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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

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1 P R O C E E D I N G S

2 (8:00 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. HUNSBERGER: Sally Hunsberger,
11 biostatistician at NIAID.

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

14 DR. RAUFMAN: Thank you.

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

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

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

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

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

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

19 **Conflict of Interest Statement**

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

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

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

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

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

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

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

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

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

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

3 Based on the agenda for today's meeting and
4 all financial interests reported by the committee
5 members and temporary voting members, a conflict of
6 interest waiver has been issued in accordance with
7 18 U.S.C. 208(b)(3) to Dr. Benjamin Lebwohl.

8 Dr. Lebwohl's waiver covers an investment in
9 Healthcare SECURA mutual fund valued between
10 \$200,000 and \$300,000. The waiver allows
11 Dr. Lebwohl to participate fully in today's
12 deliberations. FDA's reasons for issuing the
13 waiver are described in the waiver document, which
14 is posted at FDA's website at [www.fda.gov/advisory
15 committees/committeemeetingmaterials/drugs/default.
16 htm.](http://www.fda.gov/advisory/committees/committeemeetingmaterials/drugs/default.htm)

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

22 To ensure transparency, we encourage all

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

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

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

1 you.

2 DR. RAUFMAN: Thank you.

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

5 **FDA Introductory Remarks - Juli Tomaino**

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

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

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

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

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

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

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

22 Since prucalopride is a selective 5-HT₄

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

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

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

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

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

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

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

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

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

1 which there have been cardiovascular safety
2 concerns.

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

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

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

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

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

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

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

22 The NDA also contains data from three other

1 12-week phase 3 legacy trials, completed in 1999,
2 to support the generalizability of efficacy results
3 from the non-U.S. trials to the U.S. patient
4 population. In addition, data were submitted from
5 a sixth trial, a 24-week randomized double-blind,
6 placebo-controlled phase 4 trial conducted in
7 Europe.

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

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

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

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

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

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

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

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

7 We have the following questions for
8 consideration by the committee.

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

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

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

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

1 application?

2 We look forward to the discussion today.

3 Thank you.

4 DR. RAUFMAN: Thank you.

5 Dr. Crentsil, could you please identify
6 yourself?

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

12 DR. RAUFMAN: Thank you.

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

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

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

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

13 We will now proceed with the applicant's
14 presentations.

15 **Applicant Presentation - Sunil Kadam**

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

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

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

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

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

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

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

10 Prucalopride safety is further supported by
11 more than 8 years of postmarketing
12 pharmacovigilance. This provides extensive patient
13 experience since prucalopride was first approved in
14 2009.

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

1 since launch.

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

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

18 The FDA convened an advisory committee in
19 2011 to obtain advice regarding the need for
20 cardiovascular assessments, including CV outcome
21 studies for any 5-HT4 products. The committee
22 agreed that nonclinical, clinical pharmacology, and

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

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

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

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

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

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

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

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

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

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

1 unmet need for prescription medication to treat
2 chronic idiopathic constipation.

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

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

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

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

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

19 **Applicant Presentation - Michael Camilleri**

20 DR. CAMILLERI: Thank you, Dr. Kadam.

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

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

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

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

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

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

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

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

14 In the United States, an estimated
15 35 million adults are diagnosed with chronic
16 idiopathic constipation, and the related healthcare
17 costs for patients are considerable. The mean
18 annual all-cause costs were more than \$11,000, and
19 gastrointestinal-related costs were more than
20 \$4,000. Every year, constipation results in more
21 than 3 million visits to physicians, and 92,000
22 hospitalizations, and several hundred million

1 dollars spent on laxatives.

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

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

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

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

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

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

22 So what are our options for helping patients

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

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

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

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

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

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

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

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

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

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

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

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

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

1 for the 5-HT4 receptor.

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

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

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

17 **Applicant Presentation - Heinrich Achenbach**

18 DR. ACHENBACH: Thank you, Professor
19 Camilleri.

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

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

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

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

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

1 Patients meeting the protocol-specified
2 thresholds entered into the treatment period where
3 they were then randomized to receive placebo or
4 prucalopride. All studies included a 2-milligram
5 dose arm, which represents our proposed dose.

6 Three studies included the 4-milligram dose, which
7 was later omitted due to no increase in efficacy.

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

12 All studies selected adult patients with
13 chronic idiopathic constipation, defined by the
14 modified Rome Foundation's diagnostic criteria for
15 functional constipation. At randomization,
16 patients were required to have 2 or fewer
17 spontaneous bowel movements per week during the
18 2-week run-in period that resulted in the feeling
19 of complete evacuation.

20 In addition, patients must have had at least
21 1 of the criteria listed here in more than
22 25 percent of bowel movements, and symptoms must

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

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

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

17 Based on previous phase 3 studies with
18 prucalopride, the estimated proportion of patients
19 with greater than or equal to 3 CSBMs per week was
20 27 to 30 percent in the prucalopride arm and 14 to
21 15 percent in the placebo arm.

22 First, the estimated treatment effect across

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

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

11 Turning now to the demographics and results,
12 while the demographics varied across the studies,
13 each was balanced within each study. The average
14 patient age in the 6 studies was between 41 and
15 58 years. Four studies, 6, USA-11, USA-13, and
16 401, included 10 to 19 percent elderly, while study
17 3001 excluded elderly patients. Most patients were
18 female ranging from 85 to 93 percent. In contrast,
19 study 302 only enrolled men.

20 Most patients were white in 5 of the 6
21 studies. Study 3001 was based in Asia and enrolled
22 92 percent Asian patients. As expected, the

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

3 Turning now to the disease characteristics,
4 the baseline disease characteristics were similar
5 between arms. The mean duration of constipation
6 varied between studies and ranged from 9 to
7 23 years.

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

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

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

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

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

13 At the request of the FDA, we also conducted
14 a post hoc analysis called alternative endpoint A.
15 This more rigorous endpoint has been consistently
16 used in other studies for chronic constipation.
17 Alternative endpoint A required patients to have at
18 least 3 CSBMs per week and an increase of 1 CSBM
19 from baseline per week. These criteria needed to
20 occur in at least 9 out of 12 weeks and in at least
21 3 of the last 4 weeks of the study.

22 Consistent with the primary endpoint

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

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

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

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

1 significance.

2 Next, I'll review the results from important
3 secondary endpoints. Four of the 6 studies showed
4 a statistically significant difference in the
5 proportion of prucalopride patients reporting an
6 average increase of 1 or more CSBM per week from
7 baseline over the 12-week treatment period. Study
8 302 and 401 showed a numerical improvement.

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

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

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

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

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

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

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

18 **Applicant Presentation - John Caminis**

19 DR. CAMINIS: Thank you, Dr. Achenbach.

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

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

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

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

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

1 with chronic idiopathic constipation from the
2 open-label safety extensions of randomized studies,
3 patients who were in the study from three months to
4 2.6 years with a median duration of approximately
5 284 days.

6 Of the 2,759 patients enrolled in these
7 open-label studies, 1,710 were treated for at least
8 half a year and 1,052 were treated for at least
9 1 year. The data from this long-term exposure
10 supports the safety profile established by the
11 randomized studies.

12 In addition, we collected extensive safety
13 data during the open-label studies. Overall,
14 86 percent of patients who participated in the
15 double-blind placebo-controlled studies continued
16 in the open-label extensions.

17 During the open-label studies, we collected
18 safety information every 3 months until the last
19 scheduled visit or at the time of discontinuation.
20 Each visit collected adverse events, ECG, vital
21 signs, laboratory data, and PK at months 3, 6, and
22 9.

1 The clinical evidence for safety comes from
2 16 randomized, double-blind, placebo-controlled
3 studies of at least 4 weeks in duration in adult
4 patients with chronic idiopathic constipation.

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

10 Let me review the safety assessment focused
11 on a comparison between placebo and prucalopride,
12 2 milligrams. More patients on prucalopride
13 2 milligrams reported an adverse event in the
14 pooled randomized studies compared to placebo.
15 There were 2 percent more AEs that were reported as
16 severe and for AEs leading to discontinuation in
17 the prucalopride group. However, the rates of
18 SAEs -- and there are some prucalopride -- were
19 similar to placebo.

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

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

3 Turning now to AEs leading to
4 discontinuations, there are 3 event terms leading
5 to discontinuation that were reported in at least
6 1 percent of patients treated with 2 milligrams of
7 prucalopride. These are headache, diarrhea, and
8 nausea. As before, we observed a low event rate
9 across treatment arms and a similar frequency of
10 occurrence across studies for the most common AEs.

11 We will now discuss the events with fatal
12 outcome that occurred during the clinical studies
13 and their open-label extensions. There were
14 8 events reported with a fatal outcome from the
15 phase 2 to 4 studies as well as the open-label
16 extensions. Three events were from the randomized
17 studies; 2 on prucalopride, 1 on placebo. Full
18 details on each were provided in our briefing book.

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

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

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

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

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

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

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

1 study was designed and agreed to with the FDA.

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

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

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

22 Specifically, when looking at various 5-HT2,

1 5-HT1, and 5-HT7 receptors, one notices a clear
2 difference in receptor affinity between tegaserod
3 and prucalopride. Conversely, when looking at the
4 hERG receptor, we see that tegaserod has less
5 affinity than cisapride, and prucalopride has
6 negligible affinity.

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

15 Importantly, we see no relevant effects on
16 cardiovascular and cardiac electrophysiological
17 parameters. This includes no effect on the hERG
18 channel at concentrations of prucalopride up to
19 50 times the therapeutic concentration; and no
20 effect on other ion channels or proarrhythmic
21 tendencies observed at 500 times the therapeutic
22 concentration; and no effect on platelet

1 aggregation or coronary artery contractility across
2 three species.

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

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

13 In fact, the only observed cardiovascular
14 changes in healthy volunteers were small transient
15 increases in heart rate that return to baseline
16 prior to the next dose. No further increases in
17 heart rate were observed with doses up to
18 20 milligrams.

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

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

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

14 Importantly, exposure to prucalopride in the
15 open-label trials had a median duration of
16 284 days. Nonetheless, we sought the counsel of
17 independent external experts to adjudicate our
18 clinical data for possible MACE.

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

1 pre-existing cardiovascular condition or disease.

2 Four patients, 2 on placebo, 2 on
3 prucalopride, met the criteria for MACE across the
4 studies from all doses of prucalopride. This
5 results in an incidence rate of 5.2 patients per
6 1,000 patient-years exposure in the prucalopride
7 group compared to 3.5 patients per 1,000
8 patient-years for the total prucalopride group, and
9 3.1 for the 2-milligram dose.

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

14 Now we will examine the results from the
15 pharmacoepidemiology study, 802. Study 802 was a
16 robust observational population-based study that
17 included matching and used exposure propensity
18 scores to ensure comparability of cohorts. The
19 study was designed to determine whether the pooled
20 incidence rate ratio and upper bound of the
21 95 percent confidence interval for MACE excludes a
22 safety margin of 3 for patients treated with

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

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

12 Cohorts from the U.K. and Sweden were
13 balanced regarding demographic and cardiovascular
14 risk and were included in the pooled analysis. The
15 pooled dataset included 5,715 patients treated with
16 prucalopride and more than 29,000 treated with PEG.
17 Women accounted for 93 percent of the cohorts.
18 Four percent were men 55 years or older; 5 to
19 6 percent of all patients had a history of
20 hospitalization for a cardiovascular diagnosis or
21 related procedure, and more than 55 percent of
22 patients had 1 or more cardiovascular risk factors.

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

3 The pooled standardized incidence rates of
4 MACE among patients initiating prucalopride were
5 6.57 per 1,000 person-years compared to 10.24 among
6 those taking PEG. The pooled adjusted incidence
7 rate ratio for MACE of 0.64 did not show an
8 increased risk in patients treated with
9 prucalopride compared to PEG.

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

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

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

1 prucalopride compared with patients treated with
2 PEG.

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

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

14 Finally, we will review the postmarketing
15 safety experience. The clinical safety profile
16 that's supported by more than 280,000 patient-years
17 of exposure from launch through 2017, a total of
18 5,072 postmarketing adverse events were reported in
19 patients receiving prucalopride.

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

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

7 This is important, since Shire actively
8 conducts ongoing pharmacovigilance monitoring for
9 CV signals. At the time of regulatory reviews,
10 there was a desire for caution based on adverse
11 cardiovascular events reported for non-specific
12 5-HT4 products.

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

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

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

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

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

20 **Applicant Presentation - Jan Tack**

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

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

6 Since it became available in Belgium in
7 2010, I estimate I have treated about 500 patients
8 with prucalopride, and I have experienced firsthand
9 how it can advance the care for adults living with
10 chronic idiopathic constipation.

11 The pivotal trials included patients with
12 long-standing idiopathic constipation, and many had
13 a poor response to laxatives. And for those with
14 normal bowel movements, it may be hard to fully
15 comprehend what it feels like to be unable to have
16 complete spontaneous bowel movements for close to
17 2 weeks. But I can tell you that this low rate
18 correlates with substantial low quality of life and
19 high symptom severity. The vast majority of
20 patients that I see have tried and experienced
21 insufficient relief from laxatives.

