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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

THURSDAY, NOVEMBER 17, 2011

8:00 a.m. to 4:45 p.m.

Holiday Inn Washington DC/College Park

10000 Baltimore Avenue

College Park, Maryland

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10 **(Non-Voting)**

11 **Jonathan Fox, M.D., Ph.D.**

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

2                   (8:00 a.m.)

3                   **Call to Order**

4                   **Introduction of Committee**

5                   DR. RAUFMAN: Good morning. If everyone  
6 could please take their seats, we can get started.  
7 I'd like to remind everyone present to please  
8 silence your cell phones, Blackberrys, and other  
9 devices, if you have not already done so.

10                  We'll start by going around the table and  
11 introducing ourselves. My name is Jean-Pierre  
12 Raufman, head of the Division of Gastroenterology  
13 and Hepatology at the University of Maryland School  
14 of Medicine in Baltimore.

15                  Dr. Fox?

16                  DR. FOX: My name is Jonathan Fox. I'm a  
17 cardiologist with AstraZeneca, in clinical  
18 development. I'm the acting industry  
19 representative for the meeting today.

20                  DR. SOLGA: My name is Steve Solga, and I'm  
21 in private practice in gastroenterology.

22                  DR. ANDERSON: My name is Garnet Anderson.

1 I'm a biostatistician at Fred Hutchison Cancer  
2 Research Center.

3 DR. LAUER: My name is Mike Lauer. I'm a  
4 cardiologist, and I'm the director of the Division  
5 of Cardiovascular Sciences at the National Heart,  
6 Lung, and Blood Institute.

7 DR. ROSEN: My name is Rachel Rosen. I'm a  
8 pediatric gastroenterologist in the Center for  
9 Motility and Functional Bowel Disorders at  
10 Children's Hospital, Boston.

11 MR. MATSON: My name is Tracy Matson,  
12 patient representative, Little Rock, Arkansas.

13 DR. THADANI: My name is Udho Thadani,  
14 University of Oklahoma Medical and Sciences Center  
15 and VA Medical Center. I'm a cardiologist.

16 DR. SPIEGEL: My name is Brennan Spiegel.  
17 I'm a gastroenterologist at UCLA, the School of  
18 Medicine, the School of Public Health, and also at  
19 the West Los Angeles VA Medical Center.

20 DR. KAUL: Good morning. My name is Sanjay  
21 Kaul. I'm a cardiologist at Cedar Sinai Medical  
22 Center in Los Angeles.

1 DR. BLOOM: Good morning. My name is Jack  
2 Bloom. I'm a private consultant now, formerly led  
3 the Division of Diagnostics and Experimental  
4 Medicine at Eli Lilly and Company.

5 DR. ROSENBERG: Good morning. My name is  
6 Yves Rosenberg. I'm a branch chief of the  
7 Atherothrombosis and Coronary Artery Diseases  
8 Branch, Division of Cardiovascular Sciences at  
9 NHLBI. I'm an epidemiologist/clinical trialist.

10 DR. GREENE: I'm Martin Greene. I've been  
11 in practice of gastroenterology for a long time in  
12 Seattle. I've been on the governing board of the  
13 American Gastroenterological Association. I'm also  
14 interested in medical legal issues and risk  
15 management, and I've reviewed thousands of cases,  
16 including over 500 in the field of gastroenterology  
17 and medical legal issues.

18 DR. KORVICK: My name is Joyce Korvick. I'm  
19 the deputy director for safety in the Division of  
20 Gastroenterology and Inborn Error Products.

21 DR. FIORENTINO: I'm Rob Fiorentino. I'm a  
22 clinical team leader in the Division of

1 Gastroenterology and Inborn Error Products.

2 DR. PETERSON JOHNSON: My name is Aisha  
3 Peterson Johnson. I'm a clinical reviewer in the  
4 Division of Gastroenterology and Inborn Errors  
5 Products.

6 DR. LEE: My name is Sue-Chih Lee. I'm  
7 clinical pharmacology team leader with the FDA,  
8 Office of Clinical Pharmacology, FDA.

9 DR. SOUKUP: My name is Mat Soukup. I'm a  
10 team lead within the Division of Biometrics 7,  
11 Office of Biostatistics, FDA.

12 DR. TEERLINK: I'm Dr. John Teerlink. I'm a  
13 cardiologist from the University of California-San  
14 Francisco, and director of Heart Failure at the San  
15 Francisco VA Medical Center.

16 DR. RICHIG: Good morning. I'm Jeffrey  
17 Richig, CEO of ANILAB. I'm a veterinary  
18 cardiologist and a consultant for preclinical  
19 studies.

20 DR. BILD: Hi. I'm Diane Bild. My training  
21 is in internal medicine and epidemiology, and I'm  
22 with the Division of Cardiovascular Sciences at

1 NHLBI.

2 DR. BLACK: Good morning. I'm Henry Black.  
3 I'm at the New York University School of Medicine,  
4 and I'm a preventive cardiologist specializing in  
5 hypertension, in particular.

6 DR. SHEN: Hi. My name is Bo Shen. I'm a  
7 gastroenterologist at the Cleveland Clinic. Thank  
8 you.

9 DR. GRANGER: I'm Chris Granger. I'm a  
10 cardiologist at Duke University in Durham, North  
11 Carolina; also, a clinical trialist.

12 DR. KALTMAN: Good morning. My name is John  
13 Kaltman. I'm a pediatric cardiologist and medical  
14 officer at NHLBI.

15 DR. HASLER: My name is William Hasler. I'm  
16 a professor in the Division of Gastroenterology,  
17 University of Michigan Health System.

18 DR. SOUT: Good morning. I'm Dr. Gagan  
19 Sout. I'm a gastroenterologist and hepatologist at  
20 Baylor College of Medicine, Houston, Texas.

21 DR. KUMAR: Atul Kumar, gastroenterology and  
22 hepatology at Stony Brook and the Northport VA

1 Medical Center on Long Island.

2 DR. DOAN: I'm Minh Doan, acting designated  
3 federal officer.

4 DR. RAUFMAN: Thank you.

5 For topics such as those being discussed at  
6 today's meeting, there are often a variety of  
7 opinions, some of which are quite strongly held.  
8 Our goal is that today's meeting will be a fair and  
9 open forum for discussion of these issues and that  
10 individuals can express their views without  
11 interruption. Thus, as a gentle reminder,  
12 individuals will be allowed to speak into the  
13 record only if recognized by the chair. We look  
14 forward to a productive meeting.

15 In the spirit of the Federal Advisory  
16 Committee Act and the Government in the Sunshine  
17 Act, we ask that the advisory committee members  
18 take care that their conversations about the topic  
19 at hand take place in the open forum of the  
20 meeting. We are aware that members of the media  
21 are anxious to speak with the FDA about these  
22 proceedings. However, FDA will refrain from

1 discussing the details of this meeting with the  
2 media until its conclusion.

3 For the convenience of the media  
4 representatives, I would like to identify the FDA  
5 press contact, Morgan Liscinsky.

6 If present, could you please stand? Thank  
7 you.

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

11 Now, I'll pass it to Dr. Doan, who will read  
12 the conflict of interest statement.

13 **Conflict of Interest Statement**

14 DR. DOAN: The Food and Drug Administration  
15 is convening today's meeting of the  
16 Gastrointestinal Drugs Advisory Committee under the  
17 authority of the Federal Advisory Committee Act of  
18 1972. With the exception of the industry  
19 representative, all members and temporary voting  
20 members of the committee are special government  
21 employees or regular federal employees from other  
22 agencies and are subject to federal conflict of

1 interest laws and regulations.

2 The following information on the status of  
3 this committee's compliance with the federal ethics  
4 and conflict of interest laws, covered by but not  
5 limited to those found at 18 USC Section 208 and  
6 Section 712 of the Federal Food, Drug, and  
7 Cosmetics Act, is being provided to participants in  
8 today's meeting and to the public.

9 FDA has determined that members and  
10 temporary voting members of this committee are in  
11 compliance with federal ethics and conflict of  
12 interest laws. Under 18 USC Section 208, Congress  
13 has authorized FDA to grant waivers to special  
14 government employees and regular federal employees  
15 who have potential financial conflicts when it is  
16 determined that the agency's need for a particular  
17 individual's services outweighs his or her  
18 potential financial conflict of interest.

19 Under Section 712 of the Food, Drug, and  
20 Cosmetic Act, Congress has authorized FDA to grant  
21 waivers to special government employees and regular  
22 federal employees with potential financial

1 conflicts when necessary to afford the committee  
2 essential expertise.

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

14 Today's agenda involves discussion of  
15 recommendations to the agency on the design and  
16 size of premarketing cardiovascular safety  
17 development programs necessary to support approval  
18 of products in the class of serotonin,  
19 5-hydroxytryptamine, receptor 4 agonists for the  
20 proposed indications of chronic idiopathic  
21 constipation, constipation predominant irritable  
22 bowel syndrome, gastroparesis, and gastroesophageal

1 reflux disease that does not respond to a proton  
2 pump inhibitor. This is a particular matters  
3 meeting during which general issues will be  
4 discussed.

5 Based on the agenda for today's meeting and  
6 all financial interests reported by the committee  
7 members and temporary voting members, no conflict  
8 of interest waivers have been issued in connection  
9 with this meeting.

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

15 With respect to FDA's invited industry  
16 representative, we would like to disclose that  
17 Dr. Jonathan Fox is participating in this meeting as  
18 a nonvoting industry representative, acting on  
19 behalf of regulated industry. Dr. Fox's role at  
20 this meeting is to represent industry in general  
21 and not any particular company. Dr. Fox is  
22 employed with AstraZeneca.

1           We would like to remind members and  
2 temporary voting members that if the discussions  
3 involve any other products or firms not already on  
4 the agenda for which an FDA participant has a  
5 personal or imputed financial interest, the  
6 participants need to exclude themselves from such  
7 involvement, and their exclusion will be noted for  
8 the record. FDA encourages all other participants  
9 to advise the committee of any financial  
10 relationships that they may have with the firm at  
11 issue.

12           Thank you.

13           DR. RAUFMAN: Thank you.

14           We will now proceed with the FDA's  
15 presentations.

16           Dr. Korvick?

17                   **FDA Presentation - Joyce Korvick**

18           DR. KORVICK: Good morning, Mr. Chairman.  
19 We'd like to extend a welcome to our members of the  
20 advisory committee assembled here today and thank  
21 you for your participation.

22           We look forward to a lively discussion today

1 regarding the topic of the evaluation of the  
2 cardiac safety for serotonin receptor agonists as  
3 GI therapies. This is a unique moment for us  
4 because we have an equal number, as I've been told,  
5 of cardiologists and gastroenterologists at this  
6 table, although it is a GI committee. But we felt  
7 that was important to include you all because this  
8 was a particularly important issue.

9 In contrast to yesterday's meeting, where we  
10 were talking about efficacy, we're turning the page  
11 today and talking about safety. But I think that  
12 we should all remember that there is a context, and  
13 these are the gastroenterology drugs that we're  
14 talking about.

15 I'm going to give you a brief high level  
16 introduction, touch upon several guidances and ways  
17 of evaluating drugs during development, but these  
18 are non-cardiac drugs and not cardiac safety, and  
19 then introduce the questions to you that we'll be  
20 considering later today.

21 This is also a unique advisory committee,  
22 because we're going to be talking about many

1 different products, in a historical context. And  
2 in order to prepare for this meeting, it took a lot  
3 of us at the FDA. So I'd like to thank all of the  
4 members of the staff, not only the ones that are  
5 presenting today.

6 In particular, I would like to thank our  
7 regulatory project manager, Maureen Dewey; as well,  
8 the toxicologist, Dr. Niraj Mehta, for their  
9 contributions to the background package and today's  
10 meeting.

11 As you've been told, this purpose is to talk  
12 about the design size of premarketing  
13 cardiovascular evaluations necessary to support the  
14 approval of products in the serotonin 5-HT4 agonist  
15 class, and, in particular, indications which may be  
16 developed in the GI world for these drugs are  
17 targeted at chronic idiopathic constipation,  
18 irritable bowel syndrome, chronic irritable bowel  
19 syndrome with constipation predominant,  
20 gastroparesis, gastroesophageal reflux disease that  
21 does not respond to proton pump inhibitors; in  
22 other words, motility disorders.

1           When we were putting this advisory committee  
2 today together, we had to think about several  
3 things. There are a lot of new 5-HT4 agonists that  
4 are being developed in the IND phase, and the  
5 attempt in this area is to target more specifically  
6 the receptors in the GI tract and to try to avoid  
7 off-target cardiac side effects. More about that  
8 later.

9           In addition, we thought that the advice that  
10 you all would give to us and the information we  
11 discuss today at the table would probably be  
12 applicable to all of these drugs. So in that  
13 manner, we strove to bring you an open advisory  
14 committee.

15           We invited all of the sponsors presently  
16 developing drugs and those that have had drugs in  
17 the past in this class, and those presenting here  
18 today accepted the invitation.

19           We should also note that FDA was permitted  
20 to present and we are the sole presenters for the  
21 naronapride medication here today. And, finally,  
22 the goal is to be transparent in receiving

1 regarding this advice for the assessment of the new  
2 drugs in this class, and, particularly, talking  
3 about the major adverse cardiac events that should  
4 be assessed and how should they be assessed.

5           Again, we're going to review historical  
6 highlights of cardiovascular events in this class.  
7 And it should be noted that the FDA will be  
8 presenting historical notes on Zelnorm. But that  
9 sponsor is not present, so those comments will be  
10 restricted to publicly available information.

11           In consideration today, since we have  
12 cardiologists and gastroenterologists, it is  
13 important for us to consider several things. The  
14 cardiovascular safety in this drug class -- and we  
15 will touch upon the history there and particularly  
16 with regard to previous drugs.

17           So then it's important to consider what do  
18 we know about the animal toxicology and safety  
19 studies about the early phase 1/2 clinical  
20 evaluations that we have right now. And, also,  
21 it's important to think about the unmet medical  
22 need. Many gastroenterologists around the table

1 and patients come to us continuously to ask about  
2 drugs to treat motility disorders. There are not  
3 very many of them, and they have a colorful  
4 history, and you'll hear more about that today.  
5 But ones that were on the market are no longer  
6 there. So there is a need.

7 It's also important to consider the patient  
8 population for which the drug is being developed;  
9 that is, the context of use. And, hopefully, the  
10 gastroenterologists on the committee can explain  
11 some of their perspectives in that regard to the  
12 cardiology colleagues.

13 Finally, this is not an advisory committee  
14 talking about a new NDA; therefore, we do not have  
15 phase 2 data upon which to discuss the risk-benefit  
16 assessment. However, reminding ourselves about the  
17 context of use and the patient population would be  
18 helpful as you're considering safety evaluations.

19 As I mentioned, in this class, we have two  
20 drugs that are noteworthy; cisapride, which was  
21 approved in 1993, and, after it was marketed,  
22 cardiac arrhythmias were associated with drug use

1 and, also, drug-drug interactions due to metabolic  
2 pathway interruptions, especially for the  
3 cytochrome P450 system, were noted. The other  
4 drug, tegaserod, was approved later, in 2002, and  
5 it was also removed after it was approved due to  
6 excess ischemic cardiovascular events.

7 Neither of these drugs are marketed in the  
8 United States. And I would say that today we think  
9 we fairly well understand how to evaluate QT  
10 prolongation. However, the excess ischemic  
11 cardiovascular events is an issue, I think, that we  
12 will be talking about more today.

13 Just to make a point, you can see that we  
14 have now the international -- the ICH guidelines  
15 for animal evaluations, S7A and 7B, and these were  
16 actually published in 2001 and 2005, which, as  
17 you'll note, were after these drugs were pulled off  
18 the market.

19 So things have really changed of how we  
20 evaluate drugs today than how we did evaluate drugs  
21 back when cisapride and Zelnorm were approved to  
22 the market.

1           Just to say that the more complete assay,  
2 the supplemental 7B points out how to study  
3 nonclinical evaluations for QT interval  
4 prolongation, and particularly the requirements for  
5 in vitro IKr hERG assay and in vivo QT assay and  
6 ECG monitoring in canines.

7           This is adapted from the guidance, and I  
8 think it's a thoughtful way to put our discussions  
9 today in context. We start with the chemical  
10 compound in the pharmacologic class, and in this  
11 case, we have some history, as I mentioned.

12           Again, for the evaluation of the QT  
13 interval, nonclinical studies are conducted.  
14 That's added to our integrated risk assessment. If  
15 there are any questions raised by these, there may  
16 be more supplemental tests required.

17           We also draw on relevant nonclinical and  
18 clinical information, and this could come from the  
19 7A usual animal toxicology studies or other  
20 clinical information that we receive during drug  
21 development. And this all funnels together to  
22 bring the assessment to give us an understanding

1 what is the complete body of evidence for  
2 cardiovascular risk. And it should be noted that  
3 this is an iterative process during drug  
4 development, and even after drug development, as  
5 we'll see later today.

6           Again, to remind people at the table, and  
7 our cardiology friends here know this very well,  
8 but in 2005, we published, with the ICH, the  
9 guidance for the clinical evaluation of QT interval  
10 prolongation for non-antiarrhythmic drugs; that is,  
11 non-cardiac type drugs. And these guidances tell  
12 us very clearly how to conduct these studies, how  
13 to measure these intervals.

14           This is important because the QT  
15 prolongation can lead to increased susceptibility  
16 to these arrhythmias, such as ventricular  
17 tachyarrhythmias and torsades de pointes, even  
18 leading to death. We will be referring to these  
19 types of studies in our presentations today as  
20 thorough QT studies.

21           So when we look at these things, I think we  
22 fairly well believe that we understand how to

1 evaluate the drug-drug interactions. And I must  
2 say, again, that approximately 2005-2006, we as an  
3 agency updated our guidance for how you look at  
4 these, first, starting with in vitro hepatocyte  
5 assays, and then if you find metabolic issues there  
6 with CYP-P450, you proceed to clinical studies of  
7 these drugs.

8 So we believe that we can uncover, if there  
9 are suspect drugs, what the profiles look like in  
10 order to avoid the potential for higher exposure  
11 and increasing your safety profile, making it more  
12 risky to take these drugs together with other  
13 drugs.

14 Again, as I said, we have the TQT study.  
15 And, finally, people have been exploring how to use  
16 in vitro human platelet aggregation studies to look  
17 at the possibility of a reason for the ischemic  
18 cardiovascular events that were noted in Zelnorm  
19 and other drugs and that are not cardiac drugs and  
20 are not targeted to these issues.

21 We must say, though, that these are  
22 suggestive studies and of interest, but there is no

1 validated marker in this regard, and these assays  
2 are not approved by the FDA. They are variable  
3 from lab to lab, and the direct application to  
4 clinical significance is unknown at this time.

5 So, in review, we have evidence of  
6 cardiovascular risk that is accrued during drug  
7 development, and you will see in our presentation  
8 today we will review nonclinical data, clinical  
9 pharmacology data, and touch upon some phase 2  
10 data, phase 1 data. We do not have phase 3 data,  
11 but it is known by all of us here that these  
12 studies are mostly underpowered to detect rare  
13 events, and this has been discussed at many  
14 advisory committees. So for rare cardiovascular  
15 events, the standard drug evaluation paradigm may  
16 not collect those events in clinical trials.

17 So when we turn our thoughts to  
18 cardiovascular safety assessments, we have to think  
19 about is a dedicated cardiovascular study  
20 warranted. And it's not appropriate to do this for  
21 every drug that has ever come to market, because  
22 it's impractical.

1           So we have to carefully weigh the evidence  
2           which would implicate a drug or a drug class that  
3           would be required to have more intensive studies.  
4           If the cardiovascular trials are considered to be  
5           necessary prior to approval, we need to know what  
6           level of cardiovascular risk should be excluded.  
7           Of course, that needs to be in the context of the  
8           disease used.

9           Finally, to wet your whistle for our  
10          statistical presentation later this morning, I must  
11          point out that statistical considerations for the  
12          design of these studies are as follows. They would  
13          be a dedicated, randomized cardiovascular outcome  
14          trial, and this would be the gold standard for  
15          determining the hazard ratio. You need to have a  
16          comparison of the investigational treatment to a  
17          drug that is well understood or a control that's  
18          well understood; that is, what is the rate of  
19          adverse event. And, typically, these studies are  
20          being done as event-driven tests to rule out the  
21          excess risk measured by the upper bound of the  
22          95 percent confidence interval for the hazard

1 ratio.

2 Also, it should be pointed out that non-  
3 enriched populations with relatively low  
4 cardiovascular event rates require more patient  
5 years to be studied compared to enriched  
6 populations, and this would be to observe the same  
7 number of cardiovascular events and to achieve the  
8 same statistical power for a prespecified hazard  
9 ratio margin.

10 So without further ado, and not reading  
11 these verbatim, I will introduce the questions to  
12 you. You have these questions in your handout.

13 First, we are looking to see if people feel  
14 that a dedicated safety study is needed. But  
15 before we get there, we want to consider the  
16 evidence that we have and whether or not this  
17 evidence is enough to move forward to require such  
18 a study.

19 So for the new products, if you believe that  
20 they have presented enough information to convince  
21 you that they have more on-target 5-HT4 antagonist  
22 properties compared to the old and that the

1 cardiovascular issues are not important, we need to  
2 know what information you're basing that on.

3 We also want to know about the uses for  
4 which they're being developed and if you would be  
5 willing to accept an increased risk in any  
6 particular population; if so, why and what risk you  
7 would be willing to accept.

8 Then we get to whether or not you feel that  
9 a dedicated cardiovascular safety trial is needed  
10 in this group of drugs, and, if so, do you need to  
11 do it before or after, and then which indication  
12 you're doing that for; so before or after approval  
13 for each of these indications.

14 Then we would like some feedback on what an  
15 enriched population would look like; what are the  
16 characteristics for a dedicated trial? And,  
17 finally, what assessments would you like to see of  
18 cardiovascular safety in phase 3 studies for more  
19 accurate assessment of cardiovascular adverse  
20 events.

21 I'm going to turn this over then to my  
22 colleague, Dr. Peterson. But before I do, I will

1 point the committee to a handout in your package,  
2 which is a list of 5-HT receptor types. We view  
3 this as a kind of cheat sheet. We're going to be  
4 jumping back and forth and giving you a lot of  
5 information today about a lot of receptors, and our  
6 toxicologist will be regaling you with that.

7 So we thought it would be convenient to have  
8 this sheet at the ready.

9 Dr. Peterson? Thank you.

10 **FDA Presentation - Aisha Peterson Johnson**

11 DR. PETERSON JOHNSON: Thank you,

12 Dr. Korvick.

13 Hello and good morning. My name is Aisha  
14 Peterson Johnson, and I will be giving you a little  
15 bit of background.

16 During this brief presentation, I'll attempt  
17 to set the historical backdrop for today's meeting,  
18 and at the end of this overview, I will orient you  
19 to the order of today's presentations.

20 To begin our discussion, I will describe the  
21 5-HT4 drug class, starting with a broad  
22 introduction of 5-hydroxytryptamine, also known as

1 serotonin. This ubiquitous signaling molecule is  
2 found largely in the GI mucosa, and serotonin has  
3 seven main receptors subtypes. The 5-HT4 receptor  
4 subtype is the topic of today's meeting. And in  
5 the GI tract, 5-HT4 receptors are located on the  
6 terminals of myenteric neurons and on GI smooth  
7 muscle cells.

8 Now, while drug products attempt to target a  
9 single receptor subtype in a specific location,  
10 untargeted interactions with other receptor  
11 subtypes can often lead to adverse events. And I'd  
12 just like to point out that if we look at the  
13 receptor subtypes, we can see that they're located  
14 on blood vessels, in the central nervous system,  
15 peripheral nervous system, and in the GI tract, as  
16 I mentioned.

17 So as we saw in the previous slide, many  
18 5-HT receptor subtypes are located on blood  
19 vessels, and this slide just gives us more  
20 information on how activation of these subtypes  
21 affects vascular function. For example, arterial  
22 contraction, you can see the 5-HT1B and 5-HT2A

1 receptors; activation can lead to that effect.

2           So this slide is a summary slide. And in  
3 short, 5-HT4 receptor agonists increase GI  
4 motility. And these figures show that activation  
5 of the 5-HT4 receptor leads to a release of  
6 acetylcholine, causing muscle contraction, and also  
7 release of the inhibitor neurotransmitter, nitric  
8 oxide, leading to smooth muscle relaxation, and it  
9 is these two actions which lead to peristalsis.

10           Given the mechanism of action of 5-HT4  
11 agonists, there are a number of potential uses for  
12 these agonists, including chronic idiopathic  
13 constipation, GIRD, unresponsive to PPIs,  
14 gastroparesis, seen commonly in diabetes,  
15 functional dyspepsia, and the other motility  
16 disorders listed there. And this list is not meant  
17 to be exhaustive, but to give a flavor of the  
18 potential uses for these medications.

19           I'd like to turn our attention now to the  
20 limited availability of therapies for these  
21 conditions, briefly discussed by Dr. Korvick. IBSC  
22 currently approved therapies include only

1       lubiprostone, or Amitiza. For chronic idiopathic  
2       constipation, there is lactulose and lubiprostone.  
3       And for diabetic gastroparesis, there is only  
4       Reglan. Previously, there was Miralax, which  
5       underwent over-the-counter switch, and domperidone  
6       and Zelnorm are available for emergency use only.

7               This slide goes over a couple of the  
8       prevalence estimates for conditions for which 5-HT4  
9       agonists could be used. Here you see that for  
10       GIRD, it's estimated that 10 percent of the  
11       population experiences symptoms daily, with  
12       functional dyspepsia affecting 35 to 44 million  
13       people in the U.S.; gastroparesis, an estimated  
14       five million; and, other lower GI indications, with  
15       36 million people affected with chronic idiopathic  
16       constipation. It should be noted that the  
17       prevalence of these disorders rivals that of  
18       asthma, depression, and hypertension.

19               Now, we will briefly discuss and describe  
20       the history of cardiovascular adverse events  
21       associated with the 5-HT4 class of products.

22               The concern about the potential for

1 ventricular arrhythmias associated with the use of  
2 5-HT4 receptor agonists originates with cisapride.  
3 Cisapride was found to block the cardiac hERG  
4 potassium channel with associated prolongation of  
5 the repolarization phase of the ventricular action  
6 potential. The medication was removed from the  
7 market in 2000.

8           The concern with 5-HT4 agonists and  
9 cardiovascular ischemic events is related to  
10 Zelnorm. The story with Zelnorm and the reason for  
11 the imbalance in ischemic cardiovascular events  
12 compared with placebo seen in the postmarketing  
13 meta-analysis is less clear. In that  
14 meta-analysis, the event rates, which you see here,  
15 were .11 percent for Zelnorm, .01 percent for  
16 placebo. And this drug was removed from the U.S.  
17 market in 2007.

18           Now, we'll turn briefly to the order of  
19 today's presentations. First, we'll hear from  
20 Johnson & Johnson as they discuss cisapride. Next,  
21 the FDA will discuss tegaserod or Zelnorm. That  
22 will be followed by Theravance and their discussion

1 of their 5-HT4 agonists, TD-5108 and TD-8954.

2 Then the FDA will conclude with a discussion  
3 of the 5-HT4 agonists ATI-7505, also known as  
4 naronapride. And the FDA will then have a summary  
5 presentation by Dr. Fiorentino and a statistical  
6 presentation by Dr. Andraca-Carrera.

7 Thank you.

8 DR. RAUFMAN: Thank you.

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

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

1 outcome of the meeting.

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

9 We will now proceed with the Johnson &  
10 Johnson presentations, I believe starting with  
11 Dr. Sloan.

12 **Sponsor Presentation - Sheldon Sloan**

13 DR. SLOAN: Good morning. I'm Sheldon  
14 Sloan. I'm a gastroenterologist. I'm the internal  
15 medicine portfolio leader for established products  
16 in Johnson & Johnson Pharmaceutical Research and  
17 Development.

18 On behalf of J&JPRD, I would like to extend  
19 our thank you to the GI Drugs Advisory Committee  
20 and the Division of Gastroenterology-Inborn Errors  
21 Products of the FDA for the opportunity to present  
22 our experience with cisapride to you this morning.

1           We as a company feel that it is important to  
2 share with you our many years of experience with  
3 cisapride to help inform the discussions today  
4 about ongoing and future clinical research with  
5 this class of medicines for the common goal of  
6 helping address an unmet need.

7           The GI division of the U.S. FDA, as  
8 Dr. Korvick already mentioned, invited Johnson &  
9 Johnson PRD to review our cisapride experience with  
10 regard to nonclinical, clinical pharmacology,  
11 clinical safety, and the U.S. limited access  
12 program to help the GI Drugs Advisory Committee  
13 advise FDA on future 5-HT4 agonist drug development  
14 with regard to the design and size of premarketing  
15 cardiovascular safety development programs  
16 necessary to support approval of products for this  
17 class of drugs.

18           I would like to emphasize that our  
19 presentation today will focus on our experience  
20 with cisapride in all these aforementioned areas  
21 and highlight, in particular, the two following  
22 cardiovascular events of interest, ventricular

1 tachyarrhythmias and cardiac ischemia.

2 Over the course of our presentation, we will  
3 outline the different aspects of our many years of  
4 experience with cisapride and identify points to  
5 consider. We will attempt to summarize this  
6 succinctly over the next 30 minutes.

7 Here is our agenda today. We're going to  
8 start with a cisapride overview, followed by  
9 nonclinical cardiovascular safety, then the  
10 clinical pharmacology experience with cisapride,  
11 and then the clinical and postmarketing safety  
12 experience with cisapride, including the limited  
13 access program.

14 Let's start off with our overview of  
15 cisapride. Cisapride is a 5-HT<sub>4</sub> agonist which  
16 stimulates motility in the gastrointestinal tract.  
17 The mechanism of action is thought to be primarily  
18 enhancement of release acetylcholine at the level  
19 of the myenteric plexus.

20 Pharmacodynamically, cisapride has been  
21 demonstrated to increase esophageal peristaltic  
22 amplitude, increase lower esophageal sphincter

1 pressure, accelerate gastric emptying of liquids  
2 and solids, and decrease transit time in the small  
3 and large bowel.

4 Cisapride was discovered and developed by  
5 Janssen Research Foundation. The IND was filed in  
6 1983, and cisapride was approved in Europe in 1988.

7 Cisapride was approved in the United States  
8 in 1993 and it was indicated for the treatment of  
9 symptoms of nighttime heartburn due to  
10 gastroesophageal reflux disease in adults.

11 To continue with our overview, during the  
12 time period of 1988 to 1994, when we're talking  
13 here today about cardiovascular adverse events,  
14 sinus tachycardia emerged as a safety signal. This  
15 observation was published by Olsen in the British  
16 Medical Journal in 1992, reporting on seven  
17 patients. The company examined the data regarding  
18 tachycardia and submitted the data to the FDA, and  
19 the risk of tachycardia was added to the package  
20 insert.

21 Beginning in 1994, the emergence of  
22 spontaneous adverse event reports began to raise

1 suspicion of a very rare occurrence of serious and  
2 sometimes fatal ventricular arrhythmias. It was  
3 around this time that the metabolic pathway for  
4 cisapride was elucidated, with the primary enzyme  
5 responsible for metabolism described as cytochrome  
6 P450 3A4.

7 In most reports of serious ventricular  
8 arrhythmias, cisapride had been prescribed to  
9 patients who were either taking medications which  
10 inhibited the 3A4 metabolism or had underlying risk  
11 for ventricular arrhythmias. The resulting  
12 increase in steady-state plasma levels when 3A4  
13 inhibitors were co-prescribed could potentially  
14 cause a prolongation of QT interval and very  
15 rarely, torsades de pointes.

16 Because of this increased risk for patients  
17 taking drugs concomitantly with cisapride that  
18 inhibited the 3A4 enzymes, a warning was initially  
19 added to the label and subsequently changed to a  
20 box warning in mid-1995. This warning  
21 contraindicated the use of cisapride in patients  
22 taking medications that affected cisapride

1 metabolism.

2           This is not an all inclusive list here, but  
3 this included the azole antifungals, the macrolide  
4 antibiotics, and grapefruit juice. And later on,  
5 in our clinical pharmacology presentation, we'll  
6 show you some drug-drug interaction with these  
7 particular agents.

8           Between 1995 and 1998, the boxed warning was  
9 expanded, contraindicating cisapride use in  
10 patients taking medication that could prolong the  
11 QT intervals, such as the Class 1A and Class 3  
12 antiarrhythmics, or in patients with baseline heart  
13 disease, or other conditions that could predispose  
14 them to cardiac arrhythmias, including electrolyte  
15 disturbances such as hypokalemia, hypocalcemia, and  
16 hypomagnesemia.

17           Also, I'll note historically, it was really  
18 during this time period, really the mid to later  
19 1990s, that the hERG channel was discovered and  
20 found to be, in part, responsible for contributing  
21 to QT prolongation through delayed repolarization.  
22 This will be discussed in more detail by Dr. Towart

1       shortly.

2               In spite of multiple label changes with  
3       corresponding Dear Doctor letters, along with  
4       physician education programs and patient medication  
5       guides, prescribing of cisapride in patients taking  
6       contraindicated medications or with other risk  
7       factors persisted. And in discussion with the FDA,  
8       to ensure patient safety, Janssen voluntarily  
9       decided to discontinue cisapride from the market in  
10      2000. In order to continue to make cisapride  
11      available to those patients who had no alternative  
12      therapies, Janssen, in discussion with the FDA,  
13      developed a limited access program, which I will  
14      describe in more detail later.

15              I will now ask my colleague, Dr. Rob  
16      Towart, to take us through the pertinent aspects of  
17      cisapride with respect to nonclinical studies.

18                      **Sponsor Presentation - Rob Towart**

19              DR. TOWART: Thank you, Dr. Sloan.

20              Good morning, ladies and gentlemen. I am  
21      Rob Towart, a director at the Center of Excellence  
22      for Cardiovascular Safety in Janssen Research and

1 Development in Belgium.

2 Now, the topics for this morning are  
3 ischemia and arrhythmia, and I'll just point out  
4 that most ventricular arrhythmias are caused by  
5 structural damage to the heart; for example,  
6 during, after, or long after an ischemic insult  
7 such as a heart attack.

8 Now, some individuals have arrhythmias  
9 because they have congenital mutations to cardiac  
10 ion channels, and these long QT syndrome patients  
11 are very rare, about one in 10,000 individuals.  
12 Drug effects on cardiac ion channels, for example,  
13 on the hERG channel, which Dr. Peterson and  
14 Dr. Sloan have just mentioned, can be another cause  
15 of rare arrhythmias, especially in those with risk  
16 factors such as, for example, hypokalemia or  
17 metabolic inhibitors. And as has been mentioned,  
18 the importance of the hERG channel in the heart and  
19 potential QT interval prolongation was actually  
20 only recognized in the years 1995 to 1997.

21 Now, as has been pointed out in the FDA  
22 background material, a drug-induced cardiac

1 arrhythmia is not always predictive from  
2 nonclinical studies. Now, there are some reasons  
3 for this. For example, not all hERG blockers will  
4 actually prolong the QT interval, and not all QT  
5 interval prolongation is arrhythmogenic. Also,  
6 effects on other ion channels or membrane proteins  
7 can increase or decrease the propensity for  
8 arrhythmogenesis. And lastly, effects on the shape  
9 of the action potential, on dispersion, or  
10 variations of cardiac signals in the heart may also  
11 play a role.

12 Now, cisapride was invented in 1981 and, as  
13 Dr. Korvick pointed out, the guidelines only came  
14 into place in 2005, although many people were using  
15 them before that. In the 1980s, cardiovascular  
16 safety studies actually concentrated on cardiac  
17 contractility and hemodynamics. In these days, QT  
18 intervals were not corrected for heart rate and,  
19 also, ECGs were not routinely measured in chronic  
20 toxicological studies.

21 Now, in 1981, we did actually measure the  
22 action potential duration in Purkinje fiber and

1       trabecular muscle in vitro, but cisapride had no  
2       statistically significant effects on action  
3       potential duration.

4               Dog studies were carried out, five dog  
5       studies in anesthetized or conscious animals with  
6       intravenous or oral application up to  
7       2.5 milligrams per kilogram, and that corresponds  
8       to 175 milligrams per 70-kilogram patient. And  
9       these studies concluded that there was no effect of  
10      cisapride on QT interval. And this was borne out  
11      by 16 clinical pharmacology studies and 18  
12      therapeutic studies on nearly a thousand patients,  
13      which again concluded that cisapride had no  
14      clinically significant effects on ECG, blood  
15      pressure, or heart rate.

16              Now, the potential for QT prolongation in  
17      rare occasions was identified in late 1994. And in  
18      early 1995, Janssen presented an action plan to the  
19      FDA proposing a wide range of additional  
20      nonclinical and clinical studies, which were  
21      performed over the next seven years.

22              Now, it's interesting to note that a few

1 effects were noted initially as use of the more  
2 sensitive models for action potential duration  
3 prolongation was in its infancy. Such models would  
4 be the rabbit Purkinje fiber. And, in fact, we had  
5 to use bradycardia or hypokalemia in these models  
6 initially to see effects.

7 The first studies with the hERG ion channel  
8 began in 1998, shortly after academic publications  
9 in 1997 had shown the effect of cisapride. And we,  
10 in fact, found an IC-50 of 53 nanomolar, confirming  
11 that cisapride was a potent hERG block.

12 Now, hERG blockade is, in fact, a class  
13 effect of some kinds of drugs; antipsychotics and  
14 fluoroquinolones, for example. But this slide  
15 shows that hERG blockade is not a class effect of  
16 5-HT4 agonists. You can see that cisapride is the  
17 only 5-HT4 agonist which has a potent hERG  
18 blockade. And I noticed from the FDA's background  
19 book that naronapride, the ARYx compound, is also  
20 practically no effect on the hERG channel, with  
21 IC-50 of something like 24,500 nanomolar.

22 Now, let's turn our attention to ischemic

1 events. In perfused rabbit hearts, cisapride does  
2 not cause coronary vasoconstriction. In dog  
3 coronary arteries, cisapride was neither an agonist  
4 nor an antagonist of serotonin-induced relaxation.  
5 And in pig coronary arteries, cisapride blocked  
6 5-HT-induced contractions actually by a 5-HT<sub>2</sub>  
7 antagonist effect.

8 Cisapride did not significantly affect human  
9 platelet aggregation. And in volunteers, it did  
10 not significantly affect hemostatic parameters such  
11 as bleeding time, hematocrit, platelet numbers,  
12 thromboxane levels when compared to placebo when  
13 administered over, I think, three days. And,  
14 lastly, cisapride was only a weak inotropic partial  
15 agonist on human arterial 5-HT<sub>4</sub> receptors. So  
16 nonclinical studies with cisapride detected no  
17 effects related to ischemic events.

18 So, to summarize, the nonclinical points to  
19 consider for this committee are hERG blockade is  
20 not a class effect of 5-HT<sub>4</sub> agonists. Drug-induced  
21 QT interval prolongation is now known to be  
22 multifactorial and, therefore, a nonclinical

1 evaluation of cardiovascular safety should also be  
2 multifactorial, as Dr. Korvick pointed out from the  
3 ICH S7B guideline. And, lastly, there were no  
4 nonclinical signals for cardiac ischemia with  
5 cisapride.

6 I will now hand over to my colleague,  
7 Dr. Mannaert.

8 **Sponsor Presentation - Erik Mannaert**

9 DR. MANNAERT: Thank you, Dr. Towart.

10 Good morning. My name is Erik Mannaert.

11 I'm a senior director in the department of clinical  
12 pharmacology and the clinical pharmacology  
13 therapeutic area head for established products.

14 I'm also based in Beerse, Belgium. I'll give you  
15 an overview of the clinical pharmacology highlights  
16 that are relevant in the context of the  
17 cardiovascular safety of cisapride.

18 At the time of first market approval, we  
19 knew that cisapride is almost completely absorbed  
20 after oral dosing. However, its oral  
21 bioavailability is only 40 to 50 percent as a  
22 result of significant gut wall and liver first pass

1 metabolism. The oxidative metabolism is cytochrome  
2 P450 mediated, and cisapride is being eliminated  
3 mainly as metabolites, about equally split over  
4 urine and feces.

5           During the 1990s, the company started to  
6 apply new state-of-the-art methodologies and  
7 learned that the metabolism of cisapride depends  
8 primarily on a single P450 enzyme named CYP3A4,  
9 with a minor contribution of CYP2A6. From these  
10 new in vitro studies, we also predicted that there  
11 was a potential for clinically significant  
12 interactions with inhibitors of CYP3A4.

13           Consequently, and in alignment with the FDA  
14 action plan that Dr. Towart referenced to, several  
15 in vivo drug interaction studies were designed and  
16 performed, during which this potential for  
17 clinically relevant drug interactions with potent  
18 metabolic inhibitors of CYP3A4 was confirmed.

19           Such as in the case of ketoconazole, you see  
20 in the table at the bottom of the slide, peak  
21 concentrations and area under the curve increased  
22 with a factor of 2.6 to eightfold for a single dose

1 of 10 milligrams of cisapride. With erythromycin,  
2 a macrolide antibiotic, there was about a twofold  
3 increase in the steady-state peak concentrations  
4 and area under the curve. And, finally, with  
5 grapefruit juice, there is an increase of  
6 approximately 50 percent in the bioavailability.

7 It's worth noting that there were no  
8 clinically relevant interactions observed in drug  
9 interaction studies when cisapride was  
10 co-administered with potent inhibitors of  
11 cytochrome P4502D6 and 2C19.

12 At the time of first market approval, the  
13 tolerability studies in healthy volunteers had  
14 included doses in the range of 2.5 to 40 milligrams  
15 single dose, and repeated dose studies in healthy  
16 volunteers had included doses from 5 milligrams  
17 three times daily to 10 milligrams four times  
18 daily.

19 Based on these pharmacodynamic and  
20 tolerability studies in healthy volunteers, it was  
21 concluded that cisapride had no relevant effects on  
22 ECG parameters, vital signs, and hemodynamic

1 effects. It is important to note that these  
2 conclusions were made on the basis of standard  
3 safety assessments in a total of 16 clin/pharm  
4 studies, with instrumentation and methodology  
5 current in the 1980s. There was no study that  
6 could be compared with today's thorough QT study in  
7 that original application.

8 It was only post-approval that two  
9 cardiovascular safety studies in healthy volunteers  
10 were performed and for which the key results are  
11 tabulated on this slide. The first was a three-way  
12 crossover repeated dose cardiovascular safety study  
13 in healthy male volunteers.

14 Based on the data, there were no relevant  
15 increases seen in the corrected QT interval for the  
16 recommended 10 milligrams four times daily and the  
17 highest approved dose of 20 milligrams four times  
18 daily when cisapride was given as monotherapy. It  
19 should be noted that the study did not contain  
20 placebo and neither an active control.

21 The second study, at the bottom of the page,  
22 was an escalating single dose study in healthy male

1 and female volunteers, containing placebo, but no  
2 active control. Even having no moxifloxacin  
3 control arm, this study from 2000 came close to  
4 what we know today as a thorough QT study.

5 In this study, dose-dependent QTc increases  
6 were seen with cisapride plasma concentrations well  
7 above the therapeutic range following high single  
8 doses of 40 to 130 milligram. The mean average, as  
9 well as the mean maximum increases seen associated  
10 to these high doses, were in the order of magnitude  
11 of 17 to 30 and 30 to 45 milliseconds,  
12 respectively.

13 Now, QTc increases of similar extent as the  
14 one we see here with these high doses had  
15 previously been observed in drug interaction  
16 studies with potent inhibitors of CYP3A4, like  
17 ketoconazole or clarithromycin macrolide  
18 antibiotics. These drug interaction studies were  
19 done from '94 onwards and have since then led to  
20 several warnings and labeling updates, as discussed  
21 by Dr. Sloan.

22 The following are some relevant points to

1 consider from a clinical pharmacology point of  
2 view, in view of the development of future 5-HT4  
3 agonists. First, the clearance pathways of the  
4 drug need to be fully characterized both  
5 qualitatively and quantitatively. This means that  
6 all relevant factors are known that determine the  
7 absorption, metabolism and excretion of the drug.  
8 This could be factors like age from neonates until  
9 elderly, the ontogeny of the cytochrome enzymes in  
10 the newborn, factors of gender, hepatic or renal  
11 failure, body size variables, and drug  
12 interactions. When potentially relevant drug  
13 interactions are either predicted or observed,  
14 these need to be further confirmed in well designed  
15 human studies to give guidance in labeling.

16 Secondly, safety and tolerability studies  
17 should be included incorporating relevant multiples  
18 of the therapeutic dose, at least accounting for  
19 increases in plasma exposure that are expected on  
20 the basis of the pharmacokinetics of the drug.

21 In addition, the program should include a  
22 thorough QT study which is properly designed to

1 allow treatment effects to be detected. This means  
2 the other comparators should be included, as well  
3 as a placebo, and the study should be properly  
4 sized.

5 I'll now transfer back to Dr. Sloan.

6 **Sponsor Presentation - Sheldon Sloan**

7 DR. SLOAN: Thank you, Dr. Mannaert.

8 I'm going to be the final agenda item for  
9 the cisapride presentation to discuss the clinical  
10 and postmarketing safety aspects of cisapride.

11 The analysis of safety at the time of the  
12 NDA was based on about 5500 patients, of which  
13 about 4,000 were exposed to cisapride. Of the 1257  
14 subjects in U.S. trials, 979 subjects were exposed  
15 to cisapride. The total duration of exposure  
16 during clinical trials worldwide represented  
17 1263 patient years. The most common adverse events  
18 reported at the time of the NDA were headache and  
19 diarrhea.

