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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

AND

DRUG SAFETY AND RISK MANAGEMENT SUBCOMMITTEE

OF THE ADVISORY COMMITTEE FOR

PHARMACEUTICAL SCIENCE

Tuesday, April 23, 2002

8:00 a.m.

Holiday Inn Bethesda
Versailles I and II
8120 Wisconsin Avenue
Bethesda, Maryland

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Julie Beitz, M.D.
Florence Houn, M.D., M.P.H.
Victor Raczkowski, M.D.
Paul Seligman, M.D.

C O N T E N T S

PAGE

Call to Order, Introductions:
M. Michael Wolfe, M.D. 4

Meeting Statement: Thomas H. Perez, M.P.H. 9

Opening Comments:
Florence Houn, M.D., M.P.H. 13
Paul Seligman, M.D., M.P.H. 20

GlaxoSmithKline Presentation

Introduction:
James B.D. Palmer, M.D. 22
Burden of Illness & Efficacy of Alosetron:
Peter Traber, M.D. 30
Safety Assessment and Benefit-Risk Overview:
Eric Carter, M.D., Ph.D. 41
Risk Management Plan:
David Wheadon, M.D. 66
Clinician's Perspective:
Robert S. Sandler, M.D. 82
Summary and Conclusions:
James B.D. Palmer, M.D. 96

FDA Presentation

Introduction:
Victor Raczkowski, M.D. 98
Lotronex: Clinical Trial Experience:
Thomas Permutt, Ph.D. 99
Postmarketing Experience with Lotronex:
Ann Corken Mackey, R.Ph., M.P.H. 110
Lotronex Risk Management Program:
Toni Piazza-Hepp, Pharm.D. 120
Summary and Conclusions:
Victor Raczkowski, M.D. 135

Questions on Presentations 156

Open Public Hearing

Sidney M. Wolfe, M.D. 163
Public Citizen's Health Research Group

Nancy Norton 170
International Foundation for Functional
GI Disorders

Jeffrey D. Roberts 177
Irritable Bowel Syndrome Self-Help Group

C O N T E N T S(Continued)

PAGE

Corey Miller 182
Lotronex Action Group

Gary C. Stein, Ph.D. 189
American Society of Health-System Pharmacists

William Brown, Esq. 194

Lisa Kenney 197

Maria Zargo 202

Julia R. Alberino 207

Terry Olifiers 210

Diana Hoyt 213

Kathleen Kelly Ghawi 217

Bob Morris, Esq. 221

Brenda Compton 224

Dennis K. Larry, M.D. 228

Paul Stolley, M.D. 228

More Questions on Presentations 232

Introduction to Questions and Charge to the Committee:
Victor Raczkowski, M.D. 291

Discussion of Questions 295

P R O C E E D I N G S

Call to Order, Introductions

DR. WOLFE: I am Michael Wolfe. I am Professor of Medicine and Chief of the Section of Gastroenterology at Boston University. I would like to start with introductions around the table. We will start at this end.

DR. SULLIVAN: John Sullivan, clinical pharmacology, Amgen, industry rep for the Safety Committee.

DR. GOLDSTEIN: I am George Goldstein, industry rep for the Gastrointestinal Advisory Committee.

DR. KRIST: I am Alex Krist, Assistant Professor, Virginia Commonwealth University, Family Medicine.

MR. LEVIN: Arthur Levin, Center for Medical Consumers in New York, and a consultant.

DR. COHEN: Mike Cohen. I am from the Institute for Safe Medication Practices. I am on the Drug Safety and Risk Management Subcommittee.

DR. CRAWFORD: Good morning. Stephanie Crawford, University of Illinois at Chicago. I am a member of the Drug Safety and Risk Management Subcommittee.

DR. CAMPBELL: Good morning. Bill

Campbell. I am from the University of North Carolina at Chapel Hill, and Director of the Center for Education and Research in Therapeutics there, from the Drug Safety and Risk Management Subcommittee.

DR. GARDNER: I am Jacqueline Gardner, University of Washington in Seattle, School of Pharmacy, Drug Safety Committee.

DR. DAY: I am Ruth Day from Duke University. I am a member of the Drug Safety and Risk Management Committee.

DR. STROM: Brian Strom, Professor of Biostatistics and Epidemiology, and from the Center for Education and Research in Therapeutics at the University of Pennsylvania, and the Drug Safety and Risk Management Committee.

DR. GROSS: I am Peter Gross. I am Chair of the Department of Internal Medicine, Hackensack University Medical Center, Professor of Medicine, New Jersey Medical School, and I am Chair of the Drug Safety and Risk Management Subcommittee.

MR. PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. METZ: David Metz, University of Pennsylvania, Division of Gastroenterology, and on

the GI Committee.

DR. FLEMING: Thomas Fleming, Chair of the Department of Biostatistics, University of Washington.

DR. LEVINE: Robert Levine, Division of Gastroenterology, State University of New York at Syracuse, Upstate Medical Center, and I am member of the GI Committee.

DR. LaMONT: I am Tom LaMont from Harvard Medical School, Chief of Gastroenterology, Beth Israel Deaconess Medical Center, and I am a member of the GI Committee.

DR. HOLMBOE: I am Eric Holmboe from Yale University. I am a general internist. I am a member of the Drug Safety Subcommittee.

DR. VENITZ: I am Jurgen Venitz, Department of Pharmaceutics, Virginia Commonwealth University, and I am on the Drug Safety and Risk Management Committee.

DR. ANDERSON: Gloria Anderson, Callaway Professor of Chemistry, Morris Brown College in Atlanta, and I am on the Drug Safety and Risk Management Subcommittee.

DR. CRYER: Byron Cryer. I am from the University of Texas Southwestern Medical School in

Dallas, Associate Professor of Medicine, member of the Gastrointestinal Advisory Committee.

DR. RICHTER: I am Joel Richter, Chairman and Professor of Medicine, Department of Gastroenterology at the Cleveland Clinic. I am on the GI Advisory Committee.

DR. RACZKOWSKI: I am Victor Raczkowski, Director of the Gastrointestinal and Coagulation Division at FDA.

DR. HOUN: Florence Houn. I am Director of the Office of Drug Evaluation III, FDA.

DR. SELIGMAN: Paul Seligman, Director of the Office of Pharmacoepidemiology and Statistical Science, FDA.

DR. BEITZ: I am Julie Beitz with the Office of Drug Safety, FDA.

DR. WOLFE: Thank you. I failed to mention I am Chair of the GI Advisory Board for GI Drugs.

This meeting will be hopefully calm, but it is a meeting which has a lot of material to cover, so I am going to ask that persons who speak, try to be succinct and make their point as economically as possible.

We are going to start with the opening

statement by Mr. Perez.

Meeting Statement

MR. PEREZ: I wish I could be succinct, but please bear with me.

Good morning. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a 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.

Dr. Thomas Fleming has been granted a waiver under 18 U.S.C. 208(b)(3) for his unrelated consulting for the sponsor, for which he receives from $10,001 to $50,000 per year; and for his unrelated consulting for four competitors, for which he receives less than $10,001 per year per firm.

Dr. Brian Strom has been granted a waiver under 18 U.S.C. 208(b)(3) for unrelated consulting

for two of the competitors. He receives less than $10,001 per year per firm.

Dr. M. Michael Wolfe has been granted a waiver under 18 U.S.C. 208(b)(3) for his membership on an Advisory Board, regarding unrelated matters, for one of the competitors. He receives less than $10,001 a year.

Dr. Jacqueline Gardner has been granted waivers under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for her Individual Retirement Account with a competitor valued between $5,001 and $25,000.

Dr. David Metz has been granted waivers under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in a competition valued at less than $5,001 and for his spouse's stock in a competitor valued between $50,001 and $100,000.

Dr. Byron Cryer Gardner has been granted waivers under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in a competitor valued at

less than $5,001. Included in the waiver under 18 U.S.C. 208(b)(3) in his writing for a competitor. He will receive less than $5,001 a year.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Officer, Room 12A-30 of 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.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Carlar Blackman, a patient representative, would like to disclose that her supervisor at the University of North Carolina is a consultant of GlaxoSmithKline and Novartis. In addition, a division of the University of North Carolina's Functional GI and Motility Disorders Center has done drug studies on alosetron and tegaserod. Ms. Blackman is not a study coordinator or investigator

and the money received does not directly affect her salary.

In addition, Ms. Blackman is the Executive Director, on an independent contractor basis, of the Functional Brain-Gut Research Group, an international society which receives 90 percent of its financial support from unrestricted educational grants from pharmaceutical companies, including Novartis and GlaxoSmithKline.

Further, she is an Administrative Coordinator working on an independent contractor basis for the Multinational Working Teams to Develop Diagnostic Criteria for Functional Gastrointestinal Disorders, which is also supported by pharmaceutical companies.

Lastly, Ms. Blackman received a job offer from the International Foundation for Functional GI Disorders to become their Executive Director. The Foundation works with all of the pharmaceutical companies.

We would like to note for the record that Drs. John Sullivan and George Goldstein have been invited to participate as non-voting industry representatives, acting on behalf of regulated industry. As such, they have not been screened for

any conflicts of interest.

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 products they may wish to comment upon.

Thank you.

DR. WOLFE: Thank you, Mr. Perez.

We have now opening comments from Drs. Florence Houn and Paul Seligman for the FDA.

Opening Comments

Florence Houn, M.D., M.P.H.

DR. HOUN: Thank you. First, I would like to welcome Dr. Michael Wolfe, who is chairing today's meeting. I would like to welcome Dr. Peter Gross, members of the GI Advisory Committee, and members of the Drug Safety and Risk Management Subcommittee, and other guests and consultants for this joint meeting on the risk management of Lotronex.

I want to thank the staff of GSK, GlaxoSmithKline, and the staff of FDA for preparing for this meeting. I thank members of the public, the patients, the public health advocates and others for their interest in this meeting and their

desire to contribute their views to help FDA make the best possible public health decisions.

This meeting is to obtain advice on the drug Lotronex. Lotronex was approved in February of 2000 for women with diarrhea-predominant irritable bowel syndrome, IBS.

The drug was found effective in providing adequate relief of IBS symptoms. It was associated with constipation and ischemic colitis. During postmarketing in the year 2000, there were cases of severe constipation leading to serious adverse events, such as colonic obstruction and surgery, as well as serious adverse events from ischemic colitis.

A Risk Management Advisory Committee meeting was held in June of 2000 when the initial adverse event reports started coming in. The committee recommended education and communication about safe and appropriate use of Lotronex.

In the fall of 2000, death reports were received. The FDA asked GlaxoSmithKline to either, one, suspend marketing pending another Advisory Committee meeting, or, two, withdraw the drug and for patients with severe disabling IBS, to provide

IND access, and that is a type of access through research noncommercial means, or, three, to severely restrict the distribution of the drug.

GlaxoSmithKline chose to withdraw the drug in November of 2000. GSK did not allow IND access to this drug. FDA and GSK subsequently received hundreds of letters and communications requesting access to this drug by former users who had benefited from the drug's effects.

During the year 2001, FDA and GSK met to see if there was a way to provide access for Lotronex to severely disabled patients. GSK was interested in the restricted marketing of Lotronex. To this end, FDA and GSK worked on labeling, patient and physician agreements, and the medication guide, but we never came to any agreement on the overall Risk Management Program, and therefore, the pieces we did work on were without context.

I think the main hurdle has been the nature of the marketing restrictions and how they are implemented and checked. In the middle of last year, FDA asked GSK to submit all the clinical trials experience with Lotronex, so we could have a full understanding of the risks to better guide

what restrictions in the form of risk management are needed.

This submission was made in December of 2001, and we are here today to review the findings. This Advisory Committee meeting reflects FDA's responsibility in two fields that can be conflicting at times - our responsibility to ensure drugs are safe for marketing and our responsibility that the public has access to drugs that have clinical benefit.

Safe does not mean no risks. All drugs have risks. Some risks are minor and a nuisance, others are life threatening or life ending. Some risks can be managed easily, others are more difficult to manage.

FDA's major means to manage risk is to not approve marketing for a drug, or rarely, we restrict marketing. Restricted marketing under regulatory authority has occurred with four drugs - thalidomide, mifepristone, fentanyl transmucosal delivery system, and bosentan.

Each of these drugs have a risk, such as teratogenicity or predictable need for surgical intervention, or the need for proper disposal to prevent accidental use by children, such that a

program is established to ensure safe drug use through restrictions on patients, restrictions on physicians, and sometimes pharmacists.

Restricted marketing usually means only certain patients get the drug, and only certain physicians can prescribe. The drug is not carried in all pharmacies. If restrictions are not carried out, FDA can withdraw the drug more rapidly than in situations of normal marketing.

In contrast, the major way FDA provides access to drugs with clinical benefits is by approving them for marketing. We also permit investigational access to research drugs in a noncommercial setting called IND access. Contrary to public belief, FDA cannot provide access to drugs by any other means. We don't stockpile drugs, we don't manufacture drugs, we don't conduct drug research trials, we don't run drug access programs. We just don't have the drugs.

We can't force a pharmaceutical company to manufacture or market or conduct research or provide drug access programs. Thus, access to drugs that have clinical benefits, but also possess risk for serious adverse events generates complex tensions between wanting to ease a disease burden

and wanting to protect the public from drug risks.

This Advisory Committee meeting is to help FDA respond to that tension. FDA has been criticized that we don't take IBS seriously. Well, we take all disease and suffering seriously, IBS is no exception.

FDA has been criticized that we have secretly come to an agreement with GSK on the return of Lotronex. This is false. There is no done deal. The Company has made a decision about what they wish to propose for restricted marketing.

We have worked with the Company and discussed many of the controversial issues about Lotronex, such as labeling, but is the labeling final? No. New labeling has not been approved and we need your input on several aspects of this and other issues.

FDA has been criticized for treating Lotronex differently from other drugs. Well, let me say again all drugs have risks. These risks are different in frequency and type. The drug's benefits differ, too. Some very frequent risks are acceptable to the public. Some infrequent rare risks are not acceptable. Risk acceptance and perceptions of risks and benefits are value judgments. Values differ.

There is no uniform absolute way to manage drug risks for different diseases, different drugs, different adverse events, and with different risk tolerances by different people.

The input we seek today is over Lotronex. What is unusual is that Lotronex ceased marketing under safety concerns. GSK has proposed restricted marketing as a means to allow access to this drug. This meeting is to discuss should Lotronex return to marketing, if so, under what conditions, in what patients are the risks of the drug diminished compared to the benefits, who should prescribe the drug, with what expertise, what responsibilities should patients and prescribers assume, what limits and controls are feasible, acceptable, and verifiable, who is responsible for ensuring controls and that the limits are followed, what happens if these controls are not followed, how will success of the program be defined. These are many complex issues.

We hope to hear your best advice. Not only must it be your best advice, but it must be pragmatic if you want if you want it implemented in real time, real life.

Ultimately, FDA will have to make a

regulatory decision and try to negotiate a position with GSK. GSK will have to make decisions, as well. Today, your responsibility is to provide advice to FDA on these important points for negotiation mentioned above - should the drug be marketed, and if so, under what conditions.

Today's discussions do not bind the Agency. It is not a decisionmaking meeting for FDA, it's an advisory meeting. You will be voting on what is your best advice to FDA. The goal for today is to obtain your best thinking on these tough topics to help guide sound decisionmaking.

Thank you for taking your responsibilities and duties to help us seriously.

Now, Dr. Paul Seligman has a few words.

Paul Seligman, M.D., M.P.H.

DR. SELIGMAN: Thank you, Flo, and good morning everyone. I am Paul Seligman, the Director of the Office of FDA's Office of Pharmacoepidemiology and Statistical Science, and I want to welcome all of you to the first public meeting that includes the recently chartered Drug Safety and Risk Management Subcommittee, a subcommittee to the Advisory Committee on Pharmaceutical Sciences.

The purpose of the Subcommittee is to provide expert input in a forum for open public discussion on a wide range of drug safety and risk management issues.

Today, we have convened a special joint committee comprised of members of the Gastrointestinal Drugs Advisory Committee and the Subcommittee members to obtain advice on viable risk management options for the drug alosetron previously marketed under the trade name Lotronex.

The issues we are asking you to tackle are among the most challenging in the world of effective pharmaceutical risk management, and to this end, I look forward to a lively discussion.

On a somber note, I also wish to acknowledge the recent sudden death of Dr. Kenneth Melmon, a member of the Advisory Subcommittee, and a giant in the field of drug safety. His contributions, experience, and wisdom will be missed by all of us and impossible to replace.

Finally, I want to thank you the FDA staff who worked so hard to make today's meeting happen, and want to thank everyone in advance for your input into today's discussion, members of the Advisory Committees, those who have been treated

with Lotronex, and members of the public here to express their concerns and considered views. Thank you all for coming and for being so willing to bring your respective resources and expertise to bear on this important public health issue.

Thank you.

DR. WOLFE: Thank you, Dr. Seligman, Dr. Houn.

I would like to introduce Dr. James Palmer now from GlaxoSmithKline, who will introduce the Company's presentation and also will be introducing all the various speakers for the firm.

GlaxoSmithKline Presentation

Introduction

James B.D. Palmer, M.D.

DR. PALMER: Good morning, ladies and gentlemen, Dr. Wolfe, and members of the Advisory Committee, Dr. Houn, Dr. Gross. My name is James Palmer, Senior Vice President of New Product Development at GlaxoSmithKline.

[Slide.]

I have worldwide responsibility for medical, regulatory, and product strategy for the Company. We are here today to discuss the possible reintroduction of Lotronex to the U.S. market.

Before we begin our formal presentations, I would like to give a brief overview of the history of Lotronex.

[Slide.]

The original NDA was submitted in June '99, and was granted a priority review. The drug came before the GI Advisory Committee in November '99, and received a unanimous approval recommendation. At that time, the issues of ischemic colitis and constipation were discussed very thoroughly at the meeting, and, in fact, the review clock was extended in December to further discuss four cases of ischemic colitis.

[Slide.]

The original NDA was approved on February 9, 2000, with an indication that read, "For the treatment or irritable bowel syndrome in women whose predominant bowel symptom is diarrhea.

There were two prominent product label warnings relating to constipation and ischemic colitis. Specifically, for constipation, this was noted to be frequent dose-related side effect, and resulted in study withdrawal in approximately 10 percent of patients. You will hear a lot more about constipation and ischemic colitis in the

subsequent presentations.

For ischemic colitis, it was noted that it occurred infrequently with a rate of 1 in 100 to 1 in 1,000, and at the time of the drug approval, the rate was, in fact, about 1 in 700, a rate which has remained constant throughout the time the drug was on the market from the clinical trial cases.

It was noted also that a causal relationship between treatment with Lotronex and ischemic colitis had not been established, and specific risk factors for the development of this condition also had not been identified.

[Slide.]

The drug was launched on March the 13th in 2000 in the U.S., and had a very rapid product uptake with about 130,000 prescriptions written by June of 2000.

It was in May that we had the first request for a Risk Management Plan from the FDA following reports of new cases of ischemic colitis. In fact, at that in June, when we met with the Agency, we had 8 cases of ischemic colitis, 3 from clinical trials and 5 spontaneous reports.

We also had cases of complications of constipation, 2 from clinical trials and 4

spontaneous.

[Slide.]

These concerns led to a GI Drugs Advisory Committee in June of 2000, and the primary issues discussed at that time were ischemic colitis and the complications of constipation.

A Risk Management Plan was proposed at that time, and was broadly accepted by the Committee with also the inclusion of a Medication Guide.

Now, from the period from July to October 2000, quite a lot of things happened. First of all, we sent out Dear Physician and Dear Pharmacist letters following the Advisory Committee and the labeling changes relation to ischemic colitis and constipation.

The labeling changes and Medication Guide were introduced, and the elements of the Risk Management Plan were being rolled out into the physician and pharmacist community.

Also, during that time, additional serious adverse events occurred including those with fatal outcome, and we will discuss those at some length in the later presentations.

[Slide.]

This led to November 2000, which was at the time that the drug was withdrawn. We had had multiple discussions with the Agency to explore potential risk management options. These ranged from restriction of the drug, as you have heard from Dr. Houn, all the way to product withdrawal.

I think it is fair to say at that time there was also uncertainty regarding the etiology of the serious adverse events, and there was a great deal of debate at that time about whether there were primarily two entities, constipation and its complications, and ischemic colitis, or whether the paradigm of adverse events that we were seeing was being driven by a single entity, ischemic colitis.

This point is very important in the review of the cases that you see and the overall data during the day.

It is also fair to say that the concerns really at that time had raised about the benefit-risk ratio and how we could have a suitable risk management strategy to manage what were the perceived problems at that time.

We were unable to reach agreement on a viable risk management plan and the product was

withdrawn by GlaxoSmithKline on November the 28th, 2000.

[Slide.]

Following the product withdrawal during December and January 2001, there were thousands of patient testimonies to the drug, both to our own company and to the FDA. Also, many physicians lobbied the FDA and lobbied us about the fact that this drug was very effective, there was a clear unmet medical need for IBS, and I think again many people raised the question that the appreciation and significance of IBS as a disease as it affected sufferers had been underestimated.

That led in January 2001 to the reopening of discussions between GlaxoSmithKline and the FDA about possible market reintroduction.

There were many, many discussions during 2001 about how that might happen, and you have heard some of the details of those from Dr. Houn, but all those discussions culminated at the end of 2001, in December, with a supplemental sNDA submission seeking market reintroduction of Lotronex under restricted access.

[Slide.]

So, we are here today, in April 2002,

looking at the potential product reintroduction for Lotronex, and the question that a lot of people may have is what has changed.

Well, two things have changed, and I would like to go through them very briefly. One is that there is a substantial body of new data available, a lot of data that was not available at the time the drug was approved, and a lot of data that wasn't available at the time we were having all the discussions about the viability of continued marketing of the drug.

On the benefit side, we have a clear understanding and a better understanding of IBS severity and impact, and I am sure that you will hear that very eloquently from the patient testimonies today.

We have clear evidence of sustainability of beneficial effects over nearly a year of dosing, 48-week data which you will see in the presentations.

We have shown beneficial effect across a spectrum of severity of IBS symptoms, and we have also shown positive effects on quality of life and productivity.

On the risk side, we have also seen that

the relative incidence and nature of ischemic colitis from clinical trials has remained consistent since the initial product approval, and this runs at about the rate of 1 in 700.

I think there is increasing clarity that ischemic colitis and constipation are two separate entities in the overall risk profile of Lotronex.

[Slide.]

Secondly, we have a proposed risk management framework which has been developed based on a comprehensive evaluation of all the data, and the platform of this is really on four points.

Firstly, the restriction of the drug to women with diarrhea-predominant IBS who fail to respond to conventional therapy.

Secondly, patient and physician agreement processes about both the knowledge of the drug and the agreement to prescribe the drug.

Thirdly, mandatory prescription sticker and refill provisions, which you will hear details of.

Lastly, a patient/physician education and ongoing evaluation program.

I think all of these will give us a better appreciation of the benefit-to-risk ratio for

Lotronex if the drug is reintroduced.

That is a brief overview of the history of Lotronex. I would like now just to outline the formal presentations for GlaxoSmithKline for the morning.

[Slide.]

All our speakers are from GlaxoSmithKline with the exception of Dr. Robert Sandler, who we are pleased to welcome from the University of North Carolina.

So, without further ado, I would like to ask Dr. Traber to come to the podium to speak about the burden of illness and efficacy of alosetron.

Thank you.

Burden of Illness and Efficacy of Alosetron

Peter G. Traber, M.D.

DR. TRABER: Thank you, James, and good morning.

[Slide.]

My name is Peter Traber. I am the Senior Vice President for Clinical Development and Medical Affairs and the Chief Medical Officer at GlaxoSmithKline. I am also a gastroenterologist.

[Slide.]

Irritable bowel syndrome is one of over 20 functional bowel disorders. The ROME II classification represents a multinational consensus on the definition of these disorders. This important consensus document defines IBS as, "A functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habits, with features of disordered defecation and distension."

[Slide.]

The hallmark symptoms of IBS are chronic or recurrent lower abdominal pain or discomfort associated with features of altered bowel function and bloating.

Although structural or biochemical abnormalities are not found, it is likely that these disorders relate to abnormalities in motility and/or afferent neurosensitivity as modulated by the central nervous system.

[Slide.]

The diagnosis of IBS is made by clinical criteria that were developed by an expert panel and published as practice guidelines by the American Gastroenterological Association. Well-defined and easily applied symptom-based criteria in the

absence of structural or gastrointestinal disease is required for diagnosis.

Following a careful examination, clinical experience indicates that a diagnosis of IBS is rarely missed and the disorder is usually persistent in those who carry the diagnosis.

[Slide.]

IBS is a common disorder affecting up to 20 percent of the U.S. population in epidemiological surveys. The diarrhea-predominant form affects 5 to 10 percent of the U.S. population, representing 25 to 50 percent of IBS patients.

Women are more commonly affected and 30 percent of individuals report moderate to severe symptoms as self-reported in the surveys. These data provide an insight into why IBS is the most common diagnosis in U.S. gastroenterology practices and one of the top 10 reasons for primary care physician visits.

[Slide.]

Despite the benign reputation of IBS, it is increasingly recognized that patients with this disorder have worse health-related quality of life than national norms.

As shown in this one study, health-related quality of life in patients with IBS was worse for most domains when compared to normal and when compared to patients with Type II diabetes. Moreover, IBS patients have a health-related quality of life that is generally comparable to patients with clinical depression., a well-recognized and very serious functional disorder. In fact, vitality and social functioning are equally impaired in both.

[Slide.]

Symptoms of IBS and the resultant diminished quality of life have an impact on productivity. Data from the U.S. Householder Survey, shown here, demonstrated that patients with IBS missed three times as many days from work or school because of illness compared to those with no evidence of a functional GI disorder.

In data not shown on this slide, there is also an impact on health care system and productivity. This same study found that persons with IBS were more likely to see physicians for both GI and non-GI complaints than were persons with no evidence of functional GI disorders.

[Slide.]

These impacts of IBS on the quality of life and productivity result annually in 4 million physician visits, 2 million prescriptions, and countless over-the-counter drug purchases. The financial burden on the health care system and U.S. business in 1998 was estimated to total over $22 billion.

Taken together, this information indicates that IBS is a well-defined condition affecting a large number of individuals and represents a significant burden for both patients and society.

The information I have discussed thus far is well accepted in the medical and scientific community. I will now present some recently obtained data that has the potential to expand our view of IBS.

[Slide.]

As part of our post-approval commitment to FDA, we undertook an epidemiological program to obtain population-based data on background rates for serious events in IBS patients. This was done because of observed adverse events including complications of constipation and ischemic colitis, but also because there is very little knowledge about associated risks and outcomes in IBS

patients.

Dr. Alec Walker, who is Senior Vice President at Engenics, Epidemiology, and Professor of Epidemiology at Harvard, designed and performed these studies and is here today to answer any questions you may have. I will report only a brief summary of the one completed study.

[Slide.]

A retrospective cohort study was performed using medical and pharmacy claims data in the United Healthcare Research Database. Cases were identified through a multistage process including validation by individual chart review.

Because of the number of patients in the database, this approach allows the study of rare or infrequent events at a population level. Cases were identified in individuals with IBS, complications of constipation requiring hospitalization, and those diagnosed with ischemic colitis.

Incidence rates and risk estimate calculations were obtained for patients with IBS and compared to patients without IBS. It is important to note that this study period was before alosetron was introduced to the market.

[Slide.]

This figure shows the relative risk of developing complications of constipation in IBS patients as compared to non-IBS patients. In this graph, we show three different time segments following the first in-plan record of IBS in order to provide a view of how the relative risk changes over time.

The intervals shows are between 3 and 6 months, 6 months to 12 months, and greater than 12 months. The confidence intervals for relative risk are shown above the bars and indicate that the lower confidence boundary is greater than 1 in all situations.

For both men and women, the IBS patients had a marked increase in the relative rate of complications of constipation when compared to patients without IBS, and this relative risk extended out to over 12 months after the in-plan record of IBS.

[Slide.]

This figure shows that the relative risk of developing colon ischemia in IBS patients is also increased as compared to non-IBS patients. The increased risk was not gender specific and

persists 12 months following the in-plan record of IBS.

These results suggest that the risks of ischemic colitis among patients carrying a diagnosis of IBS are substantially higher than the general population. Therefore, ischemic colitis, although unusual in IBS patients, may constitute a distinct part of the natural IBS history or be a result of therapy or a manifestation of other bowel pathology that was misdiagnosed as IBS.

Taken together, these epidemiological data suggest that contrary to the general belief, IBS patients may be at substantially higher risk than the general population for serious medical disorders.

Let me take one more moment to be clear about GlaxoSmithKline's position on the relevance of these emerging epidemiological data to today's discussion. While we believe the data shed important new light on the natural history of IBS, we do not mean to suggest that they reduce the level of concern about risks associated with alosetron and the need for an appropriate risk management plan. Drs. Carter and Wheadon will address those subjects in turn.

[Slide.]

Current conventional therapy for IBS utilizes a stepped approach starting with education and reassurance, followed by dietary modification that may include fiber supplementation. The use of pharmacological agents, most of which are not approved for this indication, is directed at symptoms and has variable results.

Pain and bloating is treated with antispasmodics, and diarrhea and urgency is treated with loperamide or other antidiarrheals.

For individuals who failed this traditional therapy, tricyclic antidepressants or a number of alternative approaches including psychotherapy may be used.

[Slide.]

We were able to catalog what physicians used as traditional or conventional therapy in an open label trial. Two-thirds of patients were treated with antispasmodics, one-third with antidiarrheals, and a quarter with bulking agents. Note that some patients were taking more than one of these classes of therapy. Only 6 percent of patients were placed on antidepressants by their physicians.

[Slide.]

The success of current treatment options in addressing multiple symptoms of IBS has been quite limited. For this reason, there is a large unmet medical need for new and more effective therapies.

Alosetron is a serotonin type 3 or 5-HT3 receptor antagonist. 5-HT3 receptors are on sensory neurons of the gut and mediate gastrointestinal reflexes that control motility, secretion, and the perception of pain.

In patients with IBS, 5-HT3 receptor antagonists increase colonic compliance, slow colonic transit and improve stool consistency. An extensive preclinical and clinical research program of alosetron has established its utility in IBS.

[Slide.]

In contrast to currently available agents for IBS, the efficacy of alosetron has been confirmed in multiple large randomized, controlled trials. Ninety-three clinical trials with alosetron comprise the data in the sNDA. These trial enrolled 11,874 patients, which represents nearly 9,000 additional patients since the original file.

Thus, there is a substantial body of new evidence to evaluate the efficacy of alosetron.

[Slide.]

We found that when IBS patients were asked about their most bothersome symptom, the most frequent answer was abdominal pain, followed by the urgency and the number of bowel movements. Therefore, the primary endpoint of the clinical trials was adequate relief of abdominal pain and discomfort as assessed by the patient.

Urgency to defecate and the number and consistency of bowel movements were secondary endpoints in the trials.

[Slide.]

The efficacy of alosetron, 1 mg twice daily, in women with diarrhea-predominant IBS was established in the original NDA through the results of two, well-controlled Phase III trials. In these pivotal trials, patients with moderate to severe symptoms were enrolled after a two-week screening period.

Alosetron was compared to placebo over 12 weeks, followed by a 4-week period of monitoring to assess symptoms off therapy. The alosetron-treated groups, represented by the yellow lines on these

graphs, has significantly greater improvement in the relief of abdominal pain and discomfort than controls.

This effect was significant within 1 to 4 weeks of treatment initiation. The beneficial effects persisted through the treatment period with no evidence of tolerance, and symptoms returned rapidly upon stopping therapy.

Although not shown on this slide, it is very important to note that there were significant improvements in bowel urgencies, stool frequency, and stool consistency in these patients, and these results have been replicated in five placebo-controlled and two comparator trials.

Finally, alosetron was more effective than therapy with two smooth muscle relaxants, mebeverine, an antimuscarinic, and trimabutene, a peripheral opioid agonist. Both of these agents are widely used in Europe for IBS, but are not approved in the U.S.

[Slide.]

The efficacy of alosetron demonstrated in the original NDA has been significantly bolstered in the sNDA. An important finding is the durability of the alosetron effect. As shown in your briefing

materials, when alosetron was continued for 12 months, the effect over placebo was maintained and symptoms returned to baseline once the drug was stopped. This is important information for prescribing physicians and patients.

On the next slides, I will show additional evidence that there is efficacy in patients with severe and debilitating symptoms and that global IBS symptoms, productivity, and quality of life are improved by alosetron therapy.

[Slide.]

In our discussions with the FDA, the question arose whether patients across the spectrum of severity had relief with alosetron therapy. In order to investigate this issue, we did retrospective subgroup analyses in the six placebo-controlled studies. The weekly adequate relief data were stratified by increasing severities of baseline pain, urgency, and stool frequency.

As shown in this graph, patients with moderate severe pain scores, showed in the first two sets of bars, had greater adequate relief with alosetron than with placebo. Alosetron was also more effective than placebo in patients with

moderate and severe urgency and moderate and severe stool frequency.

Although these analyses are exploratory, they describe patterns of efficacy in moderate and severe patients that are both similar to each other and similar to those seen in patients from the studies individually.

At the same time, patients with harder stools, less urgency, and infrequent stools did not receive benefit and therefore should avoid treatment with alosetron.

[Slide.]

The benefit of alosetron in patients with severe symptoms was further illustrated in two studies completed after approval. As a surrogate for severity, only patients substantially debilitated by urgency were eligible to enter these studies. Enrolled patients in both studies experienced, on average, lack of satisfactory control of bowel urgency on approximately 80 percent of days at baseline.

This graph shows that in both studies, alosetron significantly increased from baseline the percentage of days with satisfactory control of urgency compared to placebo. Control of one's

bowels is a critical issue for patients with IBS.

[Slide.]

To understand the integrated effect of alosetron, we evaluated global improvement of IBS symptoms in the same two studies completed after approval. Global improvement was compared to baseline using a 7-point Likert scale that has been shown to reflect both clinical and quality of life-associated dimensions of IBS.

Alosetron showed improvement over placebo in both studies over the 12-week period. The magnitude of difference between placebo and alosetron in these two studies demonstrates robust efficacy of alosetron in this patient population.

[Slide.]

In this study, we examined the improvement of global symptoms on alosetron compared to traditional therapy as chosen by the principal investigator. At week 4, there was a 40 percentage point increase in the number of responders on alosetron versus traditional therapy, representing a 3-fold enhancement.

Importantly, this effect was maintained through the end of the 24-week study. This is a critical finding because it indicates the robust

effect of alosetron as compared to what is currently used in practice.

[Slide.]

Important new data in the sNDA pertains to patient outcomes as a result of the improvement in clinical symptomatology. In two placebo-controlled studies shown here, alosetron significantly improved productivity as measured by median hours of lost work time as compared to placebo. These data demonstrate that improved symptomatology translated into an important functional improvement.

[Slide.]

Further information on outcomes is shown on this slide. A disease-specific quality of life questionnaire has been developed to measure nine domains important for patients with IBS. Using this measurement tool in numerous studies, alosetron has consistently produced positive improvements over baseline.

Shown on this graph is data from a 12-month study completed since NDA approval demonstrating that patients treated with alosetron were significantly improved in the majority of quality of life domains.

[Slide.]

This graphs shows the quality of life results of the open label comparison study of alosetron versus traditional IBS therapy. Alosetron produced significantly more improvement than traditional therapy in all nine domains.

These data show that improvement in IBS symptoms with alosetron translates into a significant enhancement in the quality of life using a validated IBS-specific instrument.

[Slide.]

We draw two conclusions from this part of the presentation. Alosetron is needed and it works. It is needed because IBS is a well-defined functional bowel disorder which has a large impact on patients, health care, and society.

The fact that alosetron works is supported by a substantial body of new data presented as part of this sNDA. Indeed, it is remarkable that all of the randomized controlled trials met primary endpoints in demonstrating the efficacