DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY SUBCOMMITTEE

Wednesday, July 14, 2004

8:30 a.m.

ACS Conference Room
Room 1066
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Ronald P. Fogel, M.D., Acting Chair
Thomas H. Perez, M.P.H., R.Ph.,
Executive Secretary

MEMBERS:

Alan Lewis Buchman, M.D.
Byron Cryer, M.D.
Alexander H. Krist, M.D.
John T. LaMont, M.D.
Robert A. Levine, M.D.
David C. Metz, M.D.
Weichung Joe Shih, Ph.D.
David B. Sachar, M.D.
Jose M. Vega, M.D., Industry Representative

DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE (Voting):

Brian L. Strom, M.D., M.P.H.
Curt D. Furberg, M.D., Ph.D.
Arthur A. Levin, M.P.H., Consumer Representative

CONSULTANTS (Voting):

Ralph D'Agostino, Ph.D.
Allen Mangel, M.D., Ph.D.

FEDERAL EMPLOYEE (Voting):

Maria H. Sjogren, M.D.

FDA STAFF:

Robert Justice, M.D., Director, Division
of Gastrointestinal and Coagulation
Drug Products
Robert Prizont, M.D., Medical Officer
Garry Della'Zanna, D.O., M.Sc., Medical Officer
Julie Beitz, M.D., Deputy Director, ODE III

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order, Introductions

DR. FOGEL: Good morning. My name is Ron Fogel. I am acting chair for today's meeting of the Gastrointestinal Drugs Advisory Committee. Today's meeting deals with the new drug application of Zelnorm for the proposed indication of the treatment of patients with chronic constipation and relief of associated symptoms of straining hard or lumpy stools and infrequent defecation.

There has been one change to today's agenda. The agenda has been pushed back half an hour so the tentative time of adjournment is five o'clock. Why don't we start by going around the table and introducing ourselves? If we could start on my far left?

DR. VEGA: Jose Vega, from Amgen in California.

DR. LEVIN: Arthur Levin. I am a member of the Drug Safety and Risk Management Advisory Committee. I am a consumer representative and I am a guest as a consumer representative here today.

DR. STROM: Brian Strom, University of Pennsylvania. I am a recent graduate of the Drug Safety and Risk Management Advisory Committee--I have already forgotten the name of the committee! I am here as a special government employee, though that is not what is says there.

DR. FURBERG: I am Curt Furberg, from Wake Forrest University. I am an active member of the Drug Safety and Risk Management Advisory Committee.

DR. D'AGOSTINO: Ralph D'Agostino, from Boston University, statistician, consultant to the FDA.

DR. LAMONT: I am Tom LaMont. I am a member of the GIDAC. I work at Beth Israel Hospital in Boston and Harvard Medical School.

DR. LEVINE: I am Bob Levine, State Medical University, Syracuse, New York, and I am a member of the GI advisory committee.

DR. METZ: David Metz, University of Pennsylvania. I am on the GI drug advisory committee.

DR. PEREZ: Tom Perez, Executive Secretary

to this meeting.

DR. FOGEL: Ron Fogel, Henry Ford Health System, in Detroit.

DR. SACHAR: I am David Sachar, from Mount Sinai School of Medicine, in New York--my maiden voyage on the GI drug advisory committee.

[Laughter]

DR. BUCHMAN: Alan Buchman, from Northwestern University, in Chicago, and this is also my first cruise with today as well.

DR. MANGEL: Allen Mangel, Research Triangle Institute. I am a special government employee.

DR. CRYER: I am Byron Cryer, from the Dallas VA Medical Center and UT Southwestern Medical School. I am a member of the GI advisory committee.

DR. DELLA'ZANNA: Garry Della'Zanna, medical officer in the GI and Coagulation Drug Product Division.

DR. JUSTICE: Robert Justice, Director, Division of Gastrointestinal and Coagulation Drug

Products.

DR. BEITZ: Julie Beitz, Deputy Director in the Office of Drug Evaluation III.

DR. FOGEL: Thank you, all. At this point Tom Perez will read the meeting statement.

Meeting Statement

DR. PEREZ: Thank you and good morning. The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions:

In accordance with 18 USC Section 208(b)(3), full waivers have been granted to the following participants, Dr. Ronald Fogel has been granted a waiver for serving as a member of the

sponsor's speakers bureau. His lectures are unrelated to the matter at issue and he receives less than $10,001 per year.

Dr. Ralph D'Agostino has been granted a waiver for serving on a competitor's advisory board on unrelated matters. He receives less than $10,001 per year.

Dr. Byron Cryer has been granted a waiver under 21 USC 355(n)(4), amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in a competitor. The stock is worth less than $5,001. Because this interest falls below the de minimis exemption allowed under 5 CFR 2640.202(a)(2) a waiver underlying 18 USC 208(b)(3) is not required.

Dr. David Metz has been granted waivers under 18 USC Section 208(b)(3) and 21 USC 355(n)(4) for his spouse's ownership of stock in a competitor valued from $50,001 to $100,000.

Lastly, Dr. Allen Buchman has been granted waivers under 18 USC Section 208(b)(s) and 21 USC 355(n)(4) for owning stock in a competitor valued

from $25,001 to $50,000.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 or the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

We would also like to note that Dr. Jose Vega has been invited to participate as an industry representative, acting on behalf of regulated industry. Dr. Vega is employed by Amgen, Inc.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. FOGEL: Thank you. At this time I will turn the meeting over to Dr. Justice, of the

FDA, for opening comments.

Opening Comments

DR. JUSTICE: Good morning. I would like to welcome everyone to today's meeting of the Gastrointestinal Drugs Advisory Committee, and I would especially like to welcome members of the committee and special government employees for taking the time to provide us with your advice.

As you have heard, today we will be discussing the application for Zelnorm tablets for the proposed indication of treatment of chronic constipation. Before going on to the presentations, I would just like to briefly go through the questions so you will have them in mind as you listen to the discussions.

The first item is that we would like you to discuss the appropriateness of a primary efficacy endpoint of an increase of equal to or greater than 1 complete spontaneous bowel movement per week versus a total of greater than 3 complete spontaneous bowel movements per week.

The second question is, is the population

studied representative of patients with chronic constipation? If not, how do the populations differ?

The third question is only 9 to 16 percent of subjects were greater than or equal to 65 years of age and the treatment effect was significantly smaller in older patients. Are these data adequate for an indication that is common in the elderly?

The fourth efficacy question is that only 9 to 14 percent of the subjects were male and the treatment effect was smaller in males than females. Are these data adequate to support approval of Zelnorm for use in the treatment of chronic constipation in males?

The next question is are the clinical trial data adequate with respect to the population of non-irritable bowel syndrome patients with chronic constipation that is likely to be treated with Zelnorm?

The next efficacy question is, is Zelnorm effective for the treatment of chronic constipation and associated symptoms?

As far as the safety questions, postmarketing access of ischemic colitis and serious complications of diarrhea were not limited to patients with irritable bowel syndrome. What are the implications of these adverse events from patients with chronic constipation?

The next safety question is that the incidence of diarrhea and discontinuation due to diarrhea was higher in patients 65 years of age or older. Is there sufficient information that Zelnorm is safe for use in this age group?

The next safety question is do the adverse event data from the clinical trials and postmarketing surveillance provide adequate evidence of safety of Zelnorm for the treatment of chronic constipation?

The next safety question is should the information on the postmarketing cases of ischemic colitis and intestinal ischemia be moved from the "precautions" section to the "warning" section of the package insert?

Then, the final question will be the

overall question of should Zelnorm be approved for the proposed indication of the treatment of patients with chronic constipation and relief of associated symptoms of straining, hard or lumpy stools, and infrequent defecation?

With that, I will turn it back over to Dr. Fogel for Novartis' presentation.

DR. FOGEL: Thank you very much. At this juncture I will turn the meeting over to Dr. John Cutt, Global Head of GI Drug Regulatory Affairs for Novartis, who will introduce the speakers and the presentations. Thank you.

Novartis Presentation

Introduction

DR. CUTT: Thank you. First I would like to thank Dr. Beitz, Dr. Justice--Dr. Prizont is not here yet--and Dr. Della'Zanna and the rest of the FDA reviewers, and Dr. Fogel and the rest of the advisory committee, and say good morning to you.

My name is John Cutt. As Dr. Fogel said, I am the executive director and the global head for the gastrointestinal regulatory group at Novartis,

and it is my pleasure to share with you today the clinical data on chronic constipation that we have generated.

Let me start out with the objectives, as we see them today for the meeting. We would like to share the Zelnorm Phase 3 clinical data in support of a new indication. Dr. Fogel read that before, I will read it again. Zelnorm is indicated for the treatment of patients with chronic constipation and the relief of associated symptoms of straining, hard or lumpy stools, and infrequent defecation.

The second topic that we are going to review today is the postmarketing safety data that we have generated since the approval of the drug in the United States in July of 2002. This approval was for patients with irritable bowel syndrome with constipation.

A brief introduction of the compound, Zelnorm is tegaserod maleate. It is 5-HT

4 receptor

partial agonist with affinity for the 5-HT

4

receptor in the GI tract. For its pharmacologic

activity in the GI tract, Zelnorm enhances intestinal motility; increases intestinal secretion; and inhibits visceral sensitivity. We have also demonstrated in clinical trials that Zelnorm can improve the constipation symptoms in patients with irritable bowel syndrome with constipation.

So, these data together are the basis for the hypothesis that Zelnorm could be effective to treat patients suffering from chronic constipation.

Novartis-designed clinical development program for chronic constipation included two randomized, placebo-controlled pivotal studies. Both the studies were 12 weeks in duration to assess the efficacy, safety and tolerability of the drug. We studies both the 2 mg dose and the 6 mg dose BID versus placebo. In total, there were 2,612 patients that were studied. The program also included one extension phase study which was added on to one of the pivotal studies. This was a 13-month extension for assessing the long-term safety of the compound. The other pivotal studied

included a 4-week withdrawal period. Today what we are going to do is show you the results of these pivotal studies.

We will also share with you the postmarketing clinical data that we have collected since the approval of the drug in the United States in July of 2002. That approval was for the short-term treatment of women with irritable bowel syndrome whose primary bowel symptom is constipation. The recommended dose is 6 mg BID for a period of up to 12 weeks. At the time of the approval we demonstrated the efficacy, safety and tolerability in 5,319 patients in the clinical trial program. At this point in time, now, we have generated data on 11,600 patients in clinical trials. These patients were all treated with Zelnorm. What this means is that it translates to approximately 3,456 patient-year exposure to the drug in the clinical trials.

In terms of the worldwide clinical experience for the drug, Zelnorm is now approved in 56 countries for the indication of IBS with

constipation. We have also received approval for the drug in 10 countries for the indication of chronic constipation that we are seeking from the advisory committee and the FDA.

We first made the drug available to patients suffering from IBS-C in January of 2001 in the rest of the world. So, at this point we have over 3 years of postmarketing experience with the drug in patients. What this means is that we have treated approximately 3 million patients globally with the drug and about 2 million of those patients have been treated in the United States. This now translates to about 362,000 patient-years of experience to Zelnorm.

The safety data from the clinical trial setting and the postmarketing environment we believe supports a favorable safety profile for Zelnorm. So, our conclusion from the data that you will see today during the presentations is that Zelnorm, at the recommended dose of 6 mg BID, is efficacious and safe for the treatment of patients with multiple symptoms of chronic constipation.

What I want to do is review the agenda very briefly, the people that will be presenting for us. First we have Dr. Charlene Prather. She is from the St. Louis University and will speak about chronic constipation. Her presentation is title an unresolved problem for many patients in clinical practice.

She will be followed by Dr. Eslie Dennis. Eslie is from the Novartis clinical development and medical affairs department. Dr. Dennis will present the efficacy and safety data from the pivotal studies.

That will be followed by Dr. Bo Joelsson. He will present our overall clinical safety data and review some of the adverse events of special interest that we have agreed to talk about with the FDA.

Finally, Dr. Philip Schoenfeld, who is the chief of the gastrointestinal group at the Veterans Hospital in Ann Arbor, at the University of Michigan, will conclude historical presentation with a benefit/risk assessment for the drug.

We also have four consultants that have joined us today to answer questions that you may have. The first one is Dr. Felix Arellano. He is from the Risk Management Resources group. His expertise is pharmacovigilance, epidemiology and risk management. Then we have Dr. Gary Koch. Dr. Gary Koch is from North Carolina, Chapel Hill. He is an expert in biostatistics. We have Dr. David Lieberman. He is from the Oregon Health and Science University. He will be here to answer any questions you have on the core database which is part of the presentation.

Then we have Dr. Walter Peterson, a gastroenterologist from the University of Texas Southwestern.

We have also a number of scientists and clinicians from Novartis who can answer any of the specific questions that you have on Zelnorm.

Now I would like to invite Dr. Prather up to the podium.

Chronic Constipation:

An Unresolved Problem for Many Patients

DR. PRATHER: Thank you, Dr. Cutt. Dr. Fogel, committee members, ladies and gentlemen, my name is Charlene Prather. As you heard, I am from St. Louis University. I am a gastroenterologist. I have been in practice for over ten years. My career has been dedicated to the clinical investigation and, importantly, the clinical treatment of patients with functional bowel disorders and gastrointestinal motility disorders. Chronic constipation is one of the very common problems that I see in my clinical practice and it is, indeed, an unresolved problem for many of the patients that come to see me.

First I would like to review my presentation objectives. I will begin with a definition of chronic constipation. I will discuss epidemiology and resource utilization that is associated with chronic constipation. I will review available therapies and the limitations that some of these therapies may have. I will also summarize for you my feelings regarding the unmet medical need associated with chronic constipation.

First, beginning with the definition of chronic constipation, there are a variety of ways to define constipation. I have decided to define constipation into either primary causes of constipation or secondary causes of constipation.

First let's discuss the secondary causes of chronic constipation. Secondary causes include things such as drug-induced constipation. We are certainly familiar with this with the narcotics we may give our chronic pain patients. Metabolic factors--hypothyroidism, hypocalcemia may be associated with chronic constipation. Importantly, co-morbid medical conditions. We are certainly familiar with a variety of neurological disorders, such as Parkinson's disease, multiple sclerosis, in which constipation is an important complaint that many of these patients may bring to us. However, this is not what I am here to discuss today.

Today I would like to review primary constipation. Again, with primary constipation we have learned much in the past several years regarding what causes primary constipation. There

may be impaired colonic transit or motor function, certainly an area that I am very interested in. We often call this slow transit constipation. This may result from a failure of the neurenteric function of the digestive system or from the gastrointestinal reflexes that are involved. It may also result because there is a problem with the muscle, a failure of the muscular apparatus.

We also can look at chronic constipation as a subgroup having ineffective defecation. We also may call this functional outlet obstruction. This is really where there is a poor coordination in the muscular apparatus that is involved in the defecation process. There are some other terminologies that may be used as well, such as pelvic dyssynergia or anismus may be a term that you have also heard. Most cases of primary chronic constipation fall into neither of these categories. They are actually normal transit constipation.

Constipation really isn't defined by physiologic testing; it is defined on the basis of symptoms. In my practice the most common reported

symptoms that I see coming from my patients are complaints of hard or lumpy stools; increased straining. They may complain of infrequent bowel movements, but often the sensation of incomplete evacuation, really outcome having a satisfactory bowel movement and, not uncommonly, the complaint of gloating or fullness. Typically, the longer they have gone since they had a bowel movement, you know, they are feeling more full and they may describe that as a bloated sort of sensation.

When I think about chronic constipation, this is more persistent than intermittent or episodic constipation. We are familiar with transient constipation that may occur as a result of a dietary change. We may also see it in relation to travel. When I think about what is the definition I will use for chronicity, it needs to have been present for several months duration and quite commonly, in my practice, these patients have had their constipation for years, frequently dating back to early adolescence or sometimes even childhood.

Well, how valid are my ideas about what my patients bring me with those symptoms? There actually have been some studies that have taken a look at this. One of the first studies, performed by Dr. Robert Sandler, in North Carolina, took a look at a group of young adults, those around the university community. These were individuals who had constipation and the symptoms they reported most often were, indeed, straining 52 percent of the time; hard stools, 44 percent of the time; wanted to have a bowel movement but were unable to, 34 percent of the time; with infrequent stools being reported just 32 percent of the time.

Now let's think about this. Physicians were often called upon to think very quantitatively so we often think about the frequency as being the most important symptom in constipation. But, clearly, our patients seem to be telling us something a bit different. Now, this was not a population-based study so what actually happens in the population when we discuss symptoms and constipation?

I have two studies to review with you. First is a study on the left, a large population-based, epidemiologic study by Stewart. He took a look at the symptoms most commonly reported in constipation. Again, at the top we see the complaint--an incomplete bowel movement 83 percent of the time. Unsuccessful bowel movement, being called a stool but being unable to 65 percent of the time. We see complaints of abdominal discomfort, needing to press on the abdomen in order to have a bowel movement; some abdominal bloating in a group of patients; but, again, down at the bottom of this list is frequency, with less than 3 bowel movements per week being reported by only 13 percent of this cohort.

On the right hand of the slide is another population-based study by Pare. Again we see similar findings, with straining right at the top. Again, near the bottom less than 3 bowel movements per week being less frequent in this case, in this population, 36 percent of the time.

Now, I previously mentioned the subtypes

of primary constipation that I considered. Might it be slow transit constipation; might it be an outlet problem; or is it normal transit constipation? Well, unfortunately, the symptoms don't help me differentiate between those different physiologic groups. Fortunately, that is not necessary because in practice we don't use physiologic testing, nor do we use the patient symptoms to define which subgroup they belong in. This has been information we have really found out over the past several years. We would like to think their symptoms will tell us exactly which subgroup they belong into but that just hasn't been the case. In clinical practice and in clinical trials we really don't try to define the subtype of constipation based on either their symptoms or on physiologic testing.

However, it is important that we have criteria for the use of clinical testing and having a relatively homogenous group of patients that we can take a look at. An important stab at this has been the Rome criteria. I would like to review

with you the Rome II criteria that are used in the diagnosis of functional constipation.

The Rome II diagnostic criteria include at least 12 weeks, which not be consecutive, in the past 12 months of 2 or more of the following symptoms: These symptoms include straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction or blockage, or having to use manual maneuvers, such as digitation, to facilitate defecation. You see an asterisk by these because these need to have been present on at least a quarter of defecations. The other criterion is less than 3 defecations per week.

Looking back at the top line, we see that it is 2 or more of the following symptoms. So, a patient may have straining, lumpy or hard stools 25 percent of the time and this would be consistent with the Rome II criteria for chronic constipation. Or, it could be that they do have less than 3 defecations per week and a sensation of incomplete evacuation. For this criterion loose stools must

not be present and there should be insufficient criteria for irritable bowel syndrome.

A caveat with the Rome criteria is that one of the criteria that they say is that I cannot use these criteria if my patients are already on laxatives. So, these are criteria that are really appropriate for individuals who are not currently using laxatives.

Using these definitions and, again, the Rome I definition was for the criteria from before, how common is chronic constipation in the general population? These are some population-based studies and, depending on the criteria that have been used, we see a prevalence in the range of 4 percent up to 16 percent. This is a lot of patients that are complaining of constipation. However, not all of these patients are actually coming to see us. A few of these studies actually looked at how many of these patients or individuals had actually sought physician care for the evaluation and treatment of constipation.

What we see is that it is only about 25

percent that actually come in to the physician's office in order to seek some sort of treatment.

A little bit more about the prevalence, when we think about constipation we need to know what age groups might be affected. In the Pare study he was able to divide this out. In the green bars we see the Rome I criteria and in the magenta bars the Rome II criteria. There are some slight differences, again, depending on the definition that has been used. This is true of all of the epidemiologic studies, that we really need to understand the criteria.

Well, what we see is that actually constipation is a bit more common in the younger age group, the 18-34 year-old age group. This is consistent with my clinical practice. We see that the prevalence is relatively flat when we take a look at the 35-49 year-old age group; the 50-64 year-old age group; and even the over 64 year-ole age group. So, constipation really affects all age groups.

To summarize the epidemiology related with

constipation quite briefly, chronic constipation is, indeed, common in the general population. Again, not all of these individuals come to see us. Approximately 25 percent actually seek physician care. In data I have not presented, it is slightly more common in women than it is in men. The female to male ratio ranges from 1.3 to 2.5. Importantly, constipation affects all age groups.

Now, how does this really reflect with what I see in my clinical practice? In my clinical practice generally I see females. Now, this may be because I am a female gastroenterologist, that is the obvious. However, when I discuss this with my male colleagues they tell me that they too are seeing predominantly women that come to see them for chronic constipation. Most of my patients have been symptomatic for many years, typically over 10 years. The majority have tried life style changes. They have tried fiber. They have used over-the-counter laxatives prior to even seeking initial care from their primary care physicians. Most of them manage their constipation with

combinations of these, a combination of fiber and laxatives. The patients that come to me in my practice are predominantly referred to me by primary care physicians and I am also going to see patients that come from other gastroenterologists.

Again, I really like my patient population and I like taking care of patients with functional bowel disorders. These are not all crazy patients as I know some gastroenterologists think. They actually cope reasonably well with their condition, however, they are not completely satisfied and they are looking for something a little bit better.

So, what is the impact of this condition? Is it just kind of a minor annoyance to my patients? I would like to present some data related to the impact this condition has in patients. First I would like to take a look at quality of life. There haven't been that many studies. I will present three of the four studies I am aware of.

In Olmstead County, Minnesota, individuals with chronic constipation reported a significant

impact in quality of life with reduced SF-36 scores. Similarly, in Canada, people who have either self-reported or Rome II constipation also had worse SF-36 scores compared to the normal population. In Australia, people with constipation had significantly worse SF-12 scores on both the mental and the physical components. So, there is certainly an impact on these individuals' quality of life.

Not only does chronic constipation impact quality of life, but it is also associated with increased healthcare utilization. In this next slide we see that 5.7 million constipation-related outpatient visits do occur annually; 4.1 million of these are physician office-based visits. However, there are 991,000 emergency room visits and 587,000 hospital outpatient visits each year.

The cost is a little bit difficult to get at as it relates to how expensive is this condition. The one study that I found was from 1997, a study by Rantis and colleagues, who found in patients who had been referred for tertiary care

evaluation had costs for additional testing on the average of $2,752. Again, in 2004 dollars I am sure that may be a bit more. But the point is really that this disorder does have an impact both from a quality of life and from a healthcare utilization perspective.

So, if this is affecting my patients' lives I would like to be able to treat them appropriately, and my goal of therapy is that I would like to be able to improve GI function in order to obtain relief of the key symptoms that my patients are bringing to me, and we have reviewed what these symptoms are.

Well, what do we have available in order to do this? Certainly we have fiber; laxatives, be they osmotic or stimulant laxatives. We can use enemas or suppositories and we do have some miscellaneous agents that we use. We can use a cholinergic agonist, such as bethanchol. I don't think too many of the gastroenterologists have used that actually for treatment of constipation but it is available for us and we have used it in the

past. We may use a prostaglandin analog called misoprostil and we have also used colchicine--again, certainly not ideal agents but they are things that we do have available for us.

Well, there are some challenges with these agents. My patients tell me that they really aren't consistently getting relief. There is a variable treatment response. Importantly, for the constellation of constipation symptoms that we see the efficacy really has not been evaluated or demonstrated for most of these agents. Importantly, chronic constipation is just that, it is a chronic problem and most agents are indicated for less than or equal to 2 weeks of therapy. I would certainly like to be able to offer my patients something on an ongoing basis.

There are other limitations associated with these agents. First is the worsening of some of the constipation symptoms that I am actually trying to treat. I mean, who among us has not given fiber to patients only to have them come back a week or two later complaining of increased

bloating and gas? Likewise, these agents can also cause cramping, abdominal pain or colicky stools. Fortunately, complications are not common with the treatments that I use for treating constipation. I do worry in some patients should they develop severe diarrhea which can result in hypovolemia or electrolyte disturbance. Metabolic disturbances can occur, such as hypokalemia or hypomagnesemia depending on the agent I may have used.

There are also other adverse effects which, fortunately, also are not too common. We can see interference with concomitant drug absorption. For instance, some laxatives when given with cipro may result in poor absorption of that medication or with theophylline.

I am not too concerned about the structural changes that may occur in the gut mucosa, things such as melanosis coli or the abuse potential or dependency, although I can tell you my patients and many physicians do consider these to be obstacles to use of many of the agents that are currently available. My patients certainly tell me

that there is diminished therapeutic effect that they see that occurs over time when using these agents, causing them to have to escalate the drug usage and often with additional side effects associated with this.

I am talking to my patients not being satisfied, and can I get at is there truly a quantitative effect that tells me how satisfied are patients or physicians with these therapies? Well, there really isn't much out there. Fortunately, a colleague of mine, Dr. Larry Schiller, has shared with me an abstract that he has submitted to The American College of Gastroenterology. This is an Internet-based study that was done, and a group of physicians were asked are your patients completely satisfied with treatments for constipation? The physicians overwhelmingly, 82 percent, said no, my patients are not completely satisfied.

If you take a look at the box on the right, the reasons for dissatisfaction included lack of efficacy, 93 percent; safety or side effects, 57 percent; or other reasons such as taste

or compliance in 27 percent. In this group of physicians, 60 percent of physicians agreed that they do not have adequate products for treating their patients with chronic constipation, and 90 percent of these physicians wanted better treatment options. Physicians cited frustration with the current treatments as one of the top 3 reasons patients state for seeking care for their condition.

Another study, a population-based study, also Internet based, took a look at patients who had seen a physician for constipation within the past year. In this group of 557 patients, they were asked are you completely satisfied with your treatment for constipation? Nearly half said no, they were not completely satisfied. So, again, these are patients that have seen a physician within the past year that were obtained through a national database survey. The reasons for dissatisfaction included efficacy, similar to the physicians, in 82 percent. Patients weren't quite as concerned as physicians were about safety or

side effects but still an important concern of theirs in 16 percent. Other reasons, such as taste or not wanting to take the agents regularly, in 17 percent.

At the bottom of the slide we see two other references, one from Irvine and one from Ferrzzi. These data support the findings that they found in their studies related to patient concerns regarding the currently available treatments for constipation.

In conclusion, chronic constipation, in my opinion, is a condition that is truly in need of a better approach. Constipation is characterized by a constellation of symptoms and we need to recognize what the symptoms are that our patients bring to us as being most important, including the complaints of straining and incomplete evacuation. Certainly, we want to remember frequency but this is not our patients' primary concern. Chronic constipation is associated with high resource utilization and does have a significant negative impact on our patients' quality of life. The

current pharmacologic agents have some limitations and many patients and their physicians are not completely satisfied with the available therapies. I truly believe that better treatment options are needed for this condition.

Thank you for allowing me to share with you today my thoughts about chronic constipation. This is obviously a topic of great importance to me and to my patients. I am looking forward to hearing more from the other speakers today what I am sure will be a very lively and interesting discussion.

Zelnorm: Efficacy and Safety in Chronic Constipation

DR. DENNIS: Thank you, Dr. Prather. Dr. Fogel, members of the advisory committee, FDA representatives, ladies and gentlemen, good morning. My name is Eslie Dennis and I am one of the senior medical directors for gastroenterology at Novartis Pharmaceuticals. I am delighted to be here today to be able to share with you our chronic constipation program, and I thank you for the

opportunity to do so.

Over the next 30 minutes I will provide you with our rationale for studying patients with chronic constipation. I will then highlight the study objectives of our Phase 3 program, walk you through the study design, and provide more specifics around the patient population that was studied. Then I will present the efficacy data from our primary and secondary endpoints and, finally, the safety data for the 12-week double-blind, placebo-controlled studies and the safety data from the 13-month blinded extension study.

Zelnorm is a 5-HT 4 receptor partial agonist. It is representative of a new class, the aminoguanidine indole, and it was designed specifically to act at 5-HT 4 receptors in the GI tract. The molecular structure of Zelnorm is based on serotonin which we know plays a crucial role in the normal functioning of the GI tract. We also know that the action of serotonin at 5-HT

receptors is prokinetic.

Our mechanism of action and preclinical data have demonstrated that tegaserod is, indeed, a promotility agent. Tegaserod has been shown to augment peristalsis, thereby enhancing gut motility and decreasing transit time. Furthermore, animal studies have shown that tegaserod increases chloride and water secretion which would improve stool consistency independent of the promotile effect of the drug. In addition, we have the data from our IBS with constipation studies that confirm the significant improvement with Zelnorm compared to placebo on stool frequency, stool consistency and straining--all important benefits when treating chronic constipation.

On the basis of our IBS with constipation studies, we felt that we could proceed directly to Phase 2 trials in chronic constipation without a formal Phase 2 program, and that we would use the same doses that were tested in our IBS-C Phase 3 trials.

Let me now walk you through the Phase 3 chronic constipation program. The study objectives

were to evaluate the efficacy, tolerability and safety of 2 doses of Zelnorm, 2 mg BID and 6 mg BID, compared to placebo over a 12-week treatment period in patients with chronic constipation.

We had 2 large randomized, double-blind, placebo-controlled clinical trials in our program. Study 2301 was conducted in 128 centers in 16 countries in Europe and in Australia and South Africa. The design consisted of a 2-week baseline period, followed by a 12-week treatment period with either Zelnorm 2 mg BID, 6 mg BID or placebo.

One thousand, two hundred and sixty-four patients were randomized. We chose the time line of 12 weeks of treatment for the core studies in keeping with the Rome committee guidelines regarding duration of clinical studies in functional bowel diseases for chronic therapies. The 2 doses of Zelnorm and the BID regimen were based on our experience with the previous dose-ranging and Phase 3 studies that were conducted in IBS-C patients.

The initial 12-week treatment period was

then followed by an optional 13-month extension period. This extension period was double-blinded but there was no placebo arm. So, patients who had received Zelnorm 2 mg BID or 6 mg BID remained on these doses and patients who had received placebo then received Zelnorm 6 mg BID in the extension, and 842 patients entered the extension study.

The primary aim of the extension study was to provide long-term safety data for the 2 doses of Zelnorm. Study 2302 was conducted in 105 centers in 7 countries in North and South America. The study design was very similar, with a 2-week baseline period and a 12-week treatment period. However, in this study the 12-week treatment period was followed by a 4-week drug-free withdrawal phase. A similar number of patients were randomized, 1,348.

Patient inclusion and several of the endpoints, including the primary endpoint, were based on the number of complete, spontaneous bowel movements of CSBMs. Let me clarify this terminology that we have used. BMs refer to all

bowel movements. SBMs refer to spontaneous bowel movements. Spontaneous means a non-laxative induced stool, in other words, no laxative or enema in the preceding 24 hours. These can be stools with either complete evacuation or incomplete evacuation. CSBMs refer to complete spontaneous bowel movements. Complete is a subjective definition of a bowel movement that results in a sensation of complete evacuation. We know that there are constipated patients out there who have more than 3 bowel movements a week but these are often small amounts of hard and lumpy stools with straining and incomplete evacuation, and these are patients that are not satisfied with the quality of their bowel movements. So, complete spontaneous bowel movement captures the quality of a bowel movement that is not laxative induced and is a measure of both the quality and frequency. We felt that this endpoint best captured what patients complain of, based on expert opinion and the published literature.

A recent state-of-the-art review on

chronic constipation in The New England Journal of Medicine referred to the large study that Dr. Prather has shown you, stating that constipation had been identified in this study as an inability to evacuate stool completely and spontaneously 3 or more times a week.

Given that there is no recognized gold standard for endpoints in chronic constipation, it seemed very reasonable to use the SCBM endpoint as our primary endpoint. In fact, this is a more stringent endpoint than using just bowel movements alone. However, we recognize that different experts might request different analyses and different endpoints and so we defined a priori a number of secondary endpoints representing the multiple symptoms of chronic constipation that I will also be presenting to you today.

We included males and females over the age of 18 years with chronic constipation. Chronic was defined as at least 6 months of consistent symptoms. Constipation was defined as less than 3 complete, spontaneous bowel movements per week and

one or more of the following 25 percent of the time, very hard or hard stools, sensation of incomplete evacuation, or straining at defecation. These criteria were based on the well-established Rome criteria.

Patients were also required to have had a normal endoscopic of radiological evaluation of the bowel within the past 5 years and after the onset of symptoms. In addition, there had to be no history or evidence of alarm features such as weight loss, rectal bleeding or anemia since the evaluation was performed.

Patients were excluded if they had constipation for which the cause was known, in other words, secondary constipation as you can see listed on the slide. So, we studied patients with chronic constipation of unknown cause. In addition, patients on concomitant medications that could affect GI transit were excluded, as well as patients with fecal impaction requiring surgical or manual intervention. These criteria were excluded based on a comprehensive history, thorough physical

examination, as well as baseline ECG and laboratory assessments.

At the end of a 2-week baseline period and just prior to randomization additional exclusion criteria were applied. Patients were excluded if constipation could not be confirmed by the number of CSBMs, straining and/or very hard or hard stools recorded in daily diaries. They were also excluded if they had loose or watery stools for more than 3 of the 14 days and if they used laxatives outside of the guidelines for more than 2 of the 14 days. Patients were deemed to be non-compliant with diary completion if they entered less than 11 days in the daily diary and were subsequently also excluded.

On a daily basis we assessed a number of parameters related to bowel habits--straining, stool frequency, stool form that we measured using the Bristol Stool Scale, and whether evacuation was complete or incomplete. Patients were required to collect this data for each individual bowel movement, and we determined which bowel movement was spontaneous based on the daily diary data

reflecting the time of administration of any rescue laxatives.

On a weekly basis we asked about satisfaction with bowel habits, as well as bothersomeness of constipation, bothersomeness of a bowel movement distention or bloating and bothersomeness of abdominal discomfort or pain.

Let's look at the patient disposition. Over 80 percent of randomized patients completed the study, with fewer than 20 percent discontinuations. The most common reason for discontinuation was for unsatisfactory therapeutic effect, with the largest percentage being in the placebo group, as we might expect. Adverse events accounted for similar numbers of discontinuations in the placebo and Zelnorm 2 mg BID groups, with a slightly higher percentage in the 6 mg BID group which was not statistically significant. The pattern of disposition was similar in the 2 trials.

Let's look at the results, starting with the demographic data. These were very similar between the two studies. The vast majority of

patients, 86 and 90 percent, were female. The mean age was 46 and 47 years, with a similar age range, from 18-88 years. Fourteen percent and 12 percent were 65 years or older, and just under half the female population was postmenopausal. The vast majority were Caucasian, more so in the European study.

Patients were required to have had at least a 6-month history of constipation symptoms. As you can see, the mean duration of symptoms was considerably longer, 14.7 and 19.5 years.

The means of the characteristics of bowel habit by history and during the 14-day baseline period are shown on the slide here. However, as these baseline parameters would not be normally distributed in a constipated population it may be more relevant to look at median data at baseline. When we do so, we see from the history the duration of symptoms was 10 and 15 years, with hard or very hard stools 90 percent of the time and a median number of one SBM per week. Now, in clinical practice the Rome criteria are applied to the

history to make a diagnosis of chronic constipation.

From the baseline diary data we see that the median number of CSBMs was zero and SBMs 2.5 and 2.9. So, these patients fulfilled the inclusion criteria of having less than 3 CSBMs per week. In fact, they had less than 3 SBMs per week by history and by baseline median data. In addition, the number of SBMs with straining per week was 2.0 and 2.5 so the majority of spontaneous bowel movements were associated with straining. This confirms that the patient population was, indeed, constipated and, indeed, had chronic constipation.

I have outlined the study design, the patient population, demographics and the baseline characteristics. Now let's look at the primary efficacy variable. For this endpoint we defined a responder as having an increase of at least one complete spontaneous bowel movement per week on average during the first 4 weeks of the treatment compared to the 2 weeks at baseline. They had to

have had at least 7 days of treatment.

The results were positive. In study 2301 the responder rates for Zelnorm were 35.6 percent for 2 mg BID, 40.2 percent for 6 mg BID compared to 26.7 percent for placebo.

In study 2302 the responder rates were 41.4 percent with 2 mg, 43.2 percent with 6 mg BID compared to 25.1 percent on placebo. The p values were significant. The 6 mg BID dose was consistently more efficacious, with deltas of 13.5 percent and 18.1 percent for the 2 studies.

Now, in order to confirm sustained efficacy of Zelnorm we analyzed those patients with an increase of at least one complete spontaneous bowel movement per week on average over the entire 12-week trial duration, compared to the baseline period of 2 weeks.

Again the results were positive and consistent with the results for the primary efficacy variable. A treatment effect for the 6 mg BID dose over placebo of 13 and 18 percentage points for the 2 trials respectively was

demonstrated.

When we look at weekly responder rates using this responder definition, we can see that the effect of Zelnorm is seen early, within the first week, and is sustained throughout the entire treatment period. In study 2302 we can see that the treatment effect is lost once the drug is withdrawn. The percentage of responders in both Zelnorm groups reached the level of placebo within 2 weeks after termination of treatment. The results with the 6 mg BID dose are consistently superior to placebo, and here I am showing you the data for this dose alone so that you can more clearly see the benefit.

When we look at the number of CSBMs, there is a marked increase within the first week of treatment with a significant improvement over placebo. The number of CSBMs decreased on withdrawal of the drug, approaching but not reaching the level observed during the baseline period. There was no rebound effect demonstrated. The effect was again more consistent with the 6 mg

BID dose, which you can see more clearly on this slide.

In order to further assess the benefit of Zelnorm, we conducted analyses on other constipation assessments which we defined a priori. Let me share these results with you. Let's start with satisfaction with bowel habits. Now, this is an important endpoint and an important measure of clinically relevant benefit. The Rome committee has advocated the use of global endpoints and satisfaction really is a composite subjective assessment by the patient. We asked the question how satisfied were you with your bowel habits over the past week? We used a 5-point ordinal scale, with zero being a very great deal satisfied and 4 being not at all satisfied. So, improvement was represented by a decrease in the satisfaction score.

Here we defined a responder as having a mean decrease of 1 or more on the 5-point scale over 12 weeks compared to baseline. We subsequently have validated this data relating

satisfaction scores to a relative shift in distribution, and we have looked at baseline standard deviations and week 12 standard deviations and a 1-point change on this score is associated with significant effect sizes. We saw significant superiority of both doses of Zelnorm compared to placebo in this satisfaction endpoint.

Stool form is another important marker of constipation, and also showed significant improvement
on Zelnorm. Stool form was 2.5 and 2.8 at baseline in the 2 studies respectively and on treatment with Zelnorm. On treatment with Zelnorm this was maintained at around a score of 3.5 on the Bristol Stool Scale.

On this slide you can see the change from baseline in stool form, which showed significant benefit over placebo for nearly all weeks. Again, we can see the loss of benefit during the withdrawal period.

What about straining, yet another important symptom of constipation? For each bowel

movement we asked the question did you have any straining? This was a 3-point scale and the possible responses were zero, no straining; 1, acceptable straining; and 2, too much straining. We did not capture straining in the absence of a bowel movement. We subsequently analyzed straining scores for spontaneous bowel movements and saw significant improvement on Zelnorm compared to placebo which was consistent over time, as we saw with the other variables.

Now, what about the bothersomeness questions? On a weekly basis patients were asked to evaluate the bothersomeness of constipation. Now, this is a global assessment in keeping with the global satisfaction assessment.

In addition, we looked at the bothersomeness of a bowel movement bloating and distention and bothersomeness of abdominal discomfort. As you heard from Dr. Prather earlier, patients with chronic constipation can present with bloating and abdominal discomfort, and we can see significant improvement in the bothersomeness of

constipation on Zelnorm for both doses in both studies. For abdominal bloating and distention and abdominal discomfort and pain we saw improvement in these symptoms in both studies, reaching statistical significance for the 2 doses in study 2302.

As you also heard from Dr. Prather, many of the currently available therapies for constipation in fact aggravate the symptoms of abdominal bloating and abdominal discomfort so this is another important benefit of Zelnorm.

So, I have presented several secondary endpoints. Now the question we asked ourselves was is there an association between responders for the primary endpoint and responders for the secondary efficacy variables. Well, as you can see on this slide, there is a strong positive association between responders for the primary endpoint and response to secondary variables. Remember, the primary responder definition was an increase of at least one CSBM per week compared to baseline over the first 4 weeks of the treatment.

Improvement on stool form is represented by a positive increase, while improvement on the other variables is represented by a decrease in scores. You can see the clear-cut difference between responders and non-responders, which is significant for each endpoint, which supports the CSBM primary endpoint.

Now I will walk you through some of the additional analyses that were done. In discussions with the FDA early last year, some other responder analyses were requested prior to database lock. One of these define a responder was having at least 3 CSBMs per week for the first 4 weeks of the study.

Now, this was a fixed definition with no comparison to baseline, and this was a high hurdle to achieve considering that the patient population had a median number of CSBMs of zero and a mean number of CSBMs of 0.5 at baseline. So, reaching a level of greater than or equal to 3 CSBMs per week represents on average a 6-fold increase required to meet this responder definition. As you can see

though, Zelnorm was significantly better than placebo. Both doses in both studies were significant, with deltas of 9 percent for the 6 mg BID dose in the 2 studies. We saw similar results using this responder definition over the 12-week treatment period, with deltas of 9 and 11 percent for the 6 mg BID dose.

So, we have demonstrated significant benefit of Zelnorm compared to placebo for our primary endpoint, and we have demonstrated significant benefit of Zelnorm compared to placebo in these analyses that were requested by the FDA.

Let us now look at the effect of the number of bowel movements at baseline on response. Now, bearing in mind that we used the concept of complete spontaneous bowel movements, which is a relatively new concept, we wanted to see if baseline number of bowel movements, and that is all-comers, would affect our primary efficacy variable.

So, we looked at patients who had less than 3 bowel movements per week at baseline. What

you can see is that Zelnorm is equally effective in the group that has less than 3 bowel movements per week as it is in the group that has more than 3 bowel movements per week at baseline.

We also did various subgroup analyses. These were planned prospectively but we did not attempt to meet a minimum number of patients in any subgroup. Subsequently, some of these groups had very few subjects and this is reflected in the wide confidence intervals. It is important to remember that the purpose of subgroup analyses is not to demonstrate efficacy as these analyses are not powered to detect statistical significance. The purpose of subgroup analyses is to ensure that the effect in any subgroup is consistent with the overall effect and that we are not seeing any negative trends.

Here I am showing you the data for the 6 mg BID dose, and we can see the positive odds ratios for almost all the subjects that we analyzed. In the group 65 years and older there was a total of 88 patients in the 6 mg BID group

and 117 patients in the placebo group, with an odds ratio of 1 for the overall population.

For the male patients, there were 106 on 6 mg BID and 93 on placebo. The odds ratio was positive at 1.36, and improvement on Zelnorm was seen for most variables in men.

One of the issues I want to address now is the question how many of these patients in this chronic constipation program were, in fact, IBS patients, and did this have an effect on our results. We did not actively exclude IBS patients from the study but when we went back to the patient history only 4 percent of patients had a diagnosis of IBS in their history.

As we did not administer the Rome questionnaire for IBS, we decided to take a conservative approach to try and identify patients that we thought may be potentially IBS-like. So, we identified all patients in whom abdominal pain was the main complaint at baseline, and this was about 12 percent of our patients. In addition, we included patients who had abdominal pain that may

not necessarily have been their predominant symptom but they also had diarrhea together with this abdominal pain. So, criteria (a) and (b) on this slide come from the history and criteria (c) comes from the baseline diary data.

We came up with a total of 22 percent of our patients as possibly having IBS. These were equally represented in the 3 treatment arms. So, we felt confident that almost 80 percent of our patients were, indeed, chronic constipation patients and did not have IBS. However, we were interested to see what the efficacy results would look like if we excluded those patients who were IBS-like.

Here is the pooled data. In this group, without IS-like features, in other words, the pure chronic constipation population, you can clearly see the benefit of Zelnorm with improvement over placebo of 40 percent in the 2 mg BID group and 18 percent in the 6 mg BID group. We can compare this to the deltas in the pooled ITT primary efficacy analysis in which there was a 13 percent delta in

the 2 mg BID group and 16 percent delta in the 6 mg BID group. So, in this pooled subgroup analysis the results in the pure chronic constipation group are even more robust than in the ITT analysis.

So, I have presented data here that demonstrate the efficacy of Zelnorm in patients with chronic constipation. The onset of action is early. The effect is sustained, and there is no rebound phenomenon.

We have measured the efficacy of Zelnorm using a number of parameters and Zelnorm is efficacious for multiple symptoms of chronic constipation which include straining, hard stools and infrequent stools, with overall improved satisfaction. The 6 mg BIT dose has emerged as consistently more efficacious than the 2 mg BID dose.

Now let's look at the safety data. I am going to go through the 12-week data looking at exposure, adverse event profile, serious adverse events, and laboratory evaluations, and then the long-term safety profile from the extension study.

This was a 13-month extension study, providing a total of 16 months of data for the groups that received Zelnorm in the core study.

Let's start with overall exposure. The intended study duration was 84 days. Exposure was comparable across all treatment groups. The mean duration of treatment was 80 days, and 84 percent of patients completed at least 11 weeks of treatment and 69 percent had more than 85 days of exposure in this 12-week period. The total number of patients who experienced any adverse event was 60 percent in the placebo group, 57 percent in the 6 mg BID group and 56 percent in the 2 mg BID group. The most frequent adverse events were headache, nasopharyngitis , diarrhea, abdominal pain and nausea. The only notable adverse event seen more frequently with Zelnorm was diarrhea, as you would expect given the pharmacodynamic action of this drug.

When we look at the most frequent adverse events leading to discontinuation, we see abdominal pain, diarrhea, abdominal distension, nausea and

headache. On this table we have included all discontinuations in which there were at least 5 patients on any dose of Zelnorm. Overall, the only one where discontinuations appeared to be dose-dependent was diarrhea, with a discontinuation rate of less than 1.0 percent on the 6 mg BID dose and 0.3 percent for the 2 mg BID dose.

Let's look at the diarrhea in more detail--4.2 percent with the 2 mg BID dose, 6.6 percent with the 6 mg BID dose versus 3 percent with placebo. Over 80 percent of patients who experienced diarrhea had only a single episode, and the median duration of the first episode was about 2 days. Most diarrhea occurred on the first day of treatment.

When we look at the characteristics of the stool on the first day of diarrhea, the median number of bowel movements was 3 in the placebo group, 2 on Zelnorm 2 mg BID and 3 in the mg BID group. The median stool form was essentially similar across all treatment groups at 5.7 for placebo and 6 and 6.3 for the 2 Zelnorm doses

respectively.

Most patients who had diarrhea continued on their medication and took no action. There were more patients on 6 mg BID who adjusted their dose or temporarily interrupted therapy but there were very few patients who discontinued permanently because of diarrhea. None of these cases met the definition of a serious adverse event or the definition of clinically significant consequences of diarrhea such as hypovolemia, hypokalemia or the need for IV fluids or electrolyte replacement.

Let's look at serious adverse events. Incidence rates were comparable across all treatment groups. There were very few discontinuations due to these serious adverse events. There were no deaths during the course of the study but there was one death 67 days after the last dose of study medication in study 2302. This was an 85 year-old man who had been on Zelnorm 2 mg BID. He died from respiratory failure and mesothelioma secondary to preexisting asbestosis.

We also evaluated a number of laboratory

parameters. There was a low frequency of notable abnormalities which were essentially similar across all treatment groups.

The incidence of any abdominal or pelvic surgeries in the Zelnorm-treated group was lower than in the placebo group. One patient in study 2302, on Zelnorm 6 mg BID, had a cholecystectomy. The investigator assessed the event as not related to study medication. The incidence of other surgeries was well balanced between Zelnorm and placebo.

Now let's look at the 13-month extension study, and 842 patients entered the extension phase. And, 61.7 percent were exposed to at least 12 months of Zelnorm; 46 percent of patients discontinued over the 13 months. Most discontinuations were for unsatisfactory therapeutic responses, with very few discontinuations for adverse events. The same adverse events predominated as during the core period. Frequencies followed the same pattern as seen in the core studies, although the incidence

rates were generally higher due to the longer duration of exposure. No relevant differences were seen in the rates between the 2 doses of Zelnorm. There were no deaths in the 13-month extension.

So, to summarize our safety conclusions, the incidence of adverse events on Zelnorm in chronic constipation is similar to placebo, except for diarrhea, which is what we would expect from the pharmacodynamic profile. There were low discontinuation rates due to adverse events. The long-term safety profile was similar to the profile in the core 12-week studies. Zelnorm, therefore, as been demonstrated to be safe and well tolerated in patients with chronic constipation.

What are our final overall conclusions? Zelnorm is effective in the treatment of multiple symptoms of chronic constipation, with the 6 mg BID dose consistently more efficacious than the 2 mg BID dose. Zelnorm improves satisfaction with bowel habits; straining; hard and lumpy stools; and infrequent bowel movements. In addition, Zelnorm has a favorable safety profile.

Therefore, we are asking for an approval for Zelnorm for the treatment of patients with chronic constipation and relief of associated symptoms of straining, hard or lumpy stools, and infrequent defecation.

That concludes my presentation. Thank you very much. I would now like to introduce Dr. Bo Joelsson, vice president and head of clinical research and development for gastroenterology, who will present the general safety overview. Dr. Joelsson?

Zelnorm Safety Overview

DR. JOELSSON: Good morning, Dr. Fogel, advisory committee, representatives from the FDA, ladies and gentlemen. My name is Bo Joelsson and I am the head of GI research and development at Novartis.

Today I will review with you the overall safety experience with Zelnorm, and demonstrate to you that Zelnorm is a safe and well-tolerated drug. This is what I am going to review with you today. First I will show that the positive safety profile

of Zelnorm that was established at the time of approval in July, 2002 is confirmed in our chronic constipation clinical program. Secondly, I will briefly present a few safety topics that we have agreed with the FDA to discuss at this meeting: serious consequences of diarrhea; rectal bleeding; ischemic colitis and other forms of intestinal ischemia; biliary tract disorders and ovarian cysts. Finally, I will summarize our experience demonstrating that Zelnorm is a safe and well tolerated drug.

The three most common adverse events that were reported at approval in July, 2002 were headache, abdominal pain and diarrhea, and the incidence of diarrhea was higher on Zelnorm.

This slide shows that the adverse event data from the chronic constipation clinical trials compared favorably to the IBS constipation data. Headache incidence is similar between the treatment arms. Abdominal pain was less common in the chronic constipation studies than in the IBS trials, demonstrating that the chronic constipation

population is different from the IBS population which is characterized by abdominal pain. The incidence of abdominal pain in Zelnorm and placebo treated patients indicates that abdominal pain as an adverse event is not related to Zelnorm treatment. As in IBS, the reported incidence of diarrhea is higher on Zelnorm. Adverse events leading to discontinuation are also low in the chronic constipation clinical trials.

At approval in July, 2002 the incidence of serious adverse events was low. This was 1.6 percent on Zelnorm as compared to 1.1 percent on placebo. Serious adverse events leading to discontinuation of study drug were 0.7 percent on Zelnorm and 0.6 on placebo.

The incidence of serious adverse events in the chronic constipation clinical trials was similar to that in the IBS clinical program. The incidence of serious adverse events leading to discontinuation was lower and identical in Zelnorm and placebo treated patients.

The clinical trial adverse event data

collected in chronic constipation clinical program supports and strengthens the positive safety profile established at the time of approval. With the exception of diarrhea, the Zelnorm safety profile is similar to that of placebo.

We have at this time experience with use of Zelnorm both from clinical trials in patients with IBS, chronic constipation and upper GI indications, as well as postmarketing clinical use. In clinical trials more than 15,000 patients have been included and more than 11,000 subjects have taken Zelnorm, which corresponds to 3,456 patient-years of Zelnorm experience. More than 10,000 patients have been involved in controlled clinical trials and close to 7,000 of them have been on Zelnorm.

Zelnorm is currently registered in 56 countries worldwide. It has been available since January, 2001 and here, in the United States, since July, 2002. Approximately 3 million patients have been treated, 2 million in the United States. That corresponds to more than 350,000 patient-years of

treatment and more than 230,000 patient-years in the United States.

We have agreed with the FDA to discuss several specific safety topics at this advisory committee meeting. The first of these is serious consequences of diarrhea. Diarrhea is an expected effect of Zelnorm in some patients due to the mechanism of action. The diarrhea is generally mild, is generally transient and self-limiting, and rarely leads to serious consequences.

A patient is defined as having a serious consequence of diarrhea if one or more of the following took place: A serious adverse event was reported as defined by regulatory requirements; if hypokalemia occurred; if hypovolemia was diagnosed; if IV fluids were administered; or any medically significant events related to diarrhea occurred, such as hypotension, syncope or cardiac effects.

We carefully reviewed our clinical trial experience of more than 11,000 patients using this definition in order to identify cases of serious consequences of diarrhea, and this is our clinical

trial experience. Six cases of serious consequences of diarrhea were found in the clinical studies on Zelnorm with more than 11,000 patients. Four of these patients required hospitalization. Two received IV fluids. Two had actually possible other causes. One reported gastroenteritis and one reported antibiotic-induced diarrhea. All patients recovered without complications and four of them were actually able to continue on study medication after these episodes.

From the postmarketing experience in approximately 3 million patients, 30 cases have been reported; 16 were hospitalized; 11 received IV fluids; 8 exhibited hypotension; 4, syncope; and 4 were considered life-threatening by the reporting physician; 1 had hypokalemia. One fatality from aspiration pneumonia was reported in a patient with acute pancreatitis and chronic liver cirrhosis.

This demographic information on the 30 patients with serious consequences of diarrhea in the postmarketing experience. There was a wide age spectrum, 18 to 82 years. The median age was 49

years and only 9 patients were older than 65, indicating that this is not an elderly specific issue. As is expected, most were women, reflecting the label in most countries. Serious consequences of diarrhea mostly occurred in patients on 12 mg of Zelnorm per day but were also reported in some patients on a lower dose.

In clinical trials diarrhea usually occurred during the first days of treatment, as we heard before. This was also true for serious consequences of diarrhea in the postmarketing experience. It occurred within 5 days in all cases and the median time was 1 day.

In conclusion, serious consequences of diarrhea are rare in clinical trials and very rarely reported in the postmarketing experience. All cases resolved without sequelae.

Rectal bleeding is of special interest because of its possible relationship with serious colon conditions. We have carefully reviewed our clinical trial data for terms that indicate the presence of rectal bleeding, such as rectal

hemorrhage, melena, hematochezia, etc., etc. We found that the presence of rectal bleeding was very similar in patients on Zelnorm and placebo in our controlled clinical trials.

From the postmarketing experience of approximately 3 million patients, 82 cases of rectal bleeding were reported. Twenty-one were reported in conjunction with suspected ischemic colitis; 1 from another form of intestinal ischemia; 3 from other forms of colitis. In 23 cases hemorrhoids were a possible source of bleeding. The rest of the cases listed on this slide show varying etiologies. Fifteen of the patients were not investigated.

Our clinical trial data indicated a similar reporting rate in Zelnorm- and placebo-treated patients. There are rare reports of rectal bleeding from postmarketing experience, which indicates that Zelnorm therapy is not causally related to the rectal bleeding.

Now, the occurrence of ischemic colitis and other forms of intestinal ischemia is a concern

with drugs used to treat IBS with diarrhea. These drugs block the 5-HT 3 receptor and, thus, have a very different mechanism of action than Zelnorm, which is a 5-HT 4 receptor agonist used to treat IBS with constipation. Nonetheless, since these are potentially serious conditions and Zelnorm affects the serotonin receptor, it is important to carefully assess whether Zelnorm therapy could increase the risk of intestinal ischemia.

Ischemic colitis is a rare condition in the general population. When it occurs, it is potentially serious but is generally mild and transient. It is characterized by mucosal erosions seen at colonoscopy, with rectal bleeding and abdominal pain being the most common clinical presentations. Usually no specific treatment is needed and surgical intervention is rarely indicated.

While ischemic colitis is very rare in the general population, it is more commonly reported in IBS patients. In a study from the Medi-Cal claims database, 179 cases per 100,000 patient-years were

found in IBS patients versus 47 cases per 100,000 patient-years in non-IBS patients. In a study from the United Health Care claims database, with a younger patient population, the corresponding numbers were 43 in IBS patients and 7 in non-IBS patients. In the CORI database which collects data from endoscopy units all over the United States, ischemic colitis was found in 93 per 100,000 colonoscopies in patients with IBS-like symptoms while there were 21 cases per 100,000 screening colonoscopies in asymptomatic individuals. All of these cases were endoscopically verified and in most cases supported by histology.

It has been suggested by Dr. Brinker et al., from the FDA, that the increased incidence of ischemic colitis in IBS is the result of misdiagnosis. Dr. Brinker published this analysis from the patients from the United Health Care study. He found evidence for misdiagnosis during the first 3 weeks after IBS diagnosis. However, when patients with IBS were followed for more than a year, he still found an increased rate of

ischemic colitis, 53 per 100,000 patient-years.

Thus, ischemic colitis can be misdiagnosed as IBS during the first weeks of treatment, but patients with a stable IBS diagnosis for more than 1 year still have an increased risk of ischemic colitis diagnosis.

Now, there are two, maybe more, possible hypotheses why the rate of ischemic colitis in IBS is increased. Ascertainment bias because of the documented fact that IBS patients are investigated two to three times more than the general population, and/or because there are currently unknown common pathophysiological mechanisms that we don't know about today.

We carefully reviewed all cases of rectal bleeding, colonoscopy and reports of colitis in our clinical trials to identify possible cases of ischemic colitis and there were no cases of ischemic colitis identified in any of our clinical trials involving more than 11,000 patients on Zelnorm. However, one placebo case with ischemic colitis was identified in our clinical trials.

From postmarketing experience as of June 1, 2004, 26 cases of suspected ischemic colitis have been reported. This corresponds to a reporting rate of 7 cases per 100,000 patient-years worldwide and 12 per 100,000 patient-years in the United States. This rate is consistent with the background rate incidence in IBS patients.

The reported cases of ischemic colitis do not exhibit any distinct pattern with regard to duration of treatment, dose of drug, age of patients, co-morbid conditions, or other demographic subgroups. The absence of ischemic colitis cases in clinical studies and the low reporting rate in postmarketing experience suggest that Zelnorm treatment does not increase the risk of ischemic colitis.

Now, these findings are not surprising since Zelnorm is not expected to cause vasoconstriction as there are no 5-HT 4 receptors in the human vascular system. This is further supported by preclinical studies. In vivo animal studies have demonstrated no effect on colonic

vascular conductance which is a measure of vasal activity. In addition, although tegaserod has negligible affinity for the 5-HT 3 receptor, tegaserod has affinity for the 5-HT1B receptor but it does not cause vasoconstriction, as illustrated in this graph.

This graph depicts the results of adding sumatriptan and ergotamine, which are two known 5-HT1B agonists, and tegaserod to a preparation of isolated coronary arteries from non-human primates. As expected, ergotamine and sumatriptan cause marked contraction while tegaserod has no effect.

In conclusion, there is no evidence for a causal relationship between Zelnorm and ischemic colitis. Preclinical studies have clearly demonstrated that tegaserod has no vasoconstrictive potential. There have been no cases of ischemic colitis in clinical trials on Zelnorm, and the reporting rate in the postmarketing experience is consistent with the background rate of IC in the IBS population even taking under-reporting into account. These data indicate that Zelnorm does not

increase the risk of ischemic colitis.

Now, there have been four spontaneous reports of fatalities in patients with intestinal ischemia from postmarketing reviews. We take these reports very seriously and have investigated them thoroughly. Based on our individual and careful review of each case, we are confident that Zelnorm did not cause these fatalities.

The four fatalities are as follows: One case with untreated central line sepsis and ischemic colitis; one case of untreated chronic abdominal angina; one case with untreated hypothyroidism leading to severe fecal impaction; and one case of multi-organ failure from unknown cause.

Dr. Shetzline has carefully investigated these cases and he will now discuss them in some detail with you. Please, Dr. Shetzline?

Fatality Cases

DR. SHETZLINE: Thanks, Dr. Joelsson. I am Michael Shetzline, an gastroenterologist and a senior medical director at Novartis, responsible

for Zelnorm in the United States. Myself and Dr. Christian Avery are clinical safety experts responsible for evaluation of these cases.

I would like to review these cases in some detail. Given the complicated nature of the cases, it is important for us to go into some detail in order to separate out and look at the medical issues and make them clear. The first case is a 76 year-old woman. Her past medical history is significant for 16 years of constipation. She had IBS with constipation diagnosed in the year 2000 and started on Zelnorm in November of 2002. She also had dementia of the Alzheimer's type.

In late August of 2003, after 282 days of Zelnorm use the patient was found "down" at home. She presented at the emergency department and was admitted with abdominal pain, vomiting, hypotension, hypothermia and altered mental status. Her urine eventually grew E. coli and an abdominal CT noted dilated loops of small bowel, consistent with partial small bowel obstruction, diverticulosis and focal ischemic changes of the

left colon. She was treated with antibiotics and hydration.

During this admission she had a colonoscopy for an incidental episode of guaiac positive stool, and this revealed sigmoid and splenic flexure ulcers with areas of regeneration and healing, consistent with ischemic colitis. Zelnorm was discontinued at this time. Biopsies were consistent with ischemic colitis and she was placed on bowel rest and provided total parenteral nutrition.

She was eventually transferred to an extended care facility and had two colonoscopies on September 17th and 19th. Both noted improved colonic mucosa, resolving ischemic colitis. This is the usual expected course of ischemic colitis. However, she remained on TPN, total parenteral nutrition. She became hypotensive with E. coli UTI and was readmitted on September 26th for failure to thrive, febrile and more acutely ill.

After discussion with the family and patient, no heroic surgical interventions and/or

CPR were to be performed; only supportive care. She was diagnosed with central line sepsis and, given her medical co-morbidities and discussion with the patient and family, a "do not resuscitate" order was initiated. Her antibiotics were discontinue on October 1st and she expired. In summary, this event of ischemic colitis resulted from hypotension and possibly urosepsis.

The second case is a 66 year-old female who had a past medical history of hypertension, chronic obstructive pulmonary disease and tobacco abuse. She had a prior stroke in 1997 due to small vessel disease, and carried a prior diagnosis of non-specific chronic colitis. Significantly, she had symptoms of abdominal angina for 2-3 years characterized by chronic abdominal pain with food intake, and this resulted in 36 lbs of weight loss during this interval. Her IBS was diagnosed in January of 2000.

In October of 2003 she had continued and more severe post-prandial abdominal pain and constipation. On October 10th she was given

samples of Zelnorm, 6 mg BID, by her primary care physician. She was not given a prescription and her caregiver, who was responsible for administering all her medications, the medications taken by the patient, does not recall the patient taking Zelnorm. He does specifically recall her increasing use of Vicodin due to this more severe abdominal pain.

On October 15th she was admitted to the hospital with severe abdominal pain and bloody diarrhea. Zelnorm was not listed as an active medication in any of her admission documents.

On the 19th she developed acute abdomen and had an exploratory laparotomy for, quote, probable chronic intestinal ischemia, acutely worse, end quote. The laparotomy revealed infarcted bowel from the ligament of Treitz to the terminal ileum, cecum, and proximal ascending colon, consistent with occlusion of the superior mesenteric artery. Given the extensive bowel necrosis, comfort measures were provided and she expired. The cause of death was listed as bowel

infarction due to peripheral vascular disease. In summary, this is the natural history of end-stage chronic abdominal or mesenteric angina and it is likely Zelnorm was not taken by this patient.

The third case is a 41 year-old woman who had a very significant past medical history of chronic obstructive pulmonary disease. She had a very extensive history of tobacco abuse, with 60-90 pack-years of tobacco use for a 41 year-old woman. She also had asthma, prior alcohol and illicit drug use, as well as obsessive-compulsive disorder. She had peripheral vascular disease with claudication, constipation, recurrent urinary tract infections and hypothyroidism. She also had a significant abdominal event due to appendectomy with a rupture which resulted in abscess formation and a partial colectomy. She had medical and medication non-compliance, as noted in a primary care visit from November of 2003.

This individual was presumably prescribed Zelnorm in March of 2003, however, these documents were not available for review. We have no

follow-up from the March presumed prescription and the November primary care records which document her non-compliance. She developed severe abdominal pain and she collapsed with a cardiorespiratory arrest. After an emergency medical service call she was resuscitated and admitted.

It is important to note that admission documents list only her Lithobid and Seroquel as active medications. They do not list Zelnorm or her thyroid supplement. These documents include emergency medical service notes at home, admission notes and multiple physician evaluations.

On admission, her abdominal x-ray revealed free air in the abdomen and an exploratory laparotomy demonstrated a rectal sigmoid densely packed with rock-hard stool. She had ischemic colitis and enteritis involving the colon and terminal ileum and early gangrene of the distal bowel. She had marked dilatation, a picture consistent with toxic megacolon.

She had a sub-total colectomy with ileostomy and was treated with ventilatory support,

broad-spectrum antibiotics and vasopressors. A subsequent neurology evaluation revealed anoxic brain injury with diffuse edema and a suspicion of herniation. She developed multi-organ failure and expired three days after admission. In summary, this patient had a bowel obstruction from likely untreated hypothyroidism due to her medication non-compliance and a secondary perforation. Given her medical and medication non-compliance, it is likely she never took Zelnorm.

The last case is a 67 year-old woman who had a very significant history of heart disease, with known coronary disease, a prior coronary bypass graft procedure, angioplasty with stent placements, known occluded grafts, congestive heart failure, hypotension, atrial fibrillation and diabetes. She had chronic and acute renal failure. She was on Zelnorm 6 mg BID for an unknown indication from June 16th to August 7th, the date of this event.

She as admitted at this time with progressive shoulder and chest pain, as well as

shortness of breath, and was hospitalized, on telemetry for a rule-out myocardial infarction, on August 7th. On admission, her abdomen was soft, non-tender. Her lungs had few bibasal rales and her extremities showed trace pedal edema.

It is important to note that at this time she had no diarrhea, no melena and no bright red per rectum. On hospital day 3 she complained of abdominal pain and nausea, and surgical consult indicated a soft abdomen which was not distended. She did, however, have left lower quadrant tenderness and a questionable diverticulitis. An abdominal x-ray at this time showed a large amount of fecal material in the colon There was no gaseous distention or free air.

On the same day laboratory results indicated an amylase of over 7,000 and a lipase of over 400. A pulmonary consult for dyspnea indicated respiratory failure and she required mechanical ventilation. At this time she was evaluated for bronchitis, pneumonia, rule-out abdominal sepsis, rule-out ischemic colitis,

coronary disease and hypotension.

A clinical evaluation noted, quote, in view of her acute deterioration and chronic medical problems, her prognosis is extremely poor. Consequently, continuation of heroic interventions may be inappropriate, end of quote. A cardiologist summary indicated hypotension and it was felt that the patient had a catastrophic abdominal event. This may have included ischemic bowel, possible perforation, pancreatitis, acute renal failure, all in addition to her known co-morbidities of ischemic cardiomyopathy, congestive heart failure, renal failure and diabetes. The patient was made a "no code" and died on hospital day 4.