22 So when prescribing prucalopride in

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

8 Then thinking about how this relates to the
9 results seen in the pivotal studies, Dr. Achenbach
10 has already reviewed the data supporting how
11 prucalopride reaches its primary endpoint.

12 Achieving at least 3 CSBMs per week for a patient
13 population that started with an average of 0.3 to
14 0.5 at baseline is truly significant. It's a
15 tenfold increase.

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

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

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

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

22 I'm showing the results for abdominal

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

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

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

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

22 So what accounts for these changes? We're

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

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

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

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

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

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

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

19 Finally, with the amount of clinical trial
20 data and use in clinical practice, I'm confident
21 that prucalopride is safe and well tolerated.

22 Thank you for allowing me to share these data, and

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

3 **Applicant Presentation - Debra Silberg**

4 DR. SILBERG: Thank you, Professor Tack.

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

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

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

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

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

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

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

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

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

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

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

21 **Clarifying Questions to the Presenters**

22 DR. RAUFMAN: Thank you.

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

5 Dr. Thadani?

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

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

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

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

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

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

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

17 DR. THADANI: My cardiovascular question is
18 the increasing heart rate. You said about 5 or
19 6 beats per minute. That's average. Right?
20 What's the range? Can it go up to 20? That's
21 mean, right? Not a median?

22 DR. SILBERG: This was in healthy

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

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

12 Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 anything else that was off-target.

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

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

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

18 DR. THADANI: And the tachyphylaxis is
19 possible?

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

1 DR. RAUFMAN: Thank you. Dr. Lebwohl?

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

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

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

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

22 DR. SILBERG: Right. So I'll have

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

4 DR. CAMINIS: Thank you, Doctor Silberg.

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

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

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

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

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

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

11 DR. RAUFMAN: Thank you. Dr. Solga?

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

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

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

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

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

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

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

21 What was that study attempting to achieve at
22 that time?

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

6 DR. RAUFMAN: Thank you. Dr. Teerlink?

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

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

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

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

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

5 DR. TEERLINK: It actually doesn't. If you
6 could go on to show, as you did with the others,
7 the details about those who had greater than
8 5 percent. This triggered because you said the
9 reason you didn't go to 4 milligrams because of no
10 additional efficacy. It also looks like there was
11 actually increased adverse events, which may give
12 some insight into what we can see in case people
13 have more.

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

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

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

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

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

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

12 DR. SILBERG: No, I have that.

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

15 (Laughter.)

16 DR. TEERLINK: Thank you.

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

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

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

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

8 DR. TEERLINK: So 189.

9 DR. SILBERG: So 6.9 percent overall.

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

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

14 DR. TEERLINK: So we may be judging this on
15 112 African-Americans.

16 DR. SILBERG: Right.

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

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

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

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

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

10 DR. SILBERG: For 802?

11 DR. TEERLINK: Yes.

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

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

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

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

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

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

9 DR. SILBERG: Correct.

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

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

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

22 DR. CAMINIS: Thank you. Caminis, Shire.

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

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

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

16 DR. CAMINIS: Dr. Kowey?

17 DR. SILBERG: Dr. Kowey?

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

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

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

11 DR. SILBERG: Thank you.

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

16 DR. SILBERG: Dr. Camilleri?

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

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

4 DR. RAUFMAN: Thank you. Dr. Thadani?

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

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

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

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

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

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

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

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

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

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

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

5 DR. MARTIN: Exactly.

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

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

14 DR. SILBERG: Actually, we showed you the
15 12-week so that we could compare.

16 DR. THADANI: What happens at 24? Does it
17 keep on creeping up? Because what is impressive in
18 401? I think there's an explanation of why it
19 didn't work, because placebo responds to the
20 highest. You're running at 24 percent, and even
21 when you modify your criteria, it goes to
22 40 percent.

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

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

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

17 DR. SILBERG: Right. So let me show you
18 this. Maybe this will help. This is the
19 open-label study. Because it's long term, out to
20 18 months, patients were not recording their bowel
21 movements. What they recorded, though, was
22 satisfaction. So those are the kind of scores

1 you're seeing.

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

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

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

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

21 DR. SILBERG: Yes, yes, of course.

22 DR. THADANI: So that seems fair. What I

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

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

10 DR. THADANI: [Inaudible - off mic].

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

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

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

1 DR. RAUFMAN: Dr. Lebowhl?

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

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

11 DR. RAUFMAN: Ms. Numann?

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

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

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

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

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

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

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

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

10 DR. RAUFMAN: Dr. Thadani?

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

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

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

6 If we have that to show?

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

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

11 DR. THADANI: The question is the drug-drug
12 interaction with the CYP P450 3A4. A lot of drugs
13 have metabolites, so are there any issues with
14 that, or what?

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

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

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

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

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

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

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

1 explored others CYPs.

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

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

9 DR. SILBERG: Dr. Kowey?

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

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

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

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

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

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

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

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

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

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

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

12 (No response.)

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

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

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

1 **FDA Presentation - Babatunde Akinshola**

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

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

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

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

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

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

11 Prucalopride at concentrations of at least
12 3 micromolar prolonged the action potential
13 duration by 14 to 20 percent in isolated guinea pig
14 papillary muscles, in canine and rabbit Purkinje
15 fibers, and in rabbit hearts.

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

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

1 human isolated coronary arteries. Prucalopride at
2 200 nanomolar, which is about 10 times the Cmax in
3 humans, had no significant effect on human platelet
4 aggregation in vitro.

5 In in vivo studies, prucalopride at single
6 IV doses of at least 1.25 milligrams per kilogram,
7 which is the equivalent of 44 times the human Cmax,
8 prolonged the duration of the QTc interval by just
9 11 percent in anesthetized guinea pigs.

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

16 In anesthetized dogs, IV prucalopride up to
17 1.25 milligrams per kilogram, approximately
18 137 times human Cmax, had no adverse effect on
19 blood pressure or ECG parameters. Oral
20 prucalopride in these clinic studies in dogs at
21 30 milligrams per kilogram for 12 months had no
22 apparent effect on ECG parameters, characteristics,

1 at a dose of 872 times the human Cmax.

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

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

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

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

1 gene mutation assay.

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

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

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

1 with doses at very high multiples of human
2 exposure.

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

7 **FDA Presentation - Shen Li**

8 DR. LI: Thank you, Dr. Akinshola.

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

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

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

1 in vitro evaluation of platelet aggregation for
2 prucalopride.

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

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

15 Prucalopride is about 29 percent bound to
16 human plasma protein. In vitro, it is a substrate
17 of CYP3A. In a mass balance study, using
18 2-milligram radio-labeled prucalopride, unchanged
19 drug accounted for 92 to 94 percent of the total
20 radioactivity in plasma, while no major metabolites
21 were identified.

22 Prucalopride is mainly eliminated with renal

1 excretions. On average, 84 percent of the total
2 radioactive dose was recovered in urine and
3 13 percent of dose was recovered in feces. The
4 half-life of prucalopride was about 1 day with mean
5 values ranging from 15 to 27 hours across different
6 studies.

7 Next, I will discuss the factors that may
8 affect prucalopride exposure. As presented in the
9 upper left panel, mean AUC in subjects with mild,
10 moderate, and severe renal impairment was about
11 1.2, 1.4, and 2.4-fold compared to that in healthy
12 subjects.

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

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

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

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

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

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

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

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

5 Next, I would like to discuss the effects of
6 prucalopride on QT prolongation using data from a
7 thorough QT study conducted in healthy subjects in
8 which prucalopride was given at 2-milligram QD for
9 5 days and a supratherapeutic dose of 10-milligram
10 QD for 5 days. Moxifloxacin was used as a positive
11 control to confirm study sensitivity.

12 Based on the double-delta QTcSS, which
13 represents placebo and baseline corrected QTc based
14 on a study-specific QT correction, no clinically
15 relevant effect on the QT interval was observed at
16 2-milligram and 10-milligram doses.

17 As shown in the plot on the right, the
18 largest upper bound of the 90 percent confidence
19 interval for the mean difference between
20 prucalopride and placebo were below
21 10 milliseconds, which is a threshold level of
22 regulatory concern.

1 As shown in the concentration time plot on
2 the left, the maximum concentrations for the
3 10-milligram dose was 5.8-fold, higher than that
4 for the proposed 2-milligram dose. Therefore,
5 prucalopride concentration in this study is above
6 predicted worst-case scenario when systemic
7 exposure can be increased under conditions such as
8 renal impairment or drug-drug interactions, as
9 discussed earlier.

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

15 Prucalopride was evaluated at
16 3 concentrations of 20, 60, and 200 nanomolar,
17 which corresponds to onefold, threefold, and
18 tenfold of the mean C_{max} following 2-milligram QD
19 dosing.

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

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

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

11 To summarize, for patients with severe renal
12 impairment, a dose reduction is recommended since
13 the AUC was 2.4-fold to that in healthy subjects
14 with normal renal function. No clinically relevant
15 effect on the QT interval were observed at the
16 2-milligram and 10-milligrams once-daily doses in a
17 thorough QT study. Prucalopride did not
18 significantly potentiate platelet aggregation in
19 in vitro conditions.

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

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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

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

5 For study 3001, the eligible patients needed
6 to have less than or equal to 2 SCBMs per week.
7 For the rest of the efficacy trials, the main
8 inclusion criterion was less than or equal to
9 2 spontaneous complete bowel movements per week at
10 baseline.

11 A bowel movement was considered to be
12 spontaneous if the bowel movement was not preceded
13 by the intake of a laxative within a period of
14 24 hours. A bowel movement was considered complete
15 if the subject responded completely emptying his or
16 her bowels in the diary.

17 All phase 3 and 4 studies evaluated
18 prucalopride, 2 mg, versus placebo. For studies
19 302 and 401, patients aged 65 years or above were
20 initiated on 1 mg with the option to dose escalate
21 to the 2 mg. Therefore, the focus of this
22 application is prucalopride is less than or equal

1 to 2 mg QD.

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

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

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

22 The primary endpoint for all 6 efficacy

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

9 For a week with less than or equal to 3 days
10 of data, SCBM per week was set to missing. For a
11 12-week period with less than or equal to 13 days
12 of data, SCBM per week was also set to missing.

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

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

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

3 Given 9 to 17 percent of missing weekly
4 diary data and balance the missing pattern between
5 two treatment arms, we conducted a primary analysis
6 using observed case data for subjects with at least
7 37 days of data and non-responder imputation for
8 less than 37 days of data.

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

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

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

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

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

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

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

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

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

22 We analyzed alternative endpoint A based on

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

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

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

22 The forest plot shows that 4 of the phase 3

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

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

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

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

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

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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

1 with chronic idiopathic constipation or CIC.

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

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

13 This table summarizes the duration of
14 exposure to placebo or various doses of
15 prucalopride in weeks among patients enrolled in
16 the double-blind trials. 1,516 patients were
17 randomized to the prucalopride 2-milligram dose and
18 1,512 received at least 1 dose. 89.9 percent of
19 subjects who received the 2-milligram dose had at
20 least 4 weeks of exposure.

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

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

6 In the open-label trials, a total of 2,759
7 subjects were exposed to the study drug. Sixty-two
8 percent of the subjects received at least 180 days
9 of drug exposure regardless of dose. 38.1 percent
10 had 365 days of exposure or more, 21.1 percent had
11 545 days of exposure or more, and 3.5 percent had
12 730 days of exposure or more.

13 I will now discuss the deaths that occurred
14 in the double-blind placebo-controlled and
15 open-label CIC trials. There were 8 total deaths,
16 7 deaths occurring in patients receiving
17 prucalopride and 1 occurring in the placebo group.

18 In the double-blind trials, there were
19 2 deaths in the prucalopride group and 1 in the
20 placebo group. The treatment duration of
21 prucalopride ranged from 11 to 31 days. Five
22 deaths occurred in the open-label trials. As noted

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

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

10 The 2 cases of myocardial infarction will be
11 further described during the MACE discussion. The
12 2 cases of suicide will be further described during
13 the discussion on psychiatric events of interest.
14 None of these deaths were attributed to the study
15 drug by the investigator.

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

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

4 This table summarizes the common adverse
5 events in the double-blind placebo-controlled
6 trials directly comparing the proposed dose,
7 prucalopride 2 milligrams, to placebo. The most
8 common adverse events were headache, nausea,
9 diarrhea, and abdominal pain. The percentages of
10 these events were higher in the prucalopride
11 2-milligram group.

12 Let me draw your attention to diarrhea.
13 Though not shown in this table, the percentages of
14 diarrhea increase in a dose-dependent fashion in
15 the 0.5-milligram, 1-milligram, 2-milligram, and
16 4-milligram doses groups. Two diarrhea events were
17 associated with hypokalemia.

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

1 imbalances.

