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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEETING  
(GIDAC)

Wednesday, October 17, 2018

8:00 a.m. to 3:27 p.m.

Bethesda Marriott  
Grand Ballroom  
5151 Pooks Hill Road  
Bethesda, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Jay Fajiculay, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Joy McVey Hugick, BA**

11 *(Consumer Representative)*

12 Public Health Policy and Communication Consultant

13 Simply Joy, LLC

14 Atlanta, Georgia

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16 **Sandeep Khurana, MBBS**

17 Medical Director

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19 Geisinger Medical Center

20 Danville, Pennsylvania

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2     Assistant Professor of Medicine and Epidemiology

3     Director of Clinical Research

4     Celiac Disease Center

5     Columbia University College of Physicians &

6     Surgeons

7     New York, New York

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9     **Jean-Pierre Raufman, MD**

10    *(Chairperson)*

11    Professor and Head

12    Division of Gastroenterology & Hepatology

13    University of Maryland School of Medicine

14    Baltimore VA Maryland Health Care System

15    Baltimore, Maryland

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17    **Rachel L. Rosen, MD, MPH**

18    Associate Professor of Pediatrics

19    Boston Children's Hospital

20    Harvard Medical School

21    Boston, Massachusetts

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2       **(Non-Voting)**

3       **Douglas Levine, MD, FACC**

4       *(Industry Representative)*

5       DSL Consulting, LLC

6       Seekonk, Massachusetts

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8       **TEMPORARY MEMBERS (Voting)**

9       **Sally Hunsberger, PhD**

10       Mathematical Statistician

11       National Institute of Allergy and

12       Infectious Disease

13       National Institutes of Health

14       Bethesda, Maryland

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1     **J. John Mann, MD**

2     The Paul Janssen Professor of Translational  
3     Neuroscience (in Psychiatry and Radiology)  
4     New York State Psychiatric Institute  
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7     Columbia University  
8     New York, New York

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10    **Sabrina Numann**

11    *(Patient Representative)*  
12    New Albany, Indiana

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14    **Suzanne B. Robotti**

15    *(Acting Consumer Representative)*  
16    Executive Director  
17    DES Action USA  
18    Founder and President  
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1     **Steven F. Solga, MD**

2     Associate Professor of Clinical Medicine  
3     Program Director, Transplant Hepatology Fellowship  
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8     **John Teerlink, MD**

9     Professor of Medicine  
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11    Director, Heart Failure  
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15    San Francisco, California

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17    **Udho Thadani, MD, MRCP, FACC, FAHA**

18    Professor Emeritus of Medicine of Cardiology  
19    Consultant Cardiologist  
20    Oklahoma University Health Sciences Center and  
21    District VA Medical Center  
22    Oklahoma City, Oklahoma

1       **FDA PARTICIPANTS (Non-Voting)**

2       **Julie Beitz, MD**

3       Director

4       Office of Drug Evaluation III (ODE III)

5       Office of New Drugs (OND), CDER, FDA

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7       **Joyce Korvick, MD, MPH**

8       Deputy Director for Safety

9       Division of Gastroenterology and Inborn Errors

10      Products (DGIEP), ODE III, OND, CDER, FDA

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12      **Preeti Venkataraman, MD**

13      Clinical Team Leader

14      DGIEP, ODE III, OND, CDER, FDA

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16      **Sandhya Apparaju, PhD**

17      Safety Reviewer

18      DGIEP, ODE III, OND, CDER, FDA

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**Joel Weissfeld, MD, MPH**

Medical Officer

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CDER, FDA



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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: I would like to note for the  
6 record that today's advisory committee meeting was  
7 originally announced as a joint meeting of the  
8 Gastrointestinal Drugs Advisory Committee and the  
9 Drug Safety and Risk Management Advisory Committee.  
10 Because of the unexpected unavailability of the  
11 Drug Safety and Risk Management Advisory Committee  
12 members and consultants, this meeting was changed  
13 from a joint meeting to a meeting solely of the  
14 Gastrointestinal Drugs Advisory Committee.

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

21                   My name is Jean-Pierre Raufman. I am the  
22 chairperson of the Gastrointestinal Drugs Advisory

1 Committee, and I will be chairing this meeting. I  
2 will now call the meeting of the Gastrointestinal  
3 Drugs Advisory Committee to order. We'll start by  
4 going around the table and introducing ourselves.  
5 We will start with the FDA to my left and go around  
6 the table.

7 DR. BEITZ: Good morning. My name is Julie  
8 Beitz. I'm the director of the Office of Drug  
9 Evaluation III.

10 DR. KORVICK: Good morning. MY name is  
11 Joyce Korvick. I'm the deputy director for the  
12 Division of Gastroenterology and Inborn Errors  
13 Products.

14 DR. VENKATARAMAN: Good morning. My name is  
15 Preeti Venkataraman. I'm a clinical team leader in  
16 the same division.

17 DR. APPARAJU: Good morning. My name is  
18 Sandhya Apparaju. I'm a clinical analyst in DGIEP.

19 DR. WEISSFELD: My name is Joel Weissfeld.  
20 I'm a medical officer in the Office of Surveillance  
21 and Epidemiology.

22 DR. MANN: Good morning. My name is John

1 Mann. I'm at Columbia University. I run the  
2 Division of Newton Pathology and Molecular Imaging.

3 MR. KHURANA: Sandeep Khurana, medical  
4 director, liver transplant, Geisinger Health  
5 System.

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

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

12 DR. ROSEN: Rachael Rosen, pediatric  
13 gastroenterologist at Boston Children's Hospital  
14 with training and motility in functional GI  
15 disorders.

16 MS. McVEY HUGICK: Good morning. I'm Joy  
17 McVey Hugick. I'm the consumer representative from  
18 Atlanta, Georgia on the Gastrointestinal Drugs  
19 Advisory Committee.

20 MS. ROBOTTI: Hi. I'm Suzanne Robotti,  
21 consumer rep from Drug Safety and Risk Management.  
22 I am the president of MedShadow Foundation and the

1 executive director of DES Action.

2 MS. NUMANN: Sabrina Numann, patient  
3 representative out of New Albany, Indiana and  
4 founder of Kentuckiana Fibromyalgia and Chronic  
5 Pain Association. Thank you.

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

9 DR. SOLGA: Steve Solga, gastroenterologist  
10 and hepatologist at the University of Pennsylvania.

11 DR. TEERLINK: John Teerlink, cardiologist  
12 at San Francisco VA Medical Center and University  
13 of California San Francisco.

14 DR. HUNSBERGER: Sally Hunsberger,  
15 biostatistician at NIH, in particular NIAID.

16 DR. LEVINE: Good morning. Doug Levine.  
17 I'm the industry representative for GIDAC.

18 DR. RAUFMAN: Thank you.

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

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

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

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

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

21 Now, I'll pass it to Dr. Jay Fajiculay, who  
22 will read the conflict of interest statement.



1                                   **Conflict of Interest Statement**

2                   DR. FAJICULAY:   The Food and Drug  
3                   Administration is convening today's meeting of the  
4                   Gastrointestinal Drugs Advisory Committee under the  
5                   authority of the Federal Advisory Committee Act of  
6                   1972.   With the exception of the industry  
7                   representative, all members and temporary voting  
8                   members of the committees are special government  
9                   employees or regular federal employees from other  
10                  agencies and are subject to federal conflict of  
11                  interest laws and regulations.

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

18                  FDA has determined that members and  
19                  temporary voting members of the committees are in  
20                  compliance with the federal ethics and conflict of  
21                  interest laws.   Under 18 U.S.C., Section 208,  
22                  Congress has authorized FDA to grant waivers to

1 special government employees and regular federal  
2 employees who have potential financial conflicts  
3 when it is determined that the agency's need for a  
4 special government employee's services outweighs  
5 his or her potential financial conflict of interest  
6 or when the interests of a regular federal employee  
7 is not so substantial as to be deemed likely to  
8 affect the integrity of the services which the  
9 government may expect from the employee.

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

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

21 Today's agenda involves a discussion of  
22 supplemental new drug application 021200,

1 supplement 015 for Zelnorm, tegaserod maleate,  
2 tablets for oral administration, submitted by Sloan  
3 Pharma S.a.r.l., Bertrange, Cham Branch, proposed  
4 for the treatment of women with irritable bowel  
5 syndrome with constipation who do not have a  
6 history of cardiovascular ischemic disease such as  
7 myocardial infarction, stroke, transient ischemic  
8 attack, or angina, and do not have more than one  
9 risk factor for cardiovascular disease.

10 This is a particular matters meeting during  
11 which specific matters related to Sloan Pharma's  
12 sNDA will be discussed. Based on the agenda of  
13 today's meeting and all financial interests  
14 reported by the committee members and temporary  
15 voting members, a conflict of interest waiver has  
16 been issued in accordance with 18 U.S.C.  
17 Section 208(b)(3) to Dr. Benjamin Lebwohl.

18 Dr. Lebwohl's waiver covers an investment in  
19 Healthcare Mutual SECURA mutual fund valued between  
20 \$200,000 and \$300,000. The waiver allows  
21 Dr. Lebwohl to participate fully in today's  
22 deliberations. FDA's reasons for issuing the

1 waiver are covered in the waiver document, which is  
2 posted on FDA's website at [www.fda.gov/  
3 advisorycommittee/committeemeetingmaterials/  
4 drugs/default.htm](http://www.fda.gov/advisorycommittee/committeemeetingmaterials/drugs/default.htm). Copies of the waiver may also  
5 be obtained by submitting a written request to the  
6 agency's Freedom of Information Division at  
7 5630 Fishers Lane, Room 1035, Rockville, Maryland  
8 20857, or requests may be sent via fax to  
9 (301) 827-9267.

10 To ensure transparency, we encourage all  
11 standing committee members and temporary voting  
12 members to disclose any public statements they have  
13 made concerning the product at issue.

14 With respect to FDA's invited industry  
15 representative, we would like to disclose that  
16 Dr. Douglas Levine is participating in this meeting  
17 as a non-voting industry representative, acting on  
18 behalf of regulated industry. Dr. Levine's role at  
19 this meeting is to represent industry in general  
20 and not any particular company. Dr. Levine is an  
21 independent pharmaceutical consultant.

22 We would like to remind members and

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

8 FDA encourages all other participants to  
9 advise the committees of any financial  
10 relationships that they may have with the firm at  
11 issue. Thank you.

12 DR. RAUFMAN: Thank you. We will proceed  
13 with the opening remarks from Dr. Preeti  
14 Venkataraman.

15 **Introductory Remarks - Preeti Venkataraman**

16 DR. VENKATARAMAN: Good morning. My name is  
17 Preeti Venkataraman, and it is my pleasure to  
18 welcome everyone today. I would like to thank all  
19 the members of the committee for taking the time to  
20 participate in this important discussion.

21 Before we begin, I would like to notify  
22 participants that in addition to the FDA errata

1 published online alongside the FDA briefing  
2 document, one additional error was identified, and  
3 I would like to read the correction into the  
4 record.

5 In table 23 on page 45 of the briefing  
6 document, the confidence interval for the second  
7 external adjudication of MACE is erroneously stated  
8 as negative 0.2, 6.3. The accurate confidence  
9 interval is negative 0.1, 6.3.

10 I will now give a brief introduction to the  
11 matter being discussed today. We will discuss the  
12 risks and benefits of tegaserod treatment proposed  
13 for reintroduction after it was withdrawn from U.S.  
14 marketing due to a cardiovascular safety concern.

15 It should be noted that the NDA itself was  
16 not withdrawn. This supplemental submission  
17 proposes a reintroduction to the market for the  
18 treatment of IBS-C in females less than 65 years of  
19 age who are at low CV risk.

20 The application being discussed is a  
21 supplemental NDA submitted by US WorldMeds, the  
22 U.S. agent for Sloan Pharma, for the use of

1 tegaserod in women less than 65 years of age with  
2 IBS-C. The proposed population is further  
3 restricted to those who do not have a history of  
4 cardiovascular ischemic disease, such as myocardial  
5 infarction, stroke, transient ischemic attack, or  
6 angina, and who do not have more than one risk  
7 factor for cardiovascular disease.

8 Irritable bowel syndrome with constipation,  
9 or IBS-C, is a functional GI disorder characterized  
10 by recurrent abdominal pain related to defecation  
11 with hard or infrequent stools as characterized by  
12 the Rome IV criteria.

13 The worldwide prevalence of IBS is  
14 approximately 11 percent, with IBS-C comprising  
15 over a third of the IBS subtypes. Patients  
16 typically experience chronic symptoms with  
17 fluctuating severity and episodic flares.

18 Traditionally, IBS is thought to be  
19 primarily due to visceral hypersensitivity and GI  
20 motor disturbances. More recently, there is  
21 increasing evidence for the contributing factors of  
22 infection, immune activation, serotonin

1 dysregulation, bacterial overgrowth, central  
2 dysregulation, and brain-gut interaction, genetics,  
3 and chronic stress.

4           These underlying causes can vary by patient,  
5 and so additional treatment options with differing  
6 mechanisms of action may still be needed to achieve  
7 relief in symptoms, primarily by improving  
8 abdominal pain and stool consistency and increasing  
9 frequency of bowel movements. It should also be  
10 noted that there is a high prevalence of comorbid  
11 psychiatric disorders in IBS, including major  
12 depressive and generalized anxiety disorders, et  
13 cetera.

14           All of the currently approved treatments for  
15 patients with IBS-C are listed on this slide. It  
16 should be noted that while these three products are  
17 approved for IBS-C, they differ from tegaserod in  
18 their mechanism of action.

19           If reintroduced, tegaserod will represent  
20 the only drug in the 5-HT4 class for the treatment  
21 of IBS-C. In addition to these therapies, over-  
22 the-counter fiber supplements, laxatives, enemas,



1 and/or diet and lifestyle modification are often  
2 used to relieve symptoms, though none are  
3 specifically approved for IBS-C.

4 Now, I will provide an overview of  
5 tegaserod's key regulatory history. Tegaserod was  
6 approved in 2002 for the short-term treatment of  
7 women with IBS-C. Safety and effectiveness was not  
8 demonstrated in males. And in 2004 for the  
9 treatment of chronic idiopathic constipation, or  
10 CIC, in patients less than 65 years of age,  
11 effectiveness was not demonstrated in patients  
12 greater than or equal to 65 years.

13 On February 22, 2007, Novartis, who was the  
14 sponsor for tegaserod at that time, informed the  
15 FDA that a retrospective analysis of pooled  
16 tegaserod clinical trials revealed an imbalance in  
17 coronary ischemic events between tegaserod and  
18 placebo.

19 The Swiss regulatory authority requested  
20 that Novartis perform this retrospective analysis  
21 to evaluate all ischemic events due to  
22 postmarketing reports of ischemic colitis. On

1 March 9, 2007, a report containing a pooled  
2 analysis of ischemic events from 29 placebo-  
3 controlled trials involving over 18,000 patients  
4 was provided. The rate of CV events seen in this  
5 retrospective meta-analysis in patients taking  
6 tegaserod was 13 of 11,614 or 0.11 percent. This  
7 was compared to 1 of 7,031, or 0.01 percent, in a  
8 patient taking placebo.

9 Most tegaserod-treated patients who had an  
10 event were aged 55 years and above, had a history  
11 of CV disease at baseline, and/or had more than one  
12 CV risk factor. Additional details of these  
13 results will be discussed in subsequent  
14 presentations this morning.

15 Because of this imbalance in ischemic  
16 cardiovascular events, FDA asked Novartis to  
17 suspend the marketing and sale of tegaserod in the  
18 U.S. and a public health advisory was issued. Note  
19 that during the initial review of the tegaserod  
20 registration trials, cardiovascular adverse events  
21 were not noted to be a safety issue.

22 It should also be noted that a higher

1 incidence of suicidal ideation and behavior, or  
2 SI/B events, associated with tegaserod were  
3 identified in postmarketing, and on February 2,  
4 2007, FDA recommended to incorporate language  
5 regarding SI/B in the precautions section of the  
6 labeling. However, this labeling language was not  
7 incorporated prior to the drug being withdrawn from  
8 the market.

9           Several important regulatory events occurred  
10 following the withdrawal of tegaserod. An  
11 emergency and treatment IND program were initiated  
12 to provide drug to certain patients for whom no  
13 other treatment options were available and in whom  
14 the benefits of tegaserod treatment outweighed the  
15 chance of serious side effects.

16           In 2008, results from a second external  
17 adjudication of potential cardiovascular events  
18 were submitted. This adjudication included a  
19 reanalysis of the database comprised of 29  
20 placebo-controlled trials for CV ischemic signal  
21 identification using a broader search strategy,  
22 improved patient narratives with additional source

1 information, and prespecified definitions for CV  
2 ischemic outcomes, including major adverse  
3 cardiovascular events or MACE.

4 This is thought to be the most thorough of  
5 the three adjudications conducted, and details of  
6 these results will be discussed in subsequent  
7 presentations.

8 In 2011, a Gastrointestinal Drugs Advisory  
9 Committee meeting was convened to discuss potential  
10 recommendations on the design and size of  
11 premarketing CV safety development programs  
12 necessary to support approval of drugs in the 5-HT4  
13 receptor agonist class for indications related to  
14 CIC, IBS-C, or other GI disorders. Publicly  
15 available data regarding the risk of tegaserod was  
16 included in this discussion.

17 After withdrawal of tegaserod, FDA continued  
18 to work with then-sponsor Novartis in 2008 and  
19 after the NDA changed hands in 2015, the current  
20 applicant, in consideration of a limited  
21 reintroduction of Zelnorm if a population of  
22 patients could be identified in whom the benefits

1 of the drug outweigh the risks. It was also noted  
2 at the time that important aspects of  
3 reintroduction, including selection of an  
4 appropriate population, would need to be discussed  
5 before an advisory committee.

6 During meetings prior to this NDA  
7 supplemental submission, the applicant was asked to  
8 define a population of severely symptomatic IBS-C  
9 patients. The efficacy presentation that follows  
10 focuses on severely symptomatic patients, as this  
11 analysis will be an important consideration if the  
12 intended target population needs to be limited due  
13 to the perceived risk.

14 It should be noted that there was no final  
15 agreement between FDA and applicant on the severely  
16 symptomatic definition prior to submission of this  
17 supplement. FDA also recommended focusing  
18 reintroduction proposals to patients with IBS-C and  
19 agreed to the definition of a low CV risk patient  
20 described as those under 65 years of age and with  
21 zero or 1 cardiovascular risk factor, where risk  
22 factors include history of CV disease, active

1 smoking, hypertension, hyperlipidemia, diabetes  
2 mellitus, age greater than or equal to 55 years,  
3 and obesity.

4 This supplemental NDA includes legacy data  
5 from four trials, three of which supported approval  
6 in 2002. A fourth study, trial 351, was not  
7 included in labeling, as analysis of the primary  
8 endpoint was considered exploratory at the time.  
9 Although this trial was not relied on for the  
10 determination of efficacy to support approval,  
11 trial 351 was included to support the  
12 reintroduction to the market because the same  
13 endpoints are now being evaluated in a post hoc  
14 nature for all IBS-C trials.

15 Safety data in this application includes a  
16 database comprised of 29 placebo-controlled  
17 clinical trials of greater than or equal to  
18 4 weeks' duration and across multiple indications  
19 and from a long-term database, which includes data  
20 from 7 open-label studies of greater than or equal  
21 to 6 months' duration.

22 The inclusion of multiple indications in the

1 database cast a wide net of patients exposed to  
2 tegaserod in order to capture rare events. Reports  
3 from the three adjudications with associated  
4 patient narratives were included, and results from  
5 a non-interventional epidemiologic study to compare  
6 the incidence of cardiovascular study outcomes  
7 between tegaserod and comparator cohorts were also  
8 submitted for review.

9 Nonclinical data was also included in the  
10 submission, providing information on the  
11 mechanistic potential of tegaserod to cause CV  
12 events.

13 It should be noted that data from two  
14 postmarketing trials, studies 2306 and 2417, were  
15 also submitted. These studies were of a different  
16 design, with a short 4-week treatment period that  
17 included different types of IBS patients.  
18 Therefore, FDA did not focus on data from these two  
19 trials for the purposes of efficacy. For safety,  
20 these trials were assessed as supportive.

21 The goals of today's advisory committee  
22 discussion are to objectively assess the strength

1 of the cardiovascular imbalance noted with  
2 tegaserod use and to qualitatively weigh the  
3 benefits and risks of introducing this product in a  
4 relevant subset of patients.

5 This flowchart portrays a decision tree that  
6 may help guide the discussion. First, we seek your  
7 input on an assessment of the strength of the CV  
8 signal. If it is felt by the committee that the CV  
9 signal is weak, you might vote to reintroduce the  
10 product in all females with IBS-C.

11 In this case, the overall efficacy and  
12 safety data submitted to support approval of the  
13 product in IBS-C stand, or you may have other  
14 considerations that might prevent you from  
15 recommending approval.

16 If the CV signal associated with tegaserod  
17 is considered to be strong, we seek advice and  
18 discussion regarding whether it should be  
19 reintroduced to the U.S. market; and if so, is  
20 there a potential subset of patients in whom the  
21 benefits most outweigh the risk?

22 For example, is the CV signal serious enough



1 to warrant limiting the exposed population of  
2 female IBS-C patients to those with low CV risk,  
3 given the majority of patients who had a CV outcome  
4 were at higher CV risk?

5 Alternatively, the population could be  
6 narrowed to those who most need it, patients who  
7 have severe symptoms of IBS-C. If the signal is  
8 deemed to be very concerning, the population could  
9 be narrowed even further to include patients who  
10 are both at low CV risk and have severe symptoms  
11 who would most benefit from tegaserod treatment.

12 So we would like to discuss the strength of  
13 the CV risk signal to help guide selection of an  
14 appropriate population for a reintroduction.

15 I would also like to point out that at the  
16 time of withdrawal, only results from the sponsor's  
17 internal adjudication and a first external  
18 adjudication were available, with limited patient-  
19 level source data.

20 In addition to the limited available data,  
21 the imbalance in cardiovascular events associated  
22 with tegaserod emerged in a regulatory landscape in

1       which cardiovascular concerns had arisen with  
2       products for diabetes, and it seemed prudent at the  
3       time to withdraw tegaserod, given the residual  
4       uncertainty of cardiovascular risk.

5               Since that time, results from a second  
6       external adjudication became available, which is  
7       thought to be the most thorough of the three  
8       conducted and will be presented today.

9               I have reviewed the history leading us here  
10       today, and this morning, you will hear in some  
11       detail more information regarding the mechanistic  
12       potential of tegaserod to cause CV events,  
13       characterization of the initial signal  
14       identification, description of the three  
15       adjudications and their outcomes, as well as an  
16       analysis of risk factors, both in the full safety  
17       population and in patients who experienced a CV  
18       outcome.

19               It will be important to carefully consider  
20       the totality of cardiovascular safety data,  
21       pieced from-legacy data from clinical trials,  
22       epidemiologic studies, nonclinical data, and

1 pharmacovigilance data, as well as the presence of  
2 a suicidal ideation and behavior signal, in  
3 assessing the balance between benefit and risk and  
4 in consideration of potentially limiting the  
5 exposed population.

6 We plan to highlight these major elements of  
7 the application in an effort to focus the  
8 discussion and provide you all with as complete a  
9 picture as possible given the data that are  
10 available.

11 Next, I will present the questions to the  
12 committee. The first is for discussion.

13 Question number 1. Discuss the strength of  
14 the potential cardiovascular safety signal of  
15 tegaserod, considering the totality of available  
16 data from clinical trials, adjudications,  
17 pharmacoepidemiology studies, nonclinical data, and  
18 pharmacovigilance data.

19 Also for discussion, question number 2,  
20 discuss other potential safety concerns, including  
21 psychiatric safety, adverse events of completed  
22 suicide, and suicidal ideation and behavior when

1       considering reintroduction of tegaserod to the U.S.  
2       market.

3               Question number 3, a voting question. Is  
4       the reintroduction of tegaserod to the U.S. market  
5       supported by the available safety data? Discuss  
6       your answer.

7               Question number 4. Do you agree that the  
8       therapeutic gain for the treatment difference  
9       between tegaserod and placebo patients is generally  
10      similar in magnitude between the severely  
11      symptomatic and originally approved population?  
12      Discuss your answer.

13              Finally, number 5. In which patient  
14      population would you expect the benefits to  
15      outweigh the risks for patients treated with  
16      tegaserod? Choose from the following populations:  
17      A, IBS-C females; B, IBS-C females at low CV risk;  
18      C, IBS-C females who are severely symptomatic; D,  
19      IBS-C females at low CV risk and who are severely  
20      symptomatic; or E, other.

21              This concludes my presentation, and I thank  
22      you for taking the time to be here today.

1 DR. RAUFMAN: Thank you.

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

9 For this reason, FDA encourages all  
10 participants, including the sponsor's non-employee  
11 presenters, to advise the committee of any  
12 financial relationships that they may have with the  
13 firm at issue, such as consulting fees, travel  
14 expenses, honoraria, and interest in the sponsor,  
15 including equity interests and those based upon the  
16 outcome of the meeting.

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

1 speaking.

2 We will now proceed with the applicant's  
3 presentations.

4 **Applicant Presentation - Kristen Gullo**

5 MS. GULLO: Good morning. On behalf of my  
6 colleagues, I would like to thank the agency and  
7 panel for the opportunity to present our proposed  
8 reintroduction for Zelnorm. We look forward to  
9 your input during today's important discussions.

10 I'm Kristen Gullo, vice president of  
11 development and regulatory affairs for US  
12 WorldMeds, which is the commercial partner and U.S.  
13 agent for our sister company and NDA applicant,  
14 Sloan Pharma.

15 For my portion of the presentation, I will  
16 introduce Zelnorm and review its regulatory  
17 history. I will discuss how its removal limited  
18 the options available to manage constipation  
19 disorders, and I will outline our reevaluation  
20 efforts and proposed reintroduction for Zelnorm,  
21 aimed at ensuring a favorable benefit-risk for the  
22 product.

1           US WorldMeds is a specialty pharmaceutical  
2           company with a mission to develop and commercialize  
3           products that can meaningfully address unmet  
4           medical needs. Zelnorm is an efficacious treatment  
5           option for the management of constipation disorders  
6           and was utilized by many U.S. patients prior to its  
7           market withdrawal.

8           Despite new product approvals, a need for  
9           additional treatment options remains apparent, and  
10          some patients with unsatisfactory response to  
11          available therapies could benefit from the renewed  
12          availability of Zelnorm. This brings us here to  
13          discuss patient populations for whom its  
14          reintroduction to the U.S. market is both needed  
15          and appropriate.

16          Zelnorm's active ingredient, tegaserod, is a  
17          5-HT<sub>4</sub> serotonin receptor agonist. This mechanism  
18          of action has established pharmacologic action for  
19          the treatment of constipation disorders.

20          A large clinical program has been conducted  
21          to evaluate Zelnorm. It includes multiple  
22          controlled and open-label studies evaluating more

1 than 8,000 patients with constipation-predominant  
2 irritable bowel syndrome or IBS-C or chronic  
3 idiopathic constipation or CIC. These studies  
4 establish efficacy for both.

5 Results from the program led to clear  
6 conclusions of overall favorable benefit-risk and  
7 were the basis of U.S. approvals in 2002 and 2004  
8 and global approvals spanning 56 countries. It  
9 continues to be marketed today in Mexico, Ecuador,  
10 and Brazil and is available in the U.S. only  
11 through an expanded access program.

12 In 2007, the product was withdrawn from the  
13 market following the identification of a potential  
14 cardiovascular signal. SwissMedic requested a  
15 retrospective analysis of a large pooled clinical  
16 trial database involving 29 studies across multiple  
17 indications and more than 18,000 total subjects.

18 The events identified from this analysis  
19 have been the subject of comprehensive evaluations,  
20 including multiple adjudications. The first  
21 external adjudication committee concluded that  
22 there were 13 events or 0.11 percent in the Zelnorm



1 treatment group compared to 1 or 0.01 percent in  
2 the placebo group, a statistically significant  
3 difference.

4           Although the product was being successfully  
5 used by many patients, the reported imbalance  
6 created uncertainty about the overall benefit-risk  
7 balance in the IBS-C and CIC populations. This  
8 uncertainty resulted in a rapid withdrawal of  
9 Zelnorm from the market to enable thorough  
10 evaluation of reported cases and follow-up  
11 investigations.

12           Almost immediately following withdrawal, the  
13 sponsor and the FDA initiated efforts to consider  
14 reintroduction as well as methods to allow access  
15 to the product in the interim.

16           Our reintroduction proposal is focused on  
17 IBS-C because it represents an area of greatest  
18 unmet need. It is associated with a broad symptom  
19 complex and a significantly impaired quality of  
20 life.

21           As defined by the Rome Foundation, a medical  
22 society focused on functional GI disorders, IBS-C

1 is more than chronic constipation. It is defined  
2 by chronic, concurrent abdominal pain, and patients  
3 can also experience abdominal discomfort, bloating,  
4 and flatulence. The condition may fluctuate in  
5 severity, but persist for years and often results  
6 in patients altering eating habits, daily  
7 schedules, and social and work activities to manage  
8 their symptoms. The condition affects an estimated  
9 5 to 8 percent of the U.S. adult population and is  
10 most prevalent in younger to middle-aged women.

11 A 2016 study on disease burden and treatment  
12 needs for IBS-C showed that more than three-  
13 quarters of surveyed gastroenterologists were not  
14 satisfied with available treatments. In the  
15 patient portion of the same survey, nearly two-  
16 thirds were not satisfied with their current  
17 treatment, citing both reasons of inadequate  
18 efficacy and issues with side effects.

19 The call for additional treatment options  
20 from the IBS-C community have been the primary  
21 driver for our reassessment of the product. We  
22 have carefully evaluated the imbalance in

1 cardiovascular events from the controlled studies.  
2 Our goal in this evaluation was not to dismiss or  
3 minimize the imbalance, but to carefully  
4 characterize it in order to understand what, if  
5 any, pharmacologic contribution Zelnorm may have  
6 had to the observed higher rates in the active  
7 treatment arm. Then, with a better understanding  
8 of the safety profile, we sought to put potential  
9 product risks in the context of the product's  
10 established benefits.

11 The next few slides will illustrate the  
12 components of safety and efficacy that are  
13 available to inform overall benefit-risk  
14 characterizations.

15 This slide is an illustration of the body of  
16 data available to support benefit-risk  
17 determinations. It is not intended to be to scale,  
18 but to highlight the evolution of data over time.

19 The inner circle represents the data at the  
20 time of the original approval when favorable  
21 benefit-risk conclusions were initially made.  
22 Significant evolution in the evidence supporting

1 both benefit and risk characterization has  
2 occurred. This expands the total foundation of  
3 data on which we can rely for our proposed  
4 reintroduction.

5 The efficacy data has grown to the conduct  
6 of two post-approval randomized controlled trials.  
7 These studies were both positive and provide  
8 further confirmation of Zelnorm's efficacy in  
9 IBS-C. The total foundation of safety data has  
10 also grown.

11 The current availability of controlled  
12 studies across many indications provides a means  
13 for evaluating safety across a diverse set of  
14 patients, and the extensive marketing history of  
15 the product represents more than 1.6 million  
16 patient-years of exposure, giving us a broad base  
17 of real-world experience to confirm the product's  
18 general safety profile.

19 For today's discussion, the most important  
20 area of evidence growth is in the data available to  
21 characterize the cardiovascular safety of the  
22 product. This includes significant new sources of

1 information from work completed in the time period  
2 following Zelnorm's withdrawal from the market.

3           You will hear from Dr. Sager shortly about  
4 the work completed to characterize Zelnorm's  
5 cardiovascular safety profile. His evaluation will  
6 include detailed cardiovascular event case  
7 assessments across multiple data adjudications,  
8 analyses of relevant cardiovascular parameters,  
9 large epidemiology studies, and mechanistic  
10 evaluations.

11           You will also hear from my colleague,  
12 Dr. Gerlach, that the efficacy of the product  
13 remains robust based on current endpoint standards  
14 with established therapeutic gains consistent with  
15 other treatments in this space.

16           In addition to evaluating all of the data  
17 available to assess overall benefit-risk of the  
18 product, we also considered two approaches for  
19 defining populations to evaluate the potential for  
20 a more favorable benefit-risk profile.

21           First, we assessed populations who are less  
22 likely to have a cardiovascular event based on

1 known factors established in the general  
2 population.

3 Second, we evaluated a population with  
4 severe symptoms who may be more accepting of some  
5 remaining uncertainty of the cardiovascular safety  
6 of the product when considering their potential to  
7 benefit.

8 To best inform the discussion this  
9 afternoon, you will see data both in our  
10 presentation and the FDA's on populations defined  
11 through both of these approaches. One or the other  
12 of these approaches could be useful in enhancing  
13 the overall benefit-risk.

14 I will now walk through the populations we  
15 evaluated through these two approaches, then I will  
16 review our current proposal, which has evolved as  
17 we consider the appropriate balance between benefit  
18 and risk.

19 Again, here is a depiction of the  
20 populations that we considered. Again, it is not  
21 intended to be representative of scale; rather, an  
22 aid to help me walk through how we layered

1 additional restrictions to define populations.

2           The original cardiovascular event imbalance  
3 was reported from a pooled database across multiple  
4 indications. Because our goal was to find a  
5 population with a favorable benefit-risk, we only  
6 evaluated populations for whom benefits had been  
7 clearly established, initially including men and  
8 women with CIC and women only with IBS-C.

9           As we have discussed, our focus is solely on  
10 women with IBS-C. The diagram components in blue  
11 show the various female IBS-C populations  
12 considered. Each smaller box represents criteria  
13 used to identify populations across a spectrum of  
14 demographic variables known to pre-dispose  
15 individuals to a cardiovascular event.

16           We first narrowed the population by age to  
17 those under 65. We then added a criterion for no  
18 history of ischemic cardiovascular disease such as  
19 a history of stroke, myocardial infarction, and  
20 other clear diagnoses associated with  
21 cardiovascular ischemia.

22           Finally, the last box describes an

1 additional layer of cardiovascular health criteria;  
2 that is, to further narrow the patients with no  
3 more than 1 additional cardiovascular risk factor  
4 such as smoking, high cholesterol, and  
5 hyperlipidemia, among others.

6 This is a similar depiction of the second  
7 approach that we considered in defining  
8 populations. We separately defined this population  
9 in collaboration with the agency as one thought to  
10 represent those patients with the greatest disease  
11 burden. Patients that fit this definition may have  
12 a greater tolerance of risk uncertainty for the  
13 chance to have symptom relief.

14 The analysis population we defined is  
15 characterized by severe symptoms of pain and  
16 altered bowel habits, and we will discuss this  
17 further in the efficacy presentation.

18 Our assessment across all considered  
19 approaches and populations leads us to propose  
20 reintroduction for female IBS-C patients at low  
21 cardiovascular risk. Our definition of low  
22 cardiovascular risk is for female IBS-C patients



1 under the age of 65 with no history of ischemic  
2 cardiovascular disease.

3 This definition has been modified slightly  
4 from our original submission, but falls within the  
5 range of low cardiovascular risk populations  
6 evaluated in collaboration with the agency.

7 Throughout the rest of our presentation, we will  
8 discuss the safety and efficacy conclusions and  
9 share the clinical perspective that we considered  
10 to arrive at this proposal.

11 I am joined today by three additional  
12 presenters. Next, Dr. Sager will review the  
13 findings from targeted evaluations to assess the  
14 cardiovascular safety profile of Zelnorm.

15 Dr. Gerlach will provide an overview of the  
16 Zelnorm clinical program efficacy and general  
17 safety results, including evaluations and  
18 considered reintroduction populations.

19 Dr. Howden will put what you hear today from  
20 the clinical data into the context of current  
21 clinical practice for patients and providers, and  
22 then I will provide brief closing remarks.

1 Dr. Sager?

2 **Applicant Presentation - Philip Sager**

3 DR. SAGER: Thank you.

4 Good morning. My name is Phillip Sager. I  
5 am a cardiologist and adjunct professor of medicine  
6 at Stanford University. And as a member of the  
7 executive committee of the Cardiac Safety Research  
8 Consortium, I have been involved in the assessment  
9 of possible cardiovascular risks of 5-HT4 agonists  
10 for a number of years. Additionally, I'm the past  
11 chair of the FDA Cardiorenal Advisory Committee.

12 I am being compensated for my time and  
13 travel expenses, and I do not have any direct  
14 financial interests in the outcome of today's  
15 meeting.

16 As you heard in the introduction, in 2007,  
17 the previous sponsor observed an imbalance in  
18 cardiovascular events, which led to the withdrawal  
19 of Zelnorm. Since that time, additional data has  
20 been collected and many analyses performed, making  
21 it important to reconsider the cardiovascular  
22 safety of Zelnorm.

1 I'll review the substantial cardiovascular  
2 safety data with you, focusing on the initial  
3 cardiovascular signal in the clinical trial  
4 database and the adjudication efforts undertaken to  
5 better understand this signal; 2 epidemiologic  
6 studies that focused on cardiovascular events in  
7 different populations; nonclinical  
8 electrophysiology data and clinical evaluation of  
9 the QTc interval, blood pressure and heart rate  
10 across the clinical trials; and potential  
11 mechanisms by which Zelnorm might conceivably cause  
12 harm, including platelet receptor and arterial  
13 vasoconstriction mechanistic studies.

14 The clinical trial data has been carefully  
15 evaluated to understand the cardiovascular safety  
16 signal. The primary focus is on the dataset of all  
17 of the 29 placebo-controlled randomized trials that  
18 were of 4 weeks or longer in duration. These  
19 trials lasted up to 12 weeks and is referred to in  
20 the presentation as Db15. None of these studies  
21 were designed to assess cardiovascular safety.

22 This is a large database. There are 11,614

1 patients receiving Zelnorm and 7,031 receiving  
2 placebo, so there's some imbalance with more  
3 patients receiving Zelnorm than placebo. The mean  
4 period of exposure is 57 to 58 days.

5 In addition, later in the presentation, I  
6 will also discuss the long-term open-label trials  
7 in order to supply additional information on  
8 extended duration of Zelnorm treatment. This  
9 database is composed of 7 open-label studies of  
10 3,289 patients with a mean exposure of 277 days.