The death certificate listed cardiorespiratory failure as the primary immediate cause of death. Other factors included shock, pancreatitis and inflammatory bowel disease. In summary, this patient experienced cardiovascular collapse with a history of coronary disease and congestive heart failure, as well as other medical co-morbidities. This was likely unrelated to

Zelnorm.

Now I would like to return the safety update to Dr. Joelsson.

Zelnorm: Safety Overview (continued)

DR. JOELSSON: Thank you, Dr. Shetzline. In summary, these four cases, as you may understand, are very complicated. In two cases it is actually unclear if the patients actually took Zelnorm in the first place. In our opinion and those of external experts that have reviewed these cases, the evidence does not support that the death of these patients was caused by or contributed to by Zelnorm.

At the time of approval in July, 2002, biliary tract disorders were discussed because there was an imbalance of cholecystectomies introduction he clinical trials. When pooling the clinical trial data, there is still an imbalance in favor of placebo, although smaller than was seen in the approval trials.

An adjudication was performed with outside experts, resulting in a rate of 0.06 percent in

Zelnorm-treated patients versus 0.03 percent on placebo.

In the postmarketing experience there were 30 reports of biliary tract events in approximately 3 million patients, and 18 were cholecystectomies; 2 were cholelithiasis; and 10 were other events. There were no serious sequelae reported from these patients.

In order to further elucidate the possible effects of Zelnorm on gallbladder function a very thorough study was performed using dynamic ultrasound measurements. No effect on gallbladder function was detected. There was no impact on ejection fraction, ejection rate and period, or maximal emptying. There was no impact on fasting and residual volume, and there were no stimulus effects on gallbladder contraction during fasting. Based on this data, it is unlikely that Zelnorm affects gallbladder function.

At approval there was also discussion about ovarian cysts. However, ovarian cysts are very well balanced in the clinical trials and there

are very rare reports from the postmarketing experience. Our conclusion from these data is that Zelnorm treatment does not increase the risk of ovarian cysts.

Zelnorm has been extensively studied in clinical trials and postmarketing experience, and the safety profile of Zelnorm is very favorable. In fact, Zelnorm has the overall safety profile of placebo, with the only exception being diarrhea. However, serious consequences of diarrhea are very rare and do not result in significant clinical sequelae. Evidence from either clinical trials or postmarketing experience does not suggest that Zelnorm increases the risk of rectal bleeding, ischemic colitis, other forms of intestinal ischemia, cholecystectomies or ovarian cysts.

Zelnorm is a safe and well-tolerated drug that has a safety profile that supports its use in chronic constipation patients. Thank you. I would now like to introduce Dr. Schoenfeld who will discuss with you his benefit/risk assessment.

Benefit/Risk Assessment

DR. SCHOENFELD: Well, good morning, Dr. Fogel, members of the advisory committee, FDA officers, audience members. I am Philip Schoenfeld, a gastroenterologist at the University of Michigan School of Medicine. It is my pleasure to present a risk/benefit analysis of the use of tegaserod and traditional therapies for the management of constipation.

Now, I sympathize with the members of the advisory committee. You have been sitting here now for over an hour and a half. I imagine that I should keep this presentation brief but also as stimulating as possible to maintain your attention. I am going to present an evidence-based medicine analysis, revising the randomized, controlled trial data about the efficacy for tegaserod and traditional therapies in the management of constipation, and review the best available clinical trial data about the safety of tegaserod and traditional therapies in the management of constipation.

I think it is particularly important to

consider the risk/benefit analysis not only for tegaserod but also for alternative therapies for constipation because, as a practicing gastroenterologist, when I am treating a patient with constipation I have to consider the risk/benefit analysis for all of these possible treatments when I select the best possible treatment for my patient, and I certainly think this is an important topic. As Dr. Prather pointed out during her presentation, constipation is common. It negatively impacts the quality of life for patients who actively seek medical care, and many constipated patients are dissatisfied with available treatments.

Let's stop for a moment and think about that last statement, and look at the randomized, controlled trial data about traditional therapies for constipation to try to determine why constipated patients might not be satisfied with available therapies.

This is a partial list of the commonly used treatments for constipation. They include

surface-acting agents like dioctyl sodium sulfosuccinate--I had to practice saying that and hereafter I will refer to it as Colace; bulking agents like psyllium; stimulant laxatives and osmotic laxatives like PEG-3350. These are all FDA-approved treatments for constipation.

Dr. Prizont, in his efficacy section in the FDA briefing document, provided a brief but very balanced review about traditional therapies for constipation. He specifically noted that there are some randomized, controlled trials looking at the benefits of traditional therapies for constipation but many of these were conducted under deficient designs. In other words, many of these studies did not meet the Rome committee criteria for appropriate design of a functional GI disorder trial. They had inappropriately small sample sizes. They had inadequate blinding. They had very vague or imprecise criteria to identify patients with constipation.

Now, in the briefing document Dr. Prizont concluded that these trials revealed little

differences between laxatives and modest improvement over placebo. He actually referenced the most recent and most comprehensive meta-analysis about traditional therapies for laxatives, conducted by Jones and Nick Talley and colleagues. In fact, the actual title of that meta-analysis is "The Lack of Objective Evidence of Efficacy of Laxatives in Chronic Constipation." That is quite a provocative title.

Let's delve into that study a little bit further to see how they came up with that. In brief trials of 4 weeks or less in duration, they found that laxatives increased stool frequency by about 2 stools per week compared to baseline. Placebo increased stool frequency by about 1 stool per week compared to baseline. But as you note, the 95 percent confidence intervals here for placebo and laxatives are superimposed, not clearly demonstrating a difference in efficacy.

For trials of 5-12 weeks in duration the results are less impressive. Laxatives increased stool frequency by only 1 bowel movement per week

versus placebo-treated patients who had an increase in stool frequency of 1.5 bowel movements per week.

Now, I think we should be cautious about interpreting these results. This is a meta-analysis that provides a single summary statistic and combines the results from bulking agents, stimulant laxatives and osmotic laxatives. So, it might be more beneficial to look at a systematic review that at least separated out bulking agents from other types of laxatives.

That is actually available. The other well-designed, systematic review about traditional therapies for constipation comes from Tramonte and Cindy Mulrow and colleagues, at the Cochrane Center in San Antonio, Texas. They separated out bulking agents versus laxatives and found that bulking agents increase stool frequency by about 1.4 stools per week compared to baseline and laxatives increase stool frequency by about 1.5 stools per week compared to baseline. So, their study conclusions were that fiber and laxatives do appear to modestly increase stool frequency over placebo.

They also concluded that it was unknown if these agents would improve general well being or global satisfaction because this endpoint wasn't examined in many of these trials.

Now, it is beyond the scope of my presentation to individually review each of the randomized, controlled trials looking at traditional therapies and I am sure you wouldn't want to sit through all of that. But I will conclude by noting that the randomized, controlled trial evidence for psyllium, PEG-3355 and lactulose consistently demonstrates significant increases in stool frequency versus placebo. On the other hand, other commonly used and FDA-approved treatments for constipation, such as bisacodyl, Surfak, Colace, consistently do not demonstrate a significant increase in stool frequency versus placebo. It doesn't necessarily mean that these drugs are ineffective. As Dr. Prizont noted, most of these RCTs were carried out under deficient designs and if appropriately designed studies that met the Rome committee criteria were conducted, we might be able

to demonstrate efficacy. Nevertheless, when I am selecting a treatment for constipation I have to consider not just my clinical experience but also the randomized, controlled trial data of efficacy as well as the clinical trial data of safety.

There are several other issues for discussion today. First, whether or not the clinical trial data are adequate with respect to the chronic constipation population that is likely to be treated with tegaserod. I would just reemphasize part of Dr. Dennis' presentation, the two Novartis randomized, controlled trials contained inclusion criteria that are very similar to the Rome II committee criteria for functional constipation. In fact, in some ways they are more stringent.

Patients had to have greater than 6 months of symptoms by the Novartis criteria, whereas the Rome criteria require only 12 weeks, which need not be consecutive, of symptoms in the previous year. The Novartis criteria required that patients have fewer than 3 spontaneous bowel movements per week.

That is not an actually requirement to meet the Rome committee criteria for functional constipation. A patient, for example, who just had straining and lumpy, hard stools for 12 non-consecutive weeks would meet the Rome committee criteria for functional constipation.

Certainly, I think it is very true that 78 percent of the patients in these RCTs appear to have chronic constipation while as many as 22 percent had some symptoms of abdominal discomfort that might have led them to be classified as IBS with constipation. Nevertheless, Miss Mealey, the FDA statistical reviewer, in her very thorough and comprehensive statistical review noted that the responder rates for the constipated patients in these trials who didn't have IBS-like symptoms were similar to the overall responder rates. In fact, they tended to do better than the overall response rates that were recorded.

Certainly, the issue has been raised about whether or not we may have subtypes of patients with slow transit constipation included in this

trial. As a clinician, my main point about that would be that the AGA's medical position statement about that provides essentially identical treatment algorithms whether somebody has normal transit constipation or slow transit constipation. So, my choice of therapy wouldn't necessarily differ based on whether or not there might have been some patients with slow transit constipation included in these trials.

Another issue for discussion is the appropriateness of a primary endpoint of an increase of 1 or more complete spontaneous bowel movements per week compared to baseline versus the percentage of patients who attained 3 or more complete spontaneous bowel movements per week. This is a difficult issue. The Rome II committee actually couldn't come to a consensus about what was the most appropriate endpoint for trials of IBS and functional constipation. They recognized that there are multiple symptoms present in patients with these lower GI functional disorders. They actually stated that in addition to whatever

primary endpoint is chosen, there should be a select number of a priori defined secondary endpoints that reflect the multiple symptoms that are present in patients with these functional GI disorders.

In fact, Sander Van Zanten and his colleagues, who were on the subcommittee of the Rome committee who laid out the appropriate design of a trial of a functional GI disorder, actually stated that global improvement in satisfaction may be the most appropriate endpoint. That is an a prior defined secondary endpoint in the 2 Novartis randomized, controlled trials, that patients on tegaserod 6 mg BID were significantly more likely to be responders for global satisfaction than patients that were on placebo. This is not only a significant difference but, in my opinion, a clinically important difference where the magnitude of benefit is 9-12 percent more for patients on tegaserod 6 mg BID who were responders for global satisfaction compared to patients on placebo.

Again, there were a select number of a

priori defined secondary endpoints included, to try to contrast that with traditional therapies that patients on tegaserod 6 mg BID had 1.9 to 2 more spontaneous bowel movements per week compared to patients on placebo who had about 0.9 to 1 more spontaneous bowel movements per week. These are statistically significant differences.

If we do decide to apply the FDA's criteria that patients have to have 3 or more spontaneous bowel movements per week, and we look at the proportion of patients who attained what is a pretty high therapeutic goal, we still see that almost twice as many patients on tegaserod experienced 3 or more complete spontaneous bowel movements per week compared to patients on placebo and the magnitude of this difference, whether we look at 4 weeks or the entire 12-week trials, is approximately 10 percent. Again, in my opinion, that is a clinically important difference.

So, in conclusion for efficacy, I would state that the randomized, controlled trial data about the efficacy of tegaserod is very robust and

precise. These are the best designed, most comprehensive trials about treatments for constipation that are available among all the treatments that we have available for constipation. The study population does reflect patients with chronic constipation and the a priori defined primary and secondary endpoints do reflect the multiple symptoms that patients with constipation have, and these RCT data consistently demonstrate that tegaserod produces significant and clinically important improvement in the multiple symptoms of constipation.

Let's move on to safety. Unfortunately, there is very little data about the safety of traditional therapies for constipation. The most recent and comprehensive meta-analysis by Jones, Nick Talley and colleagues actually didn't even address the issue because the data were so scant. If we do go back to the systematic review performed by Tramonte and Cindy Mulrow and colleagues from the Cochrane Center in San Antonio, Texas, they specifically noted that few studies used

standardized techniques to assess adverse events. They also did note that they did not identify any significant differences in adverse events between laxatives and placebo. So, they concluded that although there is no evidence that laxatives are unduly harmful, the data available are very limited and short-term.

Thus, we are really left with looking at the prescribing information and case report data to try to get an idea about what adverse events are associated with commonly used laxatives. We see for bulking agents that fecal impaction and large bowel obstruction have been reported, and even acute esophageal obstruction when bulking agents aren't taken with adequate amounts of water. Anaphylaxis has been reported with psyllium. Among osmotic agents all different types of electrolyte abnormalities have been reported, specifically with magnesium-based agents that are used on a regular basis. Stimulant laxatives have been associated with both electrolyte imbalances as well as abdominal cramps. All of these agents have been

reported to have been associated with diarrhea.

So, another issue for discussion is whether or not the clinical trial data and postmarketing surveillance data provide adequate evidence of safety. I pause here for a moment, looking at the title of this slide, to just note that the clinical trial safety data where patients are followed per protocol probably provides at least the most precise safety data that we have available to us. When we look at the clinical trial safety data available for tegaserod we see that in the Novartis 2 randomized, controlled trials over 2,600 patients with constipation were enrolled. Over 1,700 received tegaserod. In the whole clinical trial safety database you have over 11,000 patients treated with tegaserod and over 3,400 patient-years of tegaserod use followed within the context of clinical trials. I would suggest that infers that there is very robust and precise clinical trial safety data for tegaserod, certainly more robust and precise clinical trial safety data than what we have available for any

other treatment of constipation.

That very precise data allows us to estimate what is the likelihood of serious adverse events for constipated patients using tegaserod or placebo. We see essentially similar rates. And, that very robust and precise safety data let's us quantify the likelihood of diarrhea as an adverse event. Among constipated patients we see that it is reported as an adverse event in 5 percent of patients in clinical trials versus 3 percent in patients on placebo. We see that 0.6 percent of patients treated with tegaserod actually discontinued the medication because of the severity of their diarrhea. When we look at the entire clinical trial database we can estimate that the likelihood of clinically serious consequences of diarrhea--going to the emergency department because of dehydration and getting IV fluids, virtually being hospitalized because of syncopal episode--occurs in 0.04 percent or 1 in 2,500 patients treated with tegaserod.

To conclude, let's turn to the safety

issue about ischemic colitis. Obviously as gastroenterologists, as primary care providers for patients, we are concerned about the issue of ischemic colitis because it has been brought to our attention by our clinical experience with alosetron. Alosetron, again, is an antagonist of the 5-HT 3 serotonin receptor as opposed to tegaserod that is an agonist of the 5-HT 4 serotonin receptor. We know from the clinical trial data that there were 17 cases of ischemic colitis among the 10,805 alosetron-treated patients in those clinical trials. That calculates out to a rate of 5.9 cases of ischemic colitis per 1,000 patient-years based on the clinical trial data.

I would also like to point out the fact that among placebo-treated patients with IBS the rate of ischemic colitis was 1.1 cases per 1,000 patient-years. Even in the context of this clinical trial, there was a background rate of ischemic colitis among patients treated with placebo.

So, what can we do about comparing the

issue of ischemic colitis with tegaserod patients treated for constipation versus other patients treated for constipation? The only other treatment for constipation that has any breadth of clinical trial safety data is PEG-3350. In their new drug application to the FDA they reported a rate of ischemic colitis in their clinical trial safety data of 3 cases per 1,000 patient-years. I want to emphasize that that is an extrapolation. The exact number is that there was 1 case of ischemic colitis among 300 patient-years of clinical trial safety data when they submitted their new drug application. That is the only other treatment for constipation where we have any breadth of clinical trial safety data to estimate the likelihood of patients experiencing ischemic colitis.

What is the data for tegaserod? Zero cases among 11,640 tegaserod-treated patients studied over 3,400 patient-years of exposure versus, among all the clinical trial database for placebo-treated patients, 1 probable case of ischemic colitis among 4,267 placebo-treated

patients followed for 780 patient-years of exposure.

Now, the FDA officials wanted to identify, based on that clinical trial data--zero cases among all the patients followed in the clinical trial database--what would be the maximal rate of ischemic colitis that still could be occurring within 95 percent confidence intervals. So, they did their statistical analysis based initially on the 7,000 tegaserod-treated patients in clinical trials that they had reviewed and they came up with a maximal ischemic colitis rate, within the confines of 95 percent confidence intervals, of 1 case in approximately 2,000 patients, based on the fact that there were zero reported cases among over 7,000 patients.

If we give the up to date analysis based on all 11,640 tegaserod-treated patients, then a similar statistical analysis would shoe that the maximal rate within 95 percent confidence intervals, considering there are zero cases among 11,640 patients, would be 1 case in 3,883 patients.

In order to be balanced, I think we should consider the placebo patients too. The same statistical analysis shows that their maximal rate would be 1 case in 867 placebo-treated patients.

This analysis is still based on very few cases of ischemic colitis. So, I certainly understand the need to look at postmarketing surveillance data. In the U.S. over 2 million prescriptions, accounting for over 233,000 patient-years of use; 26 reported cases of possible ischemic colitis, equating to a rate of approximately 12 cases per 100,0000 patient- years.

Again, as pointed out during Dr. Joelsson's presentation, patients with irritable bowel syndrome seem to be diagnosed with ischemic colitis more often than the general population. It may be an ascertainment bias because these patients tend to be scoped more frequently. It may be due to an unknown pathophysiologic factor. Obviously, there is recent research to indicate there are true pathophysiologic differences among IBS patients. But regardless of which epidemiologic study we look

at, all the available epidemiologic data indicates that patients with IBS are 3-4 times more likely to be diagnosed with ischemic colitis than is the general population, and the rates vary depending on the age of the population that is examined. Obviously, the Medi-Cal population tended to be older than the patients studied in the United Health Care study and, thus, we are seeing a higher rate of ischemic colitis both in the general population and in the IBS population.

I certainly comment Dr. Brinker. He did a very interesting analysis of the United Health Care base and identified that, clearly, when a patient is diagnosed with IBS their rate of getting subsequently diagnosed with ischemic colitis within the next 3 weeks is very high. Those patients almost certainly are patients that are misdiagnosed with IBS when they really have ischemic colitis. Nevertheless, the same analysis found that patients who had a stable IBS diagnosis for over 1 year still had a rate of 53 cases per 100,000 patient-years compared to the general population

where it was 7 cases per 100,000 patient-years.

I do want to make particular note here. When I talked about the clinical trial data my denominator was 1,000 patient-years. We have now shifted. All the postmarketing surveillance data is based on a denominator of 100,000 patient-years of use.

Postmarketing surveillance data for IBS patients treated with tegaserod is 12 cases per 100,000 patient-years, which is 4- to 15-fold lower than the expected rate, although I certainly understand there may be some under-reporting, and it very difficult to get an estimate for how often that occurs.

So, in conclusion, I certainly think that the clinical trial safety data for tegaserod is more robust and more precise than it is for any other treatment that we have available for constipation. This safety data allows us to have a very precise estimate of the likelihood of clinically serious consequences of diarrhea, but the evidence doesn't support an association between

tegaserod and ischemic colitis.

When I do a risk/benefit analysis I see the benefits being this robust clinical trial data that demonstrates that tegaserod is efficacious for the treatment of constipation, especially the multiple symptoms of constipation, and that the safety data is more robust than it is for any other treatment I might choose and that safety data from clinical trials demonstrates to me that there is a very low but finite risk of clinically serious consequences of diarrhea.

So, that analysis demonstrates to me that tegaserod has a very favorable risk/benefit profile in the management of chronic constipation, and that it compares very favorably with the risk/benefit analysis for any other therapy that I might choose to use to treat patients with constipation. Thanks very, very much for your attention and I will turn the program back over to Dr. Fogel.

Questions on Presentations

DR. FOGEL: I would like to thank the presenters for their informative presentations. At

this juncture we turn the meeting over to the committee for questions to the presenters. Dr. D'Agostino I think had his hand up first, and then Dr. Sachar.

DR. D'AGOSTINO: When I saw there was a two-hour presentation I said, my God, they will never take that long but it actually was a great presentation. Thank you very much.

I have a comment about the subset analysis, which we will have to address later. I understand that you look at subsets for consistency and not necessarily expecting to see significant results, but shouldn't we be concerned that we are not seeing the effect lying on the right side with the elderly greater than or equal to 65 and the males, and the Blacks? Can you give us some words on how we can feel comfort that you aren't seeing the effect in greater than or equal to 65 year-old individuals and also males, and I would like something on the Blacks also.

DR. DENNIS: Thank you for that question. Yes, absolutely. Can I have slide AQ-16, please?

We will start off with the elderly population since that was the question that you asked initially. As you know, we only randomized 13 percent of our patients that were 65 years or older, and this is the responders by age group looking at our primary efficacy analysis.

What we can see in the group that is 65 years and older is that we are seeing a treatment effect in the patients that are on Zelnorm. We are also seeing an effect in patients on placebo as well. So, the interesting thing though is that we can break this down further by looking at the older population by age and by gender.

If I could have the next slide, please, which is AQ-17, let me show you what happens when we break it down into further subsets. On the top row we are seeing female patients and on the bottom row we are seeing male patients. The patients that are less than 65 years old--if we start with that column on the left-hand side, we can see that the effect in the younger female population is similar to the effect in the younger male population.

Remember that we have much fewer numbers in terms of the male group so we don't reach statistical significance because, as I said before, these subgroup analyses are not powered to detect statistical significance. So, I think we are seeing a consistent effect in the men that are 65 years and younger that we are seeing in the female population.

If we look at the slide on the right-hand side, and let's turn to the elderly population, we do see an effect in female population. Of course, the effect size is slightly smaller--again, small numbers of patients, and when we will look at the male patient population that are 65 years and older we are seeing that there really is no effect looking at it on this particular analysis.

But I am going to take it one step further and take out those patients that we felt were probably IBS-like because, if you remember, in our overall efficacy analysis when we took that group out the efficacy was slightly more robust.

So, if I can have the next slide, which is

AQ-18, this shows you what happens when we take out those patients that are IBS-like. I am going to focus your attention on that male population that is 65 years and older. You can see that in the previous analysis--here we have really small numbers of patients. We are dealing with 20 patients in that group that are on 6 mg BID. So, the responders that we saw in the previous analysis were all chronic constipation patients and when we take out the other patients that have IBS obviously our denominator changes and, you know, we see a much more different effect looking at these numbers. But I do want to caution that these are very small numbers when we are looking at these subgroup analyses.

But if we look at the four different quadrants I think we can see the effect in the patients less than 65 is similar in men as it is in women. I think we are seeing an effect in elderly females, and I think we are seeing an effect in elderly males when you take out the IBS-like subset.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: With the permission of the chair, if I could address some questions to each of the four major presenters, Dr. Schoenfeld, when you presented your efficacy data in slides 13 and 14 you appeared to have limited your analysis only to the highest dose tegaserod of 6 mg BID. Yet, when you discussed the adverse effects you combined the 2 mg and the 6 mg doses. It would seem to me if you really want to look at a benefit/risk ratio we really ought to look at a comparison for the same doses. If we were to do that, we would find in your slide 21 that it really isn't 5.4 percent of patients but is actually 6.6 percent of patients who had some adverse effect with diarrhea at the equivalent dose, at the 6 mg dose.

I am not a professional statistician but if we go a little further we might say that since the number needed to treat--to get some benefit, some demonstrated benefit from this drug is approximately 10. It ranged between 9-11 in all the analyses. It is approximately 10. The number

needed to treat to see some adverse effect from diarrhea is actually about 2.8 at the equivalent dose. So, would it be fair to say that for every 3 patients who get some benefit from this drug 1 will experience some diarrhea?

DR. SCHOENFELD: No, I would not go along with that and I think there are multiple points there to address. The first one is that all of us have conducted clinical trials and, as we recognize, reporting an adverse event in the context of a clinical trial is not the same as suffering a clinically important adverse event. When these patients are followed in the context of clinical trials, to paraphrase, your study nurse may say, "anything unusual happen in the past week?" And, if the patient says, "I had a little bit of diarrhea last Thursday," that becomes an adverse event. What is probably a much more appropriate adverse event category to assess, clinically important adverse events, is how often patients stop their medication due to diarrhea. Obviously, here it is 0.6 percent.

Having said that, I certainly take your comment appropriately, that if you look at the 6 mg BID dose the rate at which diarrhea was reported as an adverse event is about 6.6 or 6.7. For the broader issue though of safety, my own experience--and there are other experts here that have far more experience in safety issues--is that when we look at efficacy we want to look at what is going to be most likely the dose that is utilized. But in safety we tend to look at multiple different dose ranges to find out what the benefit is.

Having said that, I think a subgroup analysis about what the rate would be for 6 mg BID versus 2 mg BID would be helpful, although I will mention for the most serious adverse events that we are concerned about here, which in my mind are really ischemic colitis, when you look at 6 mg BID or 2 mg BID it is still going to be zero events. You are just going to change your denominator a bit. And, the majority of patients in these trials were treated with 6 mg BID.

DR. SACHAR: Agreed. When you talk about

the diarrhea issue that brings me to the one question for Dr. Joelsson, and that is simply that you did discuss the physiologically serious consequences and those were obviously very, very low. Did anybody record whether any patient with diarrhea had any episode of incontinence?

DR. JOELSSON: We have not that recorded. I cannot answer that.

DR. SACHAR: Because that is sort of an impact thing.

DR. JOELSSON: Yes.

DR. SACHAR: And for Dr. Dennis, in slide 46--

DR. DENNIS: I will flash it up on the screen.

DR. SACHAR: Yes, it is very important, as everybody has indicated, that when you excluded IBS from the analysis you still showed efficacy. I think that is a very important point. But you showed us the data for doing that only at week 1-4.

DR. DENNIS: Yes.

DR. SACHAR: Do you have any data on that

for the 12-week point?

DR. DENNIS: It looked similar. I don't have the data on a slide but it does look similar over the 12-week treatment period.

DR. SACHAR: It is the same approximately?

DR. DENNIS: Yes.

DR. SACHAR: Great, fine. In slide 13 you showed us that, in terms of the inclusion criteria, they had to have a bowel evaluation within the past 5 years. Do I take that to mean that if some patients had early constipation symptoms 3 years ago or 4 years ago or 5 years ago and they had a barium enema, and then more recently the symptoms persisted or worsened and they represent that they would be eligible to go in this study without any new reexamination?

DR. DENNIS: If they had had a bowel evaluation that was after the onset of symptoms and the symptoms remained the same within the past 5 years there was no need for them to have a reevaluation. However, if there was any change in the symptoms or if there were any alarm features,

as I said, anything that suggested rectal bleeding, hemorrhage, anemia or any change in the pattern, those patients would have had to have a new evaluation. But it was stable patients who had been having symptoms that had remained the same within the time they had the evaluation.

DR. SACHAR: Great! My last question is for Dr. Prather. I am not actually familiar with the Canadian study of Pare et al., but you indicated it was a population study. Does the population in that study represent the group receiving and taking medications for chronic constipation? Is it a clinic-based or a true population-based study? Because if it is truly population based it doesn't reflect people who are taking medications for their constipation.

DR. PRATHER: It was, indeed, a population-based study but that would include all-comers with constipation that were actually in the population. So, it didn't discriminate against individuals who may or may not have seen a physician for their constipation.

DR. SACHAR: Right, so that means that in Larry Schiller's study that you showed in slides 19 and 20 with all the dissatisfaction, that included patients who had taken over-the-counter preparations or had seen a GP, or something, and had been perfectly satisfied? Or, was it only the dissatisfied patients who sought out GI specialists who were in that study?

DR. PRATHER: This included individuals--it was a study that was done through the Internet that was representative of the U.S. population, but with the initial questions, actually to get into the study they had to have seen a physician within the past 12 months for constipation.

DR. SACHAR: A physician or a gastroenterologist?

DR. PRATHER: Actually, these were primary care physicians predominantly, yes.

DR. FOGEL: To increase the number of questions that we can ask during our time frame, I would like the members of the committee to keep

their comments brief. I am going to take the prerogative of the chair and ask my questions of Dr. Dennis.

Can you provide us additional details regarding the question that you asked for subjective global assessment, and can you tell us how the data was analyzed and whether responders had a persistent response over the 12 weeks of the study?

DR. DENNIS: We asked the question how satisfied were you with your bowel habits over the past week? And, the responses were a very great deal satisfied; a good deal satisfied; moderately satisfied; hardly satisfied; and not at all satisfied. We defined a responder as having a decrease of 1 on the satisfaction score.

I am going to first show you some data on the persistence of satisfaction response and then I will call one of the statisticians to actually come up and explain to you the statistical analysis that was done.

If I could have slide AQ-58, please? This

is an analysis that we did where we said to those patients that met the score of a very great deal satisfied and a good deal satisfied, so zero and 1, for at least 50 percent of the weeks of the whole trial, which is 12 weeks. What we can see on the study is definitely a significant benefit of Zelnorm versus placebo when we look at patients that had satisfaction over 6 weeks of the 12-week treatment period. So, I think we are seeing persistence of the satisfaction result.

I am going to call upon Dr. Jeen Liu, who is our statistician, to come and respond to your question about how these were actually calculated.

DR. LIU: My name is Jeen Liu. I am the statistician from Novartis responsible for this project. The slide that Dr. Dennis just showed was a response rate that we defined--actually, she showed two slides for two time intervals, weeks 1-4 weeks and 1-12. What we did was we took the patient score at each week, averaged them over the respective time intervals, either 4 weeks or 12 weeks, and compared that with the baseline score

that each patient had during the 2 weeks prior to treatment, and got the difference and compared with it was a decrease of 1 or more. If it is 1 or more, it is a responder; otherwise the patient was a non-responder. Thank you.

DR. FOGEL: Thank you. Dr. Metz?

DR. METZ: Great, thanks. Just in the interest of time, I am going to float a few questions to you. I want to thank you for a nice, comprehensive presentation. Three areas to address, first of all, the problem with the subgroup analysis, as has been alluded to. Can you perhaps tell me why you chose 65 years? I would be more interested in actually seeing a median age above and below, perhaps divided into quartiles above that and see where you actually see your cut-off. I am not sure why 65 is necessarily relevant.

The second question will be a little bit about the loss of efficacy in one of your two pivotal trials in the 2 mg group. It appears to me more because of the placebo effect increasing up to

reach the 2 mg, but it makes one wonder a bit about a tolerance response, and that brings me to why you really chose the first 4 weeks. This is something people are going to be using way beyond 12 weeks. So, why the first 4 weeks; why not 12 weeks and beyond as your primary outcome measurement?

The third question is use of surrogate measurements, which you actually have in your binder but didn't talk about at all today. That is the use of rescue medication and seeing any difference there as a sort of idea of, you know, you are seeing an effect because of using less rescue? Can you address those three points, please?

DR. JOELSSON: While Dr. Dennis is thinking about the second question I can take the first question. The analysis of patients above 65 years and below 65 years is a very traditional analysis that we do, which is based on what the FDA wants us to do. This is kind of the cookbook thing you do. So, it is not that it was anything that we came up with; this is the traditional way of doing

it, and we don't have the data the way that you describe. I am sorry about that.

DR. METZ: Do you think that would be a useful examination to go through?

DR. JOELSSON: Yes, I agree.

DR. DENNIS: let me address the other questions. I am first going to tackle the question that you asked about loss of efficacy. I think what we see in these clinical studies is that the treatment effect of Zelnorm was sustained throughout the entire treatment period. We did not see a decrease in the number of responder rates. There is certainly nothing to suggest that we saw a loss of efficacy in terms of the drug response itself. Placebo responses, as we know, are not uncommon in clinical trials and we see them in all clinical trials. You know, the issue is in some clinical trials placebo responses continue to rise.

If I could go back to my core slide CE-28, this shows you the weekly responder definition over the 12-week treatment period, and I just want to really point out again that we are seeing that the

efficacy is sustained throughout the entire treatment period.

Maybe I can get a clarification, Dr. Metz. Were you referring specifically to the 2 mg dose in the 2301 study?

DR. METZ: That is correct. Clearly, you don't see that in the 2302 but you do see it in the 2301.

DR. DENNIS: Absolutely. You know, I think the 6 mg BID dose has emerged consistently as being more efficacious and that is why we are going for that dose as an indication. We have actually looked at what are the reasons that could have, you know, determined why we are seeing this in 2301 and not 2302 because these two studies were essentially identical in the core period. The only differences that we can find are geographical. 2301 was done mainly in Europe and 2302 was done in North and South America.

To address the question of why we chose a 4-week duration period, I think that was because when physicians prescribe the drug they want to

look at the effect size within 4 weeks. They want to know is this drug going to work within 4 weeks or not. So, we looked at 4 weeks as our primary endpoint but we also looked at it over 12 weeks to make sure that we would see sustained efficacy. So, we have the data for both of those two endpoints.

DR. METZ: Right, but the point I am making is that this is a chronic problem. You are defining chronic constipation as something that has been around for more than 6 months--

DR. DENNIS: Sure.

DR. METZ: --and you are not going to treat for 4 weeks and then stop.

DR. DENNIS: And that is why we have a 12-week treatment duration.

The last question that you had was laxative use. There were very strict guidelines for laxative use in these studies. Patients were only allowed to take laxatives if they had not had a bowel action for 96 hours. So, they had to wait 96 hours from the time of their last bowel action

before they could have a laxative. When we looked at laxative intake in these particular studies, we measured how many patients took at least one dose of a laxative throughout the entire 12-week treatment period, and we found that about 50 percent of patients in the study took a laxative at some point during the study. But when we really break this down and we say how frequently were laxatives actually being taken, we find that laxative intake, in fact, was quite infrequent.