2 I will now discuss the discontinuations due
3 to adverse events. Of the subjects enrolled in the
4 phase 2 through 4 double-blind placebo-controlled
5 trials, or pool D, 86.1 percent of the total
6 prucalopride group versus 87.1 percent of the
7 placebo group completed the trial in which they
8 were enrolled. 6.7 percent of subjects in the
9 total prucalopride group and 5.5 percent of
10 subjects in the prucalopride 2-milligram group
11 discontinued due to an adverse event compared to
12 2.8 percent in the placebo group.

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

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

1 prucalopride were included in this safety database.

2 Standard MACE was defined as cardiovascular
3 mortality, including sudden cardiac death, death
4 due to acute myocardial infarction, heart failure,
5 stroke, or other cardiac causes, nonfatal
6 myocardial infarction, and nonfatal stroke.

7 Extended MACE was defined as MACE plus unstable
8 angina requiring hospitalization.

9 A cardiovascular endpoint committee was
10 established, which consisted of 2 cardiologists and
11 1 neurologist specializing in strokes. Using a
12 prespecified process, all deaths, serious
13 treatment-emergent adverse events, and known
14 serious cardiovascular treatment-emergent adverse
15 events underwent blinded adjudication. The
16 cardiovascular endpoint committee chair reviewed
17 1,916 events from which 218 potential MACE cases
18 were selected for adjudication.

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

1 disease or with at least 2 other cardiovascular
2 risk factors.

3 Group 3 contained patients greater than 65
4 years of age, and group 4 contained patients with a
5 history of ischemic heart disease and/or chronic
6 renal insufficiency, defined as an estimated
7 creatinine clearance of less than 60 milliliters
8 per minute and/or peripheral vascular disease.
9 39.2 percent of subjects had at least one risk
10 factor in the all-prucalopride group, which
11 included the double-blind and open-label trials,
12 compared to 37.3 percent in the placebo group.

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

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

1 In the double-blind trials, there were
2 2 cases of standard MACE in the placebo group and
3 2 cases in the prucalopride all-doses group. There
4 were 7 additional cases of standard MACE in the
5 all-prucalopride group when the open-label trials
6 were included. I will describe these cases in a
7 later slide.

8 In general, the percentages of both MACE and
9 non-MACE events were low and comparable between the
10 2-milligram prucalopride and placebo groups. You
11 will notice some imbalances in the non-MACE events
12 listed in this table. I will display additional
13 information in the next slide regarding the non-
14 ischemic arrhythmias, other CV events, and
15 insufficient information to adjudicate groups.

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

1 small and comparable.

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

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

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

22 This table lists the subjects receiving

1 prucalopride who had an adverse event that was
2 adjudicated as standard MACE. Of these 9 cases,
3 there were 2 nonfatal MIs, 5 nonfatal strokes, and
4 2 cardiovascular deaths. 7 of the 9 subjects
5 experienced a standard MACE event while on
6 prucalopride, however, 2 of these subjects
7 experienced the event on the 2-milligram dose.

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

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

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

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

4 In the total prucalopride group, QT
5 prolongation, related ventricular arrhythmias, and
6 syncope/pre-syncope events occurred in less than
7 0.3 percent of subjects, and the percentages of
8 events were comparable between the prucalopride and
9 placebo groups.

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

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

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

1 had depression and insomnia with a 1-month history
2 of antidepressant use prior to the event, and the
3 40-year-old female had a history of depression and
4 drug abuse.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 **FDA Presentation - Joel Weissfeld**

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

16 Prucalopride entered European markets in
17 2009. To provide evidence about the cardiovascular
18 safety of prucalopride, the applicant conducted
19 study 802, which used European data sources and
20 non-randomized observational study methods to
21 examine the incidence of major adverse
22 cardiovascular events, or MACE, in adults

1 prescribed prucalopride.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 Please note that the figure on this slide
8 plots results on a logarithmic scale with tick
9 marks equally spaced between SIRRs of 0.33 and
10 3.00. The figure also shows 2 thresholds, SIRR
11 1.00, to represent SIRs equal in prucalopride and
12 PEG, and SIRR 3.00 to represent an SIR threefold
13 higher in prucalopride than PEG.

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

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

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

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

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

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

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

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

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

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

1 Pharmacoepidemiological Research Database.

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

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

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

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

3 Overall, the prucalopride and PEG cohorts
4 contain similar fractions of younger adults,
5 45.7 percent and 46.8 percent less than 55 years of
6 age, respectively.

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

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

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

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

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

11 **Clarifying Questions to the Presenters**

12 DR. RAUFMAN: Thank you.

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

17 I'd like to start with some questions for
18 Dr. Akinshola, if we can have his slide 22, please?

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

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

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

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

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

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

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

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

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

6 DR. CHAKDER: My name is Sushanta Chakder
7 from FDA. This study was for 2 years, and then
8 analyses was done. The animals are killed. The
9 surviving animals are killed at the end of 2 years,
10 and the safety analyses are done at the end of
11 2 years.

12 DR. RAUFMAN: Okay.

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

15 DR. RAUFMAN: This was at, it says,
16 194 times the clinical exposure. So can you
17 reassure us that at the clinical exposure, there's
18 no difference at a lower dose?

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

1 25-fold exposure margins. But here, these exposure
2 margins are much, much higher than the 25-fold
3 recommendations.

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

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

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

14 DR. RAUFMAN: Thank you.

15 DR. SILBERG: So particularly on breast
16 cancer?

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

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

22 DR. CAMINIS: Thank you. Caminis, Shire.

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

8 DR. RAUFMAN: Thank you. Dr. Lebwohl?

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

15 When looking at a breakdown by age and
16 gender, I don't think it was in the slide
17 presentation, but in the briefing document, FDA
18 briefing document, table 28 -- it's page
19 54 -- there were subgroup analyses. And in most of
20 them, those risk ratios were below 1, but in men 55
21 years and older, the SIRR was 2.7, with a wide
22 confidence interval but included the unity.

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

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

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

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

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

5 The subgroup analyses by age and sex are
6 shown under the heading "Subgroup Analyses for
7 MACE," subgroups of younger women, 18- to
8 54-year-old women, older women greater than or
9 equal to 55-year-old women, younger men and older
10 men, showing the breakdown of the number of MACE
11 events both in the prucalopride and PEG cohorts.

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

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

22 So I think at this point in time, we just

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

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

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

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

1 and those data sources.

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

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

12 Were there other questions?

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

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

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

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

5 DR. RAUFMAN: Dr. Thadani?

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

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

17 DR. RAUFMAN: You can go ahead and respond.

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

22 DR. CAMINIS: Thank you. John Caminis. May

1 I have the note slide, please, for prolactin?

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

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

13 DR. CAMINIS: No.

14 DR. THADANI: My other question is to
15 Dr. Akinshola. Could you show me slide number 18
16 from FDA? In this slide, it says that there was a
17 20 percent increase in atrial contractions. And
18 the reason I'm asking this question is with these
19 drugs, there was some noise on atrial fibrillation
20 in the database.

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

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

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

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

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

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

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

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

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

22 DR. THADANI: -- or you can stimulate the

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

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

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

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

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

19 My information -- and this is sort of a
20 30,000-foot view of it -- was they didn't see
21 anything, and I think that's what the FDA is
22 telling you; that even though they didn't do a

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

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

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

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

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

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

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

13 In SNR, there were 3 pru-exposed cases and
14 11 -- this is in men greater than or equal to
15 55 years of age, 3 cases of men of MACE in the pru
16 cohort; 11 in the PEG cohort, with an incidence
17 rate ratio calculated at 1.37 with a wide
18 confidence interval of 0.25 to 5.19. This would
19 mean that there was only -- the other 3 data
20 sources, the U.K. data sources only provided 1
21 additional case of MACE in the exposed cohort and
22 none in the PEG cohort.

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

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

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

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

14 DR. RAUFMAN: Dr. Solga?

15 DR. SOLGA: It's Steve Solga. A question
16 for Dr. Akinshola and follows up a theme from
17 Dr. Raufman. I read in the FDA briefing packet on
18 page 5 that this IND was put on partial hold in
19 2000 over concerns of genotoxicity in
20 carcinogenicity.

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

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

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

9 (Laughter.)

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

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

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

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

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

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

1 DR. CHAKDER: Yes, that's correct. But now
2 our standard -- as I said to you previously, the
3 standard has changed for carcinogenicity dose
4 selections. The highest dose is selected based on
5 25-fold exposure margins. So here, the highest
6 dose provided more than 200, 300 for safety
7 exposure margins.

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

11 DR. CHAKDER: Thank you.

12 DR. RAUFMAN: Dr. Hunsberger?

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

16 DR. RAUFMAN: The sponsor can address that.

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

22 DR. CAMINIS: Thank you, Dr. Silberg.

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

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

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

17 DR. CAMINIS: Open label.

18 DR. HUNSBERGER: This is just the open
19 label?

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

22 DR. HUNSBERGER: So you looked by arm, and

1 you had equal numbers of spontaneous abortions by
2 arm?

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

6 DR. HUNSBERGER: So can you look by arm?

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

9 DR. RAUFMAN: Go ahead.

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

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

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

22 This is a summary of the missing weekly

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

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

11 DR. HUNSBERGER: You said you had to impute
12 70 percent??

13 DR. LAN: Seventeen.

14 DR. HUNSBERGER: Seventeen, okay. Okay.

15 (Laughter.)

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

18 DR. HUNSBERGER: Okay. Good.

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

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

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

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

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

18 DR. LAN: Non-responder.

19 DR. HUNSBERGER: Okay. And in both groups?

20 DR. LAN: Yes.

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

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

3 DR. HUNSBERGER: Okay.

4 DR. LAN: Yes.

5 DR. RAUFMAN: Dr. Thadani?

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

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

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

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

3 DR. THADANI: Sure.

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

8 DR. THADANI: You are very far --

9 DR. TOMAINO: -- committed suicide were
10 29 days after and 52 days after. So we considered
11 the half-life of the drug as well as the time that
12 the suicide was committed to try to make a
13 determination of whether this might be related to
14 the drug. The sponsor may have additional data on
15 possible withdrawal.

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

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

1 sponsor might have addressed it.

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

6 DR. THADANI: Sure.

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

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

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

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

22 The incidence of diarrhea is up. So what

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

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

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

17 DR. RAUFMAN: Dr. Solga?

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

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

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

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

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

10 DR. LINE: Fifty-five?

11 DR. SOLGA: Fifty-five. I apologize.

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

17 DR. KORVICK: Maybe the sponsor does.

18 DR. RAUFMAN: Does the sponsor have that
19 information?

20 (No response.)

21 DR. RAUFMAN: Thank you. Ms. Hugick?

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

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

3 As a consumer representative, I want to
4 understand what you want us to do with that. It's
5 310 people, so I'm just kind of curious. I'd ask
6 that of the sponsor and FDA.

7 DR. TOMAINO: Study 401, was conducted as a
8 phase 4 trial to look at longer-term efficacy. We
9 considered this failed trial in the context of the
10 5 other trials that did show statistically
11 significant results. We were not able to identify
12 a clear reason for the treatment failure other than
13 it could happen.

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

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

2 Thanks.

3 DR. RAUFMAN: Dr. Teerlink?

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

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

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

1 15-ish percent of our U.S., but we have less than
2 3 percent in the trials.

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

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

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

18 DR. TEERLINK: Thank you.

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

22 DR. WEISSFELD: Joel Weissfeld, FDA.

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

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

7 DR. RAUFMAN: Dr. Lai?

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

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

17 DR. LAI: Correct.

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

22 DR. LAI: Okay. And were the rates of

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

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

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

16 DR. RAUFMAN: Dr. Thadani?

17 DR. THADANI: Yes, thanks. I alluded to the
18 401 study. I think the sponsor's slide 35 probably
19 really clarifies.

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

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

8 So that could be the real explanation, why
9 bad luck [indiscernible], you have a higher placebo
10 response, because average response on the active
11 medication is about 25 percent, which is maintained
12 in one of the studies, 30. And this is again
13 highlighted more in your slide 38 from the sponsor,
14 38 also.

15 Again, this one again shows sometimes it is
16 5, sometimes 12.5. So it's in the right direction,
17 but I think placebo plays havoc sometimes in
18 trials. So that could be the explanation you were
19 asking.

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

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

3 DR. RAUFMAN: Ms. Numann?

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

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

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

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

17 DR. LAI: Comparable statistically or
18 clinically?

19 DR. TOMAINO: Qualitatively, descriptively.

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

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

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

10 MS. NUMANN: Thank you.

11 DR. RAUFMAN: Additional comments, concerns?

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

14 DR. RAUFMAN: Yes.

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

17 Dr. Hunsberger, the effect size for the
18 efficacy studies ranges from 5 percent to
19 22 percent, and missing data rate is about
20 9 percent to 17 percent. So using the worst-case
21 imputation, the imputing missing to the responder
22 on the placebo and to non-responder in the

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

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

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

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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,

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

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

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

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

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

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

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

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

1 characteristics that may affect the safety and
2 efficacy of the drug such as smoking history,
3 family history of heart disease, or other medical
4 conditions and treatments causing constipation.

5 The only studies done in the American
6 population were two studies completed in 1999. In
7 addition to patients being white and relatively
8 young, they were probably less likely to be obese.
9 I say that because the prevalence of obesity in the
10 U.S. has increased dramatically in the last two
11 decades and is now 25 to 40 percent in almost all
12 states today according to the CDC.

13 The American diet has also changed, as well
14 as most sedentary habits and an increase in the use
15 of prescription medications. We can't assume that
16 a trial done in 1999 that pertains to constipation
17 is applicable today.

18 When we consider those shortcomings of the
19 old studies and the new ones, there is not enough
20 information for the FDA to evaluate whether the
21 benefits of this drug outweigh the risks for the
22 U.S. population that is likely to be prescribed

1 this drug if it is approved. There are too many
2 differences between the patients studied in all
3 those trials and patients likely to be prescribed
4 the drug in the U.S.

5 In addition to obesity, diabetes, diet, and
6 exercise, think also of the number of prescription
7 drugs that older people in the U.S. take compared
8 to younger patients from Australia, Asia, and
9 Europe. All of these health concerns could affect
10 the safety of the drug.

11 Even in terms of something as important as
12 drug interactions, we are unclear about the effect
13 of prucalopride on other medications. For example,
14 research trials done in Australia show that this
15 drug can reduce the efficacy of oral contraceptives
16 taken by some women.

17 The information is included in the Johnson
18 label for Resotran, but is not mentioned in the FDA
19 review that you received. It seems likely that the
20 drug would have a similar effect in U.S. women who
21 are taking hormones for contraception and could
22 also have an unfortunate interaction for women

1 taking hormones for menopause symptoms or to
2 prevent estrogen-receptor-positive breast cancer.

3 Biological and cultural factors affect the
4 outcomes and the severity of constipation episodes.
5 The lack of diversity and the lack of U.S. data
6 mean that we cannot predict how effective or safe
7 the drug will be in most of the patients that will
8 expect to be treated with this drug. It would be
9 impossible to know if the drug is safe in older
10 black women or men, for example.

11 Lastly, this short duration of the clinical
12 trials raises some safety concerns. The longest
13 double-blind clinical trial was only 24 weeks long.
14 This disease is a chronic condition, so patients
15 would be expected to take this drug on and off for
16 years. Many of the heart-related adverse effects
17 may take years to manifest. This is why FDA
18 typically requires longer clinical trials for such
19 drugs, so as to better identify additional safety
20 concerns such as major adverse cardiac events.

21 In summary, this drug was tested on a
22 population with limited demographic variability,

1 and we should really focus on whether this drug
2 will be effective and safe for the American
3 population. The FDA must require further
4 verification of the efficacy and the safety of this
5 drug in relevant populations in order to make an
6 informed decision. Thank you.

7 DR. RAUFMAN: Thank you. Will speaker
8 number 2 step up to the podium and introduce
9 yourself? Please state your name and any
10 organization you are representing for the record.

11 DR. STEIN: Hi. My name is Ellen Stein. I
12 have no financial disclosures. I am the clinical
13 director of gastroenterology at the Bayview Medical
14 Center and motility specialist at Johns Hopkins
15 University. I would like to thank the committee
16 and all in the room for their time and attention.

17 I spend time in my clinic helping people. I
18 take on the cases that other doctors cannot manage.
19 I partner with my colorectal surgery colleagues to
20 save colons everywhere from unnecessary resection.
21 I see patients from all walks of life, and I will
22 tell you two of their stories today.

1 One patient came to me several years ago in
2 an emergency appointment before her colon was going
3 to be removed. I was her second opinion. I offered
4 my advice to this lovely young woman in her mid-20s
5 who had dropped out of school due to the severity
6 of her symptoms. I explained that with time and
7 medication, I thought her idiopathic constipation
8 could actually be managed.

9 She was having less than 1 bowel movement a
10 week at the time, with intense bloating, pain, and
11 nausea. She trusted in me, and we went through a
12 series of medication trials. We engaged her in
13 physical therapy, psychotherapy, and we weaned her
14 off all narcotics. Then and only then was
15 linaclotide finally able to help her symptoms long
16 enough with other medical therapies to allow her
17 bowel habits to resume.

18 But it took months to achieve a good effect,
19 and she has only slowly been able to rebuild her
20 structure and function and is now considering going
21 back to school next year.

22 Without adequate medical therapy, this woman

1 would have possibly lost her colon in a vain
2 attempt to improve her quality of life. She lost
3 three years of her life with her debilitating
4 symptoms. She became depressed and isolated in her
5 challenge to have normal bowel habits again.

6 Things are finally looking up for her, as
7 she has spontaneous daily bowel movements with her
8 current regimen. She's a lucky one.

9 Another patient came to me just this past
10 week. She is at her wit's end in her late 20s.
11 She's trying to function. She has a boyfriend, a
12 job. She wants to think about pregnancy in the
13 next few years, and a colectomy would ruin those
14 plans.

15 She has no bowel movements without her
16 medications. And with the entire pharmacy of
17 over-the-counter options, she might have a bowel
18 movement every few days, but only with a lot of
19 distress.

20 She's cycled through everything available on
21 the market, Amitiza, Linzess, lactulose, senna,
22 Dulcolax, and other agents only with minimal relief

1 of her symptoms. Some days, she will spend hours
2 in distress at home, avoiding her friends and
3 family, waiting for relief. Some days, she cannot
4 go to work, the symptoms are so severe. She is
5 terrified that these things will continue to
6 decline. She has chronic idiopathic constipation.

7 We will work together, I told her, to make
8 sure her defecatory dysfunction is managed because
9 many of these patients develop dysfunction from
10 inappropriate, intense straining during years of
11 idiopathic constipation.

12 She is currently at the end of the road of
13 medical options in the U.S. We discuss thinking
14 about more intensive options like high-volume
15 enemas and more invasive maneuvers, but if there
16 were other medications with slightly different
17 mechanisms of action available, like prucalopride,
18 perhaps she would finally have the response she
19 needs and be able to restore function.

20 The effects of constipation are incredibly
21 palpable for these young women and men. They are
22 isolated, depressed, challenged to function, and

1 they often must have special accommodations to work
2 or finish schooling.

3 There are only a few approved medications to
4 try, and there are even fewer studies demonstrating
5 the true safety of years of use of the other
6 medications grandfathered into our system. I focus
7 my work on the whole patient. I always start with
8 diet and exercise. I emphasize opioid avoidance
9 and discontinuation, and we go through every
10 possible method to help augment therapy, but the
11 medications we have here in the U.S. are often not
12 enough.

13 It's hard to explain to patients that just
14 across the border in Canada or across the pond in
15 European countries, there are other possibly better
16 options that are readily available for relatively
17 safe use. And even if the efficacy of any of these
18 drugs is not 100 percent, we know that different
19 people respond to different medications
20 differently.

21 I see the patients who need more options.
22 We will someday understand at a genetic and mucosal

1 level how to predict those responses better, but in
2 the meantime, I think we need to expand our arsenal
3 in the U.S. The risks of not allowing my patients
4 to have access to these medications is great, and I
5 think it's time to approve them for use.

6 Thank you for letting me have the
7 opportunity to speak for our patients and about
8 this treatment.

9 DR. RAUFMAN: Thank you. Will speaker
10 number 3 step up to the podium and introduce
11 yourself? Please state your name and any
12 organization you are representing for the record.

13 DR. STEIN: I am going to be sharing this on
14 behalf of Baha Moshiree. I don't believe she has
15 any conflicts of interest. She was unable to be
16 here today and she sends her regrets and apologies.
17 And so I'm supposed to read this statement exactly,
18 so I'll do my best.

19 "Good afternoon. My name is Baha Moshiree.
20 I am director of motility at Carolinas Healthcare
21 System and professor medicine at the University of
22 North Carolina in Charlotte. First and foremost, I

1 would like to thank the FDA and these committees
2 for allowing me to provide testimony on behalf of
3 my patients, who suffer from severe constipation.

4 "As a gastroenterology faculty at Carolinas
5 Medical Center, now Atrium Health, I see more than
6 40 patients a month who suffer from chronic
7 idiopathic constipation or severe forms of
8 constipation such as neurogenic bowel and slow
9 transit constipation.

10 "Constipation is a relatively common and
11 debilitating condition for my patients to present
12 with. Many patients who come to my institution are
13 those who have already had moderate to severe
14 chronic idiopathic constipation, and they have
15 failed many conventional or over-the-counter
16 medications for this disorder. They also already
17 have a level of debilitation and significant
18 impairment in their quality of life. They may
19 avoid travel due to their worry about their GI
20 symptoms.

21 "Other commonly associated symptoms include
22 nausea, abdominal bloating, and pain due to their

1 underlying constipation. And many strain to have
2 bowel movements and develop hemorrhoids which can
3 bleed. They often skip meals as they may feel too
4 full due to their constipation. They can't always
5 continue working outside the home.

6 "They tend to go to pharmacies and use over-
7 the-counter medications, which may not be effective
8 for every patient, and are not covered by
9 insurance, and end up to be a financial burden for
10 them.

11 "Many times, patients come to see me after
12 they have exhausted several of these options. In
13 fact, there are more options now than in the past
14 20 years. We do have ways that we can help these
15 patients who are so in need. Despite newer
16 constipation therapies, which have now become
17 available, not all the treatments target the same
18 neurotransmitters that are found to be deficient or
19 low in patients with chronic idiopathic
20 constipation.

21 "One such neurotransmitter is serotonin,
22 which is found in the gut to a large degree.

1 Although most of the currently available
2 pharmacological agents are what are called
3 secretagogues, plecanatide, linaclotide, and
4 lubiprostone, and others as osmotic laxatives such
5 as MiraLAX or magnesium supplements, none target
6 serotonin.

7 "Prucalopride targets serotonin as an
8 agonist and has already been shown to improve
9 colonic transit and motility, thus increasing the
10 number of bowel movements, bloating, and pain
11 relief associated with constipation.

12 "Luckily, we have already had experience
13 with a similar drug, tegaserod, which was
14 clinically available for the treatment of
15 constipation previously, but which is no longer
16 available. Prucalopride has similar actions to
17 tegaserod, and I believe it could be valuable in
18 our treatment armamentarium.

19 "I am familiar with a number of my own
20 patients who have experience with prucalopride
21 already as ordered through Canadian pharmacies.
22 Their experience demonstrates it can be effective

1 for the appropriate patients. They have achieved
2 considerable benefit in their overall numbers of
3 spontaneous bowel movements over their baseline.

4 "Going from 1 bowel movement to 2 or 3 in a
5 week has a positive overall impact on people in
6 their level of comfort and satisfaction. This
7 improvement has translated into a better quality of
8 life despite the added cost of having to buy this
9 medication from Canada.

10 "I hope the FDA allows this safe medication
11 with which we already have experience to now be
12 available to our patients here and in the U.S.
13 Thank you for letting me have the opportunity to
14 speak for our patients about this new treatment."

15 DR. RAUFMAN: Thank you. Will speaker
16 number 4 step up to the podium and introduce
17 yourself? Please state your name and any
18 organization you are representing for the record.

19 DR. HASLER: Thank you, Chairman Raufman and
20 GIDAC committee attendees. My name is Dr. William
21 Hasler, and I'm speaking on behalf of the American
22 Neurogastroenterology and Motility Society or ANMS.

1 By way of disclosure, my meeting travel expenses
2 and lodging are being reimbursed by the sponsor,
3 Shire.

4 ANMS is a multidisciplinary society that
5 fosters excellence in research, education,
6 training, and patient care related to motility and
7 functional disorders of the gastrointestinal tract.
8 The ANMS applauds the U.S. Food and Drug
9 Administration review of new drug application
10 210166 for prucalopride and supports this current
11 meeting of the FDA Gastrointestinal Drugs Advisory
12 Committee to discuss its potential future clinical
13 applicability in the United States.

14 The drug is an investigational compound,
15 which acts as an agonist on serotonin 5-HT₄
16 receptors in the gastrointestinal tract.
17 Prucalopride is approved and available in Europe
18 and Canada, where it is prescribed for symptomatic
19 treatment of adults with refractory chronic
20 constipation in whom other laxatives have failed.

21 This compound is currently under evaluation
22 by the Food and Drug Administration for treatment

1 of chronic idiopathic constipation in the United
2 States. If such approval is ultimately granted,
3 prucalopride will be the only serotonin 5-HT4
4 receptor agonist accessible for adults in the U.S.
5 with this specific condition.

6 Over 35 million patients are affected by
7 chronic idiopathic constipation in the U.S. The
8 condition is characterized by infrequent or
9 incomplete passage of stools with associated
10 abdominal pain, difficult defecation, and/or
11 bloating. Chronic constipation can be very
12 debilitating for affected patients and
13 significantly decreases their quality of life.

14 In one recent U.S.-population-based survey,
15 chronic idiopathic constipation was rated as very
16 or extremely bothersome by more than 60 percent of
17 patients and disrupted productivity, including
18 missing work, more than 3 days per month.