20 In the safety update filed in February 1993,  
21 covering the period from the initial NDA filing,  
22 which was in 1991, up to that point, the medical

1 reviewer noted at that time that heart rate and  
2 cardiac rhythm disorders were reported with a  
3 similar frequency in cisapride-treated patients and  
4 in placebo-treated patients overall, but based on  
5 the aforementioned Olsen study when I gave the  
6 overview, the reviewer suggested that tachycardia  
7 should be addressed in the label.

8 I would like to now review the  
9 cardiovascular safety data for the two events of  
10 interest we're looking at today, ventricular  
11 tachyarrhythmia and cardiac ischemia.

12 During postmarketing surveillance,  
13 ventricular tachyarrhythmia was identified as a  
14 signal and subsequently well characterized.  
15 Cardiac ischemia had not been identified as a  
16 signal to date either through safety surveillance  
17 or through the review of the literature.

18 J&JPRD conducted a cumulative evaluation of  
19 cases reporting ventricular arrhythmias or cardiac  
20 ischemia-related events, and these included those  
21 cases from clinical trials, postmarketing  
22 experience, and the limited access program. This

1 cumulative review confirmed the findings from the  
2 postmarketing surveillance.

3 The cisapride limited access program was  
4 initiated in 2000 after cisapride was discontinued  
5 from the market. The intent of this program was to  
6 make cisapride available to those patients that had  
7 failed other therapies and had a critical need for  
8 cisapride, had an appropriate risk-benefit, and  
9 otherwise met the protocol eligibility  
10 requirements.

11 Within the limited access program, there are  
12 two protocols, and adult and a pediatric protocol.  
13 The diagnosis for consideration in these protocols  
14 include refractory GERD, gastroparesis, pseudo-  
15 obstruction, and severe chronic constipation.  
16 Safety is monitored and reported to the FDA.

17 Some particulars about the limited access  
18 program. Should one meet the eligibility  
19 requirements, they'd still need to undergo  
20 diagnostic evaluation. That includes radiology  
21 and/or endoscopy, baseline screening tests to rule  
22 out electrolyte disorders, electrocardiograms to

1 rule out QT prolongation, and other  
2 contraindicating risk factors.

3           Once meeting the eligibility and enrolled in  
4 the study, the subjects undergo clinical  
5 reevaluation at regular intervals. For the adult  
6 program, it's every four months during the first  
7 year and every six months thereafter. And this  
8 reevaluation includes laboratory testing,  
9 electrocardiograms, medication review in case  
10 someone started a new medicine that was  
11 contraindicated, and physician attestation of  
12 continued patient benefit.

13           This slide depicts the distribution of the  
14 over 1500 patients that have enrolled in the  
15 limited access program over the last 11 years. As  
16 you can see, in the adult protocol, the predominant  
17 diagnosis in this limited access program is  
18 gastroparesis. About 57 percent of the patients  
19 enrolled in this had gastroparesis. In the  
20 pediatric protocol, it's driven predominantly by  
21 about 55 percent of the subjects with GERD. The  
22 gender distribution in the adult studies is about

1 three to one female to male, and in the pediatric  
2 studies, it's one to one female to male.

3 Over the past five years, I would like to  
4 comment, the enrollment in the limited access  
5 program has been very stable and relatively steady  
6 by the plateau that we've seen, which includes  
7 about 300 subjects in the program at any one time.  
8 There are between 50 to 75 patients that cycle in  
9 and out of the program on a yearly basis.

10 Turning to the safety data from the limited  
11 access program, reasons why patients might  
12 discontinue is that they're cured or asymptomatic,  
13 they no longer benefit, they have appearance of  
14 risk factors, or they develop a serious adverse  
15 event, such as a QTc prolongation greater than  
16 study-defined limits. Over the past 11 years,  
17 during the course of this protocol, this limited  
18 access program, no torsades de pointes has been  
19 identified and no signal for cardiac ischemic  
20 events has been seen.

21 So, in summary, looking at our cisapride  
22 history nonclinical/clinical pharmacology, as well

1 as the safety information, I'd like to summarize  
2 some of the highlights from each of these.

3 From our nonclinical experience, Dr. Towart  
4 discussed the hERG channel blockade. Cisapride is  
5 a potent hERG channel blocker; however, this is not  
6 a 5-HT4 agonist effect, a class effect.

7 Dr. Mannaert discussed during his clinical  
8 pharmacology presentation that the science has  
9 evolved many ways, which has contributed to a  
10 better understanding of the cardiovascular safety  
11 of cisapride and hopefully for future drug  
12 development. We have a better understanding of  
13 metabolic pathways, and that's including the 3A4  
14 pathway, which has led to a better understanding of  
15 drug-drug interactions. And, lastly, we have a  
16 better understanding of evaluating QT prolongation.

17 Based on the safety review, no safety signal  
18 was identified for cardiac ischemic events with  
19 cisapride. And, finally, when we look at the U.S.  
20 limited access program, the steady enrollment  
21 suggests a continued unmet medical need driven in  
22 these protocols by GERD in children and

1       gastroparesis in adults. And today, cisapride  
2       provides an important option through the limited  
3       access program for patients with motility disorders  
4       who have no alternatives.

5               We hope our presentation this morning has  
6       provided the advisory committee with useful  
7       information to guide the agency in working with  
8       sponsors to develop future 5-HT4 agonists in order  
9       to address the continuing medical need.

10              Thank you.

11                              **Questions from the Committee**

12              DR. RAUFMAN: Thank you. We will now ask if  
13       the committee has any questions for the Johnson &  
14       Johnson presenters. It's a large group. I ask  
15       that you wait to be recognized by the chair. We'll  
16       keep track of who needs or wants to ask a question,  
17       and try to do it in some fair manner.

18              Dr. Lauer?

19              DR. LAUER: Thank you. How many  
20       patients -- throughout the history of all this, how  
21       many patients actually developed a life-threatening  
22       arrhythmia or died in arrhythmic deaths because of

1 cisapride?

2 DR. SLOAN: I don't have the exact number,  
3 Dr. Lauer. That's not something that I reviewed  
4 for today's presentation.

5 DR. LAUER: Can you give me a sense as to  
6 whether we're talking about 10, 50, 100, a  
7 thousand?

8 DR. SLOAN: Okay. So, basically, in the  
9 briefing book you saw from the FDA, there were, I  
10 believe, a little over 100 torsades de pointes  
11 described. And if you look beyond that, from what  
12 we know, that's not a great magnitude different.  
13 There are more patients because that was up until  
14 1999, but we're not talking thousands.

15 DR. RAUFMAN: Dr. Bloom I think had a  
16 question.

17 DR. BLOOM: Yes. After the tachyarrhythmia  
18 was well characterized and prior to withdrawal of  
19 that drug, as well as over the course of the  
20 limited access program, do you feel that the  
21 measures you took were successful in managing this  
22 risk; and are there other details concerning that

1 that might be helpful to the committee in managing  
2 such a well defined risk?

3 DR. SLOAN: Thank you, Dr. Bloom. Do you  
4 want me to discuss after market discontinuation or  
5 during, as well? I'm sorry.

6 DR. BLOOM: Either.

7 DR. SLOAN: Okay. Well, I think we can show  
8 a slide just showing the history of the label  
9 changes and then discuss briefly some of the  
10 information.

11 Slide up. So this is a series of label  
12 changes. In fact, after approval, there were five  
13 label changes and subsequent warnings. Each one of  
14 these warnings, after they were put into the label,  
15 there were Dear Doctor letters, as well as, at  
16 times, patient -- an improved patient medication  
17 guide. And there was evidence -- and this was  
18 published actually in -- I don't have the paper in  
19 front of me, but it may be in the background. It  
20 was published with one of the co-authors, Smalley,  
21 et al, and one of the co-authors was from the FDA,  
22 looking at the effect of the label changes on

1       prescribing behavior.

2               There were two managed-care settings, as  
3       well as one Medicare database. The two  
4       managed-care settings were somewhere in the -- 24  
5       to 30 percent of the patients were co-prescribed  
6       contraindicating medications; in the Medicare  
7       database, 60 percent of the patients. And  
8       subsequent to the regulatory action and Dear Doctor  
9       letter, the change in behavior in these three  
10      settings dropped by 2 percent.

11              So, basically, we can say that -- you can  
12      make a conclusion that it wasn't very effective.

13              In the limited access program, these  
14      patients are monitored very carefully. So, as I  
15      said, they're seen on a quarterly basis, at least  
16      in adults, four times a year for the first year and  
17      then twice a year thereafter. A thorough review of  
18      the medications are received and are taken in on  
19      the CRF, and then there's basically a judgment  
20      whether the patient should continue in the program.

21              So I would say that's a summary of the  
22      history of that.

1 DR. RAUFMAN: Dr. Thadani?

2 DR. THADANI: Two short questions. One is,  
3 mechanistically, you said the drug caused  
4 tachycardia. Is it because of the renal dilator  
5 effects and you could miss it in the animal model  
6 because they are in the supine position? So that's  
7 my first question. I'll come to the second one.

8 DR. SLOAN: Dr. Thadani, I can't answer that  
9 question. I don't know the answer to that first  
10 question.

11 DR. THADANI: Okay. The second question to  
12 you, could you tell me the age group in your  
13 limited access population? Because you showed me  
14 that data; one could tell the layman he'd be very  
15 reassured there is no torsades or adverse event,  
16 because in children, you are excluding the QT  
17 prolongation to start with.

18 Now, also, because of the labeling change,  
19 most people are not going to use ketoconazole or  
20 other stuff. But what about the, say, elderly  
21 patient with severe constipation or who is on the  
22 drug, and he is on a diuretic, and he's on the

1 CYP3A4, which is not that potent like  
2 verapamil -- or like diltiazem or other agents  
3 which you are finding could also affect it.

4           So were they also excluded, and that's the  
5 reason you are not seeing any noise, or the  
6 population size is just too small and very  
7 selective? Because the number of patients is only  
8 a thousand, and it's in millions of people?

9           DR. SLOAN: So let me just rephrase that,  
10 because, firstly, in order to be eligible for the  
11 limited access program, you cannot be taking a  
12 contraindicated medication, 3A4 inhibitor, that has  
13 been contraindicated. Secondly, if you have  
14 prolonged QT on your screening electrocardiogram,  
15 you cannot be eligible for the protocol.

16           The distribution, I don't have the exact age  
17 distribution, but I know -- I believe our oldest  
18 subject in the adult protocol is upwards in their  
19 upper 90s, but I don't have the exact age  
20 distribution.

21           DR. THADANI: So none of them had acute  
22 coronary syndrome or infarct, which would be high

1 risk -- I'm just curious-- to start with.

2 DR. SLOAN: Right. So a history of cardiac  
3 disease would not allow someone to be in the study.

4 DR. THADANI: So there could be a false  
5 reassurance for the population at large, correct?

6 DR. SLOAN: Again, let me reiterate that  
7 cisapride is not available to the public, in  
8 general, and these are for patients who have no  
9 alternative.

10 So there is a high threshold, administrative  
11 burden, actually, to get a subject or a patient in  
12 this study. So we're not here to promote; in fact,  
13 we do not go on and recruit patients for the study.  
14 This is all investigators basically or clinicians  
15 who enroll their patients when they, again, have  
16 exhausted all available therapies.

17 DR. RAUFMAN: Dr. Korvick?

18 DR. KORVICK: I just wanted to point out,  
19 for the previous question, on page 23 of the FDA  
20 backgrounder, we've abstracted some data to answer  
21 the question about the numbers of patients from the  
22 Wysowski paper.

1           Do you want me to -- just to say that in  
2 that paper, there were a total of 341 events  
3 reported. This is postmarketing. Eighty were  
4 fatal. And the total number of cardiovascular  
5 events is broken out for you in table number 12 of  
6 the backgrounder for FDA.

7           DR. THADANI: Thank you.

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

9           DR. SHEN: A question regarding this limited  
10 access program. Do you routinely do the genetic  
11 test for the hERG mutation and then stratify the  
12 patients, a risk group/non-risk group?

13          DR. SLOAN: That's a very good question.  
14 No, we do not test for hERG mutation.

15          DR. RAUFMAN: Dr. Granger?

16          DR. GRANGER: I was a little bit confused  
17 about your kind of summary statement, based on the  
18 totality of the data, about whether or not there's  
19 any effect on heart rate. Presumably, in all the  
20 randomized trials and with all the data, you must  
21 have the ability to definitively address that  
22 question, and I'm just wondering what the answer

1 is.

2 DR. SLOAN: Dr. Granger, I was really  
3 addressing the two cardiovascular events of  
4 interest that we were asked to address by FDA on  
5 our invitation to this meeting, and that was  
6 ventricular tachyarrhythmias and cardiac ischemia.

7 We were not going beyond -- our goal really  
8 was to, again, go back and look at all the cases  
9 across the life of cisapride from clinical trials,  
10 postmarketing surveillance, limited access program,  
11 compassionate use, and look to see is there a  
12 cardiac ischemic signal; and that's basically the  
13 due diligence that we did today to report out to  
14 the committee.

15 DR. GRANGER: So do we or do we not know  
16 whether there's an effect on heart rate?

17 DR. SLOAN: The effect on heart rate is in  
18 the label. So I'm not sure -- that's a known  
19 adverse event. So I'm not sure I understand the  
20 question.

21 DR. GRANGER: Heart rate is increasingly  
22 recognized as something that's relevant, at least

1 as a very strong predictor of outcome, if not as a  
2 target to improve outcome, for example, for  
3 patients with heart failure. So I think heart rate  
4 is actually quite a relevant parameter to  
5 understand the potential, at least the potential  
6 signal, including for ischemic and other outcome  
7 events, and it would seem like that might be  
8 relevant information to know whether or not there  
9 was any effect on heart rate.

10 DR. SLOAN: Okay. We don't have that  
11 information, but thank you for that comment.

12 DR. RAUFMAN: Dr. Kaul?

13 DR. KORVICK: We do have some information in  
14 our backgrounder for the dog experiment on page 25,  
15 and we go into the thorough QT on 27. So you might  
16 find that useful to look at.

17 DR. GRANGER: I'm especially interested in  
18 human beings, but that might be relevant, as well.

19 [Laughter.]

20 DR. RAUFMAN: Dr. Kaul?

21 DR. KAUL: Thank you. Drug-related safety  
22 signals, they're real. They're either drug-induced

1 or their drug-promoted or exacerbated. So I think  
2 it's important to understand what the spontaneous  
3 background event rate is.

4 So my question for you is, do we know what  
5 the cardiovascular risk profile of the cohorts that  
6 were enrolled in the NDA or in the postmarketing  
7 surveillance, or in the general real world is? And  
8 is the distribution of these cardiovascular risk  
9 factors -- does it vary across the spectrum of GI  
10 indications?

11 DR. SLOAN: That's a very good question. I  
12 don't have the answer to that.

13 DR. RAUFMAN: Dr. Spiegel?

14 DR. SPIEGEL: Thank you. In the GI  
15 community, there has been a lot of discussion  
16 recently about proton pump inhibitors and the  
17 relationship with hypomagnesemia, in particular,  
18 and it's debatable whether that's a real  
19 relationship and what the mechanism is. But,  
20 clearly, PPIs are going to be co-prescribed with  
21 most all of the conditions we're talking about  
22 today. In fact, one of the conditions involves PPI

1 as part of the definition of the condition,  
2 PPI/poorly responsive GERD.

3 So my question is, hypomagnesemia, in  
4 particular, what kind of risk does it invoke, or  
5 what is the interaction with hypomagnesemia and the  
6 risk of these tachyarrhythmias in the setting of  
7 hERG blockade?

8 DR. SLOAN: Dr. Towart will answer that  
9 question.

10 DR. TOWART: Hypomagnesemia is, in fact, a  
11 known risk factor for increasing the QT interval  
12 and increasing the -- let's say, in epidemiological  
13 studies, hypokalemia is well known, hypocalcemia is  
14 probably less known, and hypomagnesemia is probably  
15 not known really very much, but it is in the list  
16 of things to avoid.

17 DR. RAUFMAN: Dr. Teerlink?

18 DR. TEERLINK: First of all, thank you very  
19 much for taking the time out to come here and  
20 present this information to the panel. We  
21 appreciate you being here and giving us this  
22 information.

1           Just so I understand, during the  
2 course -- the limited access program has been going  
3 on for 11 years.

4           DR. SLOAN: That's correct.

5           DR. TEERLINK: And during that 11 years, it  
6 has enrolled -- may be but not less than 1600 patients  
7 during that entire time course.

8           DR. SLOAN: Right.

9           DR. TEERLINK: So on the one hand, we have a  
10 disease entity that has incredibly high prevalence  
11 throughout the U.S. population, and we're told that  
12 it's a huge unmet medical need. And yet, when  
13 patients and physicians are given the question of,  
14 well, we have this program where you can have it,  
15 but you have to accept the risks of this, a very,  
16 very, very, very, very small number of patients  
17 over the course of 11 years have decided to pursue  
18 that.

19           How do you interpret that patient and  
20 physician decision, informing how important this is  
21 as an unmet medical need when there are some safety  
22 concerns, even though you're trying to manage them?

1 DR. SLOAN: I can't speak for the community.  
2 I will say -- did you want to add something to  
3 that? Oh.

4 I will say that we don't solicit patients  
5 for this program. So I think that may be one  
6 consideration. But when I showed you the  
7 distribution of diagnoses in the two protocols,  
8 it's somewhat of a surrogate of what that unmet  
9 medical need is. It's not the totality, I think,  
10 and certainly it's a good clue, though, that  
11 this -- now, let me just finish -- the  
12 administrative burden to get patients in this  
13 program is not low, and maybe some of the  
14 gastroenterologists around the table have actually  
15 enrolled or tried to enroll patients in the  
16 program, so they can confirm that.

17 But it is an option, again, for those  
18 subjects who have failed or who did not tolerate.  
19 And these, again, are really potentially the -- I  
20 don't have the CRFs in front of me, but many of our  
21 pretty severe patients.

22 So I don't know that I can speak for the

1 community, but it is a snapshot of maybe where that  
2 unmet medical need is kind of percentage-wise.

3 DR. TEERLINK: And I completely agree with  
4 that. It's just that we're going to have to  
5 struggle with benefit-risk tradeoffs here, and this  
6 is an example where the patients and the physicians  
7 had an opportunity to evaluate that benefit-risk  
8 tradeoff with, granted, high administrative  
9 barriers. But, still, it's a profoundly low  
10 number, to me.

11 DR. RAUFMAN: I'd like to follow-up on that  
12 myself. There are two pieces of data I'm  
13 interested in, and you may not have it.

14 How many people applied for the program and  
15 were disqualified? Do you have any idea of that  
16 percentage?

17 DR. SLOAN: The answer to the first question  
18 is no.

19 DR. RAUFMAN: Okay. And I hope I'm not  
20 going to get another no, but the slide you had  
21 regarding outcomes on the LAP program, there were  
22 no numbers on that; there was no distribution, how

1 many people left the program, what percentage of  
2 people enrolled in that program left because there  
3 was no longer benefit from the drug or any of those  
4 other --

5 DR. SLOAN: Yes. So I do have a slide.  
6 Slide up. And so this is kind of discontinuation  
7 in the adult protocol, 154, and in the pediatric  
8 protocol, 156. This is those who completed  
9 treatment or cured were 71. Discontinued  
10 treatment, we don't really have the total breakdown  
11 really, but this is the information that we have  
12 today.

13 One other point that I wanted to make, but  
14 it slipped my mind, Dr. Raufman.

15 DR. RAUFMAN: I was just interested in the  
16 loss of benefit issue.

17 DR. SLOAN: Oh. That's the point I wanted  
18 to make. So I can't speak exactly to that, but we  
19 did look at how many patients actually, through  
20 physician attestation, did have benefit, so on the  
21 positive side. The loss of benefit, I don't know  
22 if we have that number of not. But, roughly,

1 again, at any one point, at any one visit, you take  
2 over the course of the enrollment in the program,  
3 it's fairly high, over 80 percent.

4 Now, that's physician attestation. This is  
5 open label, this is -- there's nothing -- we're not  
6 claiming anything, but because you asked, I'm  
7 telling you.

8 [Laughter.]

9 DR. RAUFMAN: Thank you. Dr. Bild?

10 DR. BILD: Yes. Thank you. I just want to  
11 be clear about the limited access program. People  
12 keep asking questions about the monitoring; only  
13 1263 patient years and people have been highly  
14 screened. But when you said that there was no  
15 cardiac signal, does that mean that there were no  
16 cardiac events or that it was less than something  
17 you expected?

18 DR. SLOAN: Okay. So the 1263 patient years  
19 is really just at the NDA. And the reason I  
20 pointed that out is that because of the discussions  
21 today, the event rates that are rare may be missed  
22 by something with 1200 patient years. But for the

1 limited access program, there are cardiovascular  
2 events.

3 I just pointed out torsades de pointes, but  
4 there have been deaths in the program, and, again,  
5 these are evaluated and, again, through our safety  
6 group, have not been, quote -- I don't know if you  
7 want to comment specifically, Dr. Jones, but we do  
8 look at every event and these adverse events within  
9 the program.

10 DR. BILD: I see. But then how do you  
11 determine if it's more than what you would have  
12 expected or less?

13 DR. SLOAN: This is Dr. Robyn Jones.

14 DR. JONES: Good morning. Dr. Robyn Jones,  
15 from global medical safety at J&JPRD.

16 It's not really so much a quantitative  
17 value, but cases are assessed and using a threshold  
18 criteria to determine whether it may be an actual  
19 adverse drug reaction related to the drug.

20 Slide up, please.

21 So what you see here are CIOMS threshold  
22 criteria, and this is what is used to determine

1       whether an event may be an adverse drug reaction,  
2       that is, truly has a causal association with the  
3       drug. And as you can see, initially, 1A is for  
4       those cases that are reported spontaneously, and 1B  
5       is for those cases that come in through clinical  
6       trials and studies. And then the remaining bullets  
7       are used to evaluate all other cases.

8               So, for instance, for a cardiac ischemia, as  
9       my colleague, Dr. Towart, spoke to, there does not  
10       seem to be a biologic plausibility for cardiac  
11       ischemia as it relates to cisapride.

12              DR. RAUFMAN: Dr. Rosen?

13              DR. ROSEN: So I'm going to speak as  
14       somebody who enrolls in the limited access  
15       protocol, and we have between 20 and 30 kids at any  
16       given time on the protocol. They cannot say enough  
17       how much paperwork is involved in enrolling a  
18       patient. It takes one full-time person to keep  
19       track of the 20 kids that are enrolled in the  
20       protocol, and they are meticulous. And I actually  
21       thank the FDA and to Janssen for keeping this  
22       protocol open, because it's invaluable.

1           When they put up on there that there's GERD  
2 as the diagnosis, you need to understand who these  
3 GERD patients are. These patients are kids who are  
4 on TPN because their reflux is so bad, and this is  
5 the only option for them. These are neurologically  
6 compromised patients who cannot get fundoplication.  
7 So you see GERD up there and you think about the  
8 adult who goes on to PPI. That is not who's  
9 enrolled in the limited access protocol.

10           When you look at who drops out of the  
11 limited access protocol, the main reason -- and I  
12 don't want to speak for you guys. But the main  
13 reason is that they go onto another drug that  
14 interacts with cisapride. So we have to withdraw  
15 them from the protocol because they're going to be  
16 on another long-term drug that they need for  
17 whatever reason.

18           So I think you have to keep that in mind,  
19 that the discontinuations are often involved in  
20 other drug interactions that play a role.

21           DR. SLOAN: Dr. Rosen, I just put up a slide  
22 from your center that actually describes it.

1 DR. ROSEN: Right. This is another very big  
2 use that we use. Short-gut patients are another  
3 one that fall under the reflux category, but are  
4 not a typical reflux patient.

5 So just keep that in mind, that there is a  
6 very important role for these drugs in the  
7 intractable reflux patients that are not the  
8 classic reflux patients that you think of.

9 DR. RAUFMAN: Thank you for those comments.  
10 Dr. Shen?

11 DR. SHEN: I believe this drug is still  
12 available in some other countries. And I wonder do  
13 we have safety data, has anybody reported,  
14 especially mortality?

15 DR. SLOAN: So that's actually -- the drug  
16 has been withdrawn or discontinued --

17 DR. SHEN: Worldwide?

18 DR. SLOAN: -- worldwide. And there were  
19 programs ex-U.S. more along the lines of an either  
20 registry or limited access type of program. Those  
21 have been discontinued, as well, most recently in  
22 Europe, France, Portugal, and Belgium.

1 DR. SHEN: Okay.

2 DR. RAUFMAN: Dr. Kumar?

3 DR. KUMAR: To follow-up on the question of  
4 very limited enrollment in the LAP. Is this a  
5 small group of physicians who are prescribing to a  
6 lot of patients or is it a large group of  
7 physicians who are prescribing to few patients?

8 DR. SLOAN: Dr. DeLemos, are there a lot of  
9 physicians who have one patient enrolled?

10 DR. DELEMOS: Dr. Byron DeLemos, medical  
11 affairs, Janssen Scientific Affairs.

12 There is a spectrum of physicians that  
13 participate in the program. There are some  
14 physicians that enroll a few patients. There are  
15 other physicians like Dr. Rosen that enroll a fair  
16 number of patients and follow a fair number of  
17 patients that have a need for cisapride.

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

19 DR. THADANI: I enjoyed the relevance of the  
20 presentation. Now, in the limited access program,  
21 I can realize that patients are really sick in the  
22 pediatric population, or some adults, might be

1       worth trying.

2               But you said that in adults, there were  
3 patients up to age 90, and despite that, the  
4 dropout rate is very high. Can you reassure me it  
5 is only because of the concomitant medications or  
6 people had acute coronary syndrome or died?

7               The reason I'm asking now this is, even with  
8 the cardiovascular drugs, we've been burned that  
9 drugs have been approved even on larger studies in  
10 randomized trials, and subsequently -- the example  
11 is one of the newer agents, they find it might be  
12 causing more deaths or ACS.

13              So in the older population, were there any  
14 sudden deaths? You may not have documented QTc,  
15 and we know sometimes you may not get a QTc  
16 prolongation at one time and could happen another  
17 time. So were there any sudden deaths in the  
18 overall, your smaller -- a thousand patients who  
19 were dosed, and that's why the withdrawal is  
20 greater, or any other events?

21              DR. SLOAN: Okay. So there were three  
22 deaths in the limited access program. I'm not

1 going to put up the details, but there were three  
2 deaths, and they really range from people who have  
3 previously undiagnosed type of disorders. Again,  
4 these patients come in without cardiovascular  
5 history, but people do develop cardiovascular  
6 history because they just live longer.

7 DR. THADANI: I think that's the difficulty  
8 in just observational studies. When the event rate  
9 is so low, even a thousand doesn't reassure you for  
10 a long time.

11 Are you collecting more detailed data on  
12 this?

13 DR. SLOAN: Yes.

14 DR. THADANI: And how they died, if they  
15 died in sleep suddenly or they dropped dead?

16 DR. SLOAN: We have all the data,  
17 Dr. Thadani. But I just want to point out, again,  
18 cisapride is not a marketed product. We're not  
19 promoting this. This is, therefore, absolutely  
20 patients who don't have an alternative. The fact  
21 is I think we -- and then I just want to point out,  
22 we do have regular discussions with the FDA on the

1 value of this program. And so this is an ongoing  
2 dialogue, and I think if at any one point in time  
3 we see that the value no longer exists, then we'll  
4 probably decide something different.

5 DR. RAUFMAN: Dr. Black?

6 DR. BLACK: I also want to focus on the  
7 adults. The electrolyte abnormalities that you  
8 describe are things we see with diuretics in  
9 particular. Is there any evidence from the program  
10 or from before that people on diuretics have more  
11 trouble?

12 DR. SLOAN: I'm looking at my people. And  
13 I'm sure we have that information, but -- do we  
14 have some -- okay. I don't think we have that  
15 particular information, Dr. Black.

16 DR. RAUFMAN: Are there any other questions  
17 before we move on?

18 [No response.]

19 DR. RAUFMAN: Thank you very much,  
20 Dr. Sloan.

21 We will now move to the FDA's presentations  
22 on tegaserod. Dr. Zhang?

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**FDA Presentation - Ke Zhang**

DR. ZHANG: So far we've had a very nice discussion about cisapride. Now, we'll change the topic to tegaserod.

I'm Ke Zhang, pharmacologist from FDA. I will discuss tegaserod nonclinical studies. My presentation will cover, one, serotonin receptor binding studies; two, in vitro cardiac studies; and, three, in vivo cardiovascular safety pharmacology studies. Under in vitro cardiac studies, I will discuss the hERG channel, action potential and isolated coronary artery studies.

Let's begin with the receptor binding study. It has been demonstrated tegaserod is a 5-HT<sub>4</sub> receptor agonist with moderate to high affinity for 5-HT<sub>1</sub> receptors. This table summarizes the KD from different serotonin receptors, and it compares tegaserod KD with cisapride's KD.

What is KD? KD is a dissociation constant. The smaller the KD, the higher the affinity between the drug and the receptor. You can see from this table that tegaserod has a high affinity for 5-HT<sub>4</sub>

1 receptor and a moderate to high affinity for 5-HT1  
2 receptor subtypes. In contrast, cisapride has a  
3 high affinity for 5-HT4 receptor and a high  
4 affinity for 5-HT2 receptor subtypes.

5 As we've discussed today so far, you'll  
6 notice this subtype receptor located in the blood  
7 vessel, particularly in the coronary  
8 artery -- activation of this receptor may result in  
9 vessel constriction.

10 Now, the in vitro cardiac electrophysiology  
11 studies, the hERG channel and the action potential  
12 study from isolated guinea pig ventricular  
13 papillary muscle. The study results from the hERG  
14 channel indicated tegaserod inhibits the hERG  
15 channel with IC50 of 13 micromolar. In contrast,  
16 the IC50 for cisapride is about .044 micromolar,  
17 suggesting that cisapride is more potent than  
18 tegaserod in terms of inhibition of the hERG  
19 channel.

20 Tegaserod has no effect on the action  
21 potential at concentrations up to 1 micromolar.  
22 The concentration of 1 micromolar is about 100-fold

1 higher than the human plasma level following an  
2 oral dose of 6 milligram BID.

3 Here is the isolated coronary artery study.  
4 Tegaserod has no contractile activity on isolated  
5 coronary artery from pig, nonhuman primates, and  
6 human, but it induced a small contractile response  
7 in canine coronary artery at the concentrations of  
8 5 to 10 micromolar. Five to 10 micromolar  
9 concentration is about 500 to a thousand-fold  
10 higher than the human plasma level.

11 This slide shows the dose response or  
12 concentration contraction curve from an isolated  
13 human coronary artery. 5-HT serotonin is used as  
14 positive control in this study, and serotonin  
15 induced a nice contraction which increased the  
16 dose. However, tegaserod did not induce  
17 contraction as compared to the vehicle control.

18 This slide shows similar studies in the  
19 isolated pig coronary artery on the left and the  
20 canine coronary artery on the right. Again,  
21 serotonin increased the contraction with increased  
22 dose in both studies. Tegaserod did not induce the

1 contraction as compared to the vehicle control in  
2 pig coronary artery, but induced a small  
3 contraction at a concentration of 5 to  
4 10 micromolar in the dog coronary artery.

5 Let's talk about in vivo cardiovascular  
6 safety pharmacology studies in dogs. There are two  
7 studies I'm going to discuss. One was the  
8 intraduodenal dose, and the other one was oral  
9 dose. In both studies, the doses were up to  
10 10 milligrams per kg. The results of these studies  
11 indicate tegaserod has no effect on blood pressure,  
12 heart rate, cardiac output, ECG, such as QT  
13 interval.

14 Just for comparison, the dog plasma level  
15 was about 400 nanogram per ml for males and  
16 277 nanogram per ml for females following  
17 10 milligrams per kg oral dose. In contrast, the  
18 human plasma level is about 6 nanograms per ml  
19 following the therapeutic dose, 6 milligrams BID.

20 As part of the drug development, the sponsor  
21 has conducted a number of repeated dose toxicity  
22 studies in dogs. In these studies, EKGs and the

1 cardiac histopathology were monitored.

2           Since we are evaluating the cardiac safety  
3 of tegaserod, I would like to discuss these three  
4 studies, these three repeated dose studies in dogs.  
5 Two-week IV toxicity studies and 26-week oral  
6 toxicity studies and 52-week oral toxicity studies  
7 at the doses tested listed here. The results of  
8 these studies indicate tegaserod has no effect on  
9 EKG, such as heart rate and QT interval, and did  
10 not induce histopathological change in the heart.

11           Just for comparison, the 60 milligram per kg  
12 per day dose is about 300-fold higher than the  
13 clinical dose of .2 milligram per kg per day if we  
14 assume 60 kg body weight.

15           In summary, tegaserod is a 5-HT<sub>4</sub> receptor  
16 agonist with moderate to high affinity for 5-HT<sub>1</sub>  
17 receptor subtypes. Tegaserod is a weak inhibitor  
18 of hERG potassium channel, but did not induce QT  
19 prolongation in in vivo studies in dogs. Tegaserod  
20 did not induce contractions in the isolated  
21 coronary artery from pig, dog, nonhuman primates,  
22 and humans at the clinically relevant concentration

1 and doses.

2 Thank you.

3 **FDA Presentation - Insook Kim**

4 DR. KIM: Good morning. My name is Insook  
5 Kim. I'm a clinical pharmacology reviewer, and I  
6 did not review tegaserod at the time of approval,  
7 but I'm going to go over what we know about  
8 tegaserod at this point.

9 So I'm going to talk about pharmacokinetic  
10 characteristics of tegaserod, focused on metabolic  
11 pathway and, also, in vivo drug interaction  
12 potential. And also, I'm going to talk about  
13 effect of tegaserod on the QT prolongation and,  
14 also, effect of tegaserod on platelet aggregation  
15 in vitro.

16 So the approved dose for tegaserod is  
17 6 milligrams twice daily. Upon oral  
18 administration, tegaserod is rapidly absorbed,  
19 reaching its peak plasma concentration in about one  
20 hour after dose. And the oral bioavailability of  
21 tegaserod is about 10 percent, and tegaserod is  
22 eliminated mainly by metabolism. And unchanged,

1 tegaserod was not detectable in urine.

2           There are two main metabolic pathways  
3 proposed for tegaserod. One is acid hydrolysis,  
4 presumably in the stomach before absorption of  
5 tegaserod, and the other is the direct  
6 glucuronidation after absorption to the system.

7           This is a scheme of the metabolic pathway of  
8 tegaserod. So tegaserod will undergo acid  
9 hydrolysis followed by oxidation and  
10 glucuronidation to form this major metabolite,  
11 which I will call that M29. And acid hydrolysis  
12 also produces a byproduct of tegaserod from the  
13 side chain of tegaserod, which is PAG. The PK of  
14 the PAG in human was not characterized at the time  
15 of the approval. On the other hand -- once  
16 absorbed, tegaserod undergoes N-glucuronidation to  
17 form three isomeric N-glucuronides.

18           So during the development program of  
19 tegaserod, drug-drug interaction was more focused  
20 on the effect of other drugs on tegaserod. In  
21 result, tegaserod was not shown to be an inhibitor  
22 of several enzymes in vitro, and there was no

1 remarkable in vivo drug-drug interaction via the  
2 inhibition of 2D6 and 1A2, which is not listed in  
3 this slide.

4           However, there was no drug-drug interaction  
5 study in vivo to evaluate the effect of other drugs  
6 on tegaserod during the development program.

7 However, based on this metabolism study in humans  
8 and insignificant contribution of the CYP enzymes  
9 in the metabolism of tegaserod in humans, in vivo  
10 drug-drug interaction potential with concomitant  
11 CYP enzyme inhibitors was considered low.

12           After the approval, information became  
13 available that concomitant P-glycoprotein inhibitor  
14 may increase the systemic exposure of tegaserod,  
15 based on the observation of an increased systemic  
16 exposure to tegaserod by 74 percent with a  
17 concomitant quinidine, which was used as a  
18 P-glycoprotein inhibitor in humans. This was  
19 consistent with the in vitro finding suggesting  
20 that tegaserod is a substrate of P-glycoprotein  
21 efflux pump or transporter.

22           I'm going to talk about the effect of

1 tegaserod in QT prolongation. There was no  
2 thorough QT study conducted for tegaserod. Just to  
3 remind you, guidance for a thorough QT study was  
4 published in the year 2000, whereas tegaserod was  
5 approved in the year 2002.

6           However, ECG was monitored during the  
7 phase 3 trials in IBS-C patients for the initial  
8 approval. In phase 3 trials, placebo was used and  
9 tegaserod was studied at two dose levels, which was  
10 2 milligrams or 6 milligrams twice daily, and  
11 standard 12-lead ECG was obtained after two hours  
12 post-dose, plus or minus 30 minutes, after the  
13 first and the last dose of tegaserod. Treatment  
14 duration of tegaserod was 12 weeks.

15           During this phase 3 trial, it was noted that  
16 there was no clinically relevant or significant  
17 effect of tegaserod on QT prolongation. It was  
18 based on the comparable change in QTc interval from  
19 baseline between tegaserod and placebo treatment or  
20 the similar rate of new or worsening QTc interval  
21 prolongation among treatment groups. There's no  
22 dose-dependent effect of tegaserod on any QT

1 parameters. Of note, there was no positive  
2 control.

3 On the other hand, in a small subgroup of  
4 patients aged older than 65 years, the overall rate  
5 of ECG abnormalities, primarily ST segment  
6 depression and/or T wave alterations, was  
7 numerically higher in the tegaserod group than in  
8 the placebo group. However, evidence for ischemia  
9 is unclear given the small number of subjects in  
10 the subgroup.

11 Now I'm going to talk about the effect of  
12 platelet aggregation in vitro. After the approval,  
13 there are two publications that became available in  
14 which the effect of tegaserod on in vitro plus  
15 platelet aggregation was studied using standard  
16 light transmission aggregometry.

17 Just briefly, in principle, the light  
18 transmission aggregometry is using the light  
19 transmission through platelet-rich plasma, which  
20 increases when platelet aggregation is induced by a  
21 known agonist. And light transmission through  
22 platelet-poor plasma sets a maximum light

1 transmission, and the percent platelet aggregation  
2 is determined based on the change of light  
3 transmission from the baseline with or without the  
4 drug of interest, in this case, tegaserod.

5 Two published studies share common study  
6 design features: blood samples were collected from  
7 healthy subjects, and tegaserod was preincubated in  
8 blood for one hour prior to the preparation of the  
9 platelet-rich plasma sample. And three  
10 concentrations of tegaserod were used,  
11 10 nanomolar, 33 nanomolar, and 100 nanomolar;  
12 10 nanomolar concentration was used to mimic the  
13 peak plasma concentration of tegaserod in humans  
14 after 6 milligram BID dosing, and platelet-rich  
15 plasma was prepared, and platelet aggregation was  
16 induced by agonists, such as adenosine diphosphate  
17 or agonist serotonin in the presence of low  
18 concentration of adenosine diphosphate.

19 In result, this is a table from the  
20 publication. Serebruany, et al, reported  
21 statistically significant increase in platelet  
22 aggregation with tegaserod. Compared to the

1 vehicle, there was some increase at the  
2 concentration of tegaserod close to the peak plasma  
3 concentration. When the tegaserod concentration  
4 was increased to about tenfold higher than what is  
5 observed in plasma in humans, there was a  
6 consistently significant increase in platelet  
7 aggregation compared to the vehicle group, except  
8 for the one agonist, which is TRAP.

9 So in this study, the authors showed that a  
10 mild but statistically significant increase in  
11 platelet aggregation was observed in a  
12 concentration-dependent manner. The absolute  
13 percentage of platelet aggregation was about 9 to  
14 15 percent higher, with the highest concentration  
15 of tegaserod used in this study compared to the  
16 vehicle. They also reported that consistent  
17 results were obtained when blood was collected from  
18 IBS-C patients.

19 On the other hand, in a recent publication  
20 by Higgins, et al., tegaserod did not show any  
21 significant effect on platelet aggregation in  
22 vitro. When we compared the data under the similar

1 experimental conditions in terms of the platelet  
2 concentration and agonist concentration, there was  
3 no significant effect of tegaserod shown on the  
4 platelet aggregation.

5 So, in summary, for tegaserod, although  
6 there was no in vivo drug interaction study  
7 conducted to evaluate the effect of other drugs on  
8 tegaserod, based on the primary metabolic pathway  
9 suggested in human study, in vivo drug interaction  
10 potential with CYP enzyme inhibitor appears to be  
11 low. However, systemic exposure to tegaserod may  
12 be increased by concomitant P-glycoprotein  
13 inhibitors, and there was no thorough QT study  
14 conducted for tegaserod. However, in phase 3  
15 trials, no significant effect of tegaserod on QT  
16 prolongation was noted.

17 Lastly, the effect of tegaserod on platelet  
18 aggregation is inconsistent in publications. For  
19 one study, it reported mild potentiation of  
20 platelet aggregation, and the other study reported  
21 there was no significant effect on platelet  
22 aggregation.

1           While the effect of the major metabolite  
2 M29, which has higher plasma concentration than  
3 tegaserod, was not addressed in either of the  
4 studies, interpretation of the platelet aggregation  
5 study results is really challenging in the  
6 prediction of the cardiovascular event at this  
7 point.

8           Thank you. And Dr. Johnson will continue.

9           **FDA Presentation - Aisha Peterson Johnson**

10           DR. PETERSON JOHNSON: Hello again. And  
11 during this brief presentation, I'll present  
12 clinical information on tegaserod, known as  
13 Zelnorm.

14           I'll start with the regulatory history.  
15 Tegaserod was approved in 2002 for women with  
16 irritable bowel syndrome predominated by  
17 constipation, and this diagnosis is mainly seen in  
18 women, and the drug was approved in women.

19           In 2004, the drug was approved for chronic  
20 idiopathic constipation in patients less than  
21 65 years of age, and chronic idiopathic  
22 constipation is a condition that has a more wide

1 distribution among the sexes, and there's more  
2 males seen in the patient population, and there's  
3 limited information available for patients greater  
4 than 65 years of age.

5           During the initial review of the Zelnorm  
6 NDA, it should be noted that the major safety issue  
7 was lower abdominal pain leading to abdominal and  
8 pelvic surgeries, particularly cholecystectomy.  
9 And at the time of approval, cardiovascular events  
10 was not a known safety issue.

11           Continuing on with the regulatory history.  
12 Zelnorm, in 2004, underwent labeling updates to  
13 warn about possible side effects of diarrhea and  
14 ischemic colitis. In 2006, the Swiss Regulatory  
15 Authority requested a meta-analysis of any ischemic  
16 events. And on February 22nd, 2007, Novartis  
17 informed the FDA that the retrospective analysis of  
18 pooled tegaserod clinical trials revealed an  
19 imbalance in coronary ischemic events between  
20 tegaserod and placebo. And on March 9th, 2007,  
21 Novartis submitted this full safety report to the  
22 FDA. On March 30, 2007, Zelnorm was withdrawn from

1 the U.S. market.

2 This study summarizes the results of that  
3 meta-analysis. I'd like to point out that it was  
4 retrospective, involved 29 placebo-controlled  
5 trials, and there was external adjudication of  
6 those cardiovascular events.

7 You can see that in the left column, for  
8 tegaserod, there were four events of myocardial  
9 infarction, three strokes, and six cases of  
10 unstable angina compared with one event in the  
11 right column of transient ischemic attack seen in  
12 placebo patients, and that resulted in an event  
13 rate of .11 percent for tegaserod and 0.01 percent  
14 for placebo.

15 Tegaserod availability after market  
16 withdrawal, so the sponsor, Novartis, sponsored a  
17 treatment IND, and patients in this treatment IND  
18 were given 6 milligrams twice daily, which was the  
19 approved dose. And during the time that this  
20 treatment IND was open, there were no major  
21 cardiovascular ischemic events reported, and the  
22 treatment IND was closed by the sponsor in 2008.

1 Currently, Zelnorm is available on a limited basis  
2 through emergency IND only.

3 That's the end of the clinical presentation.

4 **Questions from the Committee**

5 DR. RAUFMAN: Thank you.

6 We will now ask if the committee has any  
7 questions for the FDA regarding their presentation  
8 on tegaserod. Dr. Lauer?

9 DR. LAUER: Thank you. I am struck by the  
10 extraordinarily small number of events that's been  
11 described, a total of 13 events, of which only  
12 seven are hard, myocardial infarction and stroke.  
13 My question is whether there are reports of any  
14 other events upon which FDA made its decision  
15 besides this very tiny number of 13.

16 Then my second question is, when you say  
17 that the events were adjudicated, were there  
18 prospective definitions of myocardial infarction,  
19 stroke, and unstable angina that were used and  
20 uniformly applied to all 29 studies in this  
21 meta-analysis?

22 DR. KORVICK: So I'll answer that question.

1 For your second question first, the analysis -- the  
2 clinical trials that were included in that  
3 analysis, the 29, did not have anything other than  
4 a usual checkbox for adverse events. So this was  
5 not like a cardiology study where you would -- like  
6 we're doing today, designing these studies with  
7 prospective definitions. So the committee made a  
8 list of criteria to adjudicate cases, and the  
9 sponsor spent almost a year going back collecting  
10 additional data to firm up the diagnoses.

11 So, yes, there were potential events that  
12 may or may not have been missed because this wasn't  
13 defined prospectively in the tight way that you  
14 might do a cardiology study. And at the time that  
15 the number of events reported to us showed this  
16 imbalance, there were discussions ongoing about  
17 Avandia and the cardiovascular risk and hazard  
18 ratios and odds ratios; and although this had a  
19 broad margin, there were discussions with the  
20 sponsor about what this meant, and we were in  
21 discussions about how to perhaps more -- to  
22 restrict access. But, ultimately, they decided to

1 remove.