11 In order to best understand the  
12 cardiovascular safety of Zelnorm, multiple  
13 adjudications of the clinical trial database were  
14 performed. It is common that when a cardiovascular  
15 signal is identified, the adjudication of potential  
16 events by experts in the field is performed in  
17 order to improve the diagnostic accuracy of the  
18 events and to ensure that all cardiovascular events  
19 are appropriately collected and classified.

20 The adjudicated cardiovascular events are a  
21 very important part of the information informative  
22 to cardiovascular safety that we are considering

1 today. However, even adjudication does not  
2 overcome potential limitations of a retrospective  
3 review of trials that were not prospectively  
4 designed to assess cardiovascular safety.

5           These include an absence of a full  
6 collection of cardiovascular risk factors and  
7 cardiovascular disease data; the potential lack of  
8 specific information regarding potential  
9 cardiovascular events; and that the trials of short  
10 duration are not ideal to evaluate cardiovascular  
11 safety. As we will discuss on the next slide,  
12 three adjudications were performed using different  
13 techniques and level of sophistication.

14           After the previous sponsor, Novartis,  
15 identified a possible cardiovascular signal in the  
16 database, blinded adjudications were performed of  
17 the 29 randomized placebo-controlled trials. On  
18 the left side of the slide, after a database  
19 search, 24 cases were identified by Novartis as  
20 being potentially positive and then underwent two  
21 separate adjudications.

22           Given the potential public health issue,

1 once a signal was identified, these adjudications  
2 were rapidly performed. Thus, they were done  
3 without the necessary time for full-source document  
4 retrieval and putting in place these methodologies  
5 usually employed for standard cardiovascular event  
6 adjudication.

7 This was a two-step process. First an  
8 internal blinded adjudication was performed within  
9 Novartis, and here, source documentation was  
10 limited. Then Novartis soon afterwards convened a  
11 panel of physicians at Mount Sinai Hospital in New  
12 York City to evaluate the same cases with the  
13 benefit of some additional source documents.

14 Thereafter, once the cardiovascular signal  
15 was identified, it was deemed important to perform  
16 an extensive and thorough analysis of the clinical  
17 trial database to determine if there were  
18 additional cardiovascular cases that had not been  
19 identified or not appropriately classified.

20 This was done in conjunction with a  
21 subsequent adjudication that did use standard  
22 methodologies and was done by the Duke Clinical

1 Research Institute.

2 A very extensive search of the whole Db15  
3 database was performed, which identified 304  
4 potential cases for full committee adjudication.  
5 The process took a significant period of time of  
6 about 6 months.

7 In addition to more extensive efforts to  
8 obtain source documents, the adjudication also used  
9 pre-defined objective event definitions and a  
10 prospective use of major adverse cardiac event  
11 evaluation. It is standard now in cardiovascular  
12 outcome studies to usually focus on hard endpoints  
13 of irreversible harm such as MACE, which would be  
14 nonfatal MI, nonfatal stroke, or cardiovascular  
15 death, which is what was done here, and independent  
16 committee voting was also utilized.

17 These are all approaches recommended by the  
18 FDA-sponsored Cardiac Safety Research Committee  
19 meeting that was convened at the FDA in 2013 on  
20 event adjudication, and there's been a follow-up  
21 publication.

22 What was learned in these three

1 adjudications is that they identify a small number  
2 of cardiovascular events, and that a numerical  
3 imbalance between patients receiving Zelnorm and  
4 placebo was observed in all evaluations.

5           Shown here are the results of the three  
6 adjudications. The Novartis adjudication on the  
7 left characterized cases that were major, defined  
8 as MACE plus unstable angina. For cardiovascular  
9 ischemic events, which included MI, stroke,  
10 unstable angina, TIA, or cardiovascular death,  
11 Novartis confirmed 18 cases in the Zelnorm cohort  
12 and 2 in placebo; Mount Sinai, 13 and 1; and Duke 7  
13 and 1.

14           Slightly more than half the cases were MACE  
15 events; that's to say, nonfatal MI, nonfatal  
16 stroke, or cardiovascular death. The first  
17 external adjudication identified 7 events in  
18 patients receiving Zelnorm. Duke identified  
19 4 events, and neither identified any in the placebo  
20 cohort.

21           The Duke evaluation did not identify new  
22 cardiovascular ischemic events. However, the Duke



1 evaluation did identify other cardiac cases, which  
2 we'll discuss later in the presentation.

3 The percent of subjects experiencing events,  
4 depending on the adjudication, is small. For  
5 example, for MACE, it ranged from 0.03 to 0.06  
6 percent. While having more source documentation in  
7 the subsequent adjudications reduce the number of  
8 possibly confirmed cases, an imbalance persists.

9 Now, on the lower line, you can see the  
10 95 percent confidence intervals for the percent  
11 difference. As you'll see, the number of  
12 confidence intervals here often include unity.

13 Subjects were also evaluated for their  
14 cardiovascular risk status, and most subjects  
15 either had known cardiovascular disease or at least  
16 two cardiovascular risk factors, and this was the  
17 case in 7 of the 8 individuals adjudicated in the  
18 Duke adjudication.

19 As will be shown on the next slide, the  
20 cardiovascular events were also assessed in the  
21 intended patient population. In order to reduce  
22 the potential for cardiovascular events in patients

1 receiving Zelnorm, the sponsor's proposing that  
2 Zelnorm be limited to a lower cardiovascular risk  
3 patient population, specifically women less than  
4 65 years old without cardiovascular disease.

5           Shown on the left side are the MACE events,  
6 and the adjudicated cardiovascular ischemic events,  
7 and the entire Db15 cohort, as well on the  
8 right-hand side, those in women less than 65 years  
9 old without cardiovascular disease.

10           While these types of analyses are limited by  
11 the small number of events, women less than  
12 65 years old without cardiovascular disease had an  
13 approximately one-half to two-thirds reduction in  
14 event rates.

15           In addition, in order to evaluate  
16 cardiovascular safety of Zelnorm, the  
17 cardiovascular ischemic events in the long-term  
18 study database were also examined by Duke. This  
19 was the only external adjudication that performed  
20 this analysis. Four cardiovascular ischemic events  
21 were identified. There were 3 episodes of unstable  
22 angina and 1 MACE event, which was a stroke event.

1 All had at least two cardiovascular risk factors.

2 Overall, the frequency and pattern of  
3 cardiovascular events in the open-label long-term  
4 use database is comparable for those patients in  
5 the placebo-controlled short-term clinical trial  
6 database, Db15, suggesting that prolonged exposure  
7 to Zelnorm was not associated with an increased  
8 frequency of cardiovascular events.

9 In assessing cardiovascular safety, it can  
10 be informative to perform pharmacoepidemiology  
11 studies and two such investigations were  
12 performed. These provide a real-world evaluation  
13 and supplement the clinical trial data. Shown here  
14 from Loughlin and colleagues is a study done using  
15 the Ingenix research database, a patient health  
16 claims database with real-world data.

17 This investigation looked at new Zelnorm  
18 initiators matched with non-initiators. There were  
19 52,229 patients in each group, so the study had  
20 more than 104,000 patients, and they were followed  
21 for 6 months.

22 This database covers all healthcare for

1 these patients, maximizing case attainment. They  
2 used a new user parallel control design, and  
3 importantly, propensity score matching was utilized  
4 to reduce potential confounding bias. This was  
5 done very extensively with more than 200 factors,  
6 including cardiovascular comorbidities,  
7 cardiovascular risk factors, including diabetes,  
8 older age, and hypertension.

9 A significant and somewhat unique strength  
10 of this study is that identified cardiovascular  
11 events in the claims database were then confirmed  
12 using medical record review by blinded  
13 adjudicators.

14 While the study was designed with a greater  
15 than 80 percent power to identify a 1.7 relative  
16 risk, the power was actually greater since the  
17 number of events was approximately 50 percent  
18 higher than had been anticipated when the study was  
19 designed.

20 The Zelnorm initiator or non-initiator  
21 cohorts, which were closely balanced by propensity  
22 score matching, had similar numbers of cardiac

1 events, which included acute coronary syndrome,  
2 myocardial infarction, and coronary  
3 revascularization, as well as stroke, and shown  
4 here are the blinded medical record-confirmed  
5 cases. If the analysis is performed without the  
6 cardiovascular revascularizations, one overall gets  
7 these similar results.

8 The hazard ratio is 0.95 for cardiovascular  
9 outcomes and 0.90 for stroke outcomes. The  
10 confidence intervals are fairly narrow and include  
11 unity, indicating no difference between the two  
12 cohorts. These results are similar to what is also  
13 obtained if one looks at the whole claims database.

14 The absolute incidence of events in the  
15 cohorts was examined to assess whether the study  
16 might conceivably show a lack of increase in risk  
17 with Zelnorm due to undercounting of outcome  
18 events. The events found in the cohorts and the  
19 person, time, and risk for the cohorts are  
20 presented here along with the absolute incidence  
21 rates for the events.

22 The incidence rates of approximately 5 per

1 1,000 person-years for cardiac events and just  
2 under 1 per 1,000 patient-years for stroke events  
3 are consistent with population-based epidemiology  
4 for individuals with similar age and sex  
5 distributions.

6 This indicates that the study found  
7 appropriate events for the demographics of the  
8 cohorts and that the finding of no increased risk  
9 of cardiac and stroke outcomes for Zelnorm was not  
10 due to a lack of sensitivity for identifying cases.

11 A second smaller epidemiologic study was  
12 independently designed, executed, and analyzed by  
13 Anderson and colleagues. This is the Intermountain  
14 Healthcare database, and Zelnorm patients were  
15 matched 1 to 6 with patients based on age, sex, and  
16 date of Zelnorm initiation who had similar  
17 gastrointestinal diseases. The mean duration of  
18 therapy was 4 months, but patients were followed  
19 long term for 2 and a half years.

20 In addition, in order to evaluate short-term  
21 effects, the data were also analyzed after 3 months  
22 of therapy, and this time interval was chosen

1 because that's the length of the studies, at least  
2 many of the studies, in the clinical database.

3 Shown here are the results. Overall, the  
4 cardiovascular event rates were similar in treated  
5 versus untreated patients as well as after  
6 adjusting for baseline cardiovascular risk factors,  
7 and there was no difference during the first  
8 3 months of therapy, the time interval initially  
9 examined in the clinical database.

10 In summary, and I believe importantly, two  
11 epidemiologic studies performed in different  
12 populations have shown that the cardiovascular  
13 event incidence was similar between Zelnorm and  
14 comparative cohorts.

15 Let's now focus on mechanisms by which  
16 Zelnorm could potentially cause cardiovascular  
17 harm. Shown here are the cardiac electrophysiology  
18 evaluations. The nonclinical evaluations showed no  
19 arrhythmic signals. This data includes no hERG  
20 liability. The IC50 to Cmax margin was greater  
21 than 1300. A canine cardiovascular safety study  
22 showed no ECG effects, and in addition, there were

1 no histopathological changes in the heart of  
2 canines.

3           Ventricular repolarization studies performed  
4 in Langendorff-perfused rabbit hearts and guinea  
5 pig papillary fibers also showed no effects, and  
6 action potentials were examined in human atrial  
7 myocytes to examine any potential effects on atrial  
8 electrophysiology, and these studies were also  
9 negative.

10           The clinical evaluation demonstrate that the  
11 human ECG parameters, the QTcF interval, heart  
12 rate, the PR interval, and QRS intervals, including  
13 those whose ECGs were centrally analyzed by a core  
14 ECG laboratory that included more than 4,000  
15 patients, showed no clinically meaningful effects.

16           Shown here is the change from baseline in  
17 the QTcF interval with these ECGs measured around  
18 Cmax on days 1, weeks 1 through 6, and weeks 7  
19 through 12 in subjects whose ECGs were analyzed by  
20 a core ECG laboratory. There was no meaningful  
21 difference between patients receiving the lower  
22 dose of Zelnorm, the therapeutic 6-milligram BID



1 dose, as well as placebo. Additionally, there were  
2 no effects on the standard categorical QTc analyses  
3 identified in ICH E14.

4 The incidence of arrhythmias is shown on the  
5 next slide. Shown here are the arrhythmias that  
6 were adjudicated by the second adjudication by  
7 Duke. It's the only adjudication that evaluated  
8 the arrhythmias. There were 2 events of  
9 ventricular tachyarrhythmias identified in this  
10 adjudication, both in patients with adjudicated  
11 cardiovascular events, 1 with a cardiovascular  
12 death, and the other associated with coronary  
13 artery bypass grafting.

14 The non-significant imbalance in total  
15 adjudicated arrhythmias appears to be due to  
16 5 episodes of atrial fibrillation in the Zelnorm  
17 cohort and 1 in the placebo cohort. The 5 patients  
18 with atrial fibrillation shown on this slide were  
19 at high risk of developing the arrhythmia, so this  
20 incidence is not unexpected. Two patients had a  
21 prior history of atrial fibrillation, and thus,  
22 arrhythmia occurrence would be anticipated since

1 patients with paroxysmal forms of atrial  
2 fibrillation often do have recurrences.

3 All had significant risk factors for atrial  
4 fibrillation, all were over 60 years old, and all  
5 had either coronary artery disease or multiple  
6 cardiovascular risk factors.

7 The blood pressure evaluations are shown on  
8 this slide. There were no preclinical signals of  
9 an effect to increase blood pressure in the canine  
10 cardiovascular safety study, nor in a rat study.  
11 In the clinical trials, blood pressure was measured  
12 at multiple post-dose time points, and no effect  
13 was observed at the therapeutic 6-milligram BID  
14 dose.

15 A supratherapeutic exposure of approximately  
16 twice therapeutic, a clinical non-significant  
17 increase in systolic blood pressure ranging from 1  
18 to 1.9 millimeters of mercury, was noted.  
19 Additionally, there were no consistent increases in  
20 diastolic blood pressure.

21 Platelet aggregation could provide a  
22 potential mechanism for Zelnorm to increase

1 cardiovascular events. Thus, platelet aggregation  
2 has been carefully assessed. Zelnorm does not bind  
3 to platelets, and thus, it's very unlikely that  
4 Zelnorm would have a direct effect on platelets.

5 In vitro platelet studies have also been  
6 performed. Zelnorm did not show a consistent  
7 statistically significant effect on platelet  
8 aggregation. Platelet aggregation was not observed  
9 in the three studies listed here by Higgins,  
10 Beattie, and Conlon, et al. There was no effect on  
11 platelet aggregation in these studies.

12 However, a previous study by Serebruany did  
13 show a small increase in aggregation for some  
14 agonists. This was primarily at supratherapeutic  
15 exposures. However, this finding was not  
16 reproduced by the subsequent three studies.

17 The sponsor has conducted a platelet  
18 aggregation study of the primary metabolite, M29,  
19 which showed minor aggregation. However,  
20 interpretability of the data is very limited since  
21 samples for aggregometry in the assay were  
22 associated with platelet activation. An ex vivo

1 study in which platelet activation is being assured  
2 not to be active in that study is currently under  
3 progress.

4 The potential for Zelnorm to cause arterial  
5 vasoconstriction has been carefully examined.  
6 Three serotonergic receptors whose stimulation  
7 could potentially elicit arterial vasoconstriction  
8 include 5-HT1B, 5-HT2A, and 5-HT2B.

9 However, Zelnorm is an antagonist of all of  
10 these receptors, so even if binding existed, it  
11 would not be expected to cause vasoconstriction.  
12 In vitro and in vivo studies did not show a signal  
13 of Zelnorm on arterial vasomotor activity.

14 There's been no effect on healthy or  
15 diseased coronary arteries and no meaningful  
16 effects on human mesenteric arteries and non-human  
17 primate coronary arteries. In addition, Zelnorm or  
18 tegaserod actually blocks the vasoconstrictor  
19 effects of serotonergic agonists.

20 In summary, there's a large clinical and  
21 nonclinical safety database that meaningfully  
22 informs the cardiovascular safety of Zelnorm.

1       There is a small numerical imbalance in the  
2       cardiovascular events in the clinical trial  
3       database. This may indicate a small cardiovascular  
4       risk that needs to be considered in the benefit-  
5       risk assessment.

6               However, there is also significant  
7       reassuring data, and this includes no clinically  
8       meaningful QTc, heart rate effects, or blood  
9       pressure effects at clinical doses and no  
10      indication of a ventricular arrhythmic effect.  
11      Nonclinical studies have shown no potential  
12      mechanistic link to cardiovascular ischemic  
13      effects, and this includes studies with platelet  
14      aggregation, arterial vasoconstriction, as well as  
15      receptor binding.

16             Importantly, two epidemiologic studies  
17      performed in different populations showed no  
18      difference in the rates of CV ischemic events in  
19      Zelnorm-treated patients versus comparator groups.

20             When I independently evaluate the totality  
21      of the data, if there is a cardiovascular risk of  
22      Zelnorm, it is very small. The plans to

1 reintroduce Zelnorm in a lower risk population  
2 further reduces any potential cardiovascular risk  
3 to patients receiving the medication.

4 Thank you. Now, Dr. Gerlach will present  
5 the overview of efficacy and safety.

6 **Applicant Presentation - Rachael Gerlach**

7 DR. GERLACH: Thank you, Dr. Sager.

8 Good morning. My name is Rachael Gerlach,  
9 Zelnorm program lead at US WorldMeds. For my  
10 portion of the presentation, I will provide the  
11 rationale for the clinical benefit of this product  
12 and how we should consider efficacy as a component  
13 of the overall benefit-risk assessment. I will  
14 close with an evaluation of the efficacy and safety  
15 profile and subpopulations evaluated to support  
16 reintroduction today.

17 First, I'd like to take a moment to discuss  
18 the clinical presentation of IBS-C and the diverse  
19 nature of symptoms that are most bothersome to  
20 patients. This study, published in 2005, sought to  
21 understand the symptom most bothersome to patients  
22 entering an IBS-C clinical program. Patients

1 enrolled in this study were asked to report the one  
2 symptom they viewed as their main complaint during  
3 the 3 months preceding study entry.

4 Shown here, two-thirds reported constipation  
5 and abdominal pain as their most bothersome  
6 symptom, with no one symptom being the most  
7 bothersome in all subjects. Therefore, when  
8 evaluating the benefit of therapeutic options for  
9 these patients, it is important to look at all key  
10 symptoms.

11 Let me now take a moment to orient you to  
12 the mechanism of action that may underlie these  
13 benefits. Under normal conditions, physical and  
14 chemical stimulation, such as contents entering the  
15 intestines, induce enterochromaffin cells, lining  
16 the intestine to release serotonin, also known as  
17 5-HT, into the underlying submucosal space.

18 This serotonin release activates nerves,  
19 which then triggers neurotransmitter release,  
20 enhancing secretory function, and stimulates  
21 corollary series of intestinal contractions and  
22 relaxations, also known as peristalsis, all of

1 which play critical roles in maintaining  
2 gastrointestinal motility.

3 As you heard in the introduction, Zelnorm  
4 represents a different profile, which could benefit  
5 IBS-C patients. Dysregulation of serotonergic  
6 signaling has been implicated in gastrointestinal  
7 disorders of function. This includes IBS. This  
8 may cause constipation, bloating, and abdominal  
9 pain, all hallmark symptoms of IBS-C.

10 Zelnorm contracts this dysregulation by  
11 acting through the serotonergic mechanism.  
12 Specifically, Zelnorm acts as an agonist from the  
13 5-HT4 serotonin receptor. This activates multiple  
14 neurons and smooth muscle cells in the  
15 gastrointestinal tract, stimulating motility,  
16 secretory function, and also decreasing pain  
17 signaling.

18 As a result, Zelnorm accelerates that  
19 transit, peristalsis, and restores normal bowel  
20 function. This mechanism differs from current  
21 approved therapy options which do not stimulate the  
22 nerves and the muscles.



1           As discussed in the FDA's briefing book, the  
2 efficacy of this product is not in question.  
3 Nonetheless, it is important to consider the  
4 efficacy as a component of the overall benefit-risk  
5 assessment in support of the reintroduction today.

6           The original Zelnorm clinical development  
7 program was composed of a robust set of 4 placebo-  
8 controlled trials, which evaluated the safety and  
9 efficacy in IBS-C patients treated with Zelnorm  
10 over 12 weeks of treatment; studies 301, 351, 358,  
11 and 307.

12           All studies evaluated men and women except  
13 study 358, which studied only women. Study 307 was  
14 a dose titration study. These were the first large  
15 double-blind placebo-controlled trials to  
16 investigate efficacy of drug treatment in IBS-C  
17 utilizing the Rome II criteria. These 4 studies  
18 were part of the original submission, which  
19 resulted in Zelnorm being the first drug approved  
20 for the treatment of IBS-C.

21           As shown in the right-hand column, all  
22 studies in the IBS-C clinical development program

1 assessed the same constellation of symptoms, which  
2 included abdominal pain and discomfort, stool  
3 frequency, stool consistency, and bloating.

4 After approval, two additional studies were  
5 conducted, reconfirming the efficacy in over 3,000  
6 patients. This further expanded the clinical  
7 setting where efficacy was demonstrated.

8 These two studies, study 2306 and 2417,  
9 assessed the same symptoms as the pre-approval  
10 studies. Patients enrolled were women between the  
11 ages of 18 and 65. One assessed treatment effect  
12 upon retreatment and the other assessed treatment  
13 effect in women with IBS-C and IBS with mixed  
14 symptoms of constipation and diarrhea.

15 Both provide evidence that Zelnorm can  
16 effectively treatment women with IBS-C who also  
17 require retreatment and in patients with IBS-M.  
18 Efficacy results were consistent across both  
19 pre-approval and post-approval studies.

20 The results by symptom for the pre-approval  
21 studies will be presented in the following slide.  
22 These symptom-based endpoints demonstrate Zelnorm's

1 ability to effectively treat IBS-C symptoms. This  
2 includes a greater than or equal to 1-point  
3 improvement in abdominal pain discomfort severity,  
4 an increase in 1 or more bowel movements per week,  
5 and a greater than or equal to 1-point improvement  
6 in bloating severity assessed over the 4-week  
7 treatment period.

8 In the following slides, the therapeutic  
9 gain for these endpoints will be shown as a point  
10 estimate on a line plot. The therapeutic gain is  
11 defined as the difference in Zelnorm treatment  
12 responders compared to those in placebo. These  
13 results will be presented for the original approved  
14 female population across three of the pre-approval  
15 studies. This includes study 301, 351, and 358,  
16 all of which assessed a fixed dose of Zelnorm or  
17 placebo across a 12-week treatment duration.

18 Study 307 will not be presented in  
19 subsequent slides, as this was a dose titration  
20 study lacking a fixed 6-milligram twice-daily dose.  
21 The treatment effect trend in this study was  
22 consistent, yet statistical significance was not

1 achieved.

2 Before we move forward, let me orient you on  
3 the efficacy results we have presented from this  
4 point forward. The results by symptom in this  
5 slide and for other endpoints in the subsequent  
6 slides are presented for three studies, study 301  
7 in red, 351 in blue, and 358 in black.

8 On each plot, the vertical line at zero  
9 indicates no treatment difference. Point estimates  
10 representing the therapeutic gain to the left of  
11 zero would indicate a higher response rate in  
12 placebo. Point estimates to the right indicate a  
13 higher response rate in Zelnorm.

14 By focusing on the top-left line at month 1,  
15 significant improvement in abdominal pain  
16 discomfort with Zelnorm was demonstrated. A  
17 similar finding is seen as you go down the plots  
18 through the different studies and endpoints,  
19 including stool frequency and bloating.

20 When looking at the right plot, similar  
21 findings in the last 4 weeks of the 12-week  
22 treatment period are seen, demonstrating the

1 durability of response with Zelnorm treatment.

2 Overall, the results demonstrate consistent  
3 improvement in abdominal pain discomfort, stool  
4 frequency, and bloating across all three studies.  
5 Given that the most bothersome symptom varies from  
6 patient to patient, we also include an evaluation  
7 of the global improvement from the patient's  
8 perspective.

9 The primary assessment in the pre-approval  
10 studies was a subject's global assessment. This is  
11 also known as the SGA. This quantifies a patient's  
12 overall perception of their relief. Patients were  
13 asked weekly to consider how they felt the past  
14 week in regards to their IBS; in particular, their  
15 overall well-being.

16 Patients were asked to rate their overall  
17 relief and symptoms with responses ranging from  
18 completely relieved, considerably relieved,  
19 somewhat relieved, unchanged, or worse. This  
20 captures the variety and complexity of symptoms in  
21 IBS-C as discussed earlier.

22 A responder was defined as having either

1 50 percent of the last 4 weeks of treatment with  
2 SGA ratings of completely or considerably relieved  
3 or 100 percent of the last 4 weeks of treatment  
4 with SGA ratings of somewhat relief.

5           Importantly, in the previously approved  
6 female population, an enhanced treatment difference  
7 ranging from 13 to 14 percent at month 1 was  
8 observed with highly statistical significance seen  
9 across all three studies.

10           At endpoint, also known as the last 4 weeks  
11 of treatment, a statistically significant treatment  
12 difference was seen in 2 of the 3 studies, ranging  
13 from 4.7 to 14.9 percent. This therapeutic gain is  
14 similar to other therapies for this condition and  
15 highlights Zelnorm's ability to improve patients'  
16 overall well-being.

17           To ascertain whether the original studies  
18 support efficacy using current guidelines in IBS  
19 trials, we reevaluated the original data based on  
20 an adaptation of the standard. Current guidelines  
21 recommend a primary endpoint that measures  
22 treatment effect on 2 condition-defining IBS

1 symptoms, abdominal pain and stool frequency.

2 For the analysis, a weekly responder was  
3 defined as a patient who experiences a reduction of  
4 30 percent or more from baseline in average pain  
5 and discomfort score and an increase in 1 or more  
6 bowel movements per week from baseline for at least  
7 half the study's duration. A patient had to be a  
8 weekly responder for 6 of the 12-week treatment  
9 period.

10 The therapeutic gain seen here achieved was  
11 applying this endpoint to the three 12-week studies  
12 that were statistically significant, ranging from 9  
13 to 13 percent. This illustrates that Zelnorm  
14 maintains its efficacy with these revised  
15 standards.

16 These levels of response shown are  
17 consistent with the original SGA endpoints and  
18 reconfirm the clinical benefit of Zelnorm.

19 We are now going to move from this analysis  
20 of the original approved female population to  
21 discussion of the subpopulations analyzed to  
22 support reintroduction today. As discussed

1 earlier, we conducted comprehensive analyses to  
2 identify a population with an optimized benefit-  
3 risk profile to support reintroduction.

4 We looked to identify population at lower  
5 cardiovascular risk by evaluating restrictions  
6 based on gender, age, cardiovascular history, and  
7 cardiovascular risk factors. We also looked at  
8 disease severity.

9 Currently, there is no gold standard for  
10 defining severe IBS-C. As recognized and agreed  
11 upon with the FDA, based on the mechanism of  
12 action, the components of a definition of severely  
13 symptomatic patients should include both abdominal  
14 pain and constipation.

15 We performed independent comparative skill  
16 analyses to identify the number of days per week a  
17 subject had severe abdominal pain and discomfort or  
18 hard, very hard, or no bowel movement. These were  
19 anchored to patients' response on the subject's  
20 global assessment of their abdominal pain and  
21 discomfort and bowel habit. To be the most  
22 rigorous, we required patients to be severe for



1 both of these domains.

2 Thus, our definition of severely symptomatic  
3 female patients is having 3 or more days of severe  
4 abdominal pain and discomfort and 5 or more days of  
5 hard, very hard, or no stool per week, which will  
6 be utilized in subsequent analysis.

7 There are different statistical ways to  
8 apply this definition as described in the FDA  
9 briefing document and will be reviewed by the FDA  
10 today. Regardless of method utilized, this  
11 definition identifies roughly 20 to 35 percent of  
12 the IBS-C study population, of which the majority  
13 of patients met one of the severe domains.

14 We had focused on one statistical method in  
15 the results presented in support that the overall  
16 trend is similar in all methods evaluated,  
17 demonstrating superiority of Zelnorm treatment  
18 effect over placebo in severely symptomatic  
19 patients.

20 The next slides will walk you through  
21 analyses which support efficacy and safety in the  
22 different populations and how we support the

1 current proposed reintroduction population of  
2 females less than 65 without a history of ischemic  
3 cardiovascular disease.

4 We sought to ensure we did not lose efficacy  
5 when restricting our proposed population for  
6 reintroduction. This included a post hoc  
7 assessment of the effectiveness of Zelnorm  
8 evaluated using our endpoint definitions based on  
9 the 2012 FDA guidance and the general safety  
10 profile as compared to the original label  
11 population.

12 The top plot on this slide is what you've  
13 seen previously, demonstrating efficacy in the  
14 female population using a variation on the 2012  
15 trial guidance endpoint. When compared to this  
16 plot, the therapeutic gain is similar in magnitude  
17 and positive for the proposed population for  
18 reintroduction in the middle and in females who are  
19 severely symptomatic on the bottom. In other  
20 words, we do not lose meaningful efficacy by  
21 focusing on any one of these populations.

22 In the next slide, the overall safety

1 profile of Zelnorm was also evaluated in these  
2 subpopulations. The goal of this assessment was to  
3 understand whether the overall safety profile  
4 remains generally comparable to that established at  
5 the time of drug approval for IBS-C.

6 In the pre-approval studies, study 301, 307,  
7 351, and 358, the type and incidence of adverse  
8 events occurring in at least 1 percent of patients  
9 and more frequently on Zelnorm than placebo within  
10 the gastrointestinal, nervous system, cardiac,  
11 vascular, and psychiatric disorder system organ  
12 classes are presented here. Notably,  
13 cardiovascular and psychiatric-preferred terms do  
14 not reach this threshold.

15 In the original approved population,  
16 headache, abdominal pain, diarrhea, nausea, and  
17 flatulence were the most frequent adverse events  
18 seen in the Zelnorm treatment group. Not shown  
19 here, the frequency of adverse events in the  
20 Zelnorm treatment group were generally comparable  
21 across the IBS-C subpopulations, including those at  
22 low cardiovascular risk and those who are severely

1 symptomatic.

2 Placebo remains consistent across groups  
3 with no change to the original approved safety  
4 profile of Zelnorm. Additionally not shown on this  
5 slide, presented as part of the original approval  
6 for females with IBS-C was a low and similar  
7 incidence of serious adverse events,  
8 discontinuations, discontinuations due to adverse  
9 events, and discontinuations due to lack of  
10 efficacy for Zelnorm-treated patients compared to  
11 placebo. These low rates were similar in all  
12 subpopulations evaluated.

13 Since you will be asked to discuss  
14 psychiatric adverse events of completed suicide and  
15 suicidal ideation behavior when considering  
16 reintroduction of Zelnorm to the U.S. market today,  
17 I'll review the history of these evaluations for  
18 your consideration.

19 The IBS population is known to have a high  
20 background rate of depression and psychiatric  
21 comorbidity. As part of labeling initiatives by  
22 the FDA to standardized suicide ideation and

1 behavior language across drug classes in 2004, the  
2 FDA requested the previous sponsor evaluate the  
3 number of psychiatric adverse events in the  
4 clinical trial database.

5 The results of these analyses indicated a  
6 low incidence of suicide and suicide ideation  
7 events with a small numerical imbalance in  
8 Zelnorm-treated subjects compared to placebo.

9 All patients had a previous history of  
10 psychiatric disorders. Additional work was  
11 performed to further evaluate this imbalance. An  
12 observational study was conducted in over 50,000  
13 Zelnorm initiators and non-initiators. The hazards  
14 ratio for self-injury indicates no difference  
15 between groups. Only 1 completed suicide was  
16 observed, 1 in each cohort.

17 In postmarketing data assessments, no  
18 remarkable signals were seen for psychiatric or  
19 misused terms. Additionally, nonclinical studies  
20 support no mechanistic link with tegaserod, having  
21 minimal penetration across the blood-brain barrier.

22 Although there is a high baseline frequency

1 of psychiatric disorders among IBS patients, this  
2 does not explain the imbalance in suicide ideation  
3 and behavior events seen in the placebo-controlled  
4 trials.

5 Therefore, the FDA recommended the previous  
6 sponsor update the label in 2007 to include  
7 language describing this potential risk in the  
8 precautions section. This agreed-upon labeling was  
9 not incorporated at the time because the drug was  
10 removed from the market. This language is  
11 currently proposed for inclusion in the sponsor's  
12 labeling as a warning and precaution.

13 Overall, Zelnorm has been conclusively shown  
14 to offer a variety of benefits in the treatment of  
15 IBS-C with meaningful improvements in abdominal  
16 pain/discomfort, stool frequency, bloating, and  
17 overall symptom relief. Efficacy by current  
18 standards remains unchanged, and efficacy in  
19 subpopulations are consistent with the original  
20 approval. Using the current guidance definition,  
21 efficacy is supported in the proposed population.

22 Overall, a favorable safety profile was seen

1 in the original approved and also subpopulations  
2 evaluated with low incidence rates of adverse  
3 events, serious adverse events, and  
4 discontinuations among Zelnorm-treated patients and  
5 similar to those seen on placebo.

6 As discussed, an imbalance in suicide  
7 ideation and behavior events were observed in the  
8 placebo-controlled studies, and the sponsors  
9 committed to updating the label appropriately,  
10 given the nature of this concern and previous  
11 agreements made with the FDA.

12 I would now like to introduce Dr. Colin  
13 Howden, who will provide his clinical perspective  
14 on what the results mean to his patients.

15 **Applicant Presentation - Colin Howden**

16 DR. HOWDEN: Thank you, Dr. Gerlach.

17 Good morning. I am Dr. Colin Howden. I'm a  
18 professor of medicine and chief of the Division of  
19 Gastroenterology at the University of Tennessee  
20 Health Science Center in Memphis, Tennessee. I'm a  
21 paid consultant for the sponsor, US WorldMeds. I  
22 have no additional financial interest in the

1 outcome of today's proceedings.

2 I'd like to review for you the impact that  
3 this condition, IBS-C or irritable bowel syndrome  
4 with constipation, can have on patients' health and  
5 general well-being. I'd also like to highlight my  
6 perspective on some of the unmet medical needs in  
7 this condition in the treatment of this disorder  
8 and also look at the overall benefit-risk  
9 assessment for the anticipated treatment population  
10 and to remind you that population would comprise  
11 women with IBS-C who are under the age of 65 and do  
12 not have a history of ischemic cardiovascular  
13 events.

14 It's important to recognize that IBS is an  
15 extremely prevalent disorder. It is among the most  
16 frequent gastrointestinal disorders seen by primary  
17 care physicians, and it's also one of the most  
18 common disorders that gastroenterologists encounter  
19 in their outpatient practice.

20 IBS is not a life-threatening disorder, but  
21 it is unpleasant, and it can certainly be chronic.  
22 Affected patients have abdominal pain and they have



1 some disturbance in bowel habit. IBS-C, the  
2 condition under consideration today, is associated  
3 with abdominal pain and with predominant  
4 constipation.

5 The diagnosis of irritable bowel syndrome  
6 was once considered to be a diagnosis of exclusion,  
7 but we have moved on from that. And nowadays, the  
8 diagnosis usually can be made in the clinic based  
9 on a careful clinical history and physical  
10 examination.

11 So a positive diagnosis can often be made  
12 without recourse to much in the way of further  
13 diagnostic testing and by the application of  
14 established diagnostic criteria, the most important  
15 of which are the Rome criteria.

16 Now, in order to exclude patients with more  
17 transient upset in bowel habit, the Rome criteria  
18 require that patients with IBS-C have experienced  
19 symptoms for a minimum of 3 months.

20 As a clinician who sees many patients with  
21 this condition, I would point out that in my  
22 practice, many of the patients have had symptoms

1 for a considerably longer period than that.  
2 Sometimes, I'm the second, the third, or even the  
3 fourth gastroenterologist that a patient with IBS-C  
4 has seen.

5 By the time a patient with IBS-C sees a  
6 gastroenterologist, she's likely to have tried a  
7 variety of over-the-counter medicines, often with  
8 only very limited success. Laxatives, for example,  
9 may be helpful in alleviating constipation in IBS-C  
10 patients, but they do not address other symptoms,  
11 notably abdominal pain.

12 The symptoms of IBS-C can fluctuate in  
13 severity for months or years. They may also  
14 fluctuate in priority. That is, at sometime, a  
15 patient with IBS-C may rate pain as their most  
16 troublesome symptom; at other times, it may be  
17 constipation. And this clearly makes evaluation of  
18 the condition difficult for clinicians. The impact  
19 of these symptoms on IBS-C patients must not be  
20 underestimated.

21 It's a chronic disorder. It can  
22 substantially affect patients' quality of life.

1 It's a frequent explanation for loss of time from  
2 work or from educational activities, and  
3 furthermore, patients with IBS-C are frequent  
4 consumers of healthcare resources.

5 They make more frequent doctor visits and  
6 more frequent visits to the emergency room than  
7 age- and sex-matched controls who do not have IBS.  
8 They're more likely to undergo diagnostic  
9 procedures, and unfortunately, they're also more  
10 likely to undergo unnecessary surgical procedures,  
11 including such things as cholecystectomy and  
12 various gynecological surgeries.

13 As a clinician, I'd have to know that  
14 patients frequently express dissatisfaction with  
15 some of their physician visits, and we often get  
16 the perception that they feel that their symptoms  
17 have not been adequately addressed or taken  
18 seriously.

19 Now, despite the availability of three  
20 prescription medicines for IBS-C, there continues  
21 to be some degree of unmet medical need. And  
22 although the agents listed on this slide are highly

1 effective for many patients with IBS-C, a  
2 proportion of patients continue to express  
3 dissatisfaction with treatment, and that may be due  
4 either to an incomplete therapeutic response or to  
5 some possible adverse effect.

6 We still have a very imperfect and  
7 incomplete understanding of the underlying  
8 pathophysiology in IBS. That means that when we  
9 select a treatment option for a patient, the  
10 decision is largely empiric. It is generally not  
11 possible to determine in advance for any one  
12 particular patient which medicine would be most  
13 likely to provide benefit.

14 Therefore, as a practicing clinician, I  
15 strongly feel that it would be advantageous for  
16 prescribers and for patients to have a variety of  
17 treatment options available and options that work  
18 through different mechanisms of action.