19 Many patients try over-the-counter and
20 prescription medications, including laxatives,
21 often with unsatisfactory results. In a
22 questionnaire study published within the last year

1 of more than 1200 patients with chronic idiopathic
2 constipation, nearly 60 percent using existing
3 treatments for this condition were not satisfied
4 with their responses to therapy due to lack of
5 efficacy or side effects such as diarrhea.

6 The pathophysiology of chronic constipation
7 is multifactorial, and this condition may occur as
8 a result of impaired motility with slowed transit
9 of the gastrointestinal tract. Most of the
10 currently available therapies of chronic idiopathic
11 constipation do not act directly on these
12 underlying deficits in gastrointestinal motility
13 and transit.

14 Furthermore, none of the current
15 prescription medications for this condition utilize
16 this mechanism of action. Taken together, these
17 observations indicate that there is an important
18 unmet need for new treatments for this condition,
19 which act by different mechanisms in the
20 gastrointestinal tract.

21 Prucalopride is a selective serotonin type 4
22 receptor agonist that stimulates colonic

1 peristalsis and hastens gastrointestinal
2 propulsion, including acceleration of colon
3 transit. Prucalopride has been studied worldwide
4 in several placebo-controlled clinical trials, and
5 integrated analysis of 6 randomized controlled
6 clinical trials evaluated the global efficacy and
7 safety of prucalopride in men and women with
8 chronic constipation.

9 Compared to placebo, significantly more
10 patients treated with prucalopride achieved an
11 average of 3 or more spontaneous complete bowel
12 movements per week over the study treatment
13 periods. Adverse events were minimal and included
14 headaches as well as gastrointestinal symptoms such
15 as nausea, diarrhea, and abdominal pain.

16 Cardiac arrhythmias attributable to
17 prucalopride have not been described, and the
18 proportions of patients who experienced any adverse
19 cardiovascular events were comparable on
20 prucalopride versus placebo in the clinical trials
21 emphasizing the safety of this drug.

22 Based on the findings of these rigorous

1 investigations, the American Neurogastroenterology
2 and Motility Society, or ANMS, endorses the
3 consideration of prucalopride for treatment of
4 chronic idiopathic constipation. This medication
5 will serve as an important treatment option for the
6 millions of patients in the U.S. suffering from
7 chronic constipation. Thank you for your
8 attention.

9 DR. RAUFMAN: Thank you. Will speaker
10 number 5 step up to the podium and introduce
11 yourself? Please state your name and any
12 organization you are representing for the record.

13 MR. CONWAY: Thank you so much. My name is
14 Brad Conway. I'm here on behalf of the American
15 College of Gastroenterology. Just as way of
16 disclosure, I have no personal disclosures to let
17 you know about, but the sponsor has sponsored ACG
18 initiatives in the past at the curriculum and
19 speakers of ACG's choosing, though.

20 Just as background, American College of
21 Gastroenterology represents over 15,000 clinical
22 gastroenterologists and GI clinicians in the United

1 States and across the world. And as you had noted
2 today by the FDA, chronic constipation is one of
3 the most common functional GI disorders today with
4 a prevalence rate of roughly 15 percent, and to put
5 it in more context, that's 1 in every 7 patients
6 studied.

7 Recently, the American Journal of
8 Gastroenterology noted two issues with chronic
9 constipation, the first that no single or combined
10 current treatment option works for all patients,
11 and, secondly, there remains significant clinical
12 need for new treatment options.

13 As noted earlier today and by other
14 speakers, EMA and Canada has approved the drug, and
15 we believe that the postmarket clinical studies
16 have demonstrated both the safety and efficacy.
17 And that's why ACG appreciates the committee today
18 and the FDA for looking at this application.

19 We're also encouraged by the different
20 mechanism of action that will hopefully fulfill
21 this clinical need and for new treatment options
22 for chronic constipation. I appreciate your time

1 and thank you very much.

2 DR. RAUFMAN: Thank you. Will speaker
3 number 6 step up to the podium and introduce
4 yourself? Please state your name and any
5 organization you are representing for the record.

6 DR. NICHOLS: Hi. I'm Dr. Trent Nichols,
7 and I'm actually a neurogastroenterologist as well
8 as a previous chemist, and I'm going to try to talk
9 about some of the chemical things that may have
10 been talked about.

11 As said previously, it's a highly selective,
12 high-affinity receptor agonist, MR [ph] GI
13 prokinetic activity. And as we already talked
14 about, constipation is getting worse. This is a
15 slide in 2000, and now it's up to 63 million. At
16 that time, it was 55.

17 It has a huge significant direct cost and
18 indirect cost. About the 5-HT4 receptor site, it's
19 very important to know what it looks like. The
20 gene is a member of the family of human serotonin
21 receptors. It's a protein-coupled receptor that
22 stimulates cyclic AMP. And that's important in

1 mitochondria, and that's important to talk about
2 because this is prucalopride succinate, and I'll go
3 into that in a few minutes.

4 The gene product is glycosylated
5 transmembrane protein that functions in both the
6 peripheral and nervous system to modulate the
7 release of various neurotransmitters and release of
8 acetylcholine and muscarinic receptors in the gut.

9 The 5-HT4 receptors, 95 percent is located
10 in the elementary tract. The rest is in the
11 urinary, bladder, heart, and adrenal glands, as
12 well as the central nervous system. Prucalopride
13 has a greater than 150-fold affinity for the 5-HT4
14 receptor. And this is probably done by molecular
15 modeling. If anybody's worked in this industry,
16 you'd understand, and it has what we call less
17 bleed to other receptors.

18 Prucalopride differs from other 5-H4
19 agonists such as tegaserod and cisapride. That's
20 because it doesn't intercept the 5-H2A1BD, which
21 has the cardiac human ether-a-go-go or potassium
22 channel. It's abbreviated as hERG, respectively,

1 with cardiac arrhythmias and long QT.

2 As you know, you already went over tegaserod
3 that had ischemic cardiovascular events, which
4 maybe was brought out in the Oregon sudden death
5 study.

6 If you look at the structure of cisapride,
7 which is sort of like the father of prucalopride,
8 you notice that there's a fluorobenzene. And
9 that's at the end here; I don't think you can see
10 that. And they took the fluorobenzene ring off.

11 Also, antihistamines such as stiemazol has a
12 fluorobenzene, and that has a long QT interval, as
13 well as another, mizolastine [ph], and
14 sparfloxacin. In fact, all the fluoroquinolones
15 have the fluorobenzene ring, and they all have some
16 susceptibility to long QT.

17 Clinical trials, we previously went over.
18 This is when I was involved with Dr. Vandeplassche,
19 and this is the Moventus Group. I was at Digestive
20 Disease Week or Gastroenterology United European in
21 2008. I had 27 subjects in this.

22 One of the other things I wanted to go

1 through is that there was a trial, which one of the
2 speakers doesn't know about, which was up to
3 18 months. So it's been used longer in clinical
4 trials than she thought about because she hasn't
5 done a complete study. When you go through all the
6 literature like I have, you find out there's lots
7 of things that should be pointed out.

8 This is when it was evaluated, over 713
9 patients. Again, you've heard that mainly it's
10 headaches and abdominal pain. And again, you had
11 this in a cardiovascular thing on a previous slide,
12 which was presented earlier, I believe, where they
13 used both in vivo and in vitro studies, and there
14 was no cardiovascular. If there was, there was a
15 little bit in the guinea pig which had the heart
16 rate going up, until the drug, after about
17 15 minutes, it dropped down.

18 Prucalopride, of course, has been used in
19 Europe since 2009, Canada 2011, and Israel 2014.
20 It has now been kind of talked about in chronic
21 idiopathic constipation with Shire. And this is
22 actually not only a prokinetic problem, but

1 probably may even be mitochondrial. I'll get into
2 that in just a few minutes.

3 A study of 94 subjects found that the
4 patients saw an increase in bowel movements while
5 taking laxative and reported never having a feeling
6 of complete evacuation. These actually subjects
7 had what they call high amplitude, what we call
8 HAPCs, high-amplitude propulsive contractions,
9 which were in the colon, which was much fewer and
10 lower amplitude, and that the HAPC can have an
11 impact on having bowel movements. That may be the
12 reason why the patient is constipated.

13 There was an investigator that was at the
14 motility center at Hopkins by the name of Marvin
15 Schuster. And in 1985, he presented a paper about
16 what they called congenital constipation, and this
17 is people who were almost born to have this. They
18 had digital arches.

19 We've actually studied that, and now found
20 that this is probably a predisposing factor in
21 these IC subjects and can be identified actually by
22 looking at their fingerprints.

1 Now, the other thing I wanted to talk about
2 is just succinate for a few seconds. The succinate
3 is actually a mitochondrial cofactor. It's part of
4 the Krebs cycle. That's the tail of prucalopride,
5 and actually that's worked already in chronic
6 intestinal pseudoobstruction, which is a myocardial
7 disorder. Thank you.

8 I have no hearing subsidies whatsoever. I'm
9 presenting just for myself and QuietMIND
10 Foundation.

11 DR. RAUFMAN: Thank you. Will speaker
12 number 7 step up to the podium and introduce
13 yourself? Please state your name and any
14 organization you are representing for the record.

15 MR. ROBERTS: Members of the committee,
16 thank you again for the opportunity to appear
17 before you. My name is Jeffrey Roberts, and I'm
18 the founder of the IBS Patient Group. I'm here
19 today representing patients and sufferers. I have
20 paid all my own expenses to be here.

21 The IBS Patient Group has endeavored since
22 1987 to educate and provide support for hundreds of

1 thousands of people who have functional
2 gastrointestinal disorders, or FDIGs, and to
3 encourage both medical and pharmaceutical research
4 to make our lives easier by our patient advocacy
5 efforts.

6 I provided testimony to this committee
7 several times. I have been a sufferer of an FDIG,
8 namely IBS, for over 25 years. I face challenges
9 each and every day in order to cope with my
10 illness. It affects my family's lives, my career,
11 and I'm constantly reminded of my own physical
12 limitations because of this very burdensome
13 illness.

14 Functional constipation is a common problem
15 in our FDIG community, with its prevalence ranging
16 from 2 percent to 28 percent. As I'm a focus in
17 the community for information about functional
18 gastrointestinal disorders, I communicate with a
19 great many people who have run out of options.
20 They do not know where to turn, and their quality
21 of life has greatly suffered.

22 Many traditional current approaches to

1 chronic constipation, including the use of fiber,
2 osmotic and stimulant laxatives, biofeedback
3 training and surgery, often fail to control the
4 patients' symptoms adequately. They produce
5 problematic side effects or lose effectiveness with
6 time.

7 Newly approved drugs for constipation have
8 been successful for some patients, however, they
9 haven't quite met the needs of the majority.
10 Physicians often prescribe medications for
11 constipation with which they are familiar and
12 comfortable; in most cases anything will do.

13 Moreover, chronic constipation is a very
14 unpleasant disorder, and in some cases, individuals
15 who suffer from chronic constipation may not have a
16 satisfactory bowel movement for up to 21 days.
17 Their quality of life is greatly diminished by this
18 basic impaired function that most individuals take
19 for granted.

20 Noel, a member of the IBS Patient Group,
21 says, "People who don't deal with chronic
22 constipation have no concept of how it can destroy

1 your life, personal relationships, brain health,
2 and ability to work. It's an absolutely miserable
3 problem that affects all other areas of your
4 health."

5 While Zelnorm, a medication for chronic
6 idiopathic constipation and IBS-C, met the needs of
7 many patients, its removal from the market in 2007
8 created a gap in treatment options until new
9 treatment options were approved in the subsequent
10 years.

11 Prucalopride, the same class as Zelnorm with
12 the distinction of a diminished risk of
13 cardiovascular issues and a favorable safety
14 profile, has proven to be successful treatment by
15 patients and physicians in other countries.

16 Physicians are well versed at risk
17 management and along with patients, are risk
18 adverse. Prucalopride meets this goal as another
19 treatment option.

20 There is strong evidence that chronic
21 constipation presents itself more frequently in
22 women versus men, and its prevalence increases with

1 age. The subjective perception of chronic
2 constipation at times leads to disagreements with
3 physicians and patients as to whether someone is
4 actually suffering from constipation.

5 This leads to minimizing the illness and a
6 vicious cycle of over-the-counter remedies of
7 limited efficacy versus medications like
8 prucalopride, which are more suited to treat this
9 illness.

10 Traditionally, FDIGs were not considered to
11 be associated with an increased risk in mortality.
12 However, recent studies have shown that there is a
13 risk from constipation. Having personally
14 experienced a sudden episode of severe impacted
15 constipation with life-threatening consequences, I
16 can relate to the anguish that a chronic
17 constipation sufferer has to deal with on a
18 near-constant basis.

19 Given the fact that constipation occurs more
20 frequently in the elderly patients and that life
21 expectancy is increasing, we can likely expect an
22 increase in prevalence of constipation in the years

1 to come along with quality of life issues unless
2 more patients are taken seriously and offered a
3 chronic constipation medication like prucalopride.

4 The IBS Patient Group is prepared to place
5 educational information about prucalopride on their
6 website in order to reach out to the constipation
7 community. This provides an effective forum for
8 educating constipation sufferers about prucalopride.