This slide I am going to show you is going to show you laxative use by mean number of days. If you look at the baseline period, we see that laxatives were used about once every 11-12 days. In the double-blind, placebo group we see that laxatives were used about once every 14 days and about once every 18 days on Zelnorm.

If I could have the next slide, which is AQ-62, this is going to show you the median days data. Here we are seeing by median data of use that the baseline laxative use was about 14 days a week. The median use of laxatives in the placebo

group goes down to 0.11, which translates to 1 every 64 days. When you look at the Zelnorm-treated group we are seeing that that goes down to 0.08, which translates to once every 88 days. So, when you really look at it, laxative intake is really very infrequent.

However, to speak to your point, we are seeing that there is more laxative use in the group on placebo than there is on Zelnorm, and if we are expecting to see a confounder because of that, we would expect to see it more in the placebo than we would in the Zelnorm.

DR. FOGEL: Dr. Cryer?

DR. CRYER: Dr. Dennis, I would just like to follow-up on this theme of the subgroup analysis in those who were greater than 65 and those who were men. You very strongly make the point that Zelnorm, as you just showed us, has maintained efficacy over the 12-week period. However, all of your slides that you showed us to support its observations in the subgroups of those who were greater than 65 or those who were men were the

4-week data points. So, I am wondering whether you can show us that, in fact, the sustained 12-week data in that subgroup of men and those who were greater than 65.

DR. DENNIS: Right. The reason why we did the subgroup analysis on the 4-week data initially was because that was our primary endpoint and so that is why we determined to do that.

I don't actually have the slides with me right now to show you the actual week 12 but I will just confer with my colleagues and make sure we have those before the end of the presentation.

DR. CRYER: I think this is a very important point because when you consider the potential target group for therapy, many of them, as we have learned from Dr. Prather, are going to be greater than 65 year-old age population. So, I think in the assessment that we are making today it would be very, very helpful for us to specifically look at the effects in a target population.

DR. DENNIS: Right, and I will make sure we have those slides and we will come back to that.

DR. FOGEL: You can present those slides later.

DR. DENNIS: Right, thank you.

DR. FOGEL: The next question is by Dr. Buchman.

DR. BUCHMAN: To further follow-up on the 12-week issue, letting aside the 4-week issue, number one, I am wondering what the rationale was for the chosen 12-week interval rather than 52 weeks for example, given that this is a problem that your patients had for an average of at least 6 years. That is the first question.

Secondly, I want to know if you have any data on either on-demand or intermittent use because for a benign problem, outside of a clinical trial, compliance for medication use is very poor. So, what I am wondering is whether with intermittent use does tolerance develop, for example, and is there a loss of efficacy at that time.

In regard to the first question, and I do have a few others, my sub-question to that is if,

indeed, you have efficacy at 12 weeks, is your indication really only for 12 weeks use rather than long-term use, because you have not shown long-term use data?

DR. DENNIS: Absolutely. We chose the 12-week treatment duration in keeping with the Rome committee guidelines, and the Rome committee gives us guidelines for chronic functional GI disorders, and their recommended length for treatment trials was 8-12 weeks. So, we were within the Rome committee guidelines for doing this, and the indication that we would be seeking is for 12 weeks treatment.

DR. BUCHMAN: And what about the "on-demand" therapy? Do you have any data on that?

DR. DENNIS: We do not have any data for "on-demand" therapy in chronic constipation.

DR. JOELSSON: Maybe I can add to that. Luckily enough, we just did a study in IBS with constipation and we did show that if we had a good effect during the first treatment period it was just as good, or maybe even better, on the second

treatment period when they had a relapse. So, there is no evidence from our data that you don't respond just as well the second time as you did the first time.

DR. BUCHMAN: One quick question, and I understand that other people have to ask some other questions, there is some question whether the increase in bowel movement by one per week is clinically significant. So, my questions for that are, number one, what is the data that you have to indicate a priori that that increase of one is clinically significant? Number two, what is your data on patients who had an increase of two or more bowel movements per week?

DR. DENNIS: I showed you the slide from my core presentation that looked at the association between responders and non-responders, and we showed a clear-cut difference in terms of the means when you had a non-responder versus a responder looking at the primary endpoint and comparing it to the secondary variables.

Can I go back to the slides from my core

presentation, please? Do we have a slide from the core presentation? I am looking for the association between the endpoints. Here we are. So, this is the slide where we looked at the association to say the mean changes from baseline were quite different in the responders versus the non-responders, and this is significant at all time points.

I think what I am going to do to really delve into your question further is to say, well, is what we are seeing clinically relevant for the patient population, and I think we see this is a clinically relevant response looking at this particular analysis but I am going to ask Dr. Prather to come up and give her opinion as to whether she thinks, you know, a change of one CSBM per week is clinically relevant, bearing in mind that at baseline these patients had 0.5 CSBMs by mean values and zero CSBMs by median values at baseline. So, seeing an increase of one CSBM per week, in our minds, we felt was clinically relevant, but I will let Dr. Prather give her

opinion.

DR. PRATHER: Thank you. It is always difficult when I have my patient in the office to figure out how am I going to translate this research data to the patient in my office. What I have to remember is that I am being presented with means, meaning that there are some patients who responded well and some patients who didn't. When you are talking about constipation, for my group of patients anyway, going from having no bowel movements that are spontaneous per week or half a bowel movement per week that is spontaneous and increasing that to, you know, one or more spontaneous bowel movements, that is going to be a significant finding in my patient.

The other thing to realize is that when we are talking about bowel function we have to actually recognize that there is a balance, that we want to make them better but we can't make them too much better because too much better turns them into diarrhea, and that is just as difficult as it is to have constipation. At least, that is what my

patients tell me. So, I would rather see something that has, you know, a modest by definite effect than something that is a bit too powerful that I am going to have difficulty managing.

DR. FOGEL: Dr. Strom?

DR. STROM: Thanks. I would like to first congratulate the group on a superb series of presentations and a really very impressive pair of studies. I have three questions. One is on age breakdown. You cut it at age 65. Age 65 is becoming younger every day. Many of the people who are going to suffer from the problem who are going to use it, in fact, are a lot older than that. So, both in terms of your population data, Canadian data or other population data, and in terms of your clinical trial can you show us the breakdown of people over age 65? For example, what proportion of people over age 75 or 80 have constipation in the general population, and how many of those people do you have in your study? That is the first question.

DR. DENNIS: I think the first thing to

address is the fact that constipation, as we have defined it, is not a condition of the elderly. I mean, I think Dr. Prather showed you the data that came from the epi study and from the Pare study that really showed that constipation, as we have defined it, is actually a disorder of all ages.

DR. STROM: That is what I would like to see, to see those data greater than 65 broken down more finely in order to confirm that statement.

DR. DENNIS: For the population-based studies?

DR. STROM: I would like to see it both for the population-based studies--I mean, to make the claim that it is not a problem in the elderly I don't want to see 6 year-olds, I want to see 80 year-olds.

DR. DENNIS: Yes. I am going to ask Dr. Prather to comment as well, but would you like to see the age distribution for our particular clinical studies? This is a slide which shows you the pooled data from 2301 and 2302, looking at the breakdown of ages that we studied in the clinical

studies. As you can see, as I said, the mean age was 46 and 47 years but we did have representation of different ranges.

DR. STROM: But just to get a gestalt, over age 75, it looks like you had 10 patients?

DR. DENNIS: We had very few patients in this age group.

DR. STROM: Ten percent, sorry. And, how does that compare to the population data?

DR. DENNIS: Dr. Prater will come up and respond to that question.

DR. PRATHER: Thank you for asking that question because I actually have a special interest in GI motor and functional disorders that are associated with aging, and I have looked carefully at the epidemiologic data and, unfortunately, they are fairly flawed when it comes to taking a look at elders. For instance, the Drossman Householder study actually cut it off at age 45. The ones that actually used the Rome I or the Rome II criteria cut it off at 65. So, those were strict criteria. We really don't have a good breakdown above the age

of 65.

Now, we do have information about self-report constipation. We need to be a little bit careful when we talk about self-reports. Again thinking of my own patient population, some of my elders that don't have a bowel movement every day, or if they don't have their bowel movement in the morning and instead have it after lunch, they may not be satisfied and they may actually report that as constipation.

We do know in general from the epidemiologic studies that there appears to be an increase in self-report constipation over the age of 70. The studies that we have and, again, I don't have a slide for this but I do have information from a review--in a couple of the studies that took a look at individuals over the age of 70 we see that self-report constipation--again, not using the strict criteria but what patients think--that at the age of 55-59 it is 28 percent; 60-64, 29.7 percent; 65-69, 32.8 percent; 70-74, 37.3; 75-79, 42; 80-84 is up to 48.

But, again, we are getting very small numbers in those larger groups and, again, this is self-report constipation and, again, this isn't really a forum for me to talk about my research interests but, again, when we talk about functional bowel disorders and constipation and aging, there are also frailty issues that go along with that, locomotion, motor issues that contribute to the difficulties that these individuals do have with their bowel function.

DR. STROM: Thank you. That is very helpful because obviously it is self-report constipation that is likely to lead to treatment.

The second question--you have enormously rich data on different types of diarrhea and symptoms at baseline as well. When you see a very consistent pattern of efficacy like this but a very small increment over placebo, that sort of smells like you have some people who respond a lot and other people who don't respond at all and, in fact, we heard that as a comment. Can you give us predictors of who is going to be a responder and

who is not? You have shown us some data--age, gender race. How about baseline symptoms? Can you tell within your very rich database which baseline symptoms will lead to people likely to be responders and which will not?

DR. DENNIS: Let me show you a couple of slides. If we can start with slide AQ-81? Let's look at the responders looking at baseline characteristics, and we are going to start by looking at those patients by number of complete spontaneous bowel movements a week. So, let's look at this particular analysis.

This is responders broken down by the number of complete spontaneous bowel movements per week at baseline. We can actually see that Zelnorm is equally efficacious in all of these treatment groups. The very right-hand group obviously is very small numbers of patients and those would have been protocol violators.

If we go to slide number AQ-82, this will look at the responders by duration of constipation. So, here we are looking at whether people have had

constipation for 6-12 months all the way up to, you know, 12 years of constipation. Again we are seeing efficacy in all of these different subgroups.

The next one that we can look at as well would be responders by baseline constipation assessments. So, if we could have AQ-83, remember, we asked those bothersome questions, how bothersome was your constipation, and we broke it down by looking at baseline and whether these patients had moderately bothersome constipation or good deal bothersome constipation or a very great deal bothersome constipation and, again, we saw no difference in efficacy amongst those treatment groups.

We can also look at efficacy by looking at patients that took laxatives at baseline, if we could have AQ-67. Again we saw no difference whether patients take laxatives or don't take laxatives at baseline. So, in fact, we didn't really find any predictors to say there was one particular group in any of these baseline

characteristics that would be more likely to say, you know, Zelnorm would work more effectively in that particular group or not.

DR. STROM: How about people whose major complaint was frequency, versus people whose major complaint was straining, versus people whose major complaint was hard, lumpy stools, versus abdominal pain, versus bloating, looking at the very rich symptom data to see how well that predicts response?

DR. DENNIS: We have looked at that data as well and we haven't seen any clear-cut predictors of response looking at those baseline symptoms.

DR. STROM: The last question relates the database studies. A big point was made that it was irritable bowel syndrome that causes ischemic colitis or is associated with ischemic colitis rather than the treatments. As someone who has been using these databases for 25 years, I am very skeptical. Those are not people with irritable bowel syndrome; those are people with claims for

irritable bowel syndrome. Did you get the medical records on those patients who had irritable bowel syndrome and who had ischemic colitis and their bowel syndrome before that to be able to see whether that was really an established diagnosis or was, in fact, people who were being misdiagnosed?

DR. JOELSSON: Well, these are not studies that we have performed. These are published studies but, as far as I understand, at least in one study there was a subset of patients that were reviewed with medical records which was consistent with the overall data.

DR. FOGEL: Dr. Levine?

DR. LEVINE: I have some concerns about a lack of or presence of a dose response. First a point of information, in your IBS study initially, where you got approval, was there any difference between 2 mg and 6 mg?

DR. DENNIS: In our IBS studies 6 mg BID was consistently more efficacious for all the variables so we are seeing a consistent pattern.

DR. LEVINE: But in the current studies,

symptomatically you may have seen some differences when you pooled the data, as shown in slide 31 where you state that there is effective treatment of multiple symptoms of chronic constipation, but when you go back to looking at the weekly stool, the stool data, etc. you find a weakness in 2301 versus 2302. It is very hard for me, going through this and looking through all the data to discern whether you really think there is a difference between 2 mg and 6 mg through everything, including this particular data, page 14 and page 17 for instance, the stool change from baseline where, indeed, there is a big difference between the two suggesting perhaps dose response, and then again 2301 on page 14 where there is no difference in 2302 and there is a slight difference in 2301. So, I wondered across the board, besides symptoms, did you actually see dose response in every aspect that you looked at?

DR. DENNIS: I think we saw a more consistent dose response in study 2301. As I said earlier, we went back to say, well, what were the

reasons that we were seeing this dose response in 2301 and we didn't see it in 2302 and we looked at a number of parameters, baseline parameters, to say, well, were there any differences in the patient population because the studies were identical in design, and the only differences we could come up with were really geographic. 2301 was done in Europe mainly and 2302 was done in North and South America. Beyond that, we haven't got any explanation for why we see it in one study and not in the other study, but the bottom line is that the 6 mg BID dose is consistently efficacious across both studies, and that would be the dose that we would be looking at.

DR. STROM: Thank you.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: I have a brief question for Dr. Dennis about baseline matching. There is a table on page 21 of the Novartis briefing document, entitled Table VI-2. My question relates to the category percent SBM with sensation of complete evacuation. It looks like they are not balanced at

baseline and I would just like to hear your comment about whether these groups were balanced and comparable at baseline because the numbers look different, for example, 8 versus zero versus zero; 1.4 versus 9.1 versus 8.3. They seem to be wildly different there, and would that confound any results that we have already seen?

DR. DENNIS: I have the table up here. So, we are looking at the percentage of SBMs with the sensation of complete evacuation. I think what we have to bear in mind is that when we look at this particular analysis, percentage of SBMs, it really is a ratio. So, we are saying of the number of SBMs that you are having, how many of those are actually complete spontaneous bowel movements? I think when we looked at patients coming into the study the criteria for them to get into the study was less than 3 complete spontaneous bowel movements per week. Looking at the percentage of SBMs with sensation of complete evacuation doesn't tell us very much about how these patients are doing. For example, you could have 2 SBMs and you

could have 1 of those being complete and your percentage would be 50 percent. You could have 4 SBMs and you could have 2 of those complete and your percentage would be 50 percent. So, I think looking at just the percentage is not a very reliable statistic on its own. We should really look more at the number of SBMs and the number of CSBMs at baseline.

DR. LAMONT: So, in terms of that bottom rank there, you consider those to be matched?

DR. DENNIS: I don't think it is relevant when we look at the other members--

DR. LAMONT: You are saying it doesn't matter. I have a second question for Dr. Joelsson regarding cholecystectomies. Looking at page 20 and page 21 of your slides, it looks like there is an increase in cholecystectomies in patients that are on Zelnorm, if I am interpreting this correctly. Can you tell us then that the 14 cholecystectomies in the Zelnorm-treated patients versus 1 in the placebo is not different?

DR. JOELSSON: I think I said it was

different. I tried to say that we tried to find out does this drug really affect gallbladder or is this a chance finding. So, we did this very thorough study looking at gallbladder function and we could see no effect of tegaserod on gallbladder function.

Also the second point I would like to make is that patients with IBS do have a higher rate of cholecystectomies so the rate we have seen in our clinical trials is not higher than you would expect in patients with IBS or in our postmarketing experience. So, if anything, the placebo group is a bit low.

DR. LAMONT: On the other hand, this might be something we would want to warn clinicians about, that in fact it might increase the rate of cholecystectomy because, first of all, a comment about this statement that Zelnorm does not affect gallbladder motility, I accept your data here but don't forget that patients who have gall stones have already abnormal motility. Virtually 90 percent of them have delayed gallbladder emptying

by any clinical criteria, and I assume that this test, Fisher et al., in press is on normal subjects. Is that correct?

DR. JOELSSON: It is patients with IBS, not with gall stones.

DR. LAMONT: Right. So, you could make the case then that patients with preexisting gall stones who take Zelnorm may have an increase in contractility because of the drug that you wouldn't see in normals, and that that would force a stone into the neck of the gallbladder into the cystic duct which is the definition of what happens with acute cholecystitis and is the usual cause for cholecystectomy.

DR. JOELSSON: This issue is actually already in our prescribing information. It is not a warning but it is mentioned there as one of the issues we had at the earlier application.

DR. FOGEL: My timekeeper indicates that we already way behind schedule. There will be an opportunity for additional questions this afternoon. Are there any questions that remain to

be asked right now that cannot wait until the afternoon?

[Laughter]

Why don't we take a ten-minute break and then we will continue with the FDA presentation?

[Brief recess]

DR. FOGEL: I would like to call everybody back to their seats. Ready?

FDA Efficacy Presentation

DR. PRIZONT: My name is Robert Prizont, and Implementation an FDA medical officer in the Division of Gastrointestinal and Coagulation Drug Products.

DR. PEREZ: Excuse me, Robert, can you hold on one second? We are trying to get your slides up.

DR. PRIZONT: Ready? For those of you who don't know me and that is the majority of you, I am Robert Prizont. I am an FDA medical officer in the Division of Gastrointestinal and Coagulation Drug Products.

Zelnorm oral tablets at a dose of 6 mg

twice a day are approved for the treatment of women with constipation-predominant irritable bowel syndrome, abbreviated C-IBS. The indication for treatment was not extended to men with constipation-predominant irritable bowel syndrome. Novartis is now seeking approval for Zelnorm use at a dose of 6 mg twice a day for the treatment of chronic constipation in both women and men. To support the proposed indication Novartis submitted a prospective study protocol and results from two multicenter placebo-controlled pivotal clinical trials.

In sequential order, my presentation will review a definition of constipation, relevant issues of the prospective study protocol; provide a brief summary of the sponsor's efficacy results; discuss the patient representation for the selective constipation subtype; comment on the chosen primary efficacy endpoint; and finalize with concluding remarks.

For the last 39 years the core of defining constipation has relied on the frequency of bowel

movements. In 1965 a study on variation in bowel habits was reported in the British medical journal. In this study between 83 percent to 99 percent of 655 women and 400 men who were free of gastrointestinal symptoms had a frequency of bowel movements ranging from 3 bowel movements per week to 3 bowel movements per day. These results suggested that more than 3 bowel movements per day or fewer than 3 bowel movements per week are unusual.

The 1975 Federal Register on over-the-counter laxatives included the results of the English survey. In 1988 worldwide experts met in Rome to set guidelines for the diagnosis of functional bowel disorders and published what is now known as the Rome criteria for the diagnosis of functional bowel disorders. The criteria for the diagnosis of constipation included fewer than the 3 bowel movements per week parameter.

In 1989, the large U.S. NHANES, National Health and Nutrition Examination Survey, on bowel habits was published. This U.S. survey was

conducted in two phases. The initial phase lasted four years, from 1971 to 1975, and included 14,407 subjects. The second phase or follow-up lasted two years, from 1982 to 1984. The results on number of bowel movements revealed that over 85 percent of the U.S. men and women surveyed had 3 or more bowel movements per week.

In 1999, the Rome II criteria were published. The Rome II criteria also included fewer than 3 bowel movements per week bowel movement frequency in the definition of constipation.

In 2000, the American Gastroenterological Association published a technical report on constipation and stated as limits of normalcy the frequency range established in the first English study, i.e., 3 bowel movements per week to 3 bowel movements per day.

According to the protocol design, eligibility to participate in the Novartis studies required compliance with components included in the Rome II criteria definition of constipation. The

passage of fewer than 3 bowel movements per week and the perception of completeness in bowel evacuation were the objective and subjective components required to define patients as constipated and eligible to enter the studies. Straining was an additional subjective component included in the requirement.

Rather than applying the established definition of constipation, the protocol's primary efficacy endpoint was based on the increase of a single spontaneous and complete bowel movement per week. Moreover, efficacy response was limited to the first month of a 3-month study period.

The protocol stated that the aim of performing these studies was to demonstrate the effect of Zelnorm on bowel habits in patients suffering from chronic idiopathic constipation. Idiopathic constipation is a subtype of chronic constipation. It has generally been known as functional constipation.

The other subtypes are outlet obstruction, slow peristalsis constipation and the constipation

associated with irritable bowel syndrome, or IBS. Slow peristalsis has also been referred to as idiopathic slow transit constipation. Differentiation between slow transit constipation and outlet obstruction constipation requires specialized techniques, such as measurement of colon transit time. A potential concern in conducting clinical trials with the use of Zelnorm in idiopathic or functional chronic constipation was the inclusion of constipation-predominant IBS subjects.

The trials on Zelnorm in women with constipation-predominant IBS were conducted long before the chronic constipation trials and were initially submitted to this agency in December of the year 2000. The design of the studies for use of Zelnorm in constipation-predominant IBS had already included the Rome criteria. The Rome diagnostic criteria for irritable bowel syndrome provide the elements and parameters to separate the constipation-predominant IBS from other types and subtypes of constipation. Yet, the prospective

protocol for the Novartis studies for chronic constipation lacked any provision to exclude patients with constipation due to irritable bowel syndrome. As mentioned, since July, 2002 Zelnorm is approved for women with constipation-predominant IBS.

Novartis performed two pivotal studies. Study 2301 was conducted in Europe with contributions from centers in Australia and South Africa. Study 2302 was conducted in the U.S., Canada and a few South American centers. And, 416 to 451 patients were enrolled in each of 3 treatment groups, namely, 6 mg BID, 2 mg BID or placebo.

The first month results revealed that 40-43 percent of those assigned to Zelnorm 6 mg met the protocol's definition of efficacy. The Zelnorm response was statistically superior to 25-27 percent placebo response, and provided a therapeutic gain ranging between 15-18 percent.

Two doses of Zelnorm were tested in the trials, 2 mg BID and 6 mg BID. The average

efficacy in 12 weeks revealed a dose response in only one of the two studies. It should be noted that the Zelnorm efficacy over placebo was translated in an average weekly increase of less than one complete spontaneous bowel movement. Intermittently, 50 percent to 60 percent of treated patients, including those treated with Zelnorm, were helped by a well-known laxative, bisacodyl. A number of patients exceeded the protocol's specified use of laxatives, including between 15 percent to 25 percent of the patients treated with Zelnorm 6 mg BID.

The results from the studies raise the first question, was the treated patient population representative of idiopathic constipation? This graph illustrates the gender distribution in the various subtypes of constipation. The figure is from a large study on 10,000 subjects with various subtypes of constipation. Starting on the right side of the graph, we can see that the mixed IBS outlet obstruction subtype, the outlet obstruction subtype and the constipation IBS subtypes have a

preponderance of women, particularly the subtype of outlet obstruction constipation. This is in contrast to the almost equal proportion of men and women observed in functional or idiopathic constipation shown on the left bars of the slide.

This, in other studies, revealed considerable symptom overlap amongst subtypes. Investigators also differ on where slow peristalsis is a part of outlet obstruction or a separate subtype of constipation. Despite the overlap and differences in subtype nomenclature, there is overall concurrence that gender is the characteristic of outlet obstruction, while the predominance of abdominal symptoms distinguishes constipation-predominant irritable bowel syndrome.

The Zelnorm studies enrolled 90 percent women with a mean age of 47 years. Men 65 years and older represented around 13 percent of the patient population. The addition of completeness to the spontaneous bowel movements allowed enrollment of a large proportion of patients who otherwise would not have met the definition of

constipation based just on number of spontaneous bowel movements. Just to illustrate this point, about 50 percent of patients had an average of 3 spontaneous bowel movements per week that were not perceived as being complete. These patients would have not qualified for a constipation trial. The introduction of a complete bowel movement in the definition of constipation transformed these patients from not being constipated into being constipated. It is noteworthy that up to 45 percent of patients entering the studies referred to abdominal symptoms as the main complaint of constipation.

As a consequence of a lack of provision in the protocol to exclude IBS patients the studies did include irritable bowel syndrome patients. Novartis estimated that 23 percent of patients had IBS-like symptoms. Actually, a few patients already carried the medical diagnosis of IBS prior to entry to the studies. Though it is difficult to estimate retrospectively the characteristics of enrolled patients, it is likely that the proportion

of patients with IBS-like symptoms was higher than 23 percent, particularly if we consider the main complaint of abdominal distention as part of the constipation-predominant IBS.

Let's now examine the protocol's primary efficacy endpoint. A relevant question pertains to whether the protocol's primary efficacy endpoint represents efficacy based on the established definition of constipation included in the Rome criteria.

As mentioned, the Rome criteria defines constipation by less than 3 spontaneous bowel movements per week with a perception of completeness in less than 25 percent of bowel movements. It follows that efficacy based on the average increase of just one complete spontaneous bowel movement per week would include as responders constipated patients. Perhaps not surprisingly, estimates of efficacy by the 3 or more complete spontaneous bowel movements resulted in a drop of the proportional responders. Post study, and at the agency's request, the sponsor included efficacy

analysis based on established frequency of 3 or more bowel movements.

This table shows the results for the first month in study 2302, analyzed by the 2 endpoints. Efficacy, based on the 3 bowel movements per week rule cuts in half the proportion of responders, and there is a parallel drop in the therapeutic gain in treatment with Zelnorm 6 mg, from 18 percent when analyzed by the protocol's endpoint to 9 percent when efficacy is based by the traditional endpoint of 3 or more spontaneous bowel movements.

Although the studies were of 12 weeks duration, the sponsor's efficacy for chronic constipation was based on the first month of study results. Efficacy in the 12-week study period was the average increase of one complete spontaneous bowel movement per week extended to the 12 weeks, regardless of whether dose responders had actual participation in efficacy for the 12 weeks.

By the sponsor's analysis, the comparison of efficacy reached a 45 percent response rate in Zelnorm 6 mg if efficacy is the average increase in

one complete spontaneous bowel movement but decreases to 22 percent if efficacy is the average of 3 or more complete spontaneous bowel movements. We, therefore, decided to calculate efficacy based on the response for each one of the three months, as shown in the numerator, with participation in each one of the three months, as shown in the denominator.

This table is our analysis of responders for a 3-month study period in patients who participated in all 3 months. The first point to make is that the requirements of participation plus efficacy response to all 3 months decreases Zelnorm 6 mg efficacy to 26 percent even if calculated by the protocol's endpoint of an increase of 1 complete spontaneous bowel movement. The combination of full 3 months of participation and efficacy, analyzed by the 3 or more complete spontaneous bowel movement rule, drops the 6 mg response to a very low 12 percent.

Efficacy based on 3 or more complete spontaneous bowel movements plus full participation

results in a uniformly lower response to Zelnorm 6 mg expressed in 1-month efficacy, 2-month efficacy or efficacy for the entire 3 months of the study period.

We conclude that the clinical significance of an efficacy endpoint for constipation based on the increase of 1 complete spontaneous bowel movement per week is uncertain. Based on the definition of 3 or more complete spontaneous bowel movements per week, the proportion of responders for all 3 months is small. The intermittent use of bisacodyl, a well-known laxative, further confounds the assessment of effectiveness.

There is a plethora of laxatives presently available over-the-counter. From 1975 until 2003 6 monographs on laxative use and abuse were published in the Federal Register. I counted over 25 laxative products just in the first monograph. A few laxatives are given under prescription but so far all remedies are for occasional constipation. The sponsor now proposes the use of Zelnorm for chronic constipation seemingly for all subtypes

though the protocol aim was to study the idiopathic subtype.

It is unclear which constipation subtype benefited from Zelnorm. The contribution to efficacy of the constipation-predominant IBS and outlet obstruction patients is unresolved because 90 percent were women, many with a predominance of abdominal symptoms. A benefit of Zelnorm for laxative abusers, heralded as one reason for the studies, is unknown for laxative abusers were excluded from the trials.

Men were under-represented. In subset analyses no statistical differences between treatments were observed in men. Patients 65 years of age and older, frequent sufferers of chronic constipation, were similarly under-represented. The few treated in the studies, 10-13 percent of all patients, revealed no statistical or numerical differences between treatments. Patient representation, in whom it should be prescribed, the rationale for the indication, those inappropriately included or excluded are issues to

be resolved by this expert advisory panel. Thank you.

Questions on Presentation

DR. FOGEL: Are there questions for Dr. Prizont? Dr. Cryer?

DR. CRYER: Dr. Prizont, you make the comment that about 50-60 percent of the subjects were taking concomitant bisacodyl. I am trying to get a sense of what the response rate would be in the Zelnorm only users. Did you do an analysis which removed the bisacodyl subpopulation?

DR. PRIZONT: I did not do that analysis. Let me check with the statistician first. Dr. Joy Mele, maybe she can help.

DR. MELE: I did do an analysis where I just looked at the patients who never took a laxative at any time during the trial, and I am trying to get to that page. It is in my review that is in your packet. It is on page 31 of my review. The treatment effects were about 11 percent difference between the Zelnorm 6 mg and placebo--16 percent, actually, in the 2302 study

and 11 percent in the 3201 study.

DR. SACHAR: Just a point of information, apparently laxative use here is defined as bisacodyl use--

DR. PRIZONT: Right.

DR. SACHAR: --but there was no exclusion for the use of bulk laxatives throughout this. So, is there any information at all as to what was happening with the use of bulk laxatives during the study? I am not even sure it was recorded.

DR. PRIZONT: You mean bulk-forming agents?

DR. SACHAR: Bulk-forming agents, yes.

DR. PRIZONT: The proportion of patients who took bulk-forming agents was very, very small and, you know, those who took bulk-forming agents prior to entering the studies continued to use bulk-forming agents but the proportion was very small.

DR. FOGEL: Dr. Metz?

DR. METZ: Thank you. My earlier question to the sponsor was why they didn't divide this by a

median age and then maybe go into quartiles. I was told that that was an FDA mandate for the 65-year cut-off. Now, they managed to slice and dice everything else by all sorts of other combinations but I still haven't yet seen anything sliced by decade using the median. Do you have any kind of information for that from a statistical point of view??

My other concern, as an aside but also quite important, is that it seems to me there has been a lot of goalpost moving in this situation. Usually what happens is you will submit a protocol for review. The agency will have a look at it and say we like this protocol or we don't like this protocol. Somewhere along the way here it seems there has been a disconnect and we have a definition that should have been, I assume, agreed on up front which is now being criticized. So, can you give me a bit of the history of how that developed?

DR. PRIZONT: Let me clarify, you are talking about the efficacy endpoint?

DR. METZ: Yes.

DR. PRIZONT: Let me first go to the mandate. Dr. Justice, Dr. Beitz, do we have a mandate on 65 and older, and can we break it up? I am transferring it to management.

[Laughter]

DR. BEITZ: I would just say that 65 is the regulatory definition of elderly, over 65. So, that tends to drive analyses to look at over and under 65 but there isn't any reason why folks couldn't look at over 75 or over 80.

DR. FOGEL: Dr. Justice?

DR. JUSTICE: Dr. Mele has done an analysis on other age groups. I don't know if she would like to comment.

DR. MELE: I did look at the results by the median age and we still see an age effect even when we cut it at the median, such that the treatment effect for the patients over 46 is 10 percent. This is comparing 6 mg to placebo. For instance, for the patients under 46, the treatment effect is 21 percent.

DR. PRIZONT: Yes, but my understanding is that they are talking about 65 years old, not 46 years old.

DR. MELE: But he asked about the median so cutting it at the median--

DR. METZ: What I would like to see is whether there is an effect--in quartiles, say, is it possible that the first quartile has a great effect, the second quartile doesn't so well and you see a decline as time goes on. I mean, I think that 65 is an arbitrary number and my concern here is that the agency seems to be saying elderly patients aren't properly represented. I want to get a feel for the distribution, number one and, number two, I want to see does the effect fall off progressively in response as you go up in decades.

DR. MELE: For the cut points I used it does. I mean, when you look at 46 as a cut point the treatment difference is 10 percent. When you use 60 as a cut point it is 8 percent. When you use 65 it is 2 percent.

DR. PRIZONT: So, basically the response

is that the higher we go in age the lower the response. Now let me address the second part of your question. You are right, four years ago the agency somehow agreed with the protocol and I suppose with the endpoint. But whether we agree or disagree, we still have two points to make.

The first point is that this endpoint of the increase of one spontaneous bowel movement has not been validated, at least has not been validated independently. You know, somebody may say, well, I see patients and I think that one complete spontaneous bowel movement has a clinical significance but we don't have a trial, an independent trial or two trials validating that particular endpoint.

The other point to be made is that when we compare the prospective endpoint, the increase of one complete spontaneous bowel movement which we consider not validated, to established three bowel movements per week endpoint the results are completely different. The proportion of responders starts to drop rather markedly. Those are the two

points I can make to respond to your question.

DR. METZ: There still was statistical significance for a number of those, right?

DR. PRIZONT: Let me clarify before I go on. There was statistical significance between Zelnorm and placebo in most of the analyses, you know, with the exception of the elderly and men. But the question is are we going to rely only on the statistical significance and not placing it in light of the clinical significance of laxation? We are talking here about laxation. Ten percent of responders for a laxative would be rather small, to say the least. But, you know, that is my view; perhaps the committee has a different view.

DR. FOGEL: Dr. Mangel? Dr. Prizont, I have two questions. The first is for your slides on the primary efficacy endpoint--

DR. PRIZONT: Yes?

DR. MANGEL: --I agree with your point that the more common definition of constipation is hovering around the 3 per week.

DR. PRIZONT: Right.

DR. MANGEL: However, if I am understanding the slides correctly, and I think that is going to impact greatly upon the absolute magnitude of the numbers, these are all cut on greater than or equal to 3 complete spontaneous bowel movements per week.

DR. PRIZONT: That is correct.

DR. MANGEL: Do you have those same data for spontaneous bowel movements per week? Because the reason I am concerned is when I look at the sponsor's briefing document, page 30, and there was not a slide on that, I guess I actually see a robust response. They are looking at spontaneous bowel movements per week. Their baseline is hovering, as you said, around 3 and I think your comment was that the median was less than 3 but their baseline is hovering around 3, and with treatment it looks like it goes up to about 5.

DR. PRIZONT: You mean with completeness?

DR. MANGEL: No, just spontaneous. So, if you are going to impose the criteria of 3 being your cut-off, would it be more appropriate to look

at spontaneous bowel movements than complete spontaneous?

DR. PRIZONT: I am going to refer to Dr. Mele about the spontaneous bowel movements. Let me answer the question in a different way. We have now the Rome II criteria. The Rome II criteria include at least 25 percent or at least less than 25 percent of completeness in order to make the diagnosis of constipation and 3 bowel movements per week or less and straining as well since the baseline. The sponsor already defined that baseline. What is constipation? They picked two elements of the Rome criteria, which were frequency of bowel movements and completeness. I follow that particular definition set by the protocol. You know, that is a little bit of the paradox here that I see, that we have one definition of constipation for baseline and a different definition of no constipation-predominant for a responder.

DR. MANGEL: But the Rome criteria actually don't mandate complete spontaneous bowel movements. You know, of the criteria, straining is

one of the criteria that could be met greater than 25 percent of the time; lack of complete evacuation less than 25 percent; or the bowel frequency. It seems like a harder hurdle and, therefore, I am not surprised that the absolute responder rates go down when the entities are combined. If you would have the data cut also for your slides for spontaneous bowel movements, you know, independent of complete spontaneous--

DR. PRIZONT: Yes, you have a point, of course. Probably if I selected spontaneous bowel movements the numbers would be a little bit higher than what complete spontaneous bowel movements show. The Rome criteria state that selection of two of the elements or parameters of the list that they have in their own criteria will define constipation. The sponsor selected two criteria, completeness and frequency of bowel movements. Now, they could have selected something else but that is what they selected and I follow that selection.

DR. MANGEL: Dr. Prizont, before we move

on, the survey and epidemiology data in which you are looking at 95 percent of responders being within 3 bowel movements per day to 3 per week is talking about spontaneous bowel movements, not complete spontaneous. So, if you are coupling to the 3 number, the 3 number is derived for spontaneous bowel movements.

DR. PRIZONT: Yes.

DR. MANGEL: And that is what the Rome criteria actually use.

DR. PRIZONT: You are talking about the survey of NHANES, the one with 14,000 patients?

DR. MANGEL: Well, there have actually been several.

DR. PRIZONT: There have been several but that is probably one of the largest. The reason that they placed that is to exemplify that, other than the British study, there was a newer study which was large and had two phases, as I mentioned, and they defined, or they found because that was a survey, that most of the people responding to the survey had normal people, had between 3 or more

bowel movements per week, basically almost the same as what the British study found.

DR. MELE: Can I make a comment on this question? About half the patients, remember, had 3 spontaneous bowel movements at baseline. So, to do an analysis where you look at an increase to a level of 3 or more spontaneous, you could only do it on half the patients. What we did do is look at the baseline spontaneous bowel movements and cut it using those and looked at the primary and secondary endpoints that we have been discussing. The sponsor did this also and found significant results, statistically significant results.

DR. PRIZONT: But do you have the numbers? Because my understanding is--

DR. MELE: There are a lot of different numbers.

DR. PRIZONT: --looking at the numbers, if there was a difference between the numbers in the complete spontaneous bowel movements and the spontaneous bowel movements.

DR. MANGEL: Well, I think my point was

that you are absolutely correct when you go from greater than 1 to greater than 3, the rate of responders dramatically drops because it is a harder hurdle.

DR. PRIZONT: It is still statistically--

DR. MANGLER: Still statistical but the absolute rate, but I am not convinced that the proper comparison is comparing greater than 1 to greater than 3 complete spontaneous. If you wanted to look at greater than 1 complete spontaneous or just greater than 3 spontaneous, and I think that is what your statistician just said, but I guess the question is does the responder rate for those with less than 3 at baseline--what type of responder rates are we looking at for a primary analysis?

DR. MELE: For patients with less than 3 spontaneous bowel movements at baseline and looking at which endpoint?

DR. MANGEL: Well, it would be greater than or equal to 3 per week for spontaneous.

DR. MELE: Yes, we didn't look at it that

way. We looked at 3 or greater for complete spontaneous.

DR. PRIZONT: But, you know, I think the comparison in some ways may not be fair because we are comparing an increase of 1 complete spontaneous bowel movement to just a spontaneous bowel movement. So, I think the comparison may not be completely fair in that sense because we are including complete in one of the arms of the comparison and not in the other one.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: Regardless of whether we use spontaneous or complete spontaneous bowel movements, there is still obviously a difference between someone who goes from zero bowel movements a week to 3 bowel movements and someone who goes from 2 bowel movements to 3. So, my question for you is if we just take the responders to Zelnorm, what was the mean number of increase in bowel movements versus placebo? For example, was the mean 1; was it 2; was it 3? This would give us some sense of perhaps the clinical significance.

Rather than just looking at the percent of responders, what was actually the mean number of increase in bowel movements?

DR. MELE: I can answer that question. The average increase over the 12 weeks was 1.3 complete spontaneous bowel movements in the 6 mg group versus 0.7 complete spontaneous bowel movements in the placebo group.

DR. PRIZONT: This is for the 12-week response. The difference was 9 percent.

DR. BUCHMAN: This is actually looking at the percentage but I am actually looking at a different figure, which is the mean. But I think that is what we were just told. The difference was 0.7 versus 1.3.

DR. MELE: And that is averaged over the whole treatment period.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: Some of the questions that I was interested in have been asked but one still remaining question is I hear what you are saying in terms of the magnitude, and so forth, but

give us a feel for what clinical significance there is because you are not talking about statistical significance because it is there. So, you are moving the discussion to the clinical significance. Could you give us some reference numbers so we can judge these, why aren't they good or why are they satisfactory? Given the fact that we are moving to a different endpoint, we have this complete spontaneous, and so forth, so give us a context, please.

DR. PRIZONT: My response has to be based on what we know what is normal and what we know about constipation. The problem with my response is what I mentioned about subtypes. Not all subtypes of constipation are the same. The functional type of constipation is sort of the less severe of the types of constipation. In those cases, I would expect that 3 or more bowel movements could be clinically significant.

Now, if you take the other subtypes of constipation, if you take the outlet obstruction constipation, which is usually in women, younger

women, they have more severe type of constipation, then, you know, we can discuss but there is no uniformity. There is no universal agreement on what is the improvement for all constipation.

DR. D'AGOSTINO: Yet you are telling us, if I hear you correctly, that you are not satisfied with these numbers, that they don't show us clinical significance.

DR. PRIZONT: Because I don't know what it means, that endpoint of increase of 1 complete spontaneous bowel movement. Therefore, I am not sure how much improvement there is in the constipation.

DR. FOGEL: We all like counting bowel movements because it is easy. We have great difficulty when it comes to dealing with subjective symptoms like straining, incomplete evacuation and symptoms like that. In his work, Drossman tries to get around that issue by talking about subjective global assessment and whether or not you feel better. I mean, I think that is the important clinical outcome that we are interested in. You

haven't presented on this global assessment as to whether or not you are better by taking therapy. Do you have any information about that?

DR. PRIZONT: Well, the sponsor has information about the global assessment.

DR. FOGEL: Is there any analysis though that was done by the FDA?

DR. PRIZONT: The sponsor did an analysis on what they call secondary endpoints. They have abdominal discomfort, and so on. Referring to the secondary--

DR. FOGEL: No, not the individual endpoints, but this global assessment. Are you better taking the medication than not taking the medication? Or, are you better on tegaserod as opposed to taking placebo, and is that difference significant?

DR. PRIZONT: I will relinquish for that information to the sponsor. I think they did the analysis. I don't have any firm grasp of that.

DR. FOGEL: Dr. Beitz?

DR. BEITZ: We don't have an analysis on

the global but we have some other endpoints that you might be interested in seeing.

DR. PRIZONT: But he is not interested in the other endpoints. He is interested in the global, right?

DR. MELE: The global did show significant effects.

DR. FOGEL: Do you think that that is of clinical significance?

DR. PRIZONT: I may think that is of no clinical significance; you may think that it is of clinical significance. That is the difference in what we are dealing with now in terms of constipation, which is a sensation of infrequent evacuation and difficult evacuation, as one dictionary has defined it. That is the problem, that we don't have uniformity in terms of definition of constipation.

DR. FOGEL: Dr. Justice?

DR. JUSTICE: I think the point is we are really seeking the committee's advice on that. You know, we would appreciate your input as to the

clinical significance of these findings.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: It might be useful to consider the data as showing either complete response, that is, patients who are no longer constipated by the Rome criteria and that may have been shown, but I wonder if you could just remind us of those data again.

DR. PRIZONT: That was 3 or more bowel movements per week.

DR. LAMONT: But there are other criteria for constipation that were listed by the sponsor based on the Rome II criteria. So, I guess my question is what percent of patients were no longer constipated by those criteria, either number or subjective symptoms, at the end of 4 or 12 weeks?

The second comment I have is that in most clinical trials we look at things like partial response and complete response. For example, in rheumatology trials they look at 20 percent response, 50 percent response and 70 percent response by American Rheumatology Society criteria.

So, I wonder if we couldn't look here at complete response being no longer constipated by Rome criteria and some other partial response.

DR. PRIZONT: I am going to transfer the question you asked me to you. You know, what is complete response?

DR. LAMONT: Well, by the Rome criteria that they used for entry, that they no longer qualify for constipation by those criteria, which are established and I think validated.

DR. PRIZONT: Well, according to their criteria an increase of one single bowel movement, complete one single bowel movement is not constipated per week.

DR. LAMONT: But that wouldn't apply to the Rome criteria though. The Rome criteria wouldn't accept that as no longer being constipated, I don't think.

DR. PRIZONT: Right. That is what I was trying--

DR. LAMONT: No, no, I understand. Therefore, greater than one complete spontaneous

bowel movement per week is some sort of partial response. But I am asking what about complete response, no longer constipated by Rome criteria?

DR. PRIZONT: The data is there and I cannot add too much to the data.

DR. LAMONT: I wonder if anybody else has parsed the data.

DR. PRIZONT: As I said, you know, the Rome II criteria--and I had a small contribution in that--included two parameters to define constipation. You can pick and choose those two parameters. They already picked the two parameters which were frequency and completeness. Based on that, that is the data.

DR. FOGEL: Dr. Beitz has a comment.

DR. BEITZ: Oh, just that we were going to ask if the sponsor had done what you said.

DR. FOGEL: Does the sponsor have any comments?

DR. DENNIS: Could I have slide AQ-92, please? Remember, we have to put all these into context in terms of definitions. What we applied

here was to say, okay, let's look at the definitions we applied at the beginning at the study and we said, okay, patients had less than 3 complete spontaneous bowel movements and they had one of the others 25 percent of the time. Right? We took out the patients that were IBS-like so they weren't confounding factors. Then we said, okay, let's look throughout the course of the study with the week 12s and let's look at patients that met that definition at baseline and met that definition within the 12-week treatment trial.

Remember, we did not set out to cure constipation in this trial. We set out to improve constipation, and we have to look and see what are the placebo patients doing versus what the Zelnorm patients are doing. We see that at weeks 12 86 percent of patients on placebo are still constipated and on Zelnorm we have 72 percent of patients that would still meet that definition.

So, to speak to the previous point about complete responders, we are seeing some people that are completely responding, looking at that

reduction but, of course, we don't take into account with this definition improvement in the constipation symptoms which is what we have seen before.

Remember, patients had at baseline a median number of CSBMs of zero and a mean of 0.5. So, really to get them over that was quite a high hurdle, and this is just looking at a number but it doesn't take into account the improvement in the symptoms that we see as well.

DR. FOGEL: Thank you. One quick question and then we are going to move on.

DR. BUCHMAN: Just a quick question on that slide, why were not all the patients constipated at baseline? How did you have 15 percent of patients that were in a study on constipation that weren't constipated when they entered the study?

DR. DENNIS: Unfortunately, even though we have strict criteria for getting into the study, you always have protocol violators that come in. When you go back and analyze the data that is what

we find by these definitions.

DR. BUCHMAN: So, wouldn't they have been excluded when the monitor went by to see them before they completed the study?

DR. DENNIS: Well, that should happen in most cases but you know that the challenge of a clinical trial design is that it doesn't always happen so we have to accept that this is what we have seen in our study.

DR. BUCHMAN: Because that is a pretty high number, 15 percent; it is not like 2 percent.

DR. DENNIS: I am going to ask our statistician to come and comment on how we handled that.

DR. LIU: Jeen Liu. I am the statistician. Actually, I can only add to what Eslie said, that for the baseline constipation criteria we had criteria as she had presented. It is very difficult actually for the investigator to check that. We tried our best. The percentage that you see there, part of it comes from the fact that when we went back to double check the data

some of the patients barely missed the criteria and some of them had too many missing values to be qualified for this rigorous analysis.

DR. SACHAR: But the therapeutic aim was 4.8 percent.

DR. LIU: No, 14.

DR. SACHAR: No, no, no--

DR. LIU: I think you are looking at the wrong treatment. We should really look at the first column--

DR. SACHAR: Right, which is 1.9 and the last column which is--oh, I see, 14, yes.

DR. BUCHMAN: Did you analyze patients separately by those who were constipated at baseline and exclude the 15 percent that didn't qualify?

DR. LIU: I am not following your question.

DR. BUCHMAN: If you excluded the 15 percent of patients that were not constipated at baseline, that really failed study criteria, were they analyzed separately?

DR. LIU: No, no, we didn't do that. I think you are going to get almost the same result because you basically are just reducing the denominator by 15 percent.

DR. FOGEL: Thank you. We will move on now. The last presentation of the morning is by Dr. Della'Zanna.

FDA Safety Presentation

DR. DELLA'ZANNA: I have the benefit of being the last person presenting so I will try to keep things moving. My name is Gary Della'Zanna. I am a medical officer in the Division of Gastrointestinal and Coagulation Drug Products. I will be presenting some of the agency's concerns regarding safety issues that were identified during the postmarketing period. For some of this presentation I will be referencing postmarketing data that was received through the agency's Adverse Event Reporting System and was analyzed by the Division of Drug Risk Evaluation. At this time, I would like to acknowledge the work of Dr. Allen Brinker and Ann Corken Mackey who are members of

that Division. Following this presentation they will be available to answer any postmarketing questions.

Through 15-day postmarketing safety reports the agency became aware of several adverse events that we defined as special interest. These included serious consequences of diarrhea such as hypotension and syncope. I will also present updated information on whether the use of Zelnorm is associated with an increased risk of abdominal and pelvic surgeries in humans. I will then focus the remaining portion of the presentation on postmarketing reports of ischemic colitis and other forms of intestinal ischemia.

As already stated by Novartis, Zelnorm is a 5-HT 4 partial agonist. It also has moderate affinity for the 5-HT 1B receptor. The therapeutic mechanism of action is believed to be based primarily on its 5-HT 4 agonist properties. The proposed dose for the chronic constipation indication is the same as the approved dose for the constipation-predominant IBS. If approved, Zelnorm

would be the first drug to be granted an indication specifically for chronic constipation.

In response to postmarketing 15-day safety reports, the agency worked with Novartis to revise the Zelnorm package insert. These revisions were finalized at the end of April, 2004. The label now includes a warnings section about the serious consequences of diarrhea, including hypovolemia, hypotension and syncope. A precautions section describes ischemic colitis and other forms of intestinal ischemia. In addition to this labeling change, Novartis also mailed a "dear doctor" letter outlining these changes. Both of these documents were included in your background package as Appendix 1 and 2.

This table shows the most frequent adverse events during the 12-week portion of the chronic constipation trials. These studies did not identify any new safety concerns. The incidence and type of adverse events were similar to what is already included in the current label. Other than diarrhea, there was no appreciated dose response to

adverse events.

The incidence of adverse events was higher during the 13-month extension study. The increase in AEs was most likely due to an increase in time exposure.

Many of the Division's safety concerns that were identified during the postmarketing period were not seen in the chronic constipation trials. For the remaining portion of this presentation I will be focusing on adverse events identified during the postmarketing period as AEs of special interest. I will be referencing spontaneous postmarketing reports received through the agency's MedWatch program. This reporting program is a passive surveillance system that is designed to detect rare and unexpected events associated with drug therapy.

To help define the safety profile of Zelnorm, I will present the postmarketing data as well as relevant safety data from the chronic constipation trials and other completed trials for different indications that had similar design.

Because of the postmarketing reports, serious consequences of diarrhea were identified as an adverse event of special interest. This included cases of diarrhea or complications from diarrhea that led to an emergency room visit or hospitalization. You may notice that the numbers that we present differ from the sponsor's. This is because cases were excluded from the analysis if the diarrhea was caused by another identifiable process such as infection.

For this presentation the agency used April 15, 2004 as a cut-off data for analyzing postmarketing safety reports. As of April 15, the Office of Drug Safety received 22 reports of serious complications of diarrhea. Consistent with the prescribing patterns, the majority of the cases occurred in female patients. These patients ranged in age from 24-82 years, with an average age of 56. The time to onset of the diarrhea ranged from 1 day to 210 days, with 5 of the cases occurring on the first day of therapy and half the cases occurring during the first week. Fifteen of the 22 cases

required hospitalization; 3 were described as life-threatening. In addition to diarrhea, the complications from the diarrhea included dehydration, abdominal pain, hypotension, electrolyte disorders and shock.

During the chronic constipation trials the frequency and severity of diarrhea was dose related. These findings are not surprising considering Zelnorm's mechanism of action. And, 6.6 percent of the patients in the 6 mg group reported diarrhea as an adverse event. This compares to 3 percent in the placebo group. Eight patients in the 6 mg group discontinued from the study due to diarrhea compared to 2 in the placebo group. Additionally, 7 patients in the 6 mg group developed severe diarrhea compared to 2 in the placebo group.

There was an increase in the incidence and a slight increase in the severity of diarrhea during the 13-month extension study. A total of 840 patients continued in to the extension study. Patients who were receiving placebo during the core

study were changed to Zelnorm 6 mg BID for the extension study. Overall, 9.5 percent of the patients reported diarrhea as an adverse event during the extension study. For the proposed 6 mg BID dose this incidence was 10.2. This is relevant considering the proposed indication is for chronic therapy.

There was also a higher incidence of diarrhea in older patients. For the proposed 6 mg BID dose 12.5 percent of the patients 65 years and older reported diarrhea as an adverse event. This compares to only 6 percent in patients younger than 65. Also, there was a higher proportion of older patients who discontinued treatment due to diarrhea. This is significant considering the efficacy seen in this population and the potential number of elderly patients who will be treated for constipation.

As part of the recent labeling changes, hypotension is now listed in the warning section of the current label as one of the serious consequences of diarrhea. As of April 15, 2004 the

agency received 15 reports of hypotension. Many of these cases were confounded by underlying medical conditions and concomitant medications.

One interesting case, however, occurred in a 45 year-old female with no past medical history of cardiac or blood pressure abnormalities. Prior to starting Zelnorm, the patient's blood pressure was recorded at 138/80. Approximately 2 weeks after initiating therapy the patient experienced 2 syncopal episodes after standing. The patient's blood pressure was recorded as 75/60 at the time. Additionally, it is worth mentioning that hypotension was reported in at least 2 other cases of ischemic colitis.

During the Phase 1 development of Zelnorm rare cases of hypotension in healthy subjects were identified. Because of this, hypotension was closely evaluated during Phase 3 trials. The incidence of orthostatic hypotension was balanced between treatment groups in the IBS as well as the chronic constipation trials.

This slide demonstrates the incidence of

orthostatic hypotension during the chronic constipation trials. This was defined as a drop in systolic blood pressure of 20 or more mmHg or a diastolic drop of 10 or more after standing. Since hypotension is listed as a complication of diarrhea in the current label, it is worth noting that none of the cases of hypotension during the chronic constipation trials were associated with diarrhea.

Syncope is another adverse event of special interest. It is also listed in the warnings section of the current label as a serious complication of diarrhea. As of April 15, 2004 the agency received 8 postmarketing reports of syncope or loss of consciousness in patients receiving Zelnorm. Most of these patients had other confounding factors that may have contributed to the event, however, the role of tegaserod could not be completely ruled out.

The chronic constipation trials did not identify any signal for syncope. Four syncopal events were reported. Two occurred in the Zelnorm group and 2 in the placebo group. Again, it is

worth noting that none of the patients who developed severe diarrhea during the chronic constipation trials experienced a syncopal episode.

At the time of the original approval, there remained questions of whether the use of Zelnorm was associated with an increased risk of abdominal and pelvic surgeries. Nine cases of symptomatic ovarian cysts were reported during the IBS trials. Eight of the 9 cases occurred in patients treated with Zelnorm. Only 1 occurred in the placebo group. Five of the 9 cases required surgery, all from the Zelnorm group.

An analysis also identified an imbalance in the number of cholecystectomies performed in patients receiving Zelnorm. These differences, however, were not statistically significant.

To help identify whether the use of Zelnorm is associated with an increase in abdominal or pelvic surgeries, Novartis committed to a Phase 4 pharmacoepidemiology study which is presently ongoing. They created an adjudication board consisting of independent consultants who review

all surgeries in a blinded fashion.

As stated earlier, the agency's Adverse Event Reporting System is designed to detect rare safety signals. It is not designed to track postmarketing reports of common surgeries. Looking at the clinical trials, the number of abdominal and pelvic surgeries performed under chronic constipation trials were too small to identify an imbalance. Two ovarian cyst surgeries were performed, one in the Zelnorm group and one in the placebo group. There was also one patient in the 6 mg Zelnorm group who had a hysterectomy due to hypermenorrhea. Only one cholecystectomy was reported. This occurred on the 12-week study in a patient receiving 6 mg Zelnorm BID.

Novartis also analyzed the incidence of surgery for all completed placebo-controlled clinical trials of similar design. The frequency of abdominal and pelvic surgeries in this pooled indication population was comparable across treatment groups, but there was an imbalance in the number of cholecystectomies. Looking at all cases

of cholecystectomies, the incidence was 4 times higher in the Zelnorm treatment group. Even after the adjudication board excluded 4 cases from the Zelnorm treatment group, the incidence in the Zelnorm group was still twice the placebo group. The clinical significance of this is uncertain.

Due to postmarketing reports of ischemic colitis and other forms of intestinal ischemia, they have been identified as adverse events of special interest. From the time of approval through April, 2004 an estimated 2 million prescriptions for Zelnorm have been filled in the United States.

As stated earlier, for this presentation the agency will present cases of intestinal ischemia that were reported through April 15, 2004. As of April 15, the agency received 24 postmarketing reports of bowel ischemia. Considering the "dear doctor" letter was not finalized until the end of April, this cut-off date does not allow for the increased reporting which typically occurs when physicians become aware of a

problem. For example, the agency received 9 additional cases of intestinal ischemia between April 15 and June 1. A summary of these cases was provided in the background packet under Appendix 3.

For the safety review, the agency separated out ischemic colitis from other forms of intestinal ischemia, focusing on the 20 postmarketing cases of ischemic colitis received through April 15. Nineteen were female, ranging in age from 26-82 years, with an average age of 55. The time to onset of ischemic colitis ranged from 1 day to almost 400 days. As for the safety reports, the majority of the patients who developed ischemic colitis were treated for IBS. Four patients were treated off-label, 2 for constipation, 1 for postoperative ileus and 1 for an unknown indication.

Thirteen of the 20 patients required hospitalization. One of these required surgery and one died. The agency is concerned that these cases represent a drug-induced ischemic colitis. However, a causal relationship is difficult to

prove. But it is suggestive when one considers that these 5 of the 20 reported cases had no documented risk factors. Three cases occurred on the first day of therapy and 2 of the 3 cases occurred in patients with no documented risk factors, as in case 6 and 8 on this slide. The remaining 15 patients had 1 or more identifiable risk factor such as hormonal therapy, tobacco use or vascular disease, but that does not exclude the possible relationship with Zelnorm.

The Division assigned the definition of other intestinal ischemia to cases of ischemic bowel that resulted from a large vessel process such as a mesenteric artery occlusion. All 4 cases meeting this definition occurred in female patients ranging in age from 41 to 67 years. Postmarketing reports described 3 of the 4 patients were treated for IBS. One was treated off-label for constipation. All 4 were hospitalized, with 3 of the patients requiring surgery. One had a bowel resection. The other 2 had exploratory laparotomies. Three of the 4 patients died. The

Division acknowledges that all 4 patients had significant confounding medical conditions but the role of tegaserod cannot be completely ruled out.

The Division concluded that a thorough review of the chronic constipation trials, as well as a focused review of the IBS studies and other completed clinical trials of similar design did not identify any cases suspicious for ischemic colitis out of approximately 12,000 patients. Using the available data, the Office of Drug Safety estimated that approximately 7,000 patients were randomized to Zelnorm among the placebo-controlled trials that were at least of 3 months duration. Based on application of Poisson distribution, it would suggest that, with 95 percent confidence, ischemic colitis occurs no more often than 1 in 2,000 in this type of patient.

The agency is seeking the committee's advice on whether reference to ischemic colitis and other forms of intestinal ischemia should be moved to the warning section of the package insert. It is the agency's position that the appearance of

these events in young patients in close temporal association with Zelnorm is concerning. These conditions are generally considered a disease of the elderly. Consider 7 of the 20 cases occurred in patients less than 49 years of age, with 2 of the patients less than 30. As stated before, 5 of the 20 cases had no documented risk factors. Three cases occurred on the first day of therapy, with 2 of the 3 cases occurring in patients with no reported risk factors. In the month following the labeling change and "dear doctor" letter an additional 9 cases were reported. Since June 1, 5 more cases have been received. This brings the total to 14 new cases reported since the labeling change. These cases have not been formally adjudicated with the sponsor.

The agency would also like the committee's opinion on whether the patients with IBS have a higher background incidence of ischemic colitis. Novartis argues there is no causal relationship between the use of Zelnorm and the development of ischemic colitis. It is our position, based on

several published studies conducted within administrative claims databases, that there is a higher background incidence of ischemic colitis in IBS patients. The agency reviewed the available data Novartis used to support an association between ischemic colitis and IBS and found no compelling evidence to suggest that a clinically robust diagnosis of IBS is associated with any increased risk for ischemic colitis.

In contrast, it is the agency's position that an association between IBS and ischemic colitis is attributable to the use of a non-specific ICD9 code used in the databases. This code includes IBS and other bowel processes. We believe this resulted in a misclassification or a misdiagnosis of patients who were actually undergoing a workup, the code representing an interim diagnosis.

Novartis also defends their position stating that no mechanism of action has been identified in the animal models. It is the Division's opinion that a mechanism of action has

not been ruled out and that there may be cross reactivities with other receptors and ligands that have not been identified. Zelnorm is a 5-HT4 partial agonist with moderate affinity for the 5-HT1B receptor. There is recent medical literature proposing a link between Zelnorm and the develop of Raynaud's phenomenon, a vascular disorder that can affect the fingers and toes.

The article presents a case history of a 21 year-old female with no prior history of Raynaud's who developed painful discoloration of her fingertips after cold exposure. This occurred 2 days after initiating Zelnorm. Symptoms disappeared completely after the drug was discontinued. Although a mechanism of action for this process has not been identified, causality is strongly suggestive considering the patient had no prior history of Raynaud's, was not on any concomitant medications and the symptoms resolved after discontinuing Zelnorm.

Another article discusses the potential risk for Zelnorm-induced coronary-artery spasm.

The article, titled, "Tegaserod-Induced Myocardial Infarction: Case Report and Hypothesis," proposes that since tegaserod has moderate affinity for the 5-HT1B receptor, it is plausible that tegaserod could cause coronary-artery contraction and spasm similar to other 5-HT
1 receptor agonists on the market, such as those used for treating migraines.

Although these 2 articles are not conclusive, they do support the Division's position that a mechanism of action explaining an association between Zelnorm and ischemic colitis has not been completely ruled out. In response to the agency's concerns, Novartis has agreed to perform additional mechanistic studies.

In summary, chronic constipation trials did not identify any new safety concerns. The Division is concerned that there are limited safety and efficacy data on male patients, as well as a questionable risk/benefit profile for patients 65 years and older. Only 12 percent of the patients enrolled in the chronic constipation trials were male. The efficacy of Zelnorm in patients 65 years

and older was similar to that of placebo. These patients also had a higher incidence of diarrhea as an adverse event. Additionally, considering how common constipation is in the elderly, only 13 percent of the patients enrolled were older than 65.

Many of the Division's safety concerns that were identified during the postmarketing period have been addressed with the recent labeling changes. Serious consequences of diarrhea are now listed in the warning section of the label. However, the chronic constipation trials demonstrated that elderly patients had little efficacy and may be at higher risk for developing complications from diarrhea. The label should be revised to reflect this.

The question of whether the use of Zelnorm is associated with an increased risk of surgery remains unknown. Phase 4 studies are ongoing. The background incidence of ischemic colitis in the general population, as well as the IBS population continues to be debated. The Division questions

whether the available data justifies placing ischemic colitis in the warning section of the label.

I do have one update that I would like to share with you. We got this from an AERS MedWatch report update yesterday. It is case 25 in my background pack. Initially I just had a description term of a young female with findings consistent with ischemic colitis and I had no other information. We got an update. That patient was 31 years old. She was treated for IBS. Prior to therapy she had a clean upper and lower endoscopy. Approximately 5 months after initiating therapy she presented to the emergency room with rectal bleeding and had a colonoscopy performed that day that demonstrated superficial epithelial necrosis, acute hemorrhage, and the biopsies were consistent with ischemic colitis. Stool cultures were performed. They were negative. Hypercoagulative workup was also negative. The patient's medical history only included constipation, endometriosis and complete hysterectomy and GERD. The patient

was on no other concomitant medications.

Also of interest that I would like to comment about, the month prior to this event the patient decreased her dose to 3 mg every other day. Any questions?

Questions on Presentation

DR. FOGEL: Are there any questions for Dr. Della'Zanna? Dr. LaMont?

DR. LAMONT: Yes, has the agency or the sponsor collected any information from outside the United States on ischemic colitis? Has everything we have seen here related to U.S. patients only?

DR. MACKEY: One of the ischemic colitis cases was from Canada, and we have had no other cases outside the U.S.

DR. FOGEL: Dr. Metz?

DR. METZ: Thank you very much for a very nice summary. I am starting to realize that the older you get, the less the effect; the more concern for a confounding diagnosis that is going to end up like a secondary causal constipation or maybe, you know, not a true idiopathic constipation

patient, and maybe more of a worry about potential diarrhea or ischemia.

With the postmarketing data that is out there, I want to know how much exposure we really have to measure these patients. The briefing document, unfortunately, photocopied very badly. The IMS is really the only data we got. I mean, the other postmarketing stuff is isolated reports and it is not very robust, but with IMS you can actually get an idea. How many patients, what percentage of patients at various age groups have actually received this drug for any length of time both split by gender and split by age? That would be very useful to me.

DR. DELLA'ZANNA: I would like to introduce Dr. Allen Brinker.

DR. BRINKER: I will speak to that just briefly. Yes, IMS can give us a very good handle on drugs. The kicker with the use of Zelnorm is the short-term use. So, it has been my position and I have argued that it is very difficult to model use at all because of the short-term use

data. So, I think this is akin to the triptans in that regard because some people are going to use it for a week. It is indicated only for short-term use and people are going to stop it really quick. So, I am reluctant to try to tell you that I have a good handle on where the patient years are to help you with the denominator. Perhaps the sponsor could try to outline--I mean, we have some profiles on prescriptions only but I am not going to tell you that I know that those distributions accurately reflect how patients end up taking the drug.

DR. LAMONT: With the IMS data you actually can see when the prescription is, repeat prescription as opposed to a new prescription, and you can get that information and you can get the ages of those patients too.

DR. BRINKER: There are databases where you can do that and with claims databases you can do that, that is correct. But then you have to decide for yourself whether or not those are representative of the population at large, and we have chosen not to do that. Most of our analyses

have been qualitative.

DR. FOGEL: Dr. Joelsson, do you have a comment?

DR. JOELSSON: We have some data we can show you and we can discuss how relevant they are or not. We have a pie chart here which shows the distribution of age. As you can see, the majority is in patients under the age of 60--slightly young. Does that answer your question?

DR. LAMONT: Do you have it by gender as well?

DR. JOELSSON: I think so, yes. Can we have the gender slide? So, 7 percent male have tried this drug--mostly women. So, 7 percent male and 93 percent women.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: I was curious about the motivation for the opinion requested and changing from a precaution to a warning, considering that the label change was just a few months ago. Is it because you are concerned about the increased number of reports following the "dear doctor"

letter and label change, or is it a convenience issue because the committee happens to be meeting now? In your briefing document you mention that the first case came in, I believe, in March, 03 and the label change occurred in April, 04. To make a change now, I am curious--

DR. DELLA'ZANNA: What is our motivation?