19 As Dr. Gerlach reviewed for you, tegaserod  
20 has pro motility effects within and along the GI  
21 tract. Tegaserod also increases intestinal  
22 secretion, but it does so through a different

1 mechanism of action to the existing agents.

2 It also reduces pain signaling along the GI  
3 tract, between the GI tract and the central nervous  
4 system. And taken together, these are of course  
5 highly desirable properties for an agent used in  
6 the treatment of IBS-C.

7 As was pointed out this morning, this was  
8 the first drug ever to be approved for IBS-C, and  
9 prior to its withdrawal, I made frequent use of  
10 this agent in my clinical practice and had a high  
11 degree of success with it.

12 Therefore, given its alternative mechanism  
13 of action compared to existing agents and its  
14 demonstrated efficacy in the high-quality placebo-  
15 controlled trials that led to its initial approval,  
16 it has the potential, I feel, to address at least  
17 some of the unmet medical need in IBS-C.

18 As Dr. Gerlach showed, Zelnorm has been  
19 shown to be superior to placebo in addressing many  
20 of the individual symptoms of IBS-C. Those include  
21 abdominal pain, constipation, and bloating, and  
22 Zelnorm also improves patients' overall well-being.

1 Furthermore, it's been shown to be effective in  
2 patients with the most severe symptoms of IBS-C, as  
3 Dr. Gerlach discussed.

4 The rigorous reanalyses of the initial  
5 clinical trial data have confirmed the efficacy of  
6 this agent when more recently recommended treatment  
7 endpoints have been applied.

8 It's also been shown to be effective in a  
9 treatment discontinuation and reintroduction study.  
10 Patients in that study who initially responded to  
11 tegaserod were at least as likely to have the same  
12 level of response when the drug was reintroduced  
13 after having been offered for a few weeks.

14 Now, I think this is a potentially important  
15 observation, given that the symptoms of IBS-C  
16 typically fluctuate in severity and some patients  
17 may elect to cycle on and off treatment, depending  
18 upon their symptoms.

19 The sponsor proposes the reintroduction of  
20 Zelnorm for a specific and a relatively limited  
21 patient population, namely women with IBS-C under  
22 the age of 65 who do not have a history of ischemic

1 cardiovascular events. Reanalysis of the clinical  
2 trial data confined to this patient population  
3 demonstrates at least the same degree of efficacy  
4 as was seen in the more general IBS-C population.

5 Dr. Sager discussed that there was a small  
6 numerical imbalance in cardiovascular events noted.  
7 Among the small number of patients with confirmed  
8 MACE events, it's important to note that all have  
9 at least one potentially confounding risk factor,  
10 and most of them had a history of prior ischemic  
11 cardiovascular events.

12 Subsequent epidemiological studies in  
13 different patient populations have shown no  
14 evidence for an association between Zelnorm  
15 treatment and cardiovascular events.

16 As Dr. Gerlach showed, Zelnorm has been  
17 associated with a low incidence of adverse events  
18 in clinical trials and in postmarketing studies.  
19 The general safety profile of Zelnorm is not in  
20 question, I feel. In clinical trials, diarrhea was  
21 the side effect that was most commonly reported and  
22 had the greatest difference in incidence compared

1 to placebo. Obviously, for a drug with  
2 gastrointestinal prokinetic activity, that would  
3 not be unexpected.

4           Zelnorm offers clear, meaningful, and  
5 consistent benefits to IBS-C patients irrespective  
6 of the degree of symptom severity. And while there  
7 may be a small potential risk of cardiovascular  
8 events, although recent epidemiological studies do  
9 not support that, the level of risk, if any, is  
10 probably appropriate in the context of the unmet  
11 medical need in IBS-C.

12           Making Zelnorm available for the proposed  
13 reintroduction population, women aged under 65 with  
14 IBS-C and no history of ischemic cardiovascular  
15 events would further mitigate the risk and would  
16 help to optimize the net clinical benefit. I feel  
17 that further restrictions on the eligibility for  
18 Zelnorm would deprive many IBS-C patients from  
19 receiving a potentially effective therapy.

20           I'd like to thank you for your attention,  
21 and I would now like to reintroduce Kristen Gullo,  
22 who will conclude the sponsor's presentation.



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**Applicant Presentation - Kristen Gullo**

MS. GULLO: Thank you, Dr. Howden.

As you just heard from Dr. Howden, there are clear benefits and low risks across all evaluated populations for the proposed reintroduction. Here are the possible populations the FDA has asked you to consider in terms of overall benefit-risk. I will discuss how our evaluation of these populations has led us to our proposal.

Our evaluations started with the overall female IBS-C patient population. Even though we conclude there is favorable benefit-risk across female IBS-C patients and this would permit the greatest access to an effective therapy, out of an abundance of caution, we feel it is prudent to limit the population in some way.

We have discussed two approaches which the agency has also asked you to consider separately and in combination, first by limiting its proposed use in patients with severe symptoms who may be more willing to accept risk uncertainty for the potential to benefit, and second, by limiting to

1 those at a lower general risk of having a  
2 cardiovascular event independent of Zelnorm  
3 treatment.

4           Given the strength of the evidence  
5 supporting a low drug risk potential, if any at  
6 all, we felt it was appropriate to look at these  
7 approaches independently. In other words, the very  
8 small event rates and subsequent uncertainty about  
9 Zelnorm's contribution to them could support  
10 evaluating a more risk-tolerant population or a  
11 lower-risk population.

12           Applying both in combination was, in our  
13 assessment, so conservative that it could be to the  
14 detriment of our goal to address unmet needs in  
15 IBS-C.

16           To achieve this goal, we believe it is  
17 important to strike a balance between benefit and  
18 risk. On the benefit side of the equation,  
19 efficacy remains apparent in all considered  
20 populations, including those with severe symptoms.

21           However, when we considered a reintroduction  
22 for severely symptomatic patients only, we were

1 concerned that any single definition of severity  
2 may be limiting for translation in clinical  
3 practice. Characterization of symptom severity and  
4 frequency alone may not always be an appropriate  
5 marker for how the condition affects any individual  
6 patient.

7           You heard from Dr. Howden the improvement in  
8 individual symptoms and overall relief reported in  
9 Zelnorm-treated patients is meaningful across the  
10 symptom severity spectrum. And as he discussed, it  
11 is important to have a variety of treatment tools  
12 for a condition that is consistent in its potential  
13 to impact the overall well-being of patients,  
14 although symptom experience can vary widely among  
15 individuals.

16           So this led us to conclude that while both  
17 approaches to limiting the population may be  
18 reasonable, restrictions on the basis of  
19 cardiovascular risk are more straightforward for  
20 addressing any residual concern.

21           We have defined a low cardiovascular risk  
22 population using criteria for patient selection

1 that could also be operationalized in practice.  
2 From our review of the data, this is also  
3 appropriate to address residual cardiovascular risk  
4 uncertainty, yet preserves the role of clinical  
5 judgment to make individual benefit-risk decisions.

6           Importantly, we feel that our proposal  
7 achieves a favorable benefit-risk for the product's  
8 proposed reintroduction. It achieves our goal to  
9 introduce prudent limitations for its use without  
10 imposing criteria that could deny access to too  
11 many patients in need of an effective treatment  
12 option for IBS-C.

13           We hope that sharing our perspective on the  
14 populations you have been asked to consider is  
15 informative to explaining our proposal for  
16 reintroduction of Zelnorm in females at low  
17 cardiovascular risk. Together with Sloan, US  
18 WorldMeds is committed to an appropriate  
19 reintroduction and diligent oversight of the  
20 product if commercialization of Zelnorm is to  
21 resume.

22           Working together with the FDA, we look

1 forward to finalizing proposed updates to the label  
2 and to revise the indication statement, add any  
3 appropriate contraindications, clearly communicate  
4 important safety information through expanded  
5 warnings and precautions, and apply all current  
6 guidance, including suicidality, pregnancy, and  
7 lactation labeling rules.

8 We have also proposed a medication guide to  
9 support patient decision making. We plan to apply  
10 enhanced pharmacovigilance practices for the  
11 reporting of all events related to cardiovascular  
12 and suicidality. We also plan to focus our initial  
13 promotional efforts on those physicians who are  
14 currently diagnosing and prescribing treatments for  
15 IBS-C in support of proper utilization and patient  
16 selection through prescriber communications and  
17 patient and physician education.

18 With continued collaboration from the  
19 agency, we also look forward to continued  
20 investigation of Zelnorm to explore its utility in  
21 other areas of significant unmet need. We  
22 appreciate that this is a complex matter and that

1       there may not be a single best approach to striking  
2       an appropriate balance between benefit-risk and  
3       patient needs. We look forward to your input today  
4       to evaluate our proposed reintroduction. Thank  
5       you.

6                   **Clarifying Questions to the Presenters**

7               DR. RAUFMAN: Thank you. We now have about  
8       30 minutes for clarifying questions for the  
9       presenters. Please remember to state your name for  
10      the record before you speak. If you can, please  
11      direct questions to a specific presenter.

12              Ms. Robotti?

13              MS. ROBOTTI: Hi. Suzanne Robotti. And to  
14      Dr. Gullo, I think, I think I have three questions  
15      at the moment, and I'll give you all three. I'm  
16      interested in finding out what happens if a patient  
17      uses too much of the product. Obviously, they're  
18      uncomfortable and they may double their dosage.

19              Is it possible -- the prescription that  
20      you're requesting is 6 milligrams BID, 2 times a  
21      day. Would it be more appropriate to say as needed  
22      because it works quickly, and it may not be needed

1 every single day? From what I've read online,  
2 people seem to use it as needed, but others will be  
3 obedient. If it says use it 2 times a day, they  
4 will, whether they need it or not.

5 Thirdly, probably the most important, given  
6 the population that you're looking at, what is the  
7 effect on pregnant women and the fetus?

8 MS. GULLO: I'd like to ask Dr. Gerlach to  
9 join me so that she can explain what data are  
10 available at supratherapeutic doses. I think that  
11 will help answer your first question, and then  
12 we'll take the next two.

13 DR. GERLACH: Hi. Rachael Gerlach. To  
14 address your first question, there is a small  
15 number of studies that did assess a 12-milligram  
16 per-day dose, which is twice the dose of the  
17 reintroduction, as well as those with even greater  
18 therapeutic doses. Very similar incidence rates of  
19 adverse events were seen. Again, these were low  
20 numbers of those treated at those doses, nothing of  
21 concern in the data that we've seen. And I can  
22 bring up a clinical perspective if you feel that

1 that's necessary.

2 MS. ROBOTTI: No.

3 DR. GERLACH: To address, I believe, your  
4 third question about pregnancy and lactation,  
5 tegaserod has placental concentrations. This has  
6 not been measured in any human animal models.

7 We've committed to updating our label to discourage  
8 use in pregnant and those who are lactating without  
9 further studies being conducted in that population.

10 MS. ROBOTTI: Do you have any plans to study  
11 pregnant, lactating community?

12 MS. GULLO: No. That hasn't been discussed  
13 with the agency at this time, but we are committed  
14 to following this in a postmarketing environment,  
15 of course, and those kinds of events would be taken  
16 very seriously. But we would feel that, consistent  
17 with the pregnancy and lactation labeling rule, the  
18 information that we would provide in the label  
19 would be sufficient to inform discussions between  
20 patients and their providers.

21 I'd also like to ask Dr. Howden to try to  
22 address your question about whether the treatment



1       should be taken as needed as opposed to the way it  
2       was studied, which was twice a day for a daily  
3       basis, on a daily basis.

4               DR. HOWDEN: Thank you. You raise some  
5       interesting points, so thank you for your  
6       questions. The dose that was studied in the  
7       controlled clinical trials and were shown to be  
8       consistently efficacious was the 6-milligram BID  
9       dose, and that is the dose that was initially  
10      approved for the indication of IBS-C.

11             So if the product were to be relaunched, I  
12      would assume that that would be the recommended  
13      dosing schedule. However, in the real-world  
14      setting, I acknowledge that some patients, because  
15      of the fluctuation and the severity of their  
16      symptoms, may cycle on and off treatment. That's  
17      just a fact of life, the way that we see patients  
18      use their medicines.

19             With that in mind, I think it's important to  
20      recall that the discontinuation reintroduction  
21      study, that was conducted by Professor Jan Tack in  
22      Belgium, actually showed, as I pointed out, that

1 when the treatment was reintroduced or restarted,  
2 those women who had initially responded to it, had  
3 at least the same level of response to the drug.

4 As regarding patients taking too much,  
5 taking more than the 6-milligram BID dose, I have  
6 no personal experience of that. Prior to the  
7 drug's withdrawal, as I mentioned, I had frequent  
8 use of this in my practice, and I didn't encounter  
9 any incidences of patients escalating the dose or  
10 taking unnecessary doses. But I'm sure the sponsor  
11 has further information about any incidences of  
12 overdose, but I don't anticipate any specific  
13 problem there. Thank you.

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

15 DR. SOLGA: Hi. This is Steve Solga. I  
16 have three questions, but I'm sure the committee  
17 has many, many questions, so I invited the chair to  
18 cut me off after one or two if that's enough.

19 This question is for Dr. Gerlach. The data  
20 for efficacy did not include B307. As I'm sure you  
21 know, the FDA briefing document did include a lot  
22 of information about the study included it in its

1 analyses. B307 was a little bit less white in the  
2 population, and the efficacy was somewhat  
3 diminished compared to some of the other studies.

4 What led to the decision not to include that  
5 in the presentation this morning? And is B301,  
6 which was 97 percent white, truly extrapolatable to  
7 the U.S. population?

8 DR. GERLACH: Yes. To clarify, 307 used a  
9 dose titration design. This evaluated 2-milligram  
10 BID dose of tegaserod and then a regimen from  
11 2-milligram up to 6-milligram dose, a direct  
12 comparison to the other studies which assessed a  
13 fixed dose across a 12-week treatment duration.

14 The rationale for presenting only that data  
15 is a direct comparison. These are post hoc  
16 analyses to demonstrate the benefit, although for  
17 study 307, there is benefit seen in that study,  
18 although not statistically significant.

19 DR. SOLGA: If I may, this will be for  
20 Dr. Sager. In CC-34, when discussing possible  
21 mechanisms of possible harm, he expressed  
22 confidence that this could not be mediated through

1 a vasomotor mechanism.

2 I learned from Dr. Gerlach that drug has  
3 multiple effects on various kinds of neurons in  
4 smooth muscle. And I understand from the presented  
5 data that if there is a cardiovascular risk, it's  
6 likely small, maybe 3 to 6 out of 1,000, and not  
7 well understood.

8 What leads him, can you tell me as a non-  
9 cardiologist, please, to this confidence statement  
10 that it's unlikely to be from a vasomotal  
11 mechanism, given these activities? I don't  
12 understand how those studies were done, how many  
13 subjects were included, and the degree of  
14 confidence he has in that statement.

15 MS. GULLO: Sure. Dr. Sager?

16 DR. SAGER: So there were a number of  
17 different preparations that included  
18 suprathreshold exposures of tegaserod, and they  
19 basically were all negative. And in addition, the  
20 serotonergic receptors associated with  
21 vasoconstriction, tegaserod actually acts as an  
22 antagonist. And in two of those experiments where

1 there was shown to be no vasoconstriction, when one  
2 added in initially -- the de novo state added in  
3 either serotonin or serotonin analog, both of which  
4 are known to cause vasoconstriction, tegaserod  
5 actually blocked their effects to cause  
6 vasoconstriction.

7 So I think there's really strong data that  
8 there's not associated vasoconstriction.

9 DR. SOLGA: If I may -- thank you -- in 2007  
10 when the drug was withdrawn, there was first an  
11 emergency IND mechanism, and then a treatment IND  
12 mechanism, and then an expanded access mechanism.

13 In my practice, I did not have a lot of  
14 patients on Zelnorm at the time. Most greeted the  
15 withdrawal with a shrug, but one patient was deeply  
16 disappointed. Obviously, any of these mechanisms  
17 require a certain amount of motivation by the  
18 prescriber and the patient.

19 Can you speak to the level of interest post-  
20 withdrawal that you received in obtaining the drug  
21 by any of those mechanisms?

22 MS. GULLO: Yes. You are correct that two

1 programs started initially, both a treatment IND  
2 and an emergency IND is what it was called at the  
3 time. The treatment IND had very specific criteria  
4 to focus on patients at a very low cardiovascular  
5 risk level, and the emergency IND required them to  
6 meet very stringent criteria in terms of the nature  
7 of their condition being even considered life  
8 threatening or very serious.

9 In the environment at the time, of course,  
10 there was a lot of scrutiny on a potential  
11 cardiovascular risk signal, yet there was quite a  
12 lot of interest in the program. The treatment IND  
13 enrolled 182 patients across approximately one  
14 year, and the emergency IND later converted to a  
15 single patient use IND, but it's not broadly known  
16 that that really exists. And across both programs  
17 in total, we have around 800 patients that have  
18 accessed the program, and we still continue to  
19 receive requests today.

20 DR. RAUFMAN: Dr. Rosen?

21 DR. ROSEN: On behalf of the motility people  
22 in the community, we're very grateful that the FDA

1 is reconsidering this medication. I think all of  
2 us remember the week that this was withdrawn from  
3 the market and the barrage of calls that we got, so  
4 we're grateful for that.

5 That having been said, though, these  
6 patients are often quite sick and complicated, and  
7 they often have polypharmacy as part of their  
8 profile, which includes tricyclic antidepressants,  
9 SSRIs, other neuromodulators.

10 So when we think about cardiovascular risk  
11 and also suicidality risk, we think a lot about the  
12 interactions of these drugs. So can you guys  
13 comment on when you look at the patients who had  
14 suicidal ideation or the patients who had  
15 cardiovascular risk, what were the other  
16 medications that they were taking, including other  
17 neuromodulators that might have infected QTc  
18 intervals?

19 Then I guess along the same lines, comorbid  
20 with all of these functional disorders are things  
21 where you have vascular instability like POTS,  
22 where the adults and kids get tachycardia, and

1 hypotension, and things like that.

2 So when we think about cardiovascular risks  
3 in patients who have neurodysregulation, can you  
4 talk a little bit about the patients who may have  
5 hypotension as part of their risk profile and how  
6 you see their cardiovascular risk for that?

7 MS. GULLO: I'd like to ask Drs. Howden and  
8 Sager to both give their perspective from a  
9 practicing gastroenterology perspective and what  
10 kinds of medications would potentially be used by  
11 his patients, and also Dr. Sager then to expand on  
12 the cardiovascular considerations of concomitant  
13 therapy

14 DR. HOWDEN: Thank you for the question.  
15 Patients with IBS, as you say, may have comorbid  
16 conditions and they may be taking other medicines.  
17 As a clinician yourself, I'm sure you see that, as  
18 do I.

19 I'm not aware of any specific drug-drug  
20 interaction studies with tegaserod that are of  
21 clinical significance, but as a clinician, of  
22 course, we would always go over what medications



1 the patient was on.

2 I would like to think that a patient with  
3 IBS-C would not be receiving a tricyclic  
4 antidepressant, since that may be exacerbating  
5 their constipation. The sponsor may know of any  
6 specific pharmacokinetic or drug-drug interaction  
7 studies. But aside from taking a careful clinical  
8 history to exclude patients with known  
9 cardiovascular disease, I don't think that any  
10 other specific recommendations are required from a  
11 clinician's perspective.

12 MS. GULLO: As Dr. Sager makes his way up,  
13 we can address this from a clinical pharmacology  
14 perspective, so I'll ask Dr. Longstreth to join us,  
15 and we can review what data exists to inform what  
16 potential interactions could occur.

17 DR. SAGER: Philip Sager, Stanford  
18 University. I'd say first that the drug does not  
19 have QT effects and doesn't have hypotension  
20 effects. So that's all very positive, that you  
21 wouldn't expect to have an interaction with another  
22 drug that does those things.

1           Then in the cases of patients who develop  
2 serious cardiovascular events, I don't have, right  
3 now, a list of their medications. But in having  
4 gone through them, I don't recall a significant  
5 number who are on tricyclic or other CNS drugs.

6           Again, the nature of the events that were  
7 seen; one event was a potential arrhythmic event,  
8 the patient who had cardiovascular death, but the  
9 other people developed things like chest pain, so  
10 an arrhythmic type of mechanism didn't seem at all  
11 to be the case.

12           Again, the effects on the QTc interval, as  
13 well as all the preclinical electrophysiology is  
14 quite negative. So I do not see this as a  
15 cardiovascular concern in terms of drug  
16 interactions.

17           MS. GULLO: Dr. Longstreth can review what  
18 we know from a clinical pharmacology perspective.

19           DR. LONGSTRETH: My name is James  
20 Longstreth. I'm a consultant to US WorldMeds and  
21 have no financial interest in the outcome of this  
22 meeting. The original pharmacokinetic program that

1 was run by Novartis did include a number of  
2 drug-drug interaction studies.

3 Tegaserod is a little bit unusual in that it  
4 has no metabolism pathways that involve the CYP  
5 enzymes. Its primary metabolite is due to  
6 hydrolysis in the stomach, due to acid conditions,  
7 and that metabolite also is not active and does not  
8 bind to any of the 5-HT4 receptors or a number of  
9 the others.

10 So the typical route of drug-drug  
11 interactions via metabolism are not seen. Novartis  
12 did a further examination for drug-drug  
13 interactions due to changes in gut motility that  
14 might affect the time and amount of drug that might  
15 be absorbed by others and did not find interactions  
16 with things such as oral contraceptives with  
17 digoxin, with dextromethorphan, and some others.

18 Then further, to examine the question that  
19 you were raising about interactions in the CNS, the  
20 original program did look for drug uptake into the  
21 CNS and found it to be minimal. And the drug is a  
22 substrate for PGP and for BCRP, which will tend to

1 keep it out of the CNS anyway in addition to that.

2 MS. GULLO: Thank you, Dr. Longstreth.

3 I hope that helps to answer your question.

4 I think, overall, from a clinical pharmacology  
5 perspective and also the evidence that we've  
6 supported around understanding the cardiovascular  
7 safety potential issues with Zelnorm being overall  
8 quite strong, there is not a lot of concern around  
9 concomitant use.

10 The final point that I think I can add to  
11 the discussion is, in the Loughlin study that we  
12 presented earlier, across over 100,000 patients  
13 that did represent real-world use and accounted for  
14 a variety of concomitant medications.

15 So the results that we presented on both  
16 cardiovascular events and on suicidal events  
17 represented no change or no difference between  
18 tegaserod-treated patients, and matched cohort  
19 patients would have been representative of a broad  
20 use of additional medications.

21 DR. RAUFMAN: Dr. Thadani?

22 DR. THADANI: Thanks, Mr. Chairman.

1 Question addressed to Dr. Sager and Dr. Gerlach.

2 Obviously, you're accepting that there's a  
3 cardiovascular noise, otherwise, you would not be  
4 restricting the population to women less than 65.  
5 Given that scenario, some of them are going to have  
6 subclinical disease.

7 To give you an example, a lot of women below  
8 the age of 65 are hospitalized with chest pain,  
9 so-called acute coronary syndrome, and yet have  
10 normal coronary arteries and they have  
11 microvascular dysfunction.

12 How certain could one be that the drug in  
13 question is not affecting the small vessels that  
14 could be causing problems? And those women are  
15 also at a risk, and also, during pregnancy, young  
16 women are having coronary artery dissection as  
17 etiology for MI.

18 So I want to be reassured that you are  
19 saying that no vasomotor action is possible, that  
20 it could affect the small vessels. I don't think  
21 that was tested. All you did were coronary artery  
22 preparations from animal and human.

1           So Dr. Sager, can you allude to that so I  
2 might feel comfortable that there are millions of  
3 people who might be exposed to this? How are you  
4 going to define patients that have chest pain, but  
5 have normal coronary arteries and might have a  
6 small bump in, say, troponin assays?

7           DR. SAGER: Philip Sager, Stanford  
8 University. Well first, just to put it in  
9 perspective, the selection of the patient  
10 population for reintroduction was the sponsor's  
11 decision. My viewpoint is that in looking at the  
12 totality of the data, the risk is really very  
13 small. At most, it's very small, if the risk truly  
14 exists.

15           I think the approach that's being taken is a  
16 conservative one. There have been a number of  
17 studies that have looked at both serotonergic  
18 receptors that could play a role in  
19 vasoconstriction. And I fully appreciate your  
20 point that women can have both coronary to artery  
21 dissections but also coronary vasospasm, but those  
22 studies and receptors all showed antagonistic, in

1 fact protective effects of tegaserod in those  
2 animal studies, as well as human.

3 In addition, I think a physician will have  
4 to weigh the individual patient, but a woman who  
5 has chest pain and some bump in cardiac enzymes, I  
6 would kind of myself fit into the cardiac ischemic  
7 disease population. And based upon the proposal,  
8 that person wouldn't be a candidate. But I do feel  
9 this has been looked at really quite carefully in  
10 terms of not having vasomotor activity issues.

11 DR. THADANI: The reason I ask that is we  
12 know that if we give acetylcholine to normal  
13 coronary arteries, they dilate; diseased vessels  
14 constrict. I've not seen any data diseased  
15 vessels. You show coronaries react. There's no  
16 reaction.

17 So suppose you took a patient with a CAD,  
18 coronary artery disease, atherosclerosis, would  
19 there be no action of this agent at all? Are you  
20 pretty sure?

21 DR. SAGER: That type of experiment hasn't  
22 been done, but the fact that it doesn't affect any

1 of the receptors that play a role in  
2 vasoconstriction kind of intellectually seems to  
3 make that highly unlikely.

4 DR. THADANI: Yes. The reason I am saying  
5 that, the metabolite and some variation in platelet  
6 reactivity, some studies showing, some not, one  
7 cannot be absolutely sure.

8 DR. SAGER: I guess the only other thing  
9 we'd say with platelet reactivity is that we have  
10 three subsequent studies, all well done, that are  
11 negative.

12 DR. THADANI: I understand.

13 DR. SAGER: Let me turn it back to you.

14 MS. GULLO: We are actually joined today by  
15 Dr. Paul Gurbel, who brings specific expertise on  
16 platelet function, and I'd like to ask him to give  
17 his thoughts.

18 DR. GURBEL: Thank you. I'm Paul Gurbel.  
19 I'm director of the cardiovascular research program  
20 at Inova Heart and Vascular Institute and a  
21 professor of medicine at Duke and at Johns Hopkins.  
22 I'm a paid consultant for the sponsor, but the



1 outcome of this meeting, I have no financial  
2 interest in.

3 Sir, you asked some very important  
4 questions, and my look at the totality of the data,  
5 the evidence in preclinical studies on receptor  
6 binding, potential receptors that could be  
7 affected, affect vasoreactivity, there's really no  
8 plausible explanation for an unexpected off-target  
9 effect of tegaserod.

10 The binding to the 5-HT<sub>2A</sub> receptor has never  
11 been shown in platelets. It's only been seen in  
12 transfected cells and at almost a log higher  
13 binding than seen at C<sub>max</sub> for the platelet.

14 As far as vascular effects, the binding to  
15 potential receptors, 5-HT receptors that could be  
16 associated with vasoconstriction, when bound to  
17 serotonin, in fact tegaserod is inhibitory. So I  
18 think there's no biologic plausibility for concern  
19 of induction by vasoconstriction by tegaserod.

20 DR. RAUFMAN: Thank you. Let's move on. If  
21 we could keep the questions and the answers a  
22 little briefer and more focused.

1 Dr. Teerlink?

2 DR. TEERLINK: This is John Teerlink from  
3 USCF, and I will count on our esteemed chair to  
4 rein me in when he feels it's appropriate. So I  
5 have four questions, and I hope we can stipulate  
6 that these patients experience these symptoms and  
7 this problem over the course of decades. And I  
8 think that's something that they experience.

9 So I would like to see slide CC-23 and am  
10 interested in hearing, in the basis of disease  
11 state that progresses through decades, how do you  
12 define long-term studies?

13 MS. GULLO: Yes. I'll ask Dr. Gerlach to  
14 explain the duration of the open-label studies that  
15 are included in this database.

16 DR. TEERLINK: Then related to that, we'll  
17 be talking about the safety signal that's here, so  
18 Dr. Sager, my colleague from down south, may be  
19 wanting to also join shortly. Go ahead, quickly.

20 DR. GERLACH: So the long-term studies that  
21 are assessed here; this was the study database that  
22 Dr. Sager had presented in his presentation of

1 database 14, these consisted of 7 open-label  
2 studies across several indications, including  
3 IBS-C, CIC, and dyspepsia. The study duration  
4 ranged anywhere between 6 and 13 months with the  
5 mean duration of exposure being around 227 days.

6 DR. TEERLINK: So it's fairly short. That's  
7 fairly short, long term. And what we see here is a  
8 two- to fourfold increase in cardiovascular  
9 ischemic events compared to the studies that were  
10 shorter.

11 So I'm interested in hearing, given this  
12 two- to fourfold increase in cardiovascular  
13 ischemic events, how is that not suggestive of an  
14 ongoing increase in cardiovascular risk.

15 MS. GULLO: Right. I'll ask Dr. Sager to  
16 give us his perspective on this, but I think it is  
17 important to note here that these are represented  
18 in terms of patients experiencing events, not  
19 necessarily normalized by time, which Dr. Sager can  
20 take us through in terms of incidence rates per  
21 1,000 patient-years, which is how we would try to  
22 get a sense of whether the rates are actually

1 increasing short term to long term.

2 Dr. Sager?

3 DR. SAGER: Philip Sager, Stanford  
4 University. Thank you for that question. Of  
5 course, one of the challenges, just to start off,  
6 is we're only talking about 4 events out of almost  
7 3,300 individuals.

8 DR. TEERLINK: So are you suggesting the  
9 database is too small for us to evaluate this  
10 issue? Or when you're saying that it's so small,  
11 I'm confused.

12 DR. SAGER: I'm just saying that recognizing  
13 that there are only a few events, however, there's  
14 been an analysis done by Duke -- if I could have  
15 slide 3 up -- realizing this is in different  
16 databases, so one needs to keep that in  
17 consideration.

18 But you can see up here on the top, this is  
19 the estimated frequency per 1,000 patient-years of  
20 these events in the long-term database. And they  
21 went ahead and they compared this to what the event  
22 rate was in the placebo database in the

1 double-blind randomized controlled studies at the  
2 bottom, Db15.

3 So the point estimate was 1.95 or 0.90 with  
4 overlapping confidence intervals, but maybe most  
5 importantly, the upper confidence intervals were  
6 similar. So this provides some reassurance.

7 DR. TEERLINK: For twice the duration,  
8 there's twice the risk, so that's a proportional  
9 risk over time, so that's question one. Number 2,  
10 in terms of --

11 DR. SAGER: But can I just add that,  
12 however, the confidence intervals, the upper  
13 confidence interval in particular, is basically the  
14 same, and there's wide overlap.

15 DR. TEERLINK: That's fine, but they're also  
16 narrower, so because you have the greater exposure,  
17 so that's fine. If we look at the point estimates,  
18 it's twice as much, over about twice as much  
19 follow-up. So there's a proportional hazard.

20 In terms of number 2, the second question,  
21 this refers to slide CC-17. You've talked about  
22 the vasoconstrictor evaluations. Were those done

1 in denuded arteries or in purely intact arteries?

2 The second question is, could the sponsor  
3 please provide the frequency distribution of the  
4 systolic blood pressure responses in the  
5 6-milligram BID doses, as well as those patients  
6 who are greater than 12-milligram per day?

7 Because I'm interested in whether there is a  
8 group of patients who actually doesn't respond much  
9 to the blood pressure effect and then others who  
10 have a greater effect that actually results in a  
11 mean that's not that big of a difference. So those  
12 are the two related, and I realize the one is a  
13 data request, so we'll see that later.

14 In terms of the denuded arteries?

15 DR. SAGER: I'm going to actually let  
16 Dr. Bell, who's an expert in this particular area,  
17 kind of delve into this.

18 DR. BELL: Caroline Bell. I'm a paid  
19 consultant in safety pharmacology, nonclinical drug  
20 development. I have no financial interest in the  
21 outcome of this meeting.

22 A number of studies were done in coronary

1 arteries, not just from humans, but also in porcine  
2 and dog studies. And in all of the human studies,  
3 consistently, until we got to very, very high  
4 doses, there were many, many fold multiples that  
5 there was absolutely no effect.

6 DR. TEERLINK: In denuded and  
7 de-endothelialized?

8 DR. BELL: Yes. And studies were done in  
9 tissues that were deliberately denuded. And also,  
10 there was one study that compared diseased coronary  
11 arteries to healthy tissue, and that was determined  
12 by the use of substance P to show whether or not  
13 there was evidence of disease.

14 DR. TEERLINK: Excellent. Thank you. And  
15 then in terms of slide CC-31, so here we see a  
16 four- to fivefold increase in atrial fibrillation  
17 relationship. And the caveat down below is saying,  
18 yeah, but those patients had risk factors.

19 Now, presumably, these are placebo-  
20 controlled randomized trials, so presumably, those  
21 risk factors were equally distributed between the  
22 two groups. So I want to just see -- perhaps I

1       misunderstood what Dr. Sager was suggesting, but I  
2       wouldn't suggest that necessarily Zelnorm or  
3       tegaserod could still be a trigger for this  
4       increased rate of atrial fibrillation.

5               Maybe I misunderstood. I assume he's not  
6       trying to talk away and say there isn't an increase  
7       in atrial fibrillation here, even though it's based  
8       on small numbers.

9               MS. GULLO: I'll ask Dr. Sager to expand on  
10       that, but I do think it's important to put the  
11       database into context as far as its utility and  
12       really understanding causality to Zelnorm.

13              So you're correct. These are absolutely  
14       controlled studies, and we do typically rely on  
15       controlled studies to look for treatment  
16       differences where we can isolate effects to the  
17       investigational treatment. However, in this case,  
18       the controls were specifically built to isolate  
19       treatment effects for efficacy. We were not  
20       stratifying patients on the basis of cardiovascular  
21       risk.

22              We also have unbalanced treatment groups, so



1 for rare events, such as those reported in the less  
2 than 0.1 percent category, we do have to appreciate  
3 that there are 4,000 more patients on Zelnorm where  
4 we could have detected an event.

5 So even if those were balanced  
6 proportionally in terms of risk factors, there  
7 still then would be a higher number,  
8 proportionally -- I'm sorry. Proportionally, they  
9 would be the same, but an absolute number of then  
10 patients in the active group that would have those  
11 same higher risk factors.

12 DR. TEERLINK: I understand the concept of  
13 percentages. Okay.

14 MS. GULLO: Dr. Sager?

15 DR. SAGER: Yes. Philip Sager, Stanford  
16 University. I think to extend what was just said  
17 here, yes, there's an imbalance. Again, it looks  
18 like these are patients who one might expect to  
19 have afib. Could it be possible that Zelnorm is a  
20 precipitant of that? It's not impossible, no.

21 DR. TEERLINK: Presumably those patients in  
22 the placebo group also had prior histories of

1 atrial fibrillation and these other risk factors.

2 DR. SAGER: Some of them presumably did.  
3 However, I think it's important to keep in mind  
4 when we're looking for arrhythmias in a study, we  
5 might use some type of monitoring. This is just  
6 very kind of intermittent and isn't designed  
7 prospectively to assist arrhythmia occurrence. It  
8 has some of those drawbacks, which I'm sure you  
9 very much appreciate, Dr. Teerlink.

10 DR. TEERLINK: Thank you. The final  
11 question is in regards to CC-45. I'm just a  
12 cardiologist, so I don't understand -- in terms of  
13 the responder analysis, these seem to actually be  
14 relative low response rates, to me, in terms of the  
15 low number of patients actually benefitting from  
16 this. I don't have the perspective of that, but we  
17 usually look for a clinical response of 15 percent  
18 or so in terms of -- and that's just a ballpark  
19 number. You look for at least that kind of  
20 therapeutic gain, some kind of responder analysis.

21 So what is considered clinically important  
22 if we're going to expose patients to these risks?

1 Is this really enough patients benefitting from  
2 this to justify that risk? And is there such an  
3 MCID for this kind of responder analysis?

4 MS. GULLO: I think it might be important to  
5 revisit exactly what these data are explaining, so  
6 these particular data that you asked for are  
7 related to the variation on the FDA's guidance  
8 issued in 2012, which looks at two domains, both a  
9 minimum improvement of abdominal pain for a minimum  
10 amount of time, representing at least 50 percent of  
11 the weeks evaluated.

12 So for at least 6 weeks, patients had to  
13 report a minimum improvement in abdominal pain and  
14 also a minimum level of increase in bowel  
15 movements.

16 DR. TEERLINK: Fair enough. So let's go to  
17 CC-43. I was actually trying to help you, but  
18 CC-43. So there, it's even less.

19 MS. GULLO: Here, we're looking at the  
20 proportion of responders that have met what is  
21 considered to be a clinically meaningful  
22 improvement in each of these symptoms.

1           So this is the difference. This is the  
2 percentage of patients more than the placebo  
3 patients that experienced a clinically meaningful  
4 response. I could ask Dr. Howden to expand on how  
5 he feels if they --

6           DR. RAUFMAN: Let's hold off on that and  
7 move on to another. We'll get back to that, I'm  
8 sure. So let's move on to another question.

9           Dr. Lebwohl?

10          DR. LEBWOHL: Ben Lebwohl. So I had one  
11 question to Ms. Gullo or perhaps Dr. Howden. The  
12 greater the unmet need, the greater I would  
13 anticipate there'd be off-label use if it were  
14 reintroduced, even with restriction by age or  
15 cardiovascular risk factors.

16          Do we have data on how widespread was  
17 off-label use of tegaserod back when it was on the  
18 market, for example in men with IBS-C or people  
19 over 65 with chronic idiopathic constipation?

20          MS. GULLO: I don't believe that we have  
21 that data. Dr. Howden might be able to expand upon  
22 his clinical experience since he did use the

1 product.

2 DR. HOWDEN: Thank you. It's hard to  
3 predict, of course. There may be off-label use for  
4 any agent for any condition. I have personally  
5 seen men with IBS-C benefit from this product. I  
6 can think of no biological rationale for why men  
7 would not benefit from this product. It may just  
8 be that there were inadequate numbers of men in the  
9 clinical trials that led to its initial approval.