2 Today, in retrospect, it might look a small  
3 number, but at the time, it was felt that there was  
4 a signal.

5 DR. RAUFMAN: Dr. Kaul?

6 DR. KAUL: I'm going to follow-up on  
7 Dr. Lauer's question. I mean, I'm also struck by  
8 the paucity of the safety signal and wondering  
9 whether it was the uncertainty around the safety  
10 signal in combination with the marginal efficacy of  
11 the drug that perhaps moved the needle for you.

12 But the question I have for you is I'm also  
13 struck by the methodology. I mean, a simple  
14 pooling, 13 events from 29 trials, surely, the FDA  
15 must know the fundamental paradoxes engendered by  
16 just pooling the data together versus doing a  
17 weighted combination of data. I mean, there were  
18 many examples of ecological fallacies in Simpson's  
19 paradox that can happen. You can get a  
20 counterintuitive result if you just simply pool  
21 that.

22 DR. KORVICK: I think that in response to

1 your question, your first statement was correct,  
2 and those were the discussions that we were having  
3 internally about the risk-benefit.

4 I think that over the past several years,  
5 especially as the agency moves forward looking at  
6 things in non-cardiac drugs and how we look at  
7 epidemiology, et cetera, you can retrospectively  
8 have those comments. But at the day, there was the  
9 uncertainty and the sort of willingness to accept a  
10 risk. And so, as we apply things today, we may  
11 have a different view of this.

12 So thank you for those comments.

13 DR. KAUL: I must emphasize, if the original  
14 miss and meta-analysis had used the same flawed  
15 pooling methodology, Avandia would not have been  
16 taken off the market. In fact, it would have shown  
17 a benefit with rosiglitazone if they had used the  
18 same additional simple pooling.

19 DR. KORVICK: Yes. Your point is well  
20 taken, and we're just giving you the historical  
21 facts of how this fell together. Thank you.

22 DR. RAUFMAN: Dr. Greene?

1 DR. GREENE: Dr. Johnson, do you know how  
2 many patients are using the emergency IND? And,  
3 also, do you have any idea how much tegaserod is  
4 being brought into the country from other  
5 countries?

6 DR. PETERSON JOHNSON: Dr. Korvick is going  
7 to answer about the emergency IND.

8 DR. KORVICK: There are approximately 500  
9 active emergency INDs per month. There are people  
10 that come on and off of that, and many for lack of  
11 efficacy. So they try it for a while and then they  
12 go off.

13 We don't know what other ways people might  
14 import it into the country, but in order to  
15 actually get it from Novartis, who's the sole  
16 provider, you have to have an emergency IND number.

17 DR. RAUFMAN: Dr. Rosenberg?

18 DR. ROSENBERG: So do you know, for those  
19 patients which were in the treatment IND and now  
20 are on the emergency IND, where the patients used  
21 aforapol (ph??), do we have any information on  
22 ischemic events, and do we continue to follow those

1 patients?

2 DR. KORVICK: To the previous point, I think  
3 trying to do a quantitative analysis of an open  
4 label, open access kind of a thing would be fraught  
5 with even more hazard than the type of meta-  
6 analysis that was done before.

7 So we do not have any statistics. However,  
8 no major ischemic events were reported through that  
9 program, more in this program. However, the nature  
10 of emergency INDs and open access programs for  
11 calculating that kind of risk are flawed.

12 DR. ROSENBERG: But how many patients were  
13 in the Novartis treatment IND?

14 DR. KORVICK: At this point in time, given  
15 the fact that Novartis is not here and they can't  
16 speak to that, that's not publicly available  
17 information.

18 DR. RAUFMAN: Dr. Teerlink?

19 DR. TEERLINK: I have one question for  
20 Dr. Zhang from the preclinical information and then  
21 another clinical question.

22 In terms of the isolated coronary artery

1 studies, it's been a long time since I've done  
2 blood vessel studies myself. So when these are  
3 done for preclinical analysis, are they done on  
4 solely intact rings or are they done on denuded  
5 rings, as well, or are they done on atherosclerotic  
6 vessels, as well? Because, clearly, particularly  
7 with the serotonin agonists -- and I had done this  
8 myself in the lab years and years ago -- there's a  
9 huge range depending on what the status of the  
10 blood vessel is. That's the first question.

11 DR. ZHANG: I cannot answer that question.  
12 This study is from a publication -- I'm not sure  
13 what's the answer for that.

14 DR. TEERLINK: So this would seem to be an  
15 important way to assess the potential  
16 cardiovascular risk of these agents inasmuch as a  
17 normal blood vessel responds very differently than  
18 a diseased blood vessel to these kind of  
19 vasoconstrictors.

20 So let's look into that, and it would be  
21 useful to find that out.

22 DR. ZHANG: All right.

1 DR. TEERLINK: The second question is  
2 regarding the clinical database and the  
3 meta-analyses. There's an article that was  
4 published by Dr. Anderson in the Journal of  
5 Cardiovascular Pharmacology in 2009 where he  
6 alludes to -- and there are no references for  
7 this -- but a repeat analysis and an independent  
8 review of the updated database, where there  
9 were -- of the 14 reported events, three were not,  
10 in fact, confirmed.

11 So we even have a very small number, but  
12 then when it was independently looked at -- and,  
13 once again, I've tried to track down this  
14 information. So one question is do you have  
15 re-analysis of these endpoints. But we're trimming  
16 it down to even a smaller number of events, and  
17 we're still left with the predominant events being  
18 these unstable angina events, which we've seen  
19 traditionally have been incredibly hard to  
20 adjudicate.

21 So, first of all, is the FDA aware of that  
22 re-adjudication process or that reevaluation

1 process? Was that done in conjunction with the  
2 FDA? And, if not, how did the FDA interpret that  
3 re-analysis?

4 DR. KORVICK: I think what you say about the  
5 published report does raise similar questions to  
6 us, and the data that we based our actions on was  
7 that that we reported in our drug safety  
8 communication.

9 So you have some very good points that are  
10 germane to today's topic, and I think we have  
11 nothing else to say about that at this time. We  
12 don't have -- no. Okay. We can only talk about  
13 what's publicly available, but you do bring up some  
14 very good points, and those are very good  
15 observations.

16 DR. RAUFMAN: Dr. Fox?

17 DR. FOX: Thanks very much. A couple of  
18 questions. One is on the preclinical stuff, as a  
19 follow-on to Dr. Teerlink's question.

20 Just a clarification. On slide number 3,  
21 looking at the cross-reactivity on some of the  
22 subtypes, receptor subtypes, it states at the

1 bottom there about 5-HT1, 5-HT2 subtypes  
2 located -- it says about vasoconstriction. But the  
3 handy table that you gave us in the  
4 beginning -- and thanks for that -- actually says  
5 that the 5-HT1D is more of a vasodilator, not a  
6 vasoconstrictor.

7 So can you just confirm that that's correct  
8 and, thus, would the FDA conclude that based on  
9 this evaluation, there is no preclinical signal for  
10 coronary vasoconstriction with this agent?

11 DR. ZHANG: The first question, that is  
12 correct. And the two subtype receptors, 5-HT1B and  
13 5-HT2A, mainly induced vasoconstriction.

14 In this particular study, the sponsor did  
15 not show the 1B receptors. But in later studies,  
16 there are many studies now published that use  
17 tegaserod as a reference control and show that  
18 tegaserod has affinity for 1B. And, also, most  
19 recent publications show that tegaserod has  
20 affinity for 5-HT2 receptor subtypes.

21 DR. FOX: And do you know what the nanomolar  
22 value of those KDs are?

1 DR. ZHANG: The KDs for the 5-HT2 receptor  
2 subtypes, it's about the same range with this KDs.  
3 I do not have the precise number for that. It's  
4 relatively high, moderate to high affinity for  
5 5-HT2 receptors. You will hear this from  
6 Theravance today in later presentations.

7 DR. FOX: And the 1B, do you know that one?

8 DR. ZHANG: 1B?

9 DR. FOX: Yes.

10 DR. ZHANG: 1B is in the same range.

11 DR. FOX: So less than 100.

12 DR. ZHANG: Less than 100.

13 DR. FOX: Okay. Thanks very much.

14 The other question I had was also a  
15 follow-on on the clinical data, looking at slide  
16 26. It states -- the bottom row, there are event  
17 rates, although those are really just crude  
18 incidences, not really event rates. And do you  
19 know anything about the duration of exposure,  
20 whether it was the same with active agent versus  
21 placebo comparator, or were all of these studies  
22 double-blind? And to the -- trying to translate

1 the crude incidents into an actual annualized event  
2 rate, do you have any information about that, based  
3 on exposure?

4 DR. KORVICK: I can just say that these were  
5 selected studies because of the fact that they were  
6 blinding and placebo-controlled, and there was an  
7 equal exposure to the control in the studies.

8 When we were looking at these cases, just to  
9 say, they were in a lot of different age ranges,  
10 not concentrated to one, and exposures ranged from  
11 a few days to months. So it's really not  
12 consistent, just in a broad way of answering that  
13 question.

14 DR. FOX: Okay. Just a follow-up to that.

15 If you take out the unstable anginas, which  
16 other panelists have, I think correctly questioned  
17 the relevance of in this kind of an analysis, can  
18 you tell us whether the lower bound of the  
19 95 percent confidence interval around that point  
20 estimate of a hazard ratio is below 1?

21 DR. KORVICK: I don't have that number now,  
22 but I would --

1 DR. FOX: But I think we probably guess that  
2 it is.

3 DR. KORVICK: But I would just say one thing  
4 in defense of including the unstable anginas, these  
5 were ones that were adjudicated by the committee  
6 and really were looked at hard. And, at the time,  
7 we were not applying this sort of MACE analysis  
8 that we do so much today. And in this case, we  
9 were being conservative to cast a broad net to  
10 potential ischemic events. So it was analysis to  
11 maybe be a little more far-reaching, but certainly  
12 people apply MACE today.

13 DR. RAUFMAN: Dr. Granger?

14 DR. GRANGER: We're all kind of saying the  
15 same thing, it seems like, that there's something  
16 that seems fairly extraordinary here, to have this  
17 tiny number of events result in this drug being  
18 withdrawn from the market and kind of maybe still a  
19 lack of appreciation on what the full rationale for  
20 that would be.

21 Let me make a couple of comments. One is I  
22 think to better understand this, including what the

1       implications are now for a whole class of drugs  
2       based on this tiny number of events, it would be  
3       useful for me to have had more information about  
4       the details of these events that, again, could be  
5       driving a whole policy on just a handful of events.

6               Generally, when we see something like this,  
7       the most likely explanation is the play of chance,  
8       not something real if there's not biologic  
9       plausibility, which it seems like there's not been  
10       any evidence that I've seen about a compelling  
11       story for biologic plausibility.

12              Then a related question is when this came  
13       up, was there discussion at that time about some  
14       kind of approach to gathering more information  
15       about whether this was a real signal or not? Was  
16       there any kind of pushback or discussion about  
17       doing some type of a cardiovascular safety study at  
18       that particular time about this?

19              Then the final part to this question is what  
20       is the FDA's interpretation of this? Is it that  
21       this is something real that should really concern  
22       us for the overall -- and maybe we'll get back to

1       this -- for the overall class of drug, or are you  
2       looking for us to kind of follow the line of  
3       reasoning that we seem to be following; that it  
4       seems pretty premature, based on this information,  
5       to have kind of a broad policy change?

6               DR. KORVICK: I have to say yes to your last  
7       question. I think that we're -- these things  
8       happen in rapid succession, as you just saw  
9       Dr. Peterson's slide. We were given the data. We  
10       were looking at the data. We spoke with the  
11       sponsor.

12               There was always a question in later  
13       discussions after they took that action as to  
14       whether or not we could bring it back on the  
15       market, how could we do that, what more data we  
16       would need to have, et cetera. We were negotiating  
17       those things with them, just to speak in a broad  
18       way, as they're not here to discuss that fact.

19               So this is a chapter that perhaps remains  
20       open, but yet is closed at this point in time. So  
21       yes to your last comment.

22               DR. GRANGER: Presumably, we can't get any

1 more details today about the nature. I mea, if  
2 these were all kind of clear-cut, major -- somebody  
3 like a 30-year-old otherwise healthy woman coming  
4 in with a major MI, something like that might be  
5 more compelling than if it was a few people who had  
6 other risk factors and kind of softer events.

7 You don't have that?

8 DR. RAUFMAN: In the interest of time,  
9 because we're running a little bit late, we have a  
10 few more questioners, but I ask that people please  
11 stay focused in their questions and, as well, in  
12 their responses.

13 Dr. Spiegel?

14 DR. SPIEGEL: Thank you. Many of my  
15 questions have already been addressed, but I do  
16 want to ask -- and more of this will come back in  
17 the discussion -- about really what is the role of  
18 the hazard ratio versus a number needed to harm?

19 We can do a chi-squared on this, and I  
20 suspect the lower bound might be just barely  
21 significant, but I don't recall. I remember at the  
22 time doing that and finding it was maybe

1 significant. But the discussion at the time was  
2 the number needed to harm, which is about a  
3 thousand, if I'm doing that statistic correctly,  
4 which is, of course, much, much higher than, let's  
5 say, aspirin, which has maybe a very different  
6 risk-benefit ratio.

7 So this cuts to the bone of what we're going  
8 to be talking about today. The bottom line was  
9 tegaserod was not very effective, and that's what  
10 led that discussion. But the number needed to harm  
11 was a thousand.

12 So what is the role of number needed to  
13 harm, from the FDA's perspective, and why are we  
14 married always to a hazard ratio, which is a scaled  
15 statistic that doesn't have interpretability  
16 directly to a patient during a clinical discussion?

17 DR. KORVICK: I would just say stay tuned  
18 for -- maybe we can get into that later, in the  
19 interest of time, but we do debate that issue back  
20 and forth in the organization, and maybe we can get  
21 into that later.

22 DR. RAUFMAN: Did you want to comment?

1 DR. ZHANG: I just have a quick comment to  
2 answer question about coronary artery studies. The  
3 coronary artery comes from the heart transplant  
4 patients, and when they have a visual inspection,  
5 the area looks healthy. And the coronary artery  
6 was cut into the ring and tied into the tissue  
7 bath.

8 DR. RAUFMAN: Dr. Thadani?

9 DR. THADANI: Just two short questions.  
10 One, on the coronary artery contractions, is there  
11 any -- whether this drug or other drugs, they're  
12 looking at an ischemic model, because here the  
13 noise has been raised. The drug could have some  
14 kind of a mark on ischemic events?

15 So either in the dog model, was there acute  
16 occlusion or chronic occlusion? Because we know  
17 that in humans, if you give acetylcholine to  
18 patients who have coronary disease, they  
19 vasoconstrict rather than vasodilate. So I think  
20 it would be relevant, either for this drug or  
21 future, to look at that model, which might give you  
22 more clue. That's one.

1           Question 2 here is I think FDA probably  
2 reacted -- you could say it's an emotional  
3 reaction, but when you're getting event one in a  
4 thousand versus one in 10,000, and if you allow  
5 that and something happens -- I realize it's a  
6 retrospective analysis of data, but if the  
7 hospitalization is for unstable angina, strokes  
8 don't lie. And I'm hoping the MI was QA driven.

9           It's still an event rate, which  
10 worries -- and even cardiologists are including  
11 revascularization, a much softer endpoint than  
12 these and get away with the trials. So I think the  
13 FDA reaction, although over-reactive, is for the  
14 safety of the public. So whether that leads to  
15 larger trials is a different issue.

16           So the event rate, when it's going the wrong  
17 direction -- and I don't know what the efficacy  
18 was. Was it 20 percent, 10 percent? So if it's 10  
19 to 15, I think you probably did the right reaction  
20 barring big trials, because safety comes first.  
21 There are millions of people with irritable bowel  
22 syndrome, with chronic constipation. So I realize

1 one reacts the other way around.

2 Just a comment and question.

3 DR. RAUFMAN: Dr. Solga?

4 DR. SOLGA: I'm wondering how the FDA  
5 arrived at the emergency IND mechanism for  
6 tegaserod in contrast to what's been done with, for  
7 example, Lotronex.

8 Lotronex, for people who aren't  
9 gastroenterologists, you may recall is a 5-HT3 for  
10 irritable bowel syndrome with diarrhea, and it was  
11 withdrawn and then reintroduced after a series of  
12 very serious safety adverse events that did not  
13 involve the heart, but did result in death of some  
14 patients.

15 I am very happy with the Lotronex mechanism.  
16 There's a one-page consent form that's clear,  
17 concise, and very serious, and offers an  
18 opportunity for the patient and a prescribing  
19 physician to agree together what we're doing.

20 I'm not sure I understand the emergency IND.  
21 It seems to be some middle ground between Dear  
22 Doctor letters, which, obviously, nobody really

1 reads or pays attention to, and the very, very high  
2 administrative burden that goes along with  
3 prescribing cisapride.

4 DR. KORVICK: Again, I would say that the  
5 difference between this drug and Lotronex was the  
6 events were ischemic colitis and we figured out how  
7 to deal with that through that whole history. In  
8 this case, it was a concern about cardiovascular  
9 events, and trying to negotiate a safety program,  
10 or a REMs, in that regard would be a little bit  
11 different. So just to say we were trying to get  
12 there, but at one point, there was a decision made  
13 that that wasn't going to be pursued.

14 So we were negotiating, but the mechanism we  
15 ended up with was the one that we have today.

16 DR. SOLGA: I have prescribed Lotronex zero  
17 times since it's been reintroduced, but I have  
18 found the communications to be very useful, and I'm  
19 grateful to the FDA for them.

20 DR. RAUFMAN: Dr. Bloom?

21 DR. BLOOM: I wonder if my agency colleagues  
22 or the committee will have an opportunity sometime

1       today to put in the context of this discussion the  
2       large studies that were published fairly recently,  
3       one also by Anderson and the other by Lockland,  
4       that were unable to show any association as far as  
5       cardiovascular risk in terms of both the quality of  
6       those studies and why there would be such  
7       divergence there.

8                 DR. RAUFMAN:   Dr. Kaul?

9                 DR. KAUL:   I think this has been mentioned  
10       already, but it bears repetition just to give you  
11       the flavor for the fragility of the data.  One  
12       fewer event in the experiment arm would have  
13       negated the statistical significance.

14                If you have 13 versus 1, the lower bound is  
15       1.03, the upper bound is 60.15.  And if you have  
16       one fewer, it will be .94, and one more in the  
17       control arm, it will be .89.

18                Jonathan, to answer your question, seven  
19       fewer, the lower bound would be .54, very fragile  
20       data.  So I think the FDA has already acknowledged  
21       that it was the marginal efficacy that primarily  
22       drove the decision.

1 DR. RAUFMAN: I think we've beaten that  
2 horse sufficiently.

3 Dr. Richig?

4 DR. RICHIG: I just have two questions  
5 regarding the preclinical dog data. Number one,  
6 were the ECGs just snapshot ECGs, in other words,  
7 short duration recordings? And, number two, was  
8 the QT corrected for heart rate, and, if so, which  
9 formula was used?

10 DR. ZHANG: Slide number 4. The hERG  
11 channel study.

12 DR. RICHIG: I'm referring to the dog data.  
13 I think it's the next slide. That's it.

14 DR. ZHANG: Okay. I do not think they  
15 corrected for QT interval in this study. The thing  
16 I think you should think about is the dosing, I  
17 know the dose is very high as compared to that in  
18 clinical study. And even if they do not correct  
19 heart rate for the QT intervals, they do not see  
20 any effect at this high concentration, and the  
21 minor heart change may not affect the overall  
22 interpretation.

1 DR. RICHIG: It's just something to  
2 consider.

3 DR. ZHANG: Thank you.

4 DR. RAUFMAN: Dr. Teerlink?

5 DR. TEERLINK: So very briefly, I do  
6 understand the FDA's position and decision in  
7 things. You're damned if you delay approval of a  
8 drug; you're damned if you approve a drug too  
9 quickly. So my condolences along those lines.

10 The second point is should we -- not being a  
11 gastroenterologist, in terms of interpreting  
12 ischemic colitis, is ischemic colitis a demand  
13 ischemia, so, therefore, we should not consider it  
14 as part of the general atherosclerosis progression  
15 of disease scenario, or is it perhaps a supply  
16 issue, so we should throw it into the manifestation  
17 of ischemic and organ damage, much as we do  
18 unstable angina and other things?

19 Is there a sense of what the mechanism is  
20 there, and do we need to start -- because of this  
21 being studied in these disease entities, do we need  
22 to throw that in? I don't know. So whoever can

1 answer that.

2 DR. RAUFMAN: I'll answer. It's not my area  
3 of investigation, but I think it can be either.  
4 Certainly in terms of demand, there is certainly  
5 data on marathon runners who develop intestinal  
6 ischemia and blood loss and are otherwise perfectly  
7 normal, and, likewise, people in heart failure or  
8 whatever.

9 DR. TEERLINK: The point that I brought that  
10 up it's given that this an agent that had already  
11 an early safety signal for ischemic colitis. Was  
12 that perhaps an early signal that there was  
13 cardiovascular danger to this medicine? I don't  
14 know, but it's kind of, to me, an intriguing way to  
15 look at these groups of agents.

16 DR. KORVICK: I think it's still somewhat  
17 controversial and I would say that perhaps that is  
18 why Swiss Medic asked to expand the analysis to all  
19 ischemia. Just to say that in IBS studies and  
20 chronic constipation studies, a lot of times, these  
21 diseases are diseases of exclusion, and there are  
22 also other discussions about background rate in

1 populations, et cetera, and it gets very confusing,  
2 to answer your question directly.

3 DR. RAUFMAN: Two final questions.  
4 Dr. Lauer?

5 DR. LAUER: No.

6 DR. RAUFMAN: Dr. Greene, final question.

7 DR. GREENE: It wasn't a question. I was  
8 just going to comment on the ischemic colitis,  
9 which is multifactorial and generally not a  
10 terribly serious event as far as  
11 gastroenterologists go as opposed to mesenteric  
12 ischemia where you have a major vessel.

13 So these people generally are in and out of  
14 the hospital quickly and aren't very sick.

15 DR. TEERLINK: Kind of like unstable angina.

16 [Laughter.]

17 DR. KORVICK: May I caveat that, because the  
18 Lotronex program was raised here? And I think that  
19 when the drug was first approved and it was used  
20 broadly and people weren't aware of this issue,  
21 there were patients that continued to take their  
22 medicine and there were actually hospitalizations

1 and deaths from that. Since that time, since  
2 people have been alerted to the issue, we've not  
3 seen that as much. And it has been more looking  
4 like what you said, a reversible disease.

5 DR. RAUFMAN: At this point, we'll take a  
6 short 10-minute break. Committee members, please  
7 remember that there should be no discussion of the  
8 meeting topic during the break amongst yourselves  
9 or with any member of the audience. We'll resume  
10 at 10:40 a.m.

11 (Whereupon, a recess was taken.)

12 DR. RAUFMAN: If everyone could please take  
13 their seats, we will now resume.

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

21 For this reason, FDA encourages all  
22 participants, including the sponsor's nonemployee

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

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

14 We will now proceed with Theravance's  
15 presentations. Dr. Beattie?

16 **Sponsor Presentation - David Beattie**

17 DR. BEATTIE: Thank you. Good morning. I'm  
18 David Beattie, a senior director of pharmacology at  
19 Theravance. On behalf of Theravance, I'd like to  
20 express our appreciation for the opportunity to  
21 address the cardiovascular safety concerns with 5-  
22 HT4 receptor agonists.

1           These compounds can be divided into two  
2 separate classes; first, the previously approved  
3 agents, such as cisapride and tegaserod, which are  
4 nonselective and could be more correctly termed  
5 nonselective 5-HT receptor modulators; second, a  
6 new class of highly selective 5-HT<sub>4</sub> receptor  
7 agonists.

8           Based on the concerns raised about the early  
9 generation of nonselective pro-kinetic agents, it's  
10 important to understand any potential risks in the  
11 new class of agents, particularly in light of the  
12 needs of patient with severe disease.

13           GI functional motility disorders have a  
14 significant impact on the quality of life of  
15 patients. While patients with mild to moderate  
16 disease can often be treated effectively with  
17 available agents, regardless of the specific  
18 diagnosis, patients with disability and who don't  
19 respond to existing therapies need additional  
20 therapeutic options.

21           The impact of severe GI disease applies to  
22 all the indications being discussed today. For

1 example, in Theravance's phase 2 chronic idiopathic  
2 constipation study, patients experienced, on  
3 average, a complete spontaneous bowel movement only  
4 once every three to four weeks at baseline.

5 Although the early generation 5-HT receptor  
6 modulators, cisapride and tegaserod, were used to  
7 treat GI functional motility disorders, both were  
8 withdrawn as a result of cardiovascular safety  
9 concerns. The new class of selective 5-HT<sub>4</sub>  
10 receptor agonists have the potential to safely  
11 address the unmet medical need for patients with  
12 serious motility disorders.

13 Theravance is beyond clinical development of  
14 two highly selective 5-HT<sub>4</sub> receptor agonists for GI  
15 motility disorders, Velusetrag and TD-8954.

16 Velusetrag is also known as TD-5108.

17 Velusetrag has completed a phase 2 proof of  
18 concept study in chronic idiopathic constipation,  
19 while TD-8954 has completed phase 1 single and  
20 multiple ascending dose studies. Because both  
21 compounds are in an early stage of clinical  
22 development, the clinical safety experience is

1 limited. Therefore, this presentation will focus  
2 on preclinical properties.

3 The pharmacology of Velusetrag and TD-8954  
4 is different from that of the early generation pro-  
5 kinetic agents, cisapride and tegaserod. This  
6 unique profile has a potential to increase both  
7 efficacy and safety relative to these earlier  
8 generation medicines.

9 In order to achieve a high degree of  
10 selectivity for a targeted mechanism, Theravance  
11 uses a multivalent approach to design compounds.  
12 The selectivity is derived from simultaneous  
13 interactions of optimized primary and secondary and  
14 secondary binding groups to the protein of  
15 interest, in this case, the 5-HT4 receptor. A  
16 linker connects the primary and secondary binding  
17 groups in an optimized configuration.

18 As a result of optimization of the primary  
19 and secondary binding groups and the linker,  
20 Velusetrag and TD-8954 are structurally distinct  
21 from cisapride and tegaserod. They're not simply  
22 analogs of the older generation compounds.

1           Velusetrag has one major active metabolite  
2 and core structural analog called THRX-830449. It  
3 differs from the parent only by the absence of a  
4 methyl group. This metabolite has a nearly  
5 identical pharmacological profile to the parent.  
6 The unique structural characteristics drive the  
7 pharmacological differentiation of the new class of  
8 agents, such as Velusetrag and TD-8954, from  
9 cisapride and tegaserod.

10           Velusetrag and this metabolite and TD-8954  
11 have a high degree of 5-HT<sub>4</sub> receptor selectivity.  
12 The left column lists the individual 5-HT receptor  
13 subtypes, and the numbers in the table represent  
14 the ratios of the different binding affinities, or  
15 KI values of compounds at non-5-HT<sub>4</sub> serotonergic  
16 receptors compared to those at the human 5-HT<sub>4</sub>  
17 receptor.

18           If a number is less than 1, that means that  
19 the compound has higher affinity at the non-5-HT<sub>4</sub>  
20 subtype than at the 5-HT<sub>4</sub> receptor. And even if  
21 the number is greater than 1, but still in single  
22 digits, basically, the compound has very little

1 5-HT4 receptor selectivity.

2 Both Velusetrag and TD-8954 are at least  
3 hundreds of times more selective for the 5-HT4  
4 receptor. In stark contrast, cisapride and  
5 tegaserod lack 5-HT4 receptor selectivity, which is  
6 why they're best described as non-selective 5-HT  
7 receptor modulators.

8 Highlighted are the particular non-5-HT4  
9 serotonergic receptors at which cisapride and  
10 tegaserod have significant affinity. At several of  
11 the receptor subtypes, cisapride and tegaserod have  
12 ratios less than one, indicating the higher  
13 affinity at the non-5-HT4 receptor compared to the  
14 5-HT4 subtype.

15 This off-target activity of cisapride and  
16 tegaserod may account for their suboptimal efficacy  
17 and safety as many of these receptors, which serve  
18 both excitatory and inhibitory functions, are  
19 expressed in the GI and the cardiovascular systems.

20 With respect to the GI system, circled are  
21 several non-5-HT4 serotonergic receptors with which  
22 cisapride and tegaserod interact that may

1 counteract the 5-HT4 receptor-mediated GI pro-  
2 kinetic activity in humans.

3 There's evidence that 5-HT1B receptor  
4 activation and 5-HT2A, 5-HT2B, or 5-HT3A antagonism  
5 may reduce motility in the human GI tract. This  
6 perceived advantage of 5-HT4 selectivity isn't  
7 purely hypothetical and is borne out by available  
8 clinical data.

9 One published example is Velusetrag's  
10 clinical activity in the phase 2 chronic idiopathic  
11 constipation study. Patients had a complete  
12 spontaneous bowel movement, on average, once every  
13 three to four weeks prior to treatment. However,  
14 after four weeks of treatment with Velusetrag at  
15 15 milligrams, patients had a complete spontaneous  
16 bowel movement, on average, every two to three  
17 days, so a pretty substantial effect.

18 The efficacy advantage is reflected in the  
19 comparison of the potencies of compounds in human  
20 isolated GI tissue and binding affinities at the  
21 human recombinant 5-HT4 receptor. An interaction  
22 with non-5-HT4 receptors can influence 5-HT4

1 agonist activity in the human colon. In the human  
2 isolated colonic circular smooth muscle  
3 preparation, 5-HT4 agonists inhibit the contractile  
4 activity evoked by electrical stimulation. This  
5 action of 5-HT4 agonists is proposed to support  
6 defecation.

7 On the Y-axis is the percentage of the  
8 control response, and on the X-axis is the ratio of  
9 the test compound concentration and 5-HT4 binding  
10 affinity or KI value for each compound. This ratio  
11 gives a sense of how well the activity in human  
12 tissue is predicted by the activity at the human  
13 5HT4 receptor.

14 The tegaserod curve is substantially right-  
15 shifted from the curves for Velusetrag and TD-8954.  
16 In other words, with tegaserod, in order to achieve  
17 the same colonic response as Velusetrag or TD-8954,  
18 a much higher concentration is required, but will  
19 be predicted based on its 5-HT4 receptor binding  
20 affinity.

21 These data are consistent with an  
22 interaction of tegaserod with non-5-HT4 receptors,

1 such as antagonism of the 5-HT<sub>2B</sub> subtype, which  
2 counteracts the 5-HT<sub>4</sub> agonist activity in the  
3 colon.

4 Data like these may explain why the new  
5 class of selective 5-HT<sub>4</sub> agonists have increased  
6 efficacy in patients with GI motility disorders  
7 compared to early generation compounds like  
8 tegaserod. 5-HT<sub>4</sub> receptor selectivity may also  
9 include responsiveness of the cardiovascular  
10 system.

11 Circled are several non-5-HT<sub>4</sub> serotonergic  
12 receptors that are expressed in the cardiovascular  
13 system. Cisapride and tegaserod interact with  
14 these receptors, whereas the selective 5-HT<sub>4</sub>  
15 agonists don't. These 5-HT receptor subtypes, for  
16 example, as members of the 5-HT<sub>1</sub> and 5-HT<sub>2</sub> classes,  
17 are expressed throughout the cardiovascular system,  
18 including arteries, veins, the heart, and  
19 platelets.

20 Interactions with these receptors can be  
21 excitatory or inhibitory, and so the resultant  
22 effect can often be difficult to interpret or

1 predict. These multifactorial off-target effects  
2 don't contribute to efficacy, but could account for  
3 the cardiovascular concerns associated with  
4 cisapride and tegaserod.

5 By contrast, in preclinical studies, the  
6 cardiovascular actions of selective 5-HT<sub>4</sub> agonists  
7 appear to be limited to positive inotropic and  
8 chronotropic effects, but are generally modest in  
9 magnitude and transient. This lack of off-target  
10 activity of the new selective 5-HT<sub>4</sub> agents is also  
11 reflected in their lack of clinically relevant  
12 affinity for receptors outside the 5-H class, ion  
13 channels, and enzymes.

14 Cisapride, as we've heard today, does have  
15 clinically relevant off-target activity. Its  
16 inhibition of the hERG channel is particularly  
17 important.

18 When tested at a high concentration of  
19 3 micromolar, that's 400 to 1,000-fold higher than  
20 the plasma exposure associated with robust GI pro-  
21 kinetic activity in humans, Velusetrag, its  
22 metabolite, THRX-830449, and TD-8954 have little or

1 no effect on hERG potassium currents.

2 In contrast, when all cells are washed and  
3 then challenged with cisapride at a concentration  
4 that's 150-fold lower, or 20 nanomolar, a marked  
5 inhibition is observed. Completion of thorough  
6 concentration response curves permits the hERG  
7 potency of each compound to be compared to their  
8 5-HT4 agonist potency.

9 In this table, the hERG and human  
10 recombinant 5-HT4 receptor potencies are shown as  
11 IC50 or EC50 values together with the ratios of  
12 these potencies in the right-hand column.  
13 Cisapride clearly stands out. Its ratio is 0.2 or,  
14 in other words, it is fivefold higher potency at  
15 the hERG channel compared to its potency at the  
16 5-HT4 receptor. Cisapride's hERG channel  
17 inhibition underlies its association with cardiac  
18 arrhythmias, such as torsades de pointes due to  
19 delayed repolarization of the cardiac action  
20 potential.

21 By contrast, Velusetrag, THRX-830449, and  
22 TD-8954 have much lower potencies at the hERG

1 potassium channel compared to the 5-HT4 receptor,  
2 and the potency ratios are considerable, as is also  
3 the case for tegaserod. At doses that would be  
4 used for therapeutic effects, there is effectively  
5 no engagement of the hERG potassium channel by  
6 either Velusetrag or TD-8954.

7 5-HT4 receptor selectivity clearly  
8 differentiates Velusetrag and TD-8954 from  
9 cisapride and tegaserod, and this may be important  
10 as 5-HT receptors are expressed and exert a variety  
11 of actions in the cardiovascular system.

12 Preclinical studies with Velusetrag and  
13 TD-8954 confirm a lack of cardiovascular findings  
14 at clinically relevant exposures. As the concerns  
15 associated with tegaserod were ischemic in nature,  
16 they could be driven by coronary artery  
17 constriction or platelet aggregation. The  
18 influence of Velusetrag or TD-8954 on coronary  
19 arteries and platelets has been investigated.

20 The use of selective 5-HT4 agonists in these  
21 studies permits the definitive conclusion that the  
22 5-HT4 receptor does not interfere with coronary

1 artery or platelet function.

2 Velusetrag and TD-8954 have no significant  
3 contractile activity in human isolated coronary  
4 artery preparations. These preparations are -- the  
5 endothelium is denuded from these preparations, and  
6 the preparations appear visually healthy.

7 In these experiments, the coronary artery  
8 rings are suspended in a physiological buffer in a  
9 tissue bath and contractile responses are recorded.  
10 The study includes 5-HT or serotonin which will  
11 activate all the 5-HT receptors in the tissue. The  
12 responses on the Y-axis expresses a percentage of  
13 the maximum contraction produced by 5-HT, and the  
14 concentration of each compound is plotted on the  
15 X-axis.

16 Of the agents tested, only 5-HT was able to  
17 constrict the tissue, presumably via agonist  
18 activity at a non-5-HT4 receptor. Based on data in  
19 the literature, 5-HT contracts coronary artery  
20 preparations via activation of 5-HT2A or 5-HT1B  
21 receptors.

22 Consistent with the data from the human

1 tissue and consistent with our high 5-HT<sub>4</sub> receptor  
2 seal activity, Velusetrag and TD-8954 have no  
3 contractile activity in canine and porcine isolated  
4 coronary arteries. As in the human coronary  
5 artery, these data suggest that the 5-HT induced  
6 contraction is not due to 5-HT<sub>4</sub> receptor  
7 activation. This finding was confirmed by studying  
8 the influence of selective antagonists on the 5HT  
9 induced responses.

10 In this canine coronary artery study, all  
11 tissues are treated with 5-HT. The white curve  
12 represents the control responses to 5-HT, while the  
13 green and blue curves represent responses to 5-HT  
14 in the presence of a 5-HT<sub>4</sub> or a 5-HT<sub>2A</sub> antagonist,  
15 respectively. The fact that the green curve  
16 resembles the control white curve shows that the 5-  
17 HT<sub>4</sub> receptor is not involved in the 5-HT induced  
18 coronary artery response, because a selective 5-HT<sub>4</sub>  
19 antagonist has no effect.

20 The ability of a selective 5-HT<sub>2A</sub>  
21 antagonist, shown by the blue curve, to inhibit the  
22 5-HT concentration response curve implicates the

1 5-HT<sub>2A</sub> receptor in this response, and there were  
2 similar results using the porcine coronary artery  
3 preparation.

4 These data are consistent with a lack of  
5 effect of the selective 5-HT<sub>4</sub> receptor agonists in  
6 the coronary artery preparations. Selective 5-HT<sub>4</sub>  
7 agonists similarly show no effect on platelet  
8 aggregation.

9 Human platelets were prepared according to  
10 2008 guidelines from the Clinical and Laboratory  
11 Standards Institute, ADP at 5 micromolar, and a  
12 combination of ADP at 1 micromolar and 5-HT at  
13 5 micromolar were used in the study.

14 The positive control, thrombopoietin, was  
15 active and increased platelet aggregation in a  
16 statistically significant manner. In contrast,  
17 Velusetrag and THRX-830449, along with an active  
18 vehicle, had no effect on platelet aggregation.  
19 The concentrations of Velusetrag and its metabolite  
20 tested were up to tenfold higher than the clinical  
21 C<sub>max</sub> at steady-state, which is associated with  
22 robust clinical activity in patients with chronic

1       constipation.

2               Velusetrag and TD-8954 are highly selective  
3       5-HT<sub>4</sub> receptor agonists that can be differentiated  
4       in several respects from early generation 5-HT  
5       receptor modulators, such as cisapride and  
6       tegaserod. In terms of safety, Velusetrag and  
7       TD-8954 have no affinity for the other 5-HT  
8       receptor subtypes expressed in the cardiovascular  
9       system, and, in consequence, produce no effects on  
10      coronary arteries or on platelets. Velusetrag and  
11      TD-8954 have no clinically relevant affinity for  
12      the hERG potassium channel. In addition to the  
13      mechanistic studies, there are several  
14      opportunities to study the cardiovascular effects  
15      of compounds during the standard GLP safety  
16      program.

17              Multiple nonclinical studies support the  
18      cardiovascular safety of Velusetrag and TD-8954.  
19      The studies further highlight the cardiovascular  
20      safety of Velusetrag and TD-8954 and confirm that  
21      both compounds have high exposure margins relative  
22      to clinical concentrations associated with GI pro-

1 kinetic activity.

2 The safety margins shown in the right-hand  
3 column for effects of Velusetrag on the hERG  
4 channel, action potential duration in canine  
5 Purkinje fibers, and heart rate are 690, 40, and  
6 280-fold, respectively. The safety margins for the  
7 metabolites, THRX-830449, are also large.

8 This metabolite, which is a near identical  
9 pharmacological profile to Velusetrag, is generated  
10 by CYP3A4. In the event that concomitant medicines  
11 impair CYP3A4 mediated metabolism of Velusetrag,  
12 there should be no net impact on the overall  
13 pharmacological activity. TD-8954 showed similar  
14 results.

15 The margins for effects of TD-8954 on the  
16 hERG channel, action potential duration, and canine  
17 Purkinje fibers, and heart rate, are all greater  
18 than 1,000-fold in terms of pharmacologically  
19 active exposures, but they're associated with  
20 robust GI pro-kinetic activity in humans.

21 A dose of 0.2 milligrams, which is  
22 approximately .003 mgs per kg, is pharmacologically

1 active in humans. A dose of .67 mgs per kg cited  
2 in the FDA briefing document was based on a  
3 proposed testing of a maximal dose of  
4 40 milligrams. This dose, which is more than  
5 200-fold greater than the pharmacologically active  
6 dose, wasn't reached in the course of the phase 1  
7 studies, as maximal GI pro-kinetic activity was  
8 noted at much lower doses.

9 The studies demonstrate the differentiation  
10 of the new class of highly selective 5-HT4  
11 agonists, Velusetrag and TD-8954, from the non-  
12 selective early generation 5-HT modulators,  
13 cisapride and tegaserod. The high selectivity of  
14 Velusetrag and TD-8954 for the 5-HT4 receptor means  
15 that at therapeutic doses, there is no engagement  
16 of other potentially problematic 5-HT receptors.

17 Neither compound affects hERG currents at  
18 clinically relevant concentrations. Similarly,  
19 there were no findings with Velusetrag and TD-8954  
20 to suggest a risk for coronary artery constriction.  
21 Moreover, neither Velusetrag nor its active  
22 metabolite increased platelet aggregation. There

1 were no findings in the preclinical program to  
2 suggest a cardiovascular risk to patients.

3 Velusetrag and TD-8954 are members of the  
4 new class of highly selective 5-HT4 agonists.  
5 Because they're clearly differentiated from the  
6 early generation compounds, members of this new  
7 class should be assessed on their own merits.

8 Velusetrag and TD-8954 have the potential to  
9 address the unmet medical need for the treatment of  
10 serious functional GI motility disorders. Their  
11 preclinical properties, that is, their high 5-HT4  
12 receptor selectivity and lack of significant  
13 cardiovascular findings, suggest that the new class  
14 of selective 5-HT4 receptor agonists should not be  
15 associated with significant cardiovascular risk in  
16 humans.

17 In addition, the high selectivity and  
18 potency have the potential to translate into  
19 greater efficacy for patients. Regardless of the  
20 specific diagnosis, patients with severe disability  
21 due to their GI motility disorder, who don't  
22 respond to available therapies, need additional

1 therapeutic options. Velusetrag and TD-8954 have  
2 the potential to offer a more efficacious and safer  
3 therapy for these patients than previous  
4 treatments.

5 Thank you.

6 **Questions from the Committee**

7 DR. RAUFMAN: Thank you. Please stay at the  
8 podium. We'll now ask if the committee has any  
9 questions regarding this presentation.

10 Dr. Lauer?

11 DR. LAUER: Thank you. I'm going to echo  
12 Dr. Teerlink's earlier question. The studies that  
13 you did on isolated coronary arteries, dog, porcine  
14 and human, were those normal coronary arteries or  
15 were those atherosclerotic arteries? Were those  
16 from young individuals or old individuals? And in  
17 the case of the animal studies, did those also  
18 include animals that had been fed atherosclerotic  
19 diets?

20 DR. BEATTIE: In terms of the human coronary  
21 artery experiments -- and I can't remember the age  
22 of the particular donors -- those tissues were

1 visually healthy. However, there were  
2 atherosclerotic regions in other parts of the  
3 coronary artery, but they were visually healthy.  
4 And dogs and pigs were not treated. There were  
5 normal dogs and pigs used in those studies.

6 DR. LAUER: Thank you.

7 DR. BEATTIE: I should just add there is one  
8 published study with tegaserod demonstrating a  
9 small effect of tegaserod in human coronary  
10 arteries, and they've looked at both  
11 atherosclerotic and otherwise normal vessels and  
12 seen no apparent difference between the two.

13 DR. RAUFMAN: Dr. Kaul?

14 DR. KAUL: Yes. I have a question regarding  
15 the platelet aggregation responses. Did you study  
16 the whole spectrum of agonists, particularly  
17 collagen and thrombin, which are more naturally  
18 circulating at platelet agonists? And did you also  
19 test a higher dose of ADP, which is conventional  
20 20 micromolar?

21 Also, did you study platelets derived from  
22 individuals that are deemed to be at higher risk,

1 such as smokers, diabetic, hyperlipidemia,  
2 hypertensive individuals?

3 DR. BEATTIE: No, we did not study those  
4 subjects. These were healthy subjects in the  
5 studies. We only looked at ADP alone and in  
6 combination with 5-HT. I believe, based on the FDA  
7 briefing document, naronapride, the RX compound was  
8 tested using collagen as a stimulus and, again,  
9 found to have no effect. Naronapride, like  
10 Velusetrag and TD-8954, is a selective 5-HT4  
11 agonist.

12 DR. RAUFMAN: Dr. Teerlink?

13 DR. TEERLINK: So three sections. One is to  
14 just follow-up on Dr. Kaul's comment. I think one  
15 of the messages -- the whole purpose of this  
16 meeting is to try to get sponsors to get  
17 information to go forward. And I think one of the  
18 things is that, clearly, in terms of evaluating  
19 cardiovascular safety, if we're going to have any  
20 sense of what the preclinical studies do, the  
21 broader approach you can use in the preclinical  
22 studies, such as using collagen and other types of

1 stimulants for platelet aggregation studies would  
2 be highly recommended.

3           The second thing. In terms of the increased  
4 heart rate and blood pressure aspects, I think if  
5 we're going to be later on asked to kind of put  
6 those data into some kind of perspective and say  
7 whether they do or do not represent some kind of  
8 risk, I think it would be useful to see a little  
9 bit more of those data and also hear a bit about  
10 what you think the mechanism might be. And you may  
11 or may not be able to address that.

12           Then the final thing is about a thorough QT  
13 study, whether that has been done and completed  
14 yet, and, if so, what are the results of that. And  
15 if it's done, it would be also useful to have that  
16 information for us to give advice in terms of how  
17 to proceed with the program.

18           DR. BEATTIE: I think I can probably address  
19 your penultimate question. Looking at tegaserod's  
20 ischemic event, it's unclear if there is a  
21 mechanism that can be identified, and that's partly  
22 because tegaserod does hit a number of different

1 5-HT receptors. So actually honing in on a  
2 mechanism that may be relevant is challenging.

3 In terms of its activity at other 5-HT  
4 receptors, other non-5-HT4 receptors, tegaserod  
5 does have some 5-HT1B activity.