DR. MANGEL: yes.

DR. DELLA'ZANNA: To keep things on base, we were in negotiations for where we were going to put this in the label. We were initially hoping to put it in the warning section. We were in negotiations, that were prolonged, with the sponsor. We could not reach an agreement but we also didn't want to be completely one-sided. We agreed to meet and place it into the precautions section and discuss it at the advisory committee meeting. This was a compromise on both of our parts.

DR. MANGEL: Could I ask a follow-up to that? If there would be a label change--you probably might not have concluded this, would there

be a "dear doctor" letter, etc.? With increased communication about it, it may be confusing for the prescriber whether or not there has been a new signal in the next three months or with the original placement was just incorrect. Have you thought in terms of there would be a label change what type of communications would accompany that?

DR. DELLA'ZANNA: Well, I don't know whether I would say that the placement was incorrect. Okay? This is a developing signal possibly. We are looking at an increased number of cases which also might increase our concerns. So, I don't know if I would agree with you that we didn't place it correctly the first time. The goal was to come to an agreement; be able to get a "dear doctor" letter out to make the public aware and physicians aware of our concerns as soon as possible without having to go through any further delay of releasing this information.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: I would like to express my general unhappiness with the way the safety data

have been presented, particularly by the sponsor. It is a very one-dimensional way, basically giving the cumulative frequency. Adverse effects have other dimensions--very little about severity. The other one would, for example, be pain. They are equating a single episode of pain to constant pain for six weeks. I wish we had a little bit more information about those aspects, the other dimensions, because I am unwilling to buy the fact that the drug has very few adverse effects just based on the cumulative frequency.

DR. FOGEL: Thank you. Dr. Cryer?

DR. CRYER: As I think about this issue, I am really kind of focusing in on the subgroup analyses of the subpopulation where there was modest or no treatment effect shown, specifically again the older age and the men. In kind of making that comparison, you showed us nicely a breakout of this adverse effect of diarrhea by age. I was wondering if you have done a similar analysis by gender, the incidence of adverse effects or specifically diarrhea.

DR. DELLA'ZANNA: I do not have that with me. I have it as part of my final review. I don't remember it off the top of my head.

DR. FOGEL: Yes?

DR. DENNIS: This is a slide showing adverse events broken down by males. So, this is the slide that shows you that in the male population the adverse event that was seen more frequently was diarrhea, which is what we saw in the female population where diarrhea was more frequent than in the placebo--the males and the females.

DR. CRYER: Thank you. That answers my question.

DR. FOGEL: I would like to thank the FDA for their presentations. We are going to break now for lunch. We will resume again at 2:15. For the committee, we are going to be taken across the street to Cafe Gallery. We will start again at 2:15.

[Whereupon, at 1:10 p.m., the proceedings were recessed for lunch.]

A F T E R N O O N P R O C E E D I N G S

Open Public Session

DR. FOGEL: Good afternoon. I would like to start the afternoon session, if I can have everyone's attention, please. The first item of business this afternoon is the open public hearing and there are three presenters. Before we call the presenters to the podium, there is a statement that has to be read.

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

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

financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first speaker will be Jeffrey Roberts.

MR. ROBERTS: Thank you. I am Jeffrey Roberts, and I am here today representing patients and sufferers. I have paid all my own expenses to be here.

Members of the committee, thank you for the opportunity to appear before you. I am the president and founder of the Irritable Bowel Syndrome Self Help and Support Group and founder of the Zelnorm Action Group. The 10,000 member Irritable Bowel Syndrome Self Help Group has endeavored, since 1987, to educate and provide support for people who have functional

gastrointestinal disorders, and to encourage both medical and pharmaceutical research to make our lives easier via a successful Internet website for sufferer.

I have been a sufferer of diarrhea-predominant irritable bowel syndrome for over 25 years. Much like chronic constipated individuals, there are challenges that I face each and every day in order to cope with my functional gastrointestinal disorder. It affects my family's lives, my career and I am constantly reminded of my own physical limitations because of this very burdensome illness.

Today I have the support of the Zelnorm Action Group, Irritable Bowel Syndrome Self Help Group and Irritable Bowel Syndrome Association. I am privileged to act as the representative today for all those members who were too ill to travel here today. I would also like to acknowledge all of the efforts today.

Functional constipation is a common problem in our community, with its prevalence

rating from 2 percent to 28 percent. Its diagnosis is made by careful delineation of its duration and characteristics. Constipation classification into subtypes results in overlapping symptoms and blurring between the subtypes. The distinction between IBS with constipation and functional constipation is important as a focus in treating functional constipation is to improve bowel habits alone. In an IBS patient abdominal pain and other symptoms must also be addressed. Most chronically constipated patients do not require diagnostic studies beyond a careful history and physical examination. For clarification purposes, my presentation today refers to individuals with only functional constipation lasting longer than 6 months, and widely given the name of chronic constipation.

As I am a focus in the community for information about functional gastrointestinal intestinal disorders, I communicate with a great many people who have run out of options. They do not know where to turn and their quality of life

has greatly suffered. Many current approaches to chronic constipation, including the use of fiber, osmotic and stimulant laxatives, biofeedback training and surgery, often fail to control the patient's symptoms adequately. They produce problematic side effects or lose effectiveness with time. Most available and approved drugs for constipation have been passed down from antiquity and have not been tested in modern well-designed studies.

Primary care physicians and the sufferers believe there are very few other options available to them because chronic constipation is not usually deemed of clinical importance until it causes physical risks or impairs quality of life. Physicians often prescribe drugs for constipation with which they are familiar and comfortable and in most cases anything will do.

Chronic constipation is a very unpleasant disorder and in some cases individuals who suffer from chronic constipation do not have a bowel movement for up to 21 days. Their quality of life

is greatly diminished by this basic impaired function that most individuals take for granted. They may pass hard stools; lack the ability to defecate on demand; or strain at every bowel movement. I am here today to tell you that chronic constipation is a condition which cries out for more attention. It demands the continued use of a medication, Zelnorm, already proven in treatment of functional constipation and IBS-predominant constipation. This committee must provide clear indication to the medical community that Zelnorm should additionally be made available for the indication of chronic constipation without any further burden to the physician or patient in prescribing this medication or getting access to this medication.

As with Lotronex, a drug with the opposite effect of Zelnorm, i.e., for severe functional diarrhea individuals, this committee listened to myself and others from the Lotronex Action Group in April, 2002 make presentations as to how difficult it is to live with gastrointestinal disorders.

Although many of us do now have access to Lotronex, we are challenged by physicians who lack the knowledge or are fearful of prescribing a medication because of a negative message about its use.

Zelnorm has an admirable safety record in clinical trials in general use. Its virtue should be celebrated and not limited in its usefulness as a medication to ease the suffering of a chronic constipation individual.

An electronic survey was recently conducted by the Zelnorm Action Group. Individuals were screened so that results were recorded only for those prescribed Zelnorm after indicating their symptoms of chronic constipation to their primary care physician.

While taking Zelnorm, chronic constipation sufferers report a quality of life that is dramatically better. Seventy-nine percent of those surveyed indicated that they had no significant side effects at all.

The Zelnorm Action Group is prepared to

place educational information about Zelnorm on their website in order to reach out to the chronic constipation community. This provides an effective forum for educating chronic constipation sufferers about Zelnorm's proper use.

In conclusion, the quality of life of constipation sufferers was dramatically improved with access to Zelnorm. The medical community should be informed that a treatment is available which will improve the patient's outlook. Adverse events should not deter either the pharmaceutical or the FDA from maintaining the drug's availability.

Zelnorm has a place as an effective treatment for chronic constipation sufferers and should be indicated as such to the patient and medication community. Thank you.

DR. FOGEL: Thank you. The second speaker is Constance Hill.

MS. HILL: Good afternoon. I also am here on my own behalf and I haven't been paid by anyone. Mr. Chairman and members of the committee, my name

is Connie Hill and I have chronic IBS with constipation. I have had this terrible disease since I was about 18. Over the years my symptoms became increasingly worse and eventually became so severe and debilitating that I had to make significant life-altering changes to survive.

In 1996, I had to quit my job as a legal assistant and stop working altogether. My husband and I even moved from the hustle and bustle of Fairfax County, Virginia to the country, hoping that a slower pace of living would ease my symptoms. Even these drastic life-style changes did not help. Over the years I have consulted with many physicians and tried every remedy and drug that doctors recommended but none of the treatments worked. The doctors seem to find IBS as baffling as do the millions of Americans who suffer daily from this disease.

I was told by one well-known gastroenterologist that I have a terrible mental problem and until I came to grips with it I would never get well. I was sent to a psychiatrist for

several months, at the end of which I was no better.

One department head at Fairfax Hospital told me I have a floating rib and prescribed muscle relaxers. Others recommended biofeedback and acupuncture, which I also tried and failed. But none of these treatments gave me any relief from the daily pain and discomfort that I had to endure. I became so desperate I even resorted to exploratory surgery to determine whether or not adhesions from an earlier surgery were causing the problem. Unfortunately, this was not the case. The bottom line is the medical professionals don't really understand IBS and are very frustrated by their inability to effectively treat it. I have sensed over the years that most physicians would rather not deal with difficult cases of IBS. This was so discouraging to me, and I am sure other IBS victims encountered the same indifference from the medical community.

Zelnorm is the one and only drug that has given me any relief and restored any part of a

normal life for me. My life before Zelnorm was a living hell. I suffered daily with pain and discomfort, reaching head-banging proportions. I never got a day off from the pain and the misery. One weekend shortly after I got the definitive diagnosis, I sent my family away for the weekend and planned to kill myself. I couldn't deal with the fact that I was told I would have this pain and suffering for the rest of my life. I was working at the time. I spent a lot of time either in the ladies' room or crying at my desk. I couldn't explain to all the people at work what I was dealing with, it is so embarrassing that unless you own this problem you can't possibly understand what it does to you and your loved ones. It is degrading and demoralizing. It breaks your spirit and kills your ability to smile and enjoy anything normal.

After getting through the workday you just want to go home, rip off your clothes and crawl into the fetal position. I lived like this from 1985 until I was forced to retire from the job that

I loved, in 1996. In 1997, we moved out of the city. I became a couch potato. I would rush to get dressed by 6:00 p.m. so that when my husband came home from work he wouldn't know I spent the entire day unable to do anything. There are no vacations, movies, dinners, cookouts and other normal day-to-day activities for someone with IBS. It is not life-threatening per se but it leaves you riddled with pain, kills your spirit and makes you a prisoner in your own home.

I have been a member of the on-line support group for many years. I have tried everything that was suggested and failed. When I first heard about Zelnorm, in late 2001, from the support group it was only available in Mexico. I was planning to go there but then learned that it was also available by prescription from Switzerland. I was able to make contact with a pharmacy in Switzerland. I have a wonderful internist who agreed to write me a prescription and I received my first box of Zelnorm a few weeks later. After working to get the correct dose, I

started to be able to do a few things. I didn't spend all day on my couch. I actually had part of the day when things were relatively normal. It wasn't the panacea I had dreamed of but it was a major step forward.

I have taken Zelnorm now for two and a half years. It is a dramatic improvement for me. Although not a complete cure, it has greatly enhanced the quality of my life. Before Zelnorm was developed I prayed daily for guidance to help me out of the hell hole I was in. I thank God for the guidance to the support group which helped me find this life-altering drug.

I am not only speaking for myself but for the millions of people in the U.S. and all around the world who suffer daily with this terrible disease. There is no other effective treatment for IBS with constipation. If Zelnorm was ever taken off the market, you will be condemning me and many other IBS sufferers to the same torturous existence that we had to endure without hope before Zelnorm. If you do that, I don't know how I will be able to

go on.

I strongly object to the recommendations of some groups that a change in diet will relieve the suffering of constipation. Their suggestions for alternative treatments are so naive. Obviously, they have not had to live with this disease and do not understand that these simple steps do not bring relief to people who suffer from severe IBS with constipation. I have tried their suggestions and they don't work. Zelnorm is the only treatment that makes a difference and I beseech you to enhance its certification. Thank you.

DR. FOGEL: Thank you. The third speaker is Linda Roepke.

MS. ROEPKE: Good afternoon, everyone. Mr. Chairman, thank you for allowing me to have time today to come up and say a few words about how Zelnorm has affected my life.

Allow me first of all to introduce myself. My name is Linda Roepke and I am from St. Louis. I am very blessed in that I work at St. Louis

University and I work with a fine staff of different physicians. I work with the Chairman of Internal Medicine.

Today I am not only blessed but very lucky to have a very good GI doctor who has helped me through many years of a chronic problem with constipation. Prior to finding my specialist in the GI division today, my primary care physician for the last 20 years of my life really did not know anymore how to treat my constant stomach aches, as I will refer to them because I don't know how else to describe to you--I am sure most of you have been constipated at one time or another and you know that heavy feeling that you have. That was a very chronic thing for me. Being bloated is supposed to be a "woman" thing so, you know, I will give the medical profession part of that. However, that bloatedness can take the average waistline, whether you are male or female, from a 26 to a 30, or from a 32 to a 38 in no time.

My general health is very good, with the exception of irritable bowel which has caused more

chronic constipation than it has diarrhea. It is a most serious condition to live with. I tell you these things for two reasons. Number one, during the years that I have suffered with constipation, as anyone else who has had the same problem will tell you, life is not real normal. It is very miserable. You have many low points. You are not able to contend with a lot of daily normal life's instances. I also tell you this to testify to my own credibility.

As a child I not only knew, I had a lot of stomach aches, too much pain in my abdomen. My parents certainly knew it. I was a main topic of their conversation for years. By the time I was 12 my mother was telling me that, you know, once you start menstruating you are going to feel better. This feeling in your abdomen will get less and less. During high school years I obviously had a written excuse for the majority of our PE classes because I didn't have the energy to really do them. My family doctor at the time, our family physician, eventually, in my senior year in high school, too

me for an exploratory surgery, again, not knowing really what to do. I hopes of finding something wrong for the sake of not having to have this embarrassing problem, I was hoping for just about anything. Unfortunately, nothing was found. My bowels just move slow, quote/unquote, is what is written in my charts going back to 1964.

I had a spastic colon which would force me to go through surges of either diarrhea or then maybe five, six, seven days with not being able to go to the bathroom. During those years my mother and our family doctor would give me little Elephon [?] pills from Walgreen's. I don't know, I think most of you are of an age that you probably remember this. That was their laxative of choice, both of them. My bowels would straighten out for a while and then they would get wacky again. The sluggishness and diarrhea made even dating difficult. I continued with over-the-counter laxatives for the next 30 years, fighting abdominal pain, cramping, embarrassing situations, playing with laxatives, and I have tried them all. Many of

them have been prescribed, with it be from Metamusal, Duclolax, suppositories, it doesn't matter--been there; done that.

This is not an easy thing to try to work with your doctor and being certain that you are keeping your body physically as fit as you can. Many times I walked around, looking at though I could be four months pregnant--always not. Everywhere I worked, most people have learned--I am always a topic of conversation, I guess I should say. I have been the topic of more than one laughing piece of conversation about "don't follow her into the bathroom because you might hear just an explosion." These are embarrassing things for any of us out there. This is a delicate topic in the first place. It certainly isn't one I choose to share with my co-workers.

In 1994, I drove myself to an emergency room. The final diagnosis was that I needed a series of tests again run. I wonder how many blood samples I have had taken to find out that I am chronically constipated. The doctor did a complete

upper and lower GI series with the barium, hoping to find something. Again, nothing was found. Again, I was referred to a nutritionist. Again, I was told that I eat a far better diet than the majority of the people out here and my exercise content was pretty good.

My doctor at that time prescribed Senokot, laxatives and more fiber--35-40 grams of fiber is a lot of fiber. So, 40 years later I found myself in the same situation. When I finally walked into--I didn't walk into our GI division, I barged into my doctor's academic office, embarrassed and knowing that working for the chairman of internal medicine I resent people who try to get past me, the guard, and, yet, I just pulled the same thing with her. I had tears in my eyes. She looked up from her computer, because this is not in a clinic setting, and said, "what's up?" The tears rolled down my face, "can you help me?" to make a long story short. She continued to say, yes, there is help and I do not need to keep suffering like this. This is ridiculous and she will get me into her

clinic and she will get several tests set up for me. So, for the next many months we went through a battery of different things because, again, it is important that we stress that constipation is just constipation. I don't have cancer; I don't have a grapefruit in my stomach; I don't have a large cyst.

So, I got very lucky. I went through an anorectal manometry, colon transit and a colonoscopy. Considering the many medications I was trying to take, it is with great thankfulness that I finally was able to find Dr. Prather. At the age of 50 I finished college and I completely started a new career. Today I am planning a wedding which has been many years in the making, to someone who is healthy as what I am. My stomach feels and looks more normal, not swelled up like a puffer fish. I no longer need to stay constantly constipated. I can begin to enjoy life more today. I am looking forward to a huge mission trip through my church that I have wanted to go on for the past five years and have been too embarrassed to do

this. I could have gone last year; I look forward to it this year. Zelnorm has helped to make this possible.

Am I willing to risk any side effects from this drug today? Absolutely. I would like for any of you in this room to tell me of a drug out there that we do not have some side effects from. I see many advertisements for many medications with much worse side effects than Zelnorm and they are still on the market, indeed.

I also need to interject that I am definitely one of the few lucky ones. I just went through with you how fortunate I am to have my career path in an area where I could barge into a GI doctor's office, a specialist at that. What about these people who cannot and do not have that access, people that are in rural communities, which is probably why in 1994 my doctor didn't know what to do with me then? Of course, Zelnorm wasn't out at that time.

In conclusion, I just need to let you know that I have lived with chronic constipation for the

majority of my life and Zelnorm has been the only thing which has provided consistent relief, and it has made an entirely new person out of me today, with lost less embarrassment and a lot more regular lifestyle. Thank you so much.

Clarification of Issues

DR. FOGEL: Thank you. At this juncture we are going to turn the meeting back to Novartis for some clarification of issues that were raised in the morning's discussion.

DR. JOELSSON: Thank you, Dr. Fogel. I would like to clarify a few things that were raised during the presentations this morning. First I would like to talk a little bit about Dr. Della'Zanna. He said that we had some discussions about the label text and that in the end we agreed upon a precaution but that he felt maybe it should have been a warning.

Can I have the first slide? I would like to clarify why we think it should be a precaution and not a warning. It is really based on the regulatory definition of a warning. The labeling

shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug. A causal relationship need not be proved.

I think I made it pretty clear during the presentation earlier that we don't think there is a reasonable association of reasonable evidence of an association of a serious hazard. So, we thought that a precaution would be adequate at this time point. If things changed, we would have a discussion again.

So, this is what the precaution looks like in our label today: Ischemic colitis and other forms of intestinal ischemia have been reported in patients receiving Zelnorm during marketed use of the drug. A causal relationship has not been established.

So, this is part of the prescribing information. It is part of the "dear doctor" letter that was sent out. As you know, "dear doctor" letters are usually sent out when there are warnings but we suggested that we would include

this into our "dear doctor" warning letter too because we think this is important information to have out there.

Can I have the next slide, please? In relation to whether something has happened or not since the label change, is there any reason for us to discuss a label change, this is what the monthly reporting rate of ischemic colitis looks like in the United States right now. As you can see, after a slow uptake when the drug was marketed in August, 2002, there have been no dramatic changes in the reporting rate of ischemic colitis during the last, let's say, year. So, in my mind, nothing dramatic has happened since we had our label negotiations and currently we do see an increased reporting rate as a part of the "dear doctor" letter, and we know that is a well-documented effect of a "dear doctor" letter. However, the increase of reporting has not been dramatic.

Another point I would like to make is in relation to young patients getting ischemic colitis. In addition to the fact that there is a

background rate either in the general population or in IBS patients, misdiagnosed or not, it is also the case that some young people are diagnosed with ischemic colitis. It is less common but it is still well known in patients who don't take medication. For instance, in the United Health Care study 3 percent of the patients were between age 20-29 and 9 percent were between 30-39.

I can also say that in the CORI database, the database where endoscopies are collected from all over the United States, there are patients reported there who are also between 20-29 years of age. So, this is known. So, it is not surprising that we do get cases, young cases, also with ischemic colitis.

Next slide, please. You saw this slide before, saying that we don't have any cases of ischemic colitis in our clinical trials in more than 11,600, but we have one patient on placebo that has ischemic colitis. I would like to show you some details of that case.

May I have the next slide, please? I am

showing this case just because Dr. Della'Zanna was talking about a young patient that was recently reported. By the way, it is not a new report; it is an updating report so that is already included in the numbers--just to make sure we understand that. But it is obviously a case that raises your eyebrow because there are no factors explaining this ischemic colitis in a young patient.

This is our patient on placebo. She was 24 years old and she was part of our chronic constipation efficacy study. She was basically healthy. She had no other reasons to have an ischemic colitis. She was reported as a segmental erosive colitis on colonoscopy. We have discussed it together with Dr. Della'Zanna and we agreed that that is a probable case of ischemic colitis. So, even on placebo you can get reports on young patients without any evident reasons for why they should have ischemic colitis. So, it is not surprising that we also get such cases on tegaserod reported.

Can I have the next slide, please? Just

in relation to Dr. LaMont's question, I just want to show this slide again. After adjudication we had an imbalance, 0.03 percent versus 0.06 in the cholecystectomy indications population. As you heard from Dr. Della'Zanna, we currently have a prospective study to study abdominal operations, including cholecystectomies. There will be 10,000 patients in each arm and that will tell us what the truth is.

Finally, However, what I want to tell you is that currently there is a contraindication in our label for Zelnorm in patients with gall stone. So, it iq already there. Thank you for that. Are there questions about this?

DR. LEVIN: Could you comment on whether it wouldn't be prudent to include the postmarketing data in the precautions statement? I mean, you are only presenting the clinical trial data which says there are no cases, but we have postmarketing experience that tells there are cases. Without getting into the precautions versus the warning issue, it seems to me only reasonable to include in

the precautions statement what we know about the drug to date in ischemic colitis and that would include the postmarketing reports through some cut-off date.

DR. JOELSSON: I think we could consider having a discussion with the FDA about that.

DR. LEVIN: Again, not getting into a debate of warning versus precautions, but if you are going to have a precautions statement that then says here is the experience and we have no cases, when we know there are cases--that is not a good precautionary statement.

DR. FOGEL: Is there a comment from the FDA?

DR. LEVIN: You said there are none out of 7,000.

DR. JOELSSON: We are talking about giving numbers. I understand what you are talking about. Thank you. I think that is clear.

DR. FOGEL: Is there an FDA comment?

DR. BEITZ: Just that we think the first sentence does include postmarketing.

DR. JOELSSON: Yes, I think he is saying we should have numbers in there. We will talk about that.

DR. BEITZ: Right, the difficulty with putting in numbers is that they are out of date as soon as we print the label.

DR. BUCHMAN: It is unfairly weighted the way that it is written because there are many more words associated with the fact that there aren't any. When you read these quickly, it looks like it is a stronger emphasis that there aren't any cases. So, I would agree. I think it just needs to be reworded so that it is equal. If you have a multiple choice question, all the answers need to be the same length. If you have one that is longer, it has actually been shown that that is the one that is picked most frequently.

DR. FOGEL: Dr. Cryer?

DR. CRYER: Thank you for that very nice explanation. I would like to make a couple of comments just from my perspective after hearing your rebuttal to Dr. Della'Zanna's presentation.

That is that, you know, with respect to the comment that there have been no cases of ischemic colitis identified in the placebo-controlled trials, whether it be the 7,000 or the 11,600 patients, I would at least argue from my perspective that the risk in a younger female population may differ from a potentially older population with respect to their underlying co-morbidities.

With regard to his comment about the mechanistic plausibility of this relationship, although there has not been a definitive cause-effect relationship shown, you had a slide earlier in your presentation, which I think was your slide CS-26, which talked about its effect on isolated coronary-arteries of non-human primates, suggesting the possibility of a mechanistic plausibility. My comments about this is that, one, this would be non-human primates and so it doesn't really suggest to us what we might expect to see in a human trial, although I understand you couldn't do exactly this type of trial in human observation.

The second comment that I have would be

that my understanding of tegaserod's effects at plasma concentrations when clinically dosed is that in that slide I think the concentrations fall towards the right-hand side of the slide, at which point it looked like the two curves apparently seemed to separate from placebo.

So, all this is just to say that I do think that there is at least some mechanistic plausibility and, secondly, that the lack of observations in the clinical trial experience is probably a different patient population than we are discussing.

DR. JOELSSON: Those are very good comments. Actually, we do have data in humans also. Can I show those data? Can I get this on the screen?

Maybe Dr. Pfannkuche, who knows so much more than I do about this, could come up. He is our head of preclinical research and he has been responsible for these studies. I only showed one of them; he has done many.

DR. PFANNKUCHE: Hans Pfannkuche, I am

working in the preclinical pharmacology department. Actually, it is a very reasonable question. Dr. Della'Zanna pointed out that triptans have been associated with cases of ischemia coronary problems. I think Dr. Joelsson indicated in his slide that we did study in these monkey preparations coronary vessels, and there is no agonist activity associated with this drug. In fact, it is a silent antagonist at this receptor subtype, defined as 1B receptor.

As agreed upon with the FDA, we started looking into human preparations, and in this case human mesenteric arteries. It is interesting to know that we find exactly the same pattern as we observed in the coronary vessels. So, with the human mesenteric arteries, as you can see here, the first curve, which goes very up, is response to serotonin, our reference compound, and the second curve in between the X axis and the highest curve is the sumatriptan response that you would anticipate. It is still a low number of samples here but you have some very high and some moderate

responders here. You may ask, okay, what about its affinity? Actually, the affinity, again, translates into a silent antagonist property.

Maybe on the next slide I can give you an example, slide PI-41. On this slide you can see a parallel shift that you would expect from a competitive antagonist at this receptor site. So, you can see that the affinity translates into inhibition of sumatriptan-induced contractions in this human mesenteric artery preparation. In addition, I could show you another slide where we did the same for monkey mesenteric artery preparations.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: Yes, I just want to make a comment and then I have a question. I guess I have an alternative opinion than some of the members of the committee. I think the data that come from 11,000 patients in the clinical trial are much more robust and allow much greater degree of quantitation than the postmarketing database, especially at this juncture of time and perhaps it

won't be a question at the end of the day whether or not there is an increased incidence in IBS patients. I mean, for the clinical trials the presumption is if there is a case, you capture it, especially if there is a case of ischemic colitis. The missed cases were probably covered by the near equal frequency of rectal bleeding between the placebo and the active group. So, that is just an alternative opinion.

I did have a question though, Dr. Joelsson, on your frequency over time of ischemic colitis slide that you just showed. The question is from the FDA presentation and briefing document the impression I had is that there were 24 cases prior to April 15 reported and 7 or 9 cases afterwards. I guess on that slide where the X axis did go to June, 04 I didn't see a bump reflecting that.

DR. JOELSSON: There is actually a small bump but it gets very small because of the big denominator. But I can tell you that it is interesting what the effect of a "dear doctor"

letter has. Before the "dear doctor" letter we had between 0-4 cases maximum reported per month. During the month after the "dear doctor" letter we had 7 cases reported.

DR. MANGEL: I appreciate the fact that increased news coverage will increase reporting. I just didn't appreciate on the graph--you know, to me it looked like the rate should have gone up by about 25-30 percent and I guess I wasn't seeing it on that, unless the denominator over those 2.5 months markedly increased as well.

DR. JOELSSON: Yes, it does. The denominator increases and the number of cases accumulate. That follows each other very nicely. We don't see a quicker uptake of cases versus the use of the drug. It is very parallel, as would be expected.

DR. MANGEL: And that was even after the "dear doctor" letter.

DR. JOELSSON: There is a small bump. As I told you, it is a small bump but on that curve it doesn't look very big.

DR. FOGEL: Dr. Beitz?

DR. BEITZ: I just had a question regarding the preclinical data that were shown on the human mesenteric vessels. Are those from patients or normals? What is the source of that human material?

DR. PFANNKUCHE: This is patients who had to undergo surgery for colon cancer, with no history of IBS for example. The report has been finished right now and will be submitted to the agency shortly.

DR. BEITZ: It may just be useful to see similar types of studies done in vessels from IBS patients, if they are available.

DR. JOELSSON: They are hard to get though.

DR. BEITZ: I agree, but if you wanted to look at the vasoreactivity of the IBS vasculature you would have to look at IBS patients.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: I do have a request for a clarification but first I wanted to reinforce Dr.

Cryer's comments and maybe take a little issue with Dr. Mangel. All of the sponsor's safety presentations today have estimated the incidence of serious diarrhea and of ischemic colitis on the basis of all patients who have taken Zelnorm, but they have not presented their estimates on the basis of the populations at maximum risk, namely the oldest population. The precaution statement refers to 7,000 patients. The presentations today have referred to 11,000 trial patients and 3 million marketed patients [sic], but I am not yet convinced that these figures accurately reflect the potential incidence in the elderly population and I think that some of those estimates ought to be recalculated on the basis of a different denominator. That is just a point I might make.

The request for the clarification has to do with the data on the extended trial. We weren't given any efficacy data at 13 months. It would be nice to have them. Maybe they will come later. But we were told that 46 percent of patients discontinued the drug and evidently not because

they were all better. Did that 46 percent include the placebo patients? If not, what percent of patients on the active agent discontinued for whatever reason within that year?

DR. DENNIS: The extension study was a double-blind study, but there was no placebo arm so it was uncontrolled. Patients who had received 2 mg and 6 mg BID in the study continued on those doses in the extension study, and those patients who had been on placebo went onto 6 mg BID in the extension study.

DR. SACHAR: Well, it says 842 patients entered the extension trial--

DR. DENNIS: Correct.

DR. SACHAR: --but only 518 were exposed to Zelnorm. So, what were the other 324 taking?

DR. DENNIS: That number I gave you were exposed to Zelnorm for greater than 12 months.

DR. SACHAR: Oh, I see, the sentence continues.

DR. DENNIS: In that extension there were no patients on placebo.

DR. SACHAR: So, 46 percent of patients on Zelnorm stopped taking it within a year.

DR. DENNIS: We had discontinuations of 46 percent throughout that treatment period.

DR. SACHAR: And they were getting it free?

DR. DENNIS: They were in the study.

DR. SACHAR: And they still stopped taking it.

DR. DENNIS: Well, I think the point is that in long-term studies of this nature, it is not uncommon to see these discontinuation rates. One of the questions that you asked earlier on was for the efficacy. Remember, this was a study we designed to do safety assessments.

DR. SACHAR: Oh, sure, and I see all the reasons--unsatisfactory response, withdrew consent, administrative, adverse effects. I don't see anybody who stopped taking it because they were better.

DR. DENNIS: Patients who were better continued taking the drug.

DR. SACHAR: Exactly, and 46 percent stopped.

DR. DENNIS: Forty-six percent stopped.

DR. FOGEL: Before we begin our discussion--

DR. JOELSSON: Dr. Fogel, I have a few more points to clarify. Is that okay?

DR. FOGEL: That will be fine.

DR. JOELSSON: Thank you. Dr. Schoenfeld?

DR. SCHOENFELD: Thanks. Could I have slide CB-12? This is certainly an interesting process. It is an enjoyable one to go through.

I first wanted to try to clarify the point about appropriateness of endpoints for functional lower GI disorder studies, specifically about what the Rome committee says about those. I want to be very clear about exactly what the Rome consensus document states, first author Dr. Whitehead. It specifically stated that experts in this field recognize that people with lower functional GI disorders have multiple symptoms. The specific quote from the paper says that no consensus could

be reached on any single primary efficacy endpoint. It goes on to state specifically that they feel the best approach is to specify a primary endpoint with a few select a prior defined secondary endpoints to try to encompass the multiple symptoms in these functional lower GI disorders.

Having said that, in the section of the Rome committee document on the appropriate design of a functional GI disorder, Sander Van Zanten and colleagues said, just as Dr. Fogel alluded to, that probably the best endpoint is global satisfaction with your functional GI symptoms.

DR. PRIZONT: I think I was one of the authors.

DR. SCHOENFELD: Actually, you were, Dr. Prizont.

DR. PRIZONT: I don't recall talking about common constipation as such. We were talking about constipation-predominant irritable bowel syndrome in that particular quoting. But, in any case, you are right. Those who applied the Rome criteria had the choice of selecting the endpoints. Like you

said, you know, you can choose one endpoint, another endpoint and so on, and you chose them. You chose the 3 bowel movements with completeness. In your clinical trials in order to make the diagnosis of constipation, you said in the protocol patients will be considered constipated if they have less than 3 bowel movements per week; if those are incomplete; and if they have more straining than what is established in the Rome criteria. So, you picked them.

DR. SCHOENFELD: I think that responds to a different point but I will go ahead. Can you go to slide CB-10? I just want to make sure we are very clear about what the Rome committee criteria are for functional constipation. A patient need not have fewer than 3 bowel movements per week in order to meet the Rome committee criteria for functional constipation. If a patient, for 12 weeks which need not be consecutive in the past year, has some combination of straining, lumpy or hard stools, a sensation of incomplete evacuation, sensation of obstruction or blockage--if they have

any 2 of those 4, even if they are having 4 bowel movements per week, that meets the Rome committee criteria for functional constipation. I want to make sure we are clear on that point. Go ahead, Dr. Sachar, please.

DR. SACHAR: Well, that is the Rome criteria. I just want to be sure that you don't set up the Novartis criteria for your protocol and then dredge your outcome by the Rome criteria.