10 But I believe that the sponsor will act  
11 responsibly in this manner and make it clear to  
12 potential prescribers what the approved indications  
13 for reintroduction would be.

14 MS. GULLO: I would also note that since  
15 Zelnorm's marketing was discontinued prior to the  
16 introduction of additional agents that are  
17 available for both IBS-C and other disorders, that  
18 the data, even if we did have them, which I'm  
19 afraid we don't -- we didn't actually get all of  
20 the commercial data when we acquired the product.  
21 But even if we did, it may not be representative of  
22 any anticipated off-label use today.

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

2 DR. MANN: Thank you. I have two questions  
3 in pharmacology and one, clinical. The  
4 pharmacological question is, you actually didn't  
5 present any data about the blood-brain barrier  
6 penetration of this drug. You just stated that  
7 Novartis some time ago showed that it was not very  
8 much. I'm not sure what the word "not very much"  
9 really means.

10 It would also be useful to know how much of  
11 the drug penetrates when the person is taking this  
12 drug for weeks. There may not be much acute  
13 penetration. It might be slow getting across the  
14 blood-brain barrier, but there may be some  
15 accumulation over time.

16 Second question, a pharmacological question  
17 is affinity for the 5-HT<sub>2B</sub> receptor is comparable  
18 to your main and therapeutic target receptor, which  
19 is the 5-HT<sub>4</sub>. You describe it as an agonist at the  
20 5-HT<sub>4</sub> receptor. You described it as an antagonist  
21 at the 5-HT<sub>2B</sub> receptor. But I'm not sure when  
22 these original pharmacological studies were done,

1 and now we're familiar with concepts like biased  
2 agonism and so on and forth.

3 I'd really like to understand better what  
4 your basis is for thinking that this drug is a  
5 5-HT<sub>2B</sub> antagonist as opposed to an agonist. And  
6 obviously, that has significance for cardiovascular  
7 disease. And after that, I've got a clinical  
8 question.

9 MS. GULLO: I heard two questions. One is  
10 about the evidence around penetration of the blood-  
11 brain barrier and the other about how do we support  
12 that it's an antagonist at 5-HT<sub>2B</sub>. I'll ask  
13 Dr. Longstreth to join us to discuss that.

14 DR. LONGSTRETH: James Longstreth,  
15 consultant, US WorldMeds. The original choice of  
16 choosing tegaserod as the product to move forward  
17 in development, we have been told, is due to its  
18 high polarity, that we could reduce blood-brain  
19 barrier transport just by sheer structural  
20 components.

21 The quantitative whole body autoradiography  
22 that was conducted using rats found that less than

1 2 percent of the drug was found in the brain in  
2 those autoradiography experiments, and that was  
3 basically they couldn't observe it. So the lower  
4 limit of the quantitation of that case amounted to  
5 2 percent of the dose.

6 Now, the signal would have been the parent  
7 drug, and the three major metabolites would be able  
8 to be detected in that fashion. The drug tegaserod  
9 and also the major metabolite in 29 are both  
10 substrates for PGP and BCRP, which constitute a  
11 hefty portion of the blood-brain barrier. So those  
12 two modalities would be exporting drug out of the  
13 brain and back into the circulation, thereby  
14 enhancing it further.

15 DR. MANN: Of course, there's the  
16 possibility that means that a patient who's taking  
17 a drug that blocks the PGP would then get an  
18 unexpectedly larger CNS dose. Is that correct?

19 DR. LONGSTRETH: Yep. The original sponsor  
20 did a study where they tested digoxin and  
21 administered that simultaneously with tegaserod.  
22 They were not able to detect any increases in the



1 brain concentrations of the drug when that was  
2 done.

3 You had asked, originally when the question  
4 was put forth, about long-term exposures. The  
5 pharmacokinetic profile of tegaserod is somewhat  
6 unusual in that it peaks very rapidly, in about  
7 45 minutes post-dose, and is back down almost to  
8 baseline levels by 6 hours post-dose.

9 So of the 12-hour duration between doses,  
10 50 percent of the time, there were very, very low  
11 concentrations present. There's essentially no  
12 long-term accumulation of the drug so that you get  
13 accumulated profile. What you really see is a  
14 sequence of peaks and troughs that occur at 12-hour  
15 intervals.

16 DR. MANN: And the 2B receptor?

17 MS. GULLO: We'll ask Caroline Bell to  
18 address that. Dr. Bell?

19 DR. BELL: Caroline Bell, safety  
20 pharmacologist. Besides the binding data showing  
21 similar affinity, the functional assay showing  
22 antagonism was done in the rat fundus strip, which

1 is a selective assay for determining that.

2 DR. MANN: But with biased agonists in  
3 different systems, you can get the opposite  
4 results. You might find a drug could look like an  
5 antagonist in one effector system, but in another,  
6 it might look different. So you really need a  
7 panel of tests on a key target like the 2B receptor  
8 to really be confident about the behavior of the  
9 compound.

10 DR. BELL: You're touching on a very, very  
11 complicated subject when it comes to 5-HT  
12 pharmacology. I'm sure many people are aware. And  
13 yes, I agree that in different organs, you may have  
14 different effects. But with respect to any  
15 evidence for any pharmacology in all of the  
16 cardiovascular assessments that were made, there is  
17 absolutely no evidence for there being a vascular  
18 signal of any description.

19 DR. MANN: That sounds a little vague. I  
20 mean, the specific target 2B receptor, you have a  
21 binding study and you have one effect or signal  
22 transduction study.

1 DR. BELL: Yes. It is generally accepted  
2 that that assay is the assay in which to determine  
3 whether a drug is an agonist or an antagonist at  
4 the 5-HT<sub>2B</sub>.

5 DR. MANN: I understand that, but I'm just  
6 saying that that's an old point of view that  
7 there's one definitive assay for these things.

8 Another question for Dr. Gerlach; this won't  
9 take but just a second, slide 50. I wanted you to  
10 comment on the rates, 0.07 percent versus 0.02  
11 percent. Those rates are incredibly low. They are  
12 much lower than the general population.

13 This is a patient population that's supposed  
14 to have increased rates of psychopathology, not  
15 lower rates of psychopathology. So how do you  
16 interpret these numbers, and how does that affect  
17 your conclusions about the --

18 MS. GULLO: Dr. Gerlach can certainly  
19 discuss the numbers, but I would point out, again,  
20 that these numbers are assessed in the controlled  
21 clinical trial database, and because of the  
22 imbalance reported, they were also the subject of a

1 very large epidemiology study, where we might get  
2 more reassurance of what the rates are in the  
3 general population, in a similarly matched general  
4 population.

5 Dr. Seeger is with us today, and he was  
6 involved in that study from its inception, and he  
7 could potentially detail how this maybe compares to  
8 the rates in the general population of what we  
9 found in that study.

10 Dr. Seeger?

11 DR. SEEGER: Good morning. I'm John Seeger.  
12 I'm a pharmacoepidemiologist at Optum Epidemiology  
13 and chief scientific officer in that group. I'm  
14 also an assistant adjunct professor of epidemiology  
15 at Harvard's T.H. Chan School of Public health.  
16 And along with my colleague, Jeanne Loughlin, we  
17 conducted this large-scale epidemiology study of  
18 tegaserod.

19 We designed the study to address many of the  
20 known limitations of observational research,  
21 forming propensity-score-matched cohorts over time  
22 across the years that tegaserod was available. And

1 then we followed those cohorts within the source  
2 data for the outcomes, a range of outcomes,  
3 cardiovascular as well as suicide outcomes.

4 We see the hazard ratio that we observed in  
5 that study for self-injury or death. And these  
6 were outcomes that were identified in the claims  
7 data based on diagnosis codes for self-injury and  
8 then adjudicated by medical record review. There  
9 were fewer events in the tegaserod-treated patients  
10 in the general population, over 52,000 treated with  
11 tegaserod and 52,000 comparators.

12 DR. MANN: So translating that, you found it  
13 to be protective?

14 DR. SEEGER: With a confidence interval that  
15 includes null finding.

16 DR. RAUFMAN: Last question before the  
17 break, Dr. Khurana?

18 MR. KHURANA: My question got answered.  
19 Thank you.

20 DR. RAUFMAN: That's even better.

21 We will now take a 10-minute break. Panel  
22 members, please remember that there should be no

1 discussion of the meeting topic during the break,  
2 amongst yourselves or with any member of the  
3 audience. We will resume at approximately 10:40.

4 (Whereupon, at 10:27 a.m., a recess was  
5 taken.)

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

8 **FDA Presentation - Irena Lavine**

9 DR. LAVINE: Good morning. My name is Irena  
10 Lavine, and I am a medical officer in the Division  
11 of Gastroenterology and Inborn Errors Products. I  
12 will be presenting the clinical efficacy  
13 considerations of tegaserod reintroduction to the  
14 U.S. market. I would like to acknowledge our team  
15 statisticians, Dr. Ling Lan and Dr. George  
16 Kordzakhia, who contributed to the analyses, slide  
17 preparation, and discussion.

18 It should be noted that the review team did  
19 not reanalyze the original data that supported  
20 approval or questioned the original efficacy.  
21 Rather, the review team focused on the data  
22 submitted to support the reintroduction of

1 tegaserod to the U.S. market in female patients  
2 with IBS-C in various subpopulations.

3 As an outline of my presentation, I will  
4 first discuss the efficacy review strategy and then  
5 an overview of the clinical development program.  
6 Next, I will discuss the primary efficacy results  
7 supporting original approval.

8 If the cardiovascular safety concerns  
9 warrant narrowing the population for  
10 reintroduction, I will discuss the definition of  
11 the severely symptomatic subpopulation who would be  
12 the patients most in need. I will then discuss  
13 patient demographics and baseline characteristics  
14 of this severe subpopulation. Finally, I will  
15 discuss the efficacy results in the severely  
16 symptomatic subpopulation.

17 The data which supported approval of  
18 tegaserod established efficacy in the female IBS-C  
19 population. Because of the cardiovascular safety  
20 concerns, which will be discussed later this  
21 morning, there is the possibility of restricting  
22 use to those patients most in need and target the

1 severely symptomatic subpopulation.

2 For reintroduction, post hoc analyses of  
3 completed trials in female patients with IBS-C were  
4 used to determine if a clinical benefit was  
5 observed in a severely symptomatic subpopulation.  
6 Because cardiovascular risk is not expected to  
7 influence the efficacy of the drug, the severe  
8 subpopulation was not limited by cardiovascular  
9 risk.

10 The original trials supporting approval were  
11 301, 307, and 358. These were randomized, double-  
12 blind, placebo-controlled multi-center trials. The  
13 trials had a 4-week baseline period followed by a  
14 12-week treatment period. Trial 358 had an  
15 additional one-month withdrawal period. The trials  
16 evaluated different doses, but all trials included  
17 a 6-milligram BID dose, the FDA-approved dose in  
18 2002.

19 Trial 351 was considered exploratory at the  
20 time of original approval, but was included to  
21 support reintroduction because the same endpoints  
22 are now being evaluated in a post hoc nature for



1 all IBS-C trials. Trial 351 was similarly designed  
2 to trial 301, with the same treatment arms and  
3 12-week treatment duration.

4 This table shows the results for the primary  
5 endpoint that supported the original approval. As  
6 a reminder, we are not adjudicating the original  
7 primary efficacy results, but providing context for  
8 comparison of the original population to various  
9 subpopulations.

10 In the original trials, the patients were  
11 asked the following question, known as the subject  
12 global assessment, SGA, of relief. Please consider  
13 how you felt this past week in regard to your IBS,  
14 in particular your overall well-being and symptoms  
15 of abdominal discomfort, pain, and altered bowel  
16 habit.

17 Compared to the way you usually felt before  
18 entering the study, how would you rate your relief  
19 of symptoms during the past week? There were 5  
20 response options ranging from completely relieved  
21 to worse.

22 The original primary endpoint was response

1 in overall IBS relief with responder defined as at  
2 least 50 percent of the subject global assessments  
3 with complete or considerable relief, or all of the  
4 subject global assessments with at least somewhat  
5 relief over the last 4 weeks of treatment. The  
6 primary endpoint was the same for trials 301, 307,  
7 and 358 and was used as a post hoc analysis for  
8 trial 351.

9 This table shows the results of the primary  
10 efficacy analyses from original approval. The  
11 responders in tegaserod ranged from 39 to  
12 44 percent versus 28 to 39 percent in placebo for  
13 the three trials that supported approval. The  
14 treatment differences are shown in the last column.  
15 Of note, we tend to see a high placebo response  
16 rate in IBS trials.

17 Note that the results for trials 301, 307,  
18 and 358 are as presented in the currently approved  
19 label. Also note that the results for trial 351  
20 are a reanalysis with a new primary endpoint.  
21 Trial 351 was not included in the original label.  
22 These original treatment differences provide

1 context as we discuss the efficacy of tegaserod in  
2 various subpopulations in the coming slides.

3 During discussions between the FDA and the  
4 applicant on the approach to the reintroduction to  
5 the market, the applicant was asked to define a  
6 subpopulation of severely symptomatic IBS-C  
7 patients for whom the benefit of tegaserod may  
8 outweigh the potential cardiovascular risk.

9 There are no widely accepted clinical  
10 criteria, clinical guidelines, or literature to  
11 define a severely symptomatic IBS-C subpopulation.  
12 Although there was extensive discussion in  
13 evolution of the proposed severely symptomatic  
14 IBS-C definition, there was no final agreement  
15 reached on the specific criteria that would define  
16 the severely symptomatic subpopulation prior to  
17 submission of this efficacy supplement.

18 The applicant's proposed definition for the  
19 severely symptomatic subpopulation is female  
20 patients with IBS-C reporting an average of 3 or  
21 more days per week with severe or very severe  
22 abdominal pain and discomfort and 5 or more days

1 per week with hard, very hard, or no stools.

2 This definition of the severely symptomatic  
3 IBS-C subpopulation can be thought of as entry  
4 criteria to select the subpopulation for the  
5 post hoc analyses. Since the efficacy of tegaserod  
6 should not be affected by cardiovascular risk, this  
7 was not part of the severely symptomatic analyses.

8 Methods to interpret the severely  
9 symptomatic criteria mentioned on the previous  
10 slide can be varied because the values for the two  
11 criteria are continuous. Applying different  
12 rounding methods to determine which patients met  
13 the criteria resulted in subpopulations of varying  
14 severity.

15 The review team considered three rounding  
16 approaches to select data that met the definition  
17 of the subpopulation. These are ceiling rounding,  
18 which was the applicant's method, 0.5 rounding, and  
19 no rounding methods, which are defined on the next  
20 slide.

21 As a reminder, the pain component of the  
22 proposed definition of the severely symptomatic

1 subpopulation requires 3 or more days on average  
2 per week with severe or very severe abdominal pain  
3 and discomfort.

4 As an example, in the ceiling method, a  
5 patient with an average of 2.1 days per week of  
6 severe or very severe abdominal pain and discomfort  
7 would qualify because the ceiling method rounds 2.1  
8 to 3 days per week.

9 In the 0.5 rounding method, a patient with  
10 average of 2.5 days per week of severe or very  
11 severe abdominal pain and discomfort would qualify  
12 because 2.5 rounds to 3 days per week. In the  
13 no-rounding method, a patient is required to meet  
14 the criteria exactly as defined.

15 This table shows that the sample size for  
16 the severely symptomatic female subpopulation is  
17 almost twice as large with the ceiling rounding  
18 compared with no rounding. The sample sizes with  
19 the ceiling rounding, 0.5 rounding, and no rounding  
20 methods were considered when interpreting the  
21 results of the exploratory efficacy analyses and  
22 will be discussed later.

1           This table shows the demographics of the  
2 severely symptomatic IBS-C subpopulation, females  
3 only, no rounding for data selection for the 4  
4 premarket trials. The baseline demographics were  
5 generally similar among the trials for age, BMI,  
6 and race.

7           Patients in trial 301 were predominantly  
8 from non-U.S. countries, while patients in  
9 trials 307, 358, and 351 were predominantly from  
10 the U.S. In general, the baseline demographics  
11 were comparable between the drug and placebo arms  
12 and also between no rounding and ceiling rounding  
13 methods for the severely symptomatic subpopulation  
14 in each of the trials.

15           I will now discuss the baseline  
16 characteristics of the severely symptomatic  
17 subpopulation. I will first discuss the number of  
18 days per week with severe or very severe abdominal  
19 pain at baseline and then the number of days per  
20 week with hard, very hard, or no stools.

21           All patients had at least 3 days per week  
22 with severe or very severe abdominal pain and

1 discomfort as per the criteria used by the  
2 applicant to define the severely symptomatic  
3 subpopulation.

4           However, as shown in this table, the  
5 majority of patients in all trials were reported to  
6 have at least 4 days per week with severe or very  
7 severe abdominal pain and discomfort, indicating  
8 that patients experienced abdominal pain on most  
9 days of the week. There was a numeric pain scale  
10 used, and the severe and very severe options were  
11 at the high end of the scale.

12           This figure provides a graphical  
13 representation of the distribution of the number of  
14 days per week patients had severe abdominal pain at  
15 baseline in the three severely symptomatic  
16 subpopulations.

17           The mean number of days per week,  
18 represented by the small circle, with severe  
19 abdominal pain reported by patients at baseline is  
20 4 days or above, and the median, represented by the  
21 horizontal line, is greater than approximately 3  
22 and a half days. This suggests that the patient

1 data used to assess the clinical benefit of  
2 tegaserod in a severely symptomatic subpopulation  
3 likely reflected patients who have more severe IBS  
4 symptoms, with many patients having a greater  
5 number of days with severe pain or discomfort than  
6 required by the criteria.

7 The second component of the applicant's  
8 proposed definition for the severely symptomatic  
9 subpopulation is 5 or more days per week with hard,  
10 very hard, or no stools. Review of the baseline  
11 characteristics shows that most patients have less  
12 than 3 days per week with hard or very hard stools  
13 at baseline, approximately 79 to 95 percent across  
14 the 4 trials. However, review of the data revealed  
15 that, at baseline, most patients reported no stools  
16 rather than hard or very hard stools.

17 This table shows that most patients had at  
18 least 4 days per week with no stools and some  
19 patients reported at least 5 days per week with no  
20 stools. This suggests that the patient data used  
21 to assess the clinical benefit of tegaserod in a  
22 severely symptomatic subpopulation using the



1 no-rounding method reflected patients who have  
2 severe clinical symptoms of IBS-C.

3 The 2012 IBS guidance for industry requires  
4 fewer than 3 complete spontaneous bowel movements  
5 per week as trial entry criteria for IBS-C. This  
6 figure shows the distribution of the number of  
7 bowel movements per week in the severely  
8 symptomatic subpopulations at baseline.

9 There are a smaller number of patients who  
10 are outliers with greater than 10 bowel movements  
11 per week and not shown in the figure. Therefore,  
12 some patients in the severely symptomatic  
13 subpopulation would be excluded based on today's  
14 current guidance.

15 One limitation of the data was that the  
16 collection in the original trials was related to  
17 bowel movements. The current guidance is based on  
18 complete spontaneous bowel movements, whereas the  
19 original trials do not require the differentiation  
20 of a bowel movement from a complete spontaneous  
21 bowel movement.

22 The original trials do not collect the exact

1 time of laxative usage, the exact time of a bowel  
2 movement, or whether a bowel movement was complete.  
3 Therefore, it is not possible to determine whether  
4 a bowel movement is free of the effect of rescue  
5 medication or complete. It is important to note  
6 that the methods for data collection have evolved  
7 since the original trials were designed and  
8 conducted.

9 I will now discuss the efficacy results in  
10 the severely symptomatic subpopulation. We  
11 explored three methods for patient data selection  
12 for the severely symptomatic subpopulation and how  
13 these methods changed the sample size, and  
14 therefore impact the efficacy results.

15 We focused on the treatment difference  
16 between the patients treated with tegaserod versus  
17 placebo to determine whether the treatment effect  
18 of tegaserod demonstrated in the original approval  
19 is generally similar in magnitude to the treatment  
20 effect in the severe subpopulation.

21 With the ceiling method, the treatment  
22 differences were generally numerically similar in

1 the severely symptomatic subpopulation compared  
2 with the original population, except for trial 307,  
3 the dose titration study.

4 This figure shows the primary efficacy  
5 endpoint results for the severely symptomatic  
6 subpopulations using the three rounding methods as  
7 well as the original patient population indicated  
8 by the black bar on the right of each study panel.  
9 The treatment differences are positive for the  
10 three rounding methods in trials 301, 358, and 351,  
11 except for the no-rounding population in trial 358.

12 Trial 307 was a failed trial, and the  
13 treatment differences are negative for all rounding  
14 methods. Of note, the sample size is smaller with  
15 the no-rounding method and the confidence intervals  
16 are wide in comparison to the ceiling rounding  
17 method.

18 In conclusion, the treatment effects for the  
19 primary endpoint were notably different for various  
20 severely symptomatic subpopulations determined by  
21 different rounding methods across the trials.  
22 Overall, the treatment differences were in favor of

1 tegaserod compared with placebo in all versions of  
2 the severely symptomatic subpopulations in  
3 trials 301, 358, and 351, except for the  
4 no-rounding population in trial 358. In trial 307,  
5 placebo patients had higher response rates for all  
6 severely symptomatic subpopulations.

7 Exploratory analyses, based on a variation  
8 of the 2012 IBS guidance, also reported a treatment  
9 effect. Although there are limitations discussed  
10 in the FDA briefing book, the treatment effect  
11 numerically favored tegaserod using this endpoint  
12 in the female severely symptomatic subpopulations  
13 selected with the ceiling rounding method.

14 Collectively, the post hoc analyses suggest we  
15 would expect clinical benefit in more severely  
16 affected patients.

17 Now, I'd like to turn the podium over to  
18 Dr. Ke Zhang.

19 **FDA Presentation - Ke Zhang**

20 DR. ZHANG: Good morning. I'm Ke Zhang,  
21 pharmacologist from FDA. I will discuss the  
22 tegaserod nonclinical studies. My presentation

1 will cover in vitro cardiac studies, including  
2 study with hERG potassium channel, the study on  
3 cardiac action potential, serotonin receptor  
4 binding studies, and isolated coronary artery  
5 studies. Finally, I will also talk about the in  
6 vivo cardiovascular safety pharmacology studies.

7           Each study I present today, I will also  
8 discuss the clinical relevance of the nonclinical  
9 studies. In the next slides, I will discuss the  
10 in vitro cardiac studies.

11           This slide summarizes the study of hERG  
12 potassium channel and the study on cardiac action  
13 potential. Tegaserod inhibited hERG potassium  
14 channel with IC50 of 13 micromolar. In contrast,  
15 the IC50 for cisapride is 0.044 micromolar.  
16 Therefore, cisapride is more potent than tegaserod  
17 in terms of inhibition of hERG potassium channel.

18           Tegaserod has no effect on action potential  
19 from isolated guinea pig ventricular papillary  
20 muscle in concentrations up to 1 micromolar, and  
21 from isolated human atrial myocytes at a  
22 concentration up to 0.1 micromolar. One micromolar

1 concentration is about 100 times higher than the  
2 clinical plasma level of 0.01 following an oral  
3 dose of 6 milligrams BID.

4 It has been demonstrated that tegaserod is a  
5 5-HT4 receptor agonist with a moderate affinity for  
6 5-HT1 and 5-HT2 receptor subtypes. This table  
7 summarizes the Ki's for different serotonin  
8 receptors. Ki is an inhibitory constant, and the  
9 smaller Ki indicates a higher affinity of the drug  
10 for the receptor.

11 You can see from this table, tegaserod has a  
12 high affinity for 5-HT4 receptor, moderate affinity  
13 for 5-HT1, and 2 receptor subtypes. The major  
14 metabolite, M-29 and the two other minor  
15 metabolites, have no binding affinity for 5-HT41B  
16 or 5-HT1D receptor.

17 Why do we care about the serotonin receptor  
18 subtypes? It is because this receptor has been  
19 identified in the blood vessels such as coronary  
20 artery, and activation of this receptor may result  
21 in vasoconstriction.

22 Here is the isolated coronary artery

1 studies. Tegaserod did not induce contraction in  
2 the isolated coronary artery from the pig,  
3 non-human primates, and humans at concentrations up  
4 to 10 or 30 micromolar, but produced a small  
5 contractile response in canine coronary artery at  
6 3- to 10-micromolar concentrations. In the next  
7 slides, I will show you the study results from  
8 human coronary artery.

9 This figure shows a dose-response curve or a  
10 concentration contraction curve in isolated  
11 coronary arteries. Serotonin is used as a positive  
12 control in this study. It induces a concentration-  
13 dependent contraction. It increased the  
14 contraction with increased concentration. However,  
15 tegaserod did not induce contraction as compared to  
16 the control.

17 The next slide shows a similar study from  
18 isolated coronary artery from the pig on the left  
19 and the dog on the right. Tegaserod did not induce  
20 contraction as compared to the vehicle control in  
21 the isolated coronary artery from pigs.

22 Tegaserod produces small contraction

1 response only at 3 to 10 micromolar concentrations  
2 as compared to the vehicle control in the isolated  
3 coronary artery from dogs. The concentration of  
4 3 to 10 micromolar is about 300 to 1,000 times  
5 higher than the human plasma level of 0.01  
6 micromolar.

7 In these slides, I will discuss the in vivo  
8 cardiovascular study in dogs. There are two  
9 studies, one with intraduodenal doses and the other  
10 one with oral doses. In both studies, the doses  
11 tested were up to 10 milligrams per kg.

12 The result from this study indicates that  
13 tegaserod did not have any effect on the blood  
14 pressure, heart rate, cardiac output, and EKG such  
15 as QT interval. Just for a comparison, at  
16 10 milligrams per kg oral dose, the tegaserod  
17 plasma level in dogs is about 400 nanograms per mL  
18 for males and 277 nanograms per mL in female, which  
19 are about 100 times higher than human plasma level  
20 of 3 nanograms per mL following 6-milligram BID  
21 dose.

22 As a part of drug development, the sponsor



1 conducted a number of repeated dose toxicity  
2 studies in the dog. In these studies, EKGs and  
3 cardiac histopathology were monitored. Since our  
4 focus is on the cardiac safety of tegaserod, I will  
5 discuss the following repeated dose toxicity  
6 studies, the 2-week IV study, 26-week, and 52-week  
7 oral studies.

8 In 2-week IV toxicity studies, the doses  
9 tested were up to 1 milligram per kg per day. The  
10 oral toxicity studies used the doses up to 60 or 70  
11 milligrams per kg per day. The results indicate  
12 that tegaserod has no effect on EKG, including  
13 heart rate and QT interval, and it did not induce  
14 any histopathological changes in the heart. The  
15 high dose tested in these studies are over 300  
16 times higher than the clinical dose of 6-milligram  
17 BID or 0.2 milligram per kg per day if 60 kilograms  
18 body weight is assumed.

19 In summary, tegaserod is a weak inhibitor of  
20 hERG potassium channel, but did not induce QT  
21 prolongation in in vivo studies in dogs. Tegaserod  
22 has no effect on action potential in guinea pig

1 ventricular papillary muscle or isolated human  
2 atrial myocytes.

3 Tegaserod is a 5-HT<sub>4</sub> receptor agonist with a  
4 moderate affinity for 5-HT<sub>1</sub> and 2 receptor  
5 subtypes. Tegaserod did not induce contraction in  
6 the isolated coronary artery from pigs, dogs,  
7 non-human primates, and humans at clinically  
8 relevant concentration or doses. In conclusion,  
9 from a nonclinical standpoint, tegaserod lacks  
10 clinically relevant cardiovascular effect.

11 Thank you. Now, let me introduce our next  
12 speaker, Dr. Jenny Cheng from our clinical  
13 pharmacology team.

14 **FDA Presentation - Jie Cheng**

15 DR. CHENG: Good morning, everyone. My name  
16 is Jenny Cheng. I'm the clinical pharmacology  
17 reviewer for this application. Today, I'm going to  
18 talk about the main clinical pharmacology findings  
19 of Zelnorm with a proposed 6-mg BID dosage.

20 My presentation will cover three sections.  
21 First, I will provide pharmacokinetic information  
22 of tegaserod and its major metabolite, M29.

1 Second, I will talk about the intrinsic and  
2 extrinsic factors that may affect systemic exposure  
3 of tegaserod, including organ impairment and  
4 drug-drug interactions, and I will discuss about  
5 the effect of tegaserod and M29 on human platelet  
6 aggregation in vitro.

7 Pharmacokinetics of tegaserod information  
8 has been evaluated in healthy adults and also in  
9 patients with IBS-C. Overall, tegaserod PK in  
10 patients and healthy subjects are similar.

11 Following oral administration, tegaserod reached  
12 the maximal concentration in about 1 hour and oral  
13 bioavailability is about 10 percent.

14 Systemic exposure increases in a dose  
15 proportional manner from 2 mgs to 10 mgs, and food  
16 could reduce the drug exposure. It has high  
17 protein binding in correspondence with pronounced  
18 distribution.

19 Tegaserod is metabolized mainly by two  
20 pathways. First is majorly while presystemic acid  
21 catalyzed hydrolyzes to produce the main  
22 metabolite, M29. It is noteworthy that M29 has

1 negligible [indiscernible] affinity for 5-HT4  
2 receptors in vitro. The second metabolism pathway  
3 is the minor pathway while direct glucuronidation.  
4 Compared to tegaserod, M29 has 10-fold higher AUC  
5 and 16-fold higher Cmax.

6 For the excretion, approximately in  
7 two-thirds of oral administration, tegaserod is  
8 excreted and unchanged into feces, with the  
9 remaining one-third excreted in the urine primarily  
10 as metabolites, and half-life is around 4.6 to  
11 8.1 hours across different studies with oral  
12 administration of tegaserod.

13 Talking about the effect of the intrinsic  
14 and extrinsic factors, some PK could be divided  
15 into four sections. Based on the approved label  
16 for hepatic impairment, no dose adjustment is  
17 recommended for patients with mild hepatic  
18 impairment, although they are 31 percent and  
19 16 percent higher AUC and Cmax. Tegaserod is not  
20 recommended for patients with moderate and severe  
21 hepatic impairment.

22 Regarding renal impairment, no dose

1 adjustment is recommended for patients with mild to  
2 moderate renal impairment, and tegaserod is not  
3 recommended for patients with severe renal  
4 impairment due to the M29 accumulation. In  
5 addition, elderly female patients have higher drug  
6 exposure compared to young female and male  
7 patients, but no dose adjustment is needed.

8           Based on the studies conducted after the  
9 approval, tegaserod is a substrate of P-gp efflux  
10 transporters in vitro, and also in vivo studies  
11 show that the systemic exposure of tegaserod was  
12 increased by 70 percent and 63 percent for AUC and  
13 Cmax, with concomitant medication of quinidine,  
14 which is a P-gp inhibitor.

15           Lastly, I will be talking about the  
16 potential effects of tegaserod on platelet  
17 aggregation using blood samples from healthy  
18 subjects and IBS-C patients in 2008 with serious  
19 concentration from 10, 33, to 100 nanomolar.  
20 Please note that Cmax of tegaserod after 6-mg BID  
21 dose is around 10 nanomolar. And M29 effect on  
22 platelet aggregation was conducted on healthy

1 subjects in 2017 with 10 and 100 nanomolar. Please  
2 also note that Cmax of M29 after 6-mg BID dosing is  
3 around 160 nanomolar.

4 Platelet aggregation responses were  
5 monitored using light transmission aggregation  
6 method by an aggregometer.

7 From this table, you can see tegaserod  
8 showed a mild but statistically significant  
9 concentration-dependent increase in platelet  
10 aggregation compared to vehicle, with a  
11 physiologically relevant platelet agonist added,  
12 including ADP, collagen, TRAP, epinephrine, and  
13 serotonin. Please note that the assay was  
14 conducted without positive control added.

15 Similar results were found in IBS-C patients  
16 as well. You can see tegaserod also showed  
17 concentration-dependent increase on platelet  
18 aggregation.

19 All things considered, there are however  
20 some inconsistent results from later research. In  
21 2012, Higgins reported no significant effects on  
22 platelet aggregation at tegaserod 10, 33, and 100

1 nanomolar in a relatively small sample size. Note  
2 there is no positive control applied in this study.

3 In a recent study published in 2018, Conlon  
4 reported that tegaserod didn't potentiate platelet  
5 aggregation at high concentration of 100 nanomolar,  
6 and positive control was applied in this study and  
7 showed a positive effect.

8 Furthermore, M29 showed 5 to 16 percent  
9 increase with some of the agonists, including  
10 epinephrine and 5HT plus ADP, although there is no  
11 significant increase with the 100 nanomolar  
12 compared to the vehicle alone, and the positive  
13 control showed a significant increase with some  
14 agonists in the same assay. However, please note  
15 that the highest concentration studied is lower  
16 than M29 Cmax in this study.

17 To summarize, although there is no positive  
18 control used in the applicant study, tegaserod  
19 showed a mild but statistically significant  
20 concentration-dependent increase in platelet  
21 aggregation compared to vehicle. A similar  
22 induction pattern was observed with IBS-C patients

1 as well.

2 The results are inconsistent across all the  
3 different studies. In addition, the result of M29  
4 is inconclusive because the concentration is lower  
5 than therapeutic concentrations.

6 In summary, tegaserod is mainly eliminated  
7 by metabolism to form major inactive metabolite,  
8 M29. Also, the overall in vitro results of  
9 tegaserod and M29 effect on platelet aggregation  
10 are inconclusive. The results from an additional  
11 ex vivo study to further evaluate the effects of  
12 tegaserod and M29 on platelet aggregation are  
13 pending.

14 Next, I would invite Dr. Apparaju to present  
15 FDA clinical safety evaluation.

16 **FDA Presentation - Sandhya Apparaju**

17 DR. APPARAJU: Good morning. My name is  
18 Sandhya Apparaju. I'm a clinical analyst in the  
19 Division of Gastroenterology and Inborn Errors  
20 Products. Today, along with my colleagues from  
21 safety statistics and epidemiology, I'll be  
22 presenting the clinical safety aspects of Zelnorm,



1 tegaserod maleate, in the context of the proposed  
2 market reintroduction.

3 As previously noted, Zelnorm was withdrawn  
4 from the U.S. market in 2007 after a retrospective  
5 analysis of pooled clinical trial database  
6 suggested an imbalance in CV ischemic events in  
7 tegaserod-treated patients versus those on placebo.

8 The primary focus of this presentation,  
9 therefore, will be on the post hoc assessment of  
10 cardiovascular ischemic signal. In addition, the  
11 signal for suicidal ideation and behavior will also  
12 be presented.

13 The overall safety of tegaserod in relevant  
14 subpopulations of interest was also evaluated  
15 during this review, and the safety data in  
16 subgroups generally mirrors the labeled population.  
17 The following is a brief outline of this  
18 presentation. I will begin with an overview of the  
19 CV ischemic signal identification process, the  
20 three adjudications, and their outcomes.

21 Next, I will present the baseline CV risk  
22 characteristics of the initial cases identified by

1 Novartis and those of the overall safety  
2 population. A reassessment of the CV ischemic  
3 safety signal, including MACE, in the proposed low  
4 risk CV population will be presented next.

5 I will also summarize other relevant CV  
6 safety aspects as well as the postmarketing  
7 findings for CV ischemic signal. Finally, I will  
8 present the signal for suicidal ideation and  
9 behavior, hereafter referred to as SI/B, as well as  
10 the postmarketing data in this regard.

11 This flowchart summarizes the initial search  
12 for CV ischemic signal and Novartis' internal  
13 adjudication of the cases. Please note that the  
14 search was conducted on a pooled clinical trial  
15 database, termed Db15, which consisted of over  
16 18,000 patients from 29 randomized placebo-  
17 controlled clinical trials of at least 4 weeks in  
18 duration and across several indications, including  
19 IBS-C, CIC, functional dyspepsia, GERD, et cetera.

20 The search process primarily involved a  
21 manual search using terms for ischemic events from  
22 the adverse event and serious adverse event tables

1 and was supported by an automated search of the  
2 database, using search terms for coronary,  
3 cerebrovascular, and other ischemic events.

4 As shown, this initial search yielded 24  
5 potential cases of CV ischemia, 20 on tegaserod and  
6 4 on placebo. 18 out of the 20 initial events on  
7 tegaserod and 2 of the 4 events on placebo were  
8 deemed as CV ischemic events by the internal  
9 adjudication panel, which included 2 cardiologists.

10 The CV ischemic cases on drug included  
11 4 cases of MI, 7 cases of angina, 4 cases of  
12 coronary artery disease, 2 cases of strokes, and  
13 1 vasoconstriction. Two cases on tegaserod and 2  
14 on placebo were ruled out by the panel due to an  
15 alternative non-CV diagnosis, pre-existing  
16 condition, normal enzyme or ECG findings, or due to  
17 an event unsupported by ECG findings.

18 It should be noted that the case narratives  
19 were limited at the time of this internal  
20 adjudication due to the time constraints in  
21 gathering source data from old trials.

22 This slide presents the findings of the

1 first external adjudication, which was conducted  
2 prior to the market withdrawal in March of 2007 by  
3 a panel of two cardiologists and one neurologist at  
4 the Mount Sinai Hospital in New York.

5 This adjudication was a fresh look at the  
6 same 24 initial cases with additional source data  
7 for cases: such as hospital records, lab results,  
8 ECG findings, et cetera. As shown, 14 of the 24  
9 initial cases, 13 on tegaserod and 1 on placebo,  
10 were confirmed by the panel. 10 out of the 13  
11 confirmed events on tegaserod were coronary events,  
12 including 3 MIs, 1 CV death, 6 events of unstable  
13 angina, while the remaining 3 events were strokes.

14 Of note, 7 of the confirmed CVI events on  
15 tegaserod could be deemed as major adverse  
16 cardiovascular events, or MACE, defined as a  
17 composite endpoint of CV death, nonfatal MI, or  
18 nonfatal stroke. No MACE cases were noted on  
19 placebo.

20 Overall, 10 out of the 24 initial cases were  
21 excluded in this first external adjudication,  
22 including 7 on tegaserod and 3 on placebo. The

1 case assessment forms accompanying the adjudication  
2 report did not provide the rationale for excluding  
3 cases. However, all 7 excluded cases on tegaserod  
4 were also excluded during the second external  
5 adjudication, which was a more rigorous process and  
6 will be described next.