9 In conclusion, the quality of life of
10 constipation sufferers was dramatically improved
11 with access to prucalopride in other countries.
12 The medical communities should be informed that a
13 new treatment option is available, which will
14 improve their patients' outlook.

15 Prucalopride has a place as an effective
16 treatment for chronic constipation sufferers and
17 should be approved and indicated as such to the
18 patient and medical community. Thank you.

19 DR. RAUFMAN: Thank you. Will speaker
20 number 8 step up to the podium and introduce
21 yourself? Please state your name and any
22 organization you are representing for the record.

1 MS. ROTH: Hi. Thank you for having me here
2 and the opportunity to address the panel. My name
3 is Jessica Roth, and I am currently the director of
4 regulatory affairs for the American
5 Gastroenterological Association, which is a
6 professional society that represents nearly 16,000
7 members committed to the science and practice of
8 gastroenterology. AGA has no financial disclosures
9 to report, and today, I will read a statement that
10 is on behalf of our membership.

11 "The mission of the AGA is to advance the
12 science and practice of gastroenterology. To
13 achieve our mission, the AGA supports basic and
14 clinical research, publishes three highly respected
15 journals, and provides educational and practice
16 resources and programs to gastroenterologists.
17 These include clinical guidelines and clinical
18 practice updates aimed at helping clinical decision
19 making based on rigorous systematic reviews of the
20 clinical evidence.

21 "GI motility disorders, such as chronic
22 idiopathic constipation, or CIC, affect patients

1 not only by causing symptoms and posing a heavy
2 burden of illness, but also by decreasing quality
3 of life and work productivity. Because the causes
4 and effects of CIC are heterogeneous, it can be
5 very difficult to treat.

6 "By the time patients are referred to
7 gastroenterologists for constipation, they usually
8 have tried and failed numerous therapies.
9 Unfortunately, the number of prescription
10 medications for CIC are quite limited.

11 "Currently, there are only three
12 prescription therapies for CIC, linaclotide,
13 lubiprostone, plecanatide. These medications are
14 all secretagogues and rely on a similar mechanism
15 of action. They increase intestinal chloride
16 secretion with associated secretion of water into
17 the intestinal lumen to help accelerate intestinal
18 and colonic transit.

19 "Because of the heterogeneity of CIC, these
20 therapies work for some patients, but not all, and
21 treatment satisfaction varies widely from patient
22 to patient. Simply put, current treatments are not

1 sufficient to address the needs of all patients.

2 "Approval of prucalopride would expand the
3 number of treatments available to
4 gastroenterologists and other physicians treating
5 patients with CIC. More importantly, it would make
6 available a therapeutic option with a completely
7 different mechanism of action compared with the
8 three already FDA-approved therapies for CIC.

9 "Prucalopride is a colonic prokinetic which
10 increases colonic transit by activating submucosal
11 neurons to induce mucosal secretion. Approval of
12 prucalopride would increase the potential for
13 relief from patients affected by CIC, including
14 those who have been refractory to currently
15 available therapies.

16 "Robust clinical evidence demonstrates the
17 safety and efficacy of prucalopride for adults with
18 CIC, and the AGA encourages the FDA to support its
19 approval. AGA supports the approval of any
20 appropriate and efficacious treatment for CIC that
21 meets the FDA's strict standards.

22 "AGA also urges the FDA to consider the

1 impact CIC has on patients and the limited number
2 of available therapies when evaluating risks and
3 benefits for approval."

4 Thank you again for the opportunity to
5 address the panel.

6 **Questions to the Committee and Discussion**

7 DR. RAUFMAN: Thank you.

8 The open public hearing portion of this
9 meeting is now concluded, and we will no longer
10 take comments from the audience. The committee
11 will turn its attention to address the task at
12 hand, the careful consideration of the data before
13 the committee as well as the public comments made
14 earlier.

15 We will now proceed with the questions to
16 the committee and panel discussions. I would like
17 to remind public observers that while this meeting
18 is open for public observation, public attendees
19 may not participate except at the specific request
20 of the panel.

21 Question number 1 is a voting question. Do
22 the clinical trial data provide substantial

1 evidence of effectiveness of prucalopride for the
2 treatment of adults with chronic idiopathic
3 constipation, CIC? And this question is now open
4 for discussion. Dr. Thadani?

5 DR. THADANI: I think the data we have seen
6 so far is pretty supportive from the trials. The
7 only reservation one has is the reservations of the
8 populations studied is mostly in Caucasians, Asian,
9 and whites. The data, as previously discussed by
10 several committee members, has been a very small
11 database in African-Americans and also in the
12 Hispanic population. The U.S. Hispanic population
13 is increasing in every state, so I think that has
14 to be addressed down the road.

15 As far as the efficacy data, I think it's
16 pretty positive with the exception of 401 study,
17 which is now driven by more placebo effect. So I
18 still have just reservation for which groups.
19 Women are a majority anyway in the U.S. Whites and
20 color issue comes in.

21 But when it comes to approval, we have to
22 put some issues regarding the lack of or not

1 sufficient data in the African-American origin and
2 Hispanics. It's unfortunate the U.K. database and
3 Swedish database is very extensive, that they don't
4 capture the race issue because it's a sensitive
5 issue. I worked in the U.K. for nine years.

6 I know there are a lot of African-Americans
7 in the U.K. as well because they came from
8 Caribbean countries, so that data was there. It
9 would have probably substantiated more. I don't
10 think they can go back to this, but that
11 reservation is top of my discussion there. If they
12 can dig out that data, that'd be great, but not
13 sure of that.

14 DR. RAUFMAN: Dr. Lebowhl?

15 DR. LEBWOHL: Ben Lebowhl. I think the
16 concerns raised in the public comments about
17 generalizability are something worthy of our
18 consideration. In terms of age, I'm somewhat
19 reassured by the fact that one of the clinical
20 trials that was discussed had more than 40 percent
21 of participants older than 65, but race has been
22 pointed out. Individuals who are not white are

1 underrepresented. Of course, it's a problem. It's
2 endemic in clinical trials in general.

3 I would be interested to hear more from
4 either the FDA or the sponsor about potential
5 issues related to BMI, and smoking status, and
6 whether that could at all impact efficacy, and also
7 the question about the interaction with oral
8 contraceptives and reducing the efficacy of that
9 contraceptive.

10 DR. TOMAINO: Sure. Juli Tomaino, FDA.
11 Obviously, the application is still under review,
12 but the concern over generalizability is something
13 that we are looking at closely.

14 Just one thing to point out. The baseline
15 disease characteristics and the history of disease
16 from the patients in the two U.S. trials seemed to
17 imply that maybe they in fact had a little bit more
18 severe disease. They had a longer disease
19 duration.

20 A higher percentage of them had failed prior
21 laxatives or had tried prior laxatives, and there
22 was a larger percentage of those patients reporting

1 an average of 0 or 1 spontaneous bowel movement per
2 week in the 6 months prior. The percentages were
3 lower in the two non-U.S. trials. We still saw
4 efficacy in the U.S. trials, so just to give you a
5 little bit more information on some of the baseline
6 characteristics.

7 For BMI, we do have some data from the U.S.
8 trials. We have height and weight data, and we
9 have BMI on the two non-U.S. trials. I can find it
10 here for you.

11 The mean BMI overall in the non-U.S. trials
12 was about 22 and 26. And in the two U.S. trials,
13 we have about 15 percent, maybe a little higher,
14 BMI over 30. So there are some patients with a
15 high BMI.

16 Then you asked about smoking. I don't have
17 that information right in front of me. I don't
18 know if maybe the sponsor has additional
19 information on smoking. They did record smoking
20 status in the overall -- when we look at MACE, that
21 analysis, so we do have some information on
22 baseline risk factors. But I don't have that

1 number in front of me.

2 Then you asked about contraceptives.

3 Overall in the trials, from the sponsor's
4 integrated summary of safety, we have about
5 6 percent on conjugated estrogens at baseline. I
6 don't know. Perhaps the sponsor has additional
7 detailed data on that.

8 DR. SILBERG: If I can, I'd like to address
9 some of the issues you're talking about.

10 DR. RAUFMAN: Go ahead.

11 DR. SILBERG: I want to address a few of the
12 different issues. One thing, just in terms of
13 race, Hispanic is not a race, so it wouldn't be
14 captured that way. They would be part of either
15 whatever they identified, either white, or black,
16 or -- that's the first one.

17 Second is, in terms of DDI, we did DDI
18 studies with oral contraceptives. We showed you
19 the DDI. There is no interaction for oral
20 contraception. The second or the third point is
21 about the patient population who has chronic
22 idiopathic constipation. Dr. Camilleri's going to

1 speak to that as well, with relationship also to
2 BMI.

3 DR. LEBWOHL: Before we get there, though,
4 just to clarify, because one of the comments
5 mentioned in an insert elsewhere, that this has
6 been shown to decrease the efficacy of oral
7 contraceptives. This is not true or you've never
8 heard of this?

9 DR. SILBERG: It's not that it's not true
10 for that insert, but our studies do not support
11 that.

12 Dr. Camilleri?

13 DR. CAMILLERI: Mike Camilleri, Mayo Clinic.
14 I'd like to address the whole issue of the BMI and
15 the age of patients when they presented to us in
16 the clinic. And I happen to be the senior author
17 of a study of 1462 patients studied at our center.
18 I was the physician looking after them, the
19 gastroenterologist. And basically, I'm afraid I'm
20 going to have to read this; otherwise, I may get it
21 wrong. Forgive me.

22 That's from our paper just published in

1 2013, 1462 patients. Median age was 43 in males,
2 37 in females. The interquartile range goes up to
3 58 for males and 49 for females. And the median
4 BMI was 23.6 for males and 21.4 for females.
5 Therefore, females with constipation tend not to be
6 obese.

7 I've also done another study in 120 patients
8 with irritable bowel with diarrhea alternating or
9 constipation and showed that the diarrhea-
10 predominant patients are the ones with the BMI
11 that's 3 kilograms per meters squared higher than
12 the other patients with IBS.

13 So in summary, the patients that's
14 participated in these clinical trials, remembering
15 that three of the randomized controlled trials were
16 conducted in the United States and therefore would
17 appear to be representative of United States
18 patients, have a BMI and an age range that is
19 typical of the population that is seen in clinics
20 in the United States. Thank you, sir.

21 DR. RAUFMAN: Thank you. Dr. Khurana?

22 MR. KHURANA: I have a question, and the

1 sponsors could answer that. I really couldn't get
2 a sense of what are the actual objective
3 indications to stop this drug if it's not
4 effective. We have talked about when it's
5 effective, but I can understand subjectively, if a
6 patient has not responded, that you stop the drug.

7 So what I have not heard is what are the
8 indications for stopping the drug? And are they
9 based on some objective evidence such as colonic
10 [indiscernible] propagation or lack thereof. Could
11 you speak to that?

12 DR. SILBERG: Thank you for the question.
13 That is a very important aspect of any medication,
14 is when do you decide that something is not
15 effective? Dr. Tack has a lot of experience, of
16 course, with his patients, so I'm going to ask him
17 to address that.

18 DR. TACK: Thank you. Jan Tack,
19 gastroenterologist in Leuven, Belgium. There are
20 two aspects to look at. One is side effects. I
21 warn patients that side effects may occur, that
22 they're usually mild, transient, but typically

1 occur in the first 1 or 2 days and then go away.
2 Side effects are nausea, cramps, diarrhea, and
3 headache.

4 If they're intolerable, they stop there, but
5 you heard that the interruption rate in the
6 clinical trials is 1.5 percent on average for each
7 of these conditions, less than 5 percent in total,
8 and this is what you see in clinical practice.

9 The second thing is chronic idiopathic
10 constipation is a heterogeneous condition, probably
11 with heterogeneous underlying pathophysiology, and
12 perhaps that explains why not everybody responds.
13 And typically, I write patients a prescription for
14 one month and then have a call with them to decide
15 whether to continue or not.

16 Evaluating this is very easy. It's driven
17 by tolerance of the drug, which is usually good,
18 and second, efficacy, which translates in more
19 bowel movements and improvement of abdominal
20 symptoms, and also regaining of quality of life.

21 DR. RAUFMAN: Dr. Teerlink?

22 DR. TEERLINK: Thank you. As many of you

1 are aware, I think the FDA has approved drugs in
2 the past where absolutely no U.S. patient has ever
3 been studied, so it is not an absolute requirement
4 for approval of a drug. But I agree with
5 Dr. Srinivasan and others that it's important to
6 understand the effect of new drugs in all segments
7 of the U.S. population, including and especially
8 women, blacks, and the elderly.

9 But for safe agents that are geared towards
10 symptomatic relief, patients will probably
11 predominantly vote with their feet. So if it
12 doesn't work, they will stop taking it and move
13 away from it.

14 So in the absence of biological plausibility
15 for differential effect, I would support the
16 efficacy findings of this agent for the general
17 U.S. population, recognizing that it is always
18 incumbent upon the sponsors to try to do their very
19 best to actively study in relevant patient
20 populations.

