FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEETING

(GIDAC)

Thursday, October 18, 2018

8:00 a.m. to 2:21 p.m.

Bethesda Marriott

Grand Ballroom

5151 Pooks Hill Road

Bethesda, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jay Fajiculay, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Joy McVey Hugick, BA

(Consumer Representative)

Public Health Policy and Communication Consultant

Simply Joy, LLC

Atlanta, Georgia

Sandeep Khurana, MBBS

Medical Director

Liver Transplantation

Geisinger Medical Center

Danville, Pennsylvania

Jennifer C. Lai, MD, MBA
Associate Director of Medicine
Director of Gastroenterology/Hepatology
University of California - San Francisco
San Francisco, California

Benjamin Lebwohl, MD, MS
Assistant Professor of Medicine and Epidemiology
Director of Clinical Research
Celiac Disease Center
Columbia University College of Physicians & Surgeons
New York, New York

Jean-Pierre Raufman, MD
(Chairperson)
Professor and Head
Division of Gastroenterology & Hepatology
University of Maryland School of Medicine
Baltimore VA Maryland Health Care System
Baltimore, Maryland

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Douglas Levine, MD, FACG

(Industry Representative)

DSL Consulting, LLC

Seekonk, Massachusetts

TEMPORARY MEMBERS (Voting)

Sally Hunsberger, PhD

Mathematical Statistician

National Institute of Allergy and

Infectious Disease

National Institutes of Health

Bethesda, Maryland

Sabrina Numann

(Patient Representative)

New Albany, Indiana

Steven F. Solga, MD
Associate Professor of Clinical Medicine
Program Director, Transplant Hepatology Fellowship
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

John Teerlink, MD
Professor of Medicine
University of California San Francisco
Director, Heart Failure
Director, Echocardiography
Section of Cardiology
San Francisco Veterans Affairs Medical Center
San Francisco, California

Udho Thadani, MD, MRCP, FACC, FAHA
Professor Emeritus of Medicine of Cardiology
Consultant Cardiologist
Oklahoma University Health Sciences Center and
District VA Medical Center
Oklahoma City, Oklahoma

FDA PARTICIPANTS (Non-Voting)

Victor Crentsil, MD

Deputy Director

Office of Drug Evaluation III (ODE III)

Office of New Drugs (OND), CDER, FDA

Joyce Korvick, MD, MPH

Deputy Director for Safety

Division of Gastroenterology and Inborn Errors Products (DGIEP), ODE III, OND, CDER, FDA

Juli Tomaino, MD

Clinical Team Leader

DGIEP, ODE III, OND, CDER, FDA

Charles Line, MD

Medical Officer

DGIEP, ODE III, OND, CDER, FDA

Ling Lan, PhD

Statistical Reviewer

Division of Biometrics III

Office of Biostatistics

Office of Translational Sciences, CDER, FDA

Joel Weissfeld, MD, MPH

Medical Officer

Division of Epidemiology

Office of Pharmacovigilance and Epidemiology

Office of Surveillance and Epidemiology

CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. RAUFMAN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Deborah Kotz. If you are present, please stand.

My name is Jean-Pierre Raufman. I am the chairperson of the Gastrointestinal Drugs Advisory Committee meeting, and I will be chairing this meeting. I will now call the meeting of the Gastrointestinal Drugs Advisory Committee to order.

We'll start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. KORVICK: Joyce Korvick, deputy director for safety, DGIEP, FDA.

DR. TOMAINO: Juli Tomaino, clinical team leader, DGIEP, FDA.

DR. LINE: Charles Line, medical reviewer, DGIEP, FDA.

DR. LAN: Ling Lan, efficacy statistical reviewer, Office of Biostatistics, FDA.

DR. WEISSFELD: I'm Joel Weissfeld, medical officer, Office of Surveillance and Epidemiology at FDA.

DR. THADANI: Udho Thadani, cardiologist, University of Oklahoma and VA Medical Center, Okh City.

MR. KHURANA: Sandeep Khurana, medical director, liver transplantation, Geisinger Health System.

DR. LEBWOHL: Ben Lebwohl, director of clinical research, Celiac Disease Center at Columbia University.

DR. FAJICULAY: Jay Fajiculay, designated federal officer for the Gastrointestinal Drugs Advisory Committee, FDA.

DR. LAI: Jennifer Lai, associate professor of medicine at UCSF.

MS. McVEY HUGICK: Good morning. I'm Joy

McVey Hugick. I am the consumer representative on the Gastrointestinal Drugs Advisory Committee from Atlanta, Georgia.

MS. NUMANN: Sabrina Numann, patient representative out of Louisville, Kentucky.

DR. SOLGA: Steve Solga, hepatologist, University of Pennsylvania.

DR. TEERLINK: John Teerlink, cardiologist, San Francisco VA Medical Center and UCSF.

DR. HUNSBERGER: Sally Hunsberger, biostatistician at NIAID.

DR. LEVINE: Doug Levine, industry representative to GIDAC.

DR. RAUFMAN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the

record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass to Dr. Jay Fajiculay, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. FAJICULAY: The Food and Drug Administration is convening today's meeting of the Gastrointestinal Drugs Advisory Committee under the

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

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

FDA has determined that members and temporary voting members of the committees are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special

government employee's services outweighs his or her potential financial conflicts of interest, or when the interests of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

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

Today's agenda involves the discussion of new drug application 210166, for prucalopride tablets for oral administration, submitted by Shire Development, LLC, proposed for the treatment of chronic idiopathic constipation in adults. This is

a particular matters meeting, during which specific matters related to Shire's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. 208(b)(3) to Dr. Benjamin Lebwohl.

Dr. Lebwohl's waiver covers an investment in Healthcare SECURA mutual fund valued between $200,000 and $300,000. The waiver allows Dr. Lebwohl to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver document, which is posted at FDA's website at www.fda.gov/advisorycommittees/committeemeetingmaterials/drugs/default.htm.

Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all

standing committee members and temporary voting members to disclose any public comments that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Douglas S. Levine is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Levine's role at this meeting is to represent industry in general and not any particular company. Dr. Levine is an independent pharmaceutical consultant.

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

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

you.

DR. RAUFMAN: Thank you.

We will proceed with the opening remarks from Dr. Juli Tomaino.

FDA Introductory Remarks - Juli Tomaino

DR. TOMAINO: Good morning. My name is Juli Tomaino, and I'd like to welcome everybody today. First, I would like to thank the members of the committee for taking the time to participate in this important discussion regarding prucalopride, proposed for the treatment of chronic idiopathic constipation, or CIC, in adults.

Many of us heard a very interesting discussion of tegaserod yesterday. And although it's important to consider the potential risks associated with the 5-HT4 receptor agonist class of drugs, we are here to discuss prucalopride.

Your discussion today should be focused on the data submitted in the NDA to support the safety and efficacy of prucalopride.

Shire, the applicant, submitted the application being discussed for prucalopride, a

selective serotonin type 4 receptor agonist, administered as an oral tablet. CIC, also known as functional constipation, is diagnosed based on the Rome criteria. The Rome criteria, now in the fourth version, characterize CIC by straining during defecation, hard stools, sensation of incomplete evacuation, fewer than 3 spontaneous bowel movements per week, and loose stools rarely present without the use of laxatives.

CIC can profoundly impact patients' quality of life and not all patients will have an acceptable response to current therapy. Therefore, additional treatment options are needed.

The general goal of CIC treatment is to increase the frequency of bowel movements, improve stool consistency, and reduce straining associated with bowel movements. The currently approved and marketed therapies for CIC are summarized in this table. Please note that the information is specific to the CIC indication, as these products are also approved for other indications.

Since prucalopride is a selective 5-HT4

receptor agonist, if approved, prucalopride would offer a different class of drug compared to the currently available therapies in the United States for CIC.

The first product shown in the table was approved in 2006 and used a slightly different primary endpoint compared to the others. In general, the responder rates range from approximately 8 to 17 percent over placebo.

In addition to these therapies, probiotics, osmotic and stimulant laxatives, stool softeners, fiber, and diet and lifestyle modification are often used for treatment, but none are approved specifically for CIC.

Additional details of the regulatory history are outlined in the briefing document. I'm going to highlight the regulatory history relevant for the discussion today.

Prucalopride is unique because it has been approved in Europe since 2009 and subsequently in other countries around the world. In the United States, the IND was originally submitted in 1998 by

a different sponsor, and trials were conducted under the IND. The IND was inactivated in 2004.

The applicant acquired the prucalopride development program in 2010 and reactivated the IND in 2012. Meetings and correspondences between FDA and the applicant focused on the concern that the extent of the prucalopride exposure and the design of the clinical trials conducted may not be adequate to evaluate the potential cardiovascular safety signal associated with the 5-HT4 receptor agonist class of drugs.

During meetings prior to the NDA submission, FDA acknowledged that the applicant had already completed phase 3 trials, and the data appeared sufficient to support submission of an NDA. However, it was not clear at that time if sufficient safety data had been collected to enable an adequate evaluation of the cardiovascular risk.

The lack of controlled trials of 12 months' duration would be a significant review issue, as the division had moved towards requiring controlled trials of 12 months' duration in a drug class for

which there have been cardiovascular safety concerns.

Although we'd like to have one year of controlled trial data, we note that there were patients from open-label trials who were treated for one year in the prucalopride development program.

Because prucalopride had been approved in Europe since 2009, the division agreed that the applicant could submit results from a non-interventional epidemiologic study that used national claims data from well-recognized European data sources in lieu of obtaining controlled clinical trial data on patients treated up to one year premarketing.

These data provide an opportunity to review the safety in a broader patient population compared to the population that was studied in the controlled trial setting.

In addition to concerns with the adequacy of the safety database, FDA communicated concerns that the primary efficacy endpoint used in the completed

trials differed from the currently recommended endpoint for trials for CIC.

Given that the phase 3 trials were completed, FDA recommended that the applicant conduct post hoc analyses using the currently recommended endpoint to see if the results are consistent. This endpoint is referred to as alternative endpoint A and was considered the key supportive post hoc endpoint analysis, as this endpoint aligns with FDA's current endpoint recommendations for CIC trials.

I'm going to provide a brief overview of the contents of the NDA, which will be discussed in greater detail in the FDA presentations later this morning. The NDA includes data from two 12-week randomized double-blind, placebo-controlled phase 3 trials, studies 3001 and 302. They were completed in 2011 and 2013, respectively, as the primary basis to demonstrate efficacy in support of FDA approval and labeling. Both trials were conducted in non-U.S. populations.

The NDA also contains data from three other

12-week phase 3 legacy trials, completed in 1999, to support the generalizability of efficacy results from the non-U.S. trials to the U.S. patient population. In addition, data were submitted from a sixth trial, a 24-week randomized double-blind, placebo-controlled phase 4 trial conducted in Europe.

Because almost 10 years has passed between when the three legacy trials were completed and the current review of the application, a large proportion of source documentation at the study sites was unavailable. However, many sites for which there were no source documentation had been inspected by FDA in the past for participation in other studies.

FDA was able to conduct inspections at 5 study sites and at the applicant. We determined that the data can be used in support of the application based on the results of the inspections at the sites where source documentation was available; inspectional history of other sites; the results of the applicant inspection, including

review of monitoring reports; the history of monitoring from the previous sponsor; and results of exploratory statistical analyses.

Overall, there were no major inconsistencies between the efficacy data from study sites without source documentation and the rest of the efficacy data.

The NDA also contains safety data relevant to the evaluation of cardiovascular safety from completed comparative trials; an analysis of the non-interventional epidemiologic study; nonclinical data; platelet aggregation studies; and a thorough QT study.

We plan to highlight the important features of the application to focus today's discussion on the major issues. The goals of today's advisory committee meeting are to discuss the efficacy data submitted in support of the proposed dosing regimen for treatment of adult patients with chronic idiopathic constipation as well as the strengths and limitations of the safety database, including the data obtained from the epidemiologic study

since there exists a potential cardiovascular safety concern with this class of drugs.

We request that you consider the totality of the evidence, given that the product has been approved in Europe in 2009 and subsequently in other countries outside of the U.S.

We have the following questions for consideration by the committee.

Question 1. Do the clinical trial data provide substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation?

Question 2. Has the potential risk of cardiovascular events with the use of prucalopride in adults with CIC been adequately addressed by the applicant?

Question 2A is a nonvoting question for discussion only. If you answered "no" to question 2, what additional safety data do you recommend?

Question 3. Does the risk-benefit profile of prucalopride support the approval of this

application?

We look forward to the discussion today. Thank you.

DR. RAUFMAN: Thank you.

Dr. Crentsil, could you please identify yourself?

DR. CRENTSIL: Hello. I'm Victor Crentsil. I'm the acting deputy director for the Office of Drug Evaluation III, Office of New Drugs, FDA, and I'm really glad to be here. Thank you [sic] -- for being late. Thanks.

DR. RAUFMAN: Thank you.

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

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any

financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

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

We will now proceed with the applicant's presentations.

Applicant Presentation - Sunil Kadam

DR. KADAM: Good morning, Mr. Chairman, members of the advisory committee, and the FDA. I am Sunil Kadam, the regulatory lead for gastroenterology at Shire. Thank you for the opportunity to present our data on prucalopride for the treatment of chronic idiopathic constipation in adults.

Prucalopride is a next-generation 5-HT4 agonist that stimulates gut motility to provide effective relief to patients with chronic idiopathic constipation.

Prucalopride is a highly selective 5-HT4 receptor agonist with strong prokinetic activity that stimulates colonic peristalsis to increase intestinal motility. Blinded evaluations of colonic transit have confirmed that prucalopride induces high-amplitude contractions. But more importantly, these contractions are propagating since the contractions need to be sequential to effectively move stool through the colon.

While it functions like a 5-HT4 agonist, prucalopride is very different from previously approved non-selective 5-HT4 products. Prucalopride is highly selective for the 5-HT4 receptor.

Unlike other non-selective products, prucalopride has a low potential for off-target effects. This is an essential distinction. Off-target affinity from non-selective 5-HT4s has

been linked to QT prolongation, ventricular arrhythmias, and cardiovascular ischemic events.

Comprehensive clinical and nonclinical research demonstrate that prucalopride has substantial cardiovascular safety margins and no meaningful affinity for the hERG channel, and ECG studies have shown no effect on QT prolongation or arrhythmias when tested at up to 10 times the recommended therapeutic dose.

Prucalopride safety is further supported by more than 8 years of postmarketing pharmacovigilance. This provides extensive patient experience since prucalopride was first approved in 2009.

Today, prucalopride is marketed in 59 countries, including Canada and countries in the EU, Asia, and South America. As of October 2017, we have more than 280,000 patient-years of experience and about 1 million treated patients to support the safety of prucalopride. Importantly, there have been updates to the prucalopride label, but there have been no updates to the CV safety

since launch.

Throughout this time, periodic safety reviews continue to support the existing label. This includes annual review by global health authorities such as EMA's Pharmacovigilance Risk Assessment Committee, or PRAC, as well as pharmacovigilance where we monitored literature and postmarketing data for potential signals. These reviews have not detected any emerging CV safety signals or data that would substantiate a change to the existing labeling.

So why did it take us so long to seek approval in the United States? In 2006, prucalopride was licensed from Johnson and Johnson for Europe and other markets outside North America. In 2009, prucalopride received central marketing authorization from the EMA and launched in the EU.

The FDA convened an advisory committee in 2011 to obtain advice regarding the need for cardiovascular assessments, including CV outcome studies for any 5-HT4 products. The committee agreed that nonclinical, clinical pharmacology, and

clinical data can alleviate the need for a cardiovascular safety study and did not consider CV toxicity to be a class effect. They also overwhelmingly voted that a CV outcomes study was not merited.

Between 2012 and 2014, Shire and the FDA collaborated on safety and efficacy plans for a prucalopride submission. As a result, Shire agreed to conduct a pharmacoepidemiology study to address any real-world concern regarding cardiovascular safety.

At our pre-NDA meeting in 2017, the FDA expressed an interest in reviewing the data supporting CV safety. Shire addressed this topic in the NDA file in late 2017, which also provided an extensive clinical and postmarketing database supporting safety and efficacy.

A total of 76 studies support prucalopride's positive benefit-risk. This includes 16 phase 3 and 4 studies, 14 phase 2, and 46 phase 1 studies.

The primary evidence we will share today comes from the pivotal and supportive studies.

Taken together, we see clear evidence that prucalopride is safe and effective for patients with chronic idiopathic constipation. The primary endpoint was met in 5 of the 6 key efficacy studies.

Consistent disease characteristics and treatment standards reinforce that the results from the entire clinical program are generalizable to U.S. patients. This is supported by the studies that were conducted exclusively in the United States.

Prucalopride safety is well characterized from clinical studies and postmarketing experience. This extensive data support prucalopride approval.

Based on the clinical results and real-world experience, we are seeking an indication for the treatment of chronic idiopathic constipation in adults. Patients will be dosed at 2 milligrams once daily. Patients with severe renal impairment should be dosed at 1 milligram once daily.

Turning now to the agenda for the rest of our presentation, Dr. Camilleri will discuss the

unmet need for prescription medication to treat chronic idiopathic constipation.

Dr. Achenbach will then review the design of our clinical studies and efficacy results.

Dr. Caminis will review the safety data, including conclusions from an in-depth review of CV safety.

Professor Tack will offer his clinical perspective on the utility of prucalopride for patients with chronic idiopathic constipation, and Dr. Silberg will continue the presentation and moderate the Q&A session.

We also have additional experts to help answer questions. All external experts or their institutions have been compensated for their time and travel.

Thank you. I would now like to invite Dr. Camilleri to the lectern.

Applicant Presentation - Michael Camilleri

DR. CAMILLERI: Thank you, Dr. Kadam.

Good morning. I am Michael Camilleri, a gastroenterologist at Mayo Clinic in Rochester,

Minnesota. I was one of the primary investigators in the development of prucalopride and in fact have devoted much of my research career to studying chronic constipation and its effects.

I'm here today on behalf of the many patients living with chronic idiopathic constipation who are trying to get relief by increasing the frequency of their bowel movements.

Chronic idiopathic constipation, or CIC, is a challenging and persistent problem, where people have fewer than 3 complete spontaneous bowel movements per week. If the difficulty to pass stools lasts for at least 6 months or is recurrent, it is considered chronic.

The idiopathic component of the diagnosis is particularly frustrating for patients, as there is no underlying medical condition or medication causing the constipation.

The multiple effects of chronic idiopathic constipation can be quite debilitating and have a significant impact on quality of life. In fact, health-related quality of life scores for people

living with chronic idiopathic constipation are comparable to patients with other conditions such as musculoskeletal conditions and diabetes. For women in particular, it's comparable to those with heart disease or depression.

Additionally, chronic idiopathic constipation may lead to increased risk for serious complications and has been associated with comorbidities such as fecal impaction, diverticular disease, and rectal prolapse. Even with these multiple effects, many patients are reluctant to talk about their chronic idiopathic constipation and end up keeping it to themselves for years.

In the United States, an estimated 35 million adults are diagnosed with chronic idiopathic constipation, and the related healthcare costs for patients are considerable. The mean annual all-cause costs were more than $11,000, and gastrointestinal-related costs were more than $4,000. Every year, constipation results in more than 3 million visits to physicians, and 92,000 hospitalizations, and several hundred million

dollars spent on laxatives.

Chronic idiopathic constipation is highly disruptive. Patients with abdominal symptoms are reported to miss 0.8 days of school or work per month. Chronic constipation is more prevalent in women who also more frequently seek treatment. In fact, women are by far the predominant patients seen in a referral setting, where the patient population is more than 75 percent female. Additionally, it is more common in elderly Americans than younger adults.

Not all bowel movements are the same and categories differ based on how they were initiated and whether they deliver a feeling of completeness. The largest category is any bowel movement a person has experienced, whether it's induced by a laxative or delivers a sense of complete evacuation or not.

Next are spontaneous bowel movements, which while spontaneous and initiated without the laxative are not totally satisfying. They leave a feeling that not all of the bowel movement has been released.

Finally, we have complete spontaneous bowel movement, or CSBM, which is the most stringent definition of a bowel movement. In this case, a person is able to initiate the bowel movement on their own and feels a sense of complete evacuation. Some experts use the acronym SCBM, and both represent the same type of BM.

When it comes to interventions for treating chronic constipation, the goal is to restore normal bowel function, which generally means having at least 3 complete spontaneous bowel movements per week and improve the patient symptoms. To do so, it is important to move stool out of the colon, which can be achieved, for example, by accelerating colonic transit.

Increased bowel frequency is associated with improvements in patient symptoms. This is why achieving at least 3 complete spontaneous bowel movements per week is both clinically meaningful from an efficacy standpoint and life-changing for patients, both emotionally and physically.

So what are our options for helping patients

reach these goals? There's a range of interventions that attempt to address chronic idiopathic constipation. No one approach works for all, and unfortunately, there continues to be high patient dissatisfaction, which results in an overall unmet need.

Patients often first try lifestyle modification such as increasing their fiber intake to get relief. This has limited impact and can cause bloating. Patients also try over-the-counter laxatives, bulking agents, stool softeners, or stimulants. Again, there's limited effectiveness.

If a patient decides to seek medical care, prescription therapies are limited to those that work by increasing colonic secretions such as lubiprostone, linaclotide, and plecanatide.

As mentioned in the FDA briefing book, these therapies provide a treatment difference from placebo ranging from approximately 8 to 17 percent using a very conservative endpoint. However, due to their similar mechanism of action, if a patient is unable to achieve success with one of these

agents, they are unlikely to reach treatment goals by switching to another.

Current prescription agents do not have a direct effect on colonic peristalsis. Why is that important? Propulsion of colonic contact is regulated in part by high-amplitude propagating contractions.

Healthy individuals experience high-amplitude propagating contractions about 6 times per day, particularly after waking up and eating, and these are often followed by an urge to defecate. But the frequency of contractions in patients with chronic idiopathic constipation is reduced, as indicated by the lower percentage of patients with colonic mass movements in the graph.

So let's move now to a discussion of prokinetic systemic agents, the 5-HT4 receptor agonists that stimulate peristalsis and accelerate colonic transit.

First-generation non-selective 5-HT4 receptor agonists, cisapride and tegaserod, were previously approved in the United States for GERD

and chronic constipation, respectively. Although they successfully provided relief to many patients suffering from gut motility dysfunction, both have been withdrawn from the U.S. market due to an analysis of safety concerns versus benefits.

We now understand that the non-specificity for 5-HT4 receptors and affinity for other receptors like 5-HT1, 5-HT2, and the hERG potassium channels creates a risk for off-target effects, including cardiovascular risk.

Here, we show the receptor binding for tegaserod and cisapride with relative affinity expressed as a logarithm on the X-axis. What we see is the potential for off-target effects caused by the binding to other 5-HT4 receptors, beginning at concentrations near the pKi or affinity constant for the 5-HT4 receptor.

This lack of specificity led to the withdrawal of the only two agents with this mechanism of action, leaving a gap in the treatment of U.S. patients with chronic idiopathic constipation for a therapy with high selectivity

for the 5-HT4 receptor.

So where does that leave us? There is an unmet medical need for adults living with chronic idiopathic constipation. This condition takes its toll on patients. They often have lived with it in silence for years, and then once they seek medical help, many still find that they are unable to get sustained relief.

Patients are looking for a safe and effective treatment that increases stool frequency, uses a different mechanism of action than a secretory agent, and has the ability to improve symptoms.

Thank you. I'm pleased to invite Dr. Heinrich Achenbach to present the prucalopride program's efficacy results.

Applicant Presentation - Heinrich Achenbach

DR. ACHENBACH: Thank you, Professor Camilleri.

Good morning. I'm Heinrich Achenbach, global clinical development team lead at Shire. I'll be sharing the efficacy results supporting

that prucalopride is a compound that increases the number of complete spontaneous bowel movements, which correlates with improved quality of life.

The efficacy evidence that I will present today comes from 6 randomized double-blind, placebo-controlled studies of at least 12 weeks' duration in patients with confirmed chronic idiopathic constipation.

Although our NDA submission has described these studies as 2 pivotal and 4 supportive, we regard each study as equally important. Therefore, all results will present the totality of data across all 6 studies. The other phase 3 and 4 studies provide additional positive evidence of efficacy, but are not discussed here since they are shorter, lasting 4 weeks or less.

All 6 studies used a similar design, where patients were randomized to receive either prucalopride or placebo. Following screening, patients were observed for a 2-week run-in period to establish their baseline constipation characteristics.

Patients meeting the protocol-specified thresholds entered into the treatment period where they were then randomized to receive placebo or prucalopride. All studies included a 2-milligram dose arm, which represents our proposed dose. Three studies included the 4-milligram dose, which was later omitted due to no increase in efficacy.

The treatment period for 5 of the 6 studies was 12 weeks. Study 401 had a 24-week treatment period. Follow-up visits were conducted 7 days following the last dose of study drug.

All studies selected adult patients with chronic idiopathic constipation, defined by the modified Rome Foundation's diagnostic criteria for functional constipation. At randomization, patients were required to have 2 or fewer spontaneous bowel movements per week during the 2-week run-in period that resulted in the feeling of complete evacuation.

In addition, patients must have had at least 1 of the criteria listed here in more than 25 percent of bowel movements, and symptoms must

occur at least 6 months prior to diagnosis and should be present during the last 3 months.

The primary efficacy endpoint was the proportion of patients with an average of 3 or more complete spontaneous bowel movements per week over the 12 weeks' treatment period. CSBMs have been shown to be a clinically meaningful outcome in patients with chronic idiopathic constipation.

I will also present several clinically relevant prespecified secondary endpoints. These included the proportion of patients that have an increase of at least 1 CSBMs per week and time to first spontaneous bowel movements, or other secondary endpoints results, including the assessment of symptoms, are presented in our briefing book.

Based on previous phase 3 studies with prucalopride, the estimated proportion of patients with greater than or equal to 3 CSBMs per week was 27 to 30 percent in the prucalopride arm and 14 to 15 percent in the placebo arm.

First, the estimated treatment effect across

the studies for the strict clinical endpoint ranged from 12 to 15 percent. This was predicted to provide at least 90 percent power with a 2-sided significance level of 0.05.

Those six studies were conducted in different regions. Studies USA-11 and USA-13 were conducted in USA. only. Study 302 and 401 were conducted in Europe, and study 6 was a global study. Study 3001 was conducted solely in the Asia-Pacific region.

Turning now to the demographics and results, while the demographics varied across the studies, each was balanced within each study. The average patient age in the 6 studies was between 41 and 58 years. Four studies, 6, USA-11, USA-13, and 401, included 10 to 19 percent elderly, while study 3001 excluded elderly patients. Most patients were female ranging from 85 to 93 percent. In contrast, study 302 only enrolled men.

Most patients were white in 5 of the 6 studies. Study 3001 was based in Asia and enrolled 92 percent Asian patients. As expected, the

inter-study demographic variations were aligned for the region where the study was conducted.

Turning now to the disease characteristics, the baseline disease characteristics were similar between arms. The mean duration of constipation varied between studies and ranged from 9 to 23 years.

At baseline, patients reported having an average of 0.3 to 0.5 complete spontaneous bowel movements per week. Achieving the primary endpoint would require an up to tenfold improvement for many patients.

Turning now to the study dispositions, overall, all patients had a similar disposition up through the 12 weeks, with a similar percentage of patients withdrawing in each arm from each study.

Let's look at the primary efficacy results. Five of the 6 studies met the primary endpoint with a higher proportion of patients treated with prucalopride, achieving 3 or more CSBMs per week. The treatment effect between the arms and these studies was statistically significant.

Twenty to 38 percent of the prucalopride-treated patients met the primary endpoint of greater than 3 complete spontaneous bowel movements per week over the 12 weeks. In study 401, the primary endpoint did not meet statistical significance.

Importantly, we see quick improvement of CSBMs that persisted over time. Across all 6 efficacy studies with prucalopride, response was attained within the first week. These patients then maintained that response over the entire treatment period.

At the request of the FDA, we also conducted a post hoc analysis called alternative endpoint A. This more rigorous endpoint has been consistently used in other studies for chronic constipation. Alternative endpoint A required patients to have at least 3 CSBMs per week and an increase of 1 CSBM from baseline per week. These criteria needed to occur in at least 9 out of 12 weeks and in at least 3 of the last 4 weeks of the study.

Consistent with the primary endpoint

results, we observed a statistically significant treatment effect between the arms in the same 5 studies. Approximately 11 to 28 percent of prucalopride-treated patients met the alternative endpoint A definition. These results further support the robustness of the primary analysis and demonstrate the persistent effect of prucalopride.

Given the outcome of study 401, we conducted an extensive evaluation, but were unable to find a causal factor for the unexpected results. Since it was a 24-week study, we analyzed the data at both 12 weeks and 24 weeks, and the results were not significant at either time point.

The evaluations of baseline demographics, disease characteristics, and use of rescue medication could not explain the finding. It was noted the effect size of the study could have been driven by the placebo response rate, which was higher than in other studies.

Although study 401 was powered sufficiently at 90 percent, a 10 percent probability existed that the results would not show statistical

significance.

Next, I'll review the results from important secondary endpoints. Four of the 6 studies showed a statistically significant difference in the proportion of prucalopride patients reporting an average increase of 1 or more CSBM per week from baseline over the 12-week treatment period. Study 302 and 401 showed a numerical improvement.

Moving to time to first bowel movement, overall, patients taking prucalopride reported having their first spontaneous bowel movements within 2 to 10 hours after initiation of therapy. This means that prucalopride works promptly, usually about 24 hours sooner compared to placebo.

We also conducted several subgroup analyses, looking at the primary endpoint results by demographics. Regardless of baseline demographics, the benefit of prucalopride treatment was observed.

The consistency of results presented today, regardless of geographic location, support that the overall efficacy data are comparable and generalizable to all patients with chronic

idiopathic constipation, regardless if they were male or female, white or non-white race, or by region.

In conclusion, all efficacy evidence across all 6 studies support that prucalopride provides a meaningful benefit for patients with chronic idiopathic constipation. An overall treatment effect of 14.6 percent was observed, as shown in this forest plot.

We see that two studies that enrolled U.S. patients, USA-11 and USA-13, are consistent with the overall results. Furthermore, the benefit of prucalopride was observed across a variety of secondary efficacy endpoints, as well as the FDA requested alternative endpoint A.

Thank you. I will now ask Dr. Caminis to present our safety data.

Applicant Presentation - John Caminis

DR. CAMINIS: Thank you, Dr. Achenbach.

My name is John Caminis. I'm the therapeutic area head in global drug safety at Shire. I will now share the data related to

prucalopride's favorable safety profile, supported by a robust nonclinical and clinical program, as well as substantive information from real-world use.

More importantly, we have completed a comprehensive investigation of cardiovascular safety that includes a review of major cardiac adverse events where an increased cardiovascular risk cannot be established.

The safety information for prucalopride comes from a very large database of patients exposed to the drug. That includes randomized, double-blind, placebo-controlled studies and open-label extension studies, as well as a number of phase 1 studies; a pharmacoepidemiology study that evaluated patients taking prucalopride compared to patients on standard of care; and finally, data from our post-marketing experience, with more than 280,000 patient-years of experience with prucalopride since launch in 2009.

Our clinical program also has substantial duration of exposure to prucalopride in patients

with chronic idiopathic constipation from the open-label safety extensions of randomized studies, patients who were in the study from three months to 2.6 years with a median duration of approximately 284 days.

Of the 2,759 patients enrolled in these open-label studies, 1,710 were treated for at least half a year and 1,052 were treated for at least 1 year. The data from this long-term exposure supports the safety profile established by the randomized studies.

In addition, we collected extensive safety data during the open-label studies. Overall, 86 percent of patients who participated in the double-blind placebo-controlled studies continued in the open-label extensions.

During the open-label studies, we collected safety information every 3 months until the last scheduled visit or at the time of discontinuation. Each visit collected adverse events, ECG, vital signs, laboratory data, and PK at months 3, 6, and 9.

The clinical evidence for safety comes from 16 randomized, double-blind, placebo-controlled studies of at least 4 weeks in duration in adult patients with chronic idiopathic constipation.

These will be referred to as pooled randomized DBPC. This includes 9 phase 3 and 4 studies, including the 6 efficacy studies with a treatment duration of at least 12 weeks, as well as 7 phase 2 studies.

Let me review the safety assessment focused on a comparison between placebo and prucalopride, 2 milligrams. More patients on prucalopride 2 milligrams reported an adverse event in the pooled randomized studies compared to placebo. There were 2 percent more AEs that were reported as severe and for AEs leading to discontinuation in the prucalopride group. However, the rates of SAEs -- and there are some prucalopride -- were similar to placebo.

Four adverse event terms were reported with at least an incidence of 5 percent. These were headache, nausea, diarrhea, and abdominal pain.

The majority of events were mild to moderate in severity and typically transient in nature.

Turning now to AEs leading to discontinuations, there are 3 event terms leading to discontinuation that were reported in at least 1 percent of patients treated with 2 milligrams of prucalopride. These are headache, diarrhea, and nausea. As before, we observed a low event rate across treatment arms and a similar frequency of occurrence across studies for the most common AEs.

We will now discuss the events with fatal outcome that occurred during the clinical studies and their open-label extensions. There were 8 events reported with a fatal outcome from the phase 2 to 4 studies as well as the open-label extensions. Three events were from the randomized studies; 2 on prucalopride, 1 on placebo. Full details on each were provided in our briefing book.

Five events occurred during the open-label extension, where all patients were treated with prucalopride. Three of the events occurred after patients had been off prucalopride for about

1 month to more than 2 months. All late events were judged by the prospective study investigator as not related to prucalopride.

Following approval, 3 events of attempted suicide were reported, and this prompted us to investigate further. The results of these detailed evaluations were discussed with and provided to the relevant health authorities.

It was concluded that no change to the safety information was warranted. We found that the incidence of psychiatric adverse events was low and the double-blind, placebo-controlled studies showed them to be similar to placebo.

Here, we summarize each of the reports of suicide or suicide-related events. This includes the 2 deaths reported on the previous slide. Five of the 6 patients had a clinical history of risk factors for suicide-related psychiatric events. The one patient with no documented history had reported having personal problems. The respective investigator concluded that none of these events were attributed to prucalopride.

I would now like to present our assessment of safety for major adverse cardiac events or MACE. The results of our investigations regarding cardiovascular safety come from six different sources; an extensive number of nonclinical in vitro and in vivo studies that included supratherapeutic concentration up to 500 times the concentration of the 2-milligram dose; a thorough QT study, as well as other phase 1 studies with intensive cardiovascular monitoring; a comprehensive review of our pooled randomized, double-blind, placebo-controlled studies examining all reported preferred terms for cardiovascular adverse events; along with independent blinded expert adjudication of cases with preferred terms for MACE or cases that might suggest potential MACE. This was done for the phase 2 to 4 and open-label studies.

A pharmacoepidemiology study, 802, compared patients treated with prucalopride to patients treated with polyethylene glycol, or PEG, a commonly used product in these patients. This

study was designed and agreed to with the FDA.

In more than 8 years of post-marketing safety experience, each data source supports the cardiovascular safety profile for prucalopride. When considering the totality of the safety data, there was no evidence to indicate an increase in cardiovascular risk for patients treated with prucalopride.

Let us review each source. In order to confirm the specificity of prucalopride and investigate receptors that may lead to off-target effects, we tested 52 receptors for binding affinity based on pKi, which is a common measure used in describing binding. These include 5-HT, monoamine, peptide, and additional receptors.

Unlike the non-specific 5-HT4 products like tegaserod and cisapride, represented here by the white and red dots respectively, prucalopride is a highly selective, high affinity 5-HT4 receptor agonist. It has low affinity for other receptors associated with cardiovascular risk.

Specifically, when looking at various 5-HT2,

5-HT1, and 5-HT7 receptors, one notices a clear difference in receptor affinity between tegaserod and prucalopride. Conversely, when looking at the hERG receptor, we see that tegaserod has less affinity than cisapride, and prucalopride has negligible affinity.

This supports the biological plausibility for why prucalopride does not contribute to increased cardiovascular risk. The evidence from a number of nonclinical studies comprises efforts to exclude all potential non-5-HT4 receptor-mediated cardiovascular interactions. They show a wide cardiovascular safety margin and an absence of mechanism for cardiovascular risk.

Importantly, we see no relevant effects on cardiovascular and cardiac electrophysiological parameters. This includes no effect on the hERG channel at concentrations of prucalopride up to 50 times the therapeutic concentration; and no effect on other ion channels or proarrhythmic tendencies observed at 500 times the therapeutic concentration; and no effect on platelet

aggregation or coronary artery contractility across three species.

In addition, a thorough QT study was conducted and intense cardiovascular monitoring was included in several other phase 1 studies in healthy volunteers.

The TQT study showed that prucalopride at doses of 2 and 10 milligrams daily has no effect on cardiac repolarization. The results support our conclusion that there is no electrophysiological change with prucalopride. This is due to the high selectivity for the 5-HT4 receptor.

In fact, the only observed cardiovascular changes in healthy volunteers were small transient increases in heart rate that return to baseline prior to the next dose. No further increases in heart rate were observed with doses up to 20 milligrams.

With these data in mind, we scrutinized the clinical data for any indication of cardiovascular risk. The number of reported cardiovascular AEs from the pooled randomized placebo-controlled

studies, as well as the open-label studies, is low, is very low. The incidence of these events when looking at the 2-milligram prucalopride group are few, with no indication of a difference compared to placebo. When looking at the open-label studies, again, the incidence is low.

Now, let us look at this data corrected for exposure. Ischemic events in the clinical studies occur at a similar frequency with prucalopride as with placebo. The numbers are low. When corrected for exposure, the incidence of cardiovascular events in open label was 1 per 100 years of exposure, lower than that for placebo.

Importantly, exposure to prucalopride in the open-label trials had a median duration of 284 days. Nonetheless, we sought the counsel of independent external experts to adjudicate our clinical data for possible MACE.

Data from the adjudication found no indication of an increased risk for MACE. The number of events were low in a population with about 31 percent of enrolled patients having a

pre-existing cardiovascular condition or disease.

Four patients, 2 on placebo, 2 on prucalopride, met the criteria for MACE across the studies from all doses of prucalopride. This results in an incidence rate of 5.2 patients per 1,000 patient-years exposure in the prucalopride group compared to 3.5 patients per 1,000 patient-years for the total prucalopride group, and 3.1 for the 2-milligram dose.

Even after expanding the review to extended MACE, the conclusions of the adjudication committee remained. There was no indication of an increased cardiovascular risk for prucalopride.

Now we will examine the results from the pharmacoepidemiology study, 802. Study 802 was a robust observational population-based study that included matching and used exposure propensity scores to ensure comparability of cohorts. The study was designed to determine whether the pooled incidence rate ratio and upper bound of the 95 percent confidence interval for MACE excludes a safety margin of 3 for patients treated with

prucalopride relative to patients treated with PEG if the true relative risk is 1.

The data were collected from the U.K., Sweden, and Germany using electronic medical records, administrative claims, or national health data registries. The German data were excluded from the pooled analysis because the clinical profile between patients treated with PEG and patients treated with prucalopride differed substantially, resulting in a more favorable outcome for prucalopride.

Cohorts from the U.K. and Sweden were balanced regarding demographic and cardiovascular risk and were included in the pooled analysis. The pooled dataset included 5,715 patients treated with prucalopride and more than 29,000 treated with PEG. Women accounted for 93 percent of the cohorts. Four percent were men 55 years or older; 5 to 6 percent of all patients had a history of hospitalization for a cardiovascular diagnosis or related procedure, and more than 55 percent of patients had 1 or more cardiovascular risk factors.

This study revealed no indication of an increased risk for MACE with prucalopride.

The pooled standardized incidence rates of MACE among patients initiating prucalopride were 6.57 per 1,000 person-years compared to 10.24 among those taking PEG. The pooled adjusted incidence rate ratio for MACE of 0.64 did not show an increased risk in patients treated with prucalopride compared to PEG.

These results showed that the 95 percent confidence interval included the null value of 1 with an upper limit below 3, consistent with the original aim of the study.

The study was designed to draw conclusions from the overall population and not subgroups. However, several subgroup analyses were conducted to further characterize cardiovascular risk. It is important to remember that post hoc subgroup analyses with a small number of events limits precision.

In conclusion, study 802 did not establish an increased risk of MACE in patients treated with

prucalopride compared with patients treated with PEG.

Because bias is a concern with observational studies, sensitivity analyses were conducted to evaluate the robustness of the primary endpoint results. These included varying outcome definitions and follow-up time windows. The results were consistent with the primary analysis.

In addition, an analysis of bias revealed that the primary results did not change unless prevalence of an unmeasured confounder was greater than 70 percent in one cohort and nearly absent in the other, which is unlikely.

Finally, we will review the postmarketing safety experience. The clinical safety profile that's supported by more than 280,000 patient-years of exposure from launch through 2017, a total of 5,072 postmarketing adverse events were reported in patients receiving prucalopride.

The vast majority of these events were non-serious. 151 events were captured as cardiovascular events, most associated with

palpitations or increase in heart rate. And our investigations show no change in the annual reporting rate since launch in 2009. In fact, since launch, we have not detected any emerging cardiovascular safety signal or data that would substantiate a change in existing labeling.

This is important, since Shire actively conducts ongoing pharmacovigilance monitoring for CV signals. At the time of regulatory reviews, there was a desire for caution based on adverse cardiovascular events reported for non-specific 5-HT4 products.

In parallel, health authorities such as the European Medicines Agency periodically reviewed the safety profile for prucalopride. This includes review by the Pharmacovigilance Risk Assessment Committee, or PRAC, which is the EMA committee responsible for assessing all aspects of risk management of human medicines, including cardiovascular safety. Throughout this time, neither Shire nor regulatory agencies have identified any cardiovascular safety signal.

In summary, prucalopride has demonstrated a consistent and favorable safety profile since launch. The core safety information for prucalopride is sufficient to inform prescribers and patients of the risks and how to minimize and prevent them.

The most common side effects are headache, nausea, diarrhea, and abdominal pain. Our studies have shown that even when adverse events occur, they were mostly mild to moderate in severity and transient.

Following methodical and comprehensive investigations of all safety data, we find no evidence of an increased cardiovascular risk. This is based on the totality of the data from multiple sources throughout the program.

Thank you. I would now like to invite Professor Jan Tack to provide his clinical perspective.

Applicant Presentation - Jan Tack

DR. TACK: Good morning. I'm Jan Tack. I'm a professor of medicine at the University of Leuven

in Belgium, and I'm the head of clinic in the Department of Gastroenterology. It's a pleasure and privilege for me to be here today and discuss my experience in treating patients with prucalopride.

Since it became available in Belgium in 2010, I estimate I have treated about 500 patients with prucalopride, and I have experienced firsthand how it can advance the care for adults living with chronic idiopathic constipation.

The pivotal trials included patients with long-standing idiopathic constipation, and many had a poor response to laxatives. And for those with normal bowel movements, it may be hard to fully comprehend what it feels like to be unable to have complete spontaneous bowel movements for close to 2 weeks. But I can tell you that this low rate correlates with substantial low quality of life and high symptom severity. The vast majority of patients that I see have tried and experienced insufficient relief from laxatives.

So when prescribing prucalopride in

practice, I see that about one-third of the patients are able to achieve 3 complete spontaneous bowel movements or more per week. Importantly though, with any increase in the number of CSBMs, patients report improvement of symptoms, and taken together, this is associated with improvement of quality of life.

Then thinking about how this relates to the results seen in the pivotal studies, Dr. Achenbach has already reviewed the data supporting how prucalopride reaches its primary endpoint. Achieving at least 3 CSBMs per week for a patient population that started with an average of 0.3 to 0.5 at baseline is truly significant. It's a tenfold increase.

However, it's important to note that the regulatory threshold of 3 CSBMs may not tell the whole story in this difficult-to-treat condition. In fact, as shown in this published analysis of the first 3 key prucalopride efficacy studies, patients can achieve a gradient of that result and also feel much better.

So although 24 percent of patients taking prucalopride achieved a total response of at least 3 CSBMs per week, we see that an even higher number increased their number of CSBMs by at least 1 per week over baseline, and my patients tell me that such an increase of 1 CSBMs is clinically meaningful.

Additionally, if we look at quality-of-life assessments, we see clinically meaningful improvement in satisfaction with the stool pattern. In line with my experience, we see patient satisfaction with prucalopride going beyond a single complete spontaneous bowel movement.

In addition, prucalopride improved some of the associated symptoms in CIC that are difficult to manage. This chart shows an analysis conducted using raw data from 3 of the randomized, double-blind, placebo-controlled trials, where patients completed the PAC-SYM. This is a patient-reported outcome questionnaire focused on symptoms in chronic constipation.

I'm showing the results for abdominal

symptoms, including bloating, discomfort, pain, and cramps. And for each of these, prucalopride demonstrated moderate to large effect sizes compared to small effect sizes for patients on placebo.

So diving a little bit deeper into what is behind this increased satisfaction, I am particularly struck by the impact that an improvement in regularity can have on a patient. In fact, I found that this is one of the most important changes for patients.

Prucalopride produces a physiological response that reflects a mechanism of action that we haven't seen with other treatments. With prucalopride, patients with a good response have a bowel movement in the morning, and then they are done for the rest of the day.

This becomes their normal stool pattern. They no longer need to worry about when it will happen or stay in the neighborhood of a bathroom in case it will happen.

So what accounts for these changes? We're

probably seeing patients responding to prucalopride's mechanism of action, which is the induction of high-amplitude propagated contractions. Dr. Camilleri already reviewed earlier that patients with chronic idiopathic constipations have fewer contractions than those without chronic constipation.

These are the results from a study that compared prucalopride to PEG in patients with chronic idiopathic constipation. As you can see in blue, the mean number of high-amplitude propagated contractions in patients taking prucalopride was significantly greater, creating a propagating contraction frequency similar to the one in healthy volunteers. And it can be expected that this increase would correspondingly increase the frequency of bowel movements at times of normal high-amplitude propagated contraction incidence.

So when it comes to managing risks in my clinical practice, I inform patients about the potential occurrence of headache, diarrhea, and abdominal symptoms like cramps or nausea. I tell

them to expect these effects, if they show up, on the first day and that they are usually transient. They are rarely a cause for discontinuation.

So considering the totality of evidence presented today, the question is whether prucalopride fills a gap in the treatment of patients with chronic idiopathic constipation, and I contend that the answer is yes.

While there are therapeutic options available, they primarily target secretion. If unsuccessful for a patient, then they are left without any other option. With prucalopride, there is an opportunity to provide a unique mechanism that addresses motility.

Patients on prucalopride increase stool frequency, improve the ease and regularity of defecation, decrease associated abdominal symptoms, and increase satisfaction with their stool pattern.

Finally, with the amount of clinical trial data and use in clinical practice, I'm confident that prucalopride is safe and well tolerated. Thank you for allowing me to share these data, and

I will hand over to Dr. Silberg, who will conclude the presentation.

Applicant Presentation - Debra Silberg

DR. SILBERG: Thank you, Professor Tack.

I am Debra Silberg, therapeutic clinical area head of GI and endocrine at Shire and will make some concluding remarks.

The Shire development team has presented the efficacy and safety of prucalopride. FDA's briefing book agrees with our assessment of the efficacy benefit in adults with chronic idiopathic constipation. The main question the panel has been asked to consider is the adequacy of data to support prucalopride's cardiovascular safety.

This NDA is unique. Unlike most new molecular entities being evaluated for approval in the United States, prucalopride was first approved in the EU in 2009, and since that time, we have been accumulating significant real-world experience.

Today, prucalopride is on the market in 59 countries, and Shire estimates that approximately

1 million patients have taken prucalopride. Extensive postmarketing experience supports the use of a non-interventional pharmacoepidemiology study to examine CV safety. This approach was discussed with the FDA and agreed upon in lieu of a prospective 12-month randomized controlled trial.

Over the past 8 years, we have conducted dedicated postmarketing CV monitoring and have found no signal that prucalopride increases CV events in patients. This includes the pharmacovigilance activities, pharmacoepidemiology study 802, which was specifically designed to look at CV events. In addition, there have been no changes in the cardiovascular safety profile since approval.

The real-world data that Shire had collected is supported by a very large development program. The nonclinical and phase 1 studies show no biologic plausibility for cardiovascular risk. The double-blind placebo-controlled trials and their long-term extension studies show low rates of CV events.

Taking all of this data together, Shire is confident that prucalopride has a positive benefit-risk profile. In the end, it is for the panel to consider the treatment option for patients with chronic idiopathic constipation.

You have heard from Professor Tack and Dr. Camilleri, world-renowned motility and constipation experts. They discuss patients who suffer from chronic idiopathic constipation who are seeking relief. Prucalopride, as a highly selective 5-HT4 receptor agonist, works by promoting high-amplitude propagated contractions.

This prokinetic agent would give physicians and patients a new efficacious treatment option with a different mechanism of action. The approval of prucalopride would fill a gap that currently exists for treating chronic idiopathic constipation and provide relief for many patients.

At this time, I am pleased to moderate the question and answer portion.

Clarifying Questions to the Presenters

DR. RAUFMAN: Thank you.

We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Thadani?

DR. THADANI: A couple of points. I was a bit confused. I'm not a gastroenterologist. The definition is so variable of defining chronic idiopathic constipation. It seems the definition used here is different than what is given in your handout and sometimes being modified.

So just clarify for me which is the proper definition at the current time. Sometimes you say stools 3 times. Sometimes it's one of the two criteria. So what is the correct definition? I know there's a lot of gastroenterologists here. Then I'll ask my second question.

DR. SILBERG: I am also a gastroenterologist, so I can address this. I think the difference that you're seeing is the criteria you use to come into a study versus the criteria that would be the Rome criteria. So when you're

doing a clinical trial, each patient would have to have less than 3 bowel movements as an exact criteria, so 2 or less complete spontaneous bowel movements per week.

When you're talking about the Rome criteria, that's just one of the characteristics that you would have to have.

DR. THADANI: Yes. And I presume there's an overlap with IBS then?

DR. SILBERG: People can come in and out of IBS and chronic idiopathic constipation, but we were not looking for patients who had necessarily abdominal pain, with relief of abdominal pain with their bowel movement, which is the criteria for IBS-C. So these patients had chronic idiopathic constipation.

DR. THADANI: My cardiovascular question is the increasing heart rate. You said about 5 or 6 beats per minute. That's average. Right? What's the range? Can it go up to 20? That's mean, right? Not a median?

DR. SILBERG: This was in healthy

volunteers, and I'll have Dr. Caminis address this.

DR. CAMINIS: Caminis, Shire. In our studies in healthy volunteers, yes, it was a mean of 5.8 beats per minute at 3 hours, and the heart rate returned to baseline at steady state. But what we found also was, in doses when we increased up to 20 milligrams, we didn't have any further increases in heart rate. And when we looked even at our other studies, our longer studies, again, there was no differences from placebo or treatment in terms of heart rate overall when measured. Thank you.

DR. THADANI: And that's true for the older patients, too? Because volunteers are usually younger people in studies. What happens to elderly or --

DR. CAMINIS: Well, we did do a study in elderly patients over the age of 83, I think, or 87. Sorry, I don't recall right now. But they were elderly patients with high cardiovascular risk. And when we looked at those on placebo and treatment, there was no difference in heart rate.

And we also measured that at Cmax, and we saw no difference.

DR. THADANI: When you said there was no dose response you could observe -- I'm presume there's tachyphylaxis. Is it the first dose effect that you lose with time, or what? Because something must have happened; you're not seeing this noise.

Any receptor-mediated drug usually cause tachyphylaxis, so I was just wondering. So as the first dose effect, you won't see it subsequently? And that might be relevant to therapeutic area, too. Any data on that?

DR. SILBERG: So I'd like Dr. Kowey to comment on that. Thank you.

DR. KOWEY: Thank you, Udho. It's a very important question that we took very seriously coming out of the phase 1 trial, where you saw -- I'm sorry. Peter Kowey. I'm a cardiac electrophysiologist from Philadelphia. I was paid for my time and transportation, but I have no equity interest in any pharmaceutical companies.

We took that very seriously, Udho, because obviously an increase in heart rate can translate into cardiovascular events, so we wanted to study that more carefully.

As you heard, there were a couple of observations that were reassuring, first that there did not really appear to be a dose finding here. That is, even at higher doses, there didn't appear to be an accessory effect.

But the thing that was the most reassuring to my examination of the data, is that as they got into the clinical trials, including the elderly in that 26 trial, which was a mean age of 83 years, they didn't see it.

This is something we've observed in lots of clinical trial experience, where normal volunteers, which was the phase 1 trial experience, who have differences in autonomic tones, sometimes have a more exaggerated effect on heart rate and blood pressure. But when you get into the target population, where they're older and have a different cardiovascular profile, the effect

doesn't exist, and that's exactly what happened here.

In the clinical trials, including the patients, the 30 or 40 percent of people that you saw who had cardiovascular risk factors, the heart rate phenomenon was not observed.

DR. THADANI: Since you are on the podium, what's the mechanism? Because it says selective HT4, so I presume no cardiac effects. I got my own postulation, but what's your theory that heart rate does go up at about 3 hours, which is the peak concentration of the drug?

DR. KOWEY: Yes. I think what we're observing here is probably a very, very small autonomic effect that, again, is only observed in people who have a large baseline autonomic change in tone, that again, when you get into the older populations where autonomic tone is not the same, it's not seen anymore, it almost certainly has to be an autonomic mechanism.

As you saw, they studied just about every receptor known to man and weren't able to find

anything else that was off-target.

DR. THADANI: So the next question is, if you increase the gut motility, can that produce either increase in sympathetic activity overall to give you that or withdrawal of vagus as a negative feedback?

DR. KOWEY: So that was another hypothesis that they entertained. And one of the things you need to know about the 26 study in that 83-year-old average-age population, they did nearly continuous cardiac monitoring through that entire study and did not see what you just described because they were as concerned about it as you.

But the answer is, the 83-year-olds responded and had efficacy, and they had increased gut motility, but they did not have a delta heart rate.

DR. THADANI: And the tachyphylaxis is possible?

DR. KOWEY: Yes, I guess. And you know that better than anybody, tachyphylaxis and dysautonomia is pretty common.

DR. RAUFMAN: Thank you. Dr. Lebwohl?

DR. LEBWOHL: Ben Lebwohl. The sponsor's pointed out that this agent has been available since 2009, so as to provide reassuring safety data.

For Dr. Caminis, are there any postmarketing safety or adverse effect data on interaction between this drug and the other prosecretory agents that are available here in the U.S. and in Europe. And perhaps for Drs. Camilleri or Tack, any efficacy data to show that this drug works in patients who have failed the existing prosecretory agents that are currently available?

DR. SILBERG: I'll start this discussion and then go to Dr. Caminis and Dr. Tack. The timing of the studies would have precluded us from having both a prosecretory agent and prucalopride at the same time. So when you look at that, we don't have that type of data.

DR. LEBWOHL: I'm referring to postmarketing or claims-based data.

DR. SILBERG: Right. So I'll have

Dr. Caminis show you what we know from postmarketing and the type of GI medications that have been used.

DR. CAMINIS: Thank you, Doctor Silberg.

Dr. Caminis, Shire. Most of these prosecretory agents obviously were not available in the U.S. during the time -- in Europe. But what I can show you is the distribution of the kind of cases that were reported with other medications here. And as you can see, there's nothing with linaclotide, plecanatide, or lubiprostone here, and most of them are either over-the-counter medications or common standard of care.

DR. SILBERG: I'll refer them to Dr. Tack in terms of the prosecretory agents in Europe.

DR. TACK: So the prosecretory agents have not all been available in Europe. Lubiprostone is available at some places, linaclotide in a majority of countries. And it is clear that of the subset that does not respond to secretagogues, a substantial proportion of these patients may respond to prucalopride. the opposite is also true.

And I think this reflects the heterogeneity of chronic constipation and probably the different modes of actions of each of these classes of agents.

DR. LEBWOHL: This is based on trial data or your personal experience?

DR. TACK: This is based on personal experience. I run a large motility clinic. I see a lot of refractory constipation amongst other GI motility disorders.

DR. RAUFMAN: Thank you. Dr. Solga?

DR. SOLGA: Steve Solga. I have two questions, the first for Dr. Camilleri. There appears to be a persistent increase in nausea and headache, study drug compared to placebo. Is this chance or physiology?

DR. SILBERG: Dr. Camilleri maybe can address your thoughts on nausea and --

DR. CAMILLERI: Thank you. Michael Camilleri, Mayo Clinic. The observation of headaches with 5-HT4 receptor agonists has been something that has been essentially unexplained

since I first studied the first 5-HT4 receptor agonists we've mentioned today, which is cisapride, when I was fellow in 1984. So I'm afraid I do not have an explanation for the association of headache with 5-HT4 receptor agonists.

The nausea is quite interesting. Some patients who have acceleration of gastric emptying with delivery of food rapidly into the small intestine, part of the prokinetic action, can have some post-prandial symptoms, and that may be described as nausea.

I'd like to summarize by stating that both of these adverse effects appear to be transient when you look at the data and also from the experience of our colleagues in Europe like Professor Tack.

DR. SOLGA: Thank you. One more question. I'm curious about the inspiration for the goals for study 401. It was done in Europe post-EMA approval and pre-reactivation of the FDA IND.

What was that study attempting to achieve at that time?

DR. SILBERG: At that time, we were looking for longer-term data. We had 12-week data for multiple studies, and the question was what happens in double blind for 24 weeks. That was why it was performed.

DR. RAUFMAN: Thank you. Dr. Teerlink?

DR. TEERLINK: So three questions, and I'll leave it to Dr. Silberg to choose the appropriate folk. The first question is in regard to slide CO-26. Would you be able to just review for us the AE profile and exposure of patients who received the 4-milligrams-a-day dose of prucalopride?

DR. SILBERG: As stated, the 4-milligram dose, we stopped after the first 3 studies.

Dr. Caminis, can you go through the data on the 4 milligrams and the AE profile?

DR. CAMINIS: May I have the summary slide on AE profile, please? This slide summarizes in our double-blind, placebo-controlled trials the AE profiles for the placebo 2-4 milligrams and all of the other doses, because we also studied 0.5 and 1 milligram.

Here, we show the severe AEs related and the serious AEs, which don't differ, and AEs leading to discontinuation for the drugs. I hope this answers your question.

DR. TEERLINK: It actually doesn't. If you could go on to show, as you did with the others, the details about those who had greater than 5 percent. This triggered because you said the reason you didn't go to 4 milligrams because of no additional efficacy. It also looks like there was actually increased adverse events, which may give some insight into what we can see in case people have more.

Do you have that? And if you don't, you can present it later. That's fine.

DR. SILBERG: We can present that later. We did look at that of course, and there are slight differences but certainly nothing significant.

DR. TEERLINK: So that's one. Number two is, given that you're presenting for the United States population, I'm interested in the assessment of treatment effects in African-Americans as well

as Asians. You lumped the kind of non-white groups together.

In slide CO-42, I'd be interested in seeing that split, the race non-white split out into Asians and African-Americans. Since you did an Asian-specific study, my guess is that -- and also give a sense of what the exposure is, the numbers of patients.

So if you could do that, that would be helpful, and if you need time to present that, though I don't anticipate --

DR. SILBERG: No, I have that.

DR. TEERLINK: Yes, I would expect you would.

(Laughter.)

DR. TEERLINK: Thank you.

DR. SILBERG: I think this is what you're asking for. This is the primary endpoint based on black or African-American. We of course did a lot in Europe, so they would not be African-American.

DR. TEERLINK: That's close to what I was asking for. If you have also the numbers of

patients there that gives the -- it doesn't give the numbers of patients exposed within those areas.

DR. SILBERG: The number of patients; well, I can tell you, for black or African-American, it was 1 to 11 percent of the total population. Here's the base distribution. Maybe this will help you.

DR. TEERLINK: So 189.

DR. SILBERG: So 6.9 percent overall.

DR. TEERLINK: Or 3.5 percent in the key efficacy studies.

DR. SILBERG: Oh, sorry. That's the open label, and then the key efficacy is --

DR. TEERLINK: So we may be judging this on 112 African-Americans.

DR. SILBERG: Right.

DR. TEERLINK: Great. Then related to that is the CO-67. What's the racial distribution of that group you have? I didn't see any racial on the demographic characteristics.

DR. SILBERG: That I probably do not have this in race.

DR. TEERLINK: It's probably because -- yes, well, we'll see. But hopefully, you'll be able to provide that for us.

DR. SILBERG: So that I understand, for the demographic characteristics, you'd like race for sex and age?

DR. TEERLINK: No. What's the racial distribution? I don't see race as one of the demographic characteristics there.

DR. SILBERG: For 802?

DR. TEERLINK: Yes.

DR. SILBERG: No. Unfortunately, that is not included in the dataset for 802.

DR. TEERLINK: I'm sorry. You did an epidemiologic study where you did not collect data on race?

DR. SILBERG: Dr. Andrews from RTI can address what was collected.

DR. ANDREWS: Elizabeth Andrews, vice president, pharmacoepidemiology and risk management at RTI Health Solutions, and one of the investigators for study 802.

We based study 802 on existing health records that could be available for research. In general, race, ethnicity are not automatically collected or included in the study dataset. I will go back and verify that we don't have that, but I think that's the case.

DR. TEERLINK: So just to help me, 802 is conducted in solely Europe?

DR. SILBERG: Correct.

DR. TEERLINK: So we can anticipate that if it goes the way most European studies go, the racial distribution there will be zero to maybe, at the most, 3 percent of people from African descent. The point being here, we have very little data in terms of being able to evaluate the effect of this agent in African-Americans.

The final question is, you did an adjudication process. Who is the adjudication committee and how was that composed?

DR. SILBERG: Dr. Caminis, can you go through the adjudication?

DR. CAMINIS: Thank you. Caminis, Shire.

The adjudication committee was made up of two cardiologists and a stroke neurologist. There was a chair of the adjudication committee. One of the members was Dr. Kowey as the second cardiologist. And the way the adjudication committee was set up, they were blinded to the data.

There was a broad search of all MACE events that was provided for them, and they would each individually review these events in a blinded fashion, write their assessment. And for those where there was disagreement, they were made by committee and decided by majority vote.

DR. TEERLINK: So this wasn't a specific academic institution, but rather individual independent hires.

DR. CAMINIS: Dr. Kowey?

DR. SILBERG: Dr. Kowey?

DR. KOWEY: Peter Kowey, Philadelphia. Yes, I was the second cardiologist. The chair of the committee was William White from University of Connecticut, and the neurologist, Phil Gorelick from Chicago, Illinois.

No, there was not any specific academic institution. We were independent, and we were very independent. I don't know if you know Billy White or not, but he runs like the best CIC in the world. And that's the reason why I agreed to do it in the first place. But it was very standard operating procedures. All the definitions and everything are in your hand-outs.

Do you have any other questions, John, about that?

DR. SILBERG: Thank you.

DR. RAUFMAN: Jean-Pierre Raufman. I'd like to address a question to Dr. Camilleri, if you know the answer. Do you know what the racial distribution is of CIC in the United States?

DR. SILBERG: Dr. Camilleri?

DR. CAMILLERI: Michael Camilleri, Mayo Clinic. Yes, the prevalence of chronic idiopathic constipation or functional constipation in the United States in adults is about 15 percent. In African-Americans, it's about 20 percent; in people over the age of 65, 20 to 25 percent. Asians and

whites have the same prevalence in epidemiological studies in the United States, and therefore, that would be around 15 percent.

DR. RAUFMAN: Thank you. Dr. Thadani?

DR. THADANI: Just to follow up, two questions, short, [indiscernible] alluded to, so I presume -- which is a central effect possibly.

Does the drug cross the blood-brain barrier? The reason I'm saying, there's been noise around suicidal tendency with this class of drugs, so does it cross the BBB?

DR. SILBERG: So we do have data on blood-brain barrier. Dr. Martin will show you that data.

DR. MARTIN: Good morning. Patrick Martin. I'm the head of clinical pharmacology and pharmacokinetics at Shire. We have taken a close look at this, and the bottom line is there appears to be very, very low CNS or brain penetration of prucalopride.

First slide I'm going to show you here is just a summary of organ exposure with radio-labeled prucalopride. This is a rat study that shows that

we've got about 0.02 percent of the radioactive dose in the brain, peaking close to the times of peak plasma concentrations, and it's gone over a period of a couple hours.

The second slide just sort of summarizes, then, the number of different ways that we've looked at whether or not there seemed to be any central effects of prucalopride. So despite the lack of evidence that we're getting any reasonable amount of drug in the brain, we've looked very carefully across all of the nonclinical studies we've done that involve any sort of behavioral endpoints and see no evidence of any central activity.

DR. THADANI: Other than the headache. Headache, I presume is central, right? It's central, right?

DR. MARTIN: That is a very natural question to ask, whether it's central. Whether it is a direct result of drug in the brain or secondary to something going on in the gut, perhaps mediated through the myenteric plexus, that's a question I

think that is unresolved. I don't have a specific answer.

DR. THADANI: So maybe gut-brain acts as -- I don't know.

DR. MARTIN: Exactly.

DR. THADANI: Another relevant question to that is the time it goes away. So there is some tachyphylaxis even on headache like the heart rate, I presume. And the reason I'm asking that question, it may be relevant to your 401 study.

The 401 study you said went up to 24 weeks. And the data you show in your graph, I presume is at 24 weeks, right?

DR. SILBERG: Actually, we showed you the 12-week so that we could compare.

DR. THADANI: What happens at 24? Does it keep on creeping up? Because what is impressive in 401? I think there's an explanation of why it didn't work, because placebo responds to the highest. You're running at 24 percent, and even when you modify your criteria, it goes to 40 percent.

So is it possible, like when you get a tachyphylaxis on other -- so there's a tachyphylaxis on the gut issue, and over time, you might lose your efficacy?

DR. SILBERG: Actually, we don't see that because we've done the long-term studies, the open label. And we can see that patients who have responded, at least 75 percent continue to respond after they've responded. So we're not getting tachyphylaxis.

DR. THADANI: It would be nice for me to look at, if you have the data to show for all the studies, 12-week, 24, whatever, over time. That would be a relevant question, at least clinically, for the GI people, too, because it's long-term treatment.

DR. SILBERG: Right. So let me show you this. Maybe this will help. This is the open-label study. Because it's long term, out to 18 months, patients were not recording their bowel movements. What they recorded, though, was satisfaction. So those are the kind of scores

you're seeing.

Those patients that responded in the double blind continued to take their medication, as did placebo patients and even those who didn't respond because it was double blind.

What you can see is that you get the response you would get. Most people would respond or not respond within the first 4 weeks. Those patients who respond continue to take the medication and continue to have a sense of satisfaction over the long term, so we are not seeing tachyphylaxis.

Now, just to identify, too, because the numbers go down, 44 percent of patients in the study discontinued, but that was due to the trial stopping, not because they were withdrawing from the trial.

DR. THADANI: In this slide, you are also showing that placebo partial responders actually do respond. They go down as well, right?

DR. SILBERG: Yes, yes, of course.

DR. THADANI: So that seems fair. What I

really wanted to see is the double-blind portions if you have it. You collected the data at week 12 and 24, and it would be very useful to see the diagrams on the double-blind portions. I realize this is an open label. If you have it, it would be great.

DR. SILBERG: Yes, we do. We do. We have the individual -- you want me to show you 401's study to show you the --

DR. THADANI: [Inaudible - off mic].

DR. SILBERG: Okay. Those were 12 weeks, so can you show me -- let's not do 401 first. Let's do all studies, the maintenance of response, the one with 401 included.

DR. THADANI: Sorry. You can show it later on since I'm --

DR. SILBERG: Let me just show you this one. This is without 401. These are the 12-week efficacy studies that had statistical significance. And you can see that you get a very quick uptake of a bowel movement in the very beginning, and then it plateaus, but it's consistent over the 12 weeks.

DR. RAUFMAN: Dr. Lebwohl?

DR. LEBWOHL: Ben Lebwohl. Are there any data on psychiatric outcomes reported in those with IBS-C? Since I anticipate there will be substantial off-label use if this were approved for CIC.

DR. SILBERG: That would be difficult for us to answer since we did not study this in IBS-C. This is chronic idiopathic constipation. So I wouldn't have that type of data in IBS-C.

DR. RAUFMAN: Ms. Numann?

MS. NUMANN: Sabrina Numann, patient representative. I have a question regarding your label recommendation. I understand the CV risk recommendation, but I have a question why you are not including possible psychiatric warning label information, considering the suicide information that you have in your data, including the 1 patient with the serotonin syndrome. That information, I didn't see that particular patient in your documents. I was wondering if you could expand on that.

DR. SILBERG: The reason in terms of the psychiatric AEs and also the suicides was the evidence really wasn't there that there was a connection to the drug, and we'll have Dr. Caminis go through what we know. He has additional data on psychiatric AEs, which might be of interest to you as well.

Dr. Caminis, can you go through the psychiatric events in summary?

DR. CAMINIS: First, I'd just like to respond -- thank you. John Caminis, Shire. The first part, I'd like to respond to your question on serotonin syndrome. The one case we did have with serotonin syndrome, the patient was on a drug already that has a proclivity for serotonin syndrome.

Before the actual event manifests, she was put on another drug that is also labeled for serotonin syndrome. So we couldn't find a contributing event for that.

Now, when it comes to psychiatric events, in our double-blind and open-label studies, we didn't

see an increase in psychiatric events in patients taking prucalopride compared to placebo. And for patients who had either a history of depression, psychiatric illness, again, we didn't find an increased risk.

The analysis of a worldwide safety database yielded insufficient information of a signal, so that's why we're not looking for it in the labeling.

DR. RAUFMAN: Dr. Thadani?

DR. THADANI: I probably have a hold on my questions. Question to address regarding the QTc interval. Obviously, it's reassuring that there's no effect on hERG channel until you go to 150 times the dose or something.

So is there a risk of overdose that could happen? And the follow-up on that is, was there interaction between this drug and other drugs, which can cause torsades or issues? A lot of patients might be on cardiovascular drugs, like sotalol, dofetilide, or others? Any data on that or caution?

DR. SILBERG: We did a thorough QT study using 2- and 10-milligrams doses, so 5 times the recommended therapeutic dose, and showed no evidence of QT prolongation at all and with a positive moxifloxacin control.

If we have that to show?

DR. THADANI: I think I read it in the briefing document.

DR. SILBERG: Okay. So we don't need to show that.

DR. THADANI: The question is the drug-drug interaction with the CYP P450 3AB. A lot of drugs have metabolites, so are there any issues with that, or what?

DR. SILBERG: We actually don't have any major metabolites. We excrete in the urine without metabolizing. I'm going to have Dr. Martin go through the drug-drug interaction studies that we did and the quite substantial amount of drugs that we tested.

DR. MARTIN: Patrick Martin, Shire. As Dr. Silberg mentioned, almost all prucalopride is

excreted unchanged in the urine, but additionally, we did quite a number of drug-drug interaction studies, really, to explore specific mechanisms to ensure that there were no unexpected findings.

This is the list of studies that we did, looking both at potential effects of prucalopride on other drugs and other drugs on prucalopride. The bottom line is that there is only one interaction of any sort that was identified, and it's a small interaction. And that was with ketoconazole, resulting in about a 30 to 40 increase in prucalopride exposures, apparently because of an effect on the active renal clearance component of prucalopride excretion.

We think there's probably a very small Pgp-mediated active renal excretion that's being blocked by ketoconazole. So the bottom line on all of this is that there appears to be really a very negligible drug interaction risk with this drug.

DR. THADANI: Realizing that ketoconazole is very potent, CYP 3A and 450.

DR. MARTIN: That's correct, but we've

explored others CYPs.

DR. THADANI: I buy that. I'm glad you did that. The question is, any anti-arrhythmics I should be worried about? We get patients of all sorts, which can cause torsades or QT issues.

DR. MARTIN: From a clinical pharmacology perspective, I don't believe so, but I think Peter may have something to add.

DR. SILBERG: Dr. Kowey?

DR. KOWEY: The valuation of this drug's effect on cardiac repolarization was very important, given the class that it's in. The preclinical data that you saw, including exposures in the preclinical situation up to 500-fold, really didn't yield anything in the standard models.

Then of course, there was the need for the thorough QT study that evaluated the drug at supratherapeutic concentrations, and the results of that analysis, you heard. It was a perfect study in terms of assay sensitivity, showing no effect. But the company continued to gather data as they

went through their clinical trial experience and, again, didn't see anything.

One of the most remarkable things is in a million patient exposures worldwide, there's never been one case of torsades reported. And in addition to that, as you've heard from Patrick, there really isn't anything to suspect on the DDI.

The two ways, though, you said that drugs interact is very important. There is a PK interaction, which Patrick addressed. There's also a PD interaction. And the PD interaction you refer to is if you give this drug on top of something like sotalol, would you see anything?

Again, the reason for using supratherapeutic doses in the thorough QT study is to obviate that problem, so that for all the drugs that we've studied that have this magnitude of QT effect, we have never seen that kind of PD interaction.

So the answer to your question is we're about as solidly able to say that this drug's not torsadogenic as we could possibly be.

DR. THADANI: Thanks. It's reassuring in a

way, but as you know, in clinical practice, when patients got ischemic heart disease, the QT goes up, and --

DR. KOWEY: Yes. That's why I said, the million patient exposures in 280,000 patient-years, I can promise you, a torsadogenic drug would have reared its ugly head by this time, and it hasn't. So I think that's probably the most reassuring piece of information.

DR. RAUFMAN: Thank you. Any additional questions or issues?

(No response.)

DR. RAUFMAN: Let's take a break. We can take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves, or with any members of the audience, and we will resume at 10:10 a.m.

(Whereupon, at 9:54 a.m., a recess was taken.)

DR. RAUFMAN: We will now proceed with the presentations from the FDA.

FDA Presentation - Babatunde Akinshola

DR. AKINSHOLA: Good morning. My name is Babatunde Emmanuel Akinshola. I'm a pharmacologist at FDA from the GI division, and I will be presenting nonclinical safety data for prucalopride pertaining to cardiovascular, genetic toxicity, and carcinogenicity studies.

You've all seen this slide today, so I won't be dwelling on it. It does show you the specificity of prucalopride as a 5-HT4 agonist that has high affinity for the 5-HT4 receptor in contrast to cisapride and tegaserod.

Moving on to in vitro cardiovascular safety studies, this slide shows the in vitro cardiovascular safety data from studies performed with prucalopride in human embryonic kidney cells, isolated guinea pig ventricular myocytes, isolated guinea pig papillary muscles, canine and rabbit Purkinje fibers, and rabbit heart.

Prucalopride had no effect on the hERG current in human embryonic kidney cells at concentrations up to 1 micromolar, which is

approximately 50 times the therapeutic Cmax. The IC50 for inhibition of the hERG potassium current was 22 micromolar, which is about 1100 times the therapeutic Cmax.

Prucalopride had little or no effect on electrophysiological parameters measured in isolated guinea pig ventricular myocytes, such as the outward or inward potassium current, slow inward potassium current, fast sodium current, and L-type calcium current.

Prucalopride at concentrations of at least 3 micromolar prolonged the action potential duration by 14 to 20 percent in isolated guinea pig papillary muscles, in canine and rabbit Purkinje fibers, and in rabbit hearts.

More in vitro studies. In isolated human atrial muscle strips, prucalopride caused a minor increase in contractile force, which is the equivalent of 20 percent of serotonin-induced contractions at concentrations of 100 nanomolar.

Prucalopride at 1 nanomolar to 10 micromolar had no contractile activity on porcine, canine, and

human isolated coronary arteries. Prucalopride at 200 nanomolar, which is about 10 times the Cmax in humans, had no significant effect on human platelet aggregation in vitro.

In in vivo studies, prucalopride at single IV doses of at least 1.25 milligrams per kilogram, which is the equivalent of 44 times the human Cmax, prolonged the duration of the QTc interval by just 11 percent in anesthetized guinea pigs.

In conscious dogs, IV or oral doses of prucalopride at 2.5 milligrams per kilogram, which is the equivalent of 89 times the human Cmax, caused a slight and transient increase in blood pressure and heart rate, but no effect on the electrocardiogram.

In anesthetized dogs, IV prucalopride up to 1.25 milligrams per kilogram, approximately 137 times human Cmax, had no adverse effect on blood pressure or ECG parameters. Oral prucalopride in these clinic studies in dogs at 30 milligrams per kilogram for 12 months had no apparent effect on ECG parameters, characteristics,

at a dose of 872 times the human Cmax.

Concluding the cardiovascular safety studies in vitro [sic - in vivo], in juvenile pigs, IV prucalopride at 1.25 milligram per kilogram, the equivalent of 101 times human Cmax had no effect on cardiovascular parameters or QT and QTc intervals.

In anesthetized pro-arrhythmogenic rabbits, IV prucalopride at up to 18.6 milligram per kilogram, approximately 600 times the human Cmax, did not cause tachycardia, torsades de pointes, or cardiac arrhythmias.

Now, moving on to genetic toxicity studies, prucalopride was positive, only in the Ames test, in salmonella TA100 strength, at concentrations of at least 500 micrograms per plate with or without metabolic activation.

However, prucalopride was negative in all the following: in vitro human lymphocyte chromosomal aberration assay; in vitro unscheduled DNA synthesis assay in primary rat hepatocytes; in vivo mouse lymphoma assay; the mouse micronucleus test; and the Big Blue transgenic rat

gene mutation assay.

Moving on to carcinogenicity studies, we have two studies. In the 2-year carcinogenicity study in mice, the incidence of mammary gland adenocarcinoma in female mice was significantly higher than controls at a high dose of 80 milligram per kilogram, which is the equivalent of 194 times the clinical exposure.

Similarly, in the 2-year carcinogenicity study in rats, the incidence of pituitary, thyroid, pancreatic, mammary gland, and hepatic tumors, adrenal and hepatic tumors were significantly higher at 229 times and 196 times the clinical exposure. Mechanistic studies suggest that the tumors observed in rodents are likely through epigenetic mechanisms.

In summary, nonclinical safety data of prucalopride has been assessed in an extensive battery of studies. Nonclinical studies do not suggest significant cardiovascular safety concerns for prucalopride at the proposed clinical dose. Positive carcinogenicity findings were observed

with doses at very high multiples of human exposure.

That concludes my presentation, and I will now yield the podium to Dr. Steven Li, who will share some clinical pharmacology studies with you. Thank you.

FDA Presentation - Shen Li

DR. LI: Thank you, Dr. Akinshola.

Good morning. My name is Steven Li. I'm the clinical pharmacology reviewer for this application. Today, I will discuss the main clinical pharmacology findings of prucalopride.

Here's the outline of my presentation. First, I will provide pharmacokinetic information and discuss intrinsic and extrinsic factors that may affect the systemic exposure to prucalopride, including organ impairment and drug-drug interactions.

Next, I will briefly discuss the dose selection rationale for the proposed 2-milligram once-daily dosage, then discuss the effect of prucalopride on QT prolongation, and finally,

in vitro evaluation of platelet aggregation for prucalopride.

Pharmacokinetics of prucalopride have been evaluated in patients with chronic idiopathic constipation in healthy adults. Overall, PK in patients and healthy subjects are similar.

Following oral dosing, peak plasma concentrations are observed within 2 to 3 hours. Dose proportional increases in Cmax and AUC were observed over the dose range of 1 to 20 milligrams. Following once-daily dosing, steady state was achieved within 3 to 4 days, with about twofold accumulation. No significant food effect on PK was observed.

Prucalopride is about 29 percent bound to human plasma protein. In vitro, it is a substrate of CYP3A. In a mass balance study, using 2-milligram radio-labeled prucalopride, unchanged drug accounted for 92 to 94 percent of the total radioactivity in plasma, while no major metabolites were identified.

Prucalopride is mainly eliminated with renal

excretions. On average, 84 percent of the total radioactive dose was recovered in urine and 13 percent of dose was recovered in feces. The half-life of prucalopride was about 1 day with mean values ranging from 15 to 27 hours across different studies.

Next, I will discuss the factors that may affect prucalopride exposure. As presented in the upper left panel, mean AUC in subjects with mild, moderate, and severe renal impairment was about 1.2, 1.4, and 2.4-fold compared to that in healthy subjects.

On the other hand, prucalopride exposure in subjects with moderate to severe hepatic impairment was similar to that in healthy subjects, as shown in the lower left panel. In addition, population PK analysis identified creatinine clearance to be a significant covariate on prucalopride clearance, while sex, race, and age were not significant covariates.

Drug-drug interactions have been evaluated in multiple studies. Today's discussion will focus

on the effect of other drugs on prucalopride's PK.

In vitro, prucalopride is a substrate of CYP3A enzymes and the P-gp transporter. In in vivo studies, ketoconazole, which is a strong CYP3A inhibitor and a Pgp inhibitor, increased prucalopride exposure by about 40 percent. Co-administration of erythromycin, probenecid, cimetidine, or paroxetine did not have a significant effect on prucalopride exposure, as presented in the right panel.

Now, I will briefly discuss the dose selection rationale for the proposed 2-milligram once-daily dosage. Prucalopride at 2 milligrams and 4 milligrams QD was studied in applicant's initial phase 3 studies in patients with chronic idiopathic constipation.

This table summarizes the proportion of patients with an average of 3 or more spontaneous complete bowel movements per week over a 12-week treatment period.

As we can see here, efficacy data suggested that the 4-milligram QD dose provided no additional

benefit over the 2-milligram QD dose. Therefore, the 4-milligram dosage was not further evaluated by the applicant in additional studies, including the 2 pivotal phase 3 trials.

Next, I would like to discuss the effects of prucalopride on QT prolongation using data from a thorough QT study conducted in healthy subjects in which prucalopride was given at 2-milligram QD for 5 days and a supratherapeutic dose of 10-milligram QD for 5 days. Moxifloxacin was used as a positive control to confirm study sensitivity.

Based on the double-delta QTcSS, which represents placebo and baseline corrected QTc based on a study-specific QT correction, no clinically relevant effect on the QT interval was observed at 2-milligram and 10-milligram doses.

As shown in the plot on the right, the largest upper bound of the 90 percent confidence interval for the mean difference between prucalopride and placebo were below 10 milliseconds, which is a threshold level of regulatory concern.

As shown in the concentration time plot on the left, the maximum concentrations for the 10-milligram dose was 5.8-fold, higher than that for the proposed 2-milligram dose. Therefore, prucalopride concentration in this study is above predicted worst-case scenario when systemic exposure can be increased under conditions such as renal impairment or drug-drug interactions, as discussed earlier.

In the in vitro study, the potential effects of prucalopride on platelet aggregation was studied using blood samples from healthy subjects. Platelet aggregation was monitored using a light transmission aggregometer.

Prucalopride was evaluated at 3 concentrations of 20, 60, and 200 nanomolar, which corresponds to onefold, threefold, and tenfold of the mean Cmax following 2-milligram QD dosing.

Here are the plots for 4 different platelet agonists, including ADP, TRAP, collagen, and epinephrine plus 5-HT. As compared to the vehicle

control on the left side of each plot, prucalopride did not potentiate platelet aggregation in vitro conditions.

Over the concentration range of 20 to 200 nanomolar for prucalopride, there were also no apparent concentration-dependent changes in aggregation response. Meanwhile, the positive control, thrombopoietin, potentiated platelet aggregation, as shown on the right side of each plot, and thus demonstrated assay sensitivity.

To summarize, for patients with severe renal impairment, a dose reduction is recommended since the AUC was 2.4-fold to that in healthy subjects with normal renal function. No clinically relevant effect on the QT interval were observed at the 2-milligram and 10-milligrams once-daily doses in a thorough QT study. Prucalopride did not significantly potentiate platelet aggregation in in vitro conditions.

This concludes my presentation. Thank you for your attention. I will now turn the podium over to my colleague, Dr. Ling Lan.

FDA Presentation - Ling Lan

DR. LAN: Good morning. I will start with a brief overview of the clinical program, summarize the baseline demographics and the characteristics within each efficacy trial and across all the trials, followed by a discussion of the efficacy endpoint and results, and a summary of the efficacy.

This NDA submission included 5 phase 3 trials and 1 phase 4 trial to support an efficacy claim. The 2 trials considered as primary for the demonstration of efficacy, studies 3001 and 302, were conducted outside of the U.S.

Study 3001 primarily enrolled female Asian CIC patients and was completed in 2011. Study 302 included male Caucasian subjects and was completed in 2013. Except for the duration of study 401, which is 24 weeks, the study design was generally similar for all efficacy studies, a 12-week multicenter randomized double-blind, placebo-controlled design.

The enrollment criteria for the submitted

trials were generally similar with slight differences, which were shown by reviewer's analysis that did not influence the interpretability or outcome of the trials.

For study 3001, the eligible patients needed to have less than or equal to 2 SCBMs per week. For the rest of the efficacy trials, the main inclusion criterion was less than or equal to 2 spontaneous complete bowel movements per week at baseline.

A bowel movement was considered to be spontaneous if the bowel movement was not preceded by the intake of a laxative within a period of 24 hours. A bowel movement was considered complete if the subject responded completely emptying his or her bowels in the diary.

All phase 3 and 4 studies evaluated prucalopride, 2 mg, versus placebo. For studies 302 and 401, patients aged 65 years or above were initiated on 1 mg with the option to dose escalate to the 2 mg. Therefore, the focus of this application is prucalopride is less than or equal

to 2 mg QD.

In general, the patients' demographics and the baseline characteristics were comparable between the prucalopride arm and the placebo arm within each study. This table summarizes various demographic and baseline characteristics across the trials.

The efficacy programs included 1 Asian trial, two U.S. trials, and 3 international trials, mainly from Europe, and were completed between 1999 and 2013. A majority of the subjects enrolled in this clinical program were female less than 65 years of age. Study 302 was the only study enrolling male subjects and 42 percent patients aged 65 years and above.

The take-home message from this slide is that although patients' demographics and baseline characteristics appear heterogeneous across efficacy trials, overall, the clinical programs provide complementary efficacy information from various aspects of the indicated CIC population.

The primary endpoint for all 6 efficacy

trials was the percentage of responders defined as patients with at least 3 SCBMs per week on average over the trial week treatment period. The calculation of weekly SCBM was carried out as follows; number of SCBMs in an interval, a week, a month, or 12 weeks, divided by the number of variable diary days in the corresponding interval, multiplied by 7.

For a week with less than or equal to 3 days of data, SCBM per week was set to missing. For a 12-week period with less than or equal to 13 days of data, SCBM per week was also set to missing.

The Cochran-Mantel-Haenszel test was the primary analysis method used to compare the difference in responder rates between prucalopride and placebo, controlling for the randomization stratification factors used in each study.

The primary population for 5 of the 6 studies included randomized subjects who received at least 1 dose of treatment. Study 302 excluded subjects at 1 study site due to a violation of good clinical practice. The applicant stated that a

decision to exclude data obtained from that site was made prior to unblinding.

Given 9 to 17 percent of missing weekly diary data and balance the missing pattern between two treatment arms, we conducted a primary analysis using observed case data for subjects with at least 37 days of data and non-responder imputation for less than 37 days of data.

The applicant's primary analysis was based on LOCF imputed data by the prespecified SAP. Varying sensitivity analyses were conducted to cope with the missing data. This forest plot illustrates the primary efficacy results. Each horizontal bar indicates the treatment difference between the two treatment arms with the corresponding 95 percent confidence interval.

When the lower bound, left end of the confidence interval, locates to the right of the zero line, which is indicated by the vertical dotted line, the result is statistically significant. Otherwise, it is an non-significant finding.

Five of the 6 phase 3 and 4 studies achieved statistical significance, except for study 401. In study 3001 and study 302, prucalopride has approximately 20 percent more responder as compared to that in the placebo, with p-values of less than .001.

Studies INT-6, USA-11, and USA-13 also demonstrated a smaller significant treatment effect of 10 to 16 percent with p-values of less than .01. Study 401 reported a positive response difference of 5 percent and a p-value greater than .05.

Our findings on the primary endpoint based on observed case data were consistent with the primary result using the LOCF data by the applicant, which also demonstrated significant treatment effect, for prucalopride in 5 phase 3 studies but not for study 401.

In addition, we conducted analysis for studies 3001 and 302 to further evaluate the impact of data from sites with no source documentation. Based on the exploratory analysis, the statistical significance of the primary endpoint in study 3001

and 302 was not affected after excluding the data from sites with no source record. A similar analysis was not conducted for the rest of the positive legacy trials due to the large proportion of missing source records.

As noted previously in the regulatory history, the prespecified and primary endpoint in the efficacy trials differed from FDA's current recommendation for the CIC indication. Therefore, at a meeting in 2014, FDA requested an additional post hoc efficacy analyses using the recommended overall responder endpoint, referred to as alternative endpoint A.

An overall 12-week SCBM responder is defined as a patient who is an SCBM weekly responder for at least 9 out of the 12 weeks of the treatment period. A SCBM responder is a patient who has both at least 3 SCBMs per week and at least 1 SCBM per week increase from baseline. The analysis of alternative endpoint A is considered the key supportive analysis.

We analyzed alternative endpoint A based on

CMH tests adjusted by the pooled country, sex, and number of SCBMs per week at baseline using non-imputed data. As illustrated in this forest plot, the results were similar to the primary efficacy findings with statistically significant treatment effects in 5 of the 6 trials. While treatment effects were relatively smaller than those for the primary endpoint, study 401 again failed on this endpoint.

Each efficacy study protocol listed multiple exploratory secondary endpoints. There was no multiplicity control prespecified for the secondary endpoints. The applicant also considered one of the secondary endpoints as clinically relevant, proportion of subjects with an average increase of at least 1 SCBM per week from baseline over a trial week treatment period.

This endpoint was listed as the key secondary endpoints in studies INT-6, USA-11, and the USA-13, and one of the secondary endpoints in the other phase 3 and 4 trials.

The forest plot shows that 4 of the phase 3

and 4 trials demonstrated positive treatment effects of prucalopride on this secondary endpoint, with a nominal level of less than .001 except for studies 302 and 401.

Based on the data submitted, all trials, except for study 401, demonstrated statistically significant treatment effects for prucalopride compared with placebo as measured by the primary endpoint and alternative endpoint A.

For the primary endpoint, we conducted a sensitivity analysis for missing data using different imputation approaches per protocol and a completer analysis. The findings were consistent with the primary efficacy results. Subgroup analysis results by age, sex, and race were consistent across all studies when subgroup of sizes were reasonable.

Together, the sensitivity analysis and the subgroup analysis results further support the demonstration of efficacy in this application.

Thank you. Next, I will turn the podium to my colleague, Dr. Charles Line.

FDA Presentation - Charles Line

DR. LINE: Good morning. My name is Charles Line, and I will be presenting the safety review of the clinical trial database. My presentation will include a description of the trials comprising the safety database; extent of drug exposure; death; serious treatment-emergent adverse events; common adverse events; discontinuations; adverse events of special interest, including MACE; other cardiac events of interest; and psychiatric events of interest.

Attempted and completed suicides were evaluated due to a concern for a potential class effect. The key aspects of the safety data will be summarized and the benefit-risk analysis will be discussed.

I will now present an overview of the clinical trials contained in the applicant safety database. The applicant safety database included 16 of the 20 completed double-blind, placebo-controlled phase 2 through 4 trials of at least 4 weeks in duration conducted in adult patients

with chronic idiopathic constipation or CIC.

This trial grouping was referred to as pool D. Four trials were excluded based upon their design, and there were no controlled trials of 12 months' duration.

The phase 2 and 3 open-label trials in CIC patients were also considered for the purposes of evaluating deaths, attempted and completed suicides, and MACE. This grouping was referred to as pool E and included 7 of the 9 open-label trials. The two expanded access trials were excluded.

This table summarizes the duration of exposure to placebo or various doses of prucalopride in weeks among patients enrolled in the double-blind trials. 1,516 patients were randomized to the prucalopride 2-milligram dose and 1,512 received at least 1 dose. 89.9 percent of subjects who received the 2-milligram dose had at least 4 weeks of exposure.

As you can see, the maximum exposure to prucalopride in the double-blind trials was 26

weeks. As you consider the safety data presented in the subsequent slides, please note that the duration of exposure was similar between the placebo and prucalopride 2-milligram group, which is the proposed indicated dose.

In the open-label trials, a total of 2,759 subjects were exposed to the study drug. Sixty-two percent of the subjects received at least 180 days of drug exposure regardless of dose. 38.1 percent had 365 days of exposure or more, 21.1 percent had 545 days of exposure or more, and 3.5 percent had 730 days of exposure or more.

I will now discuss the deaths that occurred in the double-blind placebo-controlled and open-label CIC trials. There were 8 total deaths, 7 deaths occurring in patients receiving prucalopride and 1 occurring in the placebo group.

In the double-blind trials, there were 2 deaths in the prucalopride group and 1 in the placebo group. The treatment duration of prucalopride ranged from 11 to 31 days. Five deaths occurred in the open-label trials. As noted

in the right-hand column, in these 4 cases, the subject was not taking prucalopride at the time of their death.

Five of the 7 deaths in patients receiving prucalopride occurred in subjects over the age of 70. Two of the events were myocardial infarctions that were adjudicated as cardiovascular death or standard MACE. There are also two completed suicides among the deaths in the open-label trials.

The 2 cases of myocardial infarction will be further described during the MACE discussion. The 2 cases of suicide will be further described during the discussion on psychiatric events of interest. None of these deaths were attributed to the study drug by the investigator.

For the assessment of the serious adverse events, we focused on the double-blind trials where comparisons are made to placebo. This table summarizes select serious treatment adverse events of relevance occurring in higher numbers in the prucalopride 2-milligram group versus placebo in the double-blind placebo-controlled trials. As you

can see, there was one of each of these events in the prucalopride group and none in the placebo group.

This table summarizes the common adverse events in the double-blind placebo-controlled trials directly comparing the proposed dose, prucalopride 2 milligrams, to placebo. The most common adverse events were headache, nausea, diarrhea, and abdominal pain. The percentages of these events were higher in the prucalopride 2-milligram group.

Let me draw your attention to diarrhea. Though not shown in this table, the percentages of diarrhea increase in a dose-dependent fashion in the 0.5-milligram, 1-milligram, 2-milligram, and 4-milligram doses groups. Two diarrhea events were associated with hypokalemia.

Otherwise, there was no clear association between diarrhea and dehydration or hemodynamic instability. Also, there was no clear indication that any of the reported adverse cardiac events resulted from diarrhea, dehydration, or electrolyte

imbalances.

I will now discuss the discontinuations due to adverse events. Of the subjects enrolled in the phase 2 through 4 double-blind placebo-controlled trials, or pool D, 86.1 percent of the total prucalopride group versus 87.1 percent of the placebo group completed the trial in which they were enrolled. 6.7 percent of subjects in the total prucalopride group and 5.5 percent of subjects in the prucalopride 2-milligram group discontinued due to an adverse event compared to 2.8 percent in the placebo group.

In general, the other reasons for discontinuation, including withdrawal by subject, loss to follow-up, lack of efficacy, et cetera, were fairly well balanced between the placebo and the prucalopride groups.

I will now discuss the major adverse cardiac events or MACE analysis. With respect to adjudication, 19 double-blind placebo-controlled and 9 open-label trials were analyzed for standard and extended MACE. 4,476 subjects receiving

prucalopride were included in this safety database.

Standard MACE was defined as cardiovascular mortality, including sudden cardiac death, death due to acute myocardial infarction, heart failure, stroke, or other cardiac causes, nonfatal myocardial infarction, and nonfatal stroke. Extended MACE was defined as MACE plus unstable angina requiring hospitalization.

A cardiovascular endpoint committee was established, which consisted of 2 cardiologists and 1 neurologist specializing in strokes. Using a prespecified process, all deaths, serious treatment-emergent adverse events, and known serious cardiovascular treatment-emergent adverse events underwent blinded adjudication. The cardiovascular endpoint committee chair reviewed 1,916 events from which 218 potential MACE cases were selected for adjudication.

The applicant defined 4 high-risk groups in which they divided the subjects. Group 1 contained patients with ischemic heart disease. Group 2 contained patients with a history of ischemic heart

disease or with at least 2 other cardiovascular risk factors.

Group 3 contained patients greater than 65 years of age, and group 4 contained patients with a history of ischemic heart disease and/or chronic renal insufficiency, defined as an estimated creatinine clearance of less than 60 milliliters per minute and/or peripheral vascular disease. 39.2 percent of subjects had at least one risk factor in the all-prucalopride group, which included the double-blind and open-label trials, compared to 37.3 percent in the placebo group.

In general, the percentages of subjects in the high-risk groups 1 through 4 as well as in the high-risk groups 1 through 4 combined were comparable between the prucalopride and placebo groups.

This is a busy slide, but I will draw your attention to the major points. The columns which are designated with a small N indicate the number of patients with the event. All standard MACE cases are counted in the extended MACE count.

In the double-blind trials, there were 2 cases of standard MACE in the placebo group and 2 cases in the prucalopride all-doses group. There were 7 additional cases of standard MACE in the all-prucalopride group when the open-label trials were included. I will describe these cases in a later slide.

In general, the percentages of both MACE and non-MACE events were low and comparable between the 2-milligram prucalopride and placebo groups. You will notice some imbalances in the non-MACE events listed in this table. I will display additional information in the next slide regarding the non-ischemic arrhythmias, other CV events, and insufficient information to adjudicate groups.

This table describes the non-ischemic events, other CV events, and insufficient information to adjudicate groups in more detail. The percentages of the various non-ischemic arrhythmias were low, and the differences from placebo were small in the double-blind prucalopride dosing groups. The number of other CV events were

small and comparable.

There were 13 events with insufficient information to adjudicate for the double-blind and open-label trials in CIC patients. There were 5 events occurring in 5 subjects in the prucalopride groups that were not included in this table. These events were paralysis, myocardial infarction, myocardial ischemia, deep vein thrombosis, and hemiparesis.

We reviewed the rationale for not adjudicating the 13 events as MACE and determined it to be reasonable. In general, the documentation from the adjudication committee suggested that these cases had insufficient information or insufficient evidence to confirm the respective reported diagnosis.

Even if we assume these cases to be MACE, the percentage of these events with insufficient information to adjudicate were low and comparable between the prucalopride and placebo groups in the double-blind trials.

This table lists the subjects receiving

prucalopride who had an adverse event that was adjudicated as standard MACE. Of these 9 cases, there were 2 nonfatal MIs, 5 nonfatal strokes, and 2 cardiovascular deaths. 7 of the 9 subjects experienced a standard MACE event while on prucalopride, however, 2 of these subjects experienced the event on the 2-milligram dose.

There were 2 cardiovascular deaths, 1 of which occurred 67 days after prucalopride discontinuation. Of the 9 subjects with standard MACE, 8, or 88.9 percent had some degree of cardiovascular risk. A more detailed description of these cases is found in the appendix of the FDA briefing document.

Of note, the 56-year-old male that was adjudicated as cardiovascular death had a history of cardiomyopathy, atrial fibrillation, stroke, hypertension, and hypercholesterolemia. He died of a myocardial infarction that was deemed unrelated to the study medication by the investigator.

I will now discuss some other cardiovascular adverse events of interest. In the double-blind,

placebo-controlled trials, the percentages of subjects with palpitations was comparable between the total prucalopride and placebo groups.

In the total prucalopride group, QT prolongation, related ventricular arrhythmias, and syncope/pre-syncope events occurred in less than 0.3 percent of subjects, and the percentages of events were comparable between the prucalopride and placebo groups.

ECG abnormalities occurred in 1 percent or less of subjects in the total prucalopride group, and the percentages of ECG abnormalities were comparable between the prucalopride and placebo groups.

I will now discuss the psychiatric treatment-emergent adverse events of interest. There were 2 completed suicides and 4 attempted suicides in the double-blind and open-label trials.

In most of these cases, the subjects had a history of psychiatric illness. For example, both cases of completed suicide occurred in subjects with a history of depression. The 70-year-old male

had depression and insomnia with a 1-month history of antidepressant use prior to the event, and the 40-year-old female had a history of depression and drug abuse.

In addition, both suicides occurred many weeks after the discontinuation of prucalopride. None of these cases were felt to be related to study drug by the investigator.

I'll now summarize the safety analysis. The majority of the double-blind trials were 12 weeks in duration. 38.1 percent of subjects were exposed for more than a year in the open-label trials. None of these trials prospectively evaluated MACE.

There were 7 deaths in the CIC patients treated with prucalopride and none were attributed to the study drug. The differences between the placebo and prucalopride 2-milligram groups were small for serious treatment-emergent adverse events.

The most common adverse events occurring in subjects receiving prucalopride 2 milligrams, were headache, nausea, abdominal pain, and diarrhea.

The percentages of these events were higher in the prucalopride 2-milligram group compared to placebo.

There was a dose-associated increase in diarrhea, however, there was no clear association between diarrhea and dehydration or hemodynamic instability. Furthermore, there was no clear indication that any of the reported adverse cardiac events resulted from diarrhea, dehydration, or electrolyte imbalances.

In general, the percentages of standard and extended MACE cases were low for the double-blind and open-label trials. This is in alignment with the applicant's analysis. The adjudication process classified several events as "insufficient information to adjudicate," including myocardial infarction, myocardial ischemia, angina pectoris, hemiparesis, et cetera.

Though the rationale for not adjudicating these events as MACE was reviewed and appears reasonable, there doesn't appear to be enough information available to make a final determination in these cases.

However, even if we assume these cases to be MACE, the percentage of events with insufficient information to adjudicate were low and comparable between the prucalopride and placebo groups in the double-blind trials.

The numbers of other cardiovascular events of interest were low and comparable between the prucalopride and placebo groups. Finally, the numbers of subjects with either attempted or completed suicides were low, and most of them had underlying risk factors.

I will now discuss the benefit-risk analysis for the relevant clinical trials that evaluated prucalopride. With respect to the benefit, 5 out of 6 double-blind placebo-controlled trials have shown the prucalopride 2-milligram dose to have a statistically significant higher percentage of responders compared to the placebo group in adults with chronic idiopathic constipation.

In terms of the risk analysis, the numbers of MACE events, completed and attempted suicides, and other cardiovascular events of interest in the

overall safety database, including double-blind and open-label trials, were low and comparable between the prucalopride and placebo groups.

In order to complete the discussion of the MACE analysis, Dr. Weissfeld will discuss the Division of Epidemiology's review of observational study SPD555-802.

FDA Presentation - Joel Weissfeld

DR. WEISSFELD: My name is Joel Weissfeld. I am a medical officer in the CDER Office of Surveillance and Epidemiology. I am here to offer FDA's assessment of study 802, a cohort study of the relative incidence of major adverse cardiovascular events among patients initiating prucalopride versus a matched comparator cohort.

Prucalopride entered European markets in 2009. To provide evidence about the cardiovascular safety of prucalopride, the applicant conducted study 802, which used European data sources and non-randomized observational study methods to examine the incidence of major adverse cardiovascular events, or MACE, in adults

prescribed prucalopride.

For comparison, study 802 used adults prescribed enough polyethylene glycol, or PEG, to supply more than 4 days of treatment. PEG, a widely available osmotic laxative, carries no known cardiovascular risk.

Study 802 followed a common protocol to separately conduct analyses in 5 electronic data sources compared on this slide: SNR for Swedish National Registers; 3 data sources for the United Kingdom, including ISD, Information Services Division of Scotland, CPRD, Clinical Practice Research Datalink, and THIN, The Health Improvement Network; and lastly, GePaRD, for the German Pharmacoepidemiological Research Database.

In addition to study period and region, this slide summarizes several data source features, including data type, with the term "claims" referring to database used to help administer healthcare systems and "GP EHR," referring to research databases constructed from electronic health records maintained by general practitioners;

"exposure," a reference to the method used to define follow-up time covered by treatment with prucalopride or PEG; that is, prescriptions dispensed or prescriptions written; and lastly, MACE adjudication procedure.

As shown, study 802 confirmed events as MACE with variable rigor. On one extreme, ISD reviewed medical charts to confirm MACE identified by diagnosis codes. On the other extreme, SNR and GePaRD relied on diagnosis codes without additional adjudication. Study 802 conceived MACE as a composite of 3 event types: myocardial infarctions, stroke, and cardiovascular death if associated with hospitalization.

The number of studied patients by data source varied over a tenfold range from 537 patients prucalopride exposed in THIN to 5,636 prucalopride exposed in GePaRD. For reasons to be discussed later, FDA and the applicant agreed in August 2017, for purposes of the primary comparative analysis, to amend study 802 by adding SNR to replace GePaRD.

The plot on this slide summarizes MACE incidence per 1,000 patient-years of exposure to prucalopride or PEG, by data source, including the three U.K. data sources, ISD, CPRD, and THIN, and the Swedish data source SNR. These four data sources identified 6,394 patients with exposure to prucalopride and 31,968 data-source, sex-, and age matched patients with exposure to PEG.

Overall, 103 patients experienced at least 1 major adverse cardiovascular event during follow-up time covered by prescriptions written or dispensed for prucalopride or PEG. SNR contributed to 88 of these 103 MACE patients. The U.K. data source contributed the remaining 15 patients.

As shown by the red circle, study 802 estimated MACE incidence during prucalopride use in Sweden at 11.7 per 1,000 patient-years. MACE incidence during prucalopride use appeared lower in CPRD and THIN.

As indicated by the wide confidence interval, study 802 estimated MACE incidence during prucalopride use in ISD with low precision. Please

note this plot adjusts incidence for sex and age. Overall, the patient cohorts shown in this plot contained 93 percent women, 57 percent less than 55 years of age.

By design, study 802 removed or trimmed some patients from comparative analysis. This slide summarizes the number of patients available after trimming. As mentioned earlier, the primary analysis excluded GePaRD. After trimming, the prucalopride cohorts in SNR, ISD, CPRD, and THIN included 5,715 patients with mean 5.7-month exposure to prucalopride.

This slide presents the result from primary comparative analysis for MACE in patients on prucalopride relative to matched patients on PEG. To improve control for differences between patients placed on prucalopride instead of PEG, study 802 used a generally acceptable method, which I will refer to as propensity score standardization.

Following this convenient terminology, the acronym SIR refers to standardized incidence rate. SIRR refers to standardized incidence rate ratio,

the ratio between two SIRs. Combining results from SNR, ISD, CPRD, and THIN, study 802 estimated MACE incidence in patients on prucalopride relative to patients on PEG with SIRR, 0.64, and to express statistical uncertainty, 95 percent confidence interval, 0.36 to 1.14.

Please note that the figure on this slide plots results on a logarithmic scale with tick marks equally spaced between SIRRs of 0.33 and 3.00. The figure also shows 2 thresholds, SIRR 1.00, to represent SIRs equal in prucalopride and PEG, and SIRR 3.00 to represent an SIR threefold higher in prucalopride than PEG.

The latter threshold alludes to a pre-NDA agreement between FDA and the applicant, which created as a reasonable NDA requirement an expectation for results from observational studies in Europe that excluded, with 95 percent statistical confidence, threefold MACE risk from prucalopride.

As shown here, the 95 percent confidence interval included the null SIRR value of 1.00. The

upper 95 percent confidence limit fell below the upper threshold of 3.00. The applicant used these results to support a finding of no evidence of increased risk of MACE in patients using prucalopride as compared with PEG.

Our assessment viewed study 802 as a useful source of reassuring evidence about the cardiovascular safety of prucalopride. We determined that study 802 satisfied the pre-NDA expectation for an observational study that reasonably excludes threefold MACE risk from prucalopride.

However, we share this assessment with caution against over-interpretation. As shown on the previous slide, study 802 estimated an SIRR with upper confidence bound of 1.14. We caution against interpreting this upper confidence bound as evidence that reasonably excludes prucalopride-associated MACE risks greater than 1.14.

We advise caution because our assessment identified important problems in study 802, which makes study 802 especially susceptible to

confounding despite the reasonable design tools used by study 802 to mitigate confounding.

In a drug safety context, confounding refers to uncontrolled baseline differences that affect associations measured between the drug exposure and a safety outcome. We briefly summarize two factors bearing on our assessment of susceptibility to confounding.

The first factor pertains to PEG as a comparator for prucalopride. The applicant discovered that drug reimbursement policies in Germany channeled profoundly different patients to treatment with prucalopride or PEG.

These differences appeared too extreme for the reasonable design tools -- matching, trimming, and propensity score standardization -- selected by study 802 to prevent baseline differences between prucalopride and PEG cohorts from confounding comparisons for the outcome of MACE. Because of these baseline differences, the applicant proposed and FDA agreed to exclude from primary comparative analysis the results from GePaRD, the German

Pharmacoepidemiological Research Database.

With respect to our assessment of PEG as a comparator for prucalopride, our analysis also identified possibly important clinical differences between the prucalopride and PEG cohorts from Sweden and the United Kingdom. Therefore, we assessed study 802 as vulnerable to generalized clinical practices that might channel meaningfully different patients to treatment with prucalopride or PEG.

The second factor pertains to the recognition that observation time -- that is, patient years -- in the prucalopride and PEG cohorts, distributed differently on age and other baseline factors, despite matching, trimming, and stratification by propensity score decile.

The following slide illustrates this latter point with data from Swedish National Registers, the largest data source included in primary comparative analysis. Though study procedures tightly matched patients on age, patient-years in SNR distributed differently on age because of

age-related differences between prucalopride and PEG cohorts with respect to treatment durations.

Overall, the prucalopride and PEG cohorts contain similar fractions of younger adults, 45.7 percent and 46.8 percent less than 55 years of age, respectively.

The validity of the propensity score standardization method requires comparably aged cohorts when grouped by propensity score. This bar graph shows results for patients grouped according to propensity score decile cutoffs in the prucalopride cohort. Except perhaps for propensity score decile 6 and 9, the prucalopride and PEG subcohort in each propensity score decile grouping contained comparable fractions of younger adults.

However, study 802, based MACE incidence on patient-years, not patients. Overall, the prucalopride cohort accumulated relatively more patient-years in younger adults, 49.9 percent relative to 40.4 percent for the PEG cohort.

Stratification by propensity score decile did not correct this non-comparability with respect

to patient-year age, as shown by the second bar graph on the right. The bracket shows differences most pronounced in the top three propensity score decile grouping.

Therefore, in conclusion, despite important problems making study 802 especially susceptible to confounding, FDA accepted study 802 as a useful source of evidence that reasonably excludes greater than threefold MACE risk from prucalopride. This completes FDA's presentations.

Clarifying Questions to the Presenters

DR. RAUFMAN: Thank you.

We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. I'd like to start with some questions for Dr. Akinshola, if we can have his slide 22, please?

So I'd like to pursue the question about mammary gland adenocarcinomas. Most of the people who will be taking prucalopride are going to be women.

Can you provide more data on what exactly the significance was? What were the numbers? And do you have a time course for when these mice developed tumors?

DR. AKINSHOLA: Can you repeat the question, please?

DR. RAUFMAN: Yes. It says here in your first bullet point, that the incidence of mammary gland adenocarcinoma in female mice was significantly higher than controls. So I had several questions. Number 1, what were the actual numbers?

DR. AKINSHOLA: It's higher than in controls is what it says over there. But in terms of the numbers, I don't have it here. We know that it's a cause assay. It's as a result of increasing prolactin secretion. And also in rodents, we saw that there are increases in enzyme induction in the liver, and this we know results from high concentration. That's what I have.

DR. RAUFMAN: Okay. And you don't know the time course for this as well? Was this just at the

end of the 2 years, or presumably, the mice developed tumors along a 2-year time frame.

DR. AKINSHOLA: Along the 2-year time frame.

DR. RAUFMAN: But you can't be more specific about that?

DR. CHAKDER: My name is Sushanta Chakder from FDA. This study was for 2 years, and then analyses was done. The animals are killed. The surviving animals are killed at the end of 2 years, and the safety analyses are done at the end of 2 years.

DR. RAUFMAN: Okay.

DR. CHAKDER: These are significant findings based on trend analyses and pairwise comparisons.

DR. RAUFMAN: This was at, it says, 194 times the clinical exposure. So can you reassure us that at the clinical exposure, there's no difference at a lower dose?

DR. CHAKDER: Yes. If the study is conducted today, it will not be significant because FDA has changed the guidance that highest dose to be used in carcinogenic studies should provide

25-fold exposure margins. But here, these exposure margins are much, much higher than the 25-fold recommendations.

DR. RAUFMAN: My last question along these lines, probably not for the two of you, but given that a million people worldwide have now taken this drug, is there any data regarding the incidence of breast cancer in those people?

DR. CHAKDER: We don't know this one. I refer that question to the sponsor.

DR. KORVICK: This is Dr. Korvick. I think we could ask the sponsor. Maybe they have more detailed data.

DR. RAUFMAN: Thank you.

DR. SILBERG: So particularly on breast cancer?

DR. RAUFMAN: Yes, particularly breast cancer, because that's the signal that we're seeing here.

DR. SILBERG: Yes. I'll have Dr. Caminis answer that.

DR. CAMINIS: Thank you. Caminis, Shire.

May I have the notes on postmarketing for events? So in our more than 8 years of postmarketing and experience, we haven't had any cases of breast cancer per se. We've had a couple of cases of transitional cell epithelium, 1 case of metastasis without any details, and 1 case of colon cancer. Thank you.

DR. RAUFMAN: Thank you. Dr. Lebwohl?

DR. LEBWOHL: Ben Lebwohl. I was going to ask Dr. Weissfeld about study 802. Thank you for walking us through it. The overall risk ratio was, I believe, 0.64, and you explained the potential difficulties with interpreting that, given the limitations.

When looking at a breakdown by age and gender, I don't think it was in the slide presentation, but in the briefing document, FDA briefing document, table 28 -- it's page 54 -- there were subgroup analyses. And in most of them, those risk ratios were below 1, but in men 55 years and older, the SIRR was 2.7, with a wide confidence interval but included the unity.

But given that that is a subgroup that may be at higher risk for the outcome of MACE and given those public health implications, is it worth looking further at that; for example, breaking down by data source, U.K. versus Sweden, to see if all the point estimates are in the same direction?

Related to that, I'd be interested in your opinion if these are the kind of datasets that might be useful for looking at other signals we've been talking about; for example psychiatric signal, or in light of Dr. Raufman's question, breast cancer? Would these datasets be useful in analyzing these long-term effects?

DR. WEISSFELD: Can you show backup slide number 40? What we had available to us for review were results integrating the four data sources. And off the bat, I'm not certain at this point in time that we have the subgroup analyses available for the separate data sources.

I can double-check that, but my recollection is that's not available to us. I can defer back to the applicant to see if they can respond to

subgroup analyses by data source. It will be probably very evident that once you break down by individual data sources, the small numbers will get even smaller.

The subgroup analyses by age and sex are shown under the heading "Subgroup Analyses for MACE," subgroups of younger women, 18- to 54-year-old women, older women greater than or equal to 55-year-old women, younger men and older men, showing the breakdown of the number of MACE events both in the prucalopride and PEG cohorts.

The associated standardized incidence rate ratio estimates and the 95 percent confidence interval point out that the applicant showed these same results as well when the applicant demonstrated their presentation.

As with all subgroup analyses, you're faced with the conundrum of how you interpret them. You do enough subgroup analyses, you'll sooner or later find something that might cause some level of concern.

So I think at this point in time, we just

have to hold it out as an observation of uncertain importance and something to keep in mind.

Again, the subgroup analyses for greater than or equal to 50-year-old men is based upon 4 events in the exposed group. So you just have to say that's an observation that we have to attach a certain level of uncertainty and really don't know what to make out of it beyond that.

In terms of using these data sources to look at outcomes other than MACE, long-term studies in observational study settings for cancer-related outcomes are very problematic for us at FDA, but particularly if you're interested in long-term exposures greater than 3 years.

One data source, however, that's been historically useful for that purpose is the SNR data source and some of the Scandinavian data sources. Just by virtue of the fact that these data sources are population based, relatively stable populations, and the SNR data sources are linked into their national cancer registries, it's relatively easy to ascertain these long-term events

and those data sources.

Historically, the problem, however, has been that these populations, Scandinavian or small populations -- and we're dealing with a -- in this case, you're not dealing with a rare disease, that is chronic idiopathic constipation, but conceivable that the exposure to pru [ph] may be relatively uncommon in that group.

So it's worth considering. I would say that either it would be a potential in SNR to look at that kind of outcome moving down.

Were there other questions?

DR. LEBWOHL: But just to clarify, that's for outcomes psychiatric as well as cancer?

DR. WEISSFELD: Psychiatric, I would say the advantage of SNR is that it's also linked to the mortality database. So for suicide itself, you can have relatively confidence, to the extent that that's captured by a death certificate, it would be captured in SNR.

That's also true for ISD as population-based coverage against death certificate. CPRD and THIN,

historically it's been spotty in terms of linkage to the national death index, or their equivalent of the U.S. National Death Index. And going forward, I think there's uncertainty there as well.

DR. RAUFMAN: Dr. Thadani?

DR. THADANI: Thanks. Mr. Chairman, you asked a very important question. I see that concentrations were much higher that they used. To take it further out, also there's an issue of neuroendocrine tumors. Other than breast, it seems like carcinogenic pituitary, pheochromocytoma.

So is there any data, either with the FDA or with the sponsors, to allay the fear that this doesn't happen? Because that would be an important issue to at least mention it if you have any data on that.

DR. RAUFMAN: You can go ahead and respond.

DR. SILBERG: To cover those findings, we did look at prolactin. We actually did a quite extensive look at prolactin, and I'll have Dr. Caminis go through that.

DR. CAMINIS: Thank you. John Caminis. May

I have the note slide, please, for prolactin?

In our double-blind, placebo-controlled studies, the adverse events for prolactin are the same on prucalopride and placebo, 2 cases each. One serious case on 2 milligrams had a prolactin level of greater than 200 nanograms at baseline prior to study entry. We had no adverse events in the open-label trials. And we had 6 cases in postmarketing with no confirmed signal. Thank you.

DR. THADANI: What about pheochromocytoma? Because there was some noise of heart rate increase and all that. Anything there?

DR. CAMINIS: No.

DR. THADANI: My other question is to Dr. Akinshola. Could you show me slide number 18 from FDA? In this slide, it says that there was a 20 percent increase in atrial contractions. And the reason I'm asking this question is with these drugs, there was some noise on atrial fibrillation in the database.

So if you stimulate the atria, not necessarily in this context, is there any data in

the dog model to try to produce atrial fibrillation to see if this drug is proarrhythmic, as far as that's concerned. Do you know anything?

DR. AKINSHOLA: I'm not aware of that.

DR. THADANI: Maybe, sorry, or sponsors might have.

DR. CHAKDER: This is Sushanta Chakder from FDA. Yes, they have a proarrhythmic model, a rabbit model, and there is no arrhythmia.

DR. THADANI: They try to induced atrial fibrillation just in the rat model, dog model, or what?

DR. CHAKDER: No, there is no findings. Only findings we saw, in dogs there was a transient increase in blood pressure.

DR. THADANI: So they tried to induce atrial fibrillation in the dog model? Because there are dog models available. You can actually give drugs and see --

DR. CHAKDER: No, they didn't conduct a study in dog model.

DR. THADANI: -- or you can stimulate the

atria. Because if it's contracting -- the only reason I'm asking is there were issues with the drug yesterday we discussed. Maybe the sponsor's expert wants to address that?

DR. RAUFMAN: Could the sponsor please address the question?

DR. SILBERG: Sure. Dr. Kowey, can you address this, please?

DR. KOWEY: Yes, sir. There are some -- I'm sorry. Peter Kowey from Philadelphia. There are some atrial fibrillation stimulation models. To be honest about it, none of them are great.

What we generally prefer people to do, which is what the sponsor did, is to do a full set of atrialphysiologic measurements. In other words, what does the drug do to atrial refractoriness, atrial excitability, conduction times in the atrium?

My information -- and this is sort of a 30,000-foot view of it -- was they didn't see anything, and I think that's what the FDA is telling you; that even though they didn't do a

classic AF stimulation model, all the atrial electrophysiology, as well as the ventricular electrophysiology, really didn't yield more than what you saw on some of these slides.

So the answer is, there were cases of atrial fibrillation in the clinical dataset. You're absolutely correct. And we went back and looked at that very hard because it was part of our adjudication process as well as the reporting in the clinical trials.

As best we could tell, there were a potpourri of supraventricular arrhythmias, but there was not a clear AF signal for this drug. I think I can say that with confidence.

DR. THADANI: The reason I even said that is because I know in our center with Ben Scherlag and Sunny Po, they are trying to have the -- and given your autonomic heart rate increase, I was just wondering -- obviously, it's an intellectual question -- whether it could trigger it as a possibility, although you don't see it in the database.

DR. KOWEY: No. It's a logical question based on what we talked about earlier this morning, but to the best of our knowledge and to what the company's been able to achieve, no.

DR. RAUFMAN: Dr. Weissfeld, did you want to address that?

DR. WEISSFELD: Joel Weissfeld. No. I would like to offer a clarification to a previous comment if I might. And this relates to the question of the subgroup results in older men greater than 55 years of age. We do have available to us the analyses and the separate data sources.

In SNR, there were 3 pru-exposed cases and 11 -- this is in men greater than or equal to 55 years of age, 3 cases of men of MACE in the pru cohort; 11 in the PEG cohort, with an incidence rate ratio calculated at 1.37 with a wide confidence interval of 0.25 to 5.19. This would mean that there was only -- the other 3 data sources, the U.K. data sources only provided 1 additional case of MACE in the exposed cohort and none in the PEG cohort.

So the SNR is the only data source that's informative as far as the potential MACE risk in older men.

I also point out that the numerator counts are so small that the IRR and SIR incidence tend to be very unstable. As you add a case here, you get wide fluctuation in the calculations.

DR. LEBWOHL: So certainly nothing consistent we've seen between these datasets. It's too much noise. It's not enough events.

DR. WEISSFELD: It's too much noise, and the point estimate is a little bit less alarming when you just look at SNR by itself.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: It's Steve Solga. A question for Dr. Akinshola and follows up a theme from Dr. Raufman. I read in the FDA briefing packet on page 5 that this IND was put on partial hold in 2000 over concerns of genotoxicity in carcinogenicity.

If we could please have slide 21 up, please? Twelve years later, there was a complete response,

and the IND was reactivated. I can find no more information in the briefing document about the genotoxicity and the carcinogenicity. And like Dr. Raufman, I have some questions.

I understand a little bit about slide 22. I understand nothing that's on slide 21. Big Blue transgenic rat sounds like a Halloween costume to me.

(Laughter.)

DR. SOLGA: I feel inadequate and insecure about voting on a drug that is supposed to meet an important unmet need, but spent the majority of its time in the clinical development program on hold over the data on a slide, 21 and also 22, that I don't understand.

So for greater context, did the standards at the FDA change? Did the assays change? Was the sponsor simply very slow in meeting this concern? Is it something else? All I'm looking for is reassurance that this truly meets the modern expectation in 2018 so I can vote with greater confidence this afternoon. Thank you.

DR. CHAKDER: This is Sushanta Chakder. I reviewed the IND at that time in 1999. In 2000, the carcinogenicity studies, this IND was put on hold because of the carcinogenicity finding in two species, in males and females. That is correct.

But at that time, the dose selection was based on the maximum tolerated dose in animals. So we asked for some mechanistic studies. One of them is the Big Blue transgenic gene mutation assay, and that was negative. There are a lot of other mechanistic studies like thyroid hormone stimulation and prolactin secretion.

The sponsor, Johnson and Johnson, conducted all these studies. Our concern was relieved that these tumors we saw, especially the pituitary tumors, hepatic tumors, and thyroid, and some other tumors, are rodent specific, phenobarbital-like effects.

DR. SOLGA: Thank you for that. So a lot of time has elapsed. If a new IND were filed today for a different medication, these studies would satisfy the expectations.

DR. CHAKDER: Yes, that's correct. But now our standard -- as I said to you previously, the standard has changed for carcinogenicity dose selections. The highest dose is selected based on 25-fold exposure margins. So here, the highest dose provided more than 200, 300 for safety exposure margins.

DR. SOLGA: I understand the dose issue. It's really the genotoxicity I have less understanding with, but I appreciate the response.

DR. CHAKDER: Thank you.

DR. RAUFMAN: Dr. Hunsberger?

DR. HUNSBERGER: I was just wondering, in the open-label database, women on study who were pregnant? Do we have anything about that?

DR. RAUFMAN: The sponsor can address that.

DR. SILBERG: Yes, of course. We had patients who were pregnant, and I'll have Dr. Caminis go through the pregnancy data that we have, both in the double-blind and the open-label trials.

DR. CAMINIS: Thank you, Dr. Silberg.

Caminis, Shire. First of all, prucalopride is not recommended during pregnancy and in our clinical trials. Women who are pregnant or women who became pregnant were discontinued from treatment.

The nonclinical evidence that we have in our animal studies did not indicate the potential for harmful effect. In our clinical trials, we had 30 cases. In the majority of cases, pregnancy was reported without an outcome. There was some spontaneous abortion, which occurred and were in consistent range with the published data. Thank you.

DR. HUNSBERGER: So it occurred, you said, in the double blind. So were they in the placebo and the --

DR. CAMINIS: Open label.

DR. HUNSBERGER: This is just the open label?

DR. CAMINIS: No, both, in the clinical trials together.

DR. HUNSBERGER: So you looked by arm, and

you had equal numbers of spontaneous abortions by arm?

DR. CAMINIS: No, no. This is the totality of the trials. This is the cumulative double-blind and open-label. There were 30 pregnancy events.

DR. HUNSBERGER: So can you look by arm?

DR. CAMINIS: I don't have that data. Thank you.

DR. RAUFMAN: Go ahead.

DR. HUNSBERGER: This is switching gears. I just wanted to understand the missing data a little bit more in your analysis. You said you used imputation methods. I was wondering what you did, and if you did the most conservative approach, essentially.

Also, I couldn't quite understand how much data you actually had to impute, and if you could, talk about that a bit more.

DR. LAN: Thank you. Ling Lan, statistical efficacy reviewer. If we can pull up the FDA backup slide, number 18.

This is a summary of the missing weekly

diary records by study, by treatment arm. It's not quite clear, but we can see the red line represents the missing rate in the prucalopride arm, and the dotted black line represents the missing rate in the placebo arm.

So maximum, there is 17 percent [sic - missing] rate at the end of the study. And this is why we stated in the AC backgrounder saying the missing pattern is comparable between the treatment arms.

DR. HUNSBERGER: You said you had to impute 70 percent??

DR. LAN: Seventeen.

DR. HUNSBERGER: Seventeen, okay. Okay.

(Laughter.)

DR. LAN: So this is the maximum, 20 percent.

DR. HUNSBERGER: Okay. Good.

DR. LAN: Yes. So there are multiple imputation approaches. Given the time limitation, there are non-responder imputations. I will now break down by study.

The LOCF method was used here because there was no previous communication due to the age of the study, between the agency and the applicant, so we just accepted the submission as is.

We did the non-responder imputation, as we stated, the agency's approach. Most of the study used non-responder imputation for less than 14 days of diary data. We did 37 days for the primary endpoint.

As for the alternative endpoint, which is the currently recommended endpoint, that one itself is pretty good, is 9 out of the trial weeks of weekly responders. And you have to have at least 4 days of diary data per week to be eligible for weekly responder.

DR. HUNSBERGER: So if I understand, if they were missing, did you treat them as, say --

DR. LAN: Non-responder.

DR. HUNSBERGER: Okay. And in both groups?

DR. LAN: Yes.

DR. HUNSBERGER: You never did an opposite group, so a worst-case scenario.

DR. LAN: No. We didn't do that. We did just non-responder imputation for both arms.

DR. HUNSBERGER: Okay.

DR. LAN: Yes.

DR. RAUFMAN: Dr. Thadani?

DR. THADANI: Thanks. Regarding the neuropsychiatric issues, it appears that some of the patients died after withdrawal of the medication. They were off drug for a while, and given the possible CNS entry, do you think tachyphylaxis and the suggestion in the trial on headaches and all that, could it be a withdrawal phenomenon?

I know that some of the patients are too far off. So is there a possible withdrawal issue that, when you withdraw the drug, it can produce a rebound increase in the neuropsychiatric issues? I think they probably might have data for that. I don't know.

DR. TOMAINO: Right. This is Juli Tomaino, FDA. I think one thing to remember about those patients who were off their drug at the time of

their death is that the half-life of this drug is about 24 hours.

DR. THADANI: Sure.

DR. TOMAINO: So you'd think within a week or so, it should pretty much be out of the body. So the patients that died a month, 2 months later; I think the two patients that --

DR. THADANI: You are very far --

DR. TOMAINO: -- committed suicide were 29 days after and 52 days after. So we considered the half-life of the drug as well as the time that the suicide was committed to try to make a determination of whether this might be related to the drug. The sponsor may have additional data on possible withdrawal.

DR. THADANI: I buy your 5 half-lives; I understand that. But a neuropsychiatric issue is a chronic problem. Patient might be depressed. And now he was not constipated. You withdraw the drug. He gets constipated, and it gets worse over time.

So is there any noise in the database? Those are the only things you see? I'm sure the

sponsor might have addressed it.

DR. TOMAINO: Juli Tomaino, FDA. The other thing to remember, too, is that both of these patients that committed suicide did have a history of depression as well.

DR. THADANI: Sure.

DR. TOMAINO: So there's other confounding factors that are playing in as well.

DR. THADANI: Do the sponsors have any information on the early withdrawal when you switch them off the drug, any issues with the neuropsychiatric issues?

DR. SILBERG: Not in terms of the -- we agree with the FDA that the length of time that they were off the drug did not make it attributable to prucalopride.

DR. THADANI: If I may ask another question, these patients in your database are on active drug. What is the concomitant medications they were taking for constipation at that time? Some of them must be on --

The incidence of diarrhea is up. So what

are they taking? Other agents, laxatives, and all that were allowed in the study? So could that have a confounding effect on the incidence of diarrhea or anything?

DR. TOMAINO: Patients were allowed to take laxatives as per a prespecified rescue medication rule. And if they hadn't had a bowel movement in 3 days, they were allowed to take the protocol-administered laxative, which we see pretty standard across our constipation trials.

The important thing to point out is that the primary endpoint accounts for that because to have a complete spontaneous bowel movement, it cannot be preceded by a laxative. However, the rates of diarrhea -- the concomitant use of laxatives may have contributed.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: Question for Dr. Line on slide 56. I continue to stew about this headache, nausea thing along with Dr. Thadani. I think both of us were trying to understand mechanisms more.

I'm just curious to know, if you wouldn't

mind indulging me, please, the folks who had nausea and headache, were those the same patients or were they different? Do we know?

DR. LINE: To make sure I understand your question, you're asking me if patients who had headache also had nausea?

DR. SOLGA: I'm sorry. I must have the wrong slide. You had showed a slide about these adverse side effects of nausea and headache.

DR. LINE: Fifty-five?

DR. SOLGA: Fifty-five. I apologize.

DR. LINE: Nausea and headache are not mutually exclusive, Doctor. In some cases, patients had both. In some cases, patients had one or the other. In other words, do you want me to tell -- we don't have that information.

DR. KORVICK: Maybe the sponsor does.

DR. RAUFMAN: Does the sponsor have that information?

(No response.)

DR. RAUFMAN: Thank you. Ms. Hugick?

MS. McVEY HUGICK: I'm going to shift gears

a bit. Study 401, there was like a much smaller treatment effect, and nobody seems to know why.

As a consumer representative, I want to understand what you want us to do with that. It's 310 people, so I'm just kind of curious. I'd ask that of the sponsor and FDA.

DR. TOMAINO: Study 401, was conducted as a phase 4 trial to look at longer-term efficacy. We considered this failed trial in the context of the 5 other trials that did show statistically significant results. We were not able to identify a clear reason for the treatment failure other than it could happen.

The one thing that we looked at that was important in our minds was to see that there wasn't a decrease in efficacy between week 12 and week 24, and we didn't really see that. That was our concern. We wanted to make sure the patients weren't eventually losing efficacy, knowing that this is a chronic condition, and that did not seem to be the case. So we take it as part of our totality of evidence.

MS. McVEY HUGICK: The process. Got it. Thanks.

DR. RAUFMAN: Dr. Teerlink?

DR. TEERLINK: One thing regarding 401, it was interesting to me to see the differences between the reporting rates of the diary entries early on. And it looked like there was much higher absence of data in the treatment group early on compared to the placebo group. And I don't know if that contributed or not in terms of the analyses methods, but that's another hypothesis.

I guess we could go to FDA slide 46. I guess this is for Dr. Lan. One of the comments there is that the subgroup analyses had reasonable subgroup sizes.

Given that one of our mandates is to make sure this is appropriate for the U.S. population, do you believe that the subgroups that are represented in those analyses, as well as the 802 study for the black population, is appropriate for us to be able to evaluate the efficacy and safety of this agent in that population? Which represents

15-ish percent of our U.S., but we have less than 3 percent in the trials.

DR. LAN: Thank you for the question, Dr. Teerlink. This is Ling Lan, efficacy statistical reviewer. I can't comment on study 802. I didn't review that dataset, but for the 6 efficacy studies, there are in total less than 100 African-descendant subjects.

For those 3 studies who included African-American subjects, it's at most 8 or 7 percent. So break that down, 33 subjects in USA-11 or 13. Then you break that down to 2 arms. You have 15, and at most, 19 per arm.

So in that case, we cannot draw any reasonable inference based on such smaller group sizes. That's the reason we concluded it's comparable.

DR. TEERLINK: Thank you.

Dr. Weissfeld, can you address the 802, the racial composition of the 802? And hopefully, the sponsor will be able to if they can't.

DR. WEISSFELD: Joel Weissfeld, FDA.

There's no information about race in these datasets. And that's not unusual in these data sources. When race is available as a variable, it's often missing, so it's a problem in these data sources.

DR. TEERLINK: Yes, it's a challenge.

DR. RAUFMAN: Dr. Lai?

DR. LAI: Can we see slide 63 please? Yes. Can we assume from this slide 63 that there were no completed or attempted suicides among individuals in the studies who had never seen drug?

DR. TOMAINO: Juli Tomaino, FDA. I just want to make sure I understand your question. You're asking if, from this slide, we can conclude that there were no completed suicides in the patients not exposed to prucalopride?

DR. LAI: Correct.

DR. TOMAINO: So from the reported -- these are all of the reported suicides that happened on prucalopride. There were no suicides reported in the placebo group in the double-blind trials.

DR. LAI: Okay. And were the rates of

depression and/or underlying psychiatric history similar between the two groups, the exposed and unexposed?

DR. TOMAINO: I believe they were. I think we have that information in our background. I will double check.

DR. LAI: While I recognize that having and underlying history of depression certainly confounds our ability to determine an association clearly between the exposed group and the event, I would imagine that if this drug was approved in the U.S., there will be a lot individuals with depression and CIC who will be taking this medication. So it would be nice to have that information.

DR. RAUFMAN: Dr. Thadani?

DR. THADANI: Yes, thanks. I alluded to the 401 study. I think the sponsor's slide 35 probably really clarifies.

Can we have a look at that, slide 35 from the sponsor? I think it clearly shows that's the problem with the subjective trials, same with

angina. There's so much variation in the placebo-controlled study, because the response rate on placebo, here it's 10.3 and the high is 20. If it was 10.3, study 401 would look marvelous. But I think those things happen over time. We see it all the time in different patient populations here differently.

So that could be the real explanation, why bad luck [indiscernible], you have a higher placebo response, because average response on the active medication is about 25 percent, which is maintained in one of the studies, 30. And this is again highlighted more in your slide 38 from the sponsor, 38 also.

Again, this one again shows sometimes it is 5, sometimes 12.5. So it's in the right direction, but I think placebo plays havoc sometimes in trials. So that could be the explanation you were asking.

Although the sponsor in their briefing documents said they couldn't identify, I think the identification is right here because the placebo

response just varies. Some people are more subjected than others, I'm presuming.

DR. RAUFMAN: Ms. Numann?

MS. NUMANN: Sabrina Numann. Just to be clear, is the FDA not recommending a label warning for suicide risk on this product?

DR. KORVICK: This is Dr. Korvick. We'd like to address the previous question. We have the information.

DR. TOMAINO: Just to get back to Dr. Lai, and then we'll address your question.

Yes, we do. On page 56 of our background, in the double-blind studies, the percentages of the psychiatric events were comparable between the placebo and the prucalopride, and the numbers were low.

DR. LAI: Comparable statistically or clinically?

DR. TOMAINO: Qualitatively, descriptively.

DR. KORVICK: Usually, we don't do statistics on the multitudinous list of adverse events that are generated from clinical trials. So

you can see the rates are comparable because of type 1 error.

You ask about labeling. We usually don't talk about labeling here. However, if you would like to recommend your idea of what we should include in labeling, we'd be interested to discuss that. Those are issues that are discussed after we get all the input from you and complete our review. So we can't comment on that.

MS. NUMANN: Thank you.

DR. RAUFMAN: Additional comments, concerns?

DR. LAN: If I can have an opportunity to get back to Dr. Hunsberger?

DR. RAUFMAN: Yes.

DR. LAN: Thank you. Ling Lan, FDA's statistical reviewer.

Dr. Hunsberger, the effect size for the efficacy studies ranges from 5 percent to 22 percent, and missing data rate is about 9 percent to 17 percent. So using the worst-case imputation, the imputing missing to the responder on the placebo and to non-responder in the

treatment arm, none of these trials will be significant. That goes back to your earlier question. Thank you.

DR. RAUFMAN: We will now take a roughly one-hour break for lunch. Panel members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves, or with any member of the audience. We will resume at 1:00 p.m.

(Whereupon, at 11:48 a.m., a luncheon recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. RAUFMAN: Good afternoon.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors.

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

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

DR. SRINIVASAN: Good afternoon. Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivasan. I'm a physician with a master's in public health from Johns Hopkins University.

I currently work as a senior fellow for the National Center for Health Research. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

We have concerns about the drug in question today, prucalopride. One of our primary concerns is that the clinical trials are not representative of the patients in the U.S. that have chronic idiopathic constipation.

The patients in the clinical trial are younger, whiter, and non-obese, with a low risk of cardiovascular events. That is not a representative group of patients. In addition, there is no information about other patient

characteristics that may affect the safety and efficacy of the drug such as smoking history, family history of heart disease, or other medical conditions and treatments causing constipation.

The only studies done in the American population were two studies completed in 1999. In addition to patients being white and relatively young, they were probably less likely to be obese. I say that because the prevalence of obesity in the U.S. has increased dramatically in the last two decades and is now 25 to 40 percent in almost all states today according to the CDC.

The American diet has also changed, as well as most sedentary habits and an increase in the use of prescription medications. We can't assume that a trial done in 1999 that pertains to constipation is applicable today.

When we consider those shortcomings of the old studies and the new ones, there is not enough information for the FDA to evaluate whether the benefits of this drug outweigh the risks for the U.S. population that is likely to be prescribed

this drug if it is approved. There are too many differences between the patients studied in all those trials and patients likely to be prescribed the drug in the U.S.

In addition to obesity, diabetes, diet, and exercise, think also of the number of prescription drugs that older people in the U.S. take compared to younger patients from Australia, Asia, and Europe. All of these health concerns could affect the safety of the drug.

Even in terms of something as important as drug interactions, we are unclear about the effect of prucalopride on other medications. For example, research trials done in Australia show that this drug can reduce the efficacy of oral contraceptives taken by some women.

The information is included in the Johnson label for Resotran, but is not mentioned in the FDA review that you received. It seems likely that the drug would have a similar effect in U.S. women who are taking hormones for contraception and could also have an unfortunate interaction for women

taking hormones for menopause symptoms or to prevent estrogen-receptor-positive breast cancer.

Biological and cultural factors affect the outcomes and the severity of constipation episodes. The lack of diversity and the lack of U.S. data mean that we cannot predict how effective or safe the drug will be in most of the patients that will expect to be treated with this drug. It would be impossible to know if the drug is safe in older black women or men, for example.

Lastly, this short duration of the clinical trials raises some safety concerns. The longest double-blind clinical trial was only 24 weeks long. This disease is a chronic condition, so patients would be expected to take this drug on and off for years. Many of the heart-related adverse effects may take years to manifest. This is why FDA typically requires longer clinical trials for such drugs, so as to better identify additional safety concerns such as major adverse cardiac events.

In summary, this drug was tested on a population with limited demographic variability,

and we should really focus on whether this drug will be effective and safe for the American population. The FDA must require further verification of the efficacy and the safety of this drug in relevant populations in order to make an informed decision. Thank you.

DR. RAUFMAN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. STEIN: Hi. My name is Ellen Stein. I have no financial disclosures. I am the clinical director of gastroenterology at the Bayview Medical Center and motility specialist at Johns Hopkins University. I would like to thank the committee and all in the room for their time and attention.

I spend time in my clinic helping people. I take on the cases that other doctors cannot manage. I partner with my colorectal surgery colleagues to save colons everywhere from unnecessary resection. I see patients from all walks of life, and I will tell you two of their stories today.

One patient came to me several years ago in an emergency appointment before her colon was going to be removed. I was her second opinion. I offered my advice to this lovely young woman in her mid-20s who had dropped out of school due to the severity of her symptoms. I explained that with time and medication, I thought her idiopathic constipation could actually be managed.

She was having less than 1 bowel movement a week at the time, with intense bloating, pain, and nausea. She trusted in me, and we went through a series of medication trials. We engaged her in physical therapy, psychotherapy, and we weaned her off all narcotics. Then and only then was linaclotide finally able to help her symptoms long enough with other medical therapies to allow her bowel habits to resume.

But it took months to achieve a good effect, and she has only slowly been able to rebuild her structure and function and is now considering going back to school next year.

Without adequate medical therapy, this woman

would have possibly lost her colon in a vain attempt to improve her quality of life. She lost three years of her life with her debilitating symptoms. She became depressed and isolated in her challenge to have normal bowel habits again.

Things are finally looking up for her, as she has spontaneous daily bowel movements with her current regimen. She's a lucky one.

Another patient came to me just this past week. She is at her wit's end in her late 20s. She's trying to function. She has a boyfriend, a job. She wants to think about pregnancy in the next few years, and a colectomy would ruin those plans.

She has no bowel movements without her medications. And with the entire pharmacy of over-the-counter options, she might have a bowel movement every few days, but only with a lot of distress.

She's cycled through everything available on the market, Amitiza, Linzess, lactulose, senna, Dulcolax, and other agents only with minimal relief

of her symptoms. Some days, she will spend hours in distress at home, avoiding her friends and family, waiting for relief. Some days, she cannot go to work, the symptoms are so severe. She is terrified that these things will continue to decline. She has chronic idiopathic constipation.

We will work together, I told her, to make sure her defecatory dysfunction is managed because many of these patients develop dysfunction from inappropriate, intense straining during years of idiopathic constipation.

She is currently at the end of the road of medical options in the U.S. We discuss thinking about more intensive options like high-volume enemas and more invasive maneuvers, but if there were other medications with slightly different mechanisms of action available, like prucalopride, perhaps she would finally have the response she needs and be able to restore function.

The effects of constipation are incredibly palpable for these young women and men. They are isolated, depressed, challenged to function, and

they often must have special accommodations to work or finish schooling.

There are only a few approved medications to try, and there are even fewer studies demonstrating the true safety of years of use of the other medications grandfathered into our system. I focus my work on the whole patient. I always start with diet and exercise. I emphasize opioid avoidance and discontinuation, and we go through every possible method to help augment therapy, but the medications we have here in the U.S. are often not enough.

It's hard to explain to patients that just across the border in Canada or across the pond in European countries, there are other possibly better options that are readily available for relatively safe use. And even if the efficacy of any of these drugs is not 100 percent, we know that different people respond to different medications differently.

I see the patients who need more options. We will someday understand at a genetic and mucosal

level how to predict those responses better, but in the meantime, I think we need to expand our arsenal in the U.S. The risks of not allowing my patients to have access to these medications is great, and I think it's time to approve them for use.

Thank you for letting me have the opportunity to speak for our patients and about this treatment.

DR. RAUFMAN: Thank you. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. STEIN: I am going to be sharing this on behalf of Baha Moshiree. I don't believe she has any conflicts of interest. She was unable to be here today and she sends her regrets and apologies. And so I'm supposed to read this statement exactly, so I'll do my best.

"Good afternoon. My name is Baha Moshiree. I am director of motility at Carolinas Healthcare System and professor medicine at the University of North Carolina in Charlotte. First and foremost, I

would like to thank the FDA and these committees for allowing me to provide testimony on behalf of my patients, who suffer from severe constipation.

"As a gastroenterology faculty at Carolinas Medical Center, now Atrium Health, I see more than 40 patients a month who suffer from chronic idiopathic constipation or severe forms of constipation such as neurogenic bowel and slow transit constipation.

"Constipation is a relatively common and debilitating condition for my patients to present with. Many patients who come to my institution are those who have already had moderate to severe chronic idiopathic constipation, and they have failed many conventional or over-the-counter medications for this disorder. They also already have a level of debilitation and significant impairment in their quality of life. They may avoid travel due to their worry about their GI symptoms.

"Other commonly associated symptoms include nausea, abdominal bloating, and pain due to their

underlying constipation. And many strain to have bowel movements and develop hemorrhoids which can bleed. They often skip meals as they may feel too full due to their constipation. They can't always continue working outside the home.

"They tend to go to pharmacies and use over-the-counter medications, which may not be effective for every patient, and are not covered by insurance, and end up to be a financial burden for them.

"Many times, patients come to see me after they have exhausted several of these options. In fact, there are more options now than in the past 20 years. We do have ways that we can help these patients who are so in need. Despite newer constipation therapies, which have now become available, not all the treatments target the same neurotransmitters that are found to be deficient or low in patients with chronic idiopathic constipation.

"One such neurotransmitter is serotonin, which is found in the gut to a large degree.

Although most of the currently available pharmacological agents are what are called secretagogues, plecanatide, linaclotide, and lubiprostone, and others as osmotic laxatives such as MiraLAX or magnesium supplements, none target serotonin.

"Prucalopride targets serotonin as an agonist and has already been shown to improve colonic transit and motility, thus increasing the number of bowel movements, bloating, and pain relief associated with constipation.

"Luckily, we have already had experience with a similar drug, tegaserod, which was clinically available for the treatment of constipation previously, but which is no longer available. Prucalopride has similar actions to tegaserod, and I believe it could be valuable in our treatment armamentarium.

"I am familiar with a number of my own patients who have experience with prucalopride already as ordered through Canadian pharmacies. Their experience demonstrates it can be effective

for the appropriate patients. They have achieved considerable benefit in their overall numbers of spontaneous bowel movements over their baseline.

"Going from 1 bowel movement to 2 or 3 in a week has a positive overall impact on people in their level of comfort and satisfaction. This improvement has translated into a better quality of life despite the added cost of having to buy this medication from Canada.

"I hope the FDA allows this safe medication with which we already have experience to now be available to our patients here and in the U.S. Thank you for letting me have the opportunity to speak for our patients about this new treatment."

DR. RAUFMAN: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. HASLER: Thank you, Chairman Raufman and GIDAC committee attendees. My name is Dr. William Hasler, and I'm speaking on behalf of the American Neurogastroenterology and Motility Society or ANMS.

By way of disclosure, my meeting travel expenses and lodging are being reimbursed by the sponsor, Shire.

ANMS is a multidisciplinary society that fosters excellence in research, education, training, and patient care related to motility and functional disorders of the gastrointestinal tract. The ANMS applauds the U.S. Food and Drug Administration review of new drug application 210166 for prucalopride and supports this current meeting of the FDA Gastrointestinal Drugs Advisory Committee to discuss its potential future clinical applicability in the United States.

The drug is an investigational compound, which acts as an agonist on serotonin 5-HT4 receptors in the gastrointestinal tract. Prucalopride is approved and available in Europe and Canada, where it is prescribed for symptomatic treatment of adults with refractory chronic constipation in whom other laxatives have failed.

This compound is currently under evaluation by the Food and Drug Administration for treatment

of chronic idiopathic constipation in the United States. If such approval is ultimately granted, prucalopride will be the only serotonin 5-HT4 receptor agonist accessible for adults in the U.S. with this specific condition.

Over 35 million patients are affected by chronic idiopathic constipation in the U.S. The condition is characterized by infrequent or incomplete passage of stools with associated abdominal pain, difficult defecation, and/or bloating. Chronic constipation can be very debilitating for affected patients and significantly decreases their quality of life.

In one recent U.S.-population-based survey, chronic idiopathic constipation was rated as very or extremely bothersome by more than 60 percent of patients and disrupted productivity, including missing work, more than 3 days per month.

Many patients try over-the-counter and prescription medications, including laxatives, often with unsatisfactory results. In a questionnaire study published within the last year

of more than 1200 patients with chronic idiopathic constipation, nearly 60 percent using existing treatments for this condition were not satisfied with their responses to therapy due to lack of efficacy or side effects such as diarrhea.

The pathophysiology of chronic constipation is multifactorial, and this condition may occur as a result of impaired motility with slowed transit of the gastrointestinal tract. Most of the currently available therapies of chronic idiopathic constipation do not act directly on these underlying deficits in gastrointestinal motility and transit.

Furthermore, none of the current prescription medications for this condition utilize this mechanism of action. Taken together, these observations indicate that there is an important unmet need for new treatments for this condition, which act by different mechanisms in the gastrointestinal tract.

Prucalopride is a selective serotonin type 4 receptor agonist that stimulates colonic

peristalsis and hastens gastrointestinal propulsion, including acceleration of colon transit. Prucalopride has been studied worldwide in several placebo-controlled clinical trials, and integrated analysis of 6 randomized controlled clinical trials evaluated the global efficacy and safety of prucalopride in men and women with chronic constipation.

Compared to placebo, significantly more patients treated with prucalopride achieved an average of 3 or more spontaneous complete bowel movements per week over the study treatment periods. Adverse events were minimal and included headaches as well as gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain.

Cardiac arrhythmias attributable to prucalopride have not been described, and the proportions of patients who experienced any adverse cardiovascular events were comparable on prucalopride versus placebo in the clinical trials emphasizing the safety of this drug.

Based on the findings of these rigorous

investigations, the American Neurogastroenterology and Motility Society, or ANMS, endorses the consideration of prucalopride for treatment of chronic idiopathic constipation. This medication will serve as an important treatment option for the millions of patients in the U.S. suffering from chronic constipation. Thank you for your attention.

DR. RAUFMAN: Thank you. Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. CONWAY: Thank you so much. My name is Brad Conway. I'm here on behalf of the American College of Gastroenterology. Just as way of disclosure, I have no personal disclosures to let you know about, but the sponsor has sponsored ACG initiatives in the past at the curriculum and speakers of ACG's choosing, though.

Just as background, American College of Gastroenterology represents over 15,000 clinical gastroenterologists and GI clinicians in the United

States and across the world. And as you had noted today by the FDA, chronic constipation is one of the most common functional GI disorders today with a prevalence rate of roughly 15 percent, and to put it in more context, that's 1 in every 7 patients studied.

Recently, the American Journal of Gastroenterology noted two issues with chronic constipation, the first that no single or combined current treatment option works for all patients, and, secondly, there remains significant clinical need for new treatment options.

As noted earlier today and by other speakers, EMA and Canada has approved the drug, and we believe that the postmarket clinical studies have demonstrated both the safety and efficacy. And that's why ACG appreciates the committee today and the FDA for looking at this application.

We're also encouraged by the different mechanism of action that will hopefully fulfill this clinical need and for new treatment options for chronic constipation. I appreciate your time

and thank you very much.

DR. RAUFMAN: Thank you. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. NICHOLS: Hi. I'm Dr. Trent Nichols, and I'm actually a neurogastroenterologist as well as a previous chemist, and I'm going to try to talk about some of the chemical things that may have been talked about.

As said previously, it's a highly selective, high-affinity receptor agonist, MR [ph] GI prokinetic activity. And as we already talked about, constipation is getting worse. This is a slide in 2000, and now it's up to 63 million. At that time, it was 55.

It has a huge significant direct cost and indirect cost. About the 5-HT4 receptor site, it's very important to know what it looks like. The gene is a member of the family of human serotonin receptors. It's a protein-coupled receptor that stimulates cyclic AMP. And that's important in

mitochondria, and that's important to talk about because this is prucalopride succinate, and I'll go into that in a few minutes.

The gene product is glycosylated transmembrane protein that functions in both the peripheral and nervous system to modulate the release of various neurotransmitters and release of acetylcholine and muscarinic receptors in the gut.

The 5-HT4 receptors, 95 percent is located in the elementary tract. The rest is in the urinary, bladder, heart, and adrenal glands, as well as the central nervous system. Prucalopride has a greater than 150-fold affinity for the 5-HT4 receptor. And this is probably done by molecular modeling. If anybody's worked in this industry, you'd understand, and it has what we call less bleed to other receptors.

Prucalopride differs from other 5-H4 agonists such as tegaserod and cisapride. That's because it doesn't intercept the 5-H2A1BD, which has the cardiac human ether-a-go-go or potassium channel. It's abbreviated as hERG, respectively,

with cardiac arrhythmias and long QT.

As you know, you already went over tegaserod that had ischemic cardiovascular events, which maybe was brought out in the Oregon sudden death study.

If you look at the structure of cisapride, which is sort of like the father of prucalopride, you notice that there's a fluorobenzene. And that's at the end here; I don't think you can see that. And they took the fluorobenzene ring off.

Also, antihistamines such as stiemazol has a fluorobenzene, and that has a long QT interval, as well as another, mizolastine [ph], and sparfloxacin. In fact, all the fluoroquinolones have the fluorobenzene ring, and they all have some susceptibility to long QT.

Clinical trials, we previously went over. This is when I was involved with Dr. Vandeplassche, and this is the Moventus Group. I was at Digestive Disease Week or Gastroenterology United European in 2008. I had 27 subjects in this.

One of the other things I wanted to go

through is that there was a trial, which one of the speakers doesn't know about, which was up to 18 months. So it's been used longer in clinical trials than she thought about because she hasn't done a complete study. When you go through all the literature like I have, you find out there's lots of things that should be pointed out.

This is when it was evaluated, over 713 patients. Again, you've heard that mainly it's headaches and abdominal pain. And again, you had this in a cardiovascular thing on a previous slide, which was presented earlier, I believe, where they used both in vivo and in vitro studies, and there was no cardiovascular. If there was, there was a little bit in the guinea pig which had the heart rate going up, until the drug, after about 15 minutes, it dropped down.

Prucalopride, of course, has been used in Europe since 2009, Canada 2011, and Israel 2014. It has now been kind of talked about in chronic idiopathic constipation with Shire. And this is actually not only a prokinetic problem, but

probably may even be mitochondrial. I'll get into that in just a few minutes.

A study of 94 subjects found that the patients saw an increase in bowel movements while taking laxative and reported never having a feeling of complete evacuation. These actually subjects had what they call high amplitude, what we call HAPCs, high-amplitude propulsive contractions, which were in the colon, which was much fewer and lower amplitude, and that the HAPC can have an impact on having bowel movements. That may be the reason why the patient is constipated.

There was an investigator that was at the motility center at Hopkins by the name of Marvin Schuster. And in 1985, he presented a paper about what they called congenital constipation, and this is people who were almost born to have this. They had digital arches.

We've actually studied that, and now found that this is probably a predisposing factor in these IC subjects and can be identified actually by looking at their fingerprints.

Now, the other thing I wanted to talk about is just succinate for a few seconds. The succinate is actually a mitochondrial cofactor. It's part of the Krebs cycle. That's the tail of prucalopride, and actually that's worked already in chronic intestinal pseudoobstruction, which is a myocardial disorder. Thank you.

I have no hearing subsidies whatsoever. I'm presenting just for myself and QuietMIND Foundation.

DR. RAUFMAN: Thank you. Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. ROBERTS: Members of the committee, thank you again for the opportunity to appear before you. My name is Jeffrey Roberts, and I'm the founder of the IBS Patient Group. I'm here today representing patients and sufferers. I have paid all my own expenses to be here.

The IBS Patient Group has endeavored since 1987 to educate and provide support for hundreds of

thousands of people who have functional gastrointestinal disorders, or FDIGs, and to encourage both medical and pharmaceutical research to make our lives easier by our patient advocacy efforts.

I provided testimony to this committee several times. I have been a sufferer of an FDIG, namely IBS, for over 25 years. I face challenges each and every day in order to cope with my illness. It affects my family's lives, my career, and I'm constantly reminded of my own physical limitations because of this very burdensome illness.

Functional constipation is a common problem in our FDIG community, with its prevalence ranging from 2 percent to 28 percent. As I'm a focus in the community for information about functional gastrointestinal disorders, I communicate with a great many people who have run out of options. They do not know where to turn, and their quality of life has greatly suffered.

Many traditional current approaches to

chronic constipation, including the use of fiber, osmotic and stimulant laxatives, biofeedback training and surgery, often fail to control the patients' symptoms adequately. They produce problematic side effects or lose effectiveness with time.

Newly approved drugs for constipation have been successful for some patients, however, they haven't quite met the needs of the majority. Physicians often prescribe medications for constipation with which they are familiar and comfortable; in most cases anything will do.

Moreover, chronic constipation is a very unpleasant disorder, and in some cases, individuals who suffer from chronic constipation may not have a satisfactory bowel movement for up to 21 days. Their quality of life is greatly diminished by this basic impaired function that most individuals take for granted.

Noel, a member of the IBS Patient Group, says, "People who don't deal with chronic constipation have no concept of how it can destroy

your life, personal relationships, brain health, and ability to work. It's an absolutely miserable problem that affects all other areas of your health."

While Zelnorm, a medication for chronic idiopathic constipation and IBS-C, met the needs of many patients, its removal from the market in 2007 created a gap in treatment options until new treatment options were approved in the subsequent years.

Prucalopride, the same class as Zelnorm with the distinction of a diminished risk of cardiovascular issues and a favorable safety profile, has proven to be successful treatment by patients and physicians in other countries.

Physicians are well versed at risk management and along with patients, are risk adverse. Prucalopride meets this goal as another treatment option.

There is strong evidence that chronic constipation presents itself more frequently in women versus men, and its prevalence increases with

age. The subjective perception of chronic constipation at times leads to disagreements with physicians and patients as to whether someone is actually suffering from constipation.

This leads to minimizing the illness and a vicious cycle of over-the-counter remedies of limited efficacy versus medications like prucalopride, which are more suited to treat this illness.

Traditionally, FDIGs were not considered to be associated with an increased risk in mortality. However, recent studies have shown that there is a risk from constipation. Having personally experienced a sudden episode of severe impacted constipation with life-threatening consequences, I can relate to the anguish that a chronic constipation sufferer has to deal with on a near-constant basis.

Given the fact that constipation occurs more frequently in the elderly patients and that life expectancy is increasing, we can likely expect an increase in prevalence of constipation in the years

to come along with quality of life issues unless more patients are taken seriously and offered a chronic constipation medication like prucalopride.

The IBS Patient Group is prepared to place educational information about prucalopride on their website in order to reach out to the constipation community. This provides an effective forum for educating constipation suffers about prucalopride.

In conclusion, the quality of life of constipation sufferers was dramatically improved with access to prucalopride in other countries. The medical communities should be informed that a new treatment option is available, which will improve their patients' outlook.

Prucalopride has a place as an effective treatment for chronic constipation sufferers and should be approved and indicated as such to the patient and medical community. Thank you.

DR. RAUFMAN: Thank you. Will speaker number 8 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. ROTH: Hi. Thank you for having me here and the opportunity to address the panel. My name is Jessica Roth, and I am currently the director of regulatory affairs for the American Gastroenterological Association, which is a professional society that represents nearly 16,000 members committed to the science and practice of gastroenterology. AGA has no financial disclosures to report, and today, I will read a statement that is on behalf of our membership.

"The mission of the AGA is to advance the science and practice of gastroenterology. To achieve our mission, the AGA supports basic and clinical research, publishes three highly respected journals, and provides educational and practice resources and programs to gastroenterologists. These include clinical guidelines and clinical practice updates aimed at helping clinical decision making based on rigorous systematic reviews of the clinical evidence.

"GI motility disorders, such as chronic idiopathic constipation, or CIC, affect patients

not only by causing symptoms and posing a heavy burden of illness, but also by decreasing quality of life and work productivity. Because the causes and effects of CIC are heterogeneous, it can be very difficult to treat.

"By the time patients are referred to gastroenterologists for constipation, they usually have tried and failed numerous therapies. Unfortunately, the number of prescription medications for CIC are quite limited.

"Currently, there are only three prescription therapies for CIC, linaclotide, lubiprostone, plecanatide. These medications are all secretagogues and rely on a similar mechanism of action. They increase intestinal chloride secretion with associated secretion of water into the intestinal lumen to help accelerate intestinal and colonic transit.

"Because of the heterogeneity of CIC, these therapies work for some patients, but not all, and treatment satisfaction varies widely from patient to patient. Simply put, current treatments are not

sufficient to address the needs of all patients.

"Approval of prucalopride would expand the number of treatments available to gastroenterologists and other physicians treating patients with CIC. More importantly, it would make available a therapeutic option with a completely different mechanism of action compared with the three already FDA-approved therapies for CIC.

"Prucalopride is a colonic prokinetic which increases colonic transit by activating submucosal neurons to induce mucosal secretion. Approval of prucalopride would increase the potential for relief from patients affected by CIC, including those who have been refractory to currently available therapies.

"Robust clinical evidence demonstrates the safety and efficacy of prucalopride for adults with CIC, and the AGA encourages the FDA to support its approval. AGA supports the approval of any appropriate and efficacious treatment for CIC that meets the FDA's strict standards.

"AGA also urges the FDA to consider the

impact CIC has on patients and the limited number of available therapies when evaluating risks and benefits for approval."

Thank you again for the opportunity to address the panel.

Questions to the Committee and Discussion

DR. RAUFMAN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments made earlier.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Question number 1 is a voting question. Do the clinical trial data provide substantial

evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation, CIC? And this question is now open for discussion. Dr. Thadani?

DR. THADANI: I think the data we have seen so far is pretty supportive from the trials. The only reservation one has is the reservations of the populations studied is mostly in Caucasians, Asian, and whites. The data, as previously discussed by several committee members, has been a very small database in African-Americans and also in the Hispanic population. The U.S. Hispanic population is increasing in every state, so I think that has to be addressed down the road.

As far as the efficacy data, I think it's pretty positive with the exception of 401 study, which is now driven by more placebo effect. So I still have just reservation for which groups. Women are a majority anyway in the U.S. Whites and color issue comes in.

But when it comes to approval, we have to put some issues regarding the lack of or not

sufficient data in the African-American origin and Hispanics. It's unfortunate the U.K. database and Swedish database is very extensive, that they don't capture the race issue because it's a sensitive issue. I worked in the U.K. for nine years.

I know there are a lot of African-Americans in the U.K. as well because they came from Caribbean countries, so that data was there. It would have probably substantiated more. I don't think they can go back to this, but that reservation is top of my discussion there. If they can dig out that data, that'd be great, but not sure of that.

DR. RAUFMAN: Dr. Lebwohl?

DR. LEBWOHL: Ben Lebwohl. I think the concerns raised in the public comments about generalizability are something worthy of our consideration. In terms of age, I'm somewhat reassured by the fact that one of the clinical trials that was discussed had more than 40 percent of participants older than 65, but race has been pointed out. Individuals who are not white are

underrepresented. Of course, it's a problem. It's endemic in clinical trials in general.

I would be interested to hear more from either the FDA or the sponsor about potential issues related to BMI, and smoking status, and whether that could at all impact efficacy, and also the question about the interaction with oral contraceptives and reducing the efficacy of that contraceptive.

DR. TOMAINO: Sure. Juli Tomaino, FDA. Obviously, the application is still under review, but the concern over generalizability is something that we are looking at closely.

Just one thing to point out. The baseline disease characteristics and the history of disease from the patients in the two U.S. trials seemed to imply that maybe they in fact had a little bit more severe disease. They had a longer disease duration.

A higher percentage of them had failed prior laxatives or had tried prior laxatives, and there was a larger percentage of those patients reporting

an average of 0 or 1 spontaneous bowel movement per week in the 6 months prior. The percentages were lower in the two non-U.S. trials. We still saw efficacy in the U.S. trials, so just to give you a little bit more information on some of the baseline characteristics.

For BMI, we do have some data from the U.S. trials. We have height and weight data, and we have BMI on the two non-U.S. trials. I can find it here for you.

The mean BMI overall in the non-U.S. trials was about 22 and 26. And in the two U.S. trials, we have about 15 percent, maybe a little higher, BMI over 30. So there are some patients with a high BMI.

Then you asked about smoking. I don't have that information right in front of me. I don't know if maybe the sponsor has additional information on smoking. They did record smoking status in the overall -- when we look at MACE, that analysis, so we do have some information on baseline risk factors. But I don't have that

number in front of me.

Then you asked about contraceptives. Overall in the trials, from the sponsor's integrated summary of safety, we have about 6 percent on conjugated estrogens at baseline. I don't know. Perhaps the sponsor has additional detailed data on that.

DR. SILBERG: If I can, I'd like to address some of the issues you're talking about.

DR. RAUFMAN: Go ahead.

DR. SILBERG: I want to address a few of the different issues. One thing, just in terms of race, Hispanic is not a race, so it wouldn't be captured that way. They would be part of either whatever they identified, either white, or black, or -- that's the first one.

Second is, in terms of DDI, we did DDI studies with oral contraceptives. We showed you the DDI. There is no interaction for oral contraception. The second or the third point is about the patient population who has chronic idiopathic constipation. Dr. Camilleri's going to

speak to that as well, with relationship also to BMI.

DR. LEBWOHL: Before we get there, though, just to clarify, because one of the comments mentioned in an insert elsewhere, that this has been shown to decrease the efficacy of oral contraceptives. This is not true or you've never heard of this?

DR. SILBERG: It's not that it's not true for that insert, but our studies do not support that.

Dr. Camilleri?

DR. CAMILLERI: Mike Camilleri, Mayo Clinic. I'd like to address the whole issue of the BMI and the age of patients when they presented to us in the clinic. And I happen to be the senior author of a study of 1462 patients studied at our center. I was the physician looking after them, the gastroenterologist. And basically, I'm afraid I'm going to have to read this; otherwise, I may get it wrong. Forgive me.

That's from our paper just published in

2013, 1462 patients. Median age was 43 in males, 37 in females. The interquartile range goes up to 58 for males and 49 for females. And the median BMI was 23.6 for males and 21.4 for females. Therefore, females with constipation tend not to be obese.

I've also done another study in 120 patients with irritable bowel with diarrhea alternating or constipation and showed that the diarrhea-predominant patients are the ones with the BMI that's 3 kilograms per meters squared higher than the other patients with IBS.

So in summary, the patients that's participated in these clinical trials, remembering that three of the randomized controlled trials were conducted in the United States and therefore would appear to be representative of United States patients, have a BMI and an age range that is typical of the population that is seen in clinics in the United States. Thank you, sir.

DR. RAUFMAN: Thank you. Dr. Khurana?

MR. KHURANA: I have a question, and the

sponsors could answer that. I really couldn't get a sense of what are the actual objective indications to stop this drug if it's not effective. We have talked about when it's effective, but I can understand subjectively, if a patient has not responded, that you stop the drug.

So what I have not heard is what are the indications for stopping the drug? And are they based on some objective evidence such as colonic [indiscernible] propagation or lack thereof. Could you speak to that?

DR. SILBERG: Thank you for the question. That is a very important aspect of any medication, is when do you decide that something is not effective? Dr. Tack has a lot of experience, of course, with his patients, so I'm going to ask him to address that.

DR. TACK: Thank you. Jan Tack, gastroenterologist in Leuven, Belgium. There are two aspects to look at. One is side effects. I warn patients that side effects may occur, that they're usually mild, transient, but typically

occur in the first 1 or 2 days and then go away. Side effects are nausea, cramps, diarrhea, and headache.

If they're intolerable, they stop there, but you heard that the interruption rate in the clinical trials is 1.5 percent on average for each of these conditions, less than 5 percent in total, and this is what you see in clinical practice.

The second thing is chronic idiopathic constipation is a heterogeneous condition, probably with heterogeneous underlying pathophysiology, and perhaps that explains why not everybody responds. And typically, I write patients a prescription for one month and then have a call with them to decide whether to continue or not.

Evaluating this is very easy. It's driven by tolerance of the drug, which is usually good, and second, efficacy, which translates in more bowel movements and improvement of abdominal symptoms, and also regaining of quality of life.

DR. RAUFMAN: Dr. Teerlink?

DR. TEERLINK: Thank you. As many of you

are aware, I think the FDA has approved drugs in the past where absolutely no U.S. patient has ever been studied, so it is not an absolute requirement for approval of a drug. But I agree with Dr. Srinivasan and others that it's important to understand the effect of new drugs in all segments of the U.S. population, including and especially women, blacks, and the elderly.

But for safe agents that are geared towards symptomatic relief, patients will probably predominantly vote with their feet. So if it doesn't work, they will stop taking it and move away from it.

So in the absence of biological plausibility for differential effect, I would support the efficacy findings of this agent for the general U.S. population, recognizing that it is always incumbent upon the sponsors to try to do their very best to actively study in relevant patient populations.

We must also point out that the, quote, "relevant" U.S. studies are from 1999, where the

U.S. population has changed a lot over the last 20 years, unfortunately. So anyway, those are my comments.

DR. RAUFMAN: Dr. Thadani?

DR. THADANI: I think it's interesting that most of the trials done by the NIH, there's an outcry from women. Representation is very small. Here, we've gone the other way around, which is a good thing. Now the men are outcrying because there's less representation of men. Just a comment.

I hope the drug is going to be cheap because it might be an issue, because when you say non-response, you might have to keep a little diary because it's subjective. Placebo response is 20 percent. So I think the patients should be told, are you using anti-anginal drugs? I say, well, if they don't work for a month, then just quit.

So your whole database is on one more motion per week, from 2 to 3. So I think unless you make it cheap, there should be some threshold; okay, I'm

going to give you a diary rather than just talking in a busy clinic or I'm treating and going to continue it, and look at the diary. If the patient shows that there's improvement, continue it.

If not, why give an expensive drug? Because it's not working on everybody. It's working on maybe 6 percent more, so I think that'll be just an issue. I know it's difficult to put it in the labeling, but as a physician, it may be worthwhile to consider. I don't know what my gastroenterology colleagues do because that could be an important consideration, so that is not used.

My other question really is that we heard from consumer representatives and other people because this drug was only studied in chronic idiopathic constipation. It was not studied in IBS. I know there's a lot of overlap. And since a lot of those patients also have chronic constipation, you're not going to recommend those patients to take that drug, too, because they have other kinds of symptoms, too.

So I don't know how you safeguard that.

Physicians can use what they want. That might be an issue because this drug was done in chronic idiopathic constipation. And what we heard yesterday was a lot of IBS patients also have constipation as a component. I don't know. I'm not a gastroenterologist, but I think those are the issues you might have to deal with.

DR. RAUFMAN: Any other questions, or can we go ahead to a vote?

MS. McVEY HUGICK: This is Joy McVey Hugick, consumer representative. I just wanted to thank the sponsor for trying to meet this unmet need. And I also wanted to thank the public for commenting.

There were some things that were brought up that I just want to highlight and I think are important from a patient and consumer perspective, the first being that -- and I think Dr. Stein mentioned she tries to save colons.

Often, patients who are experiencing this, who have failed with all other treatment options; that's the recommendation. And it's been

recommended to me to remove my colon. So I haven't taken that step yet, but I'm grateful to know that FDA is looking at this and trying to explore other treatment options, especially with the new mechanism of action.

Something else that was brought up that I don't think we've talked about at all, and I know that FDA looks at this, is drug reimportation and substandard, falsified, and counterfeit medicines.

I know people who have ordered prucalopride online through Canada, not sure where it came from, scared about taking it because it may not be the actual product. And that's just something I think we also need to be cognizant of as well.

So I think the efficacy is there based on the data and. And while I wish we had more data certainly on the other subpopulations, I think, from my perspective, there's enough there to move forward with the vote.

DR. RAUFMAN: So in the absence of further discussion, we'll go ahead and vote, and you'll all have an opportunity to discuss why you voted how

you voted after we do that.

Let me read the question one more time, and the keypads are already blinking. Do the clinical trial data provide substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation?

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the

reason why you voted as you did if you want to.

So please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly.

After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. FAJICULAY: For the record, the results are 10 yes; zero no; zero abstain; and zero no voting.

DR. RAUFMAN: So perhaps we'll start with Dr. Hunsberger. Please state your name, how you voted, and if you want to, you can state the reason why you voted as you did.

DR. HUNSBERGER: Sally Hunsberger. I voted yes. I think it's a strong efficacy result. Seeing 5 out of 6 studies with positive results is pretty good.

A slight concern about the missing data. It's a lot of missing data, but in these type of studies, I think that's pretty typical. And I think making the assumption that missing data is a non-response is probably a fairly accurate interpretation or a fairly accurate assumption, so I feel like the results are very strong.

DR. TEERLINK: John Teerlink, and I voted yes. I wanted to reinforce that this vote does not relieve future sponsors of the responsibility of providing data to the FDA that provides information on longer-term effects and effects in subpopulations.

This packet was done before all those regulations got in place, and the original packet was before that, so it's kind of getting in under that wire. But I do think it is important to have more long-term evidence for chronic therapies, both from an efficacy and safety standpoint.

DR. SOLGA: Steve Solga, I voted yes. I think the data are compelling over multiple trials, done over multiple years on different continents

using a strict responder definition. I also felt that the additional supportive efficacy data looking at patient satisfaction, bloating, discomfort, cramps to be relevant as well.

MS. NUMANN: Sabrina Numann. I voted yes. From my perspective, I find the placebo effects of this class of 5-HT medicine to be pretty interesting and intriguing. But even if I were to assume the placebo effect into the efficacy data, there's still evidence of efficacy. So for that reason, I voted yes.

MS. McVEY HUGICK: Joy McVey Hugick. I voted yes for reasons already stated.

DR. LAI: Jennifer Lai. I voted yes, and this vote was based on my critical review of the evidence from the randomized clinical trials presented to me.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes for the reasons already stated.

DR. LEBWOHL: Ben Lebwohl. I voted yes for reasons already stated.

MR. KHURANA: Sandeep Khurana. I voted yes.

DR. THADANI: Udho Thadani. I voted yes for the positive direction, even in the 401 study, and the trials were positive. The only reservation, I'm hoping that the African-American gut motility is the same as the whites. So I think hopefully the company will provide data and a clearly reasonable sample size to tell those patients it works in you as well.

DR. RAUFMAN: We will now proceed with question 2, which is also a voting question. Has the potential risk of cardiovascular adverse events with the use of prucalopride in adults with CIC been adequately addressed by the applicant? Discuss your answer.

If there are no questions or comments concerning the wording of the question, we'll now open this question to discussion. I guess we should hear from the cardiologists on this one.

Dr. Thadani?

DR. THADANI: I think it's reassuring that the drug class affects one specific receptor, and we say HT4 rather than -- obviously in a very high

dose, you're going to use megadoses, and it's going to affect the other receptors, which is reassuring in a way because, as a cardiologist or as an internist, when you have to worry about previously reported issues with torsades, especially with the QT interval, whether it's corrected or you use formula for [indiscernible] equation, we've seen enough data it really doesn't affect it. And the ratio of hERG channel block is so high and only will be concerning in a real overdose situation, which could happen, I guess.

But given that, more specific to the receptor, it's not only the receptor. I think the database we are seeing; there's really no -- is a comparative adverse effect profile with the only exception of a couple of noises on the tachyphylaxis might have be an issue, and the neuropsychiatric issues remain.

But I think, when you look at the placebo-controlled trials, it's fairly balanced. And I think it's reassuring in the prospectively collected U.K. and Swedish registry. They are

really much more elaborate, the U.K. and Swedish. At least I'm convinced that there's no major issue with that in that population. Although there's going to be a neuropsychiatric issue, we discussed whether it's rebound or not.

But other than that, I think I fairly feel comfortable that the adverse effect on the heart as far as MI or CNS, stroke, and QT intervals are addressed. The only thing is, I'm sure there are some CNS effects of headache and all that, and we don't know the exact mechanism because it does penetrate the CNS system.

DR. RAUFMAN: Dr. Teerlink?

DR. TEERLINK: John Teerlink, UCSF. I will concur with my colleague in as much as I think the absence of biological plausibility for a cardiovascular adverse event was very helpful here. There is one of the cases where the preclinical data did provide kind of the ground work and the perspective for the rest of the clinical trial data.

In some ways, we are subjected to the

tyranny of small numbers and small events in these kind of trials, where you don't have high numbers and background of cardiovascular events, so we have to deal with these small little numbers that occur.

I think the sponsor is to be congratulated on using pharmacovigilance studies to try to help inform the safety of these agents. And I would once again caution future sponsors that this does not relieve them of the responsibility to abide by the guidance that we provided during the 2011 meeting as well. So that's my perspective.

DR. RAUFMAN: Any additional discussion before we vote?

(No response.)

DR. RAUFMAN: So let me re-read the question, and then we'll go ahead and vote.

Has the potential for cardiovascular adverse events with the use of prucalopride in adults with CIC been adequately addressed by the applicant? Please press yes or no.

(Voting.)

DR. FAJICULAY: For the record, the results

are 10 yes; zero no' zero abstain; and zero no voting.

DR. RAUFMAN: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start on my left this time with Dr. Thadani.

DR. THADANI: Thadani. I voted yes because of the preclinical data, lack of effect on the hERG channel, and also no cases of torsades as far as we can tell in the registries.

So the cardiac adverse effect profile is very similar in the double-blind trials, very low incidence, not a noise, even. It's not a disproportion zero on placebo versus that. Only issue is the neuropsychiatric issues, some noise, but again, pretty convincing that there's not a major noise there, and that's why I voted yes.

MR. KHURANA: Sandeep Khurana. I voted yes, and reasons have been extensively discussed.

DR. LEBWOHL: Ben Lebwohl. I voted yes. I

was reassured by the preclinical data, but even more so by the lack of cardiovascular signal emerging since 2009, when this was approved in Europe.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes for reasons that have already been cited.

DR. LAI: Jennifer Lai. I voted yes for reasons that have already been stated.

MS. McVEY HUGICK: Joy McVey Hugick. I reported yes for reasons already stated.

MS. NUMANN: Sabrina Numann. I did vote yes. As Dr. Thadani said, the low affinity for the other 5-HT receptors is what really changed my mind on that, so I don't find that the risk outweighs the benefits. Thank you.

DR. SOLGA: Steve Solga. I voted yes, nothing further to add.

DR. TEERLINK: John Teerlink, and I voted yes, and surprisingly, I have nothing further to add.

(Laughter.)

DR. HUNSBERGER: Sally Hunsberger. I voted

yes, and I have nothing further.

DR. RAUFMAN: We'll skip this because we all voted yes.

So question 3, this is our last question and also a voting question, and maybe we'll get a little bit more discussion here.

Does the risk-benefit profile of prucalopride support the approval of this application? If there are no questions or comments concerning the wording of the question, we'll now open this question to discussion.

Who wants to start?

DR. THADANI: I'm asking the question or a lot of them. I think we've already beaten it to death.

(Laughter.)

DR. THADANI: We discussed the efficacy. We discussed the risk. So I think risk-benefit is reasonable, given the very low incidence of side effects. Even the hard endpoint, which is MI, death, stroke, it's pretty balanced in the two and there's very low noise.

I still had a little bit of question on the neuropsychiatric issues, but again, the numbers are low, not so much in the double-blind, but mostly in the open-label studies, so I feel fairly reassured on that.

The only thing is the African-American population. We've got missing data, although they said people from Hispanic origin might have different blood, but Hispanic origin is a mixed race in the U.S. It's very different than the people from Spain because you've got mixed American Indian, a lot of different issues, so the response might be different. So I think we probably should concentrate on that in the future.

DR. RAUFMAN: Dr. Khurana?

MR. KHURANA: My only concern is with the neuropsychiatric issue, because there was really no cases in placebo, absolutely none, and they were all 7 or 8 in the treatment arm.

So I think, even if you are to approve this, then I think there should be some sort of a warning on it. Obviously, that decision has to be

discussed between the patients and the physicians prescribing it, but I think that is of a concern.

DR. RAUFMAN: No one has concerns about the carcinogenicity issues? Dr. Solga?

DR. SOLGA: Yes. I was just going to echo the residual concern about the neuropsychiatric component. I don't feel like we understand not just this drug, what this class of drugs do to serotonin on the brain. And unlike doing QTc studies and other cardiac nonclinical data, I don't know that we have the tools in the toolbox to answer these questions.

It's not going to hold back my yes vote. I don't expect the sponsor to do studies we don't know how to do or the FDA to manage risks they don't know how to measure, but that is the area that I'm going to leave and wonder about for some time to come.

DR. RAUFMAN: Dr. Lai?

DR. LAI: I also am concerned about the neuropsychiatric signal, the 7 versus 0. Although low, in both sides, zero is very concerning in the

non-placebo arm versus the 7 in the treated arm. It would just seem that, given that there is a large database to study, which was studied with respect to the MACE events, one might think that you could study this looking at maybe deaths related to suicide to look for a signal.

The reason I'm particularly worried is that while the general population of individuals with CIC may be overall a low cardiac risk population, it is a population in which depression and other psychiatric disorders is probably much higher in prevalence in the general population.

So I think this is of concern, and I wonder, maybe we should ask either the FDA or the sponsor about whether this could actually be evaluated with the data at hand.

DR. RAUFMAN: Dr. Teerlink?

DR. TEERLINK: I guess my understanding is that there were 3 events in the randomized trials. Is that not right; 3 versus 0 in terms of the attempted and others? The other events were in open label, where it's open label, so there's no

competing group. Is that not correct?

DR. RAUFMAN: I'm seeing heads nodding, so it sounds like it's correct.

DR. LINE: My name is Charles Line. I'm the medical --

DR. TEERLINK: I share that that's an issue that needs to be considered.

DR. TOMAINO: Yes. What slide is that?

DR. LINE: It's our slide, 63.

DR. TOMAINO: 63, please.

DR. LINE: So what this slide is showing you is that there were 2 completed suicides. These occurred in the open-label trials.

DR. TEERLINK: I think that's in the double-blind trial.

DR. LINE: No, these were open label.

DR. RAUFMAN: No. But they're labeled -- OL is labeled on the bottom three.

DR. TEERLINK: Yes. I believe that the first two are events that occurred in the double-blind trial but occurred well after the drug was gone. The third one was an attempted suicide

in the double-blind trial that occurred after 42 days of therapy. The fourth one was open label, and the fifth and sixth ones were open label.

That's my reading of those data. So it really is basically, of folks who are taking the drug, we have 1 versus zero in a double-blind study.

DR. RAUFMAN: Are these data correctly labeled? I see some questions.

DR. LEBWOHL: So the sponsor's slide 54, I think --

DR. SILBERG: No. It's not correctly labeled because the double-blind is only 3 months. The suicide -- I don't know if I can put it up. There we go. So you can see here it's labeled correctly.

The 2 suicides were in the open label. Since these are shorter studies, you can't go to 242 days in the double blind. So the only one that was in the double-blind placebo control is the suicide attempt. So we don't have a lot of comparison to placebo. The rest are open label,

and of course they all would be on drug.

DR. RAUFMAN: So may I ask why there's a discrepancy between the two slides, or is this the correct one? Should we go with this?

DR. TOMAINO: I don't think there's a discrepancy. I think if you go back to our slide, just to clarify, we are actually showing the same data, I think just in different ways. So you can see the third one down, the attempted suicide, is 42 days. That's what the applicant is showing as the double blind.

The first 2 completed suicides, the only 2 completed suicides in the first two rows, are not labeled for either double blind or open label because those patients were off the drug at the time, but it shows the treatment duration.

DR. KORVICK: So the bottom line is we're in agreement. We'll just have to look harder at these numbers.

DR. RAUFMAN: Got it.

DR. TOMAINO: The title of this slide is just showing you the pool that we pooled from.

DR. RAUFMAN: Dr. Hunsberger?

DR. HUNSBERGER: So I just have a slight concern. I wasn't so convinced. I'm not sure if you looked at women that were pregnant or child-bearing that closely. I didn't see a lot of data about that, and this group will be getting the drug. So I wonder if we can track that or can we do more follow-up on that. So that would be a slight concern for me.

DR. KORVICK: Thank you. Those are things that we do take into consideration. There's only so much you can put here, but those are under consideration and evaluation.

DR. RAUFMAN: Jean-Pierre Raufman. I will just say for the record that I am concerned about the preclinical carcinogenic signal, and I don't know that without doing a specific study, you have the data to address whether it's a concern in humans.

So it's not going to change my vote on this question, but I just raise it as, I think, an unresolved issue right now.

Dr. Thadani?

DR. THADANI: I think there was a comparator drug, PEG, so the database, there was no suicide or attempted suicide in that database. Right?

I know there is no placebo, but overall, from the British registry and the Swedish registry, because these are open-label trials, was there any discrepancy in the attempted suicide or confirmed suicide in that registry? Because you've got a large sample size there.

DR. SILBERG: If I can answer that, the 802 trial was only looking at MACE, so major cardiac events. It did not look at psychiatric or suicides, so we would not have that data from that database for 802.

DR. THADANI: But I am sure the database for that exists, right? Because that's one of the noises with this class of drugs. And if you have the database, it'd be reassuring to provide that to FDA if you can.

DR. SILBERG: I can only tell you what we did and that wasn't looked at. So that's the data

we have. It's not there from that study.

DR. THADANI: But I'm sure people from the U.K. registry, somebody was representing earlier, because they had the whole database on all the primary care physicians, and they captured all these things, especially if there's a death.

DR. KORVICK: This is Dr. Korvick. Just to echo what the sponsor is saying, for the answer for suicide, what we have is a large integrated summary of safety from several studies. That's the extent of the information we have on clinical trials. The other study was not designed to do that analysis.

One could ask for another analysis if you needed to, but that would have to be designed, and again, all of the definitions for the events of interest, et cetera. And all those things need to be specified, so there would be a whole other effort that would need to be taken to look at that.

We do not have that analysis as my colleague across the aisle there stated. I don't know if you want to follow with that, but what we have is what we have

DR. THADANI: I'm interested maybe in completed suicide or attempted. That would be easy to capture. Hopefully, there will be not a huge database to look at. With the cardiovascular, you've got more issues.

DR. KORVICK: Those are very particular terms of the databases. We're going to have to look and see. It's not so easy, the terms. There's an art. We have a guidance about this, actually, how you use those terms.

DR. RAUFMAN: Does the sponsor want to make a quick comment on that or no?

DR. SILBERG: I appreciate your comment. Again, we have the data that we have. We did show you also that the psychiatric AEs were balanced in the placebo versus the active treatment in our large clinical trials, the double-blind. So in that case, there really was not any kind of signal.

DR. THADANI: I'm buying that, but I think it'd be reassuring to the physicians if they know in your open-label there's no data, so you might capture it for future.

DR. SILBERG: Thank you.

DR. RAUFMAN: Dr. Lebwohl?

DR. LEBWOHL: I just want to underscore Dr. Thadani's point. These are data that are not available today. It's not something we could easily whip up, but these data are out there in specifically the Swedish registry data, for cancer as an outcome and likely suicide as an outcome.

So this is imminently doable, just not something one could do quickly. The data are out there, and I hope it gets done.

DR. RAUFMAN: Is there any additional discussion before we go ahead with the vote?

(No response.)

DR. RAUFMAN: If there's no further discussion, we will now begin the voting process. Again, you can push yes, no, or abstain.

(Voting.)

DR. FAJICULAY: For the record, the results are 10 yes; zero no; zero abstain; and zero no voting.

DR. RAUFMAN: Now that the vote is complete,

we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start with Dr. Hunsberger.

DR. HUNSBERGER: Sally Hunsberger. I voted yes based on the efficacy results and not much of a signal for the cardiovascular safety endpoint.

DR. TEERLINK: John Teerlink. I voted yes based on my comments during this entire day.

DR. SOLGA: Steve Solga. I voted yes, nothing further to add.

MS. NUMANN: Sabrina Numann. I voted yes, nothing further to add.

MS. McVEY HUGICK: Joy McVey Hugick. I voted yes for reasons already stated.

DR. LAI: Jennifer Lai. I voted yes. I remain concerned about the psychiatric effects, and believe that study could be done just to look at completed suicides, and would like it to be done. However, I do believe that there's a great unmet need and believe that the potential benefits of this drug outweigh those concerns.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes. My concerns are more for the long-term carcinogenicity potential of the drug, but with current information, benefits outweigh risks.

DR. LEBWOHL: Ben Lebwohl. I voted yes.

MR. KHURANA: Sandeep Khurana. I voted yes.

DR. THADANI: Udho Thadani. I voted yes with just one reservation on good faith that the company hopefully will dig out neuropsychiatric. I think the information is out there in the Swedish and U.K. database. It'd be easy enough to just plug two items, suicidal completed/attempted, because they all go to the hospital usually on this.

DR. RAUFMAN: Do we have any closing comments from the FDA?

DR. KORVICK: I just wanted to thank everybody for their very thoughtful comments. I don't think we have any other questions for you all at this time. Thank you.

Adjournment

DR. RAUFMAN: Thank you. We will now

adjourn the meeting. Panel members, please leave your name badge here on the table so that they may be recycled. Please also take all personal belongings with you as the room is cleaned at the end of the day. Meeting materials left on the table will be disposed of. Thank you.

(Whereupon, at 2:21 p.m., the meeting was adjourned.)