7           After the market withdrawal of Zelnorm in  
8 February of 2008, Novartis submitted the findings  
9 of a second external adjudication conducted by a  
10 panel of 3 cardiologists at the Duke Clinical  
11 Research Institute, DCRI. This slide summarizes  
12 the associated search and the adjudication process  
13 and outcomes.

14           This adjudication is thought to be thorough  
15 and included a reanalysis for CV ischemic signal  
16 identification using a broader search strategy,  
17 improved patient narratives, and prespecified  
18 criteria for CV ischemic events. This adjudication  
19 also sought to identify outcomes of MACE,  
20 arrhythmias, and those of congestive heart failure.

21           As shown on the slide, 304 potential cases  
22 were identified for adjudication by the panel,

1 which included the 24 initial cases from the prior  
2 Novartis search. Of the 304, 24 cases were  
3 confirmed by the second external adjudication, 18  
4 on drug and 6 on placebo, with a total of  
5 26 events.

6 Eight of these confirmed cases: 7 on drug  
7 and 1 on placebo, were CV ischemic events of which  
8 4 on tegaserod were also deemed as MACE-type events  
9 by the panel. A fifth MACE, an MI, was also noted  
10 in 1 patient who was adjudicated to have unstable  
11 angina, which was identified as the leading event.  
12 The remaining 16 confirmed cases were arrhythmias,  
13 11 on drug, and 5 on placebo, 14 of which were new  
14 cases.

15 As shown, a total of 254 cases were excluded  
16 by the panel during the adjudication as probably no  
17 CV event, including 158 cases on drug. These  
18 events were predominantly newly identified cases of  
19 chest pain, chest discomfort, palpitations,  
20 tachycardia, bradycardia, et cetera.

21 Eight of the initial 24 cases were also  
22 excluded as no CV events, including 4 cases of

1 angina, 2 cases of coronary artery disease, and  
2 2 MIs. In addition, 26 cases: 22 on drug and 4 on  
3 placebo, were deemed to have insufficient data to  
4 adjudicate. Of note, all three adjudications  
5 confirmed a single case of transient ischemic  
6 attack, TIA, on placebo.

7 This table summarizes the incidence of CV  
8 ischemic events, including MACE, in tegaserod  
9 versus placebo patients across the adjudications as  
10 discussed on the previous slides. Please note that  
11 the confirmed cases were scattered across the  
12 tegaserod clinical trials and indications.

13 As shown, the number of confirmed cases  
14 decreased with each adjudication compared to the  
15 initial search. Of the initial 20 cases identified  
16 in the Novartis search, the number of confirmed CV  
17 ischemic cases were 18, 13, and 7 in the internal  
18 first and second external adjudications,  
19 respectively.

20 It is noteworthy that though the reanalysis  
21 prior to the second external adjudication yielded  
22 304 potential cases for adjudication, a total of 8

1 CV ischemic cases on drug and placebo were  
2 confirmed by DCRI. These 8 cases were also part of  
3 the 24 initial cases. Thus, it should be noted  
4 that no new CVI or MACE outcomes were identified  
5 solely by the second external adjudication.

6 Overall, the number of CV ischemic events,  
7 including MACE, in tegaserod-treated patients was  
8 small relative to the size of the overall safety  
9 database as shown by the percentage values in the  
10 table. However, an imbalance on tegaserod relative  
11 to placebo persisted across all adjudications and  
12 was driven mainly by an imbalance in the coronary  
13 ischemic events.

14 With the goal of reintroducing this product  
15 in a population in whom benefits are expected to  
16 outweigh the risks, the applicant in their initial  
17 draft labeling for this submission proposed a low  
18 CV risk subpopulation. This population was  
19 comprised of female IBS-C patients less than  
20 65 years of age and not meeting the following  
21 CV-related contraindications: firstly, a prior  
22 history of CV ischemic disease such as MI, stroke,



1 transient ischemic attack, or angina, and secondly,  
2 having more than 1 CV risk factor at baseline,  
3 including hypertension, tobacco use, diabetes,  
4 hypercholesterolemia, age 55 years and older, or  
5 obesity.

6 To further understand how these risk factors  
7 may have impacted the CV outcome for an individual  
8 patient, a review of baseline characteristics was  
9 conducted in all 24 patients with an initial CV  
10 ischemic signal.

11 As shown in the table, CV ischemic events  
12 were identified in both males and females and  
13 across all age cohorts of the pooled safety  
14 database. Specifically, as it relates to the  
15 presence of CV risk at baseline, 12 out of the 20  
16 cases on tegaserod had a clear history of CV  
17 disease at baseline and 17 patients had more than  
18 1 CV risk factor.

19 The trend for baseline CV risk continued  
20 across the subgroups of all females and female  
21 IBS-C patients. Age 55 years and older,  
22 hypertension, hyperlipidemia, were the most

1 commonly noted risk factors.

2           It should be noted that there were some  
3 limitations to the risk factor data. For example,  
4 active smoking status was only collected in 15 out  
5 of the 29 clinical trials, but was obtained in all  
6 IBS-C registration trials. Diabetics were  
7 underrepresented, as they were usually excluded,  
8 except for one study in patients with diabetic  
9 gastropathy.

10           A similar trend for baseline characteristics  
11 was noted for the outcome of MACE across the  
12 populations and subgroups. All 4 patients  
13 identified to have MACE-type outcomes during the  
14 second external adjudication had more than 1 CV  
15 risk factor, and 3 patients also had a prior  
16 history of CV ischemic disease.

17           Overall, the number of cases for CV ischemia  
18 or the subset MACE was small, and a definitive  
19 pattern for an increased risk with certain CV risk  
20 factors or a combination of such factors could not  
21 be ascertained from this information.

22           For context, the baseline CV risk

1 characteristics of over 18,000 patients in  
2 tegaserod clinical trials were evaluated and are  
3 presented in the table here. Proposed restrictions  
4 are shown in bold font. In general, the  
5 demographic features, presence of CV ischemic  
6 disease, and CV risk characteristics of the safety  
7 population and subgroups were comparable across  
8 drug and placebo.

9 Eighty-eight percent of the patients in the  
10 pooled database were females and 95 percent were  
11 less than 65 years of age. Approximately 98 to  
12 99 percent of patients in Db15 did not have a  
13 history of CV ischemic disease at baseline, while  
14 75 percent of patients had 1 or no CV risk factors.

15 Predominant risk factors noted were  
16 hypotension, hyperlipidemia, obesity, or age  
17 greater than or equal to 55 years, which occurred  
18 in approximately 15 to 20 percent of patients.

19 Overall, it appears that approximately  
20 75 percent of female IBS-C patients in pooled  
21 clinical trials would fulfill the proposed criteria  
22 for a low CV risk subpopulation with the caveat

1 that the clinical trial database may not  
2 necessarily be reflective of the actual population  
3 that might receive the drug if reintroduced.

4 To reiterate, low CV risk subgroup was  
5 defined here as female IBS-C patients aged less  
6 than 65 without CV ischemic history at baseline and  
7 not having more than 1 CV risk factor.

8 As shown in the table, in the pooled  
9 clinical trial database, Db15, across several  
10 indications, both external adjudications confirmed  
11 only 1 case of CV ischemic and zero MACE on  
12 tegaserod when the patient population was  
13 restricted to low CV risk females. There were no  
14 low CV risk IBS-C patients that had CVI events  
15 using the label-proposed definition.

16 The 1 confirmed case of CV ischemia was in a  
17 patient with chronic idiopathic constipation who  
18 had unstable angina. Overall, the baseline CV risk  
19 information from cases and the pooled population  
20 supports the safety in the restricted low CV risk  
21 female IBS-C subgroup. It should be noted,  
22 however, that not all patients with a history of CV

1 ischemic disease and/or having more than 1 CV risk  
2 factor developed a CVI event.

3 This slide summarizes other relevant CV  
4 safety aspects of interest from the pooled clinical  
5 trial database analysis. There were no clinically  
6 relevant changes in blood pressure at the proposed  
7 6-milligram dose of tegaserod.

8 Systolic blood pressure increases of up to 2  
9 millimeters of mercury were noted only at doses  
10 greater than 12 milligrams per day. FDA conducted  
11 a risk analysis, which suggests that the 10-year CV  
12 risk with small to moderate increases in blood  
13 pressure will remain unaffected, especially in  
14 patients with low CV risk.

15 A formal thorough QT study was not conducted  
16 for tegaserod. Analysis of centrally read clinical  
17 trial ECG data suggested no meaningful effects on  
18 various intervals, including the QTcF. In  
19 addition, FDA analysis of findings on tegaserod  
20 versus placebo from a pooled clinical trial  
21 database concluded absence of the safety signal for  
22 clinically relevant arrhythmias.

1           The frequency of cardiovascular adverse  
2 events after a longer duration of tegaserod use was  
3 not different from that observed in short-term  
4 placebo-controlled clinical trials. A small number  
5 of CV ischemic events: 3 cases of unstable angina,  
6 and 1 case of stroke, and 6 arrhythmic events were  
7 found in a database of long-term, open-label  
8 clinical trials ranging 6 to 12 months in duration.  
9 All 4 patients with CV ischemic events had risk  
10 factors at baseline.

11           With regard to the postmarketing review for  
12 CV ischemic signal, a search of the FAERS database  
13 from product launch in 2002 to March of 2018  
14 identified a total of 67 coronary and  
15 cerebrovascular events in tegaserod-treated  
16 females. Of these, 3 of the 4 patients with  
17 cerebrovascular events were on concomitant estrogen  
18 or hormone replacement therapies.

19           In general, there are limitations associated  
20 with the use of FAERS data, including  
21 underreporting of events. In this case, there was  
22 an additional limitation of missing baseline CV

1 risk factor information in the cases identified.

2 To summarize the issue of CV safety signal,  
3 overall, the incidence of CV ischemic events,  
4 including the subset MACE, in tegaserod-treated  
5 patients was small. However, an imbalance on  
6 tegaserod related to placebo persisted across all  
7 adjudications.

8 It is difficult to interpret the CV ischemic  
9 signal given its small size relative to the size of  
10 the overall safety database as well as certain  
11 procedural and data limitations, including  
12 retrospective and pooled nature of the analysis;  
13 incomplete source data retrieval such as missing or  
14 incomplete medical history and baseline CV risk  
15 factor information; lack of objective measures to  
16 confirm some of the CV ischemic events; and  
17 differences across adjudication methodologies,  
18 including varying definitions for CV ischemic  
19 outcomes and varying methods of classifications.

20 However, the reduced number of confirmed CV  
21 ischemia or MACE events in the proposed narrow  
22 population of low CV risk females provides some

1 reassurance that the benefit-risk profile might be  
2 favorable in this subpopulation.

3           Considering the residual uncertainty in the  
4 CV ischemic risk with tegaserod and availability of  
5 treatment options for IBS-C, since its market  
6 withdrawal in 2007, a discussion of the overall  
7 benefit-risk evaluation will be important when  
8 considering the appropriate population for  
9 potential reintroduction of this product.

10           Next, we will turn our attention to the  
11 second safety signal of special interest, namely  
12 suicidal ideation and behavior. In 2005, the  
13 routine review of postmarketing reports submitted  
14 to the FAERS database indicated a potential signal  
15 for suicidal behaviors with tegaserod.

16           FDA requested then-sponsor Novartis to  
17 provide an analysis of all placebo-controlled  
18 tegaserod clinical trials for SI/B, including an  
19 exposure-adjusted risk analysis. The analysis  
20 showed a higher incidence of SI/B events in  
21 tegaserod-treated patients compared to placebo  
22 based on the Columbia classification algorithm of



1 suicide assessment criteria.

2           The frequency of SI/B events in placebo-  
3 controlled trials was 8 on drug and 1 on placebo.  
4 There was an additional case of completed suicide,  
5 which occurred in an open-label study. As shown in  
6 the table, the rate of SI/B events per 1,000  
7 person-years was 4.3 versus 0.9 in tegaserod versus  
8 placebo.

9           The 8 events on the drug included  
10 1 completed suicide, 2 suicide attempts, 4 cases of  
11 self-injurious behavior within intent unknown, and  
12 1 suicidal ideation. In comparison, there was  
13 1 suicidal attempt on placebo.

14           There is a high prevalence of primary  
15 psychiatric disorders in IBS, including major  
16 depressive, generalized anxiety, panic disorders,  
17 et cetera, all of which are risk factors for SI/B.  
18 Both patients who committed suicide on tegaserod  
19 had psychiatric illnesses. In addition, suicidal  
20 ideation was more frequent in, but not limited to,  
21 patients receiving antidepressant medications.

22           A high baseline frequency among IBS-C

1 patients, however, may not explain the treatment  
2 imbalance in drug versus placebo. In this regard,  
3 in 2007, FDA recommended inclusion of language to  
4 communicate a potential risk of SI/B in the  
5 precautions section of the labeling. The current  
6 applicant has included this language into their  
7 draft labeling.

8 In addition, the overall incidence of  
9 neuropsychiatric events in the pooled clinical  
10 trial database was found to be generally comparable  
11 between tegaserod and placebo at approximately  
12 3.1 percent versus 2.5 percent respectively.  
13 Insomnia, anxiety, depression, and nervousness were  
14 the most common AEs occurring at similar rates in  
15 drug versus placebo.

16 With regard to the postmarketing review for  
17 SI/B, a search of FAERS from 2002 through March of  
18 2018 identified 5 completed suicides and 6 cases of  
19 suicidal ideation in tegaserod-treated patients.  
20 All patients had a history of psychiatric  
21 disorders, including 1 patient with suicidal  
22 ideation who had a prior history of SI/B.

1 Overall, the postmarketing cases of SI/B did  
2 not provide clear evidence of a causal relationship  
3 between tegaserod treatment and the psychiatric  
4 adverse events. In addition, the results from an  
5 observational cohort study did not suggest  
6 differences in the incidence of suicide and self-  
7 injury among tegaserod users versus non-users.

8 However, in this study, an ascertainment of  
9 death due to suicide required patient contact with  
10 an ER or admission to a hospital. Overall, because  
11 of the small number of events and the possibility  
12 of missed cases of suicide due to an insensitive  
13 method of reporting, findings provide little  
14 additional information specifically about possible  
15 suicide from tegaserod.

16 I will now request Dr. Van Tran to present  
17 the FDA statistical perspective on the CV ischemic  
18 safety signal. Thank you.

19 **FDA Presentation - Thanh Tran**

20 DR. TRAN: Thank you, Dr. Apparaju.

21 Good morning. My name is Van Tran, and I'm  
22 presenting FDA's cardiovascular meta-analysis of

1 all 29 aforementioned clinical trials. The  
2 objective of FDA's CV assessment is to compare the  
3 CV risk in tegaserod-exposed patients to the CV  
4 risk in placebo patients for each adjudication.

5 Our analysis synthesized this information  
6 from all trials to obtain a more precise estimate  
7 of the CV risks and preserves of in-trial  
8 randomization by stratifying on trial, which is not  
9 done in a pooled analysis and includes information  
10 from trials with zero CV events.

11 For FDA's meta-analysis, all 29 randomized  
12 clinical trials were included. The following list  
13 summarizes the main features of these trials: 24  
14 out of 29 trials were double-blind, multi-center,  
15 parallel group studies; 28 out of 29 trials were  
16 less than 12 weeks in duration; the number of  
17 patients per trial ranges from 12 to approximately  
18 2600 subjects; as stated previously by  
19 Dr. Apparaju, the trials studied multiple  
20 indications and dosages; the CV cases identified by  
21 the three adjudications were assessed  
22 retrospectively and not pre-planned; lastly,

1 patient level data were available for analysis.

2 The analysis population is a safety-  
3 analyzable population defined as all patients  
4 exposed to any amount of tegaserod and with at  
5 least 1 post-baseline safety evaluation, which  
6 includes adverse events, vitals, labs, or ECG. The  
7 trial set includes all 29 randomized trials. We  
8 compared risks for two outcomes, MACE and ischemic  
9 events.

10 In our meta-analysis, we used the risk  
11 difference to measure excess or reduction in the  
12 number of CV events per 10,000 patients in the  
13 tegaserod arm compared to the placebo arm. We  
14 chose the Mantel-Haenszel risk difference estimator  
15 stratified by trial and modeled the risk difference  
16 using a fixed effects model. We did not adjust  
17 alpha level or type 1 error for multiple testing,  
18 where multiple refers to 3 adjudications and 2  
19 outcomes, one nested in the other.

20 As shown previously by Dr. Apparaju, patient  
21 baseline characteristics are approximately balanced  
22 between tegaserod and placebo arms.

1           This table shows the meta-analytic results  
2 by adjudication and by outcome. The first column  
3 list the 3 adjudications. The second column lists  
4 the 2 endpoints of interest. The next two columns  
5 shows the number of cases by treatment, and the  
6 last column show the meta-analysis Mantel-Haenszel  
7 risk difference.

8           Note that the sample size, approximately  
9 11,600 tegaserod and 7,000 placebo, differ in the  
10 two treatment groups because of unequal  
11 randomization in some trials. The internal  
12 adjudication identified 11 major ischemic events  
13 for the tegaserod arm and 1 for placebo arm,  
14 corresponding to an increase of 7.6 events per  
15 10,000 patients in the tegaserod arm with a wide  
16 95 percent confidence interval that spans 1.6 to  
17 13.7, excluding zero treatment difference.

18           Compared to the next 2 adjudications,  
19 ischemic events are major cases comprised of  
20 confirmed, unconfirmed, and probably not events.  
21 Also, MACE was not assessed.

22           Moving on to the first external

1 adjudication, which identified 13 confirmed  
2 ischemic events in the tegaserod arm, 1 in the  
3 placebo arm, corresponding to an increase of 10.1  
4 events per 10,000 patients in the tegaserod arm,  
5 again with a wide 95 percent confidence interval  
6 that excludes 0 treatment difference.

7           The same adjudications found 7 MACE cases in  
8 the tegaserod arm, 0 in the placebo arm,  
9 corresponding to an increase of 5.4 events per  
10 10,000 patients in the tegaserod arm. The final  
11 adjudication is the second external adjudication,  
12 which identified a smaller number of confirmed  
13 ischemic events, 7 tegaserod, 1 placebo, and MACE,  
14 4 tegaserod, zero placebo, with risk differences  
15 that again show an increase in the number of cases  
16 per 10,000 patients in the tegaserod arm.

17           Compared to the previous adjudications, the  
18 second external adjudication resulted in narrow  
19 confidence intervals that contain zero.

20           This is a forest plot showing the MACE risk  
21 difference and 95 percent confidence intervals by  
22 trial and overall meta-analytic risk difference

1 located at the bottom of the plot for the final  
2 second external adjudication.

3 The confidence intervals are color coded by  
4 indication. The legend is located on the right.  
5 There are 4 MACE cases from 4 different trials in  
6 the tegaserod arm and zero in placebo in the second  
7 external adjudication.

8 The plot shows that many trials have risk  
9 difference estimates equal to zero and the  
10 estimates have great variability, as seen by the  
11 wide confidence intervals that are a result of  
12 small trial sample sizes. Combined in a meta-  
13 analysis, the overall risk difference of 3.1 is  
14 greater than zero and has greater precision than  
15 the individual trials.

16 In conclusion, the adjudications identified  
17 few CV events, and as a result, few MACE cases from  
18 trials that did not have large sample sizes. All  
19 three adjudications presented an increased number  
20 of ischemic events and MACE in the tegaserod arm  
21 compared to the placebo arm.

22 Inference about the risk difference of our



1 meta-analysis is limited by short trial duration, a  
2 low CV risk population, and a retrospective  
3 assessment of CV information.

4 Next, I will turn the podium over to  
5 Dr. Joel Weissfeld.

6 **FDA Presentation - Joel Weissfeld**

7 DR. WEISSFELD: My name is Joel Weissfeld.  
8 I am a medical officer in the CDER Office of  
9 Surveillance and Epidemiology. I am here to offer  
10 FDA's assessment of a cohort study of tegaserod and  
11 cardiovascular events.

12 To support the cardiovascular safety of  
13 tegaserod, the applicant submitted a final report  
14 from an observational non-randomized study  
15 completed in 2007 by an independent contractor with  
16 direction and funding provided by a previous NDA  
17 sponsor. Documents available for NDA review  
18 included not only the final report but also a study  
19 protocol and a manuscript published in 2010.

20 Using a U.S. database of insurance claims,  
21 the investigators constructed two propensity  
22 score-matched cohorts representing patient-time

1 associated with either the initiation or  
2 non-initiation of tegaserod between September 2002  
3 and December 2006.

4 The exposed cohort contained 52,229  
5 patients, 11.8 percent of men, 23.6 percent aged  
6 greater than or equal to 55 years, with an index  
7 pharmacy claim for tegaserod and no claims for  
8 tegaserod during the preceding 6 months.

9 With index date chosen at random, the  
10 unexposed cohort contained 52,229 propensity  
11 score-matched patients sampled from a large  
12 comparator pool of patients with medical claims  
13 containing a diagnosis code frequently seen in the  
14 exposed cohort. Cohort matching occurred within 1-  
15 year blocks of calendar time. The exposed and  
16 unexposed cohorts appeared well-matched on baseline  
17 risk factors for cardiovascular disease.

18 Using diagnosis and procedure codes on  
19 hospital claims, the investigators identified  
20 events that occurred during the 6 months after each  
21 patient's index date. The investigators defined  
22 two main outcomes: cardiovascular ischemic event,

1 or CVIE, and stroke. The investigators formed the  
2 CVIE outcome as a composite of acute myocardial  
3 infarction, acute coronary syndrome, and coronary  
4 revascularization.

5 To confirm events, exposure-blind study  
6 clinicians reviewed patient chart abstracts  
7 prepared by research nurses. For chart  
8 confirmation purposes, acute myocardial infarction  
9 required an event date specified by physician  
10 diagnosis in the patient's chart or a likely  
11 clinical scenario supported by other evidence such  
12 as abnormal electrocardiogram or elevated blood  
13 creatine kinase.

14 Acute coronary syndrome required an event  
15 date specified by physician diagnosis in the  
16 patient's chart or a likely clinical scenario  
17 associated with an appropriate diagnostic procedure  
18 such as coronary catheterization. Coronary  
19 revascularization required a  
20 procedure-date-documented, coronary artery bypass  
21 graft surgery, percutaneous coronary intervention,  
22 or thrombolysis by intravenous infusion.

1           Stroke exclusive of transient ischemic  
2           attack required an event specified by physician  
3           diagnosis in a patient's chart or diagnosis  
4           supported by appropriate diagnostic test or  
5           therapeutic intervention.

6           This slide summarizes tegaserod-exposed  
7           patients with at least 1 event during fixed 6-month  
8           follow-up. The first column lists the study  
9           outcomes, the CVIE composite and stroke. The  
10          indented labels identify the three components of  
11          the CVIE outcome: acute myocardial infarction,  
12          acute coronary syndrome, and coronary  
13          revascularization.

14          This slide could be used to make several  
15          points. For today's meeting, I will use data on  
16          this slide to provide the advisory committee with  
17          some sense of the possible importance of the  
18          coronary revascularization outcome to the CVIE  
19          composite.

20          For this purpose, please focus your  
21          attention on the right-most column, which shows the  
22          number of tegaserod-exposed patients with at least

1 1 event confirmed by review of patient charts.

2 Charts confirmed a CVIE in 107 patients.  
3 Charts confirmed an acute myocardial infarction in  
4 31 patients and an acute coronary syndrome event in  
5 35 patients. Reckoning that a unique patient could  
6 experience separate AMI and ACS events, we infer  
7 that the 107 patients with chart-confirmed CVIE  
8 included at most 66 patients with chart-confirmed  
9 acute myocardial infarction or acute coronary  
10 syndrome.

11 This inference suggests that coronary  
12 revascularization alone established CVIE in at  
13 least 41 patients, the difference between the  
14 number of patients with CVIE and the maximum  
15 possible number of patients with AMI or ACS.

16 This slide summarizes main study results,  
17 chart-confirmed CVIE and stroke incidence in 52,229  
18 matched pairs by tegaserod-exposure cohort.  
19 Six-month follow-up identified 107 tegaserod-  
20 exposed and 115 unexposed patients with at least  
21 1 chart-confirmed CVIE. Adjusting for age, sex,  
22 year, geographic region, and 14 baseline

1 covariates, Cox-proportional-hazards-regression  
2 estimated relative risk at hazard ratio 0.95,  
3 95 percent confidence interval, 0.73 to 1.23.

4 Follow-up identified 16 exposed and  
5 18 unexposed patients with at least 1  
6 chart-confirmed stroke, adjusted hazard ratio 0.90,  
7 95 percent confidence interval, 0.46 to 1.77.

8 In addition to analyses conducted over fixed  
9 6-month windows, the investigators completed  
10 as-treated analyses designed to estimate risks  
11 during current tegaserod use relative to non-use.  
12 With mean 2.4 months of tegaserod use per exposed  
13 patient, as-treated analysis estimated the adjusted  
14 relative risk, 1.14, confidence interval 0.83 to  
15 1.56 for chart-confirmed CVIE, and 1.09, 95 percent  
16 confidence interval, 0.49 to 2.42 for  
17 chart-confirmed stroke.

18 Our assessment identified three issues  
19 possibly worth further discussion. By creating  
20 uncertainty, these issues affect the interpretation  
21 of results. First, non-randomized studies are  
22 susceptible to confounding. In a drug safety

1 context, confounding refers to uncontrolled  
2 baseline differences that affect associations  
3 measured between the drug exposure and safety  
4 outcome.

5           The Cohort Study of Tegaserod and  
6 Cardiovascular Events used generally acceptable  
7 methods to mitigate confounding. Second, the  
8 coronary revascularization outcome, a component of  
9 the CVIE outcome, appeared to make no distinction  
10 between interventions for acute as opposed to  
11 chronic indications. Concerned primarily about  
12 tegaserod's acute effects, our assessment regarded  
13 the elective intervention for stable cardiovascular  
14 disease as poorly suited for the CVIE composite.

15           If frequent relative to emergent  
16 interventions, elective interventions might have  
17 weakened the CVIE outcome as an indicator for  
18 cardiovascular risk from tegaserod.

19           As noted earlier, study procedures appeared  
20 to use coronary revascularization alone to  
21 establish CVIE in at least 41 of 107 tegaserod-  
22 exposed patients with CVIE. An unknown number of

1 these 41 patients, if any, had CVIE defined solely  
2 by coronary revascularization as a non-acute  
3 intervention. Finally, a small number of events  
4 limited the potential meaningfulness of results  
5 reported for stroke.

6 In conclusion, study-defined endpoints  
7 occurred no more frequently during 6-month  
8 post-index follow-up in tegaserod-exposed and  
9 unexposed patients. We assessed this study as  
10 generally sound for a non-randomized study.  
11 However, this study should not be regarded as  
12 comparable to a well-performed randomized trial  
13 with prospectively ascertained and rigorously  
14 adjudicated cardiovascular outcomes. This  
15 completes FDA's presentations.

16 **Clarifying Questions to the Presenters**

17 DR. RAUFMAN: Thank you.

18 We have 20 minutes for clarifying questions  
19 before we break for lunch. Please remember to  
20 state your name for the record before you speak.  
21 If you can, please direct questions to a specific  
22 FDA presenter. Dr. Thadani?



1 DR. THADANI: I have questions regarding the  
2 neuropsychiatric -- let me see. Who did that. I'm  
3 lost now. Regarding the neuropsychiatric  
4 evaluation, the balance is in the wrong direction.  
5 Was it in the low-risk population? Because the  
6 earlier part was shown as a separate analysis of  
7 cardiovascular events in the low risk.

8 So does it also apply to low risk or is it  
9 allcomers? I'm trying to see who --  
10 neuropsychiatric.

11 DR. VENKATARAMAN: So we didn't specifically  
12 analyze the population in terms of low or high risk  
13 in terms of SI/B. The initial analysis and signal  
14 was assessed back in 2007. And when the imbalance  
15 was assessed, we looked at specifically if there  
16 were a higher incidence in patients taking  
17 antidepressant medications, et cetera. So we  
18 didn't specifically look at it in terms of how many  
19 patients had --

20 DR. THADANI: The reason I'm asking is that  
21 you've shown a subpopulation, low risk have low  
22 cardiovascular events, down to 1 or 2, whatever.

1 And yet, it's possible that the younger people have  
2 more neuropsychiatric issues. And if your balance  
3 is you're saying, cardiovascular less,  
4 neurovascular goes the wrong way, it could have a  
5 profound impact on the whole assessment of risk-  
6 benefit ratio.

7 DR. KORVICK: So this is Dr. Korvick, FDA.  
8 I think what you're asking us is a little bit more  
9 of a description about who these patients are.

10 DR. THADANI: Yes. Are they younger rather  
11 than older?

12 DR. KORVICK: We don't have that data  
13 available to us here today, but the point you made  
14 is one well taken. I think we can look back in our  
15 briefing document. We may have patient  
16 descriptions. We can get back to you if we have  
17 that available to us today, but thank you for your  
18 point.

19 DR. THADANI: I think that would be  
20 important because I really do not want to labor it.

21 The other issue is -- sorry, second  
22 question -- the effects on the platelets was

1 inconclusive by the FDA data review and yet was  
2 very conclusive by the sponsors.

3           Perhaps the reason is because the  
4 antagonist they used in some of the trials is the  
5 different ones. They did not use all the different  
6 antagonists, and that could be the reason. And  
7 they could have some important relevance in  
8 patients with underlying cardiovascular risk or  
9 disease.

10           That was regarding the -- I think they did  
11 some only with the ADP, not with collagen and other  
12 issues, and that could be --

13           DR. KORVICK: While our colleague may want  
14 to say more, I would point out that there is, as  
15 you point out, a variety of tests done, a variety.  
16 We don't have at the FDA a specific recommended  
17 panel, so the results are what they are, and you  
18 can see that they were done over time. Are the  
19 testings done today in different labs? We also  
20 know that there's variability from lab to lab, and  
21 the earlier report was, I think, done in 2008, and  
22 more recent studies were done more recently.

1           So I don't know if that can help us  
2 understand. My colleague may want to say more.

3           DR. CHENG: Yes, I think, Dr.  
4 Korvick -- this is Jenny Cheng. I'm the clin pharm  
5 reviewer for this applicant and platelet  
6 aggregation review.

7           So far, besides the applicant's assay, also  
8 published in 2008, there are three literature  
9 available right now. And I think, across different  
10 studies, there are some different settings for the  
11 experiment, including the number of platelets,  
12 which might be important for the results.

13           So the reason we said it is inconclusive is  
14 because of the different settings for the  
15 experiment, and also, it showed us inconsistent  
16 results across different studies for tegaserod.

17           Talking about the metabolites, I think the  
18 results right now we have is -- because the  
19 concentration they use is 100 millimolar. It's  
20 less than the M29 Cmax under the proposed dose. So  
21 I think the applicant right now is  
22 conducting -- for the assay to just repeat their

1 experiment right now. Hopefully, they can have  
2 some results to provide to us soon.

3 DR. THADANI: Can I ask one last question?  
4 The response rate -- I think this is addressed to  
5 Dr. Levine and Dr. Mann -- is very variable. It  
6 seems that response could go from 4.7 to  
7 11.4 percent in different studies, and I think this  
8 is, again, substantiated. And this is in your  
9 select population they're asking for.

10 So that's great, but if you're down  
11 25 percent, that's pretty low, 12 percent. I'm not  
12 saying it's not beneficial. You're beating the  
13 placebo. I think we're reaching the same thing  
14 when we do exercise tests in the CAD population.  
15 Sometimes, you end up with that.

16 So I think that has to be taken in context  
17 with your other issues I highlighted regarding the  
18 neuropsychiatric, does it all balance the  
19 risk-benefit in your judgment?

20 DR. KORVICK: This is Dr. Korvick again from  
21 the Division of Gastroenterology. I think you  
22 bring up an interesting point of view, but we can

1 say in the GI realm that the average  
2 difference -- and we see this also in psychiatric  
3 trials -- there's a placebo effect. And these  
4 analyses, as was pointed out by my colleague,  
5 Dr. Lavine, were not intended to have statistical  
6 rigor because they're post hoc, et cetera.

7           They were trying to give the committee a  
8 feeling that, if you would eyeball this, maybe you  
9 would come to the conclusion that there are some  
10 benefits for people in a more narrow population  
11 that might approximate what we saw for the larger  
12 population.

13           I think, just going back in history, when we  
14 reintroduced Lotronex to the market, we did a  
15 similar kind of analysis, which was also of this  
16 ilk.

17           We also tried to present information on the  
18 number, the types of patients that were in that  
19 population, not having bowel movements more than 4  
20 or 5 days a week. I mean, that seems pretty  
21 substantial. So we try to give a variety of  
22 analyses for your consideration.

1 DR. RAUFMAN: Dr. Lebwohl?

2 DR. LEBWOHL: Ben Lebwohl. To follow up on  
3 what Dr. Thadani was asking about the platelet  
4 aggregation studies, can we call up slide 54? That  
5 I found to be the most maybe compelling or also  
6 frustrating of the data we saw because it appears  
7 that there is a small cardiovascular risk, and  
8 we're trying to get at the mechanism.

9 So there we're seeing what appears to be a  
10 non-significant trend that is dose dependent, and  
11 the data stop at 100 nanomolar. And it's  
12 frustrating that that doesn't reach the clinically  
13 relevant concentration, which I believe you said  
14 was 160.

15 So that's concerning. And I guess my  
16 question is, how variable is this, and how high  
17 should we be looking at this? Maybe we shouldn't  
18 even be stopping at 160. It might be higher in  
19 some individuals.

20 DR. CHENG: Yes. First of all, the sample  
21 size for this study is 20 healthy subjects, and I  
22 think the number of the subjects used in the

1 applicant's studies is for the tegaserod as well.  
2 From the data, we can see big variations for the  
3 M29. And you can see this study, if you some  
4 increase under the 100 nanomolar, it's just for  
5 some of the agonists, but not for all the agonists.

6 So basically, the basal level is pretty  
7 high, even without adding any agonist if you see  
8 the vehicle. So for this assay, I think the  
9 applicant used the 25,000 platelets to 50,000  
10 platelets, and actually the standard platelet  
11 number is 25,000 platelets.

12 So I think the platelet number is relatively  
13 high for this assay, so maybe it leads to the high  
14 basal level for platelet aggregation already. So  
15 therefore, just some of the agonists show the  
16 positive effect. And maybe it's also a reason to  
17 lead to the high variability across the 20  
18 subjects.

19 Another thing is that the concentration is  
20 as the highest, 100 millimolar, and it's less than  
21 160 millimolar. So right now, all the results  
22 considered, I don't think M29's result is



1 conclusive. We need to see the repeated result  
2 from another assay.

3 DR. LEBWOHL: At a higher concentration.

4 DR. CHENG: And a higher concentration, yes.

5 DR. RAUFMAN: This is Dr. Raufman. If I  
6 could ask, were these data -- I know it's a very  
7 small number of subjects. Did you analyze them for  
8 females alone? And what is the age of these  
9 subjects?

10 DR. CHENG: If my memory serves me  
11 correctly, I cannot -- I think -- for female --

12 DR. RAUFMAN: No, it is, but I'm talking  
13 about the analysis. Was the analysis performed for  
14 women alone?

15 DR. CHENG: This is mixed subjects.

16 DR. RAUFMAN: Right. That's why I'm asking,  
17 was the analysis performed for women alone? The  
18 answer could be no.

19 DR. KIM: Right. This Insook Kim, FDA. We  
20 didn't do that analysis. We can get back to this,  
21 and then also we can get back to you in terms of  
22 the age of this subject. Normally, those are young

1 patients -- not patients, young subjects.

2 DR. RAUFMAN: Thank you. Dr. --

3 DR. LEBWOHL: Just one other short question  
4 if you don't mind -- Ben Lebowhl again -- about  
5 actually the psychiatric safety with regard to  
6 suicidal ideation and behavior. Antidepressants  
7 were mentioned as a possible co-administered drug,  
8 but one thing that's very different now in 2018 are  
9 opioids. And I would imagine that this will be  
10 used off label for opioid-induced constipation.

11 Are there any data on co-administration of  
12 this drug with opioids with regard to these  
13 psychiatric outcomes?

14 DR. VENKATARAMAN: I don't think we're aware  
15 of that at this time. I'm sorry. This is Preeti  
16 Venkataraman. I don't believe we are aware of that  
17 information of off-label use in the OIC population  
18 at this time.

19 DR. RAUFMAN: Dr. Solga?

20 DR. SOLGA: Since Dr. Korvick brought  
21 Lotronex into the room, I wanted to go back there  
22 for a moment if you don't mind, please.

1 I wonder if FDA considered the regulatory  
2 precedent and option in this case when we talk  
3 about benefit-risk considerations and focusing on  
4 opportunity for those most in need with acceptable  
5 risk.

6 I felt like the REMS program for that drug  
7 worked quite well, and over time, actually was  
8 peeled back. And the centerpiece was the PASE  
9 acknowledgement form where the prescriber and  
10 patient had the opportunity to agree that this was  
11 a serious unmet need for the patient, all other  
12 options had been exhausted, and the patient and  
13 prescriber were both willing to tolerate a certain  
14 level of risk.

15 That obviously transfers that benefit-risk  
16 consideration from the FDA and the sponsor to the  
17 prescriber and the patient, arguably, where it  
18 belongs. I wonder if that was considered here.

19 DR. KORVICK: At this point in time, we are  
20 trying to get an answer from the committee -- this  
21 is Dr. Korvick -- for the strength of the signal.  
22 If people feel that this signal is very weak and we

1 can just label it, we don't need to talk about a  
2 REMS. If you all think that you won't put it back  
3 on the market, that's a whole other thing. If you  
4 all think this is a really bad drug, we need to  
5 know that.

6 I think we need to hear the decision about  
7 how you would think about benefit and risk and  
8 lining those things up. I will say two things  
9 about the REMS in Lotronex.

10 Number one, the REMS in Lotronex was  
11 somewhat different in the case that the side effect  
12 was ischemic colitis, so those symptoms were also  
13 symptoms that paralleled the underlying disease,  
14 pain, et cetera.

15 So people may have felt, and indeed we saw,  
16 that they thought, we'll keep taking our drug  
17 because this is going to help me with those  
18 symptoms. So the major point there was  
19 recognizing, between the physician and the patient,  
20 what those bad symptoms could look like.

21 Now, in this case, we're talking about  
22 something different. We're talking about

1 cardiovascular events. And then it drags me back  
2 to what is the weight of the evidence.

3           You are correct. Over time, the Lotronex  
4 REMS has changed, and it's now mostly an  
5 educational program. I think that there are very  
6 few highly restrictive REMS that are currently  
7 approved in the FDA. Lotronex is currently not one  
8 of them.

9           So it goes back. It brings our discussion  
10 back. And what we're trying to do today is have a  
11 discussion of what you all think the benefits and  
12 risks are.

13           At the very end, if you want to comment  
14 during your discussion of how you feel about  
15 putting it back on the market and what you would  
16 recommend for us to use, vehicles, right now the  
17 sponsor is proposing labeling, and some of the  
18 usual things that they might do in a normal way of  
19 approving a drug, your label warnings, your label  
20 precautions, sponsors reach out with educational  
21 programs. That's what they're proposing.

22           We did not ask a question about the REMS

1 today. We want to hear from you what the  
2 benefit-risk is. But if you all want to comment  
3 later, we'd be glad to hear what you have to say.

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

5 DR. MANN: Thank you. I've got a question  
6 about both the review of the data from all the  
7 randomized clinical controlled trials and the  
8 propensity analysis study that was done in regards  
9 to the very low rates of ideation and suicidal  
10 behavior that were detected, and the implications  
11 for trying to estimate what the risk is, and if  
12 there is any risk, how big is it.

13 So for clarification, can you just verify  
14 the outcome measures were assessed based on coding  
15 rather than natural language processing or kind of  
16 a text analysis of the records for each subject?

17 DR. WEISSFELD: Yes. This is Joel Weissfeld  
18 from FDA, Office of Surveillance and Epidemiology.  
19 The outcomes were assessed from insurance claims  
20 for hospitalizations and emergency room visits.  
21 The self-injury outcome was based upon, hold on --  
22 and I'm looking it up right now; hold on -- any

1 healthcare claim with a diagnosis code for suicide  
2 or self-inflicted injury. And those are based upon  
3 ICD-9 codes of E950 to E959.

4 DR. MANN: And the RCT data?

5 DR. WEISSFELD: No. These are not RCT data.  
6 This is in the observational studies.

7 DR. MANN: Right. I understand the  
8 observation study. And that's all relied on  
9 coding.

10 DR. WEISSFELD: Right. And then the chart's  
11 confirmed analyses use medical records to confirm  
12 and date outcome events identified on claims.

13 DR. MANN: But they use the coding in order  
14 to go to the charts to verify.

15 DR. WEISSFELD: Well, they were part of the  
16 chart abstraction purpose and review, with there  
17 being alternative explanations for the self-injury,  
18 this sort of thing, I believe. In terms of our  
19 assessment, I think the primary concern is that you  
20 would miss suicides that don't result in a visit to  
21 an emergency room or a hospitalization. So if  
22 they're immediately fatal suicidal events, that's

1 missed entirely by this ascertainment process. So  
2 that's a primary concern.

3 But in terms of the observational study, it  
4 was primarily ascertained by looking at claims, but  
5 there was some attempt, to the best of our  
6 knowledge, to at least pull some charts and see  
7 whether or not there is evidence in the chart to  
8 support the administrative claim.

9 In terms of the randomized clinical trials,  
10 I can't speak to that directly. Maybe someone else  
11 can. You're asking how the events were  
12 ascertained?

13 DR. MANN: Yes, right.

14 DR. WEISSFELD: I believe they were through  
15 routine adverse event reporting.

16 DR. MANN: So both of those methods are  
17 extremely flawed because there's a recent study  
18 that appeared in scientific reports, in Nature,  
19 that showed that if you look at EMRs with coding,  
20 you pick up 3 percent of the suicidal ideations and  
21 25 percent of the suicide attempts, which are  
22 clearly more dramatic. But if you go through the



1 same EMRs with natural language processing, then  
2 that's how you find out another number, which is  
3 how you get the 3 percent and the 25 percent.

4 So there is an enormous failure of  
5 ascertainment that is introduced into the method if  
6 you just rely on the coding.

7 DR. KORVICK: I think that's really very  
8 important and interesting research, and one might  
9 say that about almost anything we look into. I  
10 think it's somewhat futuristic, and these are the  
11 data that we have.

12 So I take your point about how we may be  
13 underrepresenting if we are not using the natural  
14 language searching on medical records.

15 DR. MANN: I think that that handicaps your  
16 ability to translate this into the labeling of the  
17 drug because you want to have enough information in  
18 labeling of the drug so that the doctor and the  
19 patient can try and figure out what the risk is.

20 If you're asking these patients to try and  
21 decide is it worth this percentage of improvement  
22 over placebo to take this drug versus what the

1       problem may be taking the drug, then you want to  
2       have relatively, as possible, secure estimates of  
3       risk rates. And natural language processing in  
4       these techniques, I would maintain, are new, but  
5       they're not futuristic. They're right here, now.

6               DR. KORVICK: I take your point. A lot of  
7       this data is in paper, and that's what we're  
8       dealing with right now. But point well taken.

9               DR. RAUFMAN: I think we can move on and  
10       address that again later when we have our general  
11       discussion. We have time for two brief questions.  
12       Dr. Teerlink has one.

13               DR. TEERLINK: So there seems to be some  
14       difference in terms of how the sponsor is defining  
15       low-risk cardiovascular population and the FDA has  
16       been addressing low-risk cardiovascular population.

17               In terms of the analysis on CC-67, how would  
18       that analysis of low-risk females be if it were  
19       confined to females aged less than 65 years without  
20       cardiovascular ischemic disease? In other words,  
21       we don't care about the risk factors. Would there  
22       have been a difference? So just that.

1 I'm asking the FDA for their analysis.

2 Sorry. I'm asking the FDA.

3 DR. KORVICK: Our analysis is on slide 67?

4 DR. TEERLINK: Right. Did you do analysis  
5 with just using the less than 65 years of age  
6 females and history of cardiovascular disease?

7 DR. APPARAJU: Yes. This is Sandhya  
8 Apparaju. Basically, when we restrict the  
9 population to less than 65 and only absence of CV  
10 ischemic disease, a greater percentage of patients  
11 in the database qualified, so to speak, 96 percent  
12 versus 76 percent if we were to add the CV risk  
13 factor.

14 So our analysis for the three-factor, if you  
15 want to call this three-factor, it's up there. And  
16 when we bring it down to two factors, remove the  
17 baseline CV risk factors, in the first external  
18 adjudication, for example, we found 4 CVI cases, 2  
19 of which were MACE. I believe there's a  
20 discordance between the sponsor's numbers.

21 DR. KORVICK: We have a back-up slide,  
22 number 18.

1 DR. VENKATARAMAN: Yes. Could you please  
2 pull up our FDA back-up slide, number 18, please?

3 DR. APPARAJU: So to answer the question, we  
4 did do the analysis in the sponsor's redefined way,  
5 and you can see the N in the top row. You can see  
6 there are more number of tegaserod patients that  
7 would qualify under the definition.

8 There were 4 CVI events in the first  
9 external adjudication, and 2 of which were MACE.  
10 And in the second external, that reduces down to 2  
11 and 1, respectively. The sponsor's numbers were 5  
12 and 3 in the first probably because there is a  
13 difference between the interpretation of whether or  
14 not a patient had an underlying CV ischemic disease  
15 history.

16 DR. TEERLINK: Thank you.

17 DR. RAUFMAN: Last question. Ms. Robotti?

18 MS. ROBOTTI: Thanks. Suzanne Robotti. I  
19 did not see any information about the drop-out rate  
20 for any of the studies or if there was an analysis  
21 done for the reasons for drop-outs and  
22 consequences.

1 DR. KORVICK: We did not present that  
2 because we were not reviewing all of the  
3 information from the previous approvals. I can't  
4 give you that number today, but those are in the  
5 data from the previous approvals.

6 It may be in the label, the current label.  
7 Sometimes we put those in the label. So we could  
8 check and see if we can get back to you after the  
9 break.

10 DR. RAUFMAN: We will now take a 50-minute  
11 break. Panel members, please remember there should  
12 be no discussion of the meeting topic during the  
13 break, amongst yourselves or with any member of the  
14 audience. We will resume at 1:15 p.m. We will  
15 resume at 1:15 p.m. Thank you.

16 (Whereupon, at 12:22 p.m., a lunch recess  
17 was taken.)  
18  
19  
20  
21  
22

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

(1:17 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 relationships that you may have with a sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the

1 committee if you do not have any such financial  
2 relationships. If you choose not to address this  
3 issue of financial relationships at the beginning  
4 of your statement, it will not preclude you from  
5 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. OSBORN: Good afternoon. My name is  
2 Dr. Neal Osborn from Atlanta, Georgia. I am  
3 speaking on the request of the American College of  
4 Gastroenterology. A direct member could not be  
5 present today, and as a senior member and committee  
6 member and fellow of the American College, I am  
7 reading a letter for the open statement, and I have  
8 no disclosures for that.

9 At the conclusion of that, I will make a  
10 very brief statement as a practicing  
11 gastroenterologist, and for that, I am a paid  
12 consultant in respects, but I have no financial  
13 outcome on today's session.

14 So from the American College of  
15 Gastroenterology, Docket Number FDA 218N-3223, they  
16 have asked me to present this letter.

17 "The American College of Gastroenterology  
18 appreciates the opportunity to comment in support  
19 of Zelnorm, tegaserod maleate tablets for the  
20 treatment of women with irritable bowel syndrome  
21 with constipation who do not have a history of  
22 cardiovascular ischemic disease such as myocardial



1 infarction, stroke, transient ischemic attack, or  
2 angina, as well as no more than 1 risk factor for  
3 cardiovascular disease.

4 "ACG is a physician organization  
5 representing gastroenterologists and other  
6 gastrointestinal specialists. Founded in 1932, our  
7 organization currently includes over 15,000 members  
8 providing gastroenterology specialty care. We  
9 focus on the issues confronting GI specialists and  
10 delivering high-quality patient care.

11 "The primary activities of the ACG have been  
12 and continue to be promoting evidence-based  
13 medicine and optimizing the quality of patient  
14 care. With that said, irritable bowel syndrome is  
15 the most prevalent of the functional  
16 gastrointestinal disorders that we treat. Current  
17 estimates are that IBS affects up to 12 to  
18 15 percent of adults in North America.

19 "Although it can affect all individuals  
20 regardless of age, creed, sex, et cetera, IBS is  
21 more common among women and is most commonly  
22 diagnosed in younger individuals less than age 50.

1           "Given the clinical heterogeneity that is a  
2           hallmark of the disorder and the absence of a  
3           single effective therapy for all, available  
4           therapies tend to focus on the predominant symptoms  
5           such as altered bowel habits, abdominal pain, or  
6           bloating. However, treating IBS patients can be  
7           difficult, as no validated treatment algorithm  
8           exists. Not all patients respond to treatment, and  
9           patients can be affected differently.

10           "There are no validated treatment  
11           algorithms, as mentioned. Thus, there is clinical  
12           need for a new therapy for IBS with constipation.  
13           Assuming the FDA and this advisory committee finds  
14           that the updated data and recent medical literature  
15           on Zelnorm are both safe and effective for the  
16           proposed indication and patient population, the  
17           American College of Gastroenterology supports this  
18           application in full."

19           That ends my presentation of the ACG's  
20           letter, and as a brief comment from a very busy  
21           practice gastroenterologist and one who used to be  
22           involved with designing clinical trials, I would

1 just like to mention, in follow-up this morning,  
2 there were some statements made about the delta or  
3 the treatment effect of some of these irritable  
4 bowel syndrome studies, 10 percent from placebo to  
5 drug response and does that matter.

6 I would like to offer my opinion as a  
7 resounding, yes. It really does matter in our  
8 world. With gastroenterology, we are very used to  
9 seeing these clinical trials in IBS where the  
10 treatment response rate is in the 10 to 15 percent  
11 kind of improvement range, and that really  
12 translates into clinical practice in a very  
13 significant manner because we may be treating not  
14 just the constipation, but it may treat the pain.  
15 It may treat it differently. It's how the patients  
16 feel overall, but the clinical trials can often be  
17 very difficult to look at if you just look at that  
18 little slice right there.

19 I'll give you another quick example. With  
20 inflammatory bowel disease, such as ulcerative  
21 colitis, which we treat quite frequently, keeping  
22 in mind that we use medications with significant

1 adverse events, side effects, and a long discussion  
2 with the patients, in those patients we may see a  
3 response rate or a remission rate of only  
4 18 percent for our FDA-approved drugs.

5 So with that said, I do think that that  
6 10 percent really does matter, and I'm kind of  
7 passionate about that.

8 DR. RAUFMAN: Thank you. Will speaker  
9 number 2 please step up to the podium and introduce  
10 yourself? Please state your name and any  
11 organization you are representing for the record.

12 DR. KAUFMAN: My name is Peter Kaufman, and  
13 I'm speaking on behalf of the American  
14 Gastroenterological Association as an AGA fellow.  
15 I have no financial conflicts to disclose.

16 I'm a practicing gastroenterologist with  
17 Capital Digestive Care here in Montgomery County,  
18 Maryland. Following my training at Temple  
19 University Hospital, I joined the GI faculty at  
20 Wake Forest Bowling Green School of Medicine,  
21 focusing on GI motility research. I chaired the  
22 colon motility sessions at Digestive Diseases Week

1 for three years, albeit that was quite a while ago.

2 Since leaving academics, I practiced in the  
3 Washington area for 29 years with an 18-year  
4 partial detour as chief medical officer of DrFirst,  
5 a company best known for electronic prescribing  
6 software.

7 While at DrFirst, I was named to the Health  
8 IT Standards Committee, a privacy and security  
9 workgroup for ONC, and was co-chair for Physicians  
10 EHR Coalition, and for over 10 years have served as  
11 the AGA's delegate to the AMA. In my clinical  
12 practice, I've maintained an interest in testing  
13 motility, which is why I'm here today.

14 This is the AGA's statement.

15 "The mission of the AGA is to advance the  
16 science and practice of gastroenterology. To  
17 achieve our mission, the AGA supports basic and  
18 clinical research, publishes three highly respected  
19 journals, *Gastroenterology*; *Clinical*  
20 *Gastroenterology and Hepatology*; and *Cellular and*  
21 *Molecular Gastroenterology and Hepatology*, and  
22 provides educational and practice resources and

1 programs to gastroenterologists, including clinical  
2 guidelines and clinical practice updates aimed at  
3 helping guide clinical decision-making based on  
4 rigorous, systemic reviews of the medical  
5 literature."

6 GI motility disorders, including irritable  
7 bowel syndrome with constipation, or IBS-C, affect  
8 patients by not only causing symptoms, but posing a  
9 heavy burden of illness, but also by negatively  
10 impacting daily life and productivity. Because  
11 IBS-C affects each patient differently, it can be  
12 complex and difficult to diagnose and treat.

13 Treatment options for IBS-C are limited and  
14 trial and error are often used to identify which  
15 therapy will benefit a patient. This is much  
16 better with the glasses.

17 Currently, three prescription therapies,  
18 linaclotide, lubiprostone, and plecanatide, are  
19 available for the treatment of IBS-C. These  
20 medications are all secretagogues and rely on a  
21 similar mechanism of action. They increase  
22 intestinal chloride secretion with associated

1       secretion of water into the intestinal lumen to  
2       help accelerate intestinal and colonic transit.

3               Because of the heterogeneity of IBS-C, these  
4       therapies work for some patients, but not all, and  
5       treatment satisfaction varies widely from patient  
6       to patient. Current treatments do not effectively  
7       address the needs of all patients.

8               Tegaserod was previously approved for the  
9       treatment of women with IBS-C. Concern regarding  
10      increased cardiovascular risk associated with  
11      tegaserod resulted in its voluntary withdrawal from  
12      the U.S. market. Large epidemiologic studies,  
13      however, have failed to confirm the risk identified  
14      through clinical trial databases, suggesting that  
15      the observation of increased cardiovascular risk  
16      may have been due to chance.

17              Approval of tegaserod would expand the  
18      number of treatments available to  
19      gastroenterologists and other physicians treating  
20      women with IBS-C, and the proposed restriction  
21      indicated for use should help protect against any  
22      risk that may exist. Approval would also make

1 available a therapeutic option with a different  
2 mechanism of action.

3 Tegaserod is a colonic prokinetic, which  
4 increases colonic transit by activating submucosal  
5 neurons to induce mucosal secretion. Approval of  
6 tegaserod will increase the potential for relief  
7 for patients affected by IBS-C, including those who  
8 have not benefitted from currently available  
9 secretagogues.

10 Consistent with our mission to advance the  
11 science and practice of gastroenterology, the AGA  
12 supports the approval of any appropriate and  
13 efficacious treatment that meets the FDA's strict  
14 standards. Furthermore, AGA supports the approval  
15 of tegaserod as an addition to the  
16 gastroenterologist's arsenal of available  
17 treatments for women with IBS-C who do not have a  
18 history of cardiovascular ischemic disease and who  
19 do not have more than 1 risk factor for cardiac  
20 disease.

21 Thank you to the FDA's Gastrointestinal  
22 Drugs Advisory Committee for the opportunity to



1 address this panel.

2 DR. RAUFMAN: Thank you. Will speaker  
3 number 3 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. ROBERTS: Members of the committee,  
7 thank you for the opportunity to appear before you.  
8 I am Jeffrey Roberts. I'm the founder of the IBS  
9 Patient Group. I have paid all my own expenses to  
10 be here.

11 The IBS Patient Group has endeavored since  
12 1987 to educate and provide support for hundreds of  
13 thousands of people who have IBS and to encourage  
14 both medical and pharmaceutical research to make  
15 our lives easier by our IBS patient advocacy  
16 efforts.

17 To IBS patients, IBS with constipation is  
18 not a benign illness. The burden on their quality  
19 of life along with their family's life is enormous.  
20 IBS with constipation cannot be managed simply by  
21 diet alone, by lifestyle changes, by doing more  
22 exercise. Enough research has been completed in

1 the last several decades that clearly illustrate  
2 that the quality of life of an IBS sufferer is  
3 lonely, burdensome, and there remain an unmet need  
4 for relief that are needed.

5           Meno [ph], a member of the IBS Patient  
6 Group, describes his life with IBS with  
7 constipation as if he was living in a cage with a  
8 door that isn't locked, but you are unable to open  
9 the door. Your mind is telling you what you could  
10 do, and your body is constantly telling you, no,  
11 you cannot.

12           Karen says it is as if she is living in her  
13 own world, as no one really understands the pains  
14 we go through, housebound, loss of friends,  
15 activities, loneliness, and depression.

16           I have provided testimony to this committee  
17 several times. In 2004, I testified that IBS  
18 sufferers reported that while taking Zelnorm, they  
19 felt a near complete cessation of their symptoms,  
20 and it changed their lives for the better.

21           Following the withdrawal of Zelnorm from the  
22 market in 2007, I was flooded by messages from

1 former Zelnorm users who were desperate for access  
2 to the medication. While we are grateful that  
3 industry and the FDA have developed and approved  
4 some new IBS with constipation medications since  
5 2007, some of those original Zelnorm users are  
6 still desperate for access to Zelnorm.

7 Fifty-eight percent of IBS sufferers,  
8 surveyed by the IBS Patient Group over the months  
9 of September 2018, indicated that their quality of  
10 life is greatly impacted by IBS. Ninety-one  
11 percent surveyed indicated that they used a  
12 medication to try and treat their IBS symptoms.

13 Our survey also indicates that IBS sufferers  
14 are prepared to accept risks related to treatments  
15 for IBS. The trend for their risk tolerance is  
16 between a serious side effect from a medication and  
17 a low-risk of a side effect from a medication.  
18 Only 8 percent said that it was acceptable to have  
19 no risk while taking a medication.

20 It is not a new finding that IBS sufferers  
21 are prepared to accept risks related to use of  
22 effective treatments for IBS. Patients are well

1       versed at risk management and are asked to make  
2       risk decisions every day, and are comfortable doing  
3       so if adequate information is made available to  
4       them by their physicians.

5               We believe patients are interested in  
6       participating in programs to better identify risks  
7       related to the use of treatments and to work with  
8       the FDA to reduce those risks as much as possible.  
9       The IBS Patient Group is prepared to place  
10      educational information about Zelnorm on their  
11      website in order to reach out to the IBS community.  
12      This provides an effective form for educating IBS-C  
13      sufferers about Zelnorm's proper use.

14              In 2007, we felt that removing access for  
15      Zelnorm further burdened patients and doctors and  
16      that the FDA pulled the medication from the market  
17      too quickly. Since Lotronex, for IBS with diarrhea  
18      patients, came back to the market in 2002 under a  
19      restricted access program, we have observed a  
20      positive safety record for patients and access  
21      restrictions being lessened over time. However,  
22      Lotronex has been lightly prescribed,

1       notwithstanding the benefit outweighing the risks  
2       for appropriate patients.

3               We do not want Zelnorm to also become  
4       lightly prescribed, where from its history patients  
5       reported a near cessation of their IBS-C symptoms  
6       when it was first marketed. We believe that the  
7       reapproval of Zelnorm to manage IBS-C symptoms will  
8       provide further access to a tetramer option where  
9       other new medications have not sufficiently met  
10      patients' needs.

11             Physicians and patients need options, and  
12      the more options that are available, the greater  
13      likelihood that patient symptoms can be effectively  
14      managed.

15             Noel, a former Zelnorm user and a member of  
16      the IBS Patient Group, says, "I have classic IBS-C,  
17      and while using Zelnorm, it was the first time in  
18      my life that I felt normal and my gut acted the way  
19      it should. To say it was life altering was no  
20      exaggeration. I had a normal life without  
21      complications of any kind. I was absolutely  
22      stunned at how lovely it was to simply have a

1 working gut."

2 In conclusion, IBS sufferers' quality of  
3 life was dramatically improved with access to  
4 Zelnorm. IBS sufferers are prepared to accept  
5 risks associated with any medication and want to  
6 work with the FDA to reduce those risks, but  
7 without the burden of access restrictions.

8 We believe Zelnorm to be safe and that the  
9 benefits of Zelnorm outweigh the potential risks  
10 for adverse side effects if prescribed properly.  
11 As an IBS sufferer for over 25 years, the  
12 challenges that I face are far more significant  
13 than the small risk of a cardiovascular adverse  
14 side effect from Zelnorm. Thank you.

15 **Clarifying Questions (continued)**

16 DR. RAUFMAN: Thank you. The open public  
17 hearing portion of this meeting has now concluded,  
18 and we will no longer take comments from the  
19 audience. The committee will turn its attention to  
20 address the task at hand, the careful consideration  
21 of the data before the committee as well as the  
22 public comments.

1           Before we move to the discussion and  
2           questions for the committee, we have clarifications  
3           both from the sponsor and the FDA. We'll start  
4           with the sponsor's clarifications first.

5           MS. GULLO: We have some data we can present  
6           in response to some questions that were asked of  
7           the agency, and they didn't have the data available  
8           readily, around discontinuation rates and also  
9           demographics.

10           In the patients that experienced SI/B  
11           events, Dr. Gerlach will take you through those  
12           really quickly. Then with the chair's permission,  
13           we will also provide a bit of clarification on  
14           something that came up earlier around incidence  
15           rates and short-term versus long-term exposure.  
16           The data we've provided on the screen were actually  
17           not the appropriate data to make that comparison,  
18           and we have the appropriate data.

19           DR. GERLACH: Can I have the slides we  
20           created, please? Can we show slide 1, please?  
21           There was a question on the discontinuation in the  
22           overall database that was shown here today. To

1 remind you, this is database 15 across 29  
2 placebo-controlled trials. This is the intent-to-  
3 treat population.

4 Overall, you see that 85 percent -- and  
5 roughly balanced between tegaserod and placebo  
6 treatment group -- completed the study; 15 percent  
7 did not. And the reasons for discontinuation,  
8 again, were fairly balanced between the treatment  
9 group and placebo.

10 MS. ROBOTTI: I asked that question. Can I  
11 just --

12 DR. RAUFMAN: Ms. Robotti has a question on  
13 that slide.

14 MS. ROBOTTI: Suzanne Robotti. It says  
15 5.5 percent, those on tegaserod withdrew because of  
16 adverse events. Do you have any information on the  
17 adverse events?

18 DR. GERLACH: I don't know that we have that  
19 data in this specific slide.

20 Do we have a back-up slide on the  
21 discontinuations due to adverse events?

22 MS. ROBOTTI: And is that 100 percent of the



1 15? Were you able to find out the reason for  
2 discontinuation on all of the 15 percent who  
3 discontinued and the 13 [indiscernible]?

4 DR. GERLACH: I know, without having the  
5 data in front of me, the discontinuation due to  
6 treatment adverse events, specifically, diarrhea  
7 was the most prevalent, and that's not unexpected.  
8 I believe that's all.

9 DR. RAUFMAN: Dr. Thadani?

10 DR. THADANI: On that slide, could you  
11 define for me, on therapeutic -- can we go back on  
12 the slide?

13 DR. GERLACH: I'm sorry.

14 DR. THADANI: Go back on the slide. What is  
15 unsatisfactory therapeutic event, no response or  
16 what? What does it mean?

17 DR. GERLACH: Yes. That actually appears to  
18 be a typo. It's unsatisfactory therapeutic effect.

19 DR. THADANI: Effect, so that means placebo  
20 withdrawal was about the same as the active drug.  
21 Correct?

22 DR. GERLACH: Yes.

1 DR. THADANI: And the adverse event  
2 withdrawal is higher by 2 percent?

3 DR. GERLACH: Yes.

4 DR. THADANI: So it's going against the  
5 drugs in this slide. Correct?

6 DR. GERLACH: Yes.

7 MS. GULLO: Do we want to go through the  
8 suicidal? I'm unsure that we have that actually  
9 available. But I do think it would be important to  
10 clarify something that was misstated earlier about  
11 the incidence rates and short-term treatment  
12 compared to long-term treatment.

13 I'll ask Dr. Sager. If the panel will  
14 permit, we'll go through about three slides to not  
15 only discuss the actual incidence rates we saw  
16 between short- and long-term exposure on tegaserod,  
17 but also our attempts to try to put the incidence  
18 rates that we did observe in the clinical trial  
19 database into the context of what we would expect  
20 in the general population using the resources we  
21 had available to us.

22 DR. SAGER: Yes. I'm not sure it's

1 misstated. It might have been misunderstood. But  
2 in relationship to Dr. Teerlink, your question, I  
3 showed the rate of the incidence of cardiovascular  
4 events in the long-term follow-up and then compared  
5 it to the placebo group in the placebo-controlled  
6 database from the other study.

7           So we now have actually put together the  
8 data that really compares the event rates. If I  
9 could have slide number 1 up? The event rates were  
10 randomized-controlled studies with the CV ischemic  
11 events, which was 3.9, or MACE events, 2.2 per  
12 1,000 person years, and compared this to the  
13 long-term database, 3.9 is compared to 1.95 and 2.2  
14 compared to 0.49.

15           So there's no evidence that with long-term  
16 exposure, the rates actually went up. I wouldn't  
17 want to draw any other conclusions from this slide.

18           But this raises another question, which is,  
19 what are really the background rates we might  
20 expect? We spent a lot of time looking into this.  
21 We have had Dr. Paul Ridker involved in working  
22 with us, and he was the head of the Women's Health

1 study.

2 If I could have slide 1 up? This study  
3 randomized 3,876 healthy women who had no history  
4 of previous cardiovascular disease, and were  
5 45 years or older, to either aspirin or placebo.  
6 The endpoint was MACE, and the study was conducted  
7 in a contemporaneous general time period, 1992  
8 through 2004.

9 What we've done is looked at the incidence.  
10 First of all, I'll show you the demographics for  
11 women over 45 in the two databases.

12 Slide 1, up. This compares database 15,  
13 either the Zelnorm group or the placebo group, and  
14 this was just for women greater than 45 years old  
15 because that's what the Women's Health study  
16 enrolled. The ages are similar and the breakdown  
17 of the ages are similar. The body mass indexes are  
18 similar.

19 Those who have more than 1 cardiovascular  
20 risk factors is a little bit more in the Zelnorm  
21 study, and they're equal to 2 risk factors, again a  
22 little bit more, and there's 4 percent of patients

1 in Db15 in the Zelnorm study that had a history of  
2 cardiovascular disease. Those an exclusion  
3 criteria in the Women's Health study. And not  
4 shown on this slide, the diabetes rate is also a  
5 little bit higher in Db15 as compared to the  
6 Women's Health study.

7 So the purpose of this isn't to draw any  
8 strong inferences. It's just to give some  
9 perspective of background incidence. So I want to  
10 make sure that there's no perception here that  
11 we're overstating this. This is a comparison  
12 between studies. One study is short term; one  
13 study is long term. I think that needs to be taken  
14 into consideration, but it's just to try to give  
15 some sense of perspective.

16 If we look, I now have slide 2 up. This is  
17 the incidence and events in women over 45 years  
18 old. This is from the second adjudication, which  
19 is the only adjudication that adjudicated the  
20 long-term study here. This is comparing the  
21 incidence rate with Zelnorm as compared to placebo  
22 in this study as well as the Women's Health study.

1 And these are all MACE events because MACE is what  
2 the Women's Health study looked at.

3 So again, within the confines of these  
4 differences in database, I think one thing it does  
5 also at least bring up to me when I look at it  
6 is -- and I was surprised that the placebo MACE  
7 rate was zero, given that there were older women in  
8 Db15, and there were people with cardiac disease,  
9 and diabetes, and multiple cardiac risk factors.  
10 To me, it seemed low, zero.

11 Anyway, I wanted to share this with you. I  
12 guess another -- if I can have the slide down --

13 DR. TEERLINK: Before we leave this slide,  
14 I'd just like to add that we around the table, I'm  
15 sure everybody recognizes that patients who get  
16 involved in interventional clinical trials, in  
17 general, have much lower event rates than  
18 population trials and larger-scale health outcomes  
19 trials like the Women's Health study.

20 So this doesn't surprise me at all. And I  
21 think the conclusion we can draw from this is the  
22 placebo is the drug we should be giving to protect

1       against MACE events in this population.

2               DR. SAGER:  There is one other source of  
3       data, which you're going to be looking at,  
4       prucalopride, tomorrow.  And those studies were  
5       also done for up to 12 weeks in duration and  
6       generally maybe a little bit more chronic  
7       constipation cohort, but still a somewhat similar  
8       cohort, again, up to 12 weeks.

9               The placebo group there, as you'll see  
10       discussed tomorrow, had 2 episodes of MACE in 2,019  
11       patients.  That's a rate of 0.1 percent.  The MACE  
12       event in the second adjudication was -- again, just  
13       to put this in perspective; it's across  
14       trials -- 0.03 percent.  Again, that's the placebo  
15       data.

16              DR. RAUFMAN:  Dr. Thadani, you had a  
17       follow-up?

18              DR. THADANI:  [Inaudible - off  
19       mic] -- Women's Health study.  That study went for  
20       20 years.  So the data you are showing at 2.5 is  
21       over a span of time.  Can you show me data just for  
22       3 months or one year?  Because here, we're

1 comparing apples and oranges. You've got a short-  
2 term 3-month study, maybe follow for short. I  
3 think Paul Ridker's database goes up to 20 years of  
4 follow-up.

5 So to me, it's camouflaging the whole event  
6 rate. I'm not convinced that at 1 year event rate  
7 in Women's Health study, we're all very diet  
8 conscious, exercising was as high as that.

9 You've got a comment on that?

10 MS. GULLO: As you saw on the slide, the  
11 databases account for total number of patient  
12 years, and that becomes the denominator in the  
13 incidence rate calculations. So it actually does  
14 account for differences in time, and because  
15 there's no strong predictor of when an event will  
16 occur, we actually asked Dr. Ridker about this  
17 database and the ability to look at the first  
18 12 weeks as an example. He actually said that  
19 that's not really appropriate to do to try to make  
20 it more apples to apples because it does account  
21 for total time and total events in both instances.

22 DR. THADANI: I know Paul might say that,



1 Dr. Ridker, but to me, if you have a 60-year-old  
2 person who goes for 20 years, event rate may be  
3 higher later on. So we don't necessarily buy that.  
4 This is observation when you correct it for the  
5 number of --

6 MS. GULLO: Right. And we just wanted to  
7 share this as --

8 DR. THADANI: You are deducing your data to  
9 long term, what will happen to them. Maybe it's  
10 correct. I don't know.

11 MS. GULLO: Right. We just thought it was  
12 important to clarify that we didn't actually see  
13 incident rates increase with increased exposure of  
14 the drug. And then we did have some effort behind  
15 trying to understand how that compared to rates in  
16 other databases.

17 So between both the rates that you'll see in  
18 controlled studies tomorrow and also the Women's  
19 Health study, which covered a broad spectrum of  
20 patients, and we did our best to make it apples to  
21 apples to make that comparison, we find that the  
22 incident rate for tegaserod patients is within what

1 we see in other database. And notably, we see that  
2 placebo rates are quite a bit lower than might be  
3 expected.

4 DR. RAUFMAN: Thank you.

5 Dr. Korvick will present the FDA  
6 clarifications.

7 DR. TEERLINK: Can I ask, was the sponsor  
8 not able to produce the systolic blood pressure  
9 frequency distributions that I had requested?

10 MS. GULLO: I don't believe we had an  
11 opportunity to do that. Sorry.

12 DR. KORVICK: Thank you, Raufman. This is  
13 Dr. Korvick. The sponsor might be able to look at  
14 those systolic distributions while I'm talking, but  
15 I would like to go back to our previous  
16 conversation, when we were talking about the  
17 psychiatric issues.

18 We noticed, at least in some of the  
19 documents we have with us, that in general in this  
20 population, about 11 percent of the patients had a  
21 history of current or past antidepressant  
22 treatment.

1           Subanalysis, did all those 11 end up in a  
2 serious IBS population? We don't have that  
3 analysis, but it's certainly an important one that  
4 we can do; but just to say that there were  
5 11 percent in both placebo audience treatment  
6 groups in the randomized population.

7           Then to some of the other comments that you  
8 had about ascertainment and some psychiatric  
9 issues, I'm going to call my colleague, Dr. Robert  
10 Levin, up to the microphone to give you some  
11 thoughts and further reflections.

12           DR. LEVIN: Hi. Robert Levin. I'm a  
13 medical officer in the FDA, Division of  
14 Pharmacovigilance. Dr. Mann, getting back to one  
15 of your questions about ascertainment, we agree  
16 with your point. You asked what was the  
17 methodology of obtaining or ascertaining possible  
18 suicide adverse events. And as Dr. Weissfeld  
19 mentioned, it indeed relied on spontaneous reports  
20 within the trials. There was no prospective  
21 systematic assessment for such events.

22           Later, several years after that, for various

1 reasons, FDA asked the previous sponsor of Zelnorm  
2 to go back in their entire controlled trial  
3 database, which included I think 29 studies and  
4 approximately 17,000 patients. We asked them to  
5 take their existing premarketing controlled trial  
6 database and search their adverse event data for  
7 potential SI/Bs, suicidal ideation and behavior  
8 events, which they did.

9           They do that using the methodology, the  
10 C-CASA. It's the Columbia Classification Algorithm  
11 for Suicide Assessment. They used search and  
12 string terms that could capture suicide, suicidal  
13 ideation, self-injury, and accidental injury such  
14 that they could actually look at the whole database  
15 and see whether there were maybe other adverse  
16 events related to SI/B that had not been captured.

17           They did that. In the data we presented,  
18 actually, maybe we can go back to I think slide 71.  
19 After the sponsor did that, that's the methodology  
20 that resulted in the numbers we presented about the  
21 suicidal ideation and behavior events within  
22 specifically the controlled trials.

1           So your point is correct that since there  
2 was not directed assessment, they did not ask  
3 patients during the trial about any suicidal  
4 ideation and behavior. It's quite likely that  
5 there was underreporting for such events. Most  
6 certainly, there was underreporting, especially in  
7 a fairly high-risk population, but we just don't  
8 know the extent to which there may have been  
9 underreporting. And this presents the difference,  
10 the numerical differences, between groups.

11           DR. KORVICK: Dr. Korvick again. I don't  
12 know if you have any other questions for my  
13 colleague about these issues or if we've addressed  
14 them as well as we can.

15           DR. MANN: I understand that, yes, of  
16 course. The studies were never designed with this  
17 in mind, so it's a bit like the problem that the  
18 Turks are having inside the Saudi embassy.

19           But your observation of the rates that  
20 people were receiving SSRIs is illuminating because  
21 it suggests that this pathology, psychopathology,  
22 is quite prevalent potentially in this patient

1 population, and that it would be valuable at some  
2 point to have an idea as to what the real risks and  
3 what the real numbers are for depression, suicidal  
4 ideation, and behavior in this treatment  
5 population.

6 DR. KORVICK: Yes, thank you. I would just  
7 like to make one last comment. Today's discussion  
8 is focused on the data that was analyzed and  
9 presented regarding tegaserod. Comments by the  
10 sponsor regarding other databases for other drugs  
11 may or may not be very germane to this discussion,  
12 given the fact that those populations are  
13 different. They're in the CIC group. They include  
14 males as well.

15 So the whole risk analysis might be somewhat  
16 different, so I don't know that it's really correct  
17 to consider some of those comments in your analysis  
18 today. Thank you.

19 MS. GULLO: Dr. Raufman, I made a mistake  
20 earlier when I said we were not able to respond to  
21 the systolic blood pressure question. We don't  
22 have a data slide, but Dr. Sager is able to explain

1       what he's reviewed in the data. And if  
2       appropriate, we'd also like to ask Dr. Jones to  
3       give her perspective because there's been a lot of  
4       discussion about interesting points within the full  
5       context, and she's been asked to independently  
6       assess the full picture and give us her  
7       perspective.