DR. SCHOENFELD: Absolutely. I was just going to that point. So, having said that, the criteria for Novartis studies, although they are not exactly as the Rome committee criteria, are certainly pretty darned close, and I would note also, going back to risk/benefit analysis of all laxatives, they come closer to meeting the Rome committee criteria for identifying patients with functional constipation than essentially any other randomized, controlled trial that has ever been done for a laxative.

DR. PRIZONT: I concur with that. I said that in order to define constipation, Novartis used

the wrong two criteria. You just mentioned that you are applying the wrong two criteria to define constipation. The question was not whether you defined constipation based on the Rome criteria. The question was how you define efficacy--

DR. SCHOENFELD: Absolutely, and I would like to go to that point.

DR. FOGEL: Actually, can I ask a question before you go to efficacy? What about validation of outcomes? We have a lot of data about the Rome criteria global subjective assessment, what about the Novartis outcome?

DR. SCHOENFELD: Well, what I would suggest is this, if we can go to slide CB-13, which goes back to your point which was to say are there any data about global satisfaction with bowel habits? As we see here in both studies, we see that patients who are tegaserod 6 mg BID demonstrated a statistically significant, and, what is to me, a clinically important improvement in global satisfaction with bowel habits. Now, what is that based on? Obviously, the absolute

difference is that between 9 and 12 percent more patients compared to placebo said they had global satisfaction with bowel habits.

I do want to be very careful as we talk about placebo-controlled trials. Sometimes we talk about using number needed to treat, which I am a huge proponent of, but it is probably best to use when you are comparing two alternative therapies. If I say the number needed to treat here because of an approximately 10 percent difference is a number needed to treat of 10, that infers that instead of prescribing a drug like tegaserod I am going to prescribe a placebo. That is actually not an alternative for me. Nevertheless, it gives us an idea about the incremental benefit over placebo.

Second, going back to validation of this global satisfaction endpoint, responders were defined as patients who have had an increase of 1 on a 5-point Likert Scale for their global satisfaction. Now, what does that mean clinically? In other studies of functional disorders, including functional respiratory disorders, it has

consistently been validated that an increase of 1 point on a 5-point Likert Scale is a clinically important benefit. But to be balanced, has that been validated? Not specifically for functional constipation, not to my knowledge. If you chose instead, though, to say what is the proportion of patients who get complete or near-complete satisfaction with the bowel habits, a score of 0-1 on that 5-point scale, the proportion of patients, although it is small in both the tegaserod group and the placebo group, is still significantly higher in the tegaserod group than it is in the placebo group, although I would say this was a population of patients with fairly severe constipation and that is a fairly difficult threshold to get, that they had complete or near-complete satisfaction with their bowel habits.

DR. FURBERG: Could you explain the footnote? I mean, you are really comparing baseline to any time between week 1 and 12, or are you doing it at the end of the study?

DR. SCHOENFELD: I think that question may

be better answered by Dr. Dennis.

DR. FURBERG: This question relates to some other papers you have shown as well. I mean, what is important to us is what is the global satisfaction at the end of the treatment period. You should not carryover and if you have some benefit early on take credit for that if the patient stopped taking the drug.

DR. DENNIS: Sure. What we did when we did these calculations was an average but we did look at weekly satisfaction scores, and when we look at those weekly satisfaction scores we can see significance at all weeks as well.

DR. FURBERG: I would like you to show a graph where you have the baseline and the end after 12 weeks. We need to know what is the effect on global satisfaction after 12 weeks of therapy and no carryover.

DR. DENNIS: Right. AQ-50, please. This is really showing you the weekly response for satisfaction scores by study. You can see significant difference throughout the trials. You

look at the beginning and you look at the end and we are still seeing a significant difference on these weekly analyses.

DR. FURBERG: It is hard to see the scale there.

DR. DENNIS: Remember, this was a 5-point scale and the responder improvement is shown by a decrease in the score.

DR. FURBERG: So, the improvement is less than half a point.

DR. DENNIS: We have done some statistical analyses to look at validation of these as well, and I would like to ask Dr. Gary Cook to come up and discuss the statistical significance of these results as well.

DR. COOK: Yes, I am Gary Cook from the Biostatistics Department, University of North Carolina. One of the things I wanted to see is CE-37. While that is being put up, the primary endpoint and many of the other endpoints are averages over periods so there are averages over 4 weeks for the first 4 weeks or they are an average

over 12 weeks for all 12 weeks. An analysis of the primary endpoint was done as a continuous measure. As you recall, the responder variable is a success if the patient has a change of CSBM of greater than or equal to 1. But that variable was also analyzed continuously as a continuous variable. The background standard deviation is 2. So, an improvement of 1 is half a standard deviation. Many times half a standard deviation is thought of as a meaningful effect size.

In this particular display is an analysis that is addressing the extent to which the study validates the primary endpoint. As was previously stated, there were not previous studies that address validation but these studies do address validation. Now, what are the criteria for validation? One criterion is, is the endpoint sensitive to detecting treatment effects, particularly when other criteria detect treatment effects? In these studies other criteria did detect treatment effects and the primary endpoint did as well.

Also, over here you are basically seeing the extent to which there are differences in means of some of these other criteria for responders and non-responders. The magnitudes of those differences in means vary from roughly a half to 70 percent of the standard deviation. So, the differences in means for the responders and non-responders, again by being roughly 50-70 percent of the standard deviation, are reflecting meaningful effect size differences and also reflecting the fact that the primary endpoint responder versus non-responder is, indeed, significantly correlated with other criteria.

Now, I say correlated because whenever you have a dichotomous variable and you are forming the ordinary Poisson correlation coefficient between a dichotomous variable and a continuous variable, that correlation coefficient, if you do the algebra, is proportional to the difference in means for the dichotomous variable. So, the differences in means that you are seeing here are, indeed, proportional to what the correlations would be.

The correlations are scaled by ratios of standard deviations. These differences that you are seeing, as I said, are about 50-70 percent the background standard deviation and, as I said, the criterion of a change of 1 for the CSBM parameter relative to a background standard deviation of 2 was, indeed, about 50 percent of the background standard deviation.

DR. FOGEL: If we can go back to your previous slide, I think there are some other questions. Dr. Metz?

DR. METZ: Thank you. I think a lot has been made today about what the endpoints are and how you can vary what endpoints you are discussing and which one is actually going to be better or not better. I will accept that the bottom line, as Dr. Fogel said, is if you are feeling better, you are feeling better and if you stop the drug you are feeling worse.

Let's go back to that global figure that was shown a little earlier. Do you have those sort of data divided by age? Can you show me the global

response in the elderly population?

DR. DENNIS: We don't have the analysis by age. I just want to reiterate that when we do subgroup analyses the purpose of subgroup analyses is not to prove efficacy. The purpose of subgroup analyses is to see that the effect that you are seeing within a subgroup is consistent with the overall effect and that there are no negative trends.

DR. METZ: That is exactly why it is so relevant. The whole point for me here is that we know that the dangerous potential group are going to be the elderly people who don't necessarily have functional constipation, who have outlet obstruction, who have hypothyroidism that hasn't been realized--those are the people who are going to have a lower response rate but they are the people at most risk for potentially getting into trouble. That is why I want to see that data.

DR. DENNIS: Right. Can I get AQ-17? I first of all just want to reiterate that we did not study this drug for treatment of patients who had

secondary constipation. So, that is not the patient population that we are indicated for.

Let me address the data that we do have by age and gender because I told Dr. Fogel that we would get back to you with these data so you can have a look at that. Just to remind you of what I showed you earlier this morning, this was our primary endpoint. We looked at it by age and gender. Females are in the top row, males in the bottom row. If you look at the younger patient population, which is on the left-hand side and the older population is on the right-hand side, males and females under the age of 65 were seeing a treatment effect. If we look at the older population, 65 years and older, what we see in these 65 year-old patient population is that there is a treatment effect but in each of those different treatment groups. When we look at the males younger than 65, of course, we are not seeing any benefit in that group of patients, which is the smallest group of patients where we had 98 patients.

Can I have the next slide? This is what happens when you take away the IBS-like patients. You can see what happens in that quadrant that looks at the male population.

If we go to the next slide, this is looking at the cut of the data using the FDA responder definition of patients having greater than 3 CSBMs per week. This was the fixed definition with no relation to the baseline.

Let's focus on that younger patient population that are less than 65. Females on the top and males on the bottom. I don't think there is any doubt that we are seeing a significant effect in that male population even given these are smaller numbers of patients that we are seeing here. So, I think when we are looking at that age group, males and females, the efficacy is consistent.

Let's look at the older population. The female population, the results that we are seeing for this particular responder definition are similar to what I have shown you for the primary

efficacy variable as well.

DR. PRIZONT: Let's talk about extrapolation of results from females to males. The difference between placebo and the 6 mg is about 10 percent in females. What is it in males? I think it is about 21 percent.

DR. DENNIS: Right.

DR. PRIZONT: Which, in some ways--this is my view--it may be showing that the response are different and the differences may be real. You know, somebody pointed out that males may have a different response to placebo. There was a higher placebo response. That response may be real. I see some sort of a danger of extrapolating the results that you have in females to the males because, you know, the results, although they seem to be the same, are different in some ways.

DR. DENNIS: But if we are going to look at comparing data and say we are going to accept that the negative data is real and we are not going to accept that the positive data is real--we are looking at these subgroup analyses to determine

whether there are trends. I think that is the issue. Are we seeing negative trends? I think on this slide that I am showing you we are seeing that in that older male population, yes, there is a difference between that group and the other groups that we are seeing here.

DR. CRYER: But, Dr. Dennis, I also recall from Dr. Fogel's earlier request that morning that we are interested in knowing the 12-week durable response and these, as I see it, are 4-week data.

DR. DENNIS: Yes, they are coming. I just wanted to show you these because we hadn't shown them to you earlier on.

Can I have the next slide, please? This is what happens to that FDA responder definition when you take out the IBS-like patients. Again, we see a similar effect to what happened with the primary endpoint.

Slide AQ-160. This is what happens over weeks 1-12. This is in the overall patient population.

If I can have 161, it shows you what

happens when we take out that IBS-like group.

DR. FURBERG: But you are not showing the results at 12 weeks. You are taking the average between 1 and 12.

DR. DENNIS: Correct.

DR. FURBERG: That is not the way to present the information.

DR. DENNIS: Dr. Cook is going to come and respond to that.

DR. LEVIN: Wasn't the previous slide 3 SCBM and this is 1? It is a different metric.

DR. COOK: I think your point is very well taken in terms of your concerns about average versus time point by time point. Now, previous displays have given you results time point by time point. There were any number of displays in the main presentation that went week by week. Fixating on week 12 isn't necessarily that useful in the sense that the patient probably cares about how they are doing every week, and one particular week, like week 12, may or may not be that important compared to the other weeks.

Now, if one only has one number to somehow describe what happens for every week, the average does that. When one wants to know more about what is going on week by week, then one looks at the week by week figures, which are the types of displays that have been presented previously.

DR. D'AGOSTINO: I think the concern is are the 12-week data as you are presenting the week 1-12 so overwhelmed by the early experience, and we want to get that end experience.

DR. FURBERG: Gary, the other thing is if we are talking about treatment for an extended period--this is a chronic condition, and you are mixing in the results after a week or two. I find that misleading. You can present it your way, that is fine, but in addition I think you should be honest and present the data at the end of the treatment period. That is the standard in any treatment comparison.

DR. COOK: Well, again, the sponsor is going for a treatment period of 12 weeks, as I understand, and if a patient's condition is

relieved after 12 weeks they would not receive continued treatment until again they requalified for treatment. So, I do not believe they are asking for an indication where they would be treated continuously, although it is possible that they would be treated for 12 weeks and then, if their symptoms recurred 6 months later, they might get treated for another 12 weeks.

Again, the analyses that showed the displays week by week, which Dr. Dennis can go back to, basically are looking at the real data week by week for each of the criteria. There was an analysis that she showed for percent of people that had a CSBM greater than or equal to 1, a change greater than or equal to 1. There were also analyses she showed that were for actually the mean change. Perhaps maybe she should go back over the week by week displays that are in your handout. But that is addressing the comparisons at week 12. They were not highlighted in graphs like this. But the week by week displays gave you the information at week 12.

DR. BUCHMAN: Could we have a clarification from Novartis actually as to what the indication was that was submitted? Because on the slide that was shown it said nothing about limiting treatment to 12 weeks. Has that changed since this morning?

DR. JOELSSON: No, nothing has changed since this morning, I hope. The indication that we are seeking is for chronic constipation.

DR. BUCHMAN: So, not limited to 12 weeks.

DR. JOELSSON: Obviously, somewhere in the label it will be stated that clinical trials have been performed up to 12 weeks.

DR. SACHAR: Could somebody tell us whether there would be anything useful in taking the 12-week data and dividing it into the first half and second half at least, and seeing whether the first 6 weeks have efficacy and the second 6 weeks have no efficacy? That might be useful information.

DR. JOELSSON: We have shown week by week data--

DR. SACHAR: Right.

DR. JOELSSON: --and we have shown that it is very consistent all the way through the 3 months. We showed many of those slides earlier today.

DR. CUTT: There is one point I wanted to address. The dosage and administration section of the label is where it clearly outlines the 6 mg BID dose for a period of 12 weeks. The indication is what it is indicated for. The rest of the label addresses that.

DR. FOGEL: Dr. Levine?

DR. LEVINE: You had a slide way back where you showed some global symptoms and you compared the two studies, and that was an example where it was difficult to see, in fact, if there was a dose response. I think dose response is something we have to clarify. I heard from Novartis that there was no significant dose response in this study as in the previous IBS study that originally got approved. I heard from Dr. Della'Zanna that there was no difference. Here you

are saying there was a difference, 6 mg was more efficacious than 2 mg. When I look back at the slide you showed a couple of times ago that was up there, that was one of the typical ones where I could not discern a difference between 2 mg and 6 mg. Dr. Della'Zanna said there is no dose response; you are saying there is a dose response. I think in a study like this where there are high placebo numbers and rather marginal changes, I think it is important that we know if there is or is not a dose response in all the various aspects that have been looked at.

DR. JOELSSON: Yes, when it comes to the primary endpoint, as you saw in the European study, 6 mg BID did better than 2 mg BID. In the American study there was no difference. Now, if you look at the overall picture, if you look at all the secondary endpoints, 6 mg BID is more consistent. It is more consistent, significantly better than placebo.

DR. LEVINE: You pooled the difference? Is what we are seeing in the slides the pooled

number--I assume the pooled number, the lumped number of everything when you say there is a difference in spontaneous improvement, etc. using both trials, not just the U.S. trials.

DR. JOELSSON: If you add them together there will be a small difference between 2 mg and 6 mg. I think what you need to do is to look at the overwhelming amount of data, as somebody said here, and if you look at all the endpoints that we have looked at 6 mg BID is more consistent from endpoint to endpoint. That is why we are suggesting 6 mg BID.

DR. FOGEL: Before we deal with questions from the FDA, one last question for Dr. Dennis.

DR. COOK: We wanted to show this week by week display since a number of people have decided that they would rather the difference at week 12 had been the primary endpoint rather than the average over weeks 1-4 or 1-12. This display is showing [not at microphone; inaudible]... and there is no imputation of missing data; this is the actual data, as I understand, and this is the

second study.

PARTICIPANT: You have to speak up.

DR. COOK: Sorry, but the discussion is sufficiently animated and it is easier for me to point sometimes. In this particular display the data at week 12 is the head-to-head comparison of the arms at week 12 for the responder variable, not a pre-stated primary endpoint but a descriptive analysis of the time course, and the differences at week 12 are statistically significant. So, had the primary endpoint been how did the treatment groups compare at week 12 for percent responder, which would be a change from baseline greater than or equal to 1 at week 12, this is the display that sought to address that.

DR. STROM: And you have comparable data on global satisfaction? It goes back to what David was asking for before.

DR. COOK: I believe there was a backup display that showed that. I believe statistical significance applied to that backup display. The effect size was smaller in terms of the magnitude

of the difference. But, otherwise, statistical significance was still there. It also depended upon whether you looked at the global satisfaction, I believe and maybe Dr. Dennis can clarify this, as the proportion who had at least a 1 unit improvement or whether you looked at it as a mean of the scale. I think the former was probably more meaningful. Can you clarify that, Dr. Dennis?

DR. DENNIS: I showed you some data earlier on where we looked at satisfaction, saying how many people belonged to those groups of a great deal satisfied and a very great deal satisfied for 6 out of the 12 weeks and for 2 out of the 4 weeks and, again, we showed statistically significant benefit for those patients.

DR. STROM: But I am looking for what does it look like at 12 weeks.

DR. SACHAR: That is slide 33 and it is the only one that is a bar graph instead of a linear curve.

DR. DENNIS: Here we go. So, this is the pooled data. Just to speak to the question of what

would this look like when we pool the data, we can still see that the 6 mg BID dose is more consistent with this.

DR. BUCHMAN: But in terms of this patient satisfaction though, it is interesting how subgroup analysis is only shown if it shows efficacy and it is not shown if it doesn't show efficacy. If we go back to Dr. Prather's introduction statement, she showed what she said were the only three studies that looked at quality of life in patients with idiopathic constipation. In two of the three they used the SF-36 and in one of the three they used the SF-12. Why are you only doing a subgroup analysis here with one single outcome measure? It is like looking at a tree instead of at a forest. So, the patients are happy with their bowel movements but are they happy with their life? Has it changed their life?

DR. COOK: Typically, in a regulatory environment you have protocol-planned analyses, and all of the analyses have to be planned and one will produce a certain number of analyses on an

all-patient basis for all the endpoints and on the primary endpoint one will do exploratory analyses across a variety of subgroups. Indeed, it is possible to do all possible analyses all possible ways, but at some point one has to decide when one can extrapolate.

DR. BUCHMAN: Well, the bottom line is you didn't do a validated quality of life measure on these patients.

DR. FOGEL: Last comment?

DR. DENNIS: Let me answer that. I think we have to remember that when we look at quality of life measures as an indication of treatment response, that is different to looking at what is the quality of life in a particular population at any one time. When we look at quality of life as a measure of treatment response, disease-specific tools are far more sensitive. All right?

Now, at the time that we did these studies we did not have any disease-specific tools available to us looking specifically at quality of life. So, we did look at the SF-36 and when we

looked at the SF-36--as you know, SF-36 is generic; it is non-specific. Our initial a priori analysis looked at the summary scores only, which is the broadest possible analyses for these scores. On those analyses we did not actually see any significant difference between Zelnorm and placebo. However, we have gone back and looked at the analyses of the individual scores, and this is what you can see on here. Bearing in mind this is a non-specific tool that is not designed to detect a treatment difference, we can see that we show a statistically significant benefit on three out of these eight domains for quality of life, and we see an improvement in all of the domains, albeit small, I give you that, but we are certainly seeing an improvement in quality of life as well.

Discussion of Questions

DR. FOGEL: Thank you. I am going to stop the discussion now and we are going to deal with the questions. the ground rules that we are going to follow are that every member of the committee who is voting is going to be asked for a yes or no

on each question. If you have a comment to make at that time, you can make it. In the interest of time, please try not to repeat what others have said.

Question number one with regard to efficacy, discuss the appropriateness of a primary efficacy endpoint of an increase of greater than 1 complete spontaneous bowel movement per week versus a total of 3 or greater complete spontaneous bowel movements per week. We will start with Dr. Cryer.

DR. CRYER: Well, that is not a yes or no question.

[Laughter]

DR. FOGEL: Good point!

DR. CRYER: We have had a lot of discussion about these various endpoints. You know, I have gone back and forth on this to reach my conclusion that ultimately, irrespective of which subgroup you look at or how you do an analysis and how it is defined, there was some improvement in constipation in the people who received Zelnorm.

What I am more concerned with actually than the quantitative description of number of bowel movements which define this endpoint is the duration of therapy. It is the more durable response of 12 weeks rather than their prespecified endpoint of 4 weeks because this is ultimately going to be a chronic treatment.

So, my answer in brief is that I believe that they have demonstrated in a subpopulation that there is an improvement in constipation, albeit by some people's definition they remain constipated.

DR. FOGEL: Do you think this is an appropriate endpoint? Yes or no?

DR. CRYER: Yes.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: Greater than 3 is obviously a more robust endpoint than greater than 1. I believe greater than 1 is a suitable endpoint.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: In reality, actually the difference between the Zelnorm group responders and placebo is actually only 0.6. So, it is actually

less than 1 if we look at the responders only. But if it was greater than 1, I don't think that that is clinically significant at all because that is subject to variation. If we look at the Rome II criteria, the definition was less than 3. Of course, we can't turn that around and say, in terms of treatment, if you get over 3 you are not constipated but my personal opinion is simply having 1 more bowel movement a week is not sufficient on its own to eliminate constipation so my answer is no.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: If we chose a total of equal or more than 3, I think the sponsor could say that Zelnorm relieved chronic constipation. If we choose equal to or greater than 1, I think the sponsor can say patients with chronic constipation who take Zelnorm will still be constipated but it won't be as bad. I would say it is not adequate.

DR. FOGEL: My vote is that it isn't an appropriate endpoint. I think it is far from the optimal endpoint. I would like to make a

suggestion to the FDA, since this is a huge market and I am sure you are going to see many more functional bowel disease studies in the next months and years, that you consider making the appropriate primary endpoint being subjective global assessment. Dr. Metz?

DR. METZ: I would agree entirely with those statements. I am happy with 1; happy with 3. I like global assessment.

DR. FOGEL: Dr. Levine?

DR. LEVINE: I agree with Dr. Sachar. I am not happy with 1 and I would be happier with greater than 3.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: I agree with that this is an adequate and appropriate endpoint, especially since it was discussed and apparently approved by the FDA.

DR. D'AGOSTINO: My comment is similar. It seems to have been prespecified. It also does correlate fairly well with these other measures. I also agree that the subjective global would have

been a much better endpoint.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: Inappropriate. I don't think it is fully standardized and its clinical relevance has been questioned.

DR. FOGEL: Dr. Strom?

DR. STROM: I am going to abstain, and the reason is I don't think it is a relevant question. I think, no matter how you look at it, we are seeing the same consistent results that the drug works and I think this was agreed upon beforehand and the criteria shouldn't be changed along the way. I think it is an important general broader question, not to this regulatory decision, and we haven't seen the data to be able to answer that, but I think relevant to this regulatory question it is really a non-issue.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: I do believe these patients met the Rome criteria. Actually, in some of the parameters they were stricter to enroll the patients in the study, and to evaluate the efficacy

point they followed the guidelines of the protocol. I do believe that one complete spontaneous bowel movement in patients with this type of very severe constipation adds to their quality of life. So, I do vote yes to the question.

DR. FOGEL: Thank you. Dr. Levin?

DR. LEVIN: I would agree with Dr. Strom's answers. I will pass on this or abstain. I also I think look more favorably on the global assessment.

DR. FOGEL: Thank you. Yes?

DR. BEITZ: Just a clarification on the recommendation for future studies to have as a primary endpoint a global satisfaction score, how would you also factor in the number of bowel movements? We that be composite two co-primary endpoints or a secondary endpoint? Could you say anything at this point?

DR. FOGEL: That is a very tricky question that take more thought than I can give it right now, but I would probably consider it a secondary endpoint.

DR. STROM: I think there needs to be

formal work developing that as a scale. I also think global assessment or some equivalent category makes more sense, but I think there needs to be formal development like you would develop other things. I don't have a problem that SF-36 or SF-12 weren't used because they are not responsive instruments in this kind of situation. You need a responsive constipation-based instrument and there needs to be the basic underlying quality of life work done to develop and validate it accordingly.

DR. FOGEL: Question 1(b), is the population studied representative of patients with chronic constipation? If not, how do the populations differ? We will start with Dr. Levin.

DR. LEVIN: I sort of half pass, but I think I would be remiss not to speak to the fact that in 2004 I am sort of dismayed that the participation by minorities as to race and ethnicity is not much larger in this study. I think sensitivity to the inclusion of ethnic and racial majorities in research is critical and I think it is sort of dismaying, as I said, that

there is so little participation by ethnic and racial minorities.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: During the discussion the point was made that people with IBS and constipation were not excluded from the study, and I think that was a point of contention. However, I do know that it is very difficult sometimes to make the distinction because some people with IBS may not have the symptoms all along and may present with constipation, like functional constipation. Therefore, although I agree and I would like to see more men in the study and more minorities, I do vote yes to the question.

DR. FOGEL: Dr. Strom?

DR. STROM: I think the population is not representative of those with chronic constipation but that is always the case with a premarketing clinical trial so I wouldn't expect the company could have done anything differently from that perspective. I do think there is a major issue in terms of missing--I think it is important to sort

of change the question slightly and emphasize that it is patients with chronic constipation, that is, people who are going to be coming for medical care with chronic constipation and they are mostly going to be elderly, and there clearly was a dearth of elderly here but we will talk about that more in the next question.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: I agree with Brian, the population is not representative. I think, in addition, it is not really well defined; it is a mixed bag.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: I am leaving for the next couple of responses the age and gender, and also the racial discussion, so I am taking this as being the type of constipation was the chronic constipation. They did remove the IBS and it still seemed to be significant. So, I think they have at least a subpopulation that corresponds to chronic constipation.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: yes, I think that this does represent the type of patients that I see with chronic constipation.

DR. FOGEL: Dr. Levine?

DR. LEVIN: I too am waiting for the other questions on the elderly and on males. I would say this does represent a large sub-cohort of patients.

DR. FOGEL: Dr. Metz?

DR. METZ: Yes, age and gender not withstanding, plus potential confounding with irritable bowel, I think this is the kind of patient that walks in the door and ends up in these studies. I have no problem.

DR. FOGEL: I would agree with Dr. Metz. Dr. Sachar?

DR. SACHAR: I would have said no on the basis of age and gender and confounding with IBS, but I think it is a duplicative question and I am going to roll (c) and (d) into (b) and say no.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: I am younger than Dr. Sachar so I would say--

DR. SACHAR: Everybody is younger than me!

DR. BUCHMAN: It actually does fit with the patients that I would certainly see, but I want to add a caveat and I think this is much more important than the rest of the question. That is, there is--if any--efficacy for 12 weeks, not for treatment of chronic constipation in any of these groups regardless of age, sex, gender, ethnic group or the planet that they are from.

DR. FOGEL: Dr. Mangel?/

DR. MANGEL: I agree with Dr. Prather's comment this morning that symptoms don't distinguish constipation subtypes, and Dr. Schoenfeld's comment that treatments are the same regardless, but I don't think this represents chronic constipation. I think the population which was included was a subtype of chronic constipation. The have a functional constipation. So, I say no.

DR. FOGEL: Thank you. Dr. Cryer?

DR. CRYER: I also say no. When you look at the demographic profile of the population that was studied here and then if you were to compare it

to the Pare study, the Canadian study that Dr. Prather showed us earlier, the percentages were quite similar. Fifteen percent of the people were older than 65. However, the thing that really caught my attention was when Dr. Prather spoke about her recent experience of self-reported constipation in older populations. If I remember correctly, it was 40-50 percent of the people in that older population who were self-reporting constipation. So, my suspicion is that if these observations were generalized in clinical practice ultimately, that would be the target population that would frequently request this drug.

DR. FOGEL: Thank you. The next question, only 9 to 16 percent of subjects were greater than 65 years of age and the treatment effect was significantly smaller in older populations. Are these data adequate for an indication that is common in the elderly? Yes or no, Dr. Cryer?

DR. CRYER: Following up on my recent comments, no, and I reached my conclusion when I

saw Dr. Prizont's statistical evaluation of the data in which he concluded that in subjects greater than 65 there was no statistical or numerical difference seen.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: Yes, I need a clarification of the question, if I could. I could read this question one of two ways. The first is that those greater than 65 should be excluded, contraindicated, whatever, in the label. The second interpretation of the question is because there is inadequate number of patients who were greater than 65 should, therefore, the drug not be approved for this indication? And, I just can't tell which way the question is intended.

DR. FOGEL: Dr. Justice?

DR. JUSTICE: It is the former.

DR. MANGEL: I believe individuals greater than age 65 should be excluded. So, I guess the answer is no.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: I would agree with that.

The incidence of diarrhea as a side effect was actually greater than the efficacy in these patients, at 10.5 percent. So, I would actually exclude the elderly from the indication.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: I vote no, which means yes, exclude them.

DR. FOGEL: I believe that the elderly should be excluded. Dr. Metz?

DR. METZ: No.

DR. FOGEL: Dr. Levine?

DR. LEVINE: I would say no, but I would like to point out that over 65 is maybe the elderly but there are a few of us here that don't really want to be called the old-old rather than the early-old.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: I vote no.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: No.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: No, and there is nothing

magic about 65. I think you should run further analyses. If you do your quartile analyses the cut-off maybe should be 55 or 60.

DR. FOGEL: Dr. Strom?

DR. STROM: I think the data are certainly not adequate to prove safety in those aged 65, and they are strongly suggestive of, in fact, safety problems there and lack of efficacy. So, I would support that it should not be used in those over age 65, especially given that they are most of the market.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: I think Novartis should expand their studies to people that are over 65 before they are given the green light so the answer is no.

DR. FOGEL: And Dr. Levin?

DR. LEVIN: No.

DR. FOGEL: The next question, only 9 to 14 percent of the subjects were male and the treatment effect was smaller in males than females. Are these data adequate to support approval of

Zelnorm for use in the treatment of chronic constipation in males? Dr. Levin?

DR. LEVIN: Pass.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: This is a touch one because it was a small number, 220-plus men. However, when they showed us the data this afternoon there was a statistical significance. Actually, it was pointed out that there were more percentage points for the men than the women. I would certainly hate to deny anything to my male counterparts--

[Laughter]

--that women would get. But I do think they need to expand those numbers so I will say the answer is no.

DR. FOGEL: Dr. Strom?

DR. STROM: I agree completely. I think the results are very different than in the elderly. There wasn't evidence of an increased risk. There wasn't evidence of an affirmative difference in efficacy, in contrast to the elderly. On the other hand, the numbers are still small in order to

ensure safety so I too wouldn't want to deny access to men but I would prefer to see more data before affirmatively saying yes.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: No.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: No.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: No.

DR. FOGEL: Dr. Levine?

DR. LEVINE: No.

DR. FOGEL: Dr. Metz?

DR. METZ: I would include men but I think more data are required. It is very interesting to me that in the subgroup analyses we did see differences amongst men but in a regional presentation the odds ratio was absolutely 1 and the confidence intervals went in both directions. So, I think we need more information here. I don't think it is going to be dangerous and, therefore, I would be quite willing to accept it.

DR. FOGEL: I vote no for men. The data

that was presented this afternoon showed a significant effect in the 200 or so patients. The placebo effect was only 6 percent, which is much lower than anything else we have seen. At this moment I would say no but I think that with additional data the answer could be a yes. Dr. Sachar?

DR. SACHAR: As long as we are excluding people over 65, I would say yes for the males because the data looked pretty good for the young men.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: I agree with Dr. Sachar on that. I thought that there was actually some efficacy in the young males. Obviously, the effect we saw in the subgroups this afternoon was a little bit different from the overall effect this morning but that included the elderly males which may have watered down the effect seen in the young males. So, I think young males would be appropriate.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: No.

DR. FOGEL: Dr. Cryer?

DR. CRYER: The data aren't there but the trends certainly are. I didn't see a safety signal of concern in young men and so my sense is yes, consistent with what has been commented before.

DR. FOGEL: The next question, are the clinical trial data adequate with respect to the population of non-IBS patients with chronic constipation that is likely to be treated with Zelnorm? Dr. Cryer?

DR. CRYER: In brief, yes.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: I would say yes with chronic constipation being substituted by functional constipation-predominant.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: I would say yes, although I still have some concern that 15 percent of the patients that entered and completed the trial didn't even have constipation. So, I am not sure how representative everything is.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: Strictly by the numbers, things didn't look bad when the IBS patients were subtracted, but this question specifies a population that is likely to be treated with Zelnorm and, because I think that the people who are going to get treated with Zelnorm are not going to be well distinguished between those with IBS and those without, I would have to say no.

DR. FOGEL: I would say yes. Dr. Metz?

DR. METZ: I have a concern and perhaps I need a clarification of the question. If we are talking about what is really going to go on in the big, wide world when people get their hands on this drug, I have a concern that it may potentially be given to people with other types of disease states and, therefore, I think that the answer would be no. On the other hand, if I look at what the data is as was presented, if you just take the IBS-like patients out, I am quite happy that the drug worked within the definition of the study parameters. So, I think I need a clarification on the question.

DR. FOGEL: FDA?

DR. JUSTICE: It is the population that is likely to be treated that we are concerned about.

DR. BUCHMAN: You mean including secondary causes of constipation?

DR. JUSTICE: Yes.

DR. BUCHMAN: You would be including secondary causes of constipation in that question then? Is that correct?

DR. JUSTICE: Well, any off-label use would be considered--we are specifically concerned about the labeled indication.

DR. BUCHMAN: A lot of people with secondary constipation probably would be treated if it was approved for primary constipation.

DR. FOGEL: Let me just ask the FDA, I assume the assumption is made that if the patient is evaluated and diagnosed appropriately is the drug indicated? You are not taking ownership of medical care across the country, are you?

DR. JUSTICE: That is correct. No, we are not.

DR. FOGEL: Dr. Metz?

DR. METZ: Well, that still doesn't clarify it for me. The bottom line is I can accept this label. I think the safety side is going to have to be well strengthened.

DR. FOGEL: Dr. Levine?