6 DR. TEERLINK: I wasn't asking about  
7 tegaserod.

8 DR. BEATTIE: Oh, sorry.

9 DR. TEERLINK: I'm asking about Velusetrag.

10 DR. BEATTIE: Okay. Sorry.

11 DR. TEERLINK: The drug you're presenting,  
12 right?

13 DR. BEATTIE: Sorry. Yes.

14 DR. TEERLINK: I thought that. Okay.

15 So the questions were, you showed an  
16 increase in heart rate and blood pressure with that  
17 agent. It's been suggested already that that's an  
18 early marker perhaps of cardiovascular risk.

19 If we're going to try to give you advice in  
20 terms of how to proceed in a clinical development  
21 program based on your preclinical data, it's  
22 probably useful for us to see the extent to which

1 there are heart rate and blood pressure increases  
2 with Velusetrag and its other thing.

3 The other question was related to  
4 Velusetrag, which was a thorough QT study done with  
5 Velusetrag and its metabolite or any of those  
6 things?

7 DR. COLEMAN: Thank you. I'm Becky Coleman.  
8 I'm the head of regulatory and quality at  
9 Theravance. We have a couple other people with us  
10 today, and they will speak to the questions  
11 regarding our clinical study program to date.

12 Dr. Mammen?

13 DR. MAMMEN: My name is Mathai Mammen. So  
14 on the thorough QT study, we have completed a  
15 thorough QT study with Velusetrag, but not yet with  
16 TD-8954, and we're happy to report that we have not  
17 seen any significant prolongation of the QT  
18 interval in that study; and that we feel is  
19 consistent with some of the data that my colleague,  
20 David Beattie, presented on the high margin for  
21 hERG and the Purkinje fiber studies, as well as the  
22 dog cardiovascular study.

1           That was your third question. You had a  
2 second question, though, on --

3           DR. TEERLINK: The second question was on  
4 the preclinical studies in terms of the heart rate.  
5 So just to add to that thorough QT, if you throw  
6 that out in front of us, that's great, but it's  
7 also useful to actually see the data.

8           DR. MAMMEN: So I think we agreed with FDA  
9 prior to this meeting that we can speak  
10 definitively to our nonclinical/preclinical work.  
11 The clinical studies right now, we plan on publicly  
12 discussing them in the future when the program  
13 evolves a bit. However, we want to be helpful, and  
14 we're trying to provide any top line results we  
15 can.

16           DR. TEERLINK: Fantastic. And I respect  
17 that, and I am not trying to imply any attempt on  
18 your part to hide things. It's just if it's there,  
19 it's useful for us to see it.

20           DR. RAUFMAN: Dr. Thadani?

21           DR. THADANI: You showed some data regarding  
22 the -- sorry. Go ahead.

1 DR. RAUFMAN: I didn't mean to cut you off.

2 DR. CONNER: It's Mike Conner, nonclinical  
3 safety assessment at Theravance. I just wanted to  
4 answer Dr. Teerlink's other question regarding the  
5 nonclinical data.

6 No specific slide was shown for that because  
7 of the table that was included in the FDA's package  
8 showing the heart rate and blood pressure effects  
9 at the 10, 30 and 100 milligram per kilogram dose  
10 levels for TD-8954, and those are exposures that  
11 range up to -- the 30 milligrams per kilogram, for  
12 instance, is 5,000-fold the clinical Cmax in  
13 patients receiving a pro-kinetic dose. So we  
14 didn't provide additional data showing that. Up to  
15 3 milligrams per kilogram, which is 500-fold the  
16 clinical exposure, there are no effects on heart  
17 rate or blood pressure.

18 DR. TEERLINK: And I saw that for the  
19 TD-8954, and I appreciate that. My question was in  
20 regard to Velusetrag again. That was all.

21 DR. RAUFMAN: Dr. Thadani?

22 DR. THADANI: We saw earlier data that the

1 platelet reactivity and aggregation is such a  
2 complex process. One investigator produced -- FDA  
3 showed data there was effect, and a second study, a  
4 recent trial, showed no effect.

5 I'm surprised you didn't put in your  
6 database -- you did not put a comparator which has  
7 been shown to affect platelet reactivity like  
8 tegaserod, which has adverse events. It would be  
9 nice to know that your methodology shows the effect  
10 on that, although you selected a more potent agent  
11 to show that.

12 Question one to you. Now, since the drugs  
13 are more selective on 5-HT4 receptor and you're  
14 saying others may not be relevant, but we know the  
15 other receptors can produce relaxation, especially  
16 the seven, which may be relevant, have you any data  
17 in your animal model on the transit colonic time,  
18 motility, from point A to point B -- you could tag  
19 it, and I don't know how you'd do that -- to show  
20 that your agent, because of selectivity, is better  
21 than the older agents which have other  
22 cardiovascular negative effects?

1 DR. BEATTIE: Yes. To answer your second  
2 question first, we have data from a guinea pig  
3 colonic transit model, again, suggesting that with  
4 selective 5-HT4 agonists, you do see a more robust  
5 response compared to an agent like tegaserod.

6 DR. THADANI: How robust? Because you're  
7 saying that patients -- you show very small data  
8 that patients who can't pass bowels every four  
9 weeks now can do it maybe twice a week.

10 So in terms of that, how strong is the  
11 response on colonic?

12 DR. BEATTIE: Pre-clinically, there is a  
13 robust response with Velusetrag and TD-8954 that is  
14 clearly more potent and has a higher efficacy than  
15 tegaserod.

16 DR. THADANI: Okay. So if it's more potent,  
17 is there a possibility, by increasing the  
18 contraction, you can actually produce more ischemic  
19 colitis because of the constriction? I'm just  
20 curious; some noise again in the other studies.

21 DR. BEATTIE: Again, our clinical experience  
22 with Velusetrag or 8954 is extremely limited at

1 this stage, and there has certainly been no report  
2 of ischemic colitis during the clinical program.

3 To address your first question regarding the  
4 platelet aggregation, the second study presented by  
5 the FDA was actually a Theravance study. We've  
6 since repeated that study, and, again, we find no  
7 effect of tegaserod up to tenfold higher than its  
8 clinical Cmax. We used thrombopoietin as a  
9 positive control, and thrombopoietin clearly  
10 increased platelet aggregation as expected.

11 DR. THADANI: So you think the previous  
12 studies reported are spurious because the  
13 methodology is so tricky, it depends which agent  
14 you use and all that?

15 DR. BEATTIE: I can't explain the  
16 discrepancy.

17 DR. RAUFMAN: Dr. Shen?

18 DR. SHEN: Just curious. Its efficacy.  
19 Relative potency compared to tegaserod or the  
20 cisapride -- relative affinity, your drug to the  
21 other two.

22 DR. BEATTIE: Yes. If you look at the 5-HT4

1 receptor isolated in a cell line, then tegaserod is  
2 a high affinity 5-HT4 receptor ligand -- it's  
3 similar affinity with TD-8954 and probably higher  
4 affinity than Velusetrag -- when you go to  
5 functional models, assays, then it's harder to  
6 interpret tegaserod data. In an isolated 5-HT4  
7 preparation, usually a cell-based assay, tegaserod  
8 can have full agonist activity or partial agonist  
9 activity. It depends very much on the system.

10 Of course, when you go to tissue or the  
11 whole animal, then you have the complication of  
12 other receptors, other mechanisms that potentially  
13 counteract the 5-HT4 mechanism, because tegaserod  
14 is hitting lots of other things.

15 DR. SHEN: What about in vitro data you  
16 already showed to the other serotonin receptors?  
17 What about 5-HT4? Do we have the data on that  
18 relative affinity?

19 DR. BEATTIE: Yes. In terms of 5-HT4  
20 receptor in an isolated cell system, tegaserod has  
21 high 5-HT4 receptor affinity.

22 DR. SHEN: The ratio, how much? You already

1 had a number for the other receptors. Do we have a  
2 ratio for that?

3 DR. BEATTIE: TD-8954 is approximately three  
4 to fivefold higher affinity than tegaserod.  
5 Tegaserod is approximately five to six-fold higher  
6 affinity than Velusetrag. Again, that's in the  
7 isolated receptor.

8 DR. RAUFMAN: Dr. Kaltman?

9 DR. KALTMAN: Thank you. I note here that  
10 Velusetrag's cardiovascular margin is smallest for  
11 increasing action potential duration. Do you have  
12 any thoughts on the potential mechanism there, and  
13 have you tested it for its inhibition of other  
14 cardiac ion channels?

15 DR. BEATTIE: I can perhaps address the  
16 second part of that question. We have tested a  
17 number of different potassium, sodium and calcium  
18 channels that are expressed in the cardiovascular  
19 system, and, again, there's a very high margin  
20 relative to affinities for those channels.

21 DR. RAUFMAN: Dr. Bloom?

22 DR. BLOOM: Yes. Going back to the platelet

1 aggregation in terms of suggestions for making this  
2 more robust, when there's such high expectations of  
3 this rather insensitive marker for the thrombogenic  
4 potential, it may be supplemented with ex vivo  
5 observations from animals and patients, where drug  
6 levels are established. It would complement  
7 nicely, much as we do as a pharmacokinetic marker  
8 for clopidogrel and things like that.

9 DR. RAUFMAN: Dr. Greene?

10 DR. GREENE: It's a privilege to be able to  
11 see these studies at this early phase. I  
12 appreciated the first slide, which talked about the  
13 severe patients and the impact on quality of life,  
14 and I'm just going to give you a little insight  
15 into unmet need from the Pacific Northwest.

16 These patients with severe motility  
17 disorders tend to be orphan patients. It's unusual  
18 for gastroenterologists to end up in a long-term  
19 relationship with such a patient, and they  
20 frequently get referred to larger centers or to  
21 other gastroenterologists.

22 In our group, we have one such person who is

1 interested and mentally stable enough to take care  
2 of these patients, and he has individually seen 480  
3 new referrals in the last two years. These are  
4 patients with severe gastroparesis or colonic  
5 inertia, very difficult to take care of when they  
6 fail metoclopramide. Some of them get domperidone  
7 from Canada or from compounding pharmacies. Two  
8 hundred-fifty patients have had gastric pacemakers  
9 inserted at 30 to \$40,000 each. An unknown number  
10 have had near total colectomies for severe colonic  
11 inertia.

12 There is a major need out there, and I  
13 appreciate seeing this data now.

14 DR. RAUFMAN: Thank you for those comments.

15 Dr. Bild?

16 DR. BILD: So in considering the  
17 cardiovascular safety of these drugs, it should be  
18 in the context of the efficacy for the conditions  
19 that they're being treated for. And there was  
20 interesting information presented on treating  
21 constipation.

22 Have more clinical efficacy studies been

1 done for the different conditions, including  
2 gastroparesis, that can be presented? I'm a little  
3 bit struck by the fact that we haven't been given  
4 that kind of information.

5 DR. COLEMAN: The only study we've conducted  
6 has been in chronic constipation. At this point,  
7 we're just initiating our efficacy studies with  
8 these compounds.

9 DR. RAUFMAN: Dr. Korvick?

10 DR. KORVICK: I think you point out the very  
11 important, again, unmet medical need. As those of  
12 you who were at the advisory committee yesterday  
13 realize, developing drugs for irritable bowel  
14 syndrome is very difficult, and endpoints are  
15 perhaps not very robust, and we're going under a  
16 process of trying to do those, or symptom-driven  
17 kind of, you could say, general/non-specific, in a  
18 way. And so we're improving those.

19 As we mentioned earlier, for the deltas that  
20 we saw for cisapride or Zelnorm that were put in  
21 the label for IBS, the deltas were around 10 to  
22 15 percent, even for Lotronex. And in those

1 patients, there is a large placebo effect.

2 So, as well, for some of the other drugs,  
3 it's even more difficult because of the overlay of  
4 a lot of disease to study gastroparesis. And then  
5 as my colleague here, Dr. Greene, just mentioned,  
6 these are patients that are floating around there  
7 that get to different places and not an orphan in  
8 the sense that they are perhaps small numbers of  
9 patients, because diabetic gastroparesis is pretty  
10 large, but these kind of studies are difficult to  
11 design and difficult to conduct. And previous  
12 efforts at doing so for domperidone and other  
13 products have not been, what we might say, 21st  
14 century kind of studies because of the nature of  
15 the endpoints and the assessments needed.

16 So we're trying to work with researchers,  
17 et cetera, to get a better handle on this, and we  
18 try to encourage drug companies to study those very  
19 important patient groups where the need is unmet at  
20 this point.

21 DR. RAUFMAN: We'll move on. Thank you.

22 We'll proceed with the FDA's presentations

1 on naronapride.

2 **FDA Presentation - Sushanta Chakder**

3 DR. CHAKDER: Good morning. My name is  
4 Sushanta Chakder, and I'm the pharmacologist at  
5 FDA, Division of Gastroenterology and Inborn  
6 Errors. And I will summarize the nonclinical  
7 safety data with naronapride. Naronapride is also  
8 known as ATI-7505, and so I will use both  
9 naronapride and ATI-7505 interchangeably in my  
10 presentation.

11 Naronapride is a 5-HT<sub>4</sub> receptor agonist and  
12 a structural analog of cisapride. Naronapride is a  
13 more potent and more selective 5-HT<sub>4</sub> receptor  
14 agonist than cisapride, and it is hydrolyzed to an  
15 active metabolite called ATI-7500 by plasma and  
16 tissue esterases.

17 This slide shows the binding affinities for  
18 naronapride and its metabolite, cisapride and  
19 norcisapride on 5-HT<sub>4</sub>, 5-HT<sub>3</sub>, 5-HT<sub>2B</sub>, and dopamine  
20 D<sub>2L</sub> and D<sub>2S</sub> receptors.

21 As shown here, naronapride had very high  
22 binding affinities with a carry value of

1 1.39 nanomolar, while cisapride and a carry value  
2 of 150 nanomolar. This indicates that naronapride  
3 is about 100 times more potent than cisapride on  
4 5-HT4 receptor binding. The metabolite had very  
5 low binding affinities for 5-HT4 receptors and  
6 negligible binding affinities for other receptors.  
7 Naronapride had more direct binding affinities for  
8 5-HT2B receptors and dopamine D2L receptors, and it  
9 has significant binding affinities for D2S  
10 receptors. You may ask why they used binding for  
11 dopamine D2 receptors. As you know, dopamine D2  
12 receptor antagonism is important for pro-mortality  
13 effects.

14 In addition, the sponsor also examined the  
15 binding potencies for naronapride, its metabolite,  
16 and cisapride for different L-type calcium  
17 channels, sodium channel, and potassium channel.

18 As shown in the first column, naronapride  
19 had low binding potencies for these receptors.  
20 Here the numbers are lower. The binding potency is  
21 lower. And cisapride had significant binding  
22 potencies for all L-type calcium channels and

1 sodium channels.

2 So to summarize the binding data,  
3 naronapride had high binding affinity for 5-HT<sub>4</sub>  
4 receptors. The metabolite had low or minimal  
5 affinity for the 5-HT receptors. Naronapride had  
6 moderate affinities for 5-HT<sub>2B</sub> receptors and very  
7 low affinities for 5-HT<sub>3</sub> receptors. Naronapride  
8 and its metabolite had low or no binding affinities  
9 for L-type calcium, potassium or sodium channels.

10 These are the studies conducted to exhibit  
11 the cardiac safety of naronapride. The effects of  
12 naronapride on high potassium channels were  
13 examined in HEK29 cells. In addition, the effects  
14 on non-*I*Kr cardiac channels are examined in guinea  
15 pig myocyte. And electrophysiological studies were  
16 conducted in isolated guinea pig heart. And action  
17 potential duration was examined in rabbit Purkinje  
18 fibers. In addition, cardiac safety studies,  
19 including ECGs, are examined in anesthetized dogs  
20 and anesthetized guinea pigs following intravenous  
21 administration of naronapride.

22 This slide shows that cisapride and ATI-7505

1 and ATI-7500 caused inhibition of heart potassium  
2 current. However, as you can see from these  
3 graphs, naronapride was more than 2,000 times less  
4 potent than cisapride, inhibiting the heart  
5 current.

6 This slide shows the IC50 values for  
7 inhibition of heart potassium currents by  
8 naronapride, its metabolite, cisapride, and  
9 norcisapride. As shown here, cisapride was a  
10 potent inhibitor of high potassium current in this  
11 study, and naronapride had an IC50 value of 24,521  
12 nanomolar. And this concentration is more than a  
13 thousand-fold higher than the clinical  
14 concentration, plasma concentrations, observed at  
15 the proposed clinical dose of 80 milligram BID.

16 So that's ATI-7505 and ATI-7500 caused  
17 concentrations and inhibition of heart potassium  
18 currents. However, ATI-7505 was about 2600-fold  
19 less potent than cisapride, and the metabolite was  
20 even less potent, and it was about 21,000-fold less  
21 potent than cisapride.

22 This slide shows the effects of ATI-7505,

1 its metabolite, and cisapride on non-IKr cardiac  
2 potassium channels. The channels examined are  
3 early sodium, late sodium, late L-type calcium, and  
4 slow potassium, and inward rectifying potassium  
5 channels. As shown here, ATI-7505 had very low or  
6 low effect on non-IKr channels. Cisapride was  
7 tested only for its effect on the sodium channels,  
8 and IC50 was very high. It was 11,400 nanomolar.

9 This is the graphical presentation of the  
10 effect of ATI-7505 and ATI-7500 on L-type potassium  
11 channels and slow potassium channels. As you can  
12 see here, the positive control, verapamil, caused  
13 dose-dependent inhibition of L-type calcium  
14 channels, and naronapride or its metabolite had  
15 very low effect. It's not significant. Similar  
16 data was obtained on the IKs.

17 In guinea pig isolated hERG, cisapride at a  
18 concentration of 1,000 nanomolar, that means  
19 1 micromolar -- caused about 9 -- 10 percent  
20 prolongation of QT interval. And ATI at the same  
21 concentration didn't have any effect. However, at  
22 10,000 nanomolar, it caused a very small increase

1 in the QT intervals. ATI-7505 had also some  
2 effects on the SA intervals and HB intervals.

3 This slide shows the effect of ATI-7505, its  
4 metabolite, and cisapride on action potential  
5 division in rabbit Purkinje fibers. As shown here,  
6 ATI-7505 had very small effects up to a  
7 concentration of 1,000 nanomolar, and these were  
8 not significant.

9 The metabolite had similar effects. The  
10 positive control, sotalol, was significant,  
11 increase in action potential duration. And  
12 cisapride 10 nanomolar had no effect. However,  
13 100 nanomolar caused significant increase in action  
14 potential duration. The effect of naronapride was  
15 more prominent at .2 hertz stimulation frequency.  
16 That may make bradycardia.

17 So, in summary, ATI-7505 and ATI-7500 had no  
18 effect on early and late sodium currents. ATI-7505  
19 had no effect on L-type calcium channels. ATI-7500  
20 caused a small inhibition at high concentrations.  
21 Both ATI-7505 and ATI-7500 had weak effects on IKs.  
22 In isolated guinea pig heart, ATI-7505 caused a

1 slight increase in QT intervals. In rabbit  
2 Purkinje fibers, ATI-7505 prolonged ATP [sic] at  
3 0.2 hertz stimulation. This concentration, 1,000  
4 nanomolar concentration is about 45 times the human  
5 plasma concentrations at the clinical dose.

6 In anesthetized dogs, intravenous doses of  
7 .1, .3, 1 and 2 milligram per kilogram were used,  
8 and I'm showing here the effect of 1 milligram per  
9 kilogram and 2 milligram per kilogram. The lower  
10 doses didn't have any effect.

11 As shown here, 1 milligram per kilogram dose  
12 caused about a, say, 15 millisecond increase in QTC  
13 at five minutes after dosing. And the higher dose,  
14 the 2 milligram per kilogram, caused the similar  
15 effects at five minutes and 10 minutes after  
16 dosing.

17 This slide shows the effects of ATI-7505 and  
18 its metabolite on the QTC anesthetized guinea pig,  
19 and the effect is also compared with cisapride.  
20 Cisapride was used at .3 milligram per kilogram and  
21 1 milligram per kilogram doses. At .3 milligram  
22 per kilogram doses, there was no significant effect

1 on QTC. However, at 1 milligram per kilogram, it  
2 caused an increase in QTC at all time points  
3 measured.

4 ATI-7505 at .3 and 1 milligram per kilogram  
5 had no significant effect. However, at a 3  
6 milligram per kilogram dose, ATI-7505 caused a  
7 significant prolongation of QTC at three minutes  
8 and that lasted up to five minutes after dosing.

9 To summarize, ATI-7505 is a selective 5-HT4  
10 receptor agonist with moderate to low affinities  
11 for 5-HT3 and 5-HT2B receptors. ATI-7505 caused an  
12 inhibition of heart potassium current. However,  
13 ATI-7505 was about 2600-fold less potent than  
14 cisapride. In isolated guinea pig heart, ATI-7505  
15 caused a slight increase in QT intervals. In  
16 rabbit Purkinje fibers, it caused a slight increase  
17 in action potential duration. In anesthetized dogs  
18 and anesthetized guinea pigs, intravenous ATI-7505  
19 caused a small transient increase in QTC.

20 Data not shown here, no QT prolongation was  
21 observed in the nine-month chronic toxicity studies  
22 in dogs at 3 and 10 milligram per kilogram doses.

1           Thank you. Now, Dr. Kim will present the  
2 clinical pharmacology data for naronapride.

3                           **FDA Presentation - Insook Kim**

4           DR. KIM: Hello again. I'm a clinical  
5 pharmacology reviewer for naronapride, and I'm  
6 going to talk about what we know about naronapride  
7 from a clinical pharmacology standpoint based on  
8 the data available to us at this point.

9           So I'm going to talk about the  
10 pharmacokinetic characteristics of naronapride,  
11 again, focused on the metabolic pathway of  
12 naronapride and the drug-drug interaction  
13 potential. And, also, I'm going to discuss the  
14 results of the thorough QT study done with  
15 naronapride and the results of the study -- the  
16 effect of naronapride on platelet aggregation in  
17 vitro.

18           So naronapride, which is also called  
19 ATI-7505, is a structural analog of cisapride. It  
20 has a different side chain, which has ester bond,  
21 and while naronapride is also subject to a CYP-  
22 mediated -- CYP enzyme-mediated metabolism, to a

1 certain degree, majorly because of this ester bond  
2 here, this is subject to hydrolysis by esterases,  
3 which in turn formed a major metabolite.

4 This is scheme of the proposed metabolic  
5 pathway of naronapride. So naronapride undergoes  
6 esterase hydrolysis, which is the major metabolic  
7 pathway, to produce ATI-7500, and then ATI-7500  
8 further undergoes metabolism by oxidation to form a  
9 secondary metabolite, ATI-7400, subsequently ATI-  
10 7100.

11 Esterase hydrolysis also produced a  
12 byproduct from the side chain of the naronapride,  
13 which is quinuclidinol. Naronapride also undergoes  
14 the CYP-mediated metabolism to produce  
15 norcisapride, which is a common metabolite from the  
16 cisapride, as well. But then norcisapride was not  
17 detectable in plasma, but detectable only in urine.

18 So this is the plasma concentration time  
19 profile. After a single dose of naronapride at  
20 120 milligrams, as you can see, upon oral  
21 administration, naronapride gets absorbed quickly  
22 to reach its peak plasma concentration in about one

1 or two hours later. Similarly, the metabolite also  
2 reaches peak plasma concentration in about two  
3 hours after dose.

4 Notably, the plasma concentration to major  
5 metabolites from the ester hydrolysis pathway are  
6 significantly higher than that of naronapride, as  
7 you can see. Also, the systemic exposure to the  
8 byproduct from the ester hydrolysis is also very  
9 high, as you can see from here. And at this point,  
10 activity is unknown for several metabolites, such  
11 as ATI-7400, ATI-7100, and hydrolysis by-product.

12 So to just briefly summarize, naronapride  
13 gets absorbed pretty rapidly, reaching its peak  
14 plasma concentration one or two hours later, and it  
15 exhibits nonlinear PK characteristics, meaning when  
16 you increase the dose by twofold, systemic exposure  
17 increases more than twofold, about fourfold, over  
18 the dose range 40 milligrams to 200 milligrams.

19 Naronapride is mainly eliminated by  
20 metabolism. Major metabolic pathways considered to  
21 be ester hydrolysis by esterases, and a higher  
22 systemic exposure to major metabolites from that

1 major metabolic pathway was noted.

2 As a minor metabolic pathway, CYP enzymes  
3 are also involved in the metabolism of naronapride.  
4 However, the metabolite formed by CYP enzymes,  
5 including norcisapride, are only detectable in  
6 urine. In vitro studies suggest that naronapride  
7 is a substrate of P-glycoprotein efflux  
8 transporter.

9 So, based on the data and information  
10 currently available to us, it seems that in vivo  
11 drug-drug interaction potential of the concomitant  
12 CYP enzyme inhibitors seems to be low, although no  
13 in vivo drug-drug interaction studies have been  
14 conducted yet, based on this metabolism pathway in  
15 humans.

16 However, naronapride's systemic exposure may  
17 be increased with concomitant P-gp inhibitors, such  
18 as quinidine or verapamil or cyclosporines. And  
19 there have been no studies done to evaluate the  
20 effect of organ impairment, such as hepatic or  
21 renal impairment, on the PK of naronapride yet.  
22 Because of that, naronapride exposure may increase

1 in patients with organ impairment, such as hepatic  
2 impairment. The possibility cannot be completely  
3 ruled out at this point.

4 So now I'm going to discuss the study  
5 results of the thorough QT study. The sponsor  
6 conducted a thorough QT study for naronapride. The  
7 study was single-center, randomized, double-blind,  
8 double-dummy, placebo-controlled, parallel group  
9 study in healthy male and female volunteers. About  
10 250 volunteers were enrolled for this study.  
11 Single-dose moxifloxacin at 400 milligram was used  
12 as a positive control, and multiple doses of  
13 placebo were used as a negative control.

14 The effect of naronapride on QT prolongation  
15 was studied at two dose levels, 40 milligrams,  
16 200 milligrams, given every six hours for seven  
17 days. Of note, at the time of the design of this  
18 thorough QT study, 40 milligrams QID doses, every  
19 six-hour dosing, was the proposed therapeutic dose,  
20 and the 200 milligram dose was chosen as a  
21 therapeutic dose. And each arm has about 70 to 60  
22 patients, subjects.

1           In results, there is no significant QT  
2 prolongation effect in this thorough QT study  
3 noted. The study was reviewed by the QT review  
4 team at FDA and found to be adequately conducted.

5           The sensitivity of the study was established  
6 based on the largest lower bound of 90 percent  
7 confidence interval for double-delta of QTcI.  
8 Individually corrected QT changed from baseline and  
9 the difference between placebo and the treatment  
10 group. The largest lower bound was found to be  
11 greater than 5 milliseconds, so that established  
12 the sensitivity of the study; whereas the negative  
13 effect of the naronapride on QT prolongation was  
14 concluded, based on the largest upper bound of 90  
15 percent confidence interval for double-delta QTcI  
16 which was less than 10 milliseconds. So our QT  
17 review team at FDA concluded that there was no  
18 significance effect of naronapride on QT  
19 prolongation.

20           Since the conduct of this thorough QT study,  
21 the proposed therapeutic dose was changed from  
22 40 milligrams QID to 80 milligram BID. So we

1 evaluated whether the systemic exposure provided by  
2 the therapeutic dose in the thorough QT study was  
3 adequately covering the expected plasma  
4 concentration from the proposed 80 milligram BID  
5 dosing regimen.

6 So just of note, this PK study was obtained  
7 from a separate study. But given the fact that  
8 this is a cross-study comparison and the nonlinear  
9 PK characteristics of naronapride, still we thought  
10 the mean peak Cmax of the suprathapeutic dose,  
11 which was 200 milligrams, still sufficiently  
12 covered the expected plasma concentration from the  
13 proposed 80 milligram BID, about like a three to  
14 fivefold margin.

15 So, again, I'm going to switch gears to the  
16 effect of naronapride on platelet aggregation in  
17 vitro.

18 Similarly, in studies, the effect of the  
19 naronapride on platelet aggregation was studied  
20 using standard light transmission aggregometry.  
21 Blood was collected from healthy volunteers Three  
22 concentrations of naronapride were used, 10

1 nanogram per ml, 30 milligram per ml, and 100  
2 nanogram per ml, and 10 nanogram per ml was close  
3 to the expected plasma concentration in humans.

4 In one set of the experiments, an esterase  
5 inhibitor was used to prevent hydrolysis of  
6 naronapride to produce this ATI-7500. And collagen  
7 was used as an agonist to induce platelet  
8 aggregation.

9 In results, we did not see any significant  
10 effect of naronapride on platelet aggregation under  
11 this experiment condition. However, the study  
12 design does not allow to address any potential  
13 effect of the metabolites, which, as you saw, had  
14 substantially higher systemic exposure in humans.

15 So to summarize, naronapride exhibited  
16 nonlinear PK over 40 to 200 milligram dose range.  
17 Hydrolysis by esterases is a major metabolic  
18 pathway that results in higher systemic exposure to  
19 major metabolites, such as ATI-7500 than  
20 naronapride itself. Activities are known for some  
21 metabolites, such as ATI-7400 and ATI-7100 and the  
22 byproduct of the hydrolysis.

1           As for the drug-drug interaction potential,  
2 based on the metabolic pathway in humans, the CYP  
3 enzyme-mediated drug interaction potential seemed  
4 to be low at this point. However, potentially,  
5 there is a potential drug interaction with the  
6 concomitant P-gp inhibitors.

7           As for the cardiac safety studies, there is  
8 no evidence of QT prolongation by naronapride up to  
9 200 milligram QID, every six hours. And the  
10 proposed dosage regimen for phase 3 trials is up to  
11 80 milligrams twice daily. And no effect of  
12 naronapride on platelet aggregation in vitro was  
13 observed; however, the study does not address the  
14 potential effect of metabolites on platelet  
15 aggregation.

16           So with this, Dr. Johnson will continue.

17           **FDA Presentation - Aisha Peterson Johnson**

18           DR. PETERSON JOHNSON: Hello again. So  
19 during this presentation, I'll discuss the clinical  
20 information that we have currently about  
21 naronapride.

22           I'll begin by talking about the completed

1 phase 2 studies. So the sponsor of naronapride  
2 completed a phase 2 study, which I'll refer to as  
3 Protocol 711, and the design was a phase 2  
4 randomized, double-blind, placebo-controlled, five-  
5 arm study using four dosage groups of naronapride,  
6 20 milligrams, 40 milligrams, 80 milligrams, and  
7 120 milligrams, and a placebo group. The study  
8 enrolled 212 patients and studied the indication of  
9 chronic idiopathic constipation.

10 So I'll briefly go over the efficacy  
11 results. The primary endpoint was the total number  
12 of spontaneous bowel movements during week one and  
13 just as a top-line result, only the 80 milligram  
14 twice daily group achieved a statistically  
15 significant increase in the number of spontaneous  
16 bowel movements when compared to placebo for the  
17 first week of the trial.

18 So I'll go over the top-line safety results.  
19 During this study, there were no deaths and no  
20 cardiovascular adverse events in the naronapride  
21 treatment group and no episodes of bowel  
22 perforation. Going a little bit deeper into the

1 safety results, we see that 27.8 percent of  
2 naronapride patients reported an adverse event  
3 compared with 22 percent of placebo patients, and  
4 the most commonly reported adverse events were  
5 gastrointestinal disorder adverse events reported  
6 by 11.2 percent of naronapride patients and 12.2  
7 percent of placebo patients, the most common of  
8 those events being nausea and abdominal pain.

9 The second most common system order class  
10 was the nervous system disorders, and those were  
11 reported by 6.5 percent of naronapride patients  
12 compared with 4.9 percent of placebo patients, and  
13 the most common preferred term there was headache.

14 Now, I'll move to the proposed phase 3  
15 clinical studies for naronapride. So similar to  
16 the phase 2 study, the sponsor is choosing to focus  
17 on an indication of chronic idiopathic constipation  
18 for the patients to be enrolled, and they're  
19 planning a study with 600 patients, 200 patients  
20 per arm. And they actually plan to do this  
21 Protocol 720 and 721, so they're planning two  
22 identical phase 3 studies.

1           They're planning a three-arm study using  
2           40 milligrams twice daily and 80 milligrams twice  
3           daily, along with a placebo group. And the  
4           treatment duration for this study is planned for 12  
5           weeks.

6           The objective of the study is to assess  
7           efficacy and safety of naronapride in the  
8           treatments of patients with CIC and establish an  
9           optimal dosing regimen. And for their primary  
10          efficacy endpoint, they plan to use a slightly  
11          different endpoint than that used for the phase 2  
12          study, which is complete spontaneous bowel  
13          movement, overall responder analysis.

14          So for inclusion in the study, patients have  
15          to meet Rome III criteria for chronic idiopathic  
16          constipation, and patients will be excluded if they  
17          have significant cardiovascular risks, such as the  
18          presence or suspected presence of unstable coronary  
19          artery diseases, myocardial infarction, stroke, or  
20          transient ischemic attack within six months of  
21          screening.

22          This slide lists the prohibited concomitant

1 medications, not all of them, but selective ones  
2 that we felt were important. And they want to  
3 exclude patients on laxatives or any medications  
4 which might impair bowel transit or which might be  
5 the cause of the patient's constipation, such as  
6 antipsychotics and opiates.

7           During the proposed phase 3 study, the  
8 sponsor is planning to do the following  
9 cardiovascular safety assessments. Blood pressure  
10 and pulse at screening, days 1, 15, 29, 43, 71, and  
11 99. And, basically, I don't think that I mentioned  
12 this before, but for the 12-week study treatment  
13 period, they plan prior to that a two-week run-in  
14 phase where the symptoms of constipation will be  
15 confirmed in patients.

16           So study day 1 would be day 1 of that run-in  
17 period. Study day 15 would actually be the first  
18 day of the treatment period. And so for their  
19 complete physical -- and study day 99 represents  
20 the last day of the treatment period. They plan  
21 complete physical exams at screening and day 99,  
22 and 12-lead ECGs at screening, days 15, 43, 71, and

1 99.

2 As far as cardiovascular adjudication of  
3 events goes, the sponsor is planning to have a  
4 committee comprised of cardiologists, neurologists  
5 and other physicians experienced in the  
6 adjudication of cardiovascular endpoints, and they  
7 plan to establish this committee before the  
8 initiation of the trial. And they also plan to  
9 establish diagnostic criteria for events prior to  
10 the initiation of the trial.

11 These criteria have not yet been delineated,  
12 and we do welcome the committee's comments on what  
13 they feel would be important to be included in this  
14 diagnostic criteria. This committee is going to  
15 blindly review all available clinical data, and  
16 only adjudicated events will be included in the  
17 safety reporting and stats.

18 So, currently, the following events are to  
19 be adjudicated: nonfatal MI; nonfatal ischemic  
20 stroke; cardiovascular death, including sudden  
21 death; acute coronary syndrome; angina not leading  
22 to hospitalization; transient ischemic attack; and

1 hospitalization for coronary revascularization.

2 At this point, that's the proposed phase 3  
3 study for naronapride. But if the FDA requires  
4 additional cardiac risk assessments from ARYx, they  
5 have submitted proposals. They've submitted both  
6 post-approval, if required by the FDA proposals,  
7 and a dedicated cardiovascular safety trial pre-  
8 approval, if required by the FDA.

9 So post-approval, the sponsor, ARYx, is  
10 proposing either a prospective observational cohort  
11 study using health care or insurance databases to  
12 compare the cardiovascular risk of naronapride to a  
13 matched comparator or a prospective patient  
14 registry which investigators show them from a  
15 variety of practice types.

16 If the FDA requires a pre-approval dedicated  
17 safety study, ARYx has included the following  
18 proposal: a randomized, double-blind, placebo-  
19 controlled, parallel design study in patients  
20 greater than 65 years of age. This is their  
21 attempt to enrich the population for cardiovascular  
22 ischemic events.

1           They approximate that 1,000 patients will be  
2 dosed with 80 milligrams twice daily or placebo for  
3 at least one year, with efficacy assessments every  
4 three months, using the same endpoints as the  
5 proposed phase 3 study that I described earlier,  
6 Study 720. They also plan that all cardiovascular  
7 events will be adjudicated by a blinded committee,  
8 as described earlier.

9           During this cardiovascular safety study,  
10 they plan routine chemistry and hematology, vital  
11 signs, ECG, and adverse event monitoring, with  
12 ascertainment characterization and follow-up of all  
13 cardiovascular events. Adjudication by a blinded  
14 committee, I've mentioned. And a data safety  
15 monitoring committee will review all data  
16 periodically for patient welfare.

17           So in summary, to date, approximately 950  
18 patients have been exposed to naronapride, with no  
19 deaths or cardiovascular events seen, and the most  
20 common adverse events, as we saw in that table,  
21 were nausea, diarrhea, and headache. Their Study  
22 720, which is their proposed standard phase 3

1 trial, is planned to have routine cardiac  
2 monitoring, exclusion of patients with significant  
3 risk, and adjudication of cardiovascular events.

4 Thank you.

5 **Questions from the Committee**

6 DR. RAUFMAN: Thank you. We'll now ask if  
7 the committee has any questions for the FDA on  
8 their presentations of naronapride. And I'd like  
9 to start, actually. I have a question.

10 Unless I misunderstood, when Dr. Kim  
11 reviewed the preclinical pharmacology, she showed  
12 us data up to 200 milligrams Q 6 hours, and then I  
13 think we were told that the sponsor then proposed  
14 to use 80 milligrams BID as the treatment dose  
15 based on efficacy. I believe I heard that.

16 I haven't seen any data supporting better  
17 efficacy at 80 milligrams, and I'm wondering  
18 whether they really chose to alter the dose based  
19 on concerns about the QT interval with the higher  
20 dose of drug. Could you clarify that for me?

21 DR. PETERSON JOHNSON: Sure. From what I  
22 understand, from looking at the efficacy results

1 from their phase 2 study, they had those four dose  
2 groups, but only the 80 milligram dose group showed  
3 a statistically significant difference in the  
4 primary endpoint versus placebo.

5 So I'm thinking that's why they chose to  
6 pursue, for their phase 3 study, the 80 milligram,  
7 and just go down one level to the 40 milligram  
8 dose. So they plan two dose groups for phase 3.

9 DR. RAUFMAN: I don't remember  
10 200 milligrams being tested.

11 Dr. Korvick?

12 DR. KORVICK: Dr. Fiorentino?

13 DR. FIORENTINO: Well, just to reiterate,  
14 Dr. Johnson, yes, so they proposed the 80 milligram  
15 dose because in their phase 2 exploratory study,  
16 that's the one at week 1, and an overall responder  
17 analysis was significant relative to placebo, and  
18 the TQT study supported that range.

19 DR. KORVICK: And traditionally, TQT studies  
20 look at high dose of drug to span a dose that's  
21 significantly higher than you might use clinically.

22 DR. PETERSON JOHNSON: Right. So that 200

1 was to test a supratherapeutic dose for their TQT  
2 study. It was never one of their proposed clinical  
3 doses.

4 Correct me if I'm wrong, but their sole  
5 purpose for 200 milligrams was to cover their  
6 margin for their proposed -- what was it, 40 six  
7 times a day or four times a day?

8 DR. FIORENTINO: Right. So they pick a dose  
9 that's much higher so they could say, "Well, if  
10 there's a drug-drug interaction, that raises your  
11 exposure; look, we've covered that with this high  
12 dose."

13 DR. RAUFMAN: Okay. Dr. Lauer?

14 DR. LAUER: Thank you. It's striking that  
15 in the proposed phase 3 trial, they're excluding  
16 patients with cardiovascular disease or at high  
17 risk for cardiovascular disease.

18 What proportion of patients with chronic  
19 idiopathic constipation are either over the age of  
20 65 or have established cardiovascular disease?

21 Does anyone know?

22 DR. RAUFMAN: Can anybody answer the

1 question with data?

2 DR. SPIEGEL: The proportion of patients  
3 over 65? Is that the question?

4 DR. RAUFMAN: Yes, but not anecdotal, but  
5 real data.

6 DR. LAUER: Or diabetes, or type 2 diabetes.

7 DR. RAUFMAN: So that might be an  
8 interesting question to somebody to investigate.

9 Dr. Thadani?

10 DR. THADANI: A couple of questions. You  
11 showed that the most of the interaction is with the  
12 P-gp inhibitor, and yet I didn't see any  
13 interaction data either in the animals or human  
14 subjects, or exposing them to exposing verapamil  
15 combinations. So that's one point.

16 Now, I'm actually puzzled, surprised to see  
17 that the efficacy is only shown on one week. CIC  
18 is a long-term, life-term disease. In the phase 2  
19 study, did they just do a one-week study or the  
20 data doesn't look as good on two, four, six, eight  
21 weeks, because a lot of patients initially get some  
22 effect on placebo or the drug, and with time, the

1 effect dissipates.

2 So I'm surprised that they're embarking on  
3 just one-week data and going on to, again, the  
4 study for -- to me, 12 weeks is a pretty short  
5 study, even in the phase 3 study. And excluding  
6 all the high risk patients, you want approval,  
7 without coordinating (indiscernible ??) the  
8 previous experience, why the FDA withdrew one of  
9 the drugs as a parent drug.

10 So I'm really puzzled. A, is there any data  
11 on the phase 2 study looking at four weeks, eight  
12 weeks, that effect persists or dissipates, or  
13 placebo effect is 20 percent? And this is 40,  
14 comes down to about 25. And why just stop at 12  
15 weeks and why not longer?

16 I realize that people from the company might  
17 be here or not. Just curious.

18 DR. FIORENTINO: Right. Just for a quick  
19 overview. So on the 80 milligram dose, they  
20 actually looked at an overall responder at four  
21 weeks. It was the primary endpoint, as far as we  
22 know. So the compared to a placebo, they had a

1 51 percent overall responder, the 80 milligrams  
2 compared to 24 percent responder.

3 DR. THADANI: So it's going the other way?

4 DR. FIORENTINO: No. That was in their  
5 favor.

6 DR. THADANI: You said 24 versus 50?

7 DR. FIORENTINO: It was 51 versus 24,  
8 80 milligrams to placebo, and, yes, it was greater  
9 than three spontaneous bowel movements per week  
10 over four weeks.

11 DR. THADANI: What's the actual -- percent  
12 could be -- what's the real numbers percent-wise;  
13 20 percent, 30 percent? Can you give me the  
14 number, ballgame, rather than a delta?

15 DR. FIORENTINO: So it was 51 percent in the  
16 80 milligram naronapride arm and about 24 percent  
17 overall responder in the placebo arm.

18 DR. THADANI: Okay. And why are they  
19 excluding any high risk patients at all? I'm just  
20 curious, because you are saying you got approval,  
21 then you're going to throw it to the public where  
22 all the high risk will be studied and concomitant

1 drugs.

2 Why are they doing that?

3 DR. FIORENTINO: Well, that's a very good  
4 question, and I'm not sure we endorse that going  
5 forward.

6 DR. RAUFMAN: Dr. Kaul?

7 DR. KAUL: Yes. Slide 49, I'm trying to  
8 understand how did they get to that 1,000 patients  
9 and a 65-year-old patient? By the back of my  
10 envelope calculation, even if you assume that the  
11 baseline event rate is about 2 and a half to  
12 3 percent per year, which I kind of doubt, they're  
13 willing to tolerate up to a fourfold increase in  
14 cardiovascular events and yet deem it safe with 25  
15 number of events.

16 So I'd like to understand what are the  
17 operational parameters of this cardiovascular  
18 safety trial.

19 DR. PETERSON JOHNSON: Unfortunately, we  
20 don't have the sponsor here to answer that  
21 question. What we have is the proposal they  
22 submitted without knowing how they reached the

1 thousand.

2 DR. KAUL: They're assuming that there is a  
3 cardiovascular signal that they're willing to cap.  
4 And if they're willing to accept that, this means a  
5 25-event study. And the only risk that you can cap  
6 at a 25-event study is a hazard ratio of 4. So I  
7 don't know.

8 DR. KORVICK: I think that's  
9 what -- hopefully, we'll bring that back to the  
10 discussion later today, because we have these  
11 concerns.

12 DR. RAUFMAN: Dr. Kumar?

13 DR. KUMAR: I'm not sure if I missed it, but  
14 on the last slide, there were 960 subjects who  
15 completed the study. Of these, how many were over  
16 the age of 65?

17 DR. PETERSON JOHNSON: That number included  
18 all of the phase 1 and phase 2 studies. So there  
19 were only 212 patients in that phase 2 study, and  
20 so the others are very short duration.

21 I can check real quick and see how many were  
22 greater than 65, but off the top of my head, I

1 remember the number being very small.

2 DR. RAUFMAN: Dr. Teerlink?

3 DR. TEERLINK: In regard to the phase 2  
4 studies -- I understand how, in phase 2, when  
5 you're trying to do dose finding, you keep it  
6 short -- was the 120 milligram dose not effective?  
7 So we have no dose response on an efficacy  
8 variable.

9 DR. PETERSON JOHNSON: Right. So,  
10 basically, they saw a trend toward increasing the  
11 number of spontaneous bowel movements at week 1 for  
12 each dose group, but only the 80 milligram dose  
13 group was statistically significant when compared  
14 with placebo. So we don't see like a strict dose  
15 response.

16 DR. TEERLINK: Nonetheless, it seems  
17 confusing as to why -- if one generally believes  
18 that -- you know, this is America, more is better,  
19 right?

20 [Laughter.]

21 DR. TEERLINK: Unless, of course, you have a  
22 serious safety concern. What I think they tried to

1 say from the preclinical stuff is we don't have a  
2 safety concern, and we shouldn't even have to do a  
3 cardiovascular trial. Yet, they're also saying  
4 now, we're uncomfortable going to a dose that's  
5 only 50 percent higher even though it may be more  
6 effective.