8               DR. SAGER: Dr. Teerlink, I have reviewed  
9       the categorical analyses of different ways of  
10      cutting the changes in blood pressure, both  
11      numerical increases and numerical increases with  
12      respect to higher levels of blood pressure, which I  
13      don't have a slide for you, but I can tell you in  
14      the Zelnorm cohort versus the placebo cohort, with  
15      multiple analyses, they were well balanced.

16             There wasn't any evidence of categorical  
17      changes that one saw even though one didn't see a  
18      change in the mean blood pressure, if that's  
19      helpful. Thank you.

20             DR. TEERLINK: Chair, may I ask a -- thank  
21      you for that. When I was looking at the FDA's  
22      packet, they pointed out there was a 2- to

1 3-millimeter mercury blood pressure increase in the  
2 patients who received greater than the  
3 12-milligram-per-day dose. And that can either  
4 represent 2,000 patients who had a 2-millimeter  
5 mercury difference or it can represent 2,000 who  
6 had zero difference and others who had much higher  
7 differences.

8 DR. SAGER: I can respond to that --

9 DR. TEERLINK: So given this is a stochastic  
10 event, I am concerned that there may be patients  
11 who are more susceptible to this, just as they're  
12 more susceptible to cardiovascular risk, and  
13 whether we could have a sense of how many patients  
14 there are along that and what the extent of that  
15 problem might be.

16 DR. SAGER: In the supratherapeutic group,  
17 the increase in blood pressure seemed to be across  
18 the continuum. There weren't patients who had  
19 large increases and others who did not.

20 DR. VENKATARAMAN: This is Preeti  
21 Venkataraman, FDA. I just want to clarify that in  
22 the FDA briefing document on page 55, we do make



1 reference to 2 to 3 millimeters of mercury  
2 difference, but we were actually quoting our  
3 guidance, our draft industry guidance, stating that  
4 those changes in millimeter mercury could increase  
5 in higher rates of stroke and heart attack.

6 DR. TEERLINK: You're right. It was 1 to  
7 1.19 increase.

8 DR. VENKATARAMAN: Right. Correct.

9 DR. TEERLINK: Yes. I'm still interested in  
10 knowing whether that represents mean effect, or if  
11 it's truly clustered around the mean, or whether  
12 there are people at the tail end who are having a  
13 more dramatic blood pressure response that are  
14 driving that. You have those -- somebody has those  
15 data. This is a cardiovascular issue, so --

16 DR. JONES: I'm Judith Jones, a consultant  
17 to the sponsor and paid in consultancy. I'm an  
18 adjunct professor at Georgetown University and also  
19 University of Michigan School of Health.

20 At one point in time, about three and a half  
21 decades ago, I was director of the division of what  
22 is now OSC, so I've had a fair amount of experience

1 with these types of advisory committees. And I'd  
2 just like to step back and make a couple of  
3 big-picture comments, if I may.

4 May I have the slide, please? Today, we've  
5 been hearing about a very comprehensive analysis on  
6 the part of FDA as well as the sponsor. And  
7 indeed, there is a small signal of possible  
8 cardiovascular effects and psychiatric effects.

9 It's very important to point out that  
10 neither of these are validated. These are  
11 retrospective chart reviews, but as has been  
12 described in detail, none of them have been  
13 validated. Furthermore, as was pointed out in the  
14 discussion, there is missing data, and that is  
15 always a problem in all of these things.

16 But I want to point out that we do have data  
17 on two populations, one about 52,000 and the other  
18 several thousand who have been exposed to tegaserod  
19 or not exposed. And particularly in the case of  
20 the large study, which you heard about, there was  
21 great care in trying to match the risk factors  
22 between these two populations exposed to tegaserod

1 and not, and as used and not, so two different  
2 kinds of exposures.

3 It's important to realize that there were no  
4 differences in cardiovascular effects or  
5 psychiatric effects. And I think it's just  
6 important to put all of this very good detailed  
7 data into perspective in the larger population  
8 perspective. Thank you very much.

9 **Questions to the Committee and Discussion**

10 DR. RAUFMAN: Thank you. I think we will  
11 move on.

12 We will now proceed with the questions to  
13 the committee and panel discussions. I would like  
14 to remind public observers that while this meeting  
15 is open for public observation, public attendees  
16 may not participate except at the specific request  
17 of the panel.

18 Question 1, discuss the strength of the  
19 potential cardiovascular safety signal of  
20 tegaserod, considering the totality of available  
21 data from clinical trials, adjudications,  
22 pharmacoepidemiology studies, nonclinical data, and

1 pharmacovigilance data.

2 That is open for discussion. Dr. Thadani,  
3 you can start us off.

4 DR. THADANI: It would be useful if the FDA  
5 can give some idea of the recently approved drugs.  
6 There were three of them. I know I'm going off.  
7 It's relevant to this.

8 Was there any signal on either  
9 cardiovascular, or CNS, or suicidal tendencies in  
10 that database? You approved three drugs recently  
11 for the same indication. Are we having zero signal  
12 or signal is the same? You must have the data. I  
13 just didn't see that. I know it's off the chart,  
14 but it's relevant, too.

15 DR. KORVICK: This is Dr. Korvick. There's  
16 two parts to your question. As you recall the  
17 history, when we first approved the drug tegaserod,  
18 it was based on the safety database that was  
19 smaller than that presented to you today. That was  
20 based on 3, 4 studies, some pharmacokinetic  
21 studies, and we did not see a cardiac event in  
22 those studies.

1           So I believe -- and I'll turn to my  
2           colleague -- that we did not, in a likewise  
3           fashion, see anything in those three new drugs.

4           DR. THADANI: Sure.

5           DR. KORVICK: So we cast our net broader  
6           here, as there was the meta-analysis of pooled data  
7           across many studies. So we don't have a similar  
8           database for those.

9           DR. THADANI: Sorry. I was asking for the  
10          IBS-C. There were three drugs recently approved  
11          since -- late one is 2018. Was there any signal in  
12          those?

13          DR. VENKATARAMAN: Right. So you're  
14          referring to linaclotide, plecanatide. So those  
15          drugs are of a different mechanism of action.

16          DR. THADANI: Yes, sure, sure.

17          DR. VENKATARAMAN: In those studies, there  
18          were no cardiovascular signals.

19          DR. THADANI: I think that might be relevant  
20          because you could say like placebo, there's no  
21          effect because it's a different class of drugs.  
22          But you did not see any signal, either

1 cardiovascular or neuropsychiatric issues, correct?

2 DR. VENKATARAMAN: Right. Cardiovascular  
3 effects and SI/B effects were not noted for those  
4 three trials. However, again, the databases, as  
5 Dr. Korvick mentioned, were small for the  
6 registration trials. So as the sample sizes for  
7 those trials were less, we may not be able to pick  
8 up on rare events.

9 DR. THADANI: Another point on the same  
10 basis, I would say, I sympathize with the women and  
11 men who have this syndrome; that's not the issue.  
12 You are saying that 10 or 15 percent of the  
13 population has IBS. That implies nearly several  
14 million, maybe 40 million Americans of U.S.  
15 population has that.

16 So if you just look at the natural history  
17 of women who have -- maybe gastroenterologists know  
18 better. If you just follow them up for younger age  
19 groups, say, below 55, what's the incidence of  
20 these kinds of issues?

21 Is there any data on that? I'm just  
22 throwing a general question to everybody. Follow

1 the IBS patients, the young women, and just look at  
2 3 months, how many are having cardiovascular events  
3 or neuropsychiatric issues. Because you guys treat  
4 them all the time; I don't.

5 DR. RAUFMAN: Yes, we treat them, but I  
6 don't know that I can specifically answer that  
7 question. Your estimates of the prevalence of the  
8 disease are on target. This is a large problem,  
9 and for whatever reason, it's more common in women.

10 But I can't tell you off-hand what  
11 percentages over time, and I'm not sure that's  
12 going to address this discussion point, either.  
13 This is really for the cardiologists on the  
14 committee.

15 The question for you is, after hearing both  
16 from the FDA and the sponsor regarding the  
17 available data -- and we can argue about the  
18 quality -- is it strong, and what do you take away  
19 regarding the cardiovascular safety of tegaserod?

20 DR. THADANI: I think another issue is that  
21 I know that you did three analyses, initially was  
22 adjudicated by the cardiologists for the drug

1 company. And that was in a very blinded analysis,  
2 I presume. It seems more -- the second analysis,  
3 number goes down, third goes down, fourth one goes  
4 down further.

5 I still think I've got a problem with the  
6 DCRI analysis, that when they don't have data, they  
7 throw it out. To me, if you don't have data, that  
8 counts as a patient event. So at least in the  
9 cardiorenal community, we used to say that,  
10 worst-case scenario, we're going to say an event  
11 occurred.

12 So the patient was hospitalized for stroke,  
13 so they must have some data in the database.  
14 That's why the score. And that changes the number  
15 a little bit, or the DCRI, rather than 4, it could  
16 go to 5. And they say, well, they can't adjudicate  
17 it because the event is missing somehow. But the  
18 patient was hospitalized, so he must have had  
19 either weakness or some neurological issue.

20 I'm not willing to buy that as a null event.  
21 And if I do that, in my judgment, it's a very small  
22 event rate, I realize, so you can't generalize it,



1 but it's there. So taking the cardiovascular and  
2 the CNS effects, unfortunately, they're in the  
3 wrong direction and one has to just be careful.

4           When you're giving us data on the  
5 subpopulation of younger women, those are not  
6 randomized studies; they're short term. And since  
7 there are millions of people involved, there has to  
8 be really some kind of reservation. Would that  
9 translate into adverse outcome in the long run? I  
10 really don't know for that. That's my comment.

11           DR. RAUFMAN: Dr. Korvick?

12           DR. KORVICK: I guess I'm interested -- if  
13 you would look at our slide 62 in light of the  
14 comment that you just made. I understand there is  
15 always a question about how many you throw out and  
16 how many you keep. But if you look at slide 62 and  
17 you look at that thing before they adjudicate, they  
18 had 304 cases before they got down to 7, or 3, or  
19 2, or whatever, and they excluded all these other  
20 cases.

21           But if you look at it and you do the  
22 percentages, and if you just said 198, those were

1 events and 106 were some kind of event, I would  
2 point out to you that the rates for those are very  
3 low. It's 0.017 versus 0.015.

4 I was just noodling over that fact when you  
5 were talking about this.

6 DR. THADANI: Sorry. I was alluding more to  
7 the heart event like stroke. In your other slide,  
8 I think they went from 7 to 4.

9 DR. KORVICK: Right.

10 DR. THADANI: So if it goes from 7 to 5 --

11 DR. KORVICK: But my point I was making --

12 DR. THADANI: Sure.

13 DR. KORVICK: -- is if you just don't do all  
14 of that throwing out and you just start here before  
15 you get going very far, you have small and  
16 similar --

17 DR. THADANI: See, I'm not too concerned  
18 about angina score or chest pain. I think what  
19 you're really worried about is gut, MI, or stroke,  
20 which are harder endpoints for a younger person to  
21 tolerate. In addition, you've got a  
22 neuropsychiatric issue.

1           That was more relevant, I think. If you  
2 take 100 young women between the ages of 45 and 60,  
3 a lot of them come with chest pain, but they don't  
4 necessarily have very adverse outcomes. So I think  
5 I'm more concentrating on the really hard outcomes.  
6 My issue has been, when you adjudicate data, people  
7 throw it because one person, Columbia did 7, and it  
8 differs.

9           So if you keep on doing analysis, it will  
10 come down further, but I think it's wrong when the  
11 data is not there and the patient is hospitalized,  
12 to throw that patient and it favors your analysis.

13           DR. RAUFMAN: Dr. Mann?

14           DR. MANN: Since we're trying to come up  
15 with a risk-benefit analysis, I just  
16 wondered -- and this is not my field, exactly,  
17 these statistical aspects. But isn't it easier to  
18 give us something like a number needed to harm,  
19 number needed to help, where the number needed to  
20 harm is one of these cardiovascular events and the  
21 number needed to help is some really good response  
22 clinically amongst all these different types of

1 outcome measures you've got for measuring  
2 responders?

3 DR. RAUFMAN: Dr. Hunsberger?

4 DR. HUNSBERGER: Yes. So I'm the  
5 statistician, so to me, we have to weight our  
6 evidence. And the randomized studies are what we  
7 have to really put our emphasis on. And I think  
8 the FDA did a great analysis, and I think it really  
9 does show, given the meta-analysis and everything,  
10 there is a signal there.

11 We can't really quantify what it is, but  
12 there's a signal. It could be small, but there is  
13 a signal there. And I think the randomized studies  
14 are what we have to really look at. I don't think  
15 that matched analysis -- there's so many other  
16 things that can go into play there, and I just  
17 don't put any weight on that.

18 I think the randomized studies are very  
19 solid. It's a relatively big population, and I  
20 think the meta-analysis also shows that there's a  
21 signal.

22 DR. RAUFMAN: Just around the table, does

1 anybody believe that there is no risk of  
2 cardio -- that there's no cardiovascular risk with  
3 tegaserod?

4 (No response.)

5 DR. RAUFMAN: So everybody's agreeing that  
6 there's a signal?

7 DR. LEBWOHL: Just to clarify, Ben Lebwohl  
8 here. So when we were asked to discuss the  
9 strength of the potential signal, often a weak  
10 signal, even if it's real, will correlate with  
11 one's belief of whether maybe there's no signal.  
12 Right? The smaller the point estimate, the more  
13 likely there's some sort of bias that will get you  
14 to the unit.

15 But I think the consensus here is that,  
16 given that the RCT data, using multiple differently  
17 adjudicated analyses, are all showing the same  
18 direction of these point estimates, I buy it. It's  
19 weak in that the magnitude of risk is small, but I  
20 think it's real. And I think that it's not negated  
21 by the cohort study or the propensity analysis  
22 because, as Dr. Weissfeld pointed out, that's more

1 prone to confounding and bias, which will bias you  
2 towards the null.

3 So I think there is consensus. It's real,  
4 but it is small and weak.

5 DR. RAUFMAN: I was going to ask  
6 Dr. Teerlink because I think you had your hand up.

7 DR. TEERLINK: This is John Teerlink, and I  
8 was going to concur that I think there is a real  
9 signal there. I think putting it into a more kind  
10 of global perspective, when you look at initial  
11 biological plausibility, this class of agent, any  
12 serotonergic agent raises the concern that it can  
13 precipitate cardiovascular events. But I think  
14 we've also learned that it's clearly not a class  
15 effect. We can't paint the whole class with any  
16 one specific agent, and each agent has very  
17 different pharmacologic characteristics.

18 I think the preclinical data overall has  
19 been relatively reassuring. It is concerning and  
20 disappointing -- I guess disappointing is the  
21 better response to me -- that the sponsor didn't  
22 have data on a known variable of concern with these

1 agents in terms of the distribution of blood  
2 pressure to show us.

3 I trust Dr. Sager tremendously, but show me  
4 the data. So it's too bad that that's missing  
5 because that's the one kind of dangling thing that  
6 could be precipitating cardiovascular events in  
7 this, in addition to its potential vascular  
8 effects.

9 I do believe that the signal is real, but I  
10 think the magnitude of the signal is small, so  
11 that's where I'm at.

12 DR. RAUFMAN: Dr. Thadani?

13 DR. THADANI: I think somebody raised the  
14 question, a number needed to treat. With the FDA,  
15 with the data they sent us on page 46 of 99 pages,  
16 it shows number needed to treat for IBS-C is 8, 7,  
17 and 9; otherwise figure 15 on your document with  
18 this. That's the 92-page document. It's on page  
19 46 of 99.

20 That's specific to this population, IBS-C.  
21 Am I looking at it? I just pointed it out. Sorry,  
22 that's the sponsor's; not FDA's, sponsor's. My

1 apology. That's the thick document.

2 DR. LEBWOHL: Ben Lebowhl here. My back-of-  
3 the-envelope calculation is if we give the benefit  
4 of the doubt and say it's an absolute risk-benefit  
5 of 11 percent, the number needed to treat is a  
6 little bit more than 10, unless I'm thinking about  
7 this incorrectly.

8 DR. THADANI: So what you're saying is  
9 number needed to treat is approximately 10, and  
10 you're going to harm 1 patient with a serious  
11 adverse event, maybe in 10,000, whatever number  
12 it's going to be.

13 So an important question, Chairman, would  
14 be, is a patient who is suffering from this disease  
15 willing to take the serious adverse event? I  
16 realize event rate is very low, so it could be  
17 chance observation. You need a huge database to  
18 address that. But I think that, unfortunately, the  
19 signal is there. And maybe there are some patients  
20 who are so desperate in your population that is  
21 willing to take that. That will come into the  
22 issues in the long run.



1 DR. RAUFMAN: So we'll get to that a little  
2 bit more regarding the risk and the further  
3 discussion and questions.

4 Dr. Rosen?

5 DR. ROSEN: Yes, you asked kind of the  
6 gastroenterologist's perspective, and we heard some  
7 really nice comments from the group today kind of  
8 framing things.

9 I think when you look at quality-of-life  
10 scores in patients who have IBS compared to, say,  
11 IVD, Crohn's colitis, patients with functional GI  
12 disorders actually have worse quality of life than  
13 patients with Crohn's and ulcerative colitis.

14 So while everybody presents stool data,  
15 because that's what we can count, the pain  
16 components to these disorders are very real. So I  
17 think from those of us who care for these patients,  
18 this is a really debilitating disease that takes up  
19 a lot of gastroenterologists' time and a lot of  
20 healthcare dollars.

21 When we think about the kind of risk that  
22 we're talking about, we're talking about patients

1 who are super sick and debilitated by these  
2 diseases, which is why you hear on the  
3 gastroenterologist's stuff that we feel very  
4 strongly about these drugs and the need for these  
5 drugs because there are very few options.

6           When you look, you talk about the three  
7 options that are on the market. Those drugs are on  
8 the market. They're newly on the market. But when  
9 you look at the vast majority of patients we care  
10 for, they're on multiple drugs. So this is not a  
11 one-and-done kind of situation, and I think the  
12 patients, like I said, are just more complex.

13           When you look at risk-benefit analysis, I  
14 would say that patients in general are willing to  
15 accept much more risk for these disorders because  
16 of the debilitating quality-of-life issues  
17 associated with them.

18           So I just put it out there that while I  
19 think all of us say that there's a cardiac signal  
20 here, we have to look at the converse, which is how  
21 severe the disease is, and I think it is very  
22 significant for these patients.

1           So again, just kind of putting it out there,  
2           there are not a lot of great alternatives. The  
3           FDA's done a terrific job of getting these last  
4           three drugs through the pipeline, and it's greatly  
5           appreciated. But there is really not one drug for  
6           all here, and in fact, there's often two or three  
7           or four drugs that patients are on. So just keep  
8           that in your kind of risk-benefit equation for  
9           these patients. It's a big issue.

10           Then just to get back to the other risk  
11           factors, again, I can't say enough how many drugs  
12           these patients are on. And this is not just  
13           neuromodulators, but they're also on estrogens  
14           because there's overlapping with endometriosis and  
15           other pain syndromes.

16           So I would just argue that not only are  
17           these drugs important, but postmarketing  
18           surveillance of drug interactions, including  
19           hormones, especially in women who have  
20           endometriosis associated with this, are really  
21           important comorbidities, SSRIs, tricyclics. You've  
22           got to keep data on this, whether it's with

1 tegaserod or the other drugs that are coming down  
2 the pipeline. So just kind of keep it out there  
3 that these drugs are really important for us.

4 DR. RAUFMAN: Dr. Levine?

5 DR. LEVINE: From an industry perspective,  
6 there are evolving methodologies to try to  
7 quantitate risk appetite. I believe FDA's aware of  
8 that. If the sponsor had done those kinds of  
9 studies, I'm sure it would have been presented. So  
10 feel free to decline.

11 The point is that we do have patient  
12 representatives in the room that could speak to  
13 risk appetite if the committee wanted to hear about  
14 that.

15 DR. RAUFMAN: I think we can wrap up  
16 question 1. I think the consensus is that there is  
17 a signal, but that it is not a strong signal. If  
18 anybody disagrees, please speak up around the  
19 table. But I think we can move on to the next --

20 DR. THADANI: I'll just say one thing. It's  
21 a weak signal, but it is an important signal in  
22 very young people. If you've got an 18-year-old

1 daughter who might have this issue, and suddenly  
2 she has a stroke or a heart attack, it's a big  
3 issue.

4 I realize they are suffering. It's not my  
5 personal. My daughter doesn't suffer from that.  
6 So I can speak the perspective, although weak, it  
7 may be untrue, it may be noise, but I think one has  
8 to live with the double-blind studies.

9 You raise the issue, and I would really love  
10 to know what the neuropsychiatric issue is in  
11 addition.

12 DR. RAUFMAN: So this is also a discussion,  
13 not a voting question. Discuss other potential  
14 safety concerns, including psychiatric safety,  
15 adverse events of completed suicide, and suicidal  
16 ideation and behavior when considering  
17 reintroduction of tegaserod to the U.S. market.

18 Maybe Dr. Mann can lead us off on this one.

19 DR. MANN: I'll try to share a few  
20 impressions. First of all, the dataset that we're  
21 examining is very limited because it wasn't  
22 designed to acquire the data that we're

1 particularly interested in.

2           Ascertainment problems are particularly  
3 pronounced in this situation, meaning that,  
4 whatever you see as these rights, the real rights  
5 are much higher. And you can see that from the  
6 fact of the other committee members' clinical  
7 experience and the FDA's comments about the  
8 prescription rights of relevant medications like  
9 SSRIs.

10           So there might be a signal there. I'm less  
11 confident than I would be about agreeing with the  
12 impressions regarding cardiovascular risk. But  
13 there might be a signal there, and therefore one is  
14 obliged to be cautious.

15           The FDA was proposing to address this with  
16 changes in the labeling language, which I think is  
17 good because whatever the cause of the depression  
18 and the suicidal ideation in these patients,  
19 whether it's the treatment or the comorbid  
20 psychiatric illness, they need to be cared for  
21 carefully and thoughtfully. So I would say that  
22 there's a possible signal out there, and we need to

1 be cautious about it.

2 I'm less confident about the pharmacological  
3 data suggesting that there's no potential mechanism  
4 of action that could make this drug a risk  
5 candidate because I think that the pharmacology  
6 that we heard today was insufficient to be able to  
7 make that judgment.

8 DR. RAUFMAN: One of the proposals, which  
9 we'll discuss later on, is to exclude women with  
10 cardiovascular risk factors from using this agent.  
11 Would you consider excluding women with known  
12 psychiatric disorders?

13 DR. MANN: That's an excellent question. I  
14 think that would really mean fundamentally  
15 excluding people with a mood disorder of some sort,  
16 but I would suggest that the signal that we have  
17 right now is too weak and ambiguous to recommend  
18 that. And we have much better data for other  
19 drugs, which do not carry that requirement and  
20 instead have labeling language that alerts the  
21 clinician to the need for being particularly  
22 careful. And I think that would be a better way to

1 proceed at this point in time.

2 DR. RAUFMAN: Dr. Teerlink?

3 DR. TEERLINK: John Teerlink. As a non-GI  
4 person, non-psychiatrist, I'll still go ahead and  
5 make this comment, that it's actually concerning to  
6 me that the suicidal ideation and suicide attempts  
7 weren't less in the trials because, first of all,  
8 you're selecting patients in a clinical trial who  
9 are getting continual follow-up and continual  
10 medical contact, in general do very well and  
11 actually have, in general, improvement in their  
12 mental status and mental health.

13 If they're actually getting relief of their  
14 underlying symptoms, one would have expected that  
15 one of their drivers perhaps for the suicidal  
16 ideation and other things would have been less.

17 So if there is in fact a signal, that's in  
18 some ways a little more concerning because it's  
19 going in the opposite direction of what one would  
20 have expected, and by the design would have been  
21 biased. So I think it is real, and I agree with my  
22 colleague that needs to be addressed as the FDA has



1 addressed it.

2 DR. RAUFMAN: Ms. Numann?

3 MS. NUMANN: Sabrina Numann, patient  
4 representative. There was a mention that you'd  
5 like to hear from a patient representative who  
6 represents this discussion, and I fit this bill  
7 perfectly, actually. So I do have a few things to  
8 say.

9 First, thank you to the sponsor for your  
10 information. It has been mentioned, much like the  
11 CV safety signal, that there is something there,  
12 but there hasn't been anything proven. Although,  
13 one of the things that Dr. Howden said -- and he  
14 mentioned this very quickly when he was up at the  
15 podium. He said -- and I'm paraphrasing -- that he  
16 hopes patients are not on SSRIs; it could  
17 exasperate IBS-C.

18 As a patient who may not have a history of  
19 SI/B, I am on medication, serotonin medications, so  
20 I may not quite have been the person to say I do  
21 qualify as an SI/B risk. But I am on a medication  
22 that affects my serotonin levels, and I do have

1 IBS-C.

2           So in my mind, if my doctor were to ask me  
3 if I felt the risk was worth it and I asked him,  
4 "Well, why is that on the label?" he'd say, "One  
5 person died, and they have to put it on the label."  
6 But to me, that one person is significant, whether  
7 it was related or not, or the 8 people that they  
8 have narrowed it down to, and I would proceed with  
9 caution.

10           That is because, just because I don't have a  
11 history of SI/B doesn't mean I won't, and what we  
12 don't know, we don't know. So I don't know if I  
13 would take that risk, even in the amount of pain  
14 that is disabling because I have doubt. I have to  
15 weigh those, many things, and all of those  
16 medications.

17           So that information on the label is going to  
18 be really important to me as an educated patient,  
19 let alone one that isn't educated and just is going  
20 by the faith of what their doctor has to say.

21           So I appreciate all of these comments.  
22 Dr. Mann racked up a lot of my questions very

1 easily and said a lot of what I had to say. But  
2 thank you very much for taking the time to listen  
3 to my thoughts on that. I would just ask the FDA  
4 to consider that the language in the warning  
5 label -- maybe you have to exclude a specific  
6 category of medications or include the warning on  
7 specific types of SSRIs, and a warning label to  
8 include the SI/B. Thank you very much.

9 DR. RAUFMAN: Thank you. Ms. Robotti?

10 MS. ROBOTTI: Suzanne Robotti, consumer rep.  
11 In direct response, I'm not sure I understood  
12 exactly your point in everything. Particularly, if  
13 we have an indicator and we have a reason to be  
14 concerned that SI/B is potentially exacerbated or  
15 increased by this drug, do not put it on the label  
16 because it would halt people from using it, we  
17 can't withhold that kind of information. That's  
18 probably not what you meant.

19 Is that not what you meant?

20 MS. NUMANN: No. I did not mean to withhold  
21 the information. I meant to include additional  
22 information.

1 MS. ROBOTTI: Or more fully.

2 MS. NUMANN: Even though the lack of data is  
3 there, no direct link is there, I will think that  
4 if you're going to group this kind of discussion in  
5 with the potential CV safety signal, they're very  
6 similar, and I feel that information like that  
7 should be included in the label.

8 MS. ROBOTTI: Okay. Sorry.

9 Now to get to the remarks I meant to say. I  
10 agree that I think that there's a signal for  
11 psychological effect, and I would like something on  
12 the label. And I don't think that it necessarily  
13 should tell people they shouldn't take it. It  
14 shouldn't be a black box-type label, but it should  
15 be indicated.

16 But this also asks about other risks, and I  
17 continue to worry about 4 million women becoming  
18 pregnant every single year. These are women inside  
19 the target group, the group who will be using this  
20 drug. Many will breastfeed for 3 months, a year,  
21 or more.

22 Over the course of a decade, that's

1 40 million of your drug target population who have  
2 no idea if this drug is safe for them. To say that  
3 the women should go to their doctor to then have an  
4 informed discussion is offensive because there is  
5 no information to have an informed discussion with.

6 This is a huge population of people that  
7 continuously get ignored. Pregnancy, lactation,  
8 children, major categories of people on major  
9 drugs; they are not tested against, and I think  
10 that's very dangerous. And it should, at minimum,  
11 require post-approval studies for -- I'm  
12 sorry -- yes, post-approval studies.

13 There are also registries that could be set  
14 up so that you can voluntarily register and say I'm  
15 on this. I took this drug for 3 months, and I  
16 didn't know I was pregnant, and then I stopped, so  
17 at least their information would be contained  
18 somewhere. It could potentially give a stronger  
19 signal than you might see in the FAERS because  
20 FAERS doesn't often give a strong signal.

21 I'd also worry about prescribing creep. One  
22 can predict where it might be used off label, and

1        OUD, and men, and again, children and pregnant  
2        women.  So I wish the FDA would add such  
3        considerations to the required analysis.

4                DR. RAUFMAN:  Dr. Korvick, do you want to  
5        comment on drug risks with pregnancy and lactation?

6                DR. KORVICK:  We take your points, and the  
7        FDA is very cognizant of the issues that you raise,  
8        and we take those issues seriously.  We will be  
9        doing the appropriate labeling and the analysis.

10               We don't have lactation studies, for  
11        example, currently.  So some of the things that you  
12        say, we don't have.  But we do have requirements  
13        that we can use to ask for additional studies  
14        postmarketing to address some of those concerns.

15               So we do have standard labeling that we can  
16        employ based on whatever animal data, et cetera,  
17        that we already know.  But as you say, you could  
18        collect more information postmarketing on, say, a  
19        woman that got pregnant and what was her outcome.  
20        So yes, thank you for that.

21               DR. RAUFMAN:  Dr. Thadani?

22               DR. THADANI:  I think the neuropsychiatric

1 issues is 8 versus 1. I'm talking about the  
2 double-blind trials. Forget about the propensity  
3 analysis and the observational studies. There are  
4 confounders there.

5 So if you look at the cardiovascular events,  
6 which you are saying there's a signal, to me, I  
7 think there's a signal in the neuropsychiatric,  
8 8 versus 1, and 1 patient actually completed  
9 suicide in the open label.

10 So I think it's worrisome. To me, it should  
11 be -- whether in the black box, it has been  
12 reported. If somebody has already got a  
13 neuropsychiatric problem, I want to know if there  
14 will be more chances or less. I don't know. But  
15 the signal is there. I don't think you can just  
16 bury it in the 4-page document, drug can cause it.  
17 The patient has to realize that these are the  
18 risks. I'm willing to take it. Yes or no.

19 So I think you can't just blow it off. It  
20 has to be in the risk. There are 40 million  
21 people; theoretically, maybe 10 million could take  
22 the drug. So I still don't understand why the

1 FDA -- I'm enlarging on the cardiovascular and  
2 this -- can't mandate a study of 100,000 patients,  
3 chief study for 3 months, 100,000 or 30,000 in each  
4 group, and see if this noise goes away or not  
5 before you throw this thing on the market for young  
6 people.

7           People say you can't do 100,000. I think,  
8 in this, when the population is huge, you could  
9 easily do a very large sample study, very short  
10 study, make it cheap because all you're doing is  
11 placebo versus this for 3 -- and all of you have  
12 patients. You don't have to give thousands of  
13 dollars to each doctor to do this study, and within  
14 6 months, you're going to get the answer.

15           DR. RAUFMAN: I don't think there is such a  
16 thing as a cheap study.

17           (Laughter.)

18           DR. THADANI: They are expensive because  
19 physicians get too much pay in America compared to  
20 perhaps in Asia or Europe. But when your  
21 population is so large, you've got younger people  
22 at risk with pregnancy issues. I think it's a



1 public health issue. Maybe NIH could put in some  
2 dollars and do a very quick study.

3 If you got 200,000 patients, you at least  
4 will have confidence. You could say either it's  
5 there or the signal's not there. So either you win  
6 or lose. That's up to the company, but I think FDA  
7 could mandate it if they wanted.

8 DR. RAUFMAN: I think maybe we can move on.  
9 Just in summary, the safety concerns that we just  
10 discussed were primarily the potential psychiatric  
11 adverse events, but we also discussed the issue of  
12 pregnancy and lactation in women using this agent.  
13 And it appears that, unlike the cardiovascular risk  
14 where there's going to be some risk assessment  
15 before somebody starts the drug, that these  
16 potential adverse events will be dealt with by  
17 appropriate labeling on the package insert,  
18 et cetera.

19 That pretty much summarizes the discussion,  
20 and we can move on. Now we get to actually vote on  
21 something.

22 Is the reintroduction of tegaserod in the

1 United States market supported by the available  
2 safety data? Discuss your answer. So are we  
3 voting, and then everybody going around and saying  
4 why they voted the way they did? Is that the  
5 intent here?

6 How does everybody want to do it? Do you  
7 want to discuss ahead of time or should we just go  
8 ahead and vote based on our previous discussion,  
9 and as we go around, people can explain why they  
10 voted the way they voted?

11 MS. McVEY HUGICK: This is Joy McVey Hugick,  
12 the consumer representative on the Gastrointestinal  
13 Drugs Advisory Committee. I've paused and waited  
14 because I've heard people say there will be a  
15 chance to discuss the risk. And if we're going to  
16 vote, I haven't had a chance to voice my opinion  
17 yet. So I would say, if we're going to vote, I'd  
18 like a chance to talk first, but if not --

19 DR. RAUFMAN: You've got it. Go ahead.

20 MS. McVEY HUGICK: Well, you know, a lot's  
21 been discussed today. I do want to thank the  
22 sponsor. I feel like there's definitely an unmet

1 need in the, in particular, IBS-C community. We  
2 heard from the gentleman from the IBS Patient Group  
3 that many of the patients, that Dr. Rosen talked  
4 about, it's a very debilitating disease and they're  
5 willing to take a risk.

6 They're at a point where they've tried all  
7 the other alternatives, the three new drugs, things  
8 like that, and it just has not improved their  
9 quality of life. So I would say that I definitely  
10 think it's important to have the labeling. That's  
11 very important, and I think that it comes down to  
12 the discussion with the clinician.

13 I appreciated both the comments from ACG and  
14 AGA, and I'm grateful that the clinicians are on  
15 board to wanting to find better treatment options  
16 because there really aren't a lot of them out  
17 there.

18 So I would just say that I think it's  
19 important to weigh the benefit and the risk, and I  
20 think that there is a portion of the population  
21 that is willing to do that because they've tried  
22 all the other alternatives and have not found a

1 treatment option that has been enough to  
2 accommodate an active lifestyle.

3 DR. RAUFMAN: Thank you. Additional  
4 discussion?

5 DR. THADANI: Mr. Chairman, before you vote  
6 on this, is there any data that patients with IBS  
7 who have not responded to currently approved drugs,  
8 which are relatively safe from a cardiovascular  
9 point of view, would respond to this drug, or do we  
10 have any idea whatsoever?

11 This is all old database, so how do I know  
12 that the patient was not responding to your newly  
13 approved drugs or respond to that. Maybe they're  
14 just non-responders. Don't you think that's an  
15 important chunk of information before you expose  
16 somebody to a little risk?

17 DR. RAUFMAN: I would answer, but we have  
18 others to put in. But what I'm hearing in  
19 practice, I think there's a lot of anecdotal data  
20 supporting that. I don't think there are any  
21 formal studies answering that question. It's a  
22 great question, but I think that there certainly is

1 a perception amongst patients and physicians that  
2 this would be a beneficial option that is not  
3 addressed by the existing therapies.

4 MS. McVEY HUGICK: And I would echo that.  
5 If you read the comments posted online -- again,  
6 this is Joy McVey Hugick, consumer  
7 representative -- the comments online and  
8 anecdotally, I know plenty of people who have said  
9 my life changed for the worse when Zelnorm was  
10 removed from the market.

11 So I would say I don't know numbers. I  
12 don't know the data. But I know plenty of people  
13 who have told me that it did help them, to the  
14 point to where they went from having a very poor  
15 quality of life to it made them almost back to  
16 normal.

17 DR. THADANI: I buy that. I think quality  
18 of life is a big issue, but I am surprised that in  
19 the double-blind trials, the withdrawal rate is  
20 only 2.8 on placebo and 3 on the drug. So that  
21 meant physicians don't know what they're on, so  
22 there's a lot of physician-patient interaction, and

1 I think that has to be taken into account.

2 If this is such an issue with quality of  
3 life, you would think the withdrawal rate, because  
4 of lack of therapeutic effects, will be much  
5 higher. I just don't buy that as 2.8 is too low, 3  
6 in the active drug, actually, as much as placebo.

7 I think that's the problem you run into when  
8 you have a difference between placebo and 5 and  
9 8 percent. One population shows 5, one 14.  
10 There's a lot of issues with a patient. I like my  
11 physicians; patient likes me. His response is  
12 going to be greater than --

13 I'll give you an anecdote example. People  
14 are using cell therapy for arthritis, and they're  
15 charging \$8,000 a pop, which is making a lot of  
16 money. And one physician said I don't believe in  
17 it to the patient, it surely is not going to work,  
18 as opposed to the other guy who said I got a  
19 90 percent response rate.

20 So I just want us to be careful and  
21 objective. I'm really surprised that the  
22 withdrawal rate is only 2.8 percent on placebo. I

1 value your comments. I realize what patients you  
2 see. Are you going to throw the double-blind  
3 database saying that's not as good, given the  
4 placebo effect? I'd just like your comments before  
5 we vote.

6 DR. RAUFMAN: Dr. Rosen?

7 DR. ROSEN: I mean, it's a little bit unfair  
8 to penalize Zelnorm when they weren't even on the  
9 market at the same time that linaclotide was on the  
10 market and whatever. So asking what linaclotide  
11 non-responders will do in the face of Zelnorm, I  
12 don't think that's fair to ask. They just weren't  
13 on the market at the same time.

14 That having been said, there are other  
15 serotonin drugs, such as cisapride, that were on  
16 the market that many of us had used for many years,  
17 which was a very good motility drug that was taken  
18 off the market because of cardiac effects.

19 Again, QTc prolonging; totally different  
20 mechanism, not the mechanism that we're talking  
21 about here today, but a very good motility drug.  
22 When cisapride was taken off the market and then we

1 got Zelnorm, we were happy to be able to have  
2 another serotonin drug with the same beneficial  
3 motility effects, not only lower tract, but upper  
4 tract as well.

5           So those drugs weren't on at the same time.  
6 We can't tell you -- I mean, maybe the sponsors can  
7 tell you what non-responders; I can't tell you.  
8 But I can tell you that there are some patients who  
9 respond very well to serotonin-based drugs, and we  
10 have that experience not only with cisapride, but  
11 when Zelnorm was on the market.