DR. LEVINE: I certainly agree about safety. I also have a concern about the robust amount--how robust this is and I am very disappointed in the figures. So, I am going to abstain.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: I vote yes.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: Yes.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: Well, I am struggling. I think for use over 12 weeks--is it 12 weeks?

DR. FOGEL: Yes.

DR. BUCHMAN: That is not correct. It is chronic; it is not limited to 12 weeks.

DR. FURBERG: That affects my answer. They have data for 12 weeks.

DR. BUCHMAN: It was the statistician from North Carolina that said 12 weeks; he is the only one.

DR. FOGEL: Clarification from the FDA, please.

DR. JUSTICE: Well, I think the sponsor is proposing to limit treatment to 12 weeks.

DR. BUCHMAN: So, the label indication will be 12 weeks?

DR. JUSTICE: Well, in the dosage and administration. In the indication section it will say for chronic constipation, and then in the dosage and administration section they are proposing to say for 12 weeks of treatment.

DR. BUCHMAN: The indication slide actually didn't say 12 weeks. It just said chronic constipation. That needs to be changed.

DR. FOGEL: No, no, no, the indication for the drug is chronic constipation. The duration of treatment is 12 weeks. So, the drug is only being approved for a 12-week course of therapy. I believe that is correct.

DR. CUTT: That is correct because the indication usually addresses the population and the dosage and administration section in the label addresses how you administer the drug.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: Yes, for use over 12 weeks but I am concerned. It should be pointed out that they have no data on long-term efficacy and safety.

DR. FOGEL: Dr. Strom?

DR. STROM: My answer is no and it is really for three reasons. One is that those likely to be treated with Zelnorm are likely to be mostly elderly and we haven't seen that. Second, most of the use I still think is going to be long-term use, regardless of what the label says, and we haven't seen the data on that. The third is the issue of direct-to-consumer ads which are going to have all sorts of people coming out of the woodwork who are not now coming for medical attention for treatment for constipation and would not have been included in the clinical trials.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: My answer is going to be yes if, indeed, the FDA is going to limit the age group of the patients to a population that is represented by the clinical trial.

DR. FOGEL: Dr. Levin?

DR. LEVIN: No for all the reasons that Brian stated.

DR. FOGEL: The next question is as follows, is Zelnorm effective for the treatment of chronic constipation and associated symptoms? Why don't we start with Dr. Metz this time?

DR. METZ: Yes.

DR. FOGEL: Dr. Levine?

DR. LEVINE: As I said, I didn't think it was sufficiently robust but I am going to vote yes if we limit it to the kind of populations that we are all targeting.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: Yes.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: You know, we said we don't have data on the elderly and we talked about

the males, and so forth, but all of those put aside, yes.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: I abstain.

DR. FOGEL: Dr. Strom?

DR. STROM: Yes, excluding the elderly.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: Yes.

DR. FOGEL: Dr. Levin?

DR. LEVIN: I abstain.

DR. FOGEL: Dr. Cryer?

DR. CRYER: It is a yes with a strong exclusion, and I think we really need to look very carefully at the exclusion of the elderly population because of lack of efficacy and of safety signal.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: Yes.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: I think there is a suggestion about some efficacy but not sufficient for me to vote yes. I disagreed with the primary

endpoints. I wasn't involved when that was designed, but that is not my problem. So, that is a no.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: Well, coming from New York, I think I live in the real world and I am going to say no.

DR. FOGEL: I say yes, with the caveats of age and male gender. Dr. Levine?

DR. LEVINE: I am switching my vote from yes to no.

DR. FURBERG: And so do I.

DR. FOGEL: Why don't we re-vote on this just to make sure. You got it? Okay.

The next set of questions deal with safety. Question number one, postmarketing cases of ischemic colitis and serious complications of diarrhea were not limited to patients with irritable bowel syndrome. What are the implications of these adverse events for patients with chronic constipation? Dr. Sachar?

DR. SACHAR: Is that a yes/no?

[Laughter]

I think the implications are that safety is not adequately established, especially in view of the lack of estimate with the population at highest risk being placed in the denominator. So, I am going to say I don't think it is safe.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: Given the fact that new onset of diarrhea in an elderly person who was previously constipated could actually be the only sign of ischemic bowel disease or ischemic colitis, I would have significant concern with that and would have to say no.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: I am sorry, I don't really see where this is a yes/no answer.

DR. FOGEL: It is not a yes/no.

DR. BUCHMAN: Then just strike my last sentence.

DR. MANGEL: Where we are right now, I am not quite sure we could answer this question one way or another, forgetting about the yes/no. I

think we are still going to discuss today, and obviously it won't be resolved today, is there an increased incidence of ischemic colitis in irritable bowel syndrome. The bulk of the events of ischemic colitis were in the IBS patients. I am sure that we have a good handle from the postmarketing data on how many of the constipated patients--I think there were two constipated patients with ischemic colitis but we don't know how many patients received the drug for constipation. I think it is just too early to comment on it.

DR. FOGEL: Thank you. Dr. Cryer?

DR. CRYER: I think we all acknowledge that there is clearly under-reporting in the postmarketing experience, and what I learned from this is that there is clearly a great amount of off-label use, based on the demographics of the prescribing that we saw today and what we know from other therapeutic categories. So, I do not think that 11,600 patients in the clinical trial experience to date are going to be representative

of the older population and their risk for these adverse events. I also was concerned with the very high, 12 percent, incidence of diarrhea in the population that was greater than 65, from these trials. So, the implication for these events as it relates to chronic constipation is that I do have some concern, particularly in these who are greater than 65 years of age.

DR. FOGEL: Dr. Levin?

DR. LEVIN: I would say based on what we heard today there are still serious concerns about the safety profile of the drug.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: I think the sponsor has done a very good job in presenting to us the results of the clinical trial and emphasizing that is young person in the placebo group that developed ischemic colitis. So, it is a very serious diagnosis but I do feel that if we don't address the over 65, we don't lump them into this, they have done a pretty decent job and I don't have as many concerns as with other drugs in terms of ischemic colitis.

DR. FOGEL: Dr. Strom?

DR. STROM: I vote against ischemic colitis and severe diarrhea.

[Laughter]

DR. FOGEL: Okay, thank you. Dr. Furberg?

DR. FURBERG: Those problems represent a serious concern and there should be warning included in the labeling.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: I think there are still concerns.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: Yes, it is serious and I think we are going to come to the warning versus precautions but these are serious complications and the implications are that we have to deal with them.

DR. FOGEL: Dr. Levine?

DR. LEVINE: I agree.

DR. FOGEL: Dr. Metz?

DR. METZ: Yes, implications of these issues--I am very comfortable that this drug works

in the selected population that has been targeted and I don't want to see it denied. So, I would vote to approve but the implications of these issues are that I think we have to be very careful about having the drug get over-used in populations where efficacy hasn't been shown and there might be concerns, primarily the elderly, and I am not sure in my mind what to do about the males but I think the younger males should be getting the drug. So, the implication is that I would limit the access or make people aware of the fact that this isn't something you can just dish out like M&Ms.

DR. FOGEL: I think that the adverse events are something that require additional attention, and I think a proactive postmarketing effort needs to be made to make sure that we actually quantify these adverse events. So, I think it is an issue.

Before we go on to the next questions, we are actually just going to quickly review what we already decided. Tom?

DR. PEREZ: I feel like I am on a runaway

train here. As far as the questions where we have taken clear votes, the first one was 1(c), for which we had a unanimous 13 no's. For 1(d), we had 8 no and 5 yes. Number 1(e), we had 9 yes with caveats in many of them, 3 no, 1 abstained. For 1(f), we had 7 yes, 3 no and 1 abstained.

DR. FOGEL: We are going to move on.

DR. BEITZ: Excuse me, I thought we had two abstentions.

DR. PEREZ: For what?

DR. BEITZ: For 1(f).

DR. PEREZ: One changed so we have one abstention, Furberg changed from an abstention to a no vote.

DR. SACHAR: What about 1(b), did we ever vote?

DR. PEREZ: We didn't have a clear vote on that. Let's see, we had a lot of comments but there was no clear indication of a yes or no.

DR. SACHAR: That is like the last election.

DR. PEREZ: If you would like to take a

vote on that--

DR. FOGEL: Would the committee like to take a vote on question 1(b)? The question that we are going to vote on is, is the population studied representative of patients with chronic constipation? Yes or no? Dr. Levin?

DR. LEVIN: Abstain.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: Yes.

DR. FOGEL: Dr. Strom?

DR. STROM: No because of the elderly issues.

DR. FURBERG: No.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: We went through this in terms of saying that in answering this we were anticipating also (c) and (d). So, excluding the (c) and (d) part in the IBS I said yes.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: Yes.

DR. FOGEL: Dr. Levine?

DR. LEVINE: Yes.

DR. FOGEL: Dr. Metz?

DR. METZ: Abstain.

DR. FOGEL: Yes. Dr. Sachar?

DR. SACHAR: No.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: Yes.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: No, I think it is functional constipation.

DR. FOGEL: Dr. Cryer?

DR. CRYER: No.

DR. FOGEL: Thank you. We are going to move on now--

DR. PEREZ: Wait a minute. We have 5 no, 6 yes and 2 abstentions.

DR. FOGEL: Safety question 2(b), the incidence of diarrhea and discontinuations due to diarrhea was higher in patients greater than 65 years of age. Is there sufficient information that Zelnorm is safe for use in this age group? Dr. Levin?

DR. LEVIN: Resoundingly no.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: No.

DR. FOGEL: Dr. Strom?

DR. STROM: No, and I am also worried about incidence of diarrhea but that diarrhea will have worse implications in the elderly.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: No.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: No.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: No.

DR. FOGEL: Dr. Levine?

DR. LEVINE: No.

DR. FOGEL: Dr. Metz?

DR. METZ: No.

DR. FOGEL: No. Dr. Sachar?

DR. SACHAR: No.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: No.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: No.

DR. FOGEL: Dr. Cryer?

DR. CRYER: No.

DR. PEREZ: Thirteen no.

DR. FOGEL: Question 2(c), do the adverse event data from the clinical trials and post surveillance provide adequate evidence of safety of Zelnorm for the treatment of chronic constipation? Dr. Cryer?

DR. CRYER: I was just reading the question. My answer is no.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: Well, once again, excluding the subgroups which have been spoken about I would say yes.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: I am going to abstain because although in essence it is insufficient but what else can you do, besides get the data from clinical trials and postmarketing surveillance? We don't live in a communistic society or in a society where there is a registry for everybody with constipation.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: In the grand scheme of the world, yes.

DR. FOGEL: For the population under age 65, I think that there is adequate evidence of safety of Zelnorm. But we know from other drugs that with increased use of the drug we will see increased incidence of complications. Dr. Metz?

DR. METZ: Yes, for people under 60, 65, 70, wherever the cut-off ultimately ends up.

DR. FOGEL: Dr. Levine?

DR. LEVINE: yes, if we look at a cut-off of 55, 60, 65 etc. and find a good cut-off.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: yes.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: Yes, with the same comment about the age cut-off.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: No because of the long-term safety.

DR. FOGEL: Dr. Strom?

DR. STROM: Yes for short-term use in young women.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: Yes, with the same caveats for age.

DR. FOGEL: Dr. levin?

DR. LEVIN: No because of the lack of long-term data.

DR. PEREZ: Let's see, question 2(c) had 9 yes responses, 3 no and 1 abstention.

DR. FOGEL: Question 2(d) should the information on the postmarketing cases of ischemic colitis and intestinal ischemia be moved from the precautions section to the warning section of the package insert?

The labeling regulations state that the precautions section of the labeling "shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug." The warnings section "shall describe serious adverse reactions and potential safety hazards, limitations in use

imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." In addition, the warnings section should include any potentially fatal adverse reactions.

So, to re-read the question, should the information on the postmarketing cases of ischemic colitis and intestinal ischemia be moved from the precautions section to the warnings section of the package insert?

DR. LEVINE: Clarification.

DR. FOGEL: Yes?

DR. LEVINE: Is age considered here? In other words, are you going to say a warning for over 65 and no warning for under 65?

DR. FOGEL: FDA?

DR. JUSTICE: No, we are not proposing to separate by age.

DR. BUCHMAN: Actually, I want to ask the FDA one other question for another choice in this.

Because there is no way to prevent ischemic colitis in a patient who you are not suspecting has underlying SMA disease for example, or IMA disease, the only way to prevent it is not to give the drug. That would actually not make it a warning; that would make it a contraindication. So, is the choice actually between a precaution and a contraindication with warning actually not even an issue? Are we actually being asked to choose make the correct choice here?

DR. FOGEL: Hang on one second.

DR. SCHOENFELD: I just wanted to note that the revised labeling, the revised labeling that went into effect in April, specifically says that if a patient develops ischemic colitis they shouldn't get the drug. So, if I understand Alan correctly, if a patient has ischemic colitis it specifically says that you should not prescribe it and that is now in the labeling.

DR. FOGEL: Can we get a clarification from the FDA?

DR. JUSTICE: We are only asking whether

it should be moved from precautions to warnings. We are not proposing a contraindication.

DR. BUCHMAN: But I am asking you whether you should because the thing is that if you have a patient who doesn't have a history of ischemic colitis, because it clearly would be contraindicated in that individual and I think that is probably adequate as it is stated, the question is if there is a risk of ischemic colitis in a patient who is not known to have ischemic colitis, is the drug contraindicated in that individual? If they are on birth control pills for example, should they not receive Zelnorm? That would be a contraindication for example.

DR. FOGEL: We don't have any data to support that.

DR. BUCHMAN: We don't, but then maybe it should stay as a precaution. Because the warning is in between. It means you don't know what decision you should make. If it truly is linked to ischemic colitis, for example, then clearly, in my mind, a young woman who is receiving birth control

pills should not get Zelnorm. If we don't think that it is, then we could leave it safely as a precaution because there is nothing you can do about it, other than not give it.

MS. DINGEMANSE: May I comment? We have done a study in 45 women of childbearing age receiving oral contraceptives, and we also looked at the progesterone levels to assess the lack of ovulation. This was proven. This study has been submitted with the IBS application. So, there is no increased risk of ovulation and also the pharmacokinetics have not changed the ethinyl estradiol and level of norgestrel to a significant level. They are a little lower for the level of norgestrel but there is no change in ethinyl estradiol.

DR. MANGEL: I am reading the question different from Dr. Buchman. Your different severities of regulatory statements, regulatory advice where a warning is more severe than a precaution and where actually a contraindication is a different family of material in the label than

either a precaution or a warning. In reading the question, is the threshold met that this is more severe than a precaution and warrants a warning, rather than starting to evoke whether or not there is additivity or synergism with other populations.

DR. FOGEL: Let me ask the FDA a question. What is the specific issue that you want us to address here?

DR. BEITZ: Well, before we get to that, I want to read you the regulation on contraindications. Under that heading, the labeling would describe situations in which a drug should not be used because the risk of use clearly outweighs any possible benefit. So, it is pretty strong language. Then, further on the regulations say known hazards and not theoretical possibilities shall be listed.

DR. JUSTICE: What we are asking is whether the language that is currently in the precautions section regarding ischemic colitis and intestinal ischemia should be upgraded from a precaution to a warning. We don't think we have

sufficient information to propose a contraindication.

DR. FOGEL: Thank you. Is that clear to the committee? Dr. Levin?

DR. LEVIN: We also had some discussion about the wording of the precaution. Is that appropriate to address? There was some feeling that it was a little too positive a precaution, if such a thing is possible. Forgive my ignorance, is there a medication guide required with Zelnorm? Is that an issue to be discussed today?

DR. JUSTICE: No.

DR. MANGEL: Before the vote, could I just also get a clarification. For me, when I look on the surface it looks like perhaps two and a half months after a label change when, at least my understanding from what I heard today, is that there is not a new signal; there is not a concern to upgrade the safety information within the label, I am concerned about alarming the prescribing community for another "dear doctor" letter to go out saying it goes from a precaution to a warning

when perhaps at one level it is a clarification from your previous conversations with the sponsor. I am curious if it is upgraded to a warning if you have a plan or even a preliminary plan of what the roll-out would be. Would there be a medication guide? Would there be a "dear doctor" letter? You know, what would be the nature of the explanation for the prescribing community?

DR. JUSTICE: The answer to the first question is that one of the reasons we are asking now, after having made these changes, is that if Zelnorm is approved for chronic constipation it would be expanded to a larger population with a potentially different risk/benefit ratio. So, I think it is a new question now.

I think as far as would we request a "dear doctor" letter or med guide, we have not discussed that internally so we are not prepared to give you the answer right now.

DR. FOGEL: Dr. Cryer?

DR. CRYER: I just want to echo comments which Dr. Justice just made which caught my

attention, that is that the approval of Zelnorm for a different indication will clearly lead to an expansion to different populations and a change in the risk/benefit ratio which we have seen to date, and principally younger women.

So, as I read this, what the warnings allow that differ from what the precautions would provide is a mechanism to alert the prescribing physician of what those concerns might be in brief and what we have summarized in our discussions today. The specific mechanisms that I see here in the warnings section suggest a potential safety concern, potential safety hazards and, specifically, limitations imposed by them. So, if there is not going to be any specific differentiation of a warning or a precaution based upon an age of 65, I think that that specific limitation should be implemented using the warning mechanism, specifically age.

DR. FOGEL: Dr. Mangel?

DR. MANGEL: I think the answer is still unknown with respect to IBS versus Zelnorm. I

don't see a signal for chronic constipation but, by the same token, based on the IBS data we wouldn't have seen it yet, not enough patients. I am concerned about upgrading the label with no new information. If this was the original label and you asked should it be a warning for IBS, I would have been comfortable with yes at that point. To change it now, I would say no.

DR. DELLA'ZANNA: I am just going to make a statement. Without knowing the results of whether or not this gets approved or not approved for the chronic constipation, we may be looking at a recent labeling change either way.

DR. MANGEL: And my answer would still be the same. It would be no based upon no new signal. For me, it would have been on the fence but it would have been certainly credible for IBS for there to be a warning versus a precaution. It could have gone either way since there were no cases in 11,000 individuals in clinical trials, which gives us a degree of comfort in terms of the relative rate. To make the change now with no new

data, I would say no.

DR. SACHAR: Even though it says, "in addition, the warnings section should include any potentially fatal adverse reaction?"

DR. MANGEL: Yes. I understand that and, once again, if a drug is given to three million people some people will die. You know, that is where I don't think we have robust enough data to say you have four deaths out of three million and for each of the deaths they were difficult, confounded cases--is that reasonable; unreasonable? Where we sit now, I would say it is not a clear association.

DR. FOGEL: Dr. Buchman?

DR. BUCHMAN: I would leave it as a precaution but with a significant caveat. We don't actually even know what the incidence of ischemic bowel disease is in the general population. I don't believe the data that it is increased in irritable bowel syndrome because that is an oxymoron statement because they wouldn't have irritable bowel syndrome if they had ischemic bowel

disease. But I think that the precaution should be substantially more robust, including not only what we discussed this morning, to make them equal length, but to actually make it longer. I think it specifically should list in precautions that it should be used with precaution in individuals that are taking concomitant oral contraceptives, and who smoke, and who have coexistent or known thrombotic disorders, and I think there needs to be postmarketing surveillance in those particular individuals because those would be at the highest risk for developing ischemic disease and could easily change to a warning or a contraindication, depending on what the results of that postmarketing surveillance would be.

DR. FOGEL: I just want to make sure your answer is yes, it stays as a precaution?

DR. BUCHMAN: No, my answer is no, it stays as a precaution.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: I think the best way to achieve Dr. Buchman's aims is to move it to the

warnings section. I would say yes.

DR. FOGEL: If we exclude those people over the age of 65, I would recommend that it stay as a precaution, and I agree with the comments of Dr. Buchman. Dr. Metz?

DR. METZ: I would say no, I would leave it as a precaution. I think that we have no real data to suggest that the drug has this negative impact. We are all worried about it but there is nothing that is a strong warning to me. I do, however, think it is very important that an additional precaution go into this label, and that is that idiopathic constipation is what it is indicated for. It is not indicated for secondary causes of constipation, and there is potentially concern about efficacy and risk/benefit in people over 65. So, that would be an expansion, I suppose, of the precautions section but that doesn't mean that people won't be able to use it for those specific indications.

On the other hand, I would feel uncomfortable if you took a long laundry list of

all the potential risk factors of thrombotic events because then you are going to be frightening the very people who are going to be using these drugs, and there is no data in my opinion to suggest that smoking has an effect on this particular population, that hypocholesteremia, hypotension, diabetes and other things you might put in. So, I don't think it should be so restrictive.

I am concerned about secondary causes and I am concerned about the risk/benefit ratio in the elderly, but they may well ultimately be people to benefit from this drug.

DR. FOGEL: Dr. Levine?

DR. LEVINE: I would say yes, I would put it in the warnings because in the real world what is going to happen is that this is going to be used much more frequently in non-indicated patients. Number two, I predict, as with Rezulin and a few other drugs, as more patients use it you will begin to see, very likely, signs of ischemic colitis or vasculitis or other types of things that we don't know yet. I would say if you can make a very

strong precautionary note at this point and then change it to a warning when you see the rise in the postmarketing--I think one and a half years is nothing for these figures in postmarketing. You are going to see a huge change, I predict. So, I would vote yes, move it to a warning.

DR. FOGEL: Dr. LaMont?

DR. LAMONT: Yes, I think that there is reasonable evidence of an association although it is not causal, and it is potentially fatal. So, I vote yes, to move it to the warnings section.

DR. FOGEL: Dr. D'Agostino?

DR. D'AGOSTINO: No, I don't see the data justifying it.

DR. FURBERG: I do, yes.

DR. FOGEL: Dr. Furberg is yes. Dr. D'Agostino is no. Dr. Strom?

DR. STROM: I vote yes. I think there are no data; since the "dear doctor" letter came out there is a wave of new adverse reactions. I think there isn't a strong association when you have rates of reported adverse reactions, spontaneous

reports, which are on the same order as the background rate of disease, given the available data. The only argument against that are the data suggesting that maybe people with IBS have a higher rate of ischemic colitis and I don't find that credible but I haven't seen those studies in enough detail to be able to comment on them. I am skeptical.

I feel even more strongly that wording changes that need to be made that were suggested before so that we don't give a quantitative summary of only the absence of an effect and don't provide the quantitative summary where there is an effect.

I think the other reason to put it into warnings is the issue of the elderly, and that this will be overused and shouldn't be used in the elderly, and that needs to be made loud and clear.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: Well, I feel at odds with some of my colleagues but the sponsor presented very good data in primates and in humans in coronary-arteries and mesenteric arteries that

there is no effect of the drug. So, I am puzzles by so much fear that I sense from some of my colleagues. And, we are forgetting the thousands of patients in the clinical trials where there is no evidence of ischemia.

I think the agency and we, ourselves, need to remain credible because if we are going to put in warnings for things that we are just fearful of, I think we are going in a very treacherous way. So, I would say to remain as a precaution rather than a warning.

DR. FOGEL: Thank you. Dr. Levin?

DR. LEVIN: I would move it to warnings and, obviously since I talked about it, I would strengthen the wording to at least be equitable in describing non-events and events.

I would also urge the agency to think seriously about a medication guide requirement because we are relying on patients, and this will be in the package labeling, to report immediately to their physicians certain symptoms that are indicative of serious adverse reactions and I think

patients need to have that information given to them at the time of dispensing. So, I really think, if you haven't thought about it, FDA, you ought to think about requiring a medication guide for this product.

DR. PEREZ: Dr. Levin, you said, yes, move it?

DR. LEVIN: Move it.

DR. FOGEL: Do you want to give us a summary of question two?

DR. PEREZ: Yes, 7 yes, 6 no.

DR. FOGEL: The last question, I will read it and I have a quick clarification question for FDA. The question as written is as follows: Should Zelnorm be approved for the proposed indication of the treatment of patients with chronic constipation and relief of the associated symptoms of straining, hard or lumpy stools, and infrequent defecation?

My question for clarification is as follows, we have had discussion about gender and age exclusions. Is this just a question of what the indication would be, and the modifiers of

gender and age will be added at a later date?

DR. JUSTICE: We can do that of, if the committee wants to revise the question to reflect the discussion about age and gender, they can do so.

DR. FURBERG: Can we also get in duration of treatment?

DR. FOGEL: Can we do that?

DR. BUCHMAN: To be short-term constipation?

DR. FOGEL: No, no, short-term treatment; long-term constipation is the indication.

DR. STROM: Ron, can I suggest two votes? One would be on the unqualified indication, the way it is worded. The second would be an indication for short-term use in young women.

DR. FOGEL: Actually, we have a number of different clauses to consider. Why don't we vote on the main question and we will vote on each one of these special cases.

So, excluding gender, age, duration of therapy, should Zelnorm be approved for the

proposed indication of the treatment of patients with chronic constipation and relief of the associated symptoms of straining, hard or lumpy stools, and infrequent defecation? Yes or no, Dr. Levin?

DR. STROM: Can I just clarify the question again? When you say excluding those--

DR. FOGEL: We will come to all those. Those will be separate votes.

DR. STROM: So, we are voting as written. You are asking for vote on an unrestricted indication.

DR. FOGEL: We are going to vote on the recommendation as written and we are going to add a number of different questions.

DR. STROM: I am still confused.

DR. FOGEL: We are going to vote on the question as written, and then we are going to vote on whether it should be used in people over the age of 65; whether it should be used for males.

DR. LEVIN: That is what the sponsor asked for so we are voting on what the sponsor asked for.

No.

DR. SJOGREN: I am confused. If I vote yes, that means that the sponsor will have no restrictions?

DR. FOGEL: Is that correct, FDA?

DR. JUSTICE: That is correct.

DR. SJOGREN: Then the vote is no.

DR. FOGEL: Dr. Strom?

DR. STROM: No.

DR. FURBERG: No.

DR. D'AGOSTINO: No.

DR. LAMONT: No.

DR. LEVINE: No.

DR. FOGEL: Dr. Metz?

DR. METZ: I am also still confused. If I vote yes, the precautions and warnings and issues are all jacked up--

DR. FOGEL: No, we are voting on what it says.

DR. METZ: Then I have to vote no.

DR. FOGEL: No.

DR. SACHAR: No.

DR. BUCHMAN: No.

DR. MANGEL: No.

DR. CRYER: No.

DR. PEREZ: Unanimous, 13 no.

DR. FOGEL: What I would like to do is start by adding on a number of clauses. Should Zelnorm be approved for the proposed indication of the treatment of patients with chronic constipation and relief of the associated symptoms for females only, for treatment of female patients only?

DR. BUCHMAN: That is excluding age?

DR. FOGEL: We will get to age next. For female patients only?

DR. STROM: You are saying of any age and any duration?

DR. FOGEL: Correct. Dr. Cryer?

DR. CRYER: You asked should Zelnorm be approved for females only?

DR. FOGEL: Right. The question is should we exclude males? Let's phrase it that way, the indication would exclude males from treatment.

[Multi-member discussion]

DR. JUSTICE: Could I just offer a suggestion? Maybe you could just go one by one and say what the exclusion should be.

DR. FOGEL: Okay, I think that is a better suggestion. Dr. Cryer, what exclusions would you like to place on this?

DR. CRYER: Sixty-five or older; no gender exclusion.

DR. MANGEL: Sixty-five or older. I would exclude males and I would change the nomenclature for chronic constipation to either functional or idiopathic constipation,

DR. BUCHMAN: I say no, actually, to anything because we are looking at a completely benign disorder, despite the fact that it affects lifestyle. So, I think that really almost any adverse events are unacceptable, unless the data was really quite robust, and a 10 percent benefit over placebo is not sufficient for me to waive the adverse events. I don't agree, actually, with the primary outcome variable of one bowel movement, and I looked at the three bowel movements which was

statistically significant but not clinically significant. So the bottom line is it is no for me under any circumstance.

DR. FOGEL: Dr. Sachar?

DR. SACHAR: I am with Dr. Buchman on this. We have been here for eight hours and I am convinced that we can squeeze some statistical significance out of these data but, when all is said and done, knowing how this drug is going to be marketed, advertised, prescribed, renewed, continued, passed around and consumed, for me it just doesn't cut it. I vote no approval under any circumstance.

DR. FOGEL: I vote for approval of the drug. I would exclude all individuals over the age 65. I would exclude males and I would vote for a 12-week course of therapy. Dr. Metz?

DR. METZ: I would vote for approval. I would exclude patients over 65. I would have a precaution for males, that the risk/benefit ratio has not been shown. I would suggest that there also is comment on the fact that the studies were

only done for 12 weeks but I don't think it should be restricted to only 12 weeks.

DR. FOGEL: Dr. Levine?

DR. LEVINE: I was going to support what Dr. Buchman said about specific diseases, etc. to exclude. I think the risk is so great that it will be over-utilized, I vote no.

DR. METZ: Forgive me for going back. I feel very strongly that secondary causes of constipation should be considered before people start this drug and I would put that in.

DR. FOGEL: Thank you. Dr. LaMont?

DR. LAMONT: Yes, I vote yes for 12 weeks of therapy in chronic idiopathic constipation, females only, less than 65.

DR. FOGEL: Thank you. Dr. D'Agostino?

DR. D'AGOSTINO: The same.

DR. FOGEL: Dr. Furberg?

DR. FURBERG: The same.

DR. FOGEL: Dr. Strom?

DR. STROM: The same, but only if there was a risk management plan to ensure that, in fact,

it was used that way.

DR. FOGEL: Dr. Sjogren?

DR. SJOGREN: Actually, I would like to say that it is not a benign condition. I have several patients that have undergone surgeries. Some others have contemplated suicide. It is a very serious condition for patients with constipation. We are blessed, I guess, at this table, especially my male colleagues that are not being recruited into these studies--

DR. BUCHMAN: The drug didn't prevent surgery though.

DR. SJOGREN: No, no, but it is a very serious condition. If you can treat it and there is hope with some kind of medical therapy I don't think we should deny it. I vote yes for people that are 65 or younger. I would not like to see men because the data, although very provocative, still needs to be expanded. I think I would not restrict the length of the therapy.

DR. FOGEL: Dr. Levin?

DR. LEVIN: I would vote yes under 65;

women only; 12 weeks of therapy. I would add that there be a medication guide, and I agree with Brian that there be some sort of proactive risk management program, that we do not rely on what the studies tell us isn't very effective, that is, product labeling to do the job of preventing the use of this drug inappropriately in the general population.

DR. FOGEL: Thank you. Any additional information that the FDA would like? Any clarifications that they would like?

DR. BEITZ: Yes, since you brought it up, could you elaborate on the risk management plan that you are thinking about?

DR. STROM: The answer is easy--no. It would not be an easy risk management plan because, obviously, use for IBS is very different and I am not suggesting it get stricter for IBS. How you differentiate that, it is not clear. We need a lot more thought than I have given it, and a lot more creativity I think.

I think my point is I would only be

comfortable with it being available in this way if there was a way of being sure it wasn't going to be overused. I don't know that I can come up with such a way without impairing its use for IBS, which I am not suggesting that we do. I guess one way would be just to look at things like, you know, a medication guide plus a close marketing survey about how the drug is being used, with the idea that if it is being used substantially in people over age 65 or long-term use, which are easy things to measure, that the company has to take major proactive action in order to limit use or risk losing the indication.

Certainly the things we are concerned about--gender, age, duration--are easy things to measure in a postmarketing surveillance study, and I would want to make sure it is not happening, as well as to have the company very, very actively market, plus a med guide in order to prevent that.

DR. FURBERG: Discourage off-label use.

DR. LEVIN: I would agree, med guide, tracking to see how the drug is being used, and

perhaps educational detailing is another method that the company could use to deal with off-label use and to deal with inappropriate use of the drug.

DR. FOGEL: Is there any other--

DR. METZ: I don't want to rush to a defense of the sponsor but a very important point is that the more you make these things restrictive, the more you chase the prescribing doc away and you deny drugs to patients when they certainly work for indications. I think another drug that works exactly opposite to this one has essentially died because of that kind of intervention. So, I would be wary about going overboard here and making it such a big spiel that it is just not going to happen.

DR. FOGEL: Well, I think the other drug died because it was over-prescribed and I think we are trying to save this drug from a potentially similar fate.

DR. LEVIN: The patients also died with the other drug, not just the drug.

DR. SACHAR: I need one comment on the

record because I am taking to heart the comments of Dr. Sjogren and of the patient representative who spoke to us, and I just want to make it clear that when I said I am with Dr. Buchman on this I exclude any implication that this is not a serious condition.

DR. FOGEL: Does the FDA have any other questions, clarifications that they want?

DR. BUCHMAN: I will modify my statement. The word benign is a relative term, and it is benign when compared to ischemic bowel; it is benign when compared to cancer. I, myself, have never had a suicidal patient but it obviously is a problem or we wouldn't be here today. But benign is a relative term only; so is efficacy.

DR. STROM: But I think it is also important to point out that the degree of efficacy we are dealing with here is very marginal. I guess the other thing I would like to add is if we can see analyses of predictors of responders that look in much more detail at some of the kind of things I was asking about before, I would feel much more

comfortable with it being more freely available to people who fit that requirement. My concern is broad use of the drug for a condition where there will be a very high placebo response rate and people are going to think the drug is working--patients and docs are going to think it is working when it is just placebo effect.

DR. SACHAR: you have stated well the basis of my no vote.

DR. FOGEL: Thank you all for your clarifications. At this juncture, I would like to thank the members of the committee. I would like to thank the representatives of the sponsor, Novartis. I would like to thank the FDA. And, we will close the meeting at this time. Thank you, all.

[Whereupon, at 4:45 p.m., the proceedings were adjourned.]

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