7 So I'm just trying to figure out -- and this  
8 is not fair because the sponsor is not here, though  
9 they did have an opportunity I think to join us.

10 DR. KORVICK: I think those are interesting  
11 questions. We do see sometimes this kind of  
12 response where the higher doses don't seem to work  
13 as well. So sometimes we see this in IBS trials  
14 for other drugs. It's not clear exactly what's  
15 going on, and you've raised some good questions.

16 DR. RAUFMAN: Dr. Anderson?

17 DR. ANDERSON: My question was much the  
18 same. So they were comparing four arms to placebo.  
19 So did they actually do a test for trend or were  
20 they just doing these pairwise comparisons, and, if  
21 so, did they adjust for multiple comparisons?

22 DR. FIORENTINO: Our guess is they didn't

1 completely adjust for multiple comparisons. Again,  
2 this is a phase 2 exploratory trial. We could go  
3 back and look at their statistical plan, but we may  
4 not have it in our summary documents.

5 DR. ANDERSON: And so no tests returned that  
6 you know of.

7 DR. FIORENTINO: We haven't seen any in our  
8 summary documents for their meetings.

9 DR. ANDERSON: So one more question. In the  
10 control with cardiovascular safety study that  
11 they're proposing, what's the eligibility other  
12 than greater than 65? Is it also like a ROME III  
13 questionnaire? What's the patient population.

14 DR. PETERSON JOHNSON: Yes. They're still  
15 planning CIC patients. So I would imagine a  
16 modified Rome III criteria.

17 DR. ANDERSON: One quick thing. On the over  
18 65, in our summary documents, we don't have that,  
19 but the mean age group for their phase 2 -- that's  
20 the only thing I can speak to -- was 47.8 years.  
21 So I don't think there are many older.

22 DR. RAUFMAN: Dr. Fox?

1 DR. FOX: Thanks very much. I really need  
2 to say something strong here. I think it's  
3 completely inappropriate for this committee to be  
4 picking apart this sponsor's development program,  
5 which has gotten only as far as phase 2B dose  
6 ranging. They haven't started their pivotal trials  
7 yet. They haven't accumulated really any exposure  
8 to speak of at all. They're not here to defend  
9 themselves, and here we are picking apart their  
10 sketched-out proposals.

11 I'm assuming that the agency secured their  
12 permission to show these data, which I'm sure are  
13 not otherwise in the public domain, and I just  
14 think it's inappropriate. So let's try to keep it  
15 in perspective and stay on track here.

16 DR. RAUFMAN: Dr. Korvick?

17 DR. KORVICK: I would like to respond to  
18 that. And we were given permission to discuss what  
19 we're discussing today. I take your point about  
20 picking about details, but I think that the  
21 questions that we are addressing here today are  
22 pointed toward how one would proceed. And, indeed,

1 this company is very interested in getting your  
2 preliminary comments, as we have written them in  
3 the questions today, to address just this.

4 So we realize that we're in the sort of  
5 phase 2 early planning stages, but we are not  
6 trying to sort of put down sponsors for early -- we  
7 take your point, this is early. We do have  
8 permission.

9 These are important questions. Some might  
10 say, given the history of this drug class, sure,  
11 you should exclude those patients. Others might  
12 say you should study them. Others might say how  
13 much enrichment you want. And then, finally, do  
14 you buy the argument that these are very highly  
15 targeted populations.

16 So we can argue about the dose, et cetera,  
17 and these different things, but I think given what  
18 we have today, these are questions that we're often  
19 faced with in giving comments back to the sponsor  
20 that impinge on their development program, that  
21 result in the data that come to this committee.

22 So I do take your point and, with respect,

1 we do have permission. And, hopefully, we're not  
2 all totally picking at the carcass here too much,  
3 but we're trying to get to sort of these higher  
4 level questions.

5 DR. FOX: Well, if I could just clarify, I'm  
6 actually not -- I wasn't aiming my criticism at the  
7 agency. I was aiming it at some members of the  
8 committee. I think we should try and keep to the  
9 focus that you, in fact, have put before us today.

10 DR. RAUFMAN: Dr. Shen?

11 DR. SHEN: I think that in our GI community,  
12 we need some potent agents, but just a little  
13 comment.

14 May FDA give it back to the sponsor,  
15 including the indication? CIC has different  
16 degrees. If the CIC is already very advanced, I  
17 don't think that any drug will work. You have  
18 received a surgical specimen, so a total colectomy.  
19 Those people with chronic bad CIC, the surgical  
20 specimen lay on the operating table, there's no  
21 tone. It's like a sheet of paper. I do not think  
22 that any drug can reverse that.

1           So if you have the indication, CIC probably  
2 only included patients with mild to moderate CIC,  
3 rather than those severe end-of-stage CIC.

4           Thank you.

5           DR. RAUFMAN: Dr. Richig?

6           DR. RICHIG: Well, I do appreciate Dr. Fox's  
7 comment there. I'm referring to the proposed  
8 phase 3. Although I'm not a clinical expert, I'm  
9 coming from the preclinical background. I think  
10 that what we're looking at is giving some support  
11 to a better plan, so to speak, and I just had a  
12 question.

13           I noted that blood pressure is being taken  
14 at day 1, whereas ECG is not. I just feel that ECG  
15 and blood pressure go hand-in-hand, and I'm not  
16 sure whether blood pressure is performed with  
17 standard oscillometry or high definition  
18 oscillometry.

19           DR. PETERSON JOHNSON: I don't have the  
20 details of how they'll be performing their blood  
21 pressure monitoring. But as far as you said about  
22 the ECG, day 1 involves a run-in period. So

1 they're not on any study drug at day 1, which may  
2 explain why they're going to do the first ECG on  
3 day 15, which is the first day of the study drug  
4 administration.

5 DR. RICHIG: Thank you for that  
6 clarification.

7 DR. RAUFMAN: Dr. Rosenberg?

8 DR. ROSENBERG: Yes. Related to the safety  
9 studies, there's no indication of the duration of  
10 the study. And I assume for long-term use of these  
11 drugs, you want to have longer-term follow-ups than  
12 what they've done or planned so far.

13 DR. PETERSON JOHNSON: For the dedicated  
14 cardiovascular study, they plan to study for at  
15 least one year. And for that 12-week routine phase  
16 3 study, patients can subsequently be enrolled in a  
17 long-term treatment trial. So that's just their  
18 primary endpoint.

19 DR. RAUFMAN: Dr. Bloom?

20 DR. BLOOM: I'd be curious that if in the  
21 unlikely event this committee had consensus at the  
22 end of the day that cisapride was not a class

1 effect and unlike, at that time, can be predicted  
2 with great accuracy, and that tegaserod association  
3 with ischemic disease is in doubt, would a  
4 significant amount of your guidance on this plan  
5 change?

6 DR. KORVICK: I think we hope to hear that  
7 discussion, and that certainly would inform our  
8 guidance.

9 DR. RAUFMAN: Dr. Bild?

10 DR. BILD: I want to get back briefly to  
11 Dr. Fox's comments just to make sure that I'm  
12 clear, because I appreciated seeing this proposal  
13 for the phase 3 study as a strawman perhaps. It  
14 helps the discussion.

15 My understanding was that our charge was to  
16 provide recommendations to the agency on the design  
17 and size of a premarketing cardiovascular trial or  
18 study. So I just want to make sure that I'm right  
19 about that.

20 DR. FOX: I think that's right. And what  
21 you or I might think about the robustness of their  
22 design I don't think is as important as whether a

1 study should be required, based on the preclinical  
2 and early clinical profile of the compound, the  
3 target patient population, their intrinsic CV risk  
4 and so forth.

5 So that's how I read the questions from the  
6 agency, is more towards understanding what the need  
7 for such a study might be, not the fine points of  
8 design of such a trial, what the entry criteria  
9 should be, what the endpoints should be, how long  
10 it should run and so forth.

11 DR. KORVICK: I think we can refine that  
12 when we get into the questions, but we do have some  
13 targeted questions about the assessments and  
14 studies.

15 DR. RAUFMAN: Are there any additional  
16 questions? Dr. Teerlink, did you have something?

17 DR. TEERLINK: So without really actually  
18 seeing the phase 2 data, it's hard to actually  
19 decide how much we need to do the phase 3  
20 information. So I think some of the questions here  
21 are incredibly relevant to that issue.

22 You had mentioned that they were planning on

1 running in parallel 720 and 721. Is that correct?

2 So two parallel phase 3 designs.

3 Is the total, then, patient exposure going  
4 to be 1200 patients? So 720, 600 patients, and 721  
5 will be planned to have 600 patients, as well. So  
6 we have the potential to have 1600 patients exposed  
7 to therapy for some period of time during the phase  
8 3 experience, because it's a one-to-one-to-one  
9 design, right?

10 DR. PETERSON JOHNSON: Correct. They're  
11 planning two phase 3 studies, each involving 600  
12 patients.

13 DR. RAUFMAN: Dr. Thadani?

14 DR. THADANI: Even with the phase 3 study,  
15 they're going to exclude high risk patients. So I  
16 don't think there is any way on earth -- if you  
17 take a patient with stable coronary artery disease,  
18 say, they don't have triple vessel disease, the  
19 event rate of dying or having major things is about  
20 2 or 3 percent per year. And if you have  
21 documented triple vessel diseases, you're talking  
22 about 4 or 5. So if you exclude high risk

1 patients, you're a winner-winner.

2 So I think if they're not worried about the  
3 drug being so safe in preclinical study, I'm  
4 absolutely surprised that you don't want to show  
5 that it's safe.

6 So I think even if you say they'll collect  
7 the data after three months, but then there may not  
8 be any placebo, so we'd be stuck with, again, the  
9 noise is real. What? Okay, every 65-year-old, and  
10 if you exclude disease and high risk, the event  
11 rate is going to be very low; unless it's just by  
12 chance you've got underlying CAD. You don't know.  
13 Even with the stress test, you can't predict it  
14 sometimes.

15 So I think it has to be very careful, even  
16 if you allow it, what kind of population can use  
17 the drug and all that, I'm sure it will come in the  
18 questions, but keep that mind.

19 DR. RAUFMAN: Are there any final questions  
20 or comments at this point in time?

21 [No response.]

22 DR. RAUFMAN: I'd like to make a change in

1 the schedule and break for lunch now, and then  
2 continue with the FDA presentation right after  
3 lunch. We will break for lunch. We'll reconvene  
4 again in this room in roughly one hour, at 1:15  
5 p.m. Please take any personal belongings with you.

6 Committee members, please remember that  
7 there should be no discussion of the meeting during  
8 lunch amongst yourselves, with the press, or with  
9 any member of the audience.

10 Thank you.

11 (Whereupon, at 12:22 p.m., a luncheon recess  
12 was taken.)

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

(1:17 p.m.)

DR. RAUFMAN: We'll reconvene the meeting at this time, and we'll continue with FDA's presentations.

**FDA Presentation - Rob Fiorentino**

DR. FIORENTINO: Good afternoon. I'm Rob Fiorentino. I am a clinical team leader in the Division of Gastroenterology and Inborn Error Products.

Just before I get started, I wanted to provide a little information that may help the future discussions. There was a question about the proportion of patients who are older than 65 years old in CIC trials. For one of the approved drugs for CIC, the clinical trial had a proportion greater than or equal to 65 of about 10 or 11 percent. In open label trials, that percentage is about 14 to 22 percent.

So I'd like to provide a summary of the information that was presented this morning and just discuss how the available data may help to

1 inform further evaluation of the cardiovascular  
2 safety profile of naronapride.

3 So starting with cisapride, we have a clear  
4 example where drug-drug interactions were important  
5 contributors to a drug safety profile. Cisapride  
6 also had exposure-dependent QT prolongation, which  
7 resulted in fatal ventricular arrhythmias. These  
8 two factors acted together to produce an  
9 unfavorable cardiovascular safety profile for  
10 cisapride.

11 Based on this understanding and experience  
12 gained from other drugs, we now increasingly  
13 incorporate in vitro and clinical drug-drug  
14 interaction studies into drug development programs.  
15 And the FDA now mandates thorough QT studies for  
16 all compounds, with only some exceptions.

17 So as we also saw, the post-market safety  
18 profile of tegaserod was characterized by rare  
19 cardiovascular ischemic events of unclear etiology.  
20 In tegaserod's development clinical trial, ECG data  
21 had been collected and did not appear to suggest QT  
22 effects. However, as we now know, there is no

1 thorough QT study available for this drug.

2 As Dr. Kim noted, a higher rate of ST  
3 segment and T wave abnormalities were observed in a  
4 subset of older patients who received tegaserod.  
5 However, the significance of this finding is still  
6 unclear.

7 Nonclinical studies also did not suggest a  
8 clear cardiovascular safety concern, although small  
9 contractile effects on canine coronary arteries  
10 were observed at higher doses. Tegaserod also had  
11 relatively nonspecific 5-HT<sub>4</sub> receptor binding,  
12 which, in retrospect, may have hinted at the  
13 potential, at least for off-target adverse effects,  
14 and tegaserod was also noted to be a P-gp  
15 substrate. And finally, tegaserod's effects on  
16 platelet reactivity have been very recently  
17 described, but, again, these findings remain  
18 inconclusive at this time.

19 So the lessons relevant to tegaserod are  
20 neither unique nor new to the drug development from  
21 a safety standpoint, but a number of highlights  
22 should be noted.

1           The first is that safety signals may not be  
2 detected in modestly sized clinical trials under  
3 controlled conditions. Secondly, the analysis of  
4 post-market adverse event reports is not an ideal  
5 means to evaluate safety, particularly because of  
6 the effects of confounding on risk estimation and  
7 the lack of adequate control arms.

8           It is also clear that nonclinical studies do  
9 not necessarily assure human safety. And, finally,  
10 pathophysiologics to etiologies of ischemic events  
11 can be unclear, as we still do not have a clear  
12 answer as to why tegaserod would be associated with  
13 cardiovascular ischemia.

14           So it's important to note that there are  
15 multiple highly selective 5-HT4 agonists currently  
16 under development, and Theravance's experience  
17 provides an example of what the early stages of a  
18 drug development program look like, specifically  
19 with regard to how nonclinical cardiovascular  
20 safety studies can inform the drug development  
21 process.

22           The safety profiles of these two drugs are

1 emerging and investigations are on-going. However,  
2 in general, there is nothing particularly  
3 concerning about these drugs observed to date.

4           So what do we know about naronapride? So  
5 naronapride is at a much later stage of development  
6 and, as such, has a broader characterization of its  
7 nonclinical and pharmacological safety. In vitro  
8 studies have demonstrated high 5-HT4 selectivity,  
9 which contrasts somewhat with what we saw in  
10 tegaserod and is reassuring, to some extent.

11           However, it's important to note that  
12 metabolite receptor binding has not been  
13 characterized in its entirety, including two  
14 receptors known to be active in the cardiovascular  
15 system. And as was brought up earlier, these would  
16 include the 5-HT1B and the 5-HT2A receptor  
17 subtypes.

18           Animal studies for naronapride have shown  
19 weak and generally variable findings. It should be  
20 noted that human QT study was negative, which  
21 provides some reassurance, especially in contrast  
22 to cisapride, that an arrhythmogenic potential

1 should not exist at the proposed clinical doses.

2 The in vitro studies suggested that  
3 naronapride may be a significant substrate of the  
4 P-gp transporter, but, importantly, it does not  
5 appear to have substantial CYP metabolism. But  
6 in vivo drug-drug interaction studies have not yet  
7 been done. We have also seen that platelet  
8 aggregation studies were negative, which, again,  
9 although reassuring, it is not really clear to us  
10 at this time what the clinical significance of  
11 these studies are.

12 Finally, the clinical data collected to date  
13 has not provided evidence of an early  
14 cardiovascular safety signal for this drug.

15 So one lingering concern is that although we  
16 believe that we understand the underlying cause of  
17 cisapride's safety profile, for tegaserod we do  
18 not. And that's why, typically, under these  
19 circumstances of uncertainty, we look toward the  
20 nonclinical studies to provide signals that may  
21 hint at possible clinical effects.

22 So it seems safe to assume that a closer

1 look for cardiovascular adverse events in clinical  
2 studies would be prompted by signals that emerge  
3 from non-clinical studies, such as the following  
4 examples that we discussed this morning, and these  
5 would include significant off-target receptor  
6 binding from in vitro studies, positive effects on  
7 platelet aggregation studies, nonclinical findings  
8 in supplemental cardiovascular studies, such as  
9 vasoconstriction that was discussed or possibly  
10 even hematologic or hemodynamic changes, such as  
11 increases in blood pressure or heart rate.

12 But even as we look for these early signals,  
13 we still have to keep in mind that nonclinical  
14 studies provide some but not complete assurance of  
15 human safety. A negative nonclinical program does  
16 not necessarily rule out a risk in humans.

17 Finally, for all of these drugs discussed  
18 today, early phase clinical studies can only  
19 provide limited cardiovascular safety data due to  
20 their small sample sizes and relatively short  
21 duration.

22 So how do we move forward with the

1 information we've discussed today? Is there  
2 evidence from what we've heard and discussed so far  
3 that further evaluation of cardiovascular ischemic  
4 events is needed for 5-HT4 agonists?

5 Keep in mind that we already incorporate  
6 thorough QT studies during drug development, so  
7 what we're really interested in is detecting  
8 imbalances in ischemic cardiovascular events. And  
9 we have a couple of options on how to look for an  
10 increased cardiovascular risk for 5-HT4 agonists.

11 The first is we can either collect data from  
12 routine adverse event assessments in phase 3  
13 efficacy trials, as is typically done for all  
14 drugs, or potentially improve the protocol such  
15 that cardiovascular assessments are standardized  
16 and adjudicated in a more robust manner.

17 The second and more definitive option is to  
18 perform a dedicated perspective clinical  
19 cardiovascular safety study that is specifically  
20 designed to answer whether or not the use of a 5-  
21 HT4 agonist increases cardiovascular risk. But,  
22 again, is a dedicated prospective study warranted

1 given the data currently available to us on the  
2 risk of these events and these drugs? We need to  
3 keep in mind that cardiovascular safety trials can  
4 be large and resource intensive, because, after  
5 all, these are fairly uncommon events we'll need to  
6 be looking for.

7           So if dedicated cardiovascular safety  
8 studies are done, they should be designed to rule  
9 out an increased cardiovascular risk that would be  
10 deemed unacceptable in the population with the  
11 disease. And I think it's important to consider  
12 the following questions in regard to this  
13 discussion this afternoon.

14           So the first is, what level of  
15 cardiovascular risk is unacceptable for these  
16 agents, and does it vary across each potential  
17 indication for the 5-HT4 agonists?

18           Second, how do we capture enough  
19 cardiovascular events in a GI disease population  
20 that may not, at baseline, have any major  
21 cardiovascular risk factors? And finally, should  
22 we conduct the cardiovascular safety study before

1 or after approval?

2 So I'd now like to introduce our fellow FDA  
3 statistical colleagues who will provide further  
4 insight into the design, power, and sample size  
5 issues related to the clinical evaluation of  
6 cardiovascular safety studies.

7 Thank you.

8 **FDA Presentation - Eugenio Andraca-Carrera**

9 DR. ANDRACA-CARRERA: Good afternoon. My  
10 name is Eugenio Andraca-Carrera. I am a  
11 biostatistician at the FDA. And today in this  
12 presentation, I will discuss power and sample size  
13 scenarios for dedicated cardiovascular safety  
14 trials. And while many features need to be  
15 considered in the design of clinical trials to  
16 assess cardiovascular risk, the focus of this  
17 presentation is sample size requirements for  
18 excluding different levels of risk in populations  
19 with different background risk.

20 So, first, let me define some terms that  
21 will be used in this presentation. When we say  
22 that an event is event driven, we mean to say that

1 the power of a trial is determined by the total  
2 number of events in the trial, and this is typical  
3 of trials which are analyzed using survival  
4 analysis methods.

5           Second, the hazard or hazard function is the  
6 probability of an event happening in a short  
7 interval of time. The hazard ratio is a proportion  
8 of two hazards, and it's a way to measure risk.  
9 The sample size calculations in this presentation  
10 assume that the hazard ratio is constant through  
11 time.

12           Finally, the sample size of a trial will be  
13 expressed in terms of patient years, where patient  
14 years are defined as the number of patients in the  
15 trial times the number of years that they remain in  
16 the trial.

17           At the design stage of a safety trial for  
18 cardiovascular outcomes, several design choices  
19 need to be made. First, we have to define the  
20 outcome of interest, and cardiovascular safety  
21 trials commonly use a composite MACE as their  
22 primary endpoint. Traditional MACE is composed of

1 cardiovascular death, myocardial infarction, and  
2 nonfatal stroke.

3           Second, we need to specify the amount of  
4 risk that the trial will try to rule out. This  
5 risk can be expressed in terms of the relative risk  
6 or the hazard ratio, and it is compared with the  
7 upper bound of the 95 percent confidence interval.  
8 This is essentially the same kind of reasoning that  
9 is used in non-inferiority trials.

10           Third, we need to define a population of  
11 interest. Since cardiovascular safety trials are  
12 powered by number of events, it is common to study  
13 a population based on cardiovascular risk factors.  
14 Such a population is commonly referred to as an  
15 enriched population.

16           This slide shows the hypothesis to be tested  
17 in a dedicated cardiovascular safety trial to rule  
18 out an excess amount of risk. The hazard ratio  
19 margin is shown as the green dotted line and is  
20 compared with the upper bound of the 95 percent  
21 confidence interval for the hazard ratio. So when  
22 the upper bound of the 95 percent confidence

1 interval is smaller than the hazard ratio margin,  
2 the trial is considered successful in ruling out  
3 the hazard ratio margin.

4 So in this plot, cases 1 and 3 are  
5 successful because the upper bound of the 95  
6 percent confidence interval is smaller than the  
7 hazard ratio. Case 2 is not, because the upper  
8 bound of the 95 percent confidence interval is  
9 larger than the hazard ratio margin.

10 This table shows the total number of events  
11 across both treatment arms that are needed to power  
12 a cardiovascular safety trial. There are two rows  
13 on this table, showing the number of events needed  
14 to achieve 80 percent power and 90 percent power to  
15 rule out a hazard ratio margin ranging from 1.5 to  
16 4.

17 These calculations assume that, in reality,  
18 there is no difference in risk between the two arms  
19 in the trial. In other words we assume for these  
20 calculations that the underlying hazard ratio is 1.  
21 So, for example, a trial will need to have observe  
22 66 events in order to have 80 percent power to rule

1 out a hazard ratio margin of 2.

2 If instead we want to have 90 percent power  
3 to rule out a hazard ratio margin of 2, the trial  
4 needs to observe 88 events. And notice that since  
5 cardiovascular safety trials are event driven, a  
6 trial continues until the designed number of events  
7 are observed, but the exact time at which these  
8 events are observed is not known in advance.

9 This table adds two more rows to the  
10 previous table, where the information is shown in  
11 orange, and shows the maximum value of the  
12 estimated hazard ratio that could be observing a  
13 trial and would still allow the trial to rule out a  
14 prespecified hazard ratio margin.

15 So, for example, we saw that in order to  
16 have 80 percent power to rule out a hazard ratio  
17 margin of 2, we need to observe 66 events. This  
18 means that the upper bound of the 95 percent  
19 confidence interval has to be smaller than 2. But,  
20 also, it means that the point estimate of the  
21 hazard ratio has to be smaller than 1.23.

22 So on another example, in order to rule out

1 a hazard ratio margin of 4 with 80 percent power,  
2 we need to observe 17 events. The upper bound of  
3 the 95 percent confidence interval for the hazard  
4 ratio has to be smaller than 4 or, equivalently,  
5 the point estimate of the hazard ratio has to be  
6 smaller than 1.55.

7 So the number of patients years that are  
8 needed to observe a prespecified number of events  
9 depends on the background risk of the population  
10 under study. And in this presentation, I consider  
11 two hypothetical populations with different  
12 background risks.

13 The first is a non-enriched population,  
14 consisting mostly of women under 55 years of age.  
15 This is taken from an observational study of the  
16 cardiovascular risk of tegaserod conducted -- it's  
17 barely seen on the bottom, but by Laughlin, et al.

18 In this observational study, the expected  
19 rate of MACE is calculated at between one and three  
20 events per 1,000 patient years. The second is an  
21 enriched population that consists of subjects with  
22 baseline cardiovascular risk factors and an

1 unexpected rate of events between 10 and 20 per  
2 1,000 patient years.

3 So at this point, we have discussed the  
4 number of events that are needed to rule out a  
5 hazard ratio margin. In this plot, we show how  
6 many patient years are needed to observe these  
7 events. This plot is based on scenarios to rule  
8 out a hazard ratio margin with 90 percent power in  
9 an enriched population, with a background rate  
10 between 10 and 25 events per 1,000 patient years.

11 So on the X-axis, we show the hazard ratio  
12 margin that we wish to exclude, ranging from 1.5 at  
13 the very far left, to 4 on the right. Below, on  
14 the X-axis, we show the number of events needed to  
15 rule out the corresponding hazard ratio margin with  
16 90 percent power. On the Y-axis, we have the  
17 number of expected patient years that would be  
18 required in a trial to observe these events.

19 So, for example, in order to exclude a  
20 hazard ratio margin of 2, we need a trial with 88  
21 total events. In order to observe 88 events, a  
22 trial would need approximately 8,800 patient years

1 if the background rate of events is 10 per 1,000  
2 patient years, which is the curve on top and this  
3 point here. If the background rate is 15 per 1,000  
4 patient years, which corresponds from the second  
5 line to the top, the trial will need approximately  
6 5,800 patient years.

7 So this plot shows that in order to rule out  
8 a smaller hazard ratio margin, you need a larger  
9 sample size. Also, it shows that as the background  
10 rate gets smaller, in this plot 10 per 1,000 is the  
11 smallest, the required sample size in terms of  
12 patient years also grows larger.

13 So this table shows some additional  
14 information from the previous slide. The rows with  
15 blue background show the total number of events  
16 that are needed in a trial to rule out a hazard  
17 ratio margin with 80 percent power and 90 percent  
18 power, and we have discussed these two rows  
19 previously.

20 The corresponding rows in blue text show the  
21 expected number of patient years needed to observe  
22 these events in a non-enriched population with a

1 background rate of 10 per 1,000 patient years. The  
2 rows in orange show the number of patients years  
3 needed to observe these events in an enrich  
4 population with a background rate of 20 per 1,000  
5 patient years. So in this table, the background  
6 rate in the enriched population is almost seven  
7 times as large as the background rate in the non-  
8 enriched population.

9 As an example, in order to have 90 percent  
10 power to rule out a hazard ratio margin of 2, a  
11 trial requires 88 events. In order to observe  
12 these events in an enriched population, a trial  
13 would require approximately 4,400 patient years.  
14 In order to observe the same number of events in a  
15 non-enriched population, a trial would require  
16 approximately 29,000 patient years.

17 So a trial in a non-enriched population  
18 clearly requires more patient years than a trial in  
19 an enriched population. Also, you can see that in  
20 order to rule out a smaller hazard ratio margin, a  
21 trial requires more events and also more patient  
22 years. And again, note that the number of patient

1 years needed to observe events in this table is  
2 just an estimate. In practice, a trial would  
3 continue until the prespecified numbers of events  
4 are observed, which could be before or after the  
5 patient years that are shown on this table.

6 So it's our conclusion, in order to rule out  
7 a smaller hazard ratio margin, a trial requires  
8 more events and, therefore, more patient years.  
9 The number of patient years needed to observe these  
10 events depends on the background rate in the  
11 population of the trial.

12 Here, we have discussed scenarios for power  
13 and sample size for two populations. In general, a  
14 trial in an enriched population with a high  
15 cardiovascular risk requires fewer patients and  
16 fewer patient years than a non-enriched population  
17 with low cardiovascular risk.

18 Thank you very much. And if you have any  
19 questions, I'll be happy to answer.

20 **Questions from the Committee**

21 DR. RAUFMAN: Thank you. We'll open it to  
22 questions from the committee. I guess Dr. Lauer

1 had his hand up first.

2 DR. LAUER: Thank you. I want to thank you  
3 both for very thoughtful and well prepared  
4 presentations.

5 Two questions. One question is that perhaps  
6 one of the lessons learned from the tegaserod  
7 experience is over-interpretation of small numbers.  
8 And the reason why the mechanisms may be unclear is  
9 because there is no mechanism at all. This is just  
10 a random event.

11 The second question is related to yours.  
12 There was no discussion about number needed to  
13 harm, which I think one of my colleagues brought up  
14 earlier today. If you go from 1 percent to 2  
15 percent, that's a hazard ratio of 2, that's a  
16 number needed to harm of 100. If you go from 2  
17 percent to 4 percent, that's also a hazard ratio of  
18 2, but that's a number needed to harm of 50.

19 Given that our primary concern here is  
20 safety, wouldn't number needed to harm be an  
21 important component of designing such a trial?

22 DR. ANDRACA-CARRERA: The answer is that it

1 is, and the trials are usually -- the power of the  
2 trial is determined by the number of events to rule  
3 out a hazard ratio margin. Now, the choice of the  
4 margin has to be informed by, among other things,  
5 the background rate, which gives you the number  
6 treated to harm. So, yes, the choice of the margin  
7 needs to be informed by the number needed to harm.

8 DR. RAUFMAN: Dr. Thadani?

9 DR. THADANI: Thanks for the detailed  
10 presentation. I think we have to realize it's only  
11 a new paradigm, that the cardiovascular is looking  
12 at safety trials and diabetes only recently,  
13 because most of the cardiovascular trials with  
14 large sample size have combined kind of efficacy  
15 plus the safety.

16 For example, we know that patients with  
17 coronary artery disease have events, they die, they  
18 have myocardial infarctions, so you're reducing  
19 that. And then you combine the bigger complication  
20 of new oral anticoagulants.

21 Just a comment now to you, is when your  
22 event rate, at least in the placebo study, was one

1 in 10,000 in one of the trials, you know, this  
2 point of 11 versus one out of that. So you're  
3 talking about a humongous number of patients in  
4 order to be absolutely sure that the drug in  
5 question is safe.

6 So the question to you, can I do a -- and we  
7 published something on aspirin, looking in the  
8 diabetic population who did not have a CID, and  
9 really the data is now out there for safety. And  
10 in order to be absolutely sure, efficacy/safety,  
11 we're talking about 50,000 patients done over one  
12 year or smaller numbers.

13 So the question to you, can I do -- the  
14 disease is very popular. You say millions of  
15 people have it. Can one do a 200,000-patient trial  
16 in a few months, collect very hard endpoints, which  
17 will conform to your number of years of follow-up?  
18 Because you're saying number of patients, years of  
19 follow-up; so can I increase the sample size,  
20 reduce my number of years of follow-up, realizing  
21 that the event rate is constant throughout, which  
22 may not be.

1           Just your comment from a statistical  
2 perspective.

3           DR. ANDRACA-CARRERA: Well, that's more of a  
4 question for the clinicians, whether you need to be  
5 on the drug for a certain amount of time before you  
6 expect to observe events.

7           DR. THADANI: But if the event rate stays  
8 constant -- like the QT, most of the things happen  
9 in the first two weeks, four weeks, because  
10 arrhythmia incidents is more common, unless there's  
11 a drug interaction, which could happen later. But  
12 the cardiovascular event rate, if it's due to  
13 platelet-mediated function, you would think the  
14 patient with underlying disease might present more  
15 often.

16           The dilemma I'm having, you're showing data  
17 on women who are below 55 years old. I don't know  
18 how many were on hormone replacement therapy.  
19 There could be interaction because they had  
20 strokes.

21           So could a sample size for, say, a three or  
22 six-month study on 200,000 patients address the

1 issue once and for all? Or realizing the event  
2 rate could change over time, would give me more  
3 reassurance.

4 I realize there are humans in this trial,  
5 but in my perspective, the disease is so common,  
6 perhaps, so be it. Who does it, I don't know.

7 But what's your comment? Would that be  
8 valuable from a statistical point of view?

9 DR. ANDRACA-CARRERA: Statistically, the  
10 event -- the trial is powered by number of events  
11 and the number of patient years that you need to  
12 observe these events. Whether you accrue these  
13 patient years in a short time or a long time  
14 statistically doesn't make any difference. But,  
15 however, you're making a big assumption that these  
16 events happen in three months or six months or  
17 however long your study is.

18 So perhaps whether a study like this is  
19 appropriate would be a question for my clinical  
20 colleagues.

21 DR. THADANI: The problem is if you don't  
22 have a large sample size and you start the study in

1 three months, and then you have open label design,  
2 that you don't know what would have happened in the  
3 population if you had a parallel placebo group.

4 So are there any pros and cons if one knew  
5 the event rate? I realize -- especially in the  
6 unenriched population, because the event rate is  
7 going to be low, enriched population I think will  
8 get away.

9 DR. RAUFMAN: Let's move on. Dr. Bloom?

10 DR. BLOOM: Yes. Question to  
11 Dr. Fiorentino.

12 Would it be fair to say that what you very  
13 nicely framed regarding the cardiovascular risks,  
14 challenges with these 5-HT4 agonists are based on  
15 two assumptions; one is that the association of  
16 tegaserod with ischemic cardiovascular events is  
17 conclusive; and, number two, that QT prolongation  
18 in man cannot be reliably predicted by nonclinical  
19 and early clinical testing?

20 DR. FIORENTINO: Well, I would have to -- I  
21 hope that other members of the panel will have a  
22 chance to answer that question if they have

1 thoughts.

2 Right. I think we do these studies, the  
3 platelet aggregation studies. We do look at  
4 receptor subtype studies. And they're doing it and  
5 we're evaluating those under the presumption that  
6 if they were positive, they would point to some  
7 kind of signal toward vasoconstriction or even  
8 platelet aggregation.

9 So we're looking for those signals. I'm not  
10 going to make any conclusions about whether our  
11 chief concern is platelet aggregation at this time  
12 and that somehow is relevant to tegaserod. I don't  
13 know if I can make that conclusion.

14 DR. BLOOM: But I'm not sure what being able  
15 to use platelet aggregation as a predictive marker  
16 has to do with those two assumptions and whether  
17 they're valid.

18 DR. KORVICK: I think what you're saying is  
19 that these are assumptions, and the FDA has  
20 interpreted them in a conservative manner in the  
21 past. And I do think we think that QT studies help  
22 us understand that part of the equation. So that

1 maybe it's reasonable to let a drug on the market  
2 with certain profiles that we discussed earlier.  
3 But there is this lingering concern about  
4 tegaserod, and we do want to hear what people think  
5 about the data that we have.

6 DR. RAUFMAN: Dr. Granger?

7 DR. GRANGER: I, too, would like to  
8 congratulate you. That was a terrific  
9 presentation. The issue is really nicely laid out.

10 It also reminds us back to the discussion  
11 about cardiovascular safety of drugs for treatment  
12 type 2 diabetes. One of the strong arguments there  
13 for the enriched population, in addition to  
14 reducing the number of patient years necessary to  
15 do the trials, was that the drugs were used in a  
16 population that was at high risk for cardiovascular  
17 disease. They would be used in that population,  
18 and, therefore, we needed the population to  
19 represent the information of safety that would be  
20 informing clinical practice.

21 I still don't have a great sense to what  
22 extent that's the case here, but I think that's

1 another important factor. Not only does it enrich  
2 the event rate, but it identifies that population  
3 for whom this would be the biggest issue in  
4 practice. Therefore, we need to know about that  
5 population with the events.

6 Is that a fair --

7 DR. ANDRACA-CARRERA: Yes, it is. An  
8 enriched population has to be at least  
9 representative of people who would use the drug in  
10 clinical practice, yes.

11 DR. GRANGER: And then the second is kind of  
12 a related question, and, Udho, I think you were  
13 getting at this, as well, and that is the duration  
14 of the trial also should probably reflect what the  
15 duration may end up being in practice.

16 So if we're talking about a lifelong  
17 treatment that we expect a lot of people to be on  
18 for 10 or 20 years, then it makes sense to try to  
19 go for a bit longer exposure to get relevant safety  
20 information; but if it's something where people  
21 tend to be on this for a few months and a lot of  
22 people come off of it, then if you design longer

1 trials, you run into the problem -- or if you have  
2 very high dropout rates, then, in fact, you have a  
3 paradoxical effect where you lose power to be able  
4 to look at safety in a reliable way.

5 So those are other issues I think that we  
6 have to grapple with.

7 DR. RAUFMAN: Dr. Spiegel?

8 DR. SPIEGEL: Thank you. I'd also like to  
9 thank you for that very clear presentation. If you  
10 wouldn't mind, I just want to underscore and expand  
11 the previous point about number needed to harm. I  
12 brought that up earlier.

13 This paradigm is based upon this hazard  
14 margin, which is interpretable only so far as we  
15 know that higher is worse, but that's about it.  
16 That's as interpretable as it is. And I think this  
17 whole paradigm needs to be switched -- flipped on  
18 its head.

19 This discussion begins with patients. It  
20 begins with a discussion about our understanding  
21 about the benefits and our understanding of the  
22 risks in a language that is interpretable to

1 patients. And I believe that in concert with  
2 patients and patient representatives, understanding  
3 the benefits of a drug, we can then establish what  
4 are the acceptable risks. Those risks are measured  
5 in terms of an absolute risk increase, which is the  
6 statistic that's used to calculate a number needed  
7 to harm.

8           You then power a study on number needed to  
9 harm or you have an upper bound for the 95 percent  
10 confidence intervals for a number needed to harm,  
11 and it should not exceed your acceptable number  
12 needed to harm; it should remain below that -- or  
13 above that, I should say. It's reversed.

14           It's not the case, as I'm thinking about it,  
15 that hazard ratio is a lockstep correlation with  
16 number needed to harm. They are related to each  
17 other, but I don't see, when you say that we should  
18 consider the number needed to harm in creating our  
19 hazard margin acceptability threshold, how that  
20 actually converts mathematically. Maybe there is  
21 some precedent for doing this, but, to me, that's  
22 the issue here. And I'm not sure if that's really

1       been thought about this way before.

2               DR. RAUFMAN:   Dr. Teerlink?

3               DR. HASLER:   Can I comment on that?

4               DR. RAUFMAN:   Dr. Hasler?

5               DR. HASLER:   You bring up a good point.   And  
6       for the most part, the number needed to harm, it  
7       works with attributable risk.   And you can  
8       basically get to attributable risk from the hazard  
9       ratio.

10              So if that's what you're really looking to,  
11       is you want to power a study by ruling out a  
12       certain amount of excess risk and use that to  
13       determine what you want to do, you can easily do  
14       that.   We merely presented it in this way just to  
15       kind of give an idea in terms of relative scope.

16              But, yes, we have actually looked at  
17       powering studies based upon attributable risk, so  
18       we do do that.   And I think once you have a nature  
19       underlying what you think the background risk is,  
20       then it's easy to work with attributable risk.   But  
21       without that, where we really don't know what that  
22       background risk is, it's pretty hard to get at that

1 point at this stage.

2 So these are very general considerations.

3 DR. RAUFMAN: Dr. Teerlink?

4 DR. TEERLINK: Thank you. So, once again, a  
5 very nice presentation.

6 So Drs. Granger and Spiegel actually just  
7 made some of my points. But one thing I did want  
8 to reemphasize is that if this agent is going to be  
9 used, as we would expect, in certain populations  
10 for a long period of time, that you do need to  
11 study at least for a year or so in that patient  
12 population, just because otherwise you're assuming  
13 there truly is perfect proportional hazard, which I  
14 don't think we see actually in most of these  
15 instances.

16 The other thing is I think this is a  
17 stepwise process, and I think we're never certain;  
18 even when we get this 90 percent confidence  
19 interval with the upper limit at 2.0, there is  
20 still a point-something percent chance that it's a  
21 hundredfold increase in risk. So we're looking on  
22 probabilities, and that probability evolves over

1 time.

2 So I think had we seen a study that had a  
3 positive prolongation of QT in animal studies, a  
4 positive thorough QT study, and then proceeding on  
5 to QT prolongations in phase 2 study, that's a very  
6 different animal than one where we don't see things  
7 along the way.

8 I'm wondering if there's a way to try to  
9 incorporate -- and this is one of the questions,  
10 but I think I may go even further and say where we  
11 go -- the preclinical data is not perfect, the  
12 early clinical data is not perfect, but we're  
13 comfortable enough saying you don't need to do  
14 another cardiovascular study, a specific  
15 cardiovascular study for this, and try to  
16 work -- or if you do, that you can somehow work in  
17 your pretest probability of what you think, that  
18 there's going to be cardiovascular harm, into  
19 interpreting your post-test results from your  
20 cardiovascular study.

21 So is there a way to do that?

22 DR. ANDRACA-CARRERA: I'm not sure I can

1 answer that question right now. I would actually  
2 have to think about it, how to make use of all of  
3 the data that you have collected in order to  
4 interpret the new information. I'm not sure how to  
5 answer that question at this moment.

6 DR. RAUFMAN: Dr. Kaul?

7 DR. KAUL: Yes. I have a comment and a  
8 question. The argument is do we fix the upper  
9 bound as a hazard ratio or do we fix it as an  
10 absolute difference margin.

11 Well, let me just give you an example. If  
12 you have a baseline event rate of 2 percent and you  
13 fix the margin as 2 percent absolute risk  
14 difference, so that 2-plus-2 divided by 2 is a  
15 hazard ratio of 2, 4 divided by 2; but it so  
16 happens that the observed event rate, instead of 2  
17 percent, is only 1 percent. Now, the hazard ratio  
18 becomes 1-plus-2 divided by 1. So the hazard ratio  
19 now has expanded. Are you willing to accept a  
20 worse treatment because it meets that absolute risk  
21 difference?

22 So it's very important to fix the margin in

1 terms of a hazard ratio simply because the observed  
2 event rate in the control arm not always  
3 necessarily equals the expected event rate. So  
4 that's the flipside of the argument.

5 So the question I have for the statistician  
6 is that we are basing the study estimates on what  
7 we assume the baseline event rate is, and I think  
8 we'll be on firmer ground if our assumptions are  
9 verifiable. And I have not heard, since this  
10 morning, what is the cardiovascular risk profile of  
11 these patients for us to be able to figure that  
12 out. That's the first step.

13 DR. SOUKUP: I can respond to that a little  
14 bit. You bring up a good point. All our sample  
15 size calculations, they're based upon assumptions.  
16 I mean, that's how we work in the statistical  
17 world.

18 What makes it very challenging in safety  
19 when we're looking at trial designs specifically  
20 for safety, we're not in an efficacy world where  
21 you can do a phase 2 trial to get at an estimate of  
22 what you think your treatment effect is.

1           Safety, we don't. We oftentimes go into  
2 these things somewhat blind, and that's why we're  
3 starting to work with somewhat -- we would think  
4 here a conservative estimate is you think the  
5 hazard ratio is 1, as you assume it is equal  
6 between the two groups. I don't think we have any  
7 information to maybe suggest it is more, but if you  
8 thought it was more, again, you can change sample  
9 size calculations on that. But it's very difficult  
10 to do and it's something similar that we're doing  
11 in other areas within the agency as the  
12 conservative way, as we just assume a hazard ratio  
13 of 1 and make our sample size calculations based  
14 upon that.

15           DR. KAUL: What I'm talking about is at  
16 least we have some idea of what the baseline event  
17 rate is. In diabetes, we know it's somewhere  
18 between 1-and-a-half to 3 percent per year. In  
19 obesity, probably lower than that.

20           Do we know what the cardiovascular risk  
21 profiles in these patients are? I mean, if they  
22 are younger women, then it's likely to be less than

1 1 percent per year, depending on what type of  
2 population you're studying.

3 So we need to have a better understanding of  
4 that so that we can at least be on firmer ground  
5 before we display these sample sizes.

6 DR. SOUKUP: Right. But, yes, that's where  
7 your eligibility criteria hopefully targets a  
8 specific rate. If you get there or not, that's  
9 going to -- you don't know. Again, in these  
10 trials, things happen, we don't know. But, yes,  
11 and that basically impacts the patient years you're  
12 going to need. It doesn't impact what you need in  
13 terms of the events.

14 DR. RAUFMAN: Dr. Hasler?

15 DR. HASLER: Yes. I'd like to address that,  
16 Dr. Kaul. The cardiovascular risk rate of these  
17 patients, for the most part, is going to be quite  
18 low. For example, I am part of a consortium that  
19 studies gastroparesis. It's 82 percent women. The  
20 mean age is 41 years. They have very little else  
21 in the way of morbidity. Two-thirds of them are  
22 idiopathic in nature. One-quarter, approximately,

1 are diabetic. So they may be at a slightly  
2 increased risk.

3 You'll see similar population  
4 characteristics in people who present with chronic  
5 idiopathic constipation and, for sure, constipation  
6 predominant IBS. So you're, on the whole, going to  
7 be dealing with a very low risk population, with  
8 pockets of high risk.

9 DR. RAUFMAN: Dr. Fox?

10 DR. FOX: Yes, thanks. Just a couple of  
11 comments and maybe a question to the FDA  
12 statisticians. We're focusing here on  
13 cardiovascular risk overall, but you could focus on  
14 a whole bunch of other things. In the absence of a  
15 signal, whether it's preclinical or early clinical,  
16 why would you preferentially evaluate for  
17 cardiovascular risk over, say, seizures, since  
18 these receptors are expressed in the nervous  
19 system, or any other morbidity or mortality cause  
20 for that matter?

21 So my question then is, how did you come up  
22 with an upper bound of 2, or is that just a

1 suggestion?

2 DR. ANDRACA-CARRERA: No. The upper bound  
3 of 2 was an example. It was not even a suggestion.

4 DR. FOX: Okay.

5 DR. ANDRACA-CARRERA: It was to show numbers  
6 in a specific scenario.

7 DR. FOX: Okay. Because it turns out that  
8 the publication from Steve Nissen and his  
9 statistician of Cleveland Clinic on Avandia, in  
10 fact, had an upper bound of 1.98, which started  
11 that whole discussion down that road, and everybody  
12 knows the outcome of that.

13 Then the other point I'd like to make is I'm  
14 not even talking about a hazard ratio upper  
15 boundary, but, in fact, the point estimate of risk  
16 for a drug for treating diabetes of 2.5 for  
17 cardiovascular mortality. Would anybody consider  
18 that to be acceptable? Because that's actually  
19 class labeling for the sulfonylureas. So it seems  
20 to me that we should look for parity in how we  
21 consider therapeutic agents for different target  
22 populations.

1 DR. RAUFMAN: Dr. Thadani?

2 DR. THADANI: If I remember, the data we  
3 were shown, that out of some 7,000 patients, it was  
4 one per 10,000 event rate as opposed to one in a  
5 thousand in the active group. So the event rate is  
6 low.

7 So the question to you, okay, the disease is  
8 chronic, a lot of morbidity, patients want some  
9 treatment. What kind of adverse event will you  
10 accept? If it is a younger person who dies or has  
11 a stroke, it could be the worst outcome. I would  
12 rather die with a heart attack than have a stroke.

13 So if you have that, what kind of hazard  
14 ratio are you willing to accept? Because if you  
15 have a softer endpoint on efficacy and you are  
16 saying harder really, body counts or strokes on the  
17 safety endpoint, how willing are you to even cause  
18 a hazard ratio of 2? Why not 1.3?

19 I'm just curious. I know then you run into  
20 the trouble of missing the real effect. But first  
21 there's no harm unless the patients really on  
22 parenteral lines; that's a different ballgame. But

1 we're talking about a population which is either  
2 idiopathic constipation or irritable bowel  
3 syndrome, which patients are on multiple drugs.

4           How much do you weigh that and why -- if you  
5 want to -- even cause of 100 more strokes or  
6 whatever, the real number could be different, why  
7 one is willing to accept that unless the benefit of  
8 efficacy is greater.

9           So I think you have to balance the efficacy  
10 with the safety. You can't just talk about safety.  
11 If the drug is really effective, patients come off  
12 drug and they're dancing, don't worry about it. So  
13 I think you've got to tell me the real safety, how  
14 you're going to measure the efficacy before I feel  
15 comfortable that the safety margin -- to me, 2  
16 might be too high as a ratio.

17           Just a comment. What's the FDA perspective  
18 on that?

19           DR. FIORENTINO: Well, perhaps the  
20 gastroenterologists can pipe in on that. I guess  
21 we don't know the efficacy profile yet, so we can't  
22 do that whole calculus now. I guess one thing I

1 would say is if we have a drug that doubles your  
2 relative risk -- just to keep in mind that it was  
3 alluded to that patients at a higher baseline  
4 cardiovascular risk, we may not accept a doubling  
5 of their cardiovascular risk.

6 As you said, for a younger woman who has no  
7 cardiovascular risk factors, very low  
8 cardiovascular risk, a doubling of a very, very low  
9 risk may not be that concerning. But that's  
10 something that I think this discussion needs to  
11 continue on.

12 DR. THADANI: Concerning for whom? If it is  
13 my child who ends up having a stroke -- I mean, you  
14 realize -- in a patient who already has disease,  
15 you are unwilling to accept them because they could  
16 have a heart attack or a die, but a person who is  
17 relatively young, why the threshold of 2? Why  
18 not -- I'm just curious why not lower in a larger  
19 sample size to absolutely make sure we're not  
20 causing any harm to the patients?

21 DR. FIORENTINO: And let's have the  
22 gastroenterologists, if they want, help answer that

1 question, during our question period.

2 DR. RAUFMAN: We'll take one more question.  
3 I think Dr. Rosen, and then we'll move on from  
4 there.

5 DR. ROSEN: So I just wanted to talk a  
6 little bit about what Dr. Hasler had mentioned,  
7 that baseline, their risk is low, but they're also  
8 on a lot of medicines that do affect their heart.  
9 So they're on amitriptyline, which can affect your  
10 QTc. They're on Zofran, which has effects on the  
11 QTc. They're on erythromycin. In addition to  
12 these medications, they're also on SSRIs and things  
13 like that.

14 So, while their underlying baseline risk may  
15 be low, the risk of polypharmacy is high, and it's  
16 polypharmacy with other drugs that affect their  
17 cardiac perspective. So the only thing I would  
18 throw out there is that when designing these  
19 trials, I do think you have to take into account,  
20 especially with the gastroparesis patients and the  
21 irritable bowel syndrome patients, the effect of  
22 these other medications that are known to have an

1 effect on QTc. Even though the population is  
2 younger, they are at an increased risk because of  
3 the other meds.

4 DR. RAUFMAN: That's a good point.

5 Dr. Hasler, a quick response.

6 DR. HASLER: Yes, very quick. We actually  
7 are following mortality in our gastroparesis  
8 consortium. And over five years of following  
9 nearly 600 patients, we've had, I believe, 16  
10 deaths so far. They're almost all in the  
11 diabetics. It is age-dependent, it's older. And  
12 we haven't seen any -- I agree with everything you  
13 said, and that was going to be one of my comments  
14 later on in the afternoon, is that we do deal with  
15 a lot of cardiac toxic drugs. But in the young  
16 idiopathic women, we just haven't seen much in the  
17 way of really bad consequences. I mean, they're  
18 miserable, but they don't die.

19 **Open Public Hearing**

20 DR. RAUFMAN: Thank you.

21 There were no registrants for the open  
22 public hearing portion of these proceedings. So we

1 will move on to the panel discussion.

2 **Committee Discussion and Questions to Committee**

3 DR. RAUFMAN: Although this portion is open  
4 to public observers, public attendees may not  
5 participate except at the specific request of the  
6 panel. There are both discussion questions and  
7 voting questions.

8 Just by way of introduction to that, for the  
9 voting questions, we'll be using the electronic  
10 voting system. Each of you have three voting  
11 buttons on your microphones, yes, no and abstain.  
12 Once we begin the vote, I'll ask you to please  
13 press the button that corresponds to your vote.  
14 After everyone has completed their vote, the vote  
15 will be locked in. The vote will then be displayed  
16 on the screen. I will read the vote from the  
17 screen into the record.

18 Next, we will go around the room and each  
19 individual who voted will state their name and vote  
20 into the record, as well as the reason why they  
21 voted as they did.

22 So if we could look at the first question,

1 and this is a voting question, I'll read the  
2 question and then open it up for discussion.

3 For new products in the class, can  
4 nonclinical/clinical pharmacology and clinical  
5 data, such as those presented for the newer 5-HT4  
6 agonists, dispel, i.e., alleviate the need for a  
7 dedicated safety study, the cardiovascular safety  
8 concerns, e.g., prolonged QT interval, ischemic  
9 events, raised by the clinical safety experience of  
10 the previously approved 5-HT4 agonists? If yes,  
11 specify on which data you are relying.

12 Maybe everyone will take a few seconds to  
13 read through that question.

14 Dr. Lauer?

15 DR. LAUER: I think one way of thinking  
16 about this is that these early data provide us with  
17 the prior probability of what we'll actually see in  
18 the real world. So we can look at this as a  
19 Bayesian problem. And the cisapride is a good  
20 example, where we would assume that had those kinds  
21 of preclinical data been obtained before the drug  
22 was approved, that would have increased the

1       likelihood of there being a real finding. On the  
2       other hand, tegaserod, where there probably is no  
3       real finding at all, the previous preclinical early  
4       data showed absolutely nothing.

5               So while one can never completely rule out  
6       that there is a problem, one can say, I think,  
7       based on these early types of data, that gives us a  
8       sense as to the likelihood that there's going to be  
9       a problem, and then we can make a value judgment on  
10      the basis of that.

11             So I'm going to answer yes, although the  
12      word "dispel," I have a little bit of a problem  
13      with the word "dispel," because that suggests that  
14      there's no problem at all. I would say that it  
15      would make me feel less disposed to doing a large-  
16      scale definitive study. And I would say that, in  
17      terms of what data I'm relying on, it's all the  
18      data you showed there.

19             DR. RAUFMAN: Dr. Bloom?

20             DR. BLOOM: Two complications with this  
21      question. One is safety concerns, regardless of  
22      whether they're legitimate, and, obviously,

1 tegaserod looms large there, and the other is the  
2 important but brief discussion we had, if you're  
3 incorporating into ischemic events ischemic  
4 colitis, because that complicates it considerably,  
5 if you're really having the data drive your  
6 concerns there.

7 DR. RAUFMAN: My interpretation of this  
8 question, and I'll seek clarification from FDA, is  
9 that these are cardiac ischemic events and not  
10 colonic ischemic events. Is that correct?

11 DR. FIORENTINO: Yes, that's correct. We  
12 would analyze those separately.

13 DR. RAUFMAN: Dr. Granger?

14 DR. GRANGER: I kind of have a similar  
15 approach, I think, to Michael that -- and a  
16 question of clarification here.

17 This is definitely meaning alleviate the  
18 need for a dedicated safety study, because an  
19 alternative -- a middle of the road approach, I  
20 think even the statisticians had suggested, would  
21 be to assure that the phase 3 program had a  
22 representative population that included the high

1 risk patients for which the therapy would be  
2 ultimately used.

3 For example, this very concerning comment of  
4 excluding patients with cardiovascular disease from  
5 a trial designed to look for safety, where that  
6 would be the population where one would be most  
7 concerned, I think is propagating this major  
8 problem that many of us believe we have in drug  
9 development globally, where we tend to have  
10 the -- where all too often we have relatively small  
11 trials in highly selective populations, the basis  
12 for applying these therapies in broad populations  
13 that are much higher risk and then we have no  
14 safety information.

15 So I guess the specific question is might  
16 that be -- I still have some safety concerns that  
17 cardiovascular safety needs to be better assessed,  
18 but not necessarily in a dedicated safety study.  
19 And I'm not sure how to answer this, whether that's  
20 a yes or a no.

21 DR. RAUFMAN: Dr. Thadani?

22 DR. THADANI: I think the question is

1 perhaps maybe because if your preclinical studies  
2 on  
3 the QT, at least give me some reassurance that  
4 we're not going to run into horrendous risk of long  
5 QTc issues or torsades de pointes down the road,  
6 unless there is a major drug-drug interaction.

7 But I don't think you can address the  
8 cardiovascular safety issue from the data we have  
9 seen. Maybe it's noise, it may be real, the FDA  
10 had reacted. So I think in order to do that, I  
11 feel uncomfortable to say yes, because the data on  
12 the cardiovascular safety issue has not been  
13 addressed. And since there's previous drugs of 5-  
14 HT4 agonists, I think this class of drug is going  
15 to have somehow not a black box or worrisome issue,  
16 and I think it has to be resolved for public  
17 perception and for the physicians.

18 So it's a kind of double-edged question. It  
19 should have been separated for QTc-1 and then the  
20 long-term cardiovascular safety, rather than  
21 combining the two together and yes or no.

22 DR. RAUFMAN: Dr. Spiegel?

1 DR. SPIEGEL: Thank you. To me, the  
2 question here is, is there a class effect or not.  
3 We were appropriately spooked by cisapride. Right?  
4 We had concerning results from that. We heard the  
5 story about cisapride. There is now a biologically  
6 plausible explanation for what happened. We have  
7 data that support the clinical observations. The  
8 story makes a lot of sense to me, as a non-  
9 cardiologist.

10 Then it so happens another drug comes along  
11 that happens to have some overlapping effects that  
12 had absolutely no data to suggest that there would  
13 be a cardiovascular -- or at least I shouldn't say  
14 absolutely none, but very little reason to believe  
15 there would be a problem. And then we came out  
16 with these very small numbers at a time that was a  
17 vulnerable time. There were a lot of things  
18 happening in the environment at that time. Safety  
19 concern was a big issue then, and it was put to the  
20 side largely because of efficacy, not necessarily  
21 because of safety.

22 But here, again, in hearing about this

1 preclinical data that, to me, does not raise  
2 concerns, as I'm listening to them as a  
3 gastroenterologist, in a set of conditions we'll  
4 talk about soon that we have nothing for, why are  
5 we even calling this a class effect? Why aren't we  
6 talking about seizures? Why aren't we talking  
7 about ischemic colitis? Why are we talking about  
8 this?

9           The null hypothesis is there's no problem.  
10 Cisapride is an important story we learned from. I  
11 don't see why it would repeat itself. And I'm just  
12 being very naive in saying this, at great  
13 treachery, but I throw it out there as a  
14 gastroenterologist.

15           Why are we talking about this?

16           DR. RAUFMAN: I won't answer that.

17           Dr. Solga?

18           [Laughter.]

19           DR. SOLGA: I'm going to say the same thing.  
20 I was terribly impressed all morning long about the  
21 mechanisms and the discovery, the cisapride  
22 mechanisms of action. And Dr. Fiorentino's

1 wonderful presentation, he states that we  
2 understand the underlying cause of cisapride, and  
3 just a universe of difference from where this  
4 committee was listening to yesterday. We were  
5 talking about rifaximin's possible effect on gut  
6 flora.

7 This seems like very mature science to me,  
8 and I haven't heard a cardiologist on the committee  
9 yet tell me why that may not be true, other than  
10 the fact that we don't always know everything in  
11 medicine.

12 Is there some mechanism for cisapride? Is  
13 there some concern for this class that we haven't  
14 heard? Because as an internist and a  
15 gastroenterologist, I'm feeling, wow. I agree with  
16 Dr. Spiegel. I'm echoing his sentiment.

17 So I'd like to hear more from the  
18 cardiologists in terms of concrete concerns they  
19 have with some class effect story. Otherwise, I  
20 feel like the well was poisoned, and we just need  
21 to get away from the well.

22 DR. RAUFMAN: Dr. Fox?

1 DR. FOX: I won't echo the comments that I  
2 just heard that I would otherwise agree with. I'd  
3 also like to point out that we've heard about one  
4 drug, naronapride, which has some structural  
5 similarity to cisapride, yet does not share the  
6 hERG liability nor does the thorough QT study show  
7 anything.

8 I'd like to bring up that by searching  
9 around, I found another molecule called  
10 prucalopride, which apparently is yet  
11 another -- structurally related to cisapride, but  
12 does not have hERG interaction and has also  
13 published a negative thorough QT study.

14 So, in fact, it supports what I just heard  
15 about there being -- even when there is structural  
16 similarity, there is not a class effect. And  
17 certainly, for some of the other drugs we heard  
18 about, which are not structurally related, there  
19 doesn't seem to be any hint of a problem.

20 The other comment I'll make is that the very  
21 much enhanced receptor seal activity of the newer  
22 agents I personally find reassuring. It's when you

1 get a lot of off-target activity that you tend to  
2 run into problems, especially when you've got a lot  
3 of ubiquitous expression of the other related  
4 targets in other tissues.

5 Then, Mr. Chairman, just a procedural  
6 question. I guess this is listed as a voting  
7 question, so I'm not going to make a vote, but  
8 aren't we supposed to do the blinded voting and  
9 then the explanations or how are we doing this?

10 DR. RAUFMAN: We're having discussion, then  
11 we'll vote, and then we'll go around the table and  
12 everyone will say what they voted and why.

13 Dr. Hasler?

14 DR. HASLER: I want to strongly agree with  
15 Dr. Spiegel and Dr. Solga said. I think that it  
16 looks to be an idiosyncratic effect of cisapride  
17 and in no way related to the 5-HT4 receptor.

18 However, I would comment on what Dr. Spiegel  
19 said about the community being spooked, and I think  
20 that is a very real perception that hangs over this  
21 area in general. And I don't see how we as an  
22 academic and regulatory community don't take that

1       into consideration when we're making decisions.

2               I think it would be terrible if we didn't go  
3       the extra mile and the next whatever "opride" got  
4       approved and had some sort of increased cardiac  
5       death rate from an unknown mechanism, that we  
6       didn't do our due diligence.

7               So I would actually say that although  
8       there's no evidence that there's anything other  
9       than danger from cisapride, I think that we do have  
10       to go the extra mile.

11              Dr. Fox does rightly point out prucalopride.  
12       That is approved in Europe. They use that to treat  
13       lower GI motility disorders, and I haven't heard of  
14       any cardiac toxicity from that. Likewise,  
15       mosapride is available in Asia, and I haven't heard  
16       of any cardiac toxicity of that.

17              So there is worldwide experience with this  
18       class of drugs.

19              DR. RAUFMAN: Dr. Rosenberg?

20              DR. ROSENBERG: Yes. I agree with the  
21       comments that were just made about cisapride as a  
22       class of its own. I do think that we really don't

1 have any way of really being completely reassured  
2 about the lack of effect on ischemic events. I  
3 would agree that from the result of tegaserod, I  
4 personally don't believe in them either and I  
5 expect the probability is very low that we'll ever  
6 find something with any of these agents.

7           However, given that these agents are to be  
8 seeking indications potentially affecting millions  
9 of people, I think we have to go the extra mile, it  
10 was just stated, of making sure that at least we  
11 don't find a signal, even if we go to a very high  
12 threshold as a first step to reassure us before we  
13 proceed further.

14           DR. RAUFMAN: Dr. Thadani?

15           DR. THADANI: I think I buy the part of the  
16 reassurance from the hERG channel and the  
17 selectivity of the agents. I think that perhaps  
18 cardioventricular arrhythmia is probably lower on  
19 the threshold. But I don't think on ischemic  
20 events, once the labelings are there, one can't be  
21 reassured one way or another this is a class effect  
22 or this was universal for one drug.

1           So I think it's up to us or up to the FDA to  
2           make sure the next compound which is approved has a  
3           higher threshold to prove to the society and to the  
4           patients who are going to take it that this is safe  
5           from cardiovascular adverse events. You don't have  
6           to do a three-year trial, but I think a large  
7           enough population exposed.

8           But you're talking about giving it to  
9           younger people, and unless you can show their life  
10          is so much better -- you know, gastroparesis is  
11          different, as I mentioned earlier. So I think you  
12          have to put that into context. Is it going to be  
13          IBD or are you going to chronic constipation? As  
14          my colleague on my right said, they're on a lot of  
15          other drugs.

16          So I think you have to -- because that data  
17          is out there. So I think it's up to the FDA and up  
18          to the gastroenterologists to prove that you're  
19          giving a drug which at least is safe in these  
20          patients from cardiovascular adverse outcomes. I'm  
21          not talking about torsades necessarily, because  
22          those look pretty comfortable. And you'll know

1 that by 14 days or one month if there's any issue  
2 on the QT.

3 DR. RAUFMAN: Dr. Kaul?

4 DR. KAUL: I'm somewhat uncomfortable with  
5 this process. I would respectfully urge the chair  
6 to reconsider your decision to discuss the  
7 rationale before voting, because as I understand,  
8 the whole purpose of the electronic voting system  
9 is to avoid the group mentality, the herd  
10 mentality.

11 So I've been in many meetings, and this is  
12 the first one I have seen this, and I would --

13 DR. RAUFMAN: I think you're  
14 misunderstanding -- I don't think I said anybody  
15 had to explain their rationale for voting ahead of  
16 time. We're discussing the question.

17 DR. KAUL: But the answers are being yes and  
18 no, and the answer should not be, because this is  
19 the whole idea of this electronic voting system.

20 DR. RAUFMAN: I agree, but I'm not directing  
21 anybody to say yes or no. We're discussing the  
22 merits of the question.

1 DR. KAUL: I think the point is that we --  
2 Dr. Bild?

3 DR. BILD: So without saying how I would  
4 want to vote, just to clarify the  
5 question -- because I think we need to know what  
6 we're voting on.

7 The word "dispel" and dedicated safety study  
8 I'm having a little bit of problem with, because if  
9 we didn't say that we would go that route, what is  
10 the sort of safety net? What happens later on that  
11 would identify if there actually were a problem?

12 Maybe someone from FDA could address that.

13 DR. RAUFMAN: Dr. Korvick, would you like to  
14 respond to that?:

15 DR. KORVICK: So the typical, which is  
16 something that is repeated in a lot of drug  
17 classes, is when you have a rare adverse event  
18 that's detected postmarketing, and you haven't  
19 studied it very well. And we're in a pickle  
20 because of the observational nature of many data  
21 there for our errors, MedWatch safety reporting  
22 system. There is no denominator.

1           So people always want to quantify the rate  
2 because what people want to know is what am I going  
3 to tell my patient; how rare is it; how frequent it  
4 is; what do you know. So sort of some kind of  
5 dogma is the best way to get at that, is to study  
6 it pre-approval in a more rigorous way, if there is  
7 a concern.

8           So it is always the tyranny of the small  
9 rare events that, as I said before, is well known.  
10 You don't usually pick up pre-approval.

11           DR. RAUFMAN: Dr. Granger?

12           DR. GRANGER: Without saying whether I would  
13 change my -- I apologize for hinting what I might  
14 vote, but without saying whether or not I'll change  
15 that, to answer Dr. Solga -- because you did ask, I  
16 think, for a cardiology input about what might be  
17 concerning to us.

18           Certainly, the 13 versus 1 event, well, most  
19 likely the play of chance is a signal that would  
20 prompt us to want to assure that drugs in the  
21 class -- and the other thing is with cisapride;  
22 sure, that's what we think the explanation is, but

1 we have so many examples where we're not smart  
2 enough to tell what mechanisms are of impact of  
3 these drugs on the human being.

4           When we see a couple of signals in the class  
5 and the community is sensitized and concerned about  
6 that, I think it's only prudent to be encouraging  
7 that we at least have representative populations,  
8 that we don't exclude the high risk populations  
9 when we study the drug, to assure that we're  
10 getting some safety information about the use of  
11 this class of drug in an at-risk -- in a population  
12 that includes at-risk patients.

13           I actually feel quite strongly about that  
14 aspect of it, at least.

15           DR. RAUFMAN: Dr. Fiorentino?

16           DR. FIORENTINO: So we've heard some  
17 discussion about receptor subtyping and thorough QT  
18 studies as far as how they can reassure us. I  
19 haven't really heard a discussion about the utility  
20 of platelet aggregation studies.

21           The one study that the sponsor seemed to  
22 submit are platelet aggregation studies, and if

1 people can help us understand what these negative  
2 platelet aggregation studies really mean for these  
3 drugs would be very helpful.

4 DR. RAUFMAN: Does anybody want to comment?  
5 Dr. Kaul?

6 DR. KAUL: No.

7 DR. RAUFMAN: You had your finger up.

8 DR. KAUL: I was going to ask a question.

9 DR. RAUFMAN: Dr. Lauer?

10 DR. LAUER: There is a great deal of  
11 controversy about what exactly these various  
12 platelet function tests mean? There are actually  
13 many different kinds of platelet function tests,  
14 and there have been studies done where you take the  
15 exact same patient, let's say patients with acute  
16 coronary syndromes who we know have hyperactive  
17 platelets, and you do the multiple different tests  
18 on the same patients, and you get highly disparate  
19 results.

20 So I don't find it reassuring, but it  
21 doesn't really sway me one way or the other because  
22 I think that our ability to really understand how

1 results on platelet function tests translate into  
2 the likelihood of future events years down the line  
3 is -- it's just not there. The science isn't there  
4 yet. That's my opinion.

5 DR. RAUFMAN: Dr. Kaul?

6 DR. KAUL: Yes. I can address that. I  
7 think the predict-to-accuracy of platelet  
8 reactivity tests is not sufficient enough to  
9 warrant making recommendations. It's neither  
10 prognostic nor is it predictive of treatment  
11 response. So we have to be very careful  
12 about -- the positive predictive values are in the  
13 range of 1 to 2 percent. The negative predictive  
14 values may be a little bit higher, but the positive  
15 predictive values are based on what kind of events  
16 we are looking at.

17 Stent thrombosis is such a rare event, no  
18 matter how good the test is, the positive  
19 predictive value will never be sufficiently high  
20 enough to be clinically useful.

21 The question I want -- if I may, with your  
22 permission, the question I wanted to ask is that

1 we're still not quite sure about this risk that we  
2 saw with Zelnorm, and I wish the sponsor was here  
3 to answer this question.

4 If they saw the safety signal, why did they  
5 not pursue it? Is it something that they knew all  
6 along or why did they not pursue this?

7 DR. RAUFMAN: Dr. Korvick?

8 DR. KORVICK: All I have to say is that you  
9 saw that there was a meta-analysis of 29 studies.  
10 No studies were conducted over the time period that  
11 this drug was on the market. There were only a  
12 handful of events scattered amongst several  
13 studies.

14 DR. KAUL: Well, I would have at least been  
15 curious enough to find out and do some additional  
16 due diligence studies to at least adjudicate the  
17 uncertainty around that. That's why I said I wish  
18 the sponsor were here to answer that question. It  
19 certainly raises questions, in my mind, but I'm not  
20 able to address them with any objectivity.

21 DR. RAUFMAN: Dr. Thadani?

22 DR. THADANI: I think regarding the platelet

1 reactivity, the question is up in the air. You're  
2 talking about general population. We really don't  
3 know what it means. Even in the CRE population,  
4 when they are looking at clopidogrel response, some  
5 of the European studies are coming positive, but  
6 that doesn't address the real issue in the general  
7 population.

8           So, A, the metrics are different. B, we  
9 don't know if somebody is reactive to some of the  
10 units, how it translates to outcomes. So I think  
11 that's a nice mechanistic aspect, but I don't think  
12 there's any therapeutic -- even in clopidogrel and  
13 other newer drugs, we really don't know what to  
14 make of it. And as Dr. Kaul said, the stent  
15 thrombosis is 1.6 to 2., and most of the trials are  
16 not powered to even look at that. So you're  
17 talking about 100,000 patients, and we don't have  
18 that.

19           So I think those are nice studies, but that  
20 doesn't mean what is the translation to outcome.  
21 Unfortunately, at the present, we don't have any  
22 data on that.

1 DR. RAUFMAN: Dr. Spiegel?

2 DR. SPIEGEL: I just want to briefly respond  
3 to Dr. Kaul's question. I would suggest, although  
4 the sponsor is not here, that the reason was  
5 because the medicine didn't work. It didn't work  
6 very well. And I don't say that facetiously.  
7 There just wasn't a strong demand for it. But  
8 take, in contrast, alosetron, which we heard about  
9 earlier, a therapy that was taken off the market  
10 because of ischemic colitis.

11 It's the only instance I know of, the FDA  
12 would know better, where because of patient outcry  
13 and other factors, it was brought back onto the  
14 market, because it was -- to this date, I would say  
15 the most effective -- certainly most effective FDA  
16 approved therapy we've ever seen for irritable  
17 bowel syndrome. Maybe some of you will disagree,  
18 but based upon the data, it was extremely  
19 effective. And for the right person, it's still  
20 extremely effective and still has a very favorable  
21 risk-benefit ratio.

22 So I'm just making the point that we do need

1 to continue to keep in mind the benefits, which  
2 we'll talk about, for these medications when  
3 determining how aggressively to track down these  
4 tyrannical, yet very rare events.

5 DR. KORVICK: I just have to reflect on the  
6 delta for efficacy, and it's IBSD, which may have a  
7 broader than IBSC. But the delta in those cases  
8 was 10, 15 percent, same range.

9 DR. RAUFMAN: Dr. Black?

10 DR. BLACK: Thank you. I've been really  
11 struggling with this, as I see many of the rest of  
12 you are. And the question I guess to me is, is  
13 there anything we can do, short of a study in  
14 patients, not in rabbit Purkinje fibers, that will  
15 reassure us that it's not going to be an issue?

16 I think we have to include an adequate  
17 number of high risk patients. I've been convinced,  
18 which I wasn't before I started to read this  
19 material, that this was a big unmet need. I think  
20 the gastroenterologists ought to comment a little  
21 more about how much of an unmet need it really is.  
22 And it's a very tough question.

1           I'm afraid of paralysis of the need to  
2       develop new drugs, and we have to obviously weigh  
3       the risks and the benefits, and I'm not clearly  
4       convinced that I understand how much of a risk this  
5       really is or how much of a problem it really is.  
6       So we can accept risk if there's enough benefit,  
7       and I don't think we know very much about that.

8           DR. RAUFMAN:  If I can comment.  I think  
9       Dr. Greene was very eloquent this morning in  
10      expressing how much of a need there is.

11          DR. BLACK:  He very definitely was, but I'd  
12      like to see somebody else's --

13          DR. RAUFMAN:  Perhaps Dr. Hasler would  
14      comment.

15          DR. HASLER:  I think Dr. Rosen and  
16      Dr. Spiegel and I can all comment on that.  It is  
17      an enormously morbid set of conditions which takes  
18      people away from their lives at a very, very young  
19      age.  These people are sick.  They're disabled.  
20      They cannot work.  They can't sleep.  They lose  
21      weight.  They can't eat meals.  They undergo  
22      numerous surgeries in an effort to survive.  Many

1 of them require supplemental tube feedings or TPN.

2 We're talking about the cardiac death rate  
3 of a -- possible cardiac death rate of a class of  
4 drugs, but these people die from medical  
5 interventions all the time, as I'm sure Dr. Rosen  
6 and Dr. Spiegel will tell you. I have patients who  
7 have had gastric stimulators who have died from  
8 infections. I've had patients who get TPN who die  
9 from systemic infections. I've had a handful of  
10 patients over the years commit suicide because  
11 they're so devastated by their diseases.

12 So in their most extreme forms, these  
13 conditions are as devastating as any illness that's  
14 out there.

15 DR. RAUFMAN: Dr. Rosen, would you like to  
16 comment from a pediatric perspective?

17 DR. ROSEN: Sure. So I absolutely agree  
18 with Dr. Hasler. I think these are, in many  
19 ways -- we had a drug meeting about IBD and, in  
20 many ways, these patients are much more debilitated  
21 from a quality of life perspective and it's waxing  
22 and waning, and there's no predictability to it.

1 It's any age group. And I think the need for these  
2 class of drugs is tremendous.

3 I do disagree with the tegaserod. I do  
4 think it was a very helpful drug, and I think there  
5 were a lot of patient letters written on that drug,  
6 as well, but just the company decided not to pursue  
7 it. And I think people really are desperate for a  
8 medication.

9 I just want to also just throw in -- because  
10 I think one of the things that we were asked about  
11 is reflux and the role for this class of drugs for  
12 non-PPI responsive reflux. And when you think  
13 about reflux and what PPIs do -- and this is just  
14 very briefly. PPIs don't get rid of your reflux.  
15 It just changes it to non-acidic. We all know that  
16 it doesn't decrease your reflux burden at all.

17 When you look at the drugs that we have that  
18 actually reduce your reflux burden, we have one,  
19 and that's baclofen, you know, in that class of  
20 drugs. Everything else does not treat reflux, stop  
21 reflux from coming up.

22 So I do think even for the less severe

1 diseases, such as less severe than gastroparesis,  
2 there still is a role for this class of drugs, even  
3 on the more milder spectrum. I'm not saying the  
4 spitty baby or the adult who's just fine on twice a  
5 day PPI. But there still is a role for these  
6 medicines in complicated reflux, as well, again, to  
7 avoid the surgeries that Dr. Hasler is talking  
8 about.

9 DR. RAUFMAN: Dr. Spiegel, did you want to  
10 comment on the GI need?

11 DR. SPIEGEL: I would like to add a little  
12 bit. I've spent a lot of time describing the  
13 quality of life of these patients, and you don't  
14 need to even see data. We've all had GI distress  
15 at some time in our life. We can all remember the  
16 last time you were doubled over throwing up into a  
17 toilet, just to be very blunt about it. And we  
18 remember these things, that it's awful. But to  
19 have that day in and day out, and that is literally  
20 your life, is unthinkable, unless you have these  
21 experiences.

22 So the quality of life measure on the SF-36,

1 not even for these most extreme TPN cases, but for  
2 community-based IBS, is on par with advanced  
3 diabetes and chronic kidney disease, even with  
4 dialysis. That's been repeated over and over  
5 again. The worker productivity decrements are  
6 tremendous, and even worse than that is  
7 suicidality. And we've published work on the  
8 suicidality risk of patients with chronic abdominal  
9 pain.

10 When we have abdominal pain, we hope it's  
11 going to go away. When it doesn't go away, you  
12 hope it's really going to go away. And when it  
13 stays with you day and day out and week in and week  
14 out, your life completely changes.

15 So these are conditions -- I mean, I'm a  
16 gastroenterologist. I see exsanguinating ulcer  
17 bleeds all the time. We use aspirin left and  
18 right, with a number needed to harm of about 2 to  
19 300. We're talking about rare events here. We're  
20 not throwing caution to the wind. I have a family  
21 member with a motility disorder. I would be  
22 willing to -- she would be willing to use this to

1 risk that number needed to harm, I assure you.

2 So I do want to put this into perspective,  
3 because I think it's very important.

4 DR. RAUFMAN: Dr. Bild?

5 DR. BILD: Yes. Thank you. I find the  
6 testimony of the gastroenterologists really  
7 enlightening here. One of the problems I have is  
8 that we keep saying "these patients" and we've been  
9 given these four different disorders. And my sense  
10 is that there are lots of treatments for certain  
11 types of constipation, gastroparesis, maybe less  
12 so -- and we heard a little bit about the possible  
13 efficacy with constipation. I'm not sure about  
14 gastroparesis.

15 So if at all possible, I think it would be  
16 helpful to talk about which subset people are  
17 talking about rather than just always lumping them  
18 together.

19 DR. RAUFMAN: Dr. Hasler, do you want to  
20 address that?

21 DR. HASLER: Well, why don't I just talk  
22 about the group that I follow, which is

1       gastroparesis and intestinal pseudo-obstruction,  
2       and what we use and the difficulties with  
3       management. Gastroparesis has a very limited  
4       number of therapies which are available. The one  
5       that's FDA-approved is metoclopramide or Reglan.  
6       It is a drug that all the textbooks say has a 25  
7       percent side effect rate, but I think that's low by  
8       at least a factor of 2.

9               It has a boxed warning on it for the risk of  
10       tardive dyskinesia. That is a real risk. I saw  
11       one new patient with that just less than a month  
12       ago. She's a woman my age, early 50s, who actually  
13       was put on the drug by a University of Michigan  
14       physician four years ago, who is not a motility  
15       physician, and was told to go home and follow-up  
16       with her family doctor. She came back to see me  
17       last month, chewing her lips. Her mouth is raw.  
18       She has uncontrolled movement disorders, and she's  
19       been off the metoclopramide for a year and a half.  
20       That's one drug.

21               Erythromycin is on the list of things to  
22       try. That drug works maybe in a third of patients.

1 Domperidone is another drug we use, which is not  
2 FDA approved. And in our area, we're very  
3 economically depressed. Most patients can't afford  
4 that.

5 There's the electrical stimulator, which has  
6 a humanitarian device approval, but is not formally  
7 approved by the FDA. So to get that technology,  
8 you have to go to a center that has IRB approval  
9 for such technologies.

10 There are other therapies, which, at our  
11 tertiary center, we do offer for that condition.  
12 We use a lot of tricyclics. Even though they're  
13 not motor stimulants, they do reduce some of the  
14 sensitivity of the stomach. But I think as Dr.  
15 Rosen has said, those have tremendous side effect  
16 profiles. Probably half of our patients have  
17 toxicity from that.

18 We use a moderate amount of drugs almost as  
19 rescue techniques. So, for example, in my patients  
20 with relentless nausea, I use of dronabinol, which  
21 is synthetic THC, a marijuana derivative. Michigan  
22 is a medical marijuana state, at least until the

1       Republicans take over next year.

2                 [Laughter.]

3                 DR. HASLER:   And I would say my Monday  
4 morning gastroparesis clinic, half of them show up  
5 on medical marijuana.

6                 So it's a very challenging thing.  None of  
7 those therapies is ideal.  Back in the '90s, when I  
8 started taking care of these kinds of patients,  
9 cisapride was the drug of choice.  It was a very  
10 good drug.  I think it was probably better than all  
11 of the ones we use nowadays, and I feel badly that  
12 the drug got pulled off the market.

13                I know we've talked about a number of  
14 serotonin agonists which are in development.  And  
15 I'm not entirely sure the new serotonin agonists  
16 are going to be any better than cisapride.  In  
17 fact, I would say there's a high likelihood that at  
18 least for gastroparesis, they may be worse.

19                For example, tegaserod was very poor for  
20 gastroparesis.  And I think if you had to go in and  
21 design your own boutique gastroparesis drug, you  
22 would design a drug just like cisapride, a

1       serotonin 5-HT4 agonist to stimulate antral  
2       contractions, with some weak 5-HT3 antagonist  
3       effects, to have an anti-Afrin effect, to have an  
4       antiemetic effect, some 5-HT1 effects to relax the  
5       fundus to allow the stomach to accommodate food,  
6       and, also, some weak dopamine D2 antagonist  
7       effects, also to have an anti-nausea and anti-  
8       vomiting effect.

9                So there are some significant things which  
10       could be provided by this class of drugs.

11               DR. RAUFMAN:   Dr. Rosenberg?

12               DR. ROSENBERG:   Thank you.   I'm concerned  
13       that we're heading to one end of the spectrum of  
14       the academic gastroenterologists about treating the  
15       sickest of patients, but my understanding is this  
16       drug will be marketed to more common, much less  
17       severe patients, millions of them.   And I think we  
18       need to -- for the broader perspective, the number  
19       needed to harm in those patients versus the  
20       sickest, it's a different discussion.   I think we  
21       need to keep that in mind, because if this drug  
22       comes to the market, they will be prescribed many

1 more times to these patients that you just  
2 described.

3 DR. RAUFMAN: Dr. Thadani?

4 DR. THADANI: Conflict. My wife is a  
5 gastroenterologist. But she's not practicing  
6 anymore, so it's not a conflict.

7 Now, the problem -- his point is well taken  
8 because every time you come back to the discussion,  
9 I realize there's a need, from a GI point of view,  
10 but you always bring about very sick patients who  
11 are on a TPN, gastroparesis. But you're lumping  
12 this common indication with an IBD and other  
13 chronic, and most of the time these patients end up  
14 going to a psychiatrist, they get put on  
15 amitriptyline and everything else.

16 So I think we have to talk about separate  
17 disease process, severity, rather than lumping them  
18 together. You've got so many millions of people  
19 who have minor problems.

20 DR. HASLER: I think you'll see similar  
21 morbidity with other motor disorders.

22 DR. THADANI: I realize that, but, then we

1 are told that benefit is only 5 or 10 or 15  
2 percent, which is not huge. And if there's any  
3 harm, I think we have to separate the diseases  
4 process, the severity, and if you want to get  
5 approval in patients who are severely diseased who  
6 have TPN, need surgery -- because surgical risk  
7 could be 1 percent anyway.

8 So I think you have to separate that from  
9 the GI reflux, because some people with GI reflux,  
10 you can put a clip in the stomach/esophageal  
11 junction and probably reduce the reflux. I'm not  
12 saying that's the way to go.

13 So I think we have to make sure that we  
14 separate out these four different -- rather than  
15 talking all together, which is probably in the  
16 second question.

17 DR. RAUFMAN: Dr. Spiegel?

18 DR. SPIEGEL: I just would like to respond  
19 to Dr. Rosenberg's question. Indeed, we can talk  
20 about individual cases. The data that I'm citing  
21 in terms of quality of life are amongst community-  
22 based individuals coming to see the doctor. And

1 these are individuals who have reached enough  
2 symptoms that they've come to see the doctor. And  
3 we prescribe lots of things to these individuals  
4 that are not FDA approved that probably have a  
5 worse adverse risk profile. And for that matter,  
6 we prescribe aspirin to lots of people, and we can  
7 talk about aspirin all day, number needed to harm.

8 We're not talking about prescribing  
9 chemotherapy here. We're talking about prescribing  
10 what seem to be very, hopefully, safe and effective  
11 medications, including, frankly, cisapride. We  
12 could talk about that, too.

13 These are patients that come out of the  
14 community not just to the tertiary care centers,  
15 but to primary and secondary care centers with  
16 persistent symptoms. I mean, we have to rely upon  
17 doctors to make the right decision about -- and  
18 with their patients.

19 I really think that there is an underlying  
20 concern that this is not a serious set of  
21 illnesses. And it's true that we can make it seem  
22 worse than maybe it is, and I think constipation is

1 one thing we haven't talked about that maybe  
2 doesn't quite fit with some of these other  
3 conditions. That's very fair. We could talk about  
4 that. But I don't think we're overplaying it.

5 DR. RAUFMAN: If I could just comment, and  
6 then we'll move on to other questions. This is not  
7 my area of expertise, but I've certainly sat on  
8 many committees in my role with the AGA teaching  
9 committee, participated in putting together a slide  
10 set having to do with these conditions.

11 These are, I agree -- I mean, again, just  
12 have another gastroenterologist voice an opinion  
13 that this is a highly morbid set of conditions and  
14 that the cost to society of missed days, people not  
15 working, et cetera, et cetera, is huge. This has  
16 been calculated and done many, many times.

17 I agree with my colleagues in GI that this  
18 condition or these set of conditions should not be  
19 understated.

20 Dr. Fox?

21 DR. FOX: Thank you, Mr. Chairman.

22 I just wanted to pick up on something

1 Dr. Korvick said and something Dr. Thadani said.

2 I agree with Dr. Korvick that the  
3 spontaneous adverse event reporting system, while  
4 of some utility for sort of gross signal detection,  
5 has many flaws and should not be relied upon as a  
6 quantitative assessment of risk or of crude  
7 incidence even. But that tyranny of small numbers  
8 actually extends to randomized control trials, as  
9 well, especially, as Dr. Thadani would like to see,  
10 to be able to exclude risk in the young, otherwise  
11 low risk patient, that graph you saw from the FDA  
12 statistician quickly shoots to the moon in terms of  
13 sample size and patient years of follow-up and  
14 becomes unfeasible to do those trials.

15 There could be some middle ground, though,  
16 that we should consider, which is if routine  
17 pharmacovigilance is relatively weak, there are  
18 better and better enhanced pharmacovigilance  
19 techniques now available to the industry with  
20 respect to pharmacoepidemiology study with various  
21 ways of adjusting for background confounders. And  
22 it provides -- while it doesn't have the same power

1 as a randomized control trial, especially a blinded  
2 one, it does give you the power of a very large  
3 denominator, and you can repeat those kinds of  
4 studies using databases in the United States.

5 There are several available, good ones.  
6 There are several good ones available in western  
7 and northern Europe. And that way, you can  
8 replicate, if you will, a signal or the absence of  
9 a signal to provide the kind of reassurance that  
10 everyone would like to have that we're not harming  
11 people while we're trying to take care of what are  
12 otherwise serious medical problems.

13 DR. RAUFMAN: Dr. Rosen? No?

14 DR. THADANI: I don't think -- with respect  
15 to the industry and everybody else, it's not  
16 unfeasible. I think you can easily do a hundred-  
17 thousand patient trial very quickly. I realize you  
18 want to address the later issues in a population.  
19 And keep it very simple. Just do the headcount and  
20 do the stroke, forget about the other softer  
21 endpoints of acute coronary syndrome or  
22 revascularization, which my colleagues are doing in

1 the CBS trials.

2           So it's doable. It could be very cheap, and  
3 I hope you don't have to go to China or India where  
4 they can do it in one week. But if you did it in  
5 an American population, you're telling me -- there  
6 are millions of patients out there. I can't  
7 understand. Why can't you make a simple trial,  
8 don't pay them too much money? You start with a  
9 trial, you get a large sample, follow them for  
10 five, three, six months, whatever, and just say,  
11 okay, follow-up, you're going to count the heads,  
12 we're going to count how many people had a stroke,  
13 which is a greater risk in younger people.

14           Maybe you could take an ECG for QA  
15 infarctions; I know they get hospitalized. I think  
16 you could make it simple and still do a trial  
17 rather than spending 10,000 on each patient with  
18 very sophisticated trials.

19           DR. TEERLINK: Show me one.

20           DR. THADANI: I would love to do it, but my  
21 colleagues won't go for it. Look at the GUSTO  
22 trial. The GUSTO trial had 40,000 patients. That

1 was more complicated. This is the TPA with  
2 streptokinase to show a .6 percent difference in  
3 saving lives. So then you translate it into  
4 millions.

5 I think it's doable. Here you're talking  
6 about harm, not benefit necessarily. Benefit  
7 clinically, so you put your perspective, you say,  
8 okay, I will improve 30 percent of the patients, if  
9 they are not miserable, which will be great. Who  
10 wants to be miserable and not be able to pass the  
11 bowels?

12 You could show the safety, and you could a  
13 quick trial. Come on, you've got 5, 10, 15 million  
14 people, and once and for all you address it and  
15 forget it. Sorry. I've said enough.

16 DR. RAUFMAN: I think we're hearing some  
17 variety of opinion. Maybe we'll take a few more  
18 questions and then take the vote and allow  
19 everybody to express their thinking after we've  
20 voted.

21 Dr. Bloom?

22 DR. BLOOM: Just to point out that a

1 hundred-thousand patient study was done with  
2 tegaserod. It's 50 in each arm, 50-some-thousand  
3 with tegaserod. It was an observational cohort  
4 study. It was published last year. It was  
5 negative as far as association with cardiovascular  
6 events. And I'm astonished that this committee is  
7 ignoring that. Either the study is worthless, but  
8 -- well, maybe that's it.

9 DR. THADANI: If you have an observational  
10 study, you can't control for baseline variables.  
11 If you can do observational, why not do control  
12 studies?

13 DR. BLOOM: Well, here's a second one, too,  
14 on outcomes with matched case control by Anderson.  
15 And we're ignoring those data. I understand  
16 entirely that these data are out here and we have  
17 to deal with them, but that's not necessarily  
18 science-driven as far as risk assessment.

19 DR. RAUFMAN: Again, does anyone have  
20 something new to add to the discussion? I think,  
21 again, we've heard some variety of opinion. We've  
22 heard opinion regarding the severity and perceived

1 need for this class of drugs in treating these  
2 patients.