12           Then separate from this, as we've talked  
13 about, IBS is a very waxing and waning disease.  
14 There are times where you may respond to one drug,  
15 but you may not respond to others. And then  
16 depending on what the triggers are, you may need to  
17 rotate your IBS drugs.

18           I think, again, just getting to the point of  
19 having more options for when your triggers change  
20 is a really important thing. If you're having more  
21 motility issues, you may want your serotonin drug,  
22 which is different from your neuromodulator.



1           So again, I think just having more drugs in  
2 the armamentarium is not necessarily to say you may  
3 not respond because tegaserod isn't good, but you  
4 may not respond because your IBS trigger at this  
5 time is different. So just keep that in mind when  
6 you're thinking about efficacy.

7           DR. THADANI: I'm afraid cisapride is a  
8 totally different class because of the hERG  
9 effects.

10          DR. ROSEN: I said that. I said that had  
11 nothing to do with the cardiac, but --

12          DR. THADANI: So I think you are comparing  
13 that to that drug. I just don't buy that.

14          DR. ROSEN: But we are comparing it to the  
15 motility of that.

16          DR. THADANI: I don't think you can compare  
17 that because hERG effect now, most of the companies  
18 are not even bringing those drugs on the market  
19 because of such rigorous QTc issues.

20          So I think, here, the noise is not the  
21 sudden-death syndrome here, because of the QTc.  
22 It's because of cardiovascular events. So I think

1 it's a different perspective, although you are  
2 trying to sell it that way.

3 DR. ROSEN: No. I think you misheard. What  
4 I'm saying is that the motility effects on the gut  
5 are serotonin driven. That's what I'm saying. The  
6 cardiac effects are totally different. It's a  
7 totally different mechanism. But I think you have  
8 to recognize the effect of serotonin on gut  
9 motility. That's what I'm saying.

10 DR. RAUFMAN: Ms. Numann, you're agreeing?  
11 Okay.

12 Hold on one second. I think, Dr. Teerlink,  
13 did you want to say something? Dr. Khurana?

14 MS. KHURANA: I just had a comment in  
15 response to what you were saying earlier, that I  
16 think the withdrawal rate is probably so low  
17 because the placebo effect in this patient  
18 population is so high. So you've got to take that  
19 into consideration when you're looking at  
20 withdrawal.

21 DR. THADANI: The FDA might tell them to  
22 charge one and a half times the charge of placebo

1 when they pull the drug? Sorry, you can discard my  
2 comments there.

3 DR. RAUFMAN: Dr. Korvick?

4 DR. KORVICK: The data that you were given  
5 and the number that you're quoting is all of those  
6 29 studies, but those all include different kinds  
7 of studies in different populations.

8 So when we look at the five or six studies  
9 that we were looking at for efficacy in this, we  
10 see that the withdrawal rate is approximately 15 to  
11 20 percent across these five studies, and that the  
12 withdrawal rate due to adverse events is slightly  
13 more in tegaserod than the other.

14 So your comment about placebo rate,  
15 et cetera, is -- but I just wanted to draw your  
16 attention to that. The population that we're  
17 talking about, it's more like 15 to 20 percent  
18 withdrawal rate, and there are slightly more  
19 adverse events in the treatment arm than the other,  
20 which you would expect, mostly driven probably by  
21 diarrhea and any other common adverse events. This  
22 is not 3 percent in the population we're looking.

1 DR. THADANI: No. I think I was addressing  
2 lack of efficacy. There were withdrawals because  
3 of lack of efficacy of the drug, 2.8 and 3 percent,  
4 indicating the placebo response must be pretty  
5 high. Neither the physician nor the patient can  
6 tell this.

7 DR. RAUFMAN: I think maybe we can move  
8 ahead to the vote, and then move on from there.

9 So if there's no further discussion on this  
10 question, we will now begin the voting process. We  
11 will be using an electronic voting system for this  
12 meeting. Once we begin the vote, the buttons will  
13 start flashing -- they're already flashing -- and  
14 will continue to flash even after you have entered  
15 your vote. Please press the button firmly that  
16 corresponds to your vote.

17 If you are unsure of your vote or you wish  
18 to change your vote, you may press the  
19 corresponding button until the vote is closed.  
20 After everyone has completed their vote, the vote  
21 will be locked in. The vote will then be displayed  
22 on the screen. The DFO will read the vote on the

1 screen into the record.

2 Next, we will go around the room and each  
3 individual who voted will state their name and vote  
4 into the record. You can also state the reason why  
5 you voted as you did if you want to.

6 So again, let me just read the question. Is  
7 the reintroduction of tegaserod to the United  
8 States market supported by the available safety  
9 data? Please press the button on your microphone  
10 that corresponds to your vote.

11 (Pause.)

12 DR. RAUFMAN: Push again just to be sure,  
13 everybody, please.

14 (Voting.)

15 DR. FAJICULAY: For the record, the results  
16 are 11 yes; 1 no; zero abstain; and zero no voting.

17 DR. RAUFMAN: So if we can start with  
18 Dr. Hunsberger, we'll move around the table.  
19 Please introduce yourself, what your vote was, and  
20 if you wish to discuss why you voted the way you  
21 did.

22 DR. HUNSBERGER: This is Sally Hunsberger.

1 I voted yes. I think the efficacy data is there,  
2 that it does improve symptoms. And I think we have  
3 decided there is a cardiovascular event signal that  
4 probably is somewhat small. And maybe later, we'll  
5 be discussing whether it should be in a smaller  
6 population. But I think there is this unmet need,  
7 and I think it is efficacious, so I think it does  
8 merit being considered.

9 DR. TEERLINK: This is John Teerlink. I  
10 voted yes, and I will limit my comments solely to  
11 the safety issue, and hopefully I'll get a chance  
12 to talk about efficacy the next time around. I  
13 think we agree that there is a small increase in  
14 cardiovascular events with this agent, but  
15 hopefully that can be addressed by the FDA by its  
16 Sentinel program and other ways to try to monitor  
17 it in the real world.

18 DR. SOLGA: Steve Solga. I voted yes. The  
19 efficacy data are consistent with expectations in  
20 this therapeutic class. I have been concerned  
21 about the safety issues, which we'll discuss later,  
22 but I found the public comment compelling. And

1 also the statements made by Dr. Rosen about the  
2 unmet need was important to remind me about why  
3 this drug is being considered.

4 DR. THADANI: I voted no. Efficacy; there's  
5 no issue. The drug was already approved.

6 DR. RAUFMAN: Your name, please?

7 DR. THADANI: Thadani. Efficacy is not an  
8 issue because the drug was already approved and  
9 withdrawn from the market. And efficacy is there.  
10 I'm still concerned with the safety issue.

11 I'm willing to change my vote if there's a  
12 big black box warning regarding cardiovascular and  
13 the other neuropsychiatric issue; that my vote  
14 could go yes, provided I see that combination.  
15 Efficacy is definitely there. We're not even  
16 discussing that in isolation.

17 MS. NUMANN: Sabrina Numann, patient  
18 representative. I voted yes. I do feel that the  
19 data does support safety. Thank you.

20 MS. ROBOTTI: Hi. Suzanne Robotti. I meant  
21 to object to the phrasing on the question before I  
22 voted, but too late. It's just, in my opinion, a

1 little bit too broad and too yes or no, so I'm not  
2 going to give you a yes or no.

3 I voted in favor because it's justified by  
4 the efficacy. The safety signals -- and not by the  
5 safety. The safety signals are significant, but I  
6 don't think that they're affecting a big enough  
7 number today to withhold approval and the gain to  
8 the people who need it.

9 MS. McVEY HUGICK: Joy McVey Hugick. I  
10 voted yes for reasons already stated.

11 DR. ROSEN: Rachael Rosen. I voted yes,  
12 same.

13 DR. RAUFMAN: Jean-Pierre Raufman. I voted  
14 yes for reasons already stated.

15 DR. LEBWOHL: Ben Lebwohl. I voted yes for  
16 reasons already stated.

17 MS. KHURANA: Sandeep Khurana. I voted yes  
18 for reasons stated. But I also want to state that  
19 I don't think any additional trial to look for that  
20 small signal would amplify to a much bigger signal  
21 because that amplification, even if it's 2 or  
22 3 times more by increasing the size of the study,



1 if you corroborate that, it still would not be high  
2 to warrant a large study of 100,000 patients.

3 DR. MANN: John Mann. I voted yes because I  
4 thought that the efficacy was sufficiently  
5 impressive and the signal for risk indicated a  
6 sufficiently low risk that one could come out with  
7 a meaningful, manageable risk-benefit decision that  
8 would allow a lot of patients to get some treatment  
9 that they needed

10 DR. RAUFMAN: Thank you. The next voting  
11 question, do you agree that the therapeutic gain  
12 treatment difference between tegaserod and placebo  
13 is generally similar in magnitude between the  
14 severely symptomatic and originally approved  
15 population?

16 We can open it up to discussion. If  
17 somebody has any questions about the wording of  
18 this question, feel free to opine.

19 (Laughter.)

20 DR. RAUFMAN: Discussion? Dr. Thadani, and  
21 then Dr. Solga?

22 DR. THADANI: Answer from the FDA has

1 subanalyzed the data, and this restricted group has  
2 to be yes. It's in the same direction as far as  
3 efficacy is concerned, although the sample size is  
4 small.

5 We realize it's a post hoc analysis, but  
6 it's in the right direction, the same ballpark,  
7 although placebo might be smaller, especially when  
8 you restrict the population to IBS-C. The  
9 variation is from 5 to 12 percent over placebo, but  
10 it's in the same direction.

11 So I think efficacy is not an issue. I  
12 would say it's in the same direction. Maybe it  
13 could be a little bit different. I don't know.

14 DR. RAUFMAN: Dr. Solga, and then  
15 Dr. Lebwohl.

16 DR. SOLGA: I'll just state I guess I'm  
17 somewhat frustrated by the question. It's  
18 challenging. And the frustration is really borne  
19 out of the definition of how we define severe IBS.  
20 And I understand this is from Rome I, II, III, IV,  
21 and we're trying to take a heterogeneous patient  
22 population and make it feel simple and short.

1           Two women can say these symptoms are very  
2 severe and, yes, I meet the criteria for bowel  
3 movement frequency but have entirely different  
4 outlooks on their willingness to use a medicine  
5 like tegaserod.

6           If you ask one woman, she may say, "Yes, my  
7 symptoms are very severe, but I've been managing  
8 since childhood. It's a burden that I carry. Life  
9 goes on." And somebody else may say, "It's simply  
10 everything to me today." So there's going to be  
11 just a different risk appetite.

12           One woman may say, "I tried some things, and  
13 I find some efficacy, and then it goes away, and I  
14 need another option." Another person may say, to  
15 the opposite of placebo effect -- and we've all had  
16 this patient come into our office -- "I've tried  
17 everything and nothing works." And those are  
18 dedicated non-responders for whom a perfect therapy  
19 is not going to work.

20           Then finally, there are folks who are  
21 willing to accept a lot of risk and there are folks  
22 who are really quite concerned about risk. And

1 that just speaks to the risk appetite that we were  
2 discussing when it was introduced a bit earlier.

3 So my frustration is merely just out of the  
4 concern that because these patients are so  
5 different, it's very challenging to answer this  
6 question. It's almost dehumanizing and takes away  
7 from what we do as clinicians.

8 I'm quite sure, for example, Dr. Rosen could  
9 get a much better than 10 percent response rate in  
10 her clinic with her experience than I would be able  
11 to in mine because she's going to suss that out  
12 more properly.

13 DR. RAUFMAN: Dr. Lebowhl?

14 DR. LEBWOHL: Ben Lebowhl. So I would echo  
15 many of Dr. Solga's concerns. I understand the  
16 rationale behind perhaps restricting the population  
17 to those who are severe, and the FDA shows  
18 compelling data suggesting it is just as  
19 efficacious in that context. But it strikes me as  
20 just not workable in practice because the  
21 definition of severe can be difficult.

22 Just trying to think a few moves ahead, I

1 can see this turning into, first of all, this being  
2 a wedge between physicians, patients, and insurers,  
3 who will demand that patients be severely ill.

4 I can also imagine this causing like a cat  
5 and mouse situation, where suddenly patients are  
6 classified as severe because they want to get this  
7 medicine because they need this medicine. And  
8 because it's such a subjective concept of severe  
9 IBS, despite our efforts to define them with  
10 various rounding mechanisms, it strikes me as  
11 unworkable.

12 DR. RAUFMAN: Dr. Teerlink?

13 DR. TEERLINK: So as a cardiovascular  
14 physician and as a former member of the  
15 Cardiovascular and Renal Drug Advisory Committee, I  
16 have to say that I'm kind of less than impressed  
17 with the moderate efficacy signal that we've seen.  
18 Not even all the efficacy trials were positive.  
19 This marginal additional symptomatic benefit that  
20 we're seeing in the context of a very marked  
21 placebo response suggests to me that there's really  
22 only a mild to moderate clinical benefit here, and

1 I think that does need to be put into context of a  
2 very small but what I believe to be real  
3 cardiovascular signal.

4 So because of that, I support this being  
5 limited -- difficulties acknowledged, but it be  
6 limited to patients who have the most to gain.

7 Interestingly, in many therapeutic areas,  
8 the more severe patients are the ones who actually  
9 get better responses. So this is something that  
10 also is a little different than some of the things  
11 I've seen in other settings. And maybe that's just  
12 because of my cardiovascular background, but it  
13 also adds a little additional concern to me in  
14 terms of the magnitude of benefit in terms of the  
15 efficacy.

16 So that's why I'm for balance. I think it  
17 does need to be available, but I think the  
18 appropriate restrictions need to be placed upon it  
19 to ensure that it's only used in those who truly  
20 need it.

21 DR. RAUFMAN: Dr. Levine?

22 DR. LEVINE: I'm sort of bridging to what

1 you were talking about, but also for other  
2 committee members. There's already been public  
3 comments about translating the clinical trial  
4 treatment effect to what happens in the clinic, but  
5 I think the other thing to realize is that from the  
6 industry perspective, current context is endpoints  
7 that FDA has provided in guidance. It's a  
8 different sort of responder endpoint that was  
9 different from how Zelnorm was originally  
10 conducted.

11 So I think it's one thing to look at  
12 treatment effect size where the placebo response  
13 might be as high as 40 percent, whereas the newer  
14 endpoints that current sponsors are using -- and I  
15 think that there were post hoc analyses; using  
16 those new definitions, the placebo response rate at  
17 times can be 5, 10, 15 percent.

18 So that marginal difference, however you  
19 want to classify, whether it's 5, 10, 15 percent,  
20 might be viewed differently against a placebo  
21 response that is really, really low, say around  
22 10 percent, as opposed to a placebo response that's

1 40 percent.

2 MS. McVEY HUGICK: Joy McVey Hugick.  
3 Dr. Lebowhl brought up some really valid questions  
4 and concerns, and one of them was making it a wedge  
5 issue between insurers, and clinicians, and the  
6 patients, and that is definitely something I think  
7 we need to keep top of mind.

8 I also wanted to remind the committee,  
9 sometimes the alternative, when you don't have any  
10 good treatment options, is a recommendation for a  
11 total colectomy, and that has much increased  
12 morbidity. And I just think we need to be thinking  
13 about that as well.

14 When patients don't respond to treatment,  
15 that's the next alternative. And I know plenty of  
16 people who have gone out and done that. It's been  
17 recommended to me. So I just want us to remember  
18 that that's potentially what patients are being  
19 offered as an alternative.

20 DR. RAUFMAN: Dr. Hunsberger?

21 DR. HUNSBERGER: I actually had the opposite  
22 thoughts of you. Some of my experience is that,



1 for the more severe patients, it's actually harder  
2 to get a benefit. So I was actually more assured  
3 of this data, that some of the analyses actually  
4 showed an improvement. So we've had opposite  
5 experiences.

6 I was also reassured by some of the  
7 sponsor's data where the three different components  
8 of the endpoints all kind of went in the same  
9 direction. So I actually was pretty happy with the  
10 efficacy data and the severity data.

11 DR. RAUFMAN: Can we go ahead and vote?  
12 Dr. Thadani?

13 DR. THADANI: Can I just say, John, you said  
14 in cardiovascular medicine, patients are really  
15 very symptomatic with angina; some signs the  
16 placebo response skyrockets [indiscernible]. So I  
17 think you can show the efficacy, too, but I think  
18 it goes in the wrong direction, too.

19 When I said the very restricted analysis,  
20 it's still in the right direction. So I think it  
21 didn't go the opposite way, although response is  
22 smaller. So that's why I presume it's in the right

1 direction.

2 DR. RAUFMAN: So in the absence of  
3 additional discussion, please press the button  
4 firmly that corresponds to your vote.

5 (Voting.)

6 DR. FAJICULAY: For the record, the results  
7 are 12 yes; zero no; zero abstain; and zero voting.

8 DR. RAUFMAN: So maybe we'll start on my  
9 left this time.

10 Dr. Mann, if you could, read your name, say  
11 your name into the record and why you voted the way  
12 you did.

13 DR. MANN: John Mann. I voted yes because  
14 the data indicated that there wasn't much  
15 difference in the degree of benefit between the  
16 more severe group and the total group.

17 MS. KHURANA: Sandeep Khurana. I voted yes  
18 for obviously the same reasons.

19 DR. LEBWOHL: Ben Lebwohl. I voted yes  
20 because of the FDA's data shown at their  
21 presentation.

22 DR. RAUFMAN: Jean-Pierre Raufman. I voted

1       yes for the same reasons.

2               DR. ROSEN: Rachael Rosen. I voted yes for  
3 the same reason.

4               MS. McVEY HUGICK: Joy McVey Hugick. I  
5 voted yes for the same reasons.

6               MS. ROBOTTI: Suzanne Robotti. I voted yes  
7 for reasons previously stated.

8               MS. NUMANN: Sabrina Numann, patient  
9 representative. I did vote yes due to the FDA's  
10 presentation points towards severely symptomatic,  
11 although I would not want to single out or try to  
12 limit the word "severity." Thank you.

13              DR. THADANI: Thadani. I voted yes for the  
14 data given by the FDA, which was convincing enough.

15              DR. SOLGA: Steve Solga. I voted yes,  
16 nothing further to add.

17              DR. TEERLINK: John Teerlink. I voted yes,  
18 and nothing further to add.

19              DR. HUNSBERGER: I voted yes and nothing  
20 further to add.

21              DR. RAUFMAN: Thank you.

22              Our last question, in which patient

1 population would you expect the benefits to  
2 outweigh the risks for patients treated with  
3 tegaserod? I'm not sure how we're going to use the  
4 keypads for this, so somebody will let me know.

5 We choose one of those five? Okay.

6 DR. ROSEN: Before we vote, can I just add  
7 something? Can we vote for each one separately?  
8 Because there's many groups that we may feel that  
9 this may be okay for rather than an absolute  
10 cutoff.

11 So could we vote yes/no for A, yes/no for B,  
12 yes/no for C?

13 DR. FAJICULAY: Hi. This is Jay Fajiculay,  
14 DFO for the GI advisory committee. Unfortunately,  
15 we already have these questions finalized, so we  
16 would need to vote on them as they're already  
17 projected.

18 DR. KORVICK: This is Dr. Korvick, FDA.  
19 I'll just go with our DFO here, but I think what we  
20 tried to do is put these in pairs. And if you  
21 can't find a pair that you think would be the  
22 optimal -- say you're writing a prescription for a

1 patient and this is who you want to give it  
2 to -- you could answer other and explain your  
3 answer. We tried to give the most logical pairs we  
4 could think of, but if you have another idea, you  
5 could vote for choice E. Thank you.

6 DR. RAUFMAN: I think I get it now. In  
7 which patient population would you expect the  
8 benefits to outweigh the risks for patients treated  
9 with tegaserod? A is IBS-C females; B, IBS-C  
10 females at low cardiovascular risk; C, IBS-C  
11 females who are severely symptomatic; D, IBS-C  
12 females at low cardiovascular risk who are severely  
13 symptomatic; and E is other

14 I'll open it to questions or comments.  
15 Dr. Hunsberger?

16 DR. HUNSBERGER: Yes. The CV risk, is that  
17 the FDA definition or the sponsor definition?

18 DR. KORVICK: You can choose to make that  
19 comment when you explain your answer.

20 DR. HUNSBERGER: So when we vote, we just  
21 vote whichever way we think and then we explain.  
22 Okay.

1 DR. RAUFMAN: Additional comments?

2 Dr. Lebwohl?

3 DR. LEBWOHL: Ben Lebwohl. I'm going to  
4 assume that this is also asking the advisory  
5 committee to vote in terms of what do we think the  
6 FDA should approve this for in terms of a specific  
7 indication. It's not exactly the same thing as  
8 what's being asked, but I think that it's congruent  
9 enough, that's how I'm planning to vote.

10 DR. KORVICK: Yes. We thought it was  
11 congruous enough.

12 DR. LEBWOHL: If there's not going to be  
13 further discussion, I thought I would just bring up  
14 one thing that's been bothering me about how to  
15 label, because I'm trying to look into the future,  
16 and it plays to both the small but I think real  
17 cardiovascular risk, and the question about  
18 psychiatric comorbidity, which is common in  
19 patients with IBS.

20 I think that putting low cardiovascular risk  
21 in the label will send an important message and  
22 make sure that that concern isn't just lost in a

1 package insert and actually prompts conversation.  
2 But we've been talking about high placebo effects  
3 in these trials.

4           There's also the potential for a nocebo  
5 effect and the notion that a patient may be  
6 experiencing harm without organic pathology. I  
7 think that if we present this as potentially  
8 cardiotoxic, even if rare, we're going to be seeing  
9 patients coming to the emergency room with chest  
10 pain. A proportion of such patients are going to  
11 be having that as a nocebo effect.

12           I think it's going to be hard to measure. I  
13 think we should be looking out for it, and it's  
14 just something that I'm anticipating in my own  
15 practice.

16           DR. RAUFMAN: Additional comments?

17           (No response.)

18           DR. RAUFMAN: Why don't we then go ahead and  
19 vote? So here, unlike the yes/no, as I've now been  
20 educated, we are pushing one of the letters at the  
21 bottom that best corresponds with your answer. And  
22 then we'll have a little bit more detailed

1 discussion after the vote of what you meant by how  
2 you voted. So go ahead and vote.

3 (Voting.)

4 DR. FAJICULAY: For the record, the results  
5 are 1, A, IBS-C females; 7, B, IBS-C females at low  
6 cardiovascular risk; zero, C, IBS-C females who are  
7 severely symptomatic; 3, D, IBS-C females who are  
8 low cardiovascular risk and who are severely  
9 symptomatic; and 1, E, other.

10 DR. RAUFMAN: So let's start with  
11 Dr. Hunsberger. Please say your name, how you  
12 voted, and why.

13 DR. HUNSBERGER: Sally Hunsberger. I voted  
14 B, and I like the FDA definition of CV risk. I  
15 think the efficacy is there, as I said earlier. I  
16 do think there is a CV signal, and this is our best  
17 way of trying to figure out who is at risk. I  
18 think people are at risk, and I think if we can  
19 somehow minimize this, I think that's the way we  
20 can do it. And from the numbers that the FDA put  
21 forward, it looks like we are reducing the risk  
22 somewhat.



1 DR. TEERLINK: John Teerlink, and I voted D.  
2 The reason I voted D is that I think we need to try  
3 to find a way to reduce the overall risks of the  
4 patient population. I would be tempted to ask the  
5 FDA to consider actually just limiting defining low  
6 cardiovascular risk, though, as the sponsor defined  
7 it.

8 I'm not sure you're really providing  
9 that -- you're providing a huge layer of complexity  
10 and eliminating a substantial number of patients  
11 who might benefit based on just unclear  
12 cardiovascular risk factors that didn't seem to  
13 show a definite influence on the outcomes.

14 The reason I would still limit it to  
15 severely symptomatic is because I think there is  
16 this cardiovascular risk. It is going to be  
17 related to how many patients are exposed to the  
18 agent. And so because of that, I'd want it only to  
19 be used in patients in whom you would really need  
20 that kind of benefit.

21 So I would suggest changing low  
22 cardiovascular risk to just patients with prior

1 cardiovascular ischemic events and limit it to  
2 severely symptomatic patients.

3 DR. SOLGA: Steve Solga. I voted B. I  
4 agree with Dr. Teerlink and Dr. Hunsberger that the  
5 cardiovascular risk is small but real. I think we  
6 all believe the same thing about the psychiatric  
7 risk. I think there is some real potential for  
8 harm here.

9 Unlike Dr. Teerlink, I don't want to add the  
10 symptomatic language for the reasons previously  
11 stated, so I went with B rather than D. I do  
12 think, however, this is an important high-stakes  
13 conversation between a provider and a patient, and  
14 I'm not sure that a package label alone is going to  
15 get this done.

16 I do think consideration of a REMS patient  
17 acknowledgement form à la Lotronex is a reasonable  
18 consideration here until more information comes  
19 along.

20 DR. THADANI: Thadani. I voted D for  
21 obvious reasons. I'm still concerned with the  
22 cardiovascular and the neuropsychiatric risk. I

1 think if you expose the very seriously ill  
2 population who are really in need of something, you  
3 can monitor their risk, and then you might go  
4 further to low-risk patients.

5 I think the patients who are severely  
6 constipated and have other issues also might have  
7 more neuropsychiatric issues because they are  
8 miserable. I think there's a signal, and you catch  
9 that first. So that's why I voted D rather than  
10 going for C or B.

11 MS. NUMANN: Sabrina Numann. I voted B,  
12 which combines the public comments online as well  
13 as today, the clinical discussion, and data  
14 presented. But I don't want to limit the patients  
15 who don't fit that severity scale at the time of  
16 prescription or have that severity get lost in  
17 language. Thank you.

18 MS. ROBOTTI: Hi. Suzanne Robotti. I'm E,  
19 other, and it's really D plus. I believe it should  
20 be IBS-C females at low CV risk who are severely  
21 symptomatic and have a low psychiatric risk. I  
22 didn't phrase that correctly, but I'm sure you know

1 what I mean.

2 I think the psychiatric signals are there.  
3 I think they're very poorly measured. I think that  
4 it could potentially be a big problem, so a  
5 notation should be made on the label.

6 MS. McVEY HUGICK: Joy McVey Hugick. I  
7 voted B for reasons already stated. And I would  
8 just say that I would hope that the sponsor,  
9 whether it's required or not, would put some time  
10 and energy into developing materials that would  
11 help guide the patient-provider dialogue that needs  
12 to happen.

13 DR. ROSEN: Rachael Rosen. I voted for B,  
14 and I would hope actually that the sponsor keeps  
15 track of this because I hope this cardiovascular  
16 thing goes away and you can give it to all patients  
17 with IBS-C. So please keep track of that.

18 Then the other part from an FDA perspective  
19 is that when this drug was originally released, it  
20 was prescribed for a lot of upper tract symptoms  
21 that could be confused with chest pain, so chest  
22 pain, upper tract stuff, with patients with

1 functional dyspepsia, functional heartburn, things  
2 like that.

3           So if people are going to prescribe for  
4 other indications, so in severe patients who may  
5 have IBS-C but also have other functional GI  
6 disorders, I think it's important to keep track of  
7 which patients had upper tract symptoms that maybe  
8 were mistaken for functional disease which were in  
9 fact cardiac. So just keep track of that if it  
10 comes back on.

11           DR. RAUFMAN: Jean-Pierre Raufman. I voted  
12 B. I was convinced by the data regarding the  
13 benefits of stratifying patients by cardiovascular  
14 risk. I was also convinced that there would be a  
15 lot of disagreement about determining whether  
16 patients did or did not have severe IBS-C and that  
17 it should be left up to the patient and the  
18 practitioner to make that determination regarding  
19 benefit.

20           DR. LEBWOHL: Ben Lebwohl. I voted B for  
21 the same reasons enumerated by Dr. Raufman.

22           MS. KHURANA: I voted A. And I just want to

1 explain that a little bit. I do not discount the  
2 risk factors or the signals that were discussed  
3 here. That's in spite of that.

4 First of all, the severity cannot be  
5 assessed and waxes and wanes within the same  
6 patient. So it's very hard to determine on one day  
7 when they would be severe and another day that they  
8 are not that severe.

9 That's one reason, and that's a  
10 determination that has to be made while the patient  
11 is in the office and the interaction is going on.  
12 So that's one reason. It's hard to stratify that.

13 Number two, I did not take the CV and the  
14 societal risk into consideration because that data  
15 actually shows only as a signal and not actually as  
16 an effect. So when you compare to the placebo,  
17 these differences have not reached significance.

18 Keeping that data into consideration, I  
19 think that I voted A, but despite that, I do think  
20 that there should be a discussion of these, and  
21 they should be put on label, and there should be a  
22 postmarketing registry of some sort to track this

1 and does this really pan out or not.

2 DR. MANN: John Mann. I voted D. And the  
3 reason for that is that I thought that the domains  
4 of risk, the data for that were sufficiently  
5 compelling to pay attention to that. I was  
6 concerned that there would be indication creep in  
7 terms of who would be offered this medication.

8 I would hope that the FDA would pursue the  
9 matter of clarifying and quantifying these risk  
10 levels more precisely, and that would be best done  
11 in a smaller group of patients rather than a bigger  
12 group of patients. So I went for the more  
13 incremental and cautious strategy for the  
14 reintroduction of this medication.

15 DR. RAUFMAN: I would just comment that I  
16 think it's interesting that the gastroenterologists  
17 uniformly voted for either A or B and the non-  
18 gastroenterology physicians on the panel voted for  
19 D. I think that says something about those of us  
20 who interact with these patients and understand the  
21 complexity and difficulties.

22 Dr. Korvick?

1 DR. KORVICK: Thank you for that comment. I  
2 think that we've gotten a lot of good answers from  
3 the panel, but I have one last more answer that I'd  
4 like to get from you all.

5 For the people that voted for B or D, where  
6 you say at low cardiovascular risk, would people  
7 opine on -- some of you did -- whether you think  
8 the definition should be that proposed by the  
9 sponsor or even more restrictive with the  
10 additional factors that we used on the FDA  
11 analysis?

12 We'd like to get your input into what is the  
13 low CV risk that you want to characterize, so if we  
14 could hear from those people.

15 DR. RAUFMAN: Perhaps the cardiologists  
16 would like to start this off.

17 DR. THADANI: On the slide, the differences  
18 on the two?

19 DR. KORVICK: Slide 64 maybe.

20 DR. THADANI: No. He's going to put what is  
21 the low cardiovascular risk.

22 DR. KORVICK: Here we go. This is the



1 one -- why don't you explain?

2 DR. VENKATARAMAN: So this is the proposed  
3 definition. The sponsor initially proposed this  
4 definition. This is what most of our analyses are  
5 based on. What we're calling today is the sponsor-  
6 proposed definition is just discounting that last  
7 sub-bullet. So it's only female IBS-C patients  
8 less than 65 years without a history of CV ischemic  
9 disease.

10 Is that clear?

11 DR. THADANI: Sorry. Thadani. So you are  
12 saying your data analysis is based on both? The  
13 data we saw is for both?

14 DR. VENKATARAMAN: Right. So the data that  
15 we presented and called as low CV risk was this  
16 whole definition as you see it on the slide.

17 DR. THADANI: Yes. So why are you  
18 discarding the second part? The sponsor doesn't  
19 want it, right?

20 DR. VENKATARAMAN: That's the applicant's  
21 proposed definition of low CV risk, so we're asking  
22 you to consider both, and if there's one that you

1 think is more or less appropriate.

2 DR. THADANI: My feeling would be to leave  
3 both in because even though the signal may be very  
4 small, the population of treatment is huge. So I  
5 think once you get more cautious and no signal in  
6 your mandatory registry, then you can expand it.

7 Safety first. These are young people, and I  
8 think all you need is one or two going the wrong  
9 way by chance. You're going to pay for it. So my  
10 personal bias would be to keep both as you  
11 analyzed.

12 DR. TEERLINK: So this is John Teerlink.  
13 I'll give my opinion. I already gave my previous  
14 opinion, but that was with restricting it to  
15 severely symptomatic. If you decide to expand it  
16 to beyond severely symptomatic patients, then I  
17 would be very much in favor of having more than one  
18 cardiovascular risk factor and have it go back to  
19 the FDA definition.

20 The reason being that I think until we get  
21 more experience with this and the indication creep  
22 and other issues that are going to come up, I'm

1 very concerned that there are going to be millions  
2 of patients who are going to get this and the  
3 excess of 3 per 10,000 cardiovascular events.

4 These aren't, oh, I'm feeling bad. This is  
5 myocardial infarction, stroke, or death. So even  
6 though it's a small number, when you jack it up to  
7 millions of patients treated, I'm concerned about  
8 the possible public health impact.

9 So if you go to all females who are not  
10 severely symptomatic, then you should have both of  
11 those factors in there, please.

12 DR. RAUFMAN: If I could ask for  
13 clarification, for example, hypercholesterolemia;  
14 if someone is on a statin and their lipids are  
15 normal, that's okay?

16 DR. TEERLINK: No. It's still a risk  
17 factor.

18 DR. RAUFMAN: It's still a risk factor.

19 DR. TEERLINK: Tobacco use; if they've quit,  
20 then it's okay. Hypertension, treated hypertension  
21 should still be an exclusion. Diabetes treated  
22 should be an exclusion. And if you find a way to

1 treat age over 55 years, please let me know.

2 (Laughter.)

3 DR. THADANI: Thadani. I think you can go  
4 further because you're 64 years and 11 months, and  
5 when you become 65 next year, you're going to stop  
6 it? There are a lot of caveats in that.

7 How do we define hypertension? The current  
8 definition used to be 160, then came the 140, and  
9 now the best thing is 130. So I realize it's very  
10 tough. You may find a lot of your patients are  
11 going to be excluded, but you're cautious about the  
12 effect.

13 This is what you showed; the lowest signal  
14 is in this population. And I think if there was  
15 zero risk, then we wouldn't be discussing it here.  
16 So I think, initially, you start with that. As  
17 you get more confident, FDA will review the data.  
18 I would even suggest to put a black box for the  
19 cardiovascular risk and neuropsychiatric issues.  
20 If I want to take the drug, I want to know I am  
21 miserable; I'm going to take a chance. I'll take  
22 it.

1           But if you don't have a box, all the GI  
2 people will use for other indications because all  
3 you have to do is show the patient a paper. He's  
4 going to read it on Google. He said, "This drug  
5 works. Use it." So I would really like to see a  
6 black box warning.

7           I think we did have the cardiorenal  
8 committee on sotalol. The signal was low there,  
9 too, but I think we are dealing with very serious  
10 issues, which is death, MI, and stroke. I'm not  
11 worried about squirrely chest pain. So I would  
12 like to see in addition a black box warning.

13           DR. RAUFMAN: I think you might have wanted  
14 to see this as a voting question because I think  
15 that there's going to be disagreement around the  
16 table regarding these two options.

17           I think that the diabetes,  
18 hypercholesterolemia, et cetera is going to  
19 restrict use. You're going to cut out obesity.  
20 And the age, you're just going to cut out a lot of  
21 women who would potentially benefit from the drug  
22 and be at very low risk.

1 DR. TEERLINK: And your basis of saying that  
2 they're at low risk is for a symptomatic benefit?

3 DR. RAUFMAN: Overall, we said the signal is  
4 weak. Right? So overall, we're saying that there  
5 is a risk, but it seems to be a low risk.

6 DR. MANN: I don't know. Millions of people  
7 are going to get this drug. I think let's see how  
8 it works in a more confined population, and then  
9 reassess.

10 DR. LEBWOHL: Ben Lebwohl. I, too, wish  
11 that it were a little more granular, and I  
12 personally would probably be comfortable in a  
13 55-year-old woman who's taking atorvastatin to take  
14 this drug, but not a smoker with uncontrolled  
15 hypertension.

16 That said, given the discernible signal  
17 we're seeing, I'd err on the side of casting a more  
18 cautious net and using this FDA definition for now.

19 DR. RAUFMAN: Additional comments?

20 (No response.)

21 DR. RAUFMAN: Would the FDA like to make a  
22 closing comment?

1 DR. KORVICK: I think we'd like to thank  
2 everybody for their thoughtful comments. And I  
3 didn't know if there -- I counted 7 people that  
4 answered B or D. So did everybody who answered B  
5 or D comment for us?

6 (No response.)

7 DR. KORVICK: Thank you.

8 MS. NUMANN: As a patient, I would be  
9 considered SI/B risk. I have a history of  
10 hypertension. I smoked 20 years ago. I had high  
11 cholesterol for about 5 years that I got under  
12 control with diet. I was obese at one time and  
13 took off 85 pounds, but that could come back. I  
14 can keep going.

15 So I think that I chose B with the  
16 understanding that this should be between a patient  
17 and a physician, and the physician knowing their  
18 patient more than anybody should be able to make  
19 that kind of decision. Thank you.

20 DR. RAUFMAN: I think, with that, if there  
21 are no additional comments? All right. Steve?

22 DR. SOLGA: Steve Solga. I feel obliged

1 because Dr. Korvick asked. I feel like this is  
2 something where we want the patients who may  
3 benefit the most to have access. And I had said  
4 previously, maybe a patient acknowledgement form  
5 would be helpful or maybe it wouldn't be.

6 I think it's just a matter of communicating  
7 to the providers something that's important and  
8 workable and getting it through to patients that  
9 this is important.

10 Dr. Teerlink thinks severe symptomatic is  
11 the answer. I don't. We disagree on that. I feel  
12 like the sponsor's definition of cardiovascular  
13 risk is not unreasonable. I'm a little bit  
14 concerned that a lot of folks are going to get  
15 caught up if it's the FDA's definition, and there  
16 are going to be a lot of folks that get excluded.  
17 I don't know that that's the intent, so I actually  
18 kind of favor the sponsor's definition here.

19 **Adjournment**

20 DR. RAUFMAN: With that, we will now adjourn  
21 the meeting. Panel members, please leave your name  
22 badges here on the table so they can be recycled.



1 Please also take all personal belongings with you,  
2 as the room will be cleaned at the end of the  
3 meeting day. Meeting materials left on the table  
4 will be disposed of. Thank you all.

5 (Whereupon, at 3:27 p.m., the meeting was  
6 adjourned.)

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