21 We must also point out that the, quote,
22 "relevant" U.S. studies are from 1999, where the

1 U.S. population has changed a lot over the last 20
2 years, unfortunately. So anyway, those are my
3 comments.

4 DR. RAUFMAN: Dr. Thadani?

5 DR. THADANI: I think it's interesting that
6 most of the trials done by the NIH, there's an
7 outcry from women. Representation is very small.
8 Here, we've gone the other way around, which is a
9 good thing. Now the men are outcrying because
10 there's less representation of men. Just a
11 comment.

12 I hope the drug is going to be cheap because
13 it might be an issue, because when you say
14 non-response, you might have to keep a little diary
15 because it's subjective. Placebo response is
16 20 percent. So I think the patients should be
17 told, are you using anti-anginal drugs? I say,
18 well, if they don't work for a month, then just
19 quit.

20 So your whole database is on one more motion
21 per week, from 2 to 3. So I think unless you make
22 it cheap, there should be some threshold; okay, I'm

1 going to give you a diary rather than just talking
2 in a busy clinic or I'm treating and going to
3 continue it, and look at the diary. If the patient
4 shows that there's improvement, continue it.

5 If not, why give an expensive drug? Because
6 it's not working on everybody. It's working on
7 maybe 6 percent more, so I think that'll be just an
8 issue. I know it's difficult to put it in the
9 labeling, but as a physician, it may be worthwhile
10 to consider. I don't know what my gastroenterology
11 colleagues do because that could be an important
12 consideration, so that is not used.

13 My other question really is that we heard
14 from consumer representatives and other people
15 because this drug was only studied in chronic
16 idiopathic constipation. It was not studied in
17 IBS. I know there's a lot of overlap. And since a
18 lot of those patients also have chronic
19 constipation, you're not going to recommend those
20 patients to take that drug, too, because they have
21 other kinds of symptoms, too.

22 So I don't know how you safeguard that.

1 Physicians can use what they want. That might be
2 an issue because this drug was done in chronic
3 idiopathic constipation. And what we heard
4 yesterday was a lot of IBS patients also have
5 constipation as a component. I don't know. I'm
6 not a gastroenterologist, but I think those are the
7 issues you might have to deal with.

8 DR. RAUFMAN: Any other questions, or can we
9 go ahead to a vote?

10 MS. McVEY HUGICK: This is Joy McVey Hugick,
11 consumer representative. I just wanted to thank
12 the sponsor for trying to meet this unmet need.
13 And I also wanted to thank the public for
14 commenting.

15 There were some things that were brought up
16 that I just want to highlight and I think are
17 important from a patient and consumer perspective,
18 the first being that -- and I think Dr. Stein
19 mentioned she tries to save colons.

20 Often, patients who are experiencing this,
21 who have failed with all other treatment options;
22 that's the recommendation. And it's been

1 recommended to me to remove my colon. So I haven't
2 taken that step yet, but I'm grateful to know that
3 FDA is looking at this and trying to explore other
4 treatment options, especially with the new
5 mechanism of action.

6 Something else that was brought up that I
7 don't think we've talked about at all, and I know
8 that FDA looks at this, is drug reimportation and
9 substandard, falsified, and counterfeit medicines.

10 I know people who have ordered prucalopride
11 online through Canada, not sure where it came from,
12 scared about taking it because it may not be the
13 actual product. And that's just something I think
14 we also need to be cognizant of as well.

15 So I think the efficacy is there based on
16 the data and. And while I wish we had more data
17 certainly on the other subpopulations, I think,
18 from my perspective, there's enough there to move
19 forward with the vote.

20 DR. RAUFMAN: So in the absence of further
21 discussion, we'll go ahead and vote, and you'll all
22 have an opportunity to discuss why you voted how

1 you voted after we do that.

2 Let me read the question one more time, and
3 the keypads are already blinking. Do the clinical
4 trial data provide substantial evidence of
5 effectiveness of prucalopride for the treatment of
6 adults with chronic idiopathic constipation?

7 We will be using an electronic voting system
8 for this meeting. Once we begin the vote, the
9 buttons will start flashing and will continue to
10 flash even after you have entered your vote.
11 Please press the button firmly that corresponds to
12 your vote.

13 If you are unsure of your vote or you wish
14 to change your vote, you may press the
15 corresponding button until the vote is closed.
16 After everyone has completed their vote, the vote
17 will be locked in.

18 The vote will then be displayed on the
19 screen. The DFO will read the vote from the screen
20 into the record. Next, we will go around the room
21 and each individual who voted will state their name
22 and vote into the record. You can also state the

1 reason why you voted as you did if you want to.

2 So please press the button on your
3 microphone that corresponds to your vote. You will
4 have approximately 20 seconds to vote. Please
5 press the button firmly.

6 After you have made your selection, the
7 light may continue to flash. If you are unsure of
8 your vote or you wish to change your vote, please
9 press the corresponding button again before the
10 vote is closed.

11 (Voting.)

12 DR. FAJICULAY: For the record, the results
13 are 10 yes; zero no; zero abstain; and zero no
14 voting.

15 DR. RAUFMAN: So perhaps we'll start with
16 Dr. Hunsberger. Please state your name, how you
17 voted, and if you want to, you can state the reason
18 why you voted as you did.

19 DR. HUNSBERGER: Sally Hunsberger. I voted
20 yes. I think it's a strong efficacy result.
21 Seeing 5 out of 6 studies with positive results is
22 pretty good.

1 A slight concern about the missing data.
2 It's a lot of missing data, but in these type of
3 studies, I think that's pretty typical. And I
4 think making the assumption that missing data is a
5 non-response is probably a fairly accurate
6 interpretation or a fairly accurate assumption, so
7 I feel like the results are very strong.

8 DR. TEERLINK: John Teerlink, and I voted
9 yes. I wanted to reinforce that this vote does not
10 relieve future sponsors of the responsibility of
11 providing data to the FDA that provides information
12 on longer-term effects and effects in
13 subpopulations.

14 This packet was done before all those
15 regulations got in place, and the original packet
16 was before that, so it's kind of getting in under
17 that wire. But I do think it is important to have
18 more long-term evidence for chronic therapies, both
19 from an efficacy and safety standpoint.

20 DR. SOLGA: Steve Solga, I voted yes. I
21 think the data are compelling over multiple trials,
22 done over multiple years on different continents

1 using a strict responder definition. I also felt
2 that the additional supportive efficacy data
3 looking at patient satisfaction, bloating,
4 discomfort, cramps to be relevant as well.

5 MS. NUMANN: Sabrina Numann. I voted yes.
6 From my perspective, I find the placebo effects of
7 this class of 5-HT medicine to be pretty
8 interesting and intriguing. But even if I were to
9 assume the placebo effect into the efficacy data,
10 there's still evidence of efficacy. So for that
11 reason, I voted yes.

12 MS. McVEY HUGICK: Joy McVey Hugick. I
13 voted yes for reasons already stated.

14 DR. LAI: Jennifer Lai. I voted yes, and
15 this vote was based on my critical review of the
16 evidence from the randomized clinical trials
17 presented to me.

18 DR. RAUFMAN: Jean-Pierre Raufman. I voted
19 yes for the reasons already stated.

20 DR. LEBWOHL: Ben Lebwohl. I voted yes for
21 reasons already stated.

22 MR. KHURANA: Sandeep Khurana. I voted yes.

1 DR. THADANI: Udho Thadani. I voted yes for
2 the positive direction, even in the 401 study, and
3 the trials were positive. The only reservation,
4 I'm hoping that the African-American gut motility
5 is the same as the whites. So I think hopefully
6 the company will provide data and a clearly
7 reasonable sample size to tell those patients it
8 works in you as well.

9 DR. RAUFMAN: We will now proceed with
10 question 2, which is also a voting question. Has
11 the potential risk of cardiovascular adverse events
12 with the use of prucalopride in adults with CIC
13 been adequately addressed by the applicant?
14 Discuss your answer.

15 If there are no questions or comments
16 concerning the wording of the question, we'll now
17 open this question to discussion. I guess we
18 should hear from the cardiologists on this one.

19 Dr. Thadani?

20 DR. THADANI: I think it's reassuring that
21 the drug class affects one specific receptor, and
22 we say HT4 rather than -- obviously in a very high

1 dose, you're going to use megadoses, and it's going
2 to affect the other receptors, which is reassuring
3 in a way because, as a cardiologist or as an
4 internist, when you have to worry about previously
5 reported issues with torsades, especially with the
6 QT interval, whether it's corrected or you use
7 formula for [indiscernible] equation, we've seen
8 enough data it really doesn't affect it. And the
9 ratio of hERG channel block is so high and only
10 will be concerning in a real overdose situation,
11 which could happen, I guess.

12 But given that, more specific to the
13 receptor, it's not only the receptor. I think the
14 database we are seeing; there's really no -- is a
15 comparative adverse effect profile with the only
16 exception of a couple of noises on the
17 tachyphylaxis might have be an issue, and the
18 neuropsychiatric issues remain.

19 But I think, when you look at the placebo-
20 controlled trials, it's fairly balanced. And I
21 think it's reassuring in the prospectively
22 collected U.K. and Swedish registry. They are

1 really much more elaborate, the U.K. and Swedish.
2 At least I'm convinced that there's no major issue
3 with that in that population. Although there's
4 going to be a neuropsychiatric issue, we discussed
5 whether it's rebound or not.

6 But other than that, I think I fairly feel
7 comfortable that the adverse effect on the heart as
8 far as MI or CNS, stroke, and QT intervals are
9 addressed. The only thing is, I'm sure there are
10 some CNS effects of headache and all that, and we
11 don't know the exact mechanism because it does
12 penetrate the CNS system.

13 DR. RAUFMAN: Dr. Teerlink?

14 DR. TEERLINK: John Teerlink, UCSF. I will
15 concur with my colleague in as much as I think the
16 absence of biological plausibility for a
17 cardiovascular adverse event was very helpful here.
18 There is one of the cases where the preclinical
19 data did provide kind of the ground work and the
20 perspective for the rest of the clinical trial
21 data.

22 In some ways, we are subjected to the

1 tyranny of small numbers and small events in these
2 kind of trials, where you don't have high numbers
3 and background of cardiovascular events, so we have
4 to deal with these small little numbers that occur.

5 I think the sponsor is to be congratulated
6 on using pharmacovigilance studies to try to help
7 inform the safety of these agents. And I would
8 once again caution future sponsors that this does
9 not relieve them of the responsibility to abide by
10 the guidance that we provided during the 2011
11 meeting as well. So that's my perspective.

12 DR. RAUFMAN: Any additional discussion
13 before we vote?

14 (No response.)

15 DR. RAUFMAN: So let me re-read the
16 question, and then we'll go ahead and vote.

17 Has the potential for cardiovascular adverse
18 events with the use of prucalopride in adults with
19 CIC been adequately addressed by the applicant?
20 Please press yes or no.

21 (Voting.)

22 DR. FAJICULAY: For the record, the results

1 are 10 yes; zero no' zero abstain; and zero no
2 voting.

3 DR. RAUFMAN: Now that the vote is complete,
4 we'll go around the table and have everyone who
5 voted state their name, vote, and if you want to,
6 you can state the reason why you voted as you did
7 into the record. We'll start on my left this time
8 with Dr. Thadani.

9 DR. THADANI: Thadani. I voted yes because
10 of the preclinical data, lack of effect on the hERG
11 channel, and also no cases of torsades as far as we
12 can tell in the registries.

13 So the cardiac adverse effect profile is
14 very similar in the double-blind trials, very low
15 incidence, not a noise, even. It's not a
16 disproportion zero on placebo versus that. Only
17 issue is the neuropsychiatric issues, some noise,
18 but again, pretty convincing that there's not a
19 major noise there, and that's why I voted yes.

20 MR. KHURANA: Sandeep Khurana. I voted yes,
21 and reasons have been extensively discussed.

22 DR. LEBWOHL: Ben Lebowhl. I voted yes. I

1 was reassured by the preclinical data, but even
2 more so by the lack of cardiovascular signal
3 emerging since 2009, when this was approved in
4 Europe.

5 DR. RAUFMAN: Jean-Pierre Raufman. I voted
6 yes for reasons that have already been cited.

7 DR. LAI: Jennifer Lai. I voted yes for
8 reasons that have already been stated.

9 MS. McVEY HUGICK: Joy McVey Hugick. I
10 reported yes for reasons already stated.

11 MS. NUMANN: Sabrina Numann. I did vote
12 yes. As Dr. Thadani said, the low affinity for the
13 other 5-HT receptors is what really changed my mind
14 on that, so I don't find that the risk outweighs
15 the benefits. Thank you.

16 DR. SOLGA: Steve Solga. I voted yes,
17 nothing further to add.

18 DR. TEERLINK: John Teerlink, and I voted
19 yes, and surprisingly, I have nothing further to
20 add.

21 (Laughter.)

22 DR. HUNSBERGER: Sally Hunsberger. I voted

1 yes, and I have nothing further.

2 DR. RAUFMAN: We'll skip this because we all
3 voted yes.

4 So question 3, this is our last question and
5 also a voting question, and maybe we'll get a
6 little bit more discussion here.