3 So with that, I would ask, if there's no  
4 further discussion on the question, we'll now begin  
5 the voting process. Please press the button on  
6 your microphone that corresponds to your vote. The  
7 votes will then be locked in.

8 [Vote taken.]

9 DR. RAUFMAN: I will read the vote results  
10 into the record. There were 14 yes votes, 8 no  
11 votes, no abstentions, and everyone voted. And  
12 we'll go around, starting with Dr. Kumar. Please  
13 tell us how you voted and why.

14 DR. KUMAR: I voted yes, that the data, as  
15 we heard this morning and afternoon, does dispel,  
16 because even if such a study were conducted, would  
17 it fully dispel the notion that there could be a  
18 risk. And then I thought about several personal  
19 anecdotes. Would I take it on those lines? Would  
20 I take it? Would I give it to my family member?  
21 And in the context of the disease and then looking  
22 at it from a pragmatic standpoint on a population

1 basis, I think the risk is small enough such that  
2 the benefit of the drug exceeds the risk inherent  
3 to it.

4 Then there's also this whole issue of  
5 perfect is the enemy of good. I don't think we'll  
6 ever have perfect data, but at this point, I think  
7 to move forward with the trial and then to analyze  
8 the risk factors within the trial probably makes  
9 the most sense to me.

10 Thank you.

11 DR. RAUFMAN: Dr. Sood?

12 DR. SOOD: Yes. I said yes, based on the  
13 need of these medications, which our patients, have  
14 and the data from the preclinical studies in vitro  
15 and in vivo was pretty convincing to me for the  
16 safety of these medications.

17 DR. RAUFMAN: Dr. Hasler?

18 DR. HASLER: I voted no. And I wasn't  
19 really a solid no on this, because I certainly  
20 acknowledge that it will be very tough to do any  
21 sort of a dedicated study. But the reason I voted  
22 no is I'm not sure we know the exact reasons why

1 these drugs had their cardiac toxicities. That's  
2 especially true for tegaserod. So that was my  
3 vote.

4 DR. RAUFMAN: Dr. Kaltman?

5 DR. KALTMAN: I was a hesitant yes. I agree  
6 there's an important need for these drugs. Their  
7 safety profile with the preclinical data seems  
8 reassuring, although not convincing to me. There  
9 was some effect of naronapride on some of the ion  
10 channels. So I think that needs to be further  
11 evaluated. But I think a clinical trial looking at  
12 safety, unless it's powered to the millions,  
13 probably is not going to be very convincing. But I  
14 do feel there's a need for some kind of vigilance  
15 following the approval of these drugs.

16 DR. RAUFMAN: Dr. Granger?

17 DR. GRANGER: I voted yes, and it's because,  
18 as we've all been saying, the QT data I think is  
19 relatively clear, and the tegaserod data I think is  
20 unconvincing for a real safety issue, mostly likely  
21 related to the play of chance.

22 But I do have two caveats that are important

1 for me. One is that I really think there needs to  
2 be due diligence, because I might change my mind if  
3 I -- really, if those events were really looked  
4 through very carefully, and there was a more clear  
5 signal that these were really entirely unexpected,  
6 convincing, hard events, these 13 to 1 in that  
7 trial.

8 The second caveat is I do think that safety  
9 of these drugs and all drugs used in patients who  
10 are at risk for cardiovascular disease, because it  
11 is the number one cause of death and disability in  
12 the world. They are used in the aging population  
13 and that we do have a responsibility. When we look  
14 at safety -- if we haven't looked at cardiovascular  
15 safety and it's being used in a population of  
16 patients at risk, we haven't assured safety of the  
17 drug, and that's one of the responsibilities of the  
18 FDA.

19 So I do think the trials -- even though I  
20 don't think a dedicated cardiovascular safety trial  
21 would end up needing to be 10,000 patients or  
22 whatever is necessary. I do think there needs to

1 be -- that the trials need to be designed in a way  
2 to provide information regarding the at- risk  
3 patient.

4 DR. RAUFMAN: Dr. Shen?

5 DR. SHEN: I voted yes, for several reasons.  
6 So, actually, in my tertiary care clinical  
7 practice, I probably encounter -- at least every  
8 year, the patient died from aspiration pneumonia,  
9 from bad GERD reflux, gastroparesis, general GI  
10 dysmotility. So I think mortality is there, and  
11 then you sort of balance these medicines' potential  
12 lethal side effect; its mortality for the bad GI  
13 disease, GI motility disease even more.

14 The second one is one is about they run the  
15 clinical trial for these safety issues, the trial.  
16 Yes, you can do the 10,000 and 20,000 patients and  
17 100,000 patients. But in my clinical practice, if  
18 we'd run the trial, and then my institution and my  
19 chairman said we don't want to lose money -- so the  
20 average trial you do is like minimal; you have  
21 \$6,000 per patient enrolled. Now, this is  
22 like -- there's an ideal world, there's a practical

1 world.

2 The third thing is what are the drugs we  
3 have? Dr. Hasler mentioned about erythromycin.  
4 Erythromycin has tachyphylaxis. It worked, worked  
5 for three days. Second is you have Reglan as a  
6 black box. The third one is domperidone, cross-  
7 border.

8 So as a gastroenterologist, what is the tool  
9 I have? For the severe disease, we have a TPN, can  
10 cause death; we have a gastric pacer, can cause  
11 death; we have the ventilating pack tube, can cause  
12 complications, which the major complication is  
13 1 percent.

14 So this is like my rationale; I voted for  
15 yes. Thank you.

16 DR. RAUFMAN: Dr. Black?

17 DR. BLACK: I also voted yes. I didn't have  
18 the courage to abstain, which is what I really  
19 wanted to do.

20 [Laughter.]

21 DR. BLACK: It was very difficult, I think,  
22 as we talked about, to really decide what side of

1 the fence. But I was convinced that there is a  
2 need. I'm convinced that my colleagues who have to  
3 deal with it that they could use some help. And I  
4 don't think we need to -- it's going to be  
5 appropriate to do the large clinical trial that  
6 might somewhat reassure us, but even that's not  
7 necessarily reassuring.

8 So I think the studies presented are  
9 helpful, but I can't pick any one out, and I think  
10 probably cisapride is a little different than some.  
11 And I'm interested that it probably was the most  
12 effective drug you had, and maybe we ought to think  
13 about that a little more carefully.

14 DR. RAUFMAN: Dr. Bild?

15 DR. BILD: Yes. I found this discussion  
16 very helpful. I found myself flipping back and  
17 forth several times, but I decided to come down on  
18 yes. I thought the preclinical data showing the  
19 better selectivity of this drug compared to the  
20 earlier ones; but I guess I really would have liked  
21 to have said "yes, but," and one of the buts would  
22 have been a better pharmacovigilance study

1 afterwards so that, again, we could identify a  
2 signal if it emerges later.

3 The other is that I found it a little more  
4 compelling for the gastroparesis patients than  
5 perhaps for patients with constipation, and maybe,  
6 if the drug is approved, it would be indicated for  
7 some conditions and not others.

8 Then, finally, I know that the feasibility  
9 of doing a really well done clinical trial can be  
10 difficult.

11 DR. RAUFMAN: Dr. Richig?

12 DR. RICHIG: I voted no, and it's based on  
13 the fact that I'm not a hundred percent secure in  
14 the safety of these compounds. Based on a new  
15 compound coming through, if it is changed in some  
16 way, could that make it even worse? It's just not  
17 convincing to me as it's written here for the  
18 "dispel" and dedicated studies. I had to say no;  
19 also, based on the fact that we're dealing with a  
20 huge population of people here and the diversity of  
21 age, not just young patients, but older ones, as  
22 well.

1 DR. RAUFMAN: Dr. Teerlink?

2 DR. TEERLINK: So I voted yes, and I voted  
3 yes in the context of framing this as a general  
4 question, since we were really -- none of us  
5 received enough information on any specific  
6 compound, even tegaserod or any of these compounds,  
7 to really do a specific case analysis.

8 I viewed this as a general question. I do  
9 believe that these can, in fact -- those other bits  
10 of information can ameliorate the need for a  
11 specific large-scale cardiovascular safety study.  
12 I'm not saying, though, that I think they have the  
13 data -- the extant data has excluded that  
14 possibility in currently available therapies.

15 I agree that there's a need. Actually, in  
16 my heart failure clinic, I have lots of patients  
17 who have problems in terms of constipation all the  
18 time, and I have one patient who begs me to put her  
19 on cisapride continuously because she had good  
20 effects with it before and had to get off of it.  
21 So I feel that need in things.

22 I don't believe that either of the events,

1 or pseudo-events, that we've seen are class effects  
2 of the 5-HT4 agonists. And so I'm not going to  
3 impugn the whole body, and I believe we should use  
4 a Bayesian approach to this.

5 So I think that thorough QT data does help  
6 us predict whether there's going to be bad effects  
7 in terms of QT prolongation and torsades de  
8 pointes, which is the main side effect we had with  
9 cisapride. And I think we can kind of say reduce  
10 the risk of that in these oncoming agents.

11 Finally, I will say that I think large-scale  
12 cardiovascular studies certainly can be done  
13 particularly in this kind of case, where it's  
14 basically outpatient therapy, and it can be just  
15 done starting patients on therapy, following them,  
16 and just doing basically safety assessments.

17 We just got done doing a 7,000-patient, and  
18 none were near that big, but the acute heart  
19 failure study with ASCEND, and it was a very  
20 intense study, and that was easily done. So I  
21 think they can be done. The question is whether  
22 they should or need to be done.

1 DR. RAUFMAN: Dr. Greene?

2 DR. GREENE: Despite many decades of my  
3 cardiology friends telling me that the heart is the  
4 most important organ in the body, I did vote yes.  
5 I think the preclinical data is very good. I'm  
6 willing to accept some risks for the great need  
7 that we have in these patients. I also have a  
8 concern that if we try to be too perfect in this  
9 and mandate these huge studies, they may inhibit  
10 pharmaceutical companies from developing drugs.  
11 And if they do these studies, then the cost of the  
12 studies will get somehow passed on to the patients  
13 in the future.

14 DR. RAUFMAN: Dr. Rosenberg?

15 DR. ROSENBERG: Yes. As many have said, it  
16 was a difficult decision. I voted no; no, but,  
17 maybe. But based on the strict interpretation I  
18 had of the question, which was based on the  
19 available data, does this need dispel the  
20 cardiovascular safety concerns, just answering that  
21 question, I could not say yes. We've been burned  
22 too many times with prepared clinical data and all

1 the even early clinical data showing a favorable  
2 safety profile such that we can be reassured.  
3 However, I'm not sure that the best way to answer  
4 this question for the cardiovascular safety profile  
5 is dedicated safety studies. There may be other  
6 ways to address that.

7 So, again, my response is based on strictly  
8 answering your question; tried, like some of my  
9 colleagues, not to consider the medical needs, the  
10 feasibility of a large clinical trial. I didn't  
11 think that's what we were asked to answer here.

12 DR. RAUFMAN: Dr. Bloom?

13 DR. BLOOM: Yes. I voted yes, and it was on  
14 the basis of the two considerations of the elevated  
15 QT and the ischemic disease. The vast majority of  
16 elevated QT goes through the hERG channel.

17 I urge those of you interested to look at  
18 the data -- many of you are familiar with  
19 it -- that's come out of ILSI and HESI studies  
20 product that have defined, with the appropriate  
21 numbers, the sensitivity/specificity for supporting  
22 the concordance for hERG, along with the conscious

1 dog, to predict the clinical outcomes for elevated  
2 QT and torsades de pointes. And when you add the  
3 total QT studies, the data are very compelling on  
4 being able to manage that risk.

5 As it relates to ischemic disease, I think  
6 the association is poor. I think that even if  
7 there was a hint of association there, whether that  
8 is a class effect. And I think to do all the  
9 things that are implied that we've talked about  
10 today based on that is wrongheaded, in my view.

11 Now, that doesn't preclude including in  
12 phase 3 safety studies additional things that allow  
13 you to manage the perception of cardiovascular risk  
14 and the remote possibility that it's real.

15 So the operative word there was "dedicated,"  
16 and that's the basis on which I voted.

17 DR. RAUFMAN: Dr. Kaul?

18 DR. KAUL: I voted no. These studies are  
19 conducted in a sanitized and reductionist  
20 environment that, in my opinion, do not faithfully  
21 replicate the complex phenotype and pathobiology of  
22 the disease process and the associated

1 vulnerability to potential safety signals that  
2 might be modulated by a variety of factors,  
3 including co-morbid conditions, drug interactions,  
4 genotype interactions.

5 So I agree with the FDA that the negative  
6 outcomes of nonclinical studies do not rule out  
7 potential safety concerns in humans, but they can  
8 be helpful. They can help set the roadmap  
9 especially if there are some signals.

10 So I clearly acknowledge that there is an  
11 unmet need, and that is one of the reasons why we  
12 should persuade and encourage the sponsors to  
13 determine efficacy validly, to detect risk  
14 prudently, and to do both in a timely and efficient  
15 way. Only this way we can avoid controversies like  
16 Vioxx and rosiglitazone and Meridia, and cisapride.

17 DR. RAUFMAN: Dr. Spiegel?

18 DR. SPIEGEL: I voted yes. I've sort of  
19 made my points, more or less, already. So I'll  
20 keep it short. I do agree with the sentiment that  
21 we can't always let perfect be the enemy of good  
22 enough. I understand the points that were just

1 made. We probably can do a safety trial for  
2 ischemic colitis. That may be a more relevant  
3 study to do, but we're not here to talk about that.

4 We could do lots of things. But I'm not, at  
5 this point, seeing the data strong enough to turn  
6 back the clock right now. I think it's more  
7 important to move forward.

8 DR. RAUFMAN: Dr. Thadani?

9 DR. THADANI: I voted no, for the main  
10 reason that the question doesn't address all the  
11 safety concerns that are out there. We have to  
12 address that. Given the very large population who  
13 will be exposed, which will be in question 2, for  
14 the overall, I said no for that reason, as to the  
15 vulnerability issue; and not for so much the  
16 QT -- again, that will come out in the trials;  
17 mostly the ischemic events. The fact it is out  
18 there, I think we'll have to make sure that we  
19 either disprove or prove if it's true or not.

20 DR. RAUFMAN: Mr. Matson?

21 MR. MATSON: I voted no. I almost voted  
22 yes. I waffled back and forth. But as a patient

1 who experienced what probably should have been  
2 fatal lymphoma from a medication linked to Crohn's  
3 disease, I decided if I was going to err on a vote,  
4 I was going to err on the side of caution and on  
5 the side of the patients.

6 DR. RAUFMAN: Dr. Rosen?

7 DR. ROSEN: I voted no. I would go through  
8 withdrawal without my every two-month EKGs from  
9 cisapride. But mostly because of the cisapride,  
10 I'm still concerned about drug interactions, and I  
11 do think this is a heterogeneous population that  
12 does get into issues with electrolyte problems.

13 DR. RAUFMAN: Dr. Lauer?

14 DR. LAUER: I voted yes. Three issues.  
15 Number one is this is a small number problem. In  
16 1971, Daniel Kahneman wrote a Nobel prize-winning  
17 paper about the law of small numbers, and he writes  
18 that "People have strong intuitions about random  
19 samplings. These intuitions are wrong in  
20 fundamental respects. These intuitions are shared  
21 by naive subjects and by trained scientists, and  
22 they are applied with unfortunate consequences in

1 the course of scientific inquiry." We see this  
2 here in two respects. Number one is that we're  
3 being overly convinced by small numbers, and number  
4 two is failure to take into account prior  
5 probabilities.

6 So I do think, I agree with Dr. Teerlink, we  
7 should take a Bayesian approach. This is  
8 essentially what we're asking for in this question,  
9 and I think that's correct.

10 I agree with some of my colleagues here who  
11 have argued that the preclinical studies could be  
12 better done. For example, the studies in coronary  
13 arteries could be done in animals that have  
14 atherosclerosis or that have been fed an  
15 atherosclerotic diet. That would probably give us  
16 a more convincing assessment as to what's going on.  
17 And I also agree with Dr. Granger that any trial,  
18 any phase 3 trial that is done should not  
19 deliberately exclude patients with cardiovascular  
20 disease or patients who are at high risk. It  
21 should include the kind of patients who are going  
22 to actually get put on these drugs.

1 Thank you.

2 DR. RAUFMAN: Dr. Anderson?

3 DR. ANDERSON: Yes. I voted no, and it was  
4 a "no, but," with considerable hesitation here. I  
5 found the discussion of the kinds of patients that  
6 you all are facing very compelling, and I hope that  
7 the sponsors will feel encouraged to evaluate these  
8 drugs. However, I -- and I also appreciated all  
9 the mechanistic arguments that were put in front of  
10 me, but I don't find them compelling, and so I  
11 could not answer yes to the question of were my  
12 concerns dispelled.

13 I do think we need somewhat larger trials,  
14 but I would not require a dedicated safety study.  
15 I just think we need some reliable estimates for  
16 the numbers needed to treat and numbers needed to  
17 harm, and I don't think we will get that with the  
18 kind of -- the one example of a trial that was  
19 given to us, I don't think we'll have adequate  
20 numbers to allow those decisions to be made, which  
21 will be condition dependent.

22 Thank you.

1 DR. RAUFMAN: Dr. Solga?

2 DR. SOLGA: I voted yes. Nothing new to add

3 DR. RAUFMAN: And I voted yes, as well,  
4 based on a number of factors. One is the  
5 compelling need for effective drugs for these  
6 patients, what I perceived as the absence of a  
7 strong toxicity signal in any of the data we were  
8 shown this morning and a presence of what I thought  
9 was a very strong specificity signal in terms of  
10 the receptor we were interested in and lack of  
11 significant interaction with the receptors we  
12 weren't interested in or that could potentially  
13 cause toxicity.

14 So I will try to summarize the opinions of  
15 22 people. Let me just hit on what I took as the  
16 key points, that those voting yes voter pretty much  
17 along the lines that I said, that they didn't see a  
18 very strong signal suggesting toxicity; that there  
19 was some consideration that decisions were made on  
20 previous drugs, for example, tegaserod, on very  
21 limited and small numbers.

22 I will say that even those voting yes, like

1 myself, still voiced some potential concern about  
2 these agents and certainly didn't write off the  
3 possibility of drug-induced cardiovascular  
4 toxicity, but thought that that could be addressed  
5 within the context of studies that are proposed to  
6 evaluate the efficacy of these agents and don't  
7 require a dedicated cardiovascular toxicity study.

8 My sense from the people who voted no is  
9 that there was some lingering question, I thought,  
10 about still the need for these drugs; that perhaps  
11 the conditions weren't as compelling, the  
12 indications weren't as compelling, and concern  
13 about potential cardiovascular toxicity from one of  
14 these agents.

15 Something that I think came through from  
16 everyone is that when these drugs are studied, they  
17 should include -- the studies should include people  
18 from at risk populations so that a true index of  
19 cardiovascular risk is obtained, not just to study  
20 young otherwise healthy people who only have the GI  
21 indication for the drug.

22 One of the other issues that was raised,

1 also, was to be sure that these folks were also on  
2 other agents that are commonly used to treat these  
3 disorders.

4 If I'm missing anything, please say  
5 something.

6 So we'll go on to the next, question 2, and  
7 I'll read it, and this is a voting question.

8 Among the uses for which 5-HT4 agonists are  
9 being developed, chronic idiopathic constipation,  
10 constipation predominant irritable bowel syndrome,  
11 gastroparesis, other functional motility disorders,  
12 is there an indication for which you would be  
13 unwilling to accept an increased cardiovascular  
14 risk?

15 A, if yes, which ones and why; B, for those  
16 uses that you are willing to accept an increased  
17 risk, state the level of risk you would find  
18 unacceptable, e.g., hazard ratio.

19 So, again, I'll open this to discussion.  
20 I'm not asking people what they're going to vote,  
21 just what your thoughts are.

22 Dr. Bloom?

1 DR. BLOOM: A quick clarification. Is an  
2 increased cardiovascular risk hypothetical here or  
3 is it related to what we've been discussing? I  
4 mean, is it a hypothetical, real, significant risk?

5 DR. RAUFMAN: A hypothetical, real,  
6 significant risk.

7 [Laughter.]

8 DR. BLOOM: Sorry about that.

9 DR. FIORENTINO: So I guess we can say  
10 assuming there was a risk there, no matter how big,  
11 because that's part B, I suppose, but assuming  
12 there is a risk.

13 DR. RAUFMAN: Dr. Spiegel?

14 DR. SPIEGEL: Thank you.

15 Just my own perspective about these  
16 different conditions. It's difficult to generalize  
17 patients within a condition, especially these  
18 conditions which can be very, very heterogeneous  
19 not only in their symptom expression, but even in  
20 their underlying pathophysiology, because we're  
21 still struggling to understand what these  
22 conditions even are, much less how to characterize

1 patients within conditions.

2 But with that caveat, it's my  
3 perception -- I'd be interested in the other  
4 GIs -- that if I had to rank order from generally  
5 more burdensome to less burdensome -- and I hate to  
6 even do this, but maybe it's helpful -- on average,  
7 it would be my opinion that true gastroparesis  
8 would be probably at the top, from my experience,  
9 in terms of the quality of life impact, impact on  
10 daily living and so forth, followed by a pretty  
11 close second with irritable bowel syndrome.

12 Keep in mind, the difference between  
13 irritable bowel syndrome and constipation and  
14 chronic idiopathic constipation is really the  
15 presence of abdominal pain. So that's how we  
16 distinguish them clinically. When there's a  
17 predominant pain or discomfort in the belly and  
18 constipation, we tend to say that's IBS with  
19 constipation. When pain or discomfort is not a  
20 major component, but constipation is, we generally  
21 call that constipation, with various caveats.

22 So just by virtue of that distinction, the

1        constipation patient has one less symptom, namely,  
2        pain, still has quality of life decrement, for  
3        sure. But it's been my experience that that order  
4        would probably make the most sense, with a larger  
5        drop-off between IBS and CC; closer packed, the IBS  
6        and the gastroparesis.

7                In terms of the acceptable number needed to  
8        harm, I'm not quite prepared to give that answer.  
9        I think that requires some patient input, too. But  
10       I'd be curious, if you wouldn't mind asking the  
11       other GIs.

12               DR. RAUFMAN: As we move to the next  
13       question, one thing I'd like somebody from GI to  
14       address, and not necessarily me, is somebody opined  
15       earlier that -- for this question, we're thinking,  
16       gee, whose disease is so trivial that the risk  
17       isn't worth it, but somebody opined earlier that  
18       when you have very advanced disease, you're not  
19       likely to respond to anything, including these  
20       drugs, anyway, and is the risk acceptable in that  
21       situation.

22               So we'll go around, but just think about

1 that.

2 Dr. Solga?

3 DR. SOLGA: In the absence of Dr. Ronald  
4 Fogel being here today, I really am the practicing  
5 gastroenterologist on the committee, because I  
6 don't have the subspecialty focus of Dr. Hasler or  
7 Dr. Rosen, et cetera. So I'll jump into the  
8 conversation at this point about who we see.

9 Sort of a little bit of a replay of  
10 yesterday, folks come into the office, they've got  
11 these symptoms. You have to ask, "Why are you  
12 here?" And at the outset, a lot of patients will  
13 self-select and say, "Because my primary doc sent  
14 me, my family member sent me, I didn't want to  
15 come. Okie-doke."

16 If they wanted to come, then we're ruling  
17 out other things and looking for danger. Once that  
18 gets done, okay, now we're looking to provide  
19 comfort. How are we going to provide comfort?  
20 Talking therapy first, second, third, and fourth,  
21 and then a certain number, a small number of  
22 patients will need prescription therapy.

1           I do see the sick people that Dr. Hasler  
2 sees. I don't see children, so I don't see  
3 Dr. Rosen's populations. But I do see very, very  
4 sick people, and that minority of people really do  
5 need these medicines. So there needs to be a lot  
6 of thoughtful constraint practiced by practicing  
7 physicians.

8           It's been brought up several times today  
9 that in the real world, there'll be a lot of  
10 misprescriptions written to millions of people who  
11 aren't so sick. Sadly, I'm sure that's true, to a  
12 degree. But representing the real world, I don't  
13 know that it's as true as we think it is, and I  
14 certainly don't think that should tie the hands of  
15 thoughtful prescribing physicians in terms of what  
16 their options are.

17           On the flipside, you also can't forget the  
18 patient. A lot of patients will come saying, "I am  
19 very sick. I have terrible symptoms. But I don't  
20 want a medicine. I just don't want it. I want you  
21 to do your evaluation and then we want to talk  
22 about dietary interventions."

1           Even when I see that they're very sick, when  
2 I brought up the Lotronex example earlier, said,  
3 "Look, you're asking me to write excuses to your  
4 university about why you can't sit through your  
5 exams because of irritable bowel. You need  
6 Lotronex." And I pull out the Lotronex consent.  
7 Then they say, "I don't want it."

8           So for better or for worse, there are a lot  
9 of patients out there that aren't going to be  
10 jumping on the bandwagon saying, "I want this, I  
11 want this, I want this." There is a pushback  
12 there, too, and that's a good thing.

13           DR. RAUFMAN: Dr. Shen?

14           DR. SHEN: So to voice Dr. Spiegel's  
15 comments, also, it's my rank of the order,  
16 gastroparesis, IBS/constipation, and then chronic  
17 constipation and CIC. But also we said what kind  
18 of medicine, available alternative do we have.  
19 Chronic constipation, if not good, end of stage, we  
20 have Miralax, we have lactulose. For the bad  
21 gastroparesis, we have nothing except a TPN and a  
22 ventilation pack.

1 Thank you.

2 DR. RAUFMAN: Dr. Lauer?

3 DR. LAUER: And, in fact, what we're being  
4 asked to do is make a value judgment, and this is a  
5 value judgment that ultimately needs to be made by  
6 individual patients. It reminds me of what  
7 happened with multiple sclerosis. There was a drug  
8 which was exceedingly effective for controlling  
9 multiple sclerosis symptoms, but it caused PMLE,  
10 which is a devastating disorder in a very small  
11 percentage. And what was done was that the  
12 multiple sclerosis community, and I believe the FDA  
13 was involved with this, got together and figured  
14 out a way of presenting this to patients so that  
15 patients could make a careful, thoughtful,  
16 informed, value decision about what was going on.

17 Now there was a case where the risk was  
18 real, and here, the risk may not be real. But that  
19 may be another way of approaching this, would be to  
20 say if the risk actually is real, think about  
21 developing a program by which patients can be  
22 brought into this conversation on an individual

1 basis, and they can then make a decision as to  
2 whether or not their symptoms are so bad that  
3 they're willing to accept a theoretical increased  
4 risk in cardiovascular events.

5 DR. RAUFMAN: I might opine, and I think  
6 this is somewhat similar to what you just said. I  
7 don't know that I would stratify these disorders by  
8 indication, that gastroparesis is really terrible  
9 and I would accept more risk. I think it's more a  
10 question of severity at each level of disease, and  
11 that I could see somebody with constipation that is  
12 so severe that I would accept a higher  
13 cardiovascular risk. And I would also include in  
14 that category failure to respond to other approved  
15 agents, that people who have one of these disorders  
16 and has tried whatever it is. They've developed  
17 tardive dyskinesias or whatever, a loss of  
18 concentration from metoclopramide, whatever  
19 problems with erythromycin and so on, and they have  
20 nothing left that that might also allow me or cause  
21 me and the patient to accept more cardiovascular  
22 risk, because that's the question here, too. It's

1 not whether we will accept the cardiovascular risk.

2 Does the patient accept that cardiovascular risk?

3 DR. Korvick?

4 DR. KORVICK: I think you stated my  
5 concerns, as well, but I would just say that at  
6 some point, we have to ask the professionals about  
7 benefit and risk, but, also, we will be -- as these  
8 things move on, as we accumulate more data, we will  
9 be talking to patient groups, and we do have a  
10 representative here.

11 DR. RAUFMAN: Dr. Thadani?

12 DR. THADANI: I realize that  
13 gastroenterologists want an indication. I would  
14 say, yes, especially in the patients with the CIC,  
15 irritable bowel syndrome, which is not extreme,  
16 patients have symptoms. He alluded to the patient  
17 comes in. He gave him the drug. He didn't want to  
18 take it because of the -- those are the risks  
19 you're taking when there's a large population.

20 I think you've got extreme examples on  
21 gastroparesis. Nobody wants to hear parenteral  
22 nutrition or surgery. So I think if you focus on

1 that group, I'll accept the risk-benefit, and that  
2 probably will be greater. But to generalize all  
3 together, I think it's wrong, in my perception.

4 If it was my young child, I would try  
5 everything else before, if there's a cardiovascular  
6 risk. Obviously, if we show there is no risk, that  
7 is not the issue. But the question specifically  
8 asks if there is a risk. And my answer is I would  
9 limit it to very sick patients that are chronically  
10 constipated to the extent that life is totally  
11 miserable, and the patient is given a choice, would  
12 I rather die or have a heart attack, and he accepts  
13 it, that'd be okay for me.

14 DR. RAUFMAN: Dr. Hasler?

15 DR. HASLER: Yes. Dr. Raufman, I agree with  
16 your comments. I also think there's another  
17 factor, which is the drug itself. There are  
18 different splice variants to the 5-HT4 receptor in  
19 the stomach, colon, and mid gut. And I think we  
20 know from our experiences with the different 5-HT4  
21 agonists that they have different efficacies in  
22 different regions. So cisapride I personally think

1 was better in the upper gut, whereas tegaserod was  
2 better in the lower gut. So if a next generation  
3 5-HT4 agonist is marketed that is more selective  
4 proximately or distally, then that would be the  
5 patient subset you would focus on.

6 DR. RAUFMAN: Are there any other comments  
7 on this question, because we can vote? Dr. Kumar?

8 DR. KUMAR: My other colleagues commented in  
9 the first three that are listed here, chronic  
10 idiopathic constipation and so on, but not the last  
11 one, the functional motility disorders, which I  
12 feel is a wastebasket term, because a lot of these  
13 tests are not tell all. They are not very  
14 sensitive or specific, and even based on  
15 objective -- or subjective criteria, patients'  
16 complaints, I think it's easy to either diagnose or  
17 not diagnose. A lot of the patients could be  
18 diagnosed with this condition and thereby given the  
19 medication, which, I think, given the unsurety of  
20 its side effect, I think might be problematic.

21 So that one I think would be the one to  
22 exclude, I think.

1 DR. RAUFMAN: Other comments?

2 DR. THADANI: Can I ask a generic question  
3 to my colleagues?

4 You showed us that a smaller number of  
5 patients, either in the pediatric population or  
6 adults, ends up having a very severe form of  
7 disease. Are those patients a different  
8 protoplasm? Because I don't think everybody with  
9 an idiopathic disorder ends up having colons which  
10 are operating -- are totally nonfunctional or have  
11 extreme gastroparesis.

12 Are there co-morbidities which explain this,  
13 or are there difference in the population?

14 DR. RAUFMAN: Dr. Hasler?

15 DR. HASLER: Well, I only have my own  
16 experience, which is in a tertiary center, but  
17 there certainly is a spectrum of disease. And in  
18 many of these milder cases, they're handled by  
19 primary care gastroenterologists or even sometimes  
20 primary care physicians. So I think, of course,  
21 you're right, and I think that what Dr. Rosen sees,  
22 what I see, what Dr. Spiegel sees, we see it as

1 kind of the tip of the iceberg.

2 But just to give you a feel for the group  
3 I'm currently following, like I said, I'm the PI at  
4 Michigan of a seven center consortium, and we're in  
5 the process of -- we've already published one paper  
6 on symptom manifestations of gastroparesis.

7 There's another one going out in the next couple of  
8 weeks. And we actually quantified symptom severity  
9 in our patients, and we use a survey called the  
10 Gastroparesis Cardinal Symptom Index, which is a  
11 six- number scale of a whole range of symptoms.

12 And in our group -- granted, they're tertiary  
13 patients, but about two-thirds of them were in the  
14 moderate, severe, or very severe range.

15 So at least what we see at academic centers  
16 is a fairly sick group of people.

17 DR. THADANI: Would the mild become severe?  
18 If you took 100 patients, how many with mild would  
19 convert into severe form?

20 DR. HASLER: I don't know the answer to  
21 that. I think if you took a community sample,  
22 perhaps 15 to 20 percent would be in the severe

1 range.

2 DR. RAUFMAN: Dr. Spiegel?

3 DR. SPIEGEL: Just a brief comment. Because  
4 these conditions are driven by patient-reported  
5 outcomes, it makes it especially challenging for us  
6 to determine who is severe and who isn't. We don't  
7 really have a reliable biomarker that we can use,  
8 like blood pressure, to establish risk; we rely on  
9 the patients.

10 The Rome Foundation, which is the origin of  
11 the Rome criteria, I happen to be on the Rome  
12 Foundation, and there's a working group on just  
13 severity measurement. And this has also been very  
14 important to the FDA, because for clinical trials,  
15 we need to be able to measure, in a reliable and  
16 valid way, somebody's symptom severity, much less  
17 their quality of life or maybe much more.

18 So my point is that there needs to be better  
19 ways, not just for clinical trials, but even for  
20 clinical practice, for establishing who is severe  
21 and who isn't. And there are efforts underway to  
22 do such a thing so that we have a more reliable

1 method of establishing severity based upon the  
2 patient-reported outcomes and the combinations of  
3 symptoms they're experiencing.

4 DR. RAUFMAN: I think the discussion has  
5 matured and we can go ahead to a vote on this. So  
6 I won't re-read the question. Select yes, no, or  
7 abstain.

8 [Vote taken.]

9 DR. RAUFMAN: So the results are 9 voted  
10 yes, 11 voted no, 2 abstentions. Everyone voted.

11 We'll go around the room, starting with  
12 Dr. Solga this time.

13 DR. SOLGA: It falls on the lines of mild,  
14 moderate, severe. I wouldn't call it a disease  
15 that I would say no to this and yes to that. I  
16 would say 78 percent of what I see is mild, another  
17 15 to 20 percent thereafter is going to be moderate  
18 to severe, and that runs across these different  
19 disease categories.

20 So I want the medicines for the moderate to  
21 severe. If I could have said -- I could answer  
22 this question by saying yes and snuck in mild up

1       there somewhere, but you get the idea.

2               DR. RAUFMAN:   Dr. Anderson?

3               DR. ANDERSON:   Yes.   I voted no for the same  
4 reasons.   I feel like it should be based on  
5 severity of disease and symptoms.

6               DR. RAUFMAN:   Dr. Lauer?

7               DR. LAUER:   I voted no, and I agree with the  
8 two previous speakers.   I think that if something  
9 is going to be done in this regard, there should be  
10 some kind of a program that formally and  
11 thoughtfully incorporates individual patient  
12 assessments.   And the drug that I was talking about  
13 with multiple sclerosis was Tysabri, and I think  
14 that's a nice example of how to do it.

15              DR. RAUFMAN:   Dr. Rosen?

16              DR. ROSEN:   I voted no for all of the  
17 reasons that everybody else has stated.

18              DR. RAUFMAN:   Mr. Matson?

19              MR. MATSON:   I abstained.   I'm neither a  
20 prescriber of these drugs nor am I a sufferer of  
21 any of these conditions, and I would want to leave  
22 those decisions to the individual patient and

1 doctor.

2 DR. RAUFMAN: Dr. Thadani?

3 DR. THADANI: I think the question was for  
4 which you would be unwilling to accept an increased  
5 cardiovascular risk, so I said yes. And for the  
6 indications, it will be chronic idiopathic  
7 constipation, predominant irritable bowel syndrome,  
8 functional motility disorders, I won't accept it if  
9 there's a cardiovascular risk.

10 So it's a double negative question. I hope  
11 people really aren't confused. And the only  
12 probable area will be gastroparesis extreme, which  
13 I'll buy, probably, maybe.

14 DR. RAUFMAN: Dr. Spiegel?

15 DR. SPIEGEL: I voted no, and I have no  
16 additional comments.

17 DR. RAUFMAN: Dr. Kaul?

18 DR. KAUL: I voted no. Clinical  
19 decision making is all about accepting tradeoffs,  
20 and if there's a very small increase in a very soft  
21 endpoint of cardiovascular risk, of course, I'm  
22 willing to accept that if the return, the tradeoff

1 is acceptable.

2 So that's how I read the question. I took  
3 the best case scenario and I said, yes, that that  
4 is acceptable of me. So the answer would be no, if  
5 you're not already confused.

6 [Laughter.]

7 DR. RAUFMAN: Dr. Bloom?

8 DR. BLOOM: Yes. I abstained. While I'm  
9 sympathetic with the chair's and others' notion of  
10 it should be on the basis of severity and would  
11 have been inclined to vote no, I don't feel I have  
12 an informed clinical perspective to do a risk-  
13 benefit on this.

14 DR. RAUFMAN: Dr. Rosenberg?

15 DR. ROSENBERG: I voted no, more or less,  
16 for the same question Dr. Kaul and others stated.  
17 I voted yes. Yes.

18 [Laughter.]

19 DR. RAUFMAN: Dr. Greene?

20 DR. GREENE: Yes. I found the question a  
21 very confusing question, and I'm not particularly  
22 interested in exposing a lot of patients with

1 so-called functional motility disorders or other  
2 things, which I think we can treat in very safe  
3 ways, to increased risk. But I've agreed with  
4 everything that everybody has said so far. So I'm  
5 not sure what I should have voted.

6 [Laughter.]

7 DR. RAUFMAN: Dr. Teerlink?

8 DR. TEERLINK: So using Sanjay's exact  
9 reasoning, but I took the worst case, I voted -- I  
10 voted yes. But I agree with everything everybody  
11 else said so far, too. So there you go.

12 DR. RAUFMAN: Dr. Richig?

13 DR. RICHIG: I voted yes, also, and  
14 predominantly for lesser degrees of this illness,  
15 I'd be unwilling to accept the risk.

16 DR. RAUFMAN: Dr. Bild?

17 DR. BILD: I voted no. And I agree with  
18 what has been said about it being a discussion with  
19 the patient about what they're suffering, what  
20 they're willing to accept in terms of risk.

21 DR. RAUFMAN: Dr. Black?

22 DR. BLACK: I also voted no for many of the

1 same, if not all of the same reasons that have  
2 already been mentioned.

3 DR. RAUFMAN: Dr. Shen?

4 DR. SHEN: I vote for yes. Actually, there  
5 is a particular indication I want to point out,  
6 which is CIC. No matter what kind of degree, we  
7 always have the backup. If you're mild to  
8 moderate, laxative; if you're really severe,  
9 actually the dream patient for our surgical  
10 esophageal colectomy. And other things, other  
11 side, you put the patient almost lifelong on the  
12 medicine. We're really not sure if there's a  
13 cardiovascular risk. So that group of patients  
14 I -- just to point that out.

15 Thank you.

16 DR. RAUFMAN: Dr. Granger?

17 DR. GRANGER: I voted no for the reasons  
18 that have been outlined. And I think the place to  
19 deal with this, from the FDA perspective,  
20 is -- well, I guess Mike Lauer had examples of  
21 otherwise, but it would include careful labeling as  
22 second line therapy.

1 DR. RAUFMAN: Dr. Kaltman?

2 DR. KALTMAN: I voted yes, but I sort of  
3 read it as stratified by severity and patient  
4 preference rather than a specific indication.

5 DR. RAUFMAN: Dr. Hasler?

6 DR. HASLER: I voted no for many of the  
7 reasons which have already been stated.

8 DR. RAUFMAN: Dr. Sood?

9 DR. SOOD: I voted yes, because I believe  
10 there are a subset of patients for which I'm  
11 unwilling to accept the risk, and there are other  
12 options for the treatment.

13 DR. RAUFMAN: Dr. Kumar?

14 DR. KUMAR: I voted yes, because the first  
15 three indications probably capture most of our  
16 needy patients. And the last group, especially the  
17 functional motility disorders, as I stated, would  
18 then result in its use being in a wider population.

19 In those patients where the condition was  
20 unlikely to kill -- and, potentially, I think we  
21 are unaware of the long term consequences of the  
22 drug. There is still a cloud hanging over it. To

1 then use it for those patients, I felt it wasn't  
2 warranted in that group.

3 DR. RAUFMAN: I voted no, again, as I  
4 indicated before, because I'd be more focused on  
5 severity rather than the actual diagnosis, and with  
6 the proviso that other drugs have been tried and  
7 failed before I used one of these agents.

8 Nobody who, like myself, voted no addressed  
9 part B of this, which is for those that you were  
10 willing to accept an increased risk. State the  
11 level of risk you would find unacceptable; e.g.,  
12 hazard ratio.

13 I don't have a clue as to how to answer  
14 that. Dr. Spiegel has said repeatedly how  
15 dangerous aspirin is, and I'm now concerned about  
16 my daily 81 milligrams. So I don't really know. I  
17 don't know what the hazard ratio is for my 81  
18 milligrams of aspirin, so I don't know.

19 If anybody else here who voted no would like  
20 to address that question, again, of what level of  
21 risk they would find unacceptable, please speak.

22 Dr. Lauer?

1 DR. LAUER: So to echo on what I said  
2 before, I think that's a patient-specific question.  
3 So instead of presenting it in terms of relative  
4 risk, I would present it in absolute risk. So one  
5 would ask someone -- and this is like a gamble  
6 tradeoff -- are you willing to accept a one in a  
7 thousand risks that you're going to have a fatal  
8 heart attack in exchange for the improvement of  
9 symptoms that you would get with this drug, and  
10 then you would keep titrating that until you see  
11 what that actually is.

12 One could potentially study this in a large  
13 number of subjects, and then that could potentially  
14 then inform future studies.

15 DR. RAUFMAN: Dr. Kaul?

16 DR. KAUL: Ruling out unacceptable harm  
17 depends on what the clinical context is, and  
18 everybody has already mentioned that -- it depends  
19 on what the seriousness and the magnitude of the  
20 adverse event is. What are the alternatives? What  
21 is the patient preference?

22 It should be not driven by trial

1 feasibility. It should be driven by dispassionate  
2 objectivity. And there are already two examples,  
3 or one solid example and one still in evolution,  
4 that we can borrow from, which is the diabetes drug  
5 guidance.

6 They came up with a hazard ratio of 1.8 in  
7 the pre-approval study and 1.3 post-approval study,  
8 and most of us didn't feel very comfortable with  
9 it, saying that this is arbitrary. But it was  
10 based on a trial that is currently ongoing, looking  
11 at the non-steroidals and COX-1 and COX-2  
12 inhibitors. The trial is called PRECISION. That  
13 was the basis of that.

14 Everybody sort of started saying that this  
15 is going to stagnate innovation, this is going to  
16 stifle diabetes drug development. But when you  
17 look at the new applications to the FDA, there have  
18 been about 10 trials since 2008 when this was  
19 implemented, including 115,000 patients, including  
20 those trials that are currently underway.

21 So there is no reason why we can't borrow  
22 from the diabetes guidance example and set some

1 boundaries, but these boundaries should not be  
2 fixed. They should be based on what are the  
3 tradeoffs.

4 The obesity drug development program is also  
5 undergoing these discussions. So I don't find the  
6 GI motility drugs to be unique enough not to  
7 undergo the same process.

8 DR. RAUFMAN: Any other comments on the  
9 hazards ratio part of that? Dr. Thadani?

10 DR. THADANI: Can I ask a generic question?  
11 A patient comes to you and you say, okay, you show  
12 him a form, you could die at this, and he says I  
13 won't. Usually they ask you, "What would you do,  
14 Doctor?" And my answer is I don't know, because  
15 what I'll do may not necessarily be right for you.  
16 Like, you're on aspirin and I'm not, because I'm  
17 worried about the intracranial bleed, maybe low  
18 incidence.

19 So I can't tell the patient, "Look, I won't  
20 take it." So I think that's the dilemma. And I  
21 assure you, most of the patients rely on you. They  
22 ask you what would you do. And I'd tell them this

1 is the data. It's up to you to decide, your family  
2 members, discuss it with them, I can't -- because  
3 most of the time, I tell the physician or tell them  
4 I think you should take it.

5 So if you want to put a question that you  
6 should also stay away from that, because I don't  
7 know how you find in your practice, that most of  
8 the patients say, "Doctor, what should I do?" And  
9 we are influenced -- if I was a patient, I'm going  
10 to be influenced by that.

11 Any comments on that?

12 DR. RAUFMAN: Well, again, personally, I  
13 would just comment that it varies. And if I really  
14 think that there is a clear answer, I would feel  
15 ethically bound to answer the question of what I  
16 would do, and make it clear that's what I would do.  
17 But that becomes very individual, and it also  
18 depends on how well you know the patient and so on.  
19 So there are a lot of factors there.

20 So to, again, very quickly summarize 22  
21 different opinions. There were people who voted  
22 yes on this who felt that some of the disorders

1 listed were perhaps not that severe or did not  
2 warrant the degree, any significant degree of risk,  
3 whereas others felt that, I guess like I did, that  
4 the severity was perhaps a more important feature  
5 than the actual condition, and that led to their  
6 votes. And then the two people abstained and they  
7 made their reasons for that clear.

8 We have one more voting question. I would  
9 propose that we do that voting question next and  
10 then take a short break, and we have three  
11 discussion questions to follow that, if that's  
12 alright with everyone.

13 So question number 3, again, a voting  
14 question, does the committee recommend a dedicated  
15 cardiovascular safety trial, a trial in which the  
16 primary objective is to define cardiovascular risk  
17 to demonstrate the safety of 5-HT4 agonists?

18 So I see some similarity in this question to  
19 question number 1, but I'll open it to discussion.

20 Dr. Rosenberg?

21 DR. ROSENBERG: Well, I guess for those who  
22 answered yes to question 1, they already answered

1 that question. They shouldn't vote.

2 [Laughter.]

3 DR. RAUFMAN: Well, it's worded differently,  
4 and we may get a different outcome.

5 Is there any discussion on this? Again,  
6 this is something we've already quite discussed at  
7 length several times today. But are there any  
8 additional comments that anyone would like to make?

9 [No response.]

10 DR. RAUFMAN: Take it to a vote, and then  
11 everybody can give their opinion. So let's go  
12 ahead and vote on this question.

13 [Vote taken.]

14 DR. RAUFMAN: So on the question -- this is  
15 question number 3 -- does the committee recommend a  
16 dedicated cardiovascular safety trial, a trial in  
17 which the primary objective is to define  
18 cardiovascular risk to determine the safety of  
19 5-HT4 agonists, 4 voted yes, 17 voted no,  
20 1 abstention, and, again, everyone voted.

21 I'll start this time, and then we'll go to  
22 my right. So I voted no on this, consistent with

1 my vote on the first question. I think that  
2 because of the adverse events with prior drugs used  
3 to treat this disorder, there is a lot of attention  
4 now paid to potential cardiovascular risk.

5 I think that the data we saw today doesn't  
6 indicate a strong signal suggesting a risk, a  
7 cardiovascular risk, and, in fact, that there's a  
8 strong signal suggesting highly specific HT4  
9 receptor interactions of these new drugs.

10 Dr. Kumar?

11 DR. KUMAR: I also voted no, consistent with  
12 my earlier response. Although it does not  
13 completely allay my concerns about the possibility  
14 of a side effect, there continues to be a cloud  
15 over this, especially when it may likely be used in  
16 the long term. We are completely unaware of what  
17 its consequences might be in such a patient. So I  
18 think one has to be sensitive in the context of any  
19 clinical trial that is conducted and, also, if  
20 approved in the postmarketing surveillance of the  
21 drug.

22 DR. RAUFMAN: Dr. Sood?

1 DR. SOOD: I voted yes. I think this is not  
2 consistent with my prior response. My concern is  
3 I'm pretty much kind of satisfied with the data we  
4 were presented about the safety. But my concern is  
5 about the select population who are high risk for  
6 these cardiovascular events.

7 So I'm not sure how we'll be selecting those  
8 patients. So if we have to do a trial, I don't  
9 know. I'm saying it's a dedicated trial, but this  
10 should be an enriched population who are high risk  
11 for the cardiovascular events.

12 DR. RAUFMAN: Dr. Hasler?

13 DR. HASLER: I voted no. I don't consider  
14 my vote to be totally inconsistent with my first  
15 vote. The thing that bothered me most about  
16 question 1 was whether the data available dispelled  
17 my concerns, and they did not. But I think from a  
18 practical standpoint, I think if we're going to be  
19 enrolling patients in trials of any of these  
20 disorders, which would be largely 80 percent women,  
21 median age of 35 or 40, you're going to have to  
22 design a trial of tens of thousands of patients.

1 I know we've heard that in non-GI  
2 specialties, you can accumulate that number of  
3 patients. But to my way of thinking -- Brennan,  
4 maybe you can tell me, but I believe the biggest  
5 trial that's been done in constipation is about  
6 1500 people. So that sort of sample size is not  
7 practical, so I voted no.

8 DR. RAUFMAN: Dr. Kaltman?

9 DR. KALTMAN: I voted no, as well. But sort  
10 of to echo my statement on the first question, I  
11 think there needs to be some type of vigilance  
12 following approval, more than just spontaneous case  
13 reporting.

14 DR. RAUFMAN: Dr. Granger?

15 DR. GRANGER: I voted no. And similarly, I  
16 think that's in the context of the desire in what I  
17 think should be the requirement for nevertheless a  
18 more comprehensive approach towards accurate  
19 safety, appraisal for these patients at risk.

20 DR. RAUFMAN: Dr. Shen?

21 DR. SHEN: I voted for no, and reason number  
22 one is the feasibility to run the trial. Number

1 two, is I think that I would have liked to have had  
2 the postmarketing registry to monitor this safety.

3 Thank you.

4 DR. RAUFMAN: Dr. Black?

5 DR. BLACK: I also voted no, consistent with  
6 my first vote. I think the practical aspects of  
7 trying to do what would perhaps answer the question  
8 would make it very, very hard to do and perhaps  
9 make us wait much too long to use it. But I think,  
10 as said, the pharmacovigilance after this is  
11 approved has to be extremely good.

12 DR. RAUFMAN: Dr. Bild?

13 DR. BILD: I voted no, consistent with  
14 what's been said and endorsing the idea of some  
15 pharmacovigilance down the road.

16 DR. RAUFMAN: Dr. Richig?

17 DR. RICHIG: I voted yes. I just feel that  
18 not enough is done in cardiovascular safety. In  
19 light of all the drugs that have been taken off the  
20 market to date, I think that something else needs  
21 to be done.

22 DR. RAUFMAN: Dr. Teerlink?

1 DR. TEERLINK: So I voted no, meaning no,  
2 not yet. But, they need to enroll real world  
3 patients. The studies need to be not powered  
4 solely for efficacy, but rather actually powered  
5 for a reasonable degree of substantial drug  
6 exposure in the at risk population.

7 As has been previously mentioned, it has to  
8 be followed by vigilant postmarketing observations,  
9 including adjudications. And if a signal arises in  
10 that phase 3 experience or later, then a dedicated  
11 cardiovascular risk study absolutely needs to be  
12 performed.

13 This is said with the caveat that some  
14 sponsors may actually look at the risk-benefit and  
15 suggest that doing the safety study upfront, a  
16 dedicated separate cardiovascular safety study,  
17 might be considered to be actually cheaper and a  
18 lower risk strategy. So I would encourage sponsors  
19 listening to this to consider that those kind of  
20 safety studies, contrary to what some of the GI  
21 colleagues are suggesting, are actually relatively  
22 inexpensive and can be generally relatively easily

1 enrolled.

2 DR. RAUFMAN: Dr. Greene?

3 DR. GREENE: Well, I abstained, but my vote  
4 is basically a no. I was just a little unsure  
5 about generalizing this to all patients. So,  
6 either way, I can change it to no or leave it  
7 abstain.

8 DR. RAUFMAN: Dr. Rosenberg?

9 DR. ROSENBERG: I answered no, despite the  
10 fact that I said no to question 1. I don't think  
11 we necessarily need a large safety study. Also,  
12 the comment was made that it may be more cost  
13 efficient to do it. So I would think that a  
14 properly sized phase 3 trial, enrolling the  
15 appropriate population, including high risk  
16 patients with appropriate population post-trial  
17 follow-up. And if the drug is marketed, carefully  
18 designed postmarketing studies where we have an  
19 idea of what the real denominator is will also do  
20 the trick.

21 DR. RAUFMAN: Dr. Bloom?

22 DR. BLOOM: I voted no, for, as before, the

1 signals that are translating to risk that need to  
2 be managed in justifying such trial are either  
3 manageable, as in the case of QT, or uncertain in  
4 terms of the validity of the signals, in the case  
5 of tegaserod.

6 DR. RAUFMAN: Dr. Kaul?

7 DR. KAUL: I voted yes, simply because we  
8 don't have the sophisticated tools to detect low  
9 frequency signals. Epidemiologic studies are  
10 reasonably good at capturing strength of  
11 associations, of odds ratios greater than 3 and 4.

12 Numerator-based pharmacovigilance programs,  
13 such as the adverse event reporting system, they  
14 are just numerator-based. We don't know what the  
15 denominator is. The insurance claims databases are  
16 denominator-based, but we don't know what the  
17 numerator is.

18 So if you want to capture a 5200 percent  
19 increase in risk, the only efficient and effective  
20 tool we have is a randomized control trial. And I  
21 have heard nothing here to persuade me that a trial  
22 of 10,000 patients followed for one or two years is

1 not feasible.

2 We just had an obesity drug that got a  
3 complete response letter last year that had  
4 negotiated with the FDA and said that they're  
5 willing to conduct a trial, 10,000 patients  
6 followed for three to four years, to rule out a  
7 pre-approval unacceptable margin of 2 and a post-  
8 approval unacceptable margin of 1.4.

9 So I don't see any reason why this cannot be  
10 done with these types of drugs.

11 DR. RAUFMAN: Dr. Spiegel?

12 DR. SPIEGEL: I voted no. I think it's  
13 important to emphasize, probably on behalf of  
14 everybody voting no, that this is not a flip and  
15 vote, it's not cavalier, not throwing caution to  
16 the wind, and I think we're all in agreement with  
17 that.

18 We've heard a lot of good ideas today about  
19 how to be cautious, how to employ case selection,  
20 perhaps employing a patient report of severity  
21 filter or ensuring that this therapy is used as  
22 second or third line therapy, or having a

1 postmarketing registry.

2 I think that what we heard earlier about the  
3 law of small numbers is extremely compelling and  
4 very, very important. It's human nature to latch  
5 onto these things. We have to keep that in mind.

6 We still need to be vigilant, we still need  
7 to be careful, and we need to look out for the  
8 wellbeing of our patients. I think the way we do  
9 that is we move forward at this point without doing  
10 large scale cardiovascular safety studies.

11 DR. RAUFMAN: Dr. Thadani?

12 DR. THADANI: I voted yes for my previous  
13 discussions. I think the only way we can address  
14 this issue is by doing very large randomized  
15 trials. And given the sheer number of people out  
16 there, millions, I'm sure the drug companies, if  
17 they prove it's effective and safe, they will make  
18 multi-million, billion dollars. So I have no  
19 problem recommending a very large trial, 50,000,  
20 100,000 patients. It is doable. Keep it simple.

21 So I voted yes for that reason, to not  
22 expose everybody -- with a low risk population to

1 even some increase, which you're willing to accept.

2 DR. RAUFMAN: Mr. Matson?

3 MR. MATSON: I voted no consistent with my  
4 answer on question 1.

5 DR. RAUFMAN: Dr. Rosen?

6 DR. ROSEN: I voted no. I agree with  
7 Dr. Hasler.

8 DR. RAUFMAN: Dr. Lauer?

9 DR. LAUER: I voted no. I agree that it is  
10 certainly possible to do a trial. The question is,  
11 given that our resources are limited, is this an  
12 appropriate place to send it?

13 Based on the data that have been presented  
14 today, I'm not at all convinced that there's a  
15 problem. And given that my pretrial likelihood  
16 that there is a problem is low, I would rather send  
17 our resources elsewhere.

18 Let me just add one other thing. I would  
19 strongly recommend that the paradigm for  
20 preclinical studies change; that the specimens that  
21 are used should represent, as closely as possible,  
22 represent the atherosclerotic state, because that's

1 what we're concerned about here.

2 I would also strongly recommend that the  
3 phase 3 study that is done have as few exclusion  
4 criteria as possible. It should certainly not  
5 exclude people with cardiovascular disease and  
6 rather should be representative of the real  
7 population.

8 DR. RAUFMAN: Dr. Anderson?

9 DR. ANDERSON: Yes. I voted no. But I do  
10 think that the phase 3 trials that are to be done  
11 should have several characteristics, and many have  
12 been mentioned. They should be a broader, more  
13 representative population that reflects the way  
14 practice would go forward. I would like to see  
15 longer-term use, not the three months, but at least  
16 a year of use being examined.

17 I think there should be standardized  
18 cardiovascular risk assessment. This need not be  
19 excessive, but that it's comparable in all the  
20 trials that are done so that they can be pooled and  
21 used to assess the risk. And I think they should  
22 be larger than the example put before us. I'm not

1 asking for 50,000, but I think 12,000 for three  
2 months is not enough person years to have any  
3 reliable statistical information.

4 DR. RAUFMAN: Dr. Solga?

5 DR. SOLGA: I voted no. I agree with  
6 Dr. Lauer that I just haven't heard the rationale  
7 that we need this, and the resources are better  
8 spent elsewhere. I'm concerned about both the time  
9 and cost delay. The charge of this committee, of  
10 course, is always efficacy and safety. But the  
11 moment I step back in the office tomorrow morning,  
12 it's going to be about cost and cost and cost in  
13 terms of whether patients actually can get a  
14 medicine. You can't entirely uncouple these issues  
15 in the real world.

16 DR. RAUFMAN: So just by way of a quick  
17 summary, those who voted no regarding a dedicated  
18 cardiovascular trial still voiced concerns about  
19 potential side effects, cardiovascular side  
20 effects. And that these should be carefully  
21 monitored in any efficacy trials that should not  
22 exclude patients with cardiovascular risk or are on

1 other drugs and so on.

2 There was some opinion that doing a  
3 dedicated trial would take time and be expensive.  
4 There was also opinion that it might not take as  
5 much time as thought and might not be as expensive  
6 as one might think.

7 I think that pretty much summarizes it.

8 Any other comments?

9 [No response.]

10 DR. RAUFMAN: So we're going to take a  
11 15-minute break.

12 Dr. Kaul, Dr. Thadani, Dr. Richig, and  
13 Dr. Sood have to think about their answers to the  
14 next question -

15 [Laughter.]

16 DR. RAUFMAN: -- because it's specifically  
17 geared to those who voted yes to question number 3.

18 So we'll take a 15-minute break. We'll  
19 reconvene at 4:10. Please don't discuss the issues  
20 of the meeting.

21 (Whereupon, a recess was taken.)

22 DR. RAUFMAN: If I could get everybody to

1 please resume their seats. I know people are  
2 interested in leaving. Again, if we could get  
3 everybody to please sit down and let's finish up.  
4 We have three discussion issues.

5 So on question number 4, since it is  
6 targeted just to four specific members of the  
7 committee, I think as a first go, we can just go  
8 around, in no particular order, and ask them to  
9 respond to this particular question.

10 Dr. Kaul, would you like to?

11 DR. KAUL: Yes. Discuss the characteristics  
12 which would define the enriched population for a  
13 dedicated cardiovascular study. I think the  
14 patient should be at increased risk for  
15 cardiovascular disease. They should have advanced  
16 cardiovascular disease, patients with chronic  
17 kidney disease, they should be --

18 DR. RAUFMAN: Question 4 -- you jumped ahead  
19 I think.

20 DR. KAUL: Sorry. I thought we had already  
21 answered that. Let me just read the questions.

22 If anybody has already read the question,

1 please go ahead and I'll catch up.

2 DR. RAUFMAN: Drs. Thadani, Richig and Sood.  
3 I'll take anybody.

4 DR. THADANI: I'll take that. I think the  
5 question is if you answered yes, discuss whether  
6 you recommend that the trial be conducted prior to  
7 post-approval.

8 I recommend trials to be done prior for, A,  
9 CIC, B, IBCC, D, other gastro functional motility  
10 diseases, because, to me, that's a larger  
11 population. I want to make sure that we're not  
12 harming anybody in that. So that's my answer.

13 DR. RAUFMAN: So gastroparesis you leave.

14 DR. THADANI: I might take a chance if it's  
15 bad enough and you think you guys are going to put  
16 a line to feed them and do surgeries. I think  
17 that's a high risk, then you can do a smaller trial  
18 and get away with it.

19 DR. RAUFMAN: Dr. Kaul?

20 DR. KAUL: Yes. For consistency, I would  
21 say that this can be -- the trial can be done in  
22 two phases, both pre-approval and post-approval.

1           You can have an interim unacceptable safety  
2 margin assigned where the pre-approval trial has to  
3 overcome that burden, and then the final analysis  
4 could be done in a post-approval fashion. So the  
5 drug can be given a conditional approval based on  
6 the pre-approval higher margin and a post-approval  
7 lower margin.

8           That's how I would do it. I'll make it very  
9 simple. I won't differentiate between the  
10 different categories of these disorders.

11           DR. RAUFMAN: Dr. Richig?

12           DR. RICHIG: Yes. I'd have to say E, all of  
13 the above, and that would be prior to. I think I'd  
14 want to know as early as possible what the  
15 cardiovascular effects are. So that's where I'm  
16 coming from.

17           DR. RAUFMAN: Dr. Sood?

18           DR. SOOD: Yes. To the specific answer for  
19 this question, I go back to the question 2, where  
20 we said that I'm willing to accept an increased  
21 cardiovascular risk for certain conditions, for  
22 which probably the other options are available.

1           Again, I just want to rephrase; probably a  
2 little confusion here. I probably differ from  
3 Dr. Thadani and Dr. Kaul. I don't believe there's  
4 a feasibility of a dedicated cardiovascular safety  
5 trial. I was pretty convinced about the  
6 preclinical data, but we did not have much clinical  
7 information about the high risk group.

8           So that's my point, is the high risk group  
9 for the cardiovascular events and risk. And the  
10 other side of the GI, the group, which is at low  
11 risk or which can have other options, probably they  
12 should go to some trial, but it's not a dedicated  
13 cardiovascular big trial.

14           I don't think there's a feasibility of a  
15 large-scale trial to be done here. There's a  
16 definite need for these agents to be released into  
17 the market.

18           DR. RAUFMAN: So just to summarize the  
19 sentiment I just heard, I think the general  
20 sentiment is that it should be for all four of  
21 these disorders, although gastroparesis might be  
22 left out from one of the respondents and that,

1 generally, it should be prior to approval is what  
2 I'm hearing as a sentiment.

3 I'll open it up to the rest of the  
4 committee, if anybody has an opinion or who wants  
5 to add anything to this question.

6 Dr. Granger?

7 DR. GRANGER: I'll just comment, and I  
8 think, Sanjay, this is what you were implying, that  
9 it might be reasonable to be parallel to what's  
10 happening in the diabetes example. And we think  
11 that's working reasonably well, but there's still  
12 some uncertainty actually about how that's going to  
13 unfold. So it might be worthwhile to track how  
14 that works and see.

15 DR. KAUL: Actually, it's working better  
16 than before the guidance development. We have 13  
17 trials ranging from 4,000 to 16,000, a total of  
18 115,000 patients. And so it had the opposite  
19 effect as was predicted.

20 DR. GRANGER: I'm involved in a couple of  
21 these. I would say there's still some uncertainty  
22 about how exactly it's going to unfold.

1 DR. KAUL: Granted, I would acknowledge  
2 that. But you can borrow from a guidance that's  
3 already out there perhaps more mature. And you can  
4 borrow strength from that, what works and what  
5 doesn't work, and perhaps use that to inform the  
6 guidance for the GI motility drugs.

7 DR. RAUFMAN: Any other comments on this  
8 issue? Dr. Rosenberg?

9 DR. ROSENBERG: Well, if we are going to do  
10 a trial, I don't think there's a need for the  
11 population with chronic idiopathic constipation. I  
12 would do it pre-approval, because that's the  
13 population where you are more likely to find  
14 patients at higher cardiovascular risk anyway. And  
15 if you have the other trials, say, you have the  
16 answer to the other trials, well, for the patient  
17 who was sick, his medication would be available.

18 DR. RAUFMAN: Anything else, or we'll move  
19 on to the next?

20 DR. FIORENTINO: Just a comment. I guess  
21 one thing I wonder about is for the diabetes  
22 trials, diabetes is a cardiac risk equivalent. So

1 it's possible that the treatment for diabetes can  
2 improve your cardiac outcome.

3 I wonder if it truly is -- if that approach  
4 is truly comparable to this indication, for those  
5 who made that comment.

6 DR. KAUL: So far we have not seen any  
7 evidence of improved cardiovascular risk profile  
8 with any diabetic drug. The one that comes closest  
9 is based on a set of a subgroup of UKPDS study,  
10 metformin in obese individuals that were not on  
11 sulfonylurea. That's the closest we have come.

12 The second one is pioglitazone and the  
13 proactive study, where it failed to meet its  
14 primary endpoint, but a secondary endpoint made it.  
15 It's kind of hard to interpret a trial where the  
16 primary endpoint is not met and a secondary  
17 endpoint is met, because the possibility of a false  
18 positive is quite high with that secondary  
19 endpoint.

20 So far we have 11 different classes of  
21 drugs, and we don't have any compelling evidence  
22 that reducing or improving glycemic control

1 translates into conclusive evidence of  
2 cardiovascular benefit.

3 DR. RAUFMAN: Dr. Thadani?

4 DR. THADANI: I think on that aspect,  
5 diabetes has been considered as equal  
6 cardiovascular risk, but that's not a fact. They  
7 have macrovascular, as in microvascular disease,  
8 and most of the trials haven't shown much on  
9 macrovascular, as Sanjay was saying.

10 Also, aspirin data in diabetics is almost  
11 neutral. The more and more -- again, based on the  
12 trials which have been published, there is no data  
13 that aspirin is cardio protective in diabetes  
14 patients if you do not have underlying CID or  
15 otherwise core diseases. So I'm not  
16 sure -- realizing that the adverse outcome is  
17 greater in a diabetic patient, but it's not the  
18 same thing as having underlying CID.

19 DR. KAUL: I might just add one more  
20 comment. We used to believe that diabetes is a CHD  
21 risk equivalent. This was based on the East-West  
22 Finland study by Steven Haffner. That's the only

1 study that the risk ratio of 2 was shown in  
2 diabetic individuals without a previous  
3 cardiovascular event, never replicated in  
4 subsequent studies.

5 We have recent trials, about four or five of  
6 them, where the event rates were very low. They  
7 were actually 1 to 1 and a half percent per year,  
8 which would put them in an intermediate Framingham  
9 risk category.

10 These trials are the DIAD study, the VA  
11 diabetes study, the ACCORD study, and the ADVANCE  
12 study. So the totality of data seems to suggest  
13 that perhaps diabetes may not be a CHD equivalent.  
14 Maybe perhaps we have modified risk factors more  
15 aggressively. These patients are better treated  
16 more aggressively than the East-West Finland study  
17 seemed to indicate.

18 So we have to be very careful that even when  
19 we design the diabetes trials, they're not  
20 designing them with a 3 percent event rate per  
21 year. They're designing them with somewhere  
22 between 1 and a half to 2 percent per year.

1 DR. RAUFMAN: Any other comments on  
2 question 4?

3 DR. FOX: Mr. Chairman?

4 DR. RAUFMAN: Dr. Fox?

5 DR. FOX: Just a comment to Dr. Kaul and  
6 this idea that the implementation of the diabetes  
7 CV outcomes guidance is working well. If the  
8 launching and implementation of those large 15 to  
9 20,000-patient trials is evidence of working well,  
10 I just want to point out that all of those are  
11 postmarketing requirements under FDAAA, and, thus,  
12 the sponsors of those studies don't have a choice.

13 DR. KAUL: But they are still pursuing it.  
14 That's their decision. They can choose not to do  
15 it, just like Novartis chose not to pursue the  
16 Zelnorm risk.

17 DR. RAUFMAN: If we could bring up the next  
18 question, please.

19 So question 5, discuss the characteristics  
20 which would define the enriched population for a  
21 dedicated cardiovascular study. So you could take  
22 this as a hypothetical. If a dedicated

1 cardiovascular study were to be done, would you and  
2 how would you enrich the population in that study?

3 Is that a fair statement? Dr. Korvick, did  
4 you want to --

5 DR. KORVICK: We're kind of interested in  
6 understanding -- since the last vote was more  
7 overwhelming to not have a dedicated study, we're  
8 really interested in what characteristics -- I  
9 think that was why Dr. Fiorentino probed the last  
10 question he asked about how would you enrich this.

11 Then I think this sort of overlaps into the  
12 next question, where we're looking at how  
13 to -- what kind of people you want to enroll in  
14 these studies to maybe enrich it. I think we heard  
15 people comment a little bit, but we'd like to get a  
16 little more specific, also, how would you assess  
17 cardiovascular events in that kind of a phase 3  
18 study where it might be bigger preapproval.

19 So it could overlap, since we're in the  
20 discussion zone and not voting.

21 DR. RAUFMAN: Right. I would say that I've  
22 also heard some sentiment for not enriching, that

1 we should be studying a, quote, "real world  
2 population," taking all comers of this disease, not  
3 focusing -- I'm taking enrichment here as putting  
4 more people in it with some cardiovascular risk,  
5 but others who have said that it should just be  
6 reflective of the population that's going to be  
7 taking these drugs.

8 Dr. Thadani?

9 DR. THADANI: I think one has to be very  
10 careful, because if you take a sample size of a  
11 thousand patients and put a hundred patients with  
12 cardiovascular risk, you may not come to any  
13 conclusion. So if you're going to do a trial in  
14 younger people who are 35 years old, the  
15 cardiovascular risk is going to be low, unless all  
16 your women are on contraceptive pills, which  
17 exposes them to more thrombotic events.

18 So if you're going to do an enriched  
19 population, you have to concentrate on older people  
20 with documented CID. Even then the event rate is  
21 about 3 percent. And then they also have to have  
22 either irritable bowel or chronic constipation.

1 You can't just do it on patients who don't have  
2 underlying disease.

3 So I think I would probably put it separate  
4 in order to be absolutely sure. Do the other trial  
5 in the low risk population, what you're  
6 postulating, and do a separate trial in the  
7 enriched population, diabetes plus CID, which will  
8 enhance your large number of patients in the  
9 highest risk, including hypertension.

10 DR. RAUFMAN: If I could ask Dr. Hasler, I  
11 think you threw this number out before, what  
12 percentage of your gastroparesis patients are  
13 diabetic?

14 DR. HASLER: Around a quarter, between 25  
15 and 30 percent. And I think that will hold up not  
16 just for severe gastroparesis, but also nationwide.  
17 It really has become -- I guess because of  
18 increased awareness of the disease, changes in  
19 diagnostic criteria, whatever, it's become  
20 predominately an idiopathic condition.

21 DR. THADANI: Sorry. Are they diabetic  
22 because they -- the fact they can't even eat, they

1 are still diabetic? They are skinny or they are  
2 fat? I don't know.

3 DR. HASLER: Most of the patients are  
4 diabetic for a decade or more before they start  
5 developing GI disease. So it's a long-term  
6 diabetic complication, like neuropathy,  
7 nephropathy, et cetera.

8 DR. RAUFMAN: Dr. Bloom?

9 DR. BLOOM: I just wanted to remind the  
10 group that we just went from reviewing a  
11 development plan that excluded people of  
12 cardiovascular risk, and I think that may have been  
13 with the assumption that there may well have been a  
14 dedicated cardiovascular study. But now we're  
15 debating whether to enrich or take all comers.

16 Is it appropriate for the committee to weigh  
17 in on that?

18 DR. RAUFMAN: Does FDA want to respond to  
19 that?

20 DR. FIORENTINO: Well, I guess I would say  
21 if -- one thing is, if we had a study and we have  
22 the inclusion criteria, what are the points that we

1       could add to the inclusion criteria to enrich the  
2       population?  And I think we've already heard  
3       diabetics, older patients.  But to maybe get the  
4       diabetics and to get that from hearing it, we would  
5       want to open it up to an all comers, being all the  
6       indications that potentially such an agent could  
7       cover.

8               DR. BLOOM:  I don't think that was the  
9       question.  It was we have a clinical development  
10      plan that this group reviewed that excludes  
11      patients with cardiovascular risk.

12             DR. FIORENTINO:  Right.  So I think going  
13      forward with that, we have to revisit that.  That's  
14      not something that we're endorsing right now.

15             DR. KORVICK:  But you've recommended that we  
16      study patients with cardiovascular risk.

17             DR. FIORENTINO:  Right.  Yes.

18             DR. RAUFMAN:  Dr. Lauer?

19             DR. LAUER:  So an enriched population would  
20      include people who have established cardiovascular  
21      disease.  That means they have a documented prior  
22      myocardial infarction.  They've undergone prior

1 coronary revascularization, or they've undergone a  
2 coronary angiogram which demonstrates at least one  
3 50 percent lesion in a major epicardial artery.

4 Another group would be patients who have a  
5 stroke, who've had a documented stroke, and there  
6 are standard definitions for that. And then  
7 another high risk group are patients who have  
8 symptomatic peripheral vascular disease. Actually,  
9 patients with symptomatic peripheral vascular  
10 disease are exceedingly high risk. They have  
11 mortality risks of about 4 to 5 percent per year.

12 I think that the specific types of outcomes  
13 that you would look at would be what we refer to as  
14 major adverse cardiac events. Unfortunately, major  
15 adverse cardiac events is an endpoint that gets  
16 defined differently in every major trial.

17 But I think for something like this, I would  
18 focus on what we often refer to as hard events. So  
19 hard events would be deaths, and I would include  
20 deaths from all causes, definite  
21 cardiovascular -- or cardiovascular deaths, which  
22 are often hard to assess, and nonfatal myocardial

1 infarction, and nonfatal stroke; amputation of a  
2 limb because of ischemic disease.

3 I would not include revascularization as an  
4 endpoint. That's a rather soft endpoint. I would  
5 not include unstable angina. That's, these days,  
6 particularly, a very soft endpoint. I would not  
7 include the development of anginas in outpatient,  
8 which I saw was one of the criteria that had been  
9 listed.

10 DR. RAUFMAN: Thank you for being very  
11 specific.

12 Dr. Spiegel?

13 DR. SPIEGEL: Actually, my comment has  
14 already been made.

15 DR. RAUFMAN: Dr. Richig?

16 DR. RICHIG: Yes. I agree with  
17 Dr. Raufman's suggestion of the enriched population  
18 to cover all aspects of age group and types of  
19 people, race and so forth.

20 This is the luxury of human studies.  
21 Unfortunately, in the pre-clinical realm, we're  
22 dealing with a set group of animals. You're just

1 dealing with a beagle dog of a restricted age  
2 group, of, let's say, six months to nine months of  
3 age; nonhuman primate that are sub- adult,  
4 restricted numbers, they don't -- the luxury isn't  
5 there for that. Why not mongrels? Why not  
6 different aged animals to kind of fill the gap, so  
7 to speak? That's just something to consider.

8 DR. RAUFMAN: Dr. Kaul?

9 DR. KAUL: Yes. As a general rule, I also  
10 believe in trials being designed to inform and  
11 guide clinical practice. So, ideally, I would  
12 recommend that the type of patient population that  
13 would be enrolled and this would be an all comer.  
14 But that's even bigger a hurdle for them to  
15 overcome in terms of the trial numbers, and it  
16 might actually end up creating a lot more noise and  
17 diluting out any signals.

18 So I would prefer, given that, that they  
19 enrich this population. And to what Dr. Lauer  
20 already described, I would also add chronic kidney  
21 disease, as well. And I agree that we should focus  
22 only on the so called hard, robust cardiovascular

1 endpoints and not include recurring ischemia,  
2 unstable angina, TIA, or revascularization.

3 I would also recommend that we have an  
4 independent committee that should prospectively and  
5 blindly adjudicate these hard, major, at-risk  
6 cardiac events. A trial should be followed for a  
7 minimum of about a year, ideally, up to two years  
8 in order to expose the patients and maximize the  
9 possibility of separating out signal from noise.

10 DR. RAUFMAN: Dr. Teerlink?

11 DR. TEERLINK: So I agree with everything  
12 that Dr. Lauer and Dr. Kaul said so far, and I  
13 would add that the sponsor should also  
14 consider -- it's actually in their best interest to  
15 enroll a higher risk population because that gives  
16 them the confidence intervals and the event number  
17 that gives some certainty that might have them be  
18 able to maybe avoid, in this Bayesian approach, a  
19 full-on, solely dedicated cardiovascular safety  
20 study.

21 So my recommendation of saying, yes, they  
22 can get by without a cardiovascular study was

1 dependent upon them actually enrolling a patient  
2 population that was at least real world and most  
3 likely enriched, and based on the characteristics  
4 so far discussed.

5 DR. RAUFMAN: Dr. Granger?

6 DR. GRANGER: I agree with everybody else,  
7 too, and two other minor points. The  
8 enrichment -- one of the reasons the enrichment is  
9 important is because in trials, we always  
10 underrepresent high risk patients. So the  
11 enrichment will simply get us to kind of what the  
12 general population is that we want to be studying.

13 Then in terms of other features, somebody  
14 had mentioned including patients who are on these  
15 other drugs, that these patients are on, to assure  
16 that we do that and don't exclude patients on other  
17 drugs; and that we assure -- because I think this  
18 is probably a particular issue in this  
19 population -- that patients continue to be followed  
20 until the end of the study, not just while they're  
21 on the treatment, which all too often we tend to  
22 do.

1 DR. RAUFMAN: Dr. Bild?

2 DR. BILD: So I also agree with the  
3 suggestions to enrich the population for high  
4 cardiovascular risk. And not that we're designing  
5 this trial, but another way to do that is to  
6 include people with high coronary calcium scores.

7 DR. RAUFMAN: Any other comments?  
8 Dr. Thadani?

9 DR. THADANI: I think enrichment is fine,  
10 but you must insist what kind of -- in 30 percent  
11 of the population or 40, because enrichment in just  
12 numbers won't be enough.

13 So depending on the sample size, you might  
14 say, okay, 30 percent of the population is going to  
15 be high risk. And in addition, you might include  
16 patients -- because a lot of patients are getting  
17 exercise studies, so they don't necessarily have to  
18 do an MI to be in the study or a previous known  
19 coronary angiogram.

20 If they've got a positive nuclear study or  
21 positive dobutamine stress study, realizing  
22 especially in women, they will be false positive at

1 a younger age, you might include that to enhance  
2 your population.

3 DR. RAUFMAN: So if I could summarize at  
4 this point, I think there's a consensus that the  
5 population for the cardiovascular portion of this  
6 study should, at the very least, not have the kinds  
7 of exclusion criteria we saw before; that patients  
8 with cardiovascular risk should be included in the  
9 trials; that subjects on various drugs for their  
10 disorder should be included in the trials.

11 Then if you truly want to enrich with people  
12 at greater risk, there were some very specific  
13 means of doing that proposed.

14 If we could see the last question. So this  
15 is question 6. What elements to assess  
16 cardiovascular safety should be included in a  
17 standard phase 3 efficacy trial to assure accurate  
18 ascertainment of cardiovascular adverse events?

19 So the cardiologists on the panel should  
20 opine here.

21 DR. KAUL: I think we already covered that,  
22 the endpoints, the adjudication committee, blinded,

1 prospective, and hard endpoints, not  
2 revascularization.

3 DR. RAUFMAN: That's what I said, the  
4 cardiologists should opine.

5 [Laughter.]

6 DR. KAUL: I think we did.

7 DR. RAUFMAN: Anything else to add to what's  
8 already been said? Is there anything else the FDA  
9 is specifically looking for on this question that  
10 they haven't heard before as of now?

11 DR. FIORENTINO: Well, I see people getting  
12 up to leave, but --

13 DR. KORVICK: They have to catch a plane.

14 DR. FIORENTINO: You have to get a plane.  
15 So I guess this idea of a large -- I guess it would  
16 be a large, simple trial, a pragmatic trial that  
17 was -- it doesn't have to be the actual efficacy  
18 trial. It could be done in parallel, I thought I  
19 heard, or something like that. Maybe people could  
20 just spend a few moments commenting on how that  
21 would operate.

22 So in one hand, it's a phase 3 efficacy

1 trial; in another hand, it's a large, simple safety  
2 trial to answer a cardiovascular question, if I  
3 kind of judged their conversation right.

4 Maybe people can comment on, operationally,  
5 how that would work, especially as far as detecting  
6 cardiovascular events. I'm assuming they wouldn't  
7 have the frequency of assessments with that.

8 DR. RAUFMAN: Dr. Teerlink?

9 DR. TEERLINK: Right. So oftentimes in the  
10 other disciplines, what we'll do is they'll have a  
11 programmatic safety program. So they'll have  
12 one -- they'll have an efficacy trial in chronic  
13 constipation, another efficacy trial in  
14 inflammatory bowel disease with constipation,  
15 another efficacy trial in GERD, refractory to PPIs.  
16 And then they will do a -- you can do another large  
17 trial that enrolls patients with all of those  
18 indications and enrich them for the cardiovascular  
19 disease, but you don't do the efficacy assessments.  
20 You don't do the high overhead type of assessments,  
21 and you look and follow in terms of their outcomes.  
22 And that approach seems to be a reasonable approach

1 in other disciplines.

2 DR. RAUFMAN: Dr. Lauer?

3 DR. LAUER: The traditional way of  
4 approaching this, which is what we do in a number  
5 of our trials, is that we contact subjects on a  
6 regular basis, every six months, every year, or  
7 whatever is appropriate, and then ask them whether  
8 or not anything happened, and then follow that up  
9 with formal adjudication.

10 There are ways that one can do this with a  
11 much lesser degree of intensity that might be  
12 acceptable here. One really nice example was  
13 actually published in last week's issue of the New  
14 England Journal, which was an insurance company  
15 trial in which the investigators randomized people  
16 to full prescription coverage or co-pay, and these  
17 were patients with established cardiovascular  
18 disease, and then they follow them up over time.

19 They ascertain the events solely on the  
20 basis of claims data, and they did not adjudicate  
21 the events. You know, I see some heads nodding  
22 here or not nodding here. But that is a

1 potentially valid approach to look for a safety  
2 signal.

3           Rory Collins did an interesting analysis of  
4 the heart protection study. The heart protection  
5 study was a 20,000-patient mega trial of  
6 simvastatin to see whether or not simvastatin  
7 reduces the risk of events in patients with  
8 established vascular disease or patients at very  
9 high risk.

10           All the events were adjudicated, and then he  
11 did an analysis in which he looked at the events as  
12 they were non-adjudicated events, they events as  
13 they were ascertained by the individual sites,  
14 which would have cost a lot less.

15           It turns out the results of the trial were  
16 virtually identical. The adjudication added  
17 essentially no additional value.

18           So for something like this, where you're  
19 looking for a strong safety signal, one way in  
20 which one could approach this and do it at  
21 reasonable cost would be to consider using a  
22 creative mechanism.

1 DR. RAUFMAN: Dr. Thadani?

2 DR. THADANI: I think you can do that with  
3 computerized electronic records, because then  
4 you're not going to miss anything. So if you just  
5 give the hard endpoints, which I said before, long  
6 time ago, as death, stroke, and a major MI, those  
7 patients are going to come to the hospital or die.

8 So I think keep it simple, have large  
9 trials, you're going to address the issue. Whether  
10 you enrich the whole population or address it in  
11 two trials and combine them is a different issue,  
12 because the population is going to be very  
13 different, low risk versus high risk, with the  
14 different conditions.

15 So I think it's doable. You could keep it  
16 cheaper, and I see no reason why it can't be done.

17 DR. RAUFMAN: Dr. Rosenberg?

18 DR. ROSENBERG: Yes. I agree that in a  
19 large-scale, randomized, blinded trial,  
20 adjudication adds just a minor noise and you don't  
21 get many examples; you don't get any difference.

22 I agree with the previous comment that was

1 made that you need to look at that separately from  
2 the registration trials, because you don't want be  
3 encumbered by all the money treating for adverse  
4 events that have nothing related to safety.

5 That's where the major cost is. You don't  
6 want any money treating, you don't want any  
7 reporting ulcers of the cardiovascular outcomes  
8 you're interested in.

9 DR. RAUFMAN: Dr. Granger?

10 DR. GRANGER: I'll just comment. I  
11 think -- and we've published some on this, too,  
12 including several trials showing almost the  
13 identical thing. It rarely seems to make much of a  
14 difference. And the main reason we still  
15 adjudicate still most of our trials is because the  
16 FDA likes us to do it.

17 [Laughter.]

18 DR. GRANGER: And we're working with Bob  
19 Temple and others to try to soften that a bit.

20 The key thing is to have predefined  
21 definitions and case report forms that capture  
22 things in a systematic way about whether or not the

1 events occurred. I think that's more important  
2 than the adjudication process itself.

3 DR. RAUFMAN: Dr. Kaul?

4 DR. KAUL: I agree with everything that has  
5 been said, except how we define the endpoints. I  
6 think Dr. Thadani got it right when he said major  
7 MI's. If you're going to use peri-procedure and  
8 biomarker elevation criteria for MI's, better make  
9 sure you have an adjudication committee, because  
10 there are a lot of examples of discordance between  
11 investigator site-reported MI's and adjudicated MI  
12 events.

13 So, again, if you're going to take the easy  
14 route, do a pragmatic design and not have them  
15 adjudicated, please make sure that these are hard  
16 endpoints that we don't need committee members to  
17 decide whether it's a true event or not; large, new  
18 queue of MI's in the right clinical setting.

19 DR. RAUFMAN: Dr. Lauer?

20 DR. LAUER: I would agree with that. I  
21 would be careful about over-interpreting peri-  
22 procedural events.

1           I also wanted to say that one potentially  
2 could do a trial with electronic medical records if  
3 one were to do it within integrated health care  
4 systems. The advantage of an integrated health  
5 care system is just that even if a person has an  
6 event at a facility outside of the system, they'll  
7 find out about it.

8           DR. RAUFMAN: Dr. Rosenberg?

9           DR. ROSENBERG: Also, adjudication has a  
10 significant cost. I think the overwhelming cost in  
11 most large-scale registration trials is the money  
12 treating and the reporting of events. So we need  
13 to get rid of that before the start of trial.

14          DR. RAUFMAN: Dr. Thadani?

15          DR. THADANI: Adjudication and another  
16 problem. I know that people who are on the  
17 adjudicating committee can go to nice places and  
18 adjudicate events. I'm not questioning that.

19                 There's always a problem with the smaller  
20 MI's because you take a target of somebody's  
21 troponin is slightly up or CKMB. So the  
22 investigator clicks it yes because the guidelines

1 say it has to be twice, three times, four times,  
2 that's the difference.

3 So I think it's absolutely crucial that we  
4 do not include these smaller -- so it has to be a  
5 spontaneous MI with a marker so that it's the WHO  
6 definition rather than small, peri-procedural or  
7 even small MIs.

8 A patient comes with unstable angina.  
9 Right? He has got an associated CKD or heart  
10 failure. His troponin is slightly high. People  
11 are going to call it MI. So I think you'd want to  
12 stay away from that. Otherwise, there's going to  
13 be issues.

14 DR. RAUFMAN: Are there any additional  
15 comments regarding this question?

16 DR. FIORENTINO: Just one more question. So  
17 could we hear some thoughts perhaps on what the  
18 most appropriate comparator would have to be for a  
19 large safety trial, and, again, circle back to  
20 really what level of cardiovascular risk we would  
21 want to rule out?

22 Is there any guidance about what kind of

1 number we could pin down?

2 DR. LAUER: I don't understand. What's the  
3 question? I don't understand the question.

4 DR. FIORENTINO: So for a large safety  
5 trial, just from a designing it standpoint,  
6 presumably, you would have to design it to  
7 statistically rule out a hazard ratio.

8 Is there something in these trials that  
9 would require a number be pinned down before it's  
10 designed? I guess we haven't heard that. I know  
11 it's difficult.

12 DR. RAUFMAN: I think Dr. Kaul was using  
13 some numbers from the diabetes.

14 DR. KAUL: If we assume that the  
15 cardiovascular event rate in these populations is  
16 lower than the obesity population, then I would  
17 recommend -- I would be okay with ruling out  
18 provisional 2.5 -- 2 or 2.5 and, in the final  
19 analysis, somewhere between 1.5 and 1.8, I would be  
20 okay, if the cardiovascular event rate is lower  
21 than what we see in obesity. If it is similar,  
22 then 2 and 1.5 would be okay.

1 DR. RAUFMAN: Any other thoughts about that?

2 DR. THADANI: The only thing would be the  
3 age group we are discussing. If it's younger  
4 people, your threshold might be different than  
5 older people.

6 DR. RAUFMAN: But Dr. Granger agreed, and  
7 you put in the proviso about whether it's the same  
8 as in the obesity population or not.

9 DR. KAUL: Or lower than that. If it's  
10 lower than that, then we will be willing to accept  
11 a higher margin, 2.5 and 1.8 maybe. I mean, these  
12 are arbitrary. I'm just pulling them out of my  
13 hat, but there is some precedence for it.

14 DR. RAUFMAN: Does that answer -- is that  
15 what you're looking for?

16 DR. FIORENTINO: That's a good start, I  
17 think.

18 DR. RAUFMAN: Dr. Lauer?

19 DR. LAUER: I think another interesting  
20 question -- I don't know what the answer to this  
21 is -- is whether or not the comparator should be a  
22 placebo. In this particular case, since you're

1 looking for hard clinical events and this is a  
2 safety study, I'm not sure that a placebo is  
3 necessary. It may be possible to do a simple  
4 controlled study where one group gets the drug and  
5 one group gets nothing.

6 I'm not sure that's right, but I think  
7 that's something that's worthy of conversation.

8 DR. THADANI: Thadani again. It's important  
9 to put a placebo because treatment method differs,  
10 physician or tension might be different. So if you  
11 don't know, you can control the co-morbidities in  
12 probably a similar way.

13 DR. KAUL: I would agree. I would stay away  
14 from non-controlled conditions, a lot of spurious  
15 results.

16 DR. RAUFMAN: Dr. Rosenberg?

17 DR. ROSENBERG: That might depend on the  
18 condition you're studying and the severity,  
19 because, again, as a gastroenterologist, I'm afraid  
20 that if you don't have a rigorous control, a  
21 placebo, there may be imbalance in terms of the  
22 background therapy in those patients.

1 DR. TEERLINK: But that's taken into the  
2 safety benefit of your drug. So it's basically  
3 standard of care plus your comparator plus  
4 your -- and the placebo.

5 DR. ROSENBERG: Well, but these are -- it's  
6 a bygone case, not the same. You will have problem  
7 just discerning what is really due to your new drug  
8 versus what other differences there may be.

9 DR. THADANI: It's important because you're  
10 saying the efficacy is only 15 or 20 percent, down  
11 the road, some of the studies. So if you don't  
12 have a placebo, I think you're doomed because  
13 you're just doing a trial which is on safety. I  
14 think it has to be efficacy combined with safety;  
15 otherwise, you'll never know.

16 DR. RAUFMAN: Any additional comments?

17 [No response.]

18 **Adjournment**

19 DR. RAUFMAN: I'd like to thank the FDA, the  
20 sponsors, the members of the committee for some  
21 very thoughtful and intense discussion. I really  
22 enjoyed it, and I hope we've answered some

1 important questions. So my thanks. We are  
2 adjourned.

3 (Whereupon, at 4:46 p.m., the meeting was  
4 adjourned.)

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