7 Does the risk-benefit profile of
8 prucalopride support the approval of this
9 application? If there are no questions or comments
10 concerning the wording of the question, we'll now
11 open this question to discussion.

12 Who wants to start?

13 DR. THADANI: I'm asking the question or a
14 lot of them. I think we've already beaten it to
15 death.

16 (Laughter.)

17 DR. THADANI: We discussed the efficacy. We
18 discussed the risk. So I think risk-benefit is
19 reasonable, given the very low incidence of side
20 effects. Even the hard endpoint, which is MI,
21 death, stroke, it's pretty balanced in the two and
22 there's very low noise.

1 I still had a little bit of question on the
2 neuropsychiatric issues, but again, the numbers are
3 low, not so much in the double-blind, but mostly in
4 the open-label studies, so I feel fairly reassured
5 on that.

6 The only thing is the African-American
7 population. We've got missing data, although they
8 said people from Hispanic origin might have
9 different blood, but Hispanic origin is a mixed
10 race in the U.S. It's very different than the
11 people from Spain because you've got mixed American
12 Indian, a lot of different issues, so the response
13 might be different. So I think we probably should
14 concentrate on that in the future.

15 DR. RAUFMAN: Dr. Khurana?

16 MR. KHURANA: My only concern is with the
17 neuropsychiatric issue, because there was really no
18 cases in placebo, absolutely none, and they were
19 all 7 or 8 in the treatment arm.

20 So I think, even if you are to approve this,
21 then I think there should be some sort of a warning
22 on it. Obviously, that decision has to be

1 discussed between the patients and the physicians
2 prescribing it, but I think that is of a concern.

3 DR. RAUFMAN: No one has concerns about the
4 carcinogenicity issues? Dr. Solga?

5 DR. SOLGA: Yes. I was just going to echo
6 the residual concern about the neuropsychiatric
7 component. I don't feel like we understand not
8 just this drug, what this class of drugs do to
9 serotonin on the brain. And unlike doing QTc
10 studies and other cardiac nonclinical data, I don't
11 know that we have the tools in the toolbox to
12 answer these questions.

13 It's not going to hold back my yes vote. I
14 don't expect the sponsor to do studies we don't
15 know how to do or the FDA to manage risks they
16 don't know how to measure, but that is the area
17 that I'm going to leave and wonder about for some
18 time to come.

19 DR. RAUFMAN: Dr. Lai?

20 DR. LAI: I also am concerned about the
21 neuropsychiatric signal, the 7 versus 0. Although
22 low, in both sides, zero is very concerning in the

1 non-placebo arm versus the 7 in the treated arm.
2 It would just seem that, given that there is a
3 large database to study, which was studied with
4 respect to the MACE events, one might think that
5 you could study this looking at maybe deaths
6 related to suicide to look for a signal.

7 The reason I'm particularly worried is that
8 while the general population of individuals with
9 CIC may be overall a low cardiac risk population,
10 it is a population in which depression and other
11 psychiatric disorders is probably much higher in
12 prevalence in the general population.

13 So I think this is of concern, and I wonder,
14 maybe we should ask either the FDA or the sponsor
15 about whether this could actually be evaluated with
16 the data at hand.

17 DR. RAUFMAN: Dr. Teerlink?

18 DR. TEERLINK: I guess my understanding is
19 that there were 3 events in the randomized trials.
20 Is that not right; 3 versus 0 in terms of the
21 attempted and others? The other events were in
22 open label, where it's open label, so there's no

1 competing group. Is that not correct?

2 DR. RAUFMAN: I'm seeing heads nodding, so
3 it sounds like it's correct.

4 DR. LINE: My name is Charles Line. I'm the
5 medical --

6 DR. TEERLINK: I share that that's an issue
7 that needs to be considered.

8 DR. TOMAINO: Yes. What slide is that?

9 DR. LINE: It's our slide, 63.

10 DR. TOMAINO: 63, please.

11 DR. LINE: So what this slide is showing you
12 is that there were 2 completed suicides. These
13 occurred in the open-label trials.

14 DR. TEERLINK: I think that's in the
15 double-blind trial.

16 DR. LINE: No, these were open label.

17 DR. RAUFMAN: No. But they're labeled -- OL
18 is labeled on the bottom three.

19 DR. TEERLINK: Yes. I believe that the
20 first two are events that occurred in the
21 double-blind trial but occurred well after the drug
22 was gone. The third one was an attempted suicide

1 in the double-blind trial that occurred after
2 42 days of therapy. The fourth one was open label,
3 and the fifth and sixth ones were open label.

4 That's my reading of those data. So it
5 really is basically, of folks who are taking the
6 drug, we have 1 versus zero in a double-blind
7 study.

8 DR. RAUFMAN: Are these data correctly
9 labeled? I see some questions.

10 DR. LEBWOHL: So the sponsor's slide 54, I
11 think --

12 DR. SILBERG: No. It's not correctly
13 labeled because the double-blind is only 3 months.
14 The suicide -- I don't know if I can put it up.
15 There we go. So you can see here it's labeled
16 correctly.

17 The 2 suicides were in the open label.
18 Since these are shorter studies, you can't go to
19 242 days in the double blind. So the only one that
20 was in the double-blind placebo control is the
21 suicide attempt. So we don't have a lot of
22 comparison to placebo. The rest are open label,

1 and of course they all would be on drug.

2 DR. RAUFMAN: So may I ask why there's a
3 discrepancy between the two slides, or is this the
4 correct one? Should we go with this?

5 DR. TOMAINO: I don't think there's a
6 discrepancy. I think if you go back to our slide,
7 just to clarify, we are actually showing the same
8 data, I think just in different ways. So you can
9 see the third one down, the attempted suicide, is
10 42 days. That's what the applicant is showing as
11 the double blind.

12 The first 2 completed suicides, the only 2
13 completed suicides in the first two rows, are not
14 labeled for either double blind or open label
15 because those patients were off the drug at the
16 time, but it shows the treatment duration.

17 DR. KORVICK: So the bottom line is we're in
18 agreement. We'll just have to look harder at these
19 numbers.

20 DR. RAUFMAN: Got it.

21 DR. TOMAINO: The title of this slide is
22 just showing you the pool that we pooled from.

1 DR. RAUFMAN: Dr. Hunsberger?

2 DR. HUNSBERGER: So I just have a slight
3 concern. I wasn't so convinced. I'm not sure if
4 you looked at women that were pregnant or
5 child-bearing that closely. I didn't see a lot of
6 data about that, and this group will be getting the
7 drug. So I wonder if we can track that or can we
8 do more follow-up on that. So that would be a
9 slight concern for me.

10 DR. KORVICK: Thank you. Those are things
11 that we do take into consideration. There's only
12 so much you can put here, but those are under
13 consideration and evaluation.

14 DR. RAUFMAN: Jean-Pierre Raufman. I will
15 just say for the record that I am concerned about
16 the preclinical carcinogenic signal, and I don't
17 know that without doing a specific study, you have
18 the data to address whether it's a concern in
19 humans.

20 So it's not going to change my vote on this
21 question, but I just raise it as, I think, an
22 unresolved issue right now.

1 Dr. Thadani?

2 DR. THADANI: I think there was a comparator
3 drug, PEG, so the database, there was no suicide or
4 attempted suicide in that database. Right?

5 I know there is no placebo, but overall,
6 from the British registry and the Swedish registry,
7 because these are open-label trials, was there any
8 discrepancy in the attempted suicide or confirmed
9 suicide in that registry? Because you've got a
10 large sample size there.

11 DR. SILBERG: If I can answer that, the
12 802 trial was only looking at MACE, so major
13 cardiac events. It did not look at psychiatric or
14 suicides, so we would not have that data from that
15 database for 802.

16 DR. THADANI: But I am sure the database for
17 that exists, right? Because that's one of the
18 noises with this class of drugs. And if you have
19 the database, it'd be reassuring to provide that to
20 FDA if you can.

21 DR. SILBERG: I can only tell you what we
22 did and that wasn't looked at. So that's the data

1 we have. It's not there from that study.

2 DR. THADANI: But I'm sure people from the
3 U.K. registry, somebody was representing earlier,
4 because they had the whole database on all the
5 primary care physicians, and they captured all
6 these things, especially if there's a death.

7 DR. KORVICK: This is Dr. Korvick. Just to
8 echo what the sponsor is saying, for the answer for
9 suicide, what we have is a large integrated summary
10 of safety from several studies. That's the extent
11 of the information we have on clinical trials. The
12 other study was not designed to do that analysis.

13 One could ask for another analysis if you
14 needed to, but that would have to be designed, and
15 again, all of the definitions for the events of
16 interest, et cetera. And all those things need to
17 be specified, so there would be a whole other
18 effort that would need to be taken to look at that.

19 We do not have that analysis as my colleague
20 across the aisle there stated. I don't know if you
21 want to follow with that, but what we have is what
22 we have

1 DR. THADANI: I'm interested maybe in
2 completed suicide or attempted. That would be easy
3 to capture. Hopefully, there will be not a huge
4 database to look at. With the cardiovascular,
5 you've got more issues.

6 DR. KORVICK: Those are very particular
7 terms of the databases. We're going to have to
8 look and see. It's not so easy, the terms.
9 There's an art. We have a guidance about this,
10 actually, how you use those terms.

11 DR. RAUFMAN: Does the sponsor want to make
12 a quick comment on that or no?

13 DR. SILBERG: I appreciate your comment.
14 Again, we have the data that we have. We did show
15 you also that the psychiatric AEs were balanced in
16 the placebo versus the active treatment in our
17 large clinical trials, the double-blind. So in
18 that case, there really was not any kind of signal.

19 DR. THADANI: I'm buying that, but I think
20 it'd be reassuring to the physicians if they know
21 in your open-label there's no data, so you might
22 capture it for future.

1 DR. SILBERG: Thank you.

2 DR. RAUFMAN: Dr. Lebowhl?

3 DR. LEBWOHL: I just want to underscore
4 Dr. Thadani's point. These are data that are not
5 available today. It's not something we could
6 easily whip up, but these data are out there in
7 specifically the Swedish registry data, for cancer
8 as an outcome and likely suicide as an outcome.

9 So this is imminently doable, just not
10 something one could do quickly. The data are out
11 there, and I hope it gets done.

12 DR. RAUFMAN: Is there any additional
13 discussion before we go ahead with the vote?

14 (No response.)

15 DR. RAUFMAN: If there's no further
16 discussion, we will now begin the voting process.
17 Again, you can push yes, no, or abstain.

18 (Voting.)

19 DR. FAJICULAY: For the record, the results
20 are 10 yes; zero no; zero abstain; and zero no
21 voting.

22 DR. RAUFMAN: Now that the vote is complete,

1 we will go around the table and have everyone who
2 voted state their name, vote, and if you want to,
3 you can state the reason why you voted as you did
4 into the record. We'll start with Dr. Hunsberger.

5 DR. HUNSBERGER: Sally Hunsberger. I voted
6 yes based on the efficacy results and not much of a
7 signal for the cardiovascular safety endpoint.

8 DR. TEERLINK: John Teerlink. I voted yes
9 based on my comments during this entire day.

10 DR. SOLGA: Steve Solga. I voted yes,
11 nothing further to add.

12 MS. NUMANN: Sabrina Numann. I voted yes,
13 nothing further to add.

14 MS. McVEY HUGICK: Joy McVey Hugick. I
15 voted yes for reasons already stated.

16 DR. LAI: Jennifer Lai. I voted yes. I
17 remain concerned about the psychiatric effects, and
18 believe that study could be done just to look at
19 completed suicides, and would like it to be done.
20 However, I do believe that there's a great unmet
21 need and believe that the potential benefits of
22 this drug outweigh those concerns.

1 DR. RAUFMAN: Jean-Pierre Raufman. I voted
2 yes. My concerns are more for the long-term
3 carcinogenicity potential of the drug, but with
4 current information, benefits outweigh risks.

5 DR. LEBWOHL: Ben Lebwohl. I voted yes.

6 MR. KHURANA: Sandeep Khurana. I voted yes.

7 DR. THADANI: Udho Thadani. I voted yes
8 with just one reservation on good faith that the
9 company hopefully will dig out neuropsychiatric. I
10 think the information is out there in the Swedish
11 and U.K. database. It'd be easy enough to just
12 plug two items, suicidal completed/attempted,
13 because they all go to the hospital usually on
14 this.

15 DR. RAUFMAN: Do we have any closing
16 comments from the FDA?

17 DR. KORVICK: I just wanted to thank
18 everybody for their very thoughtful comments. I
19 don't think we have any other questions for you all
20 at this time. Thank you.

21 **Adjournment**

22 DR. RAUFMAN: Thank you. We will now

1 adjourn the meeting. Panel members, please leave
2 your name badge here on the table so that they may
3 be recycled. Please also take all personal
4 belongings with you as the room is cleaned at the
5 end of the day. Meeting materials left on the
6 table will be disposed of. Thank you.

7 (Whereupon, at 2:21 p.m., the meeting was
8 adjourned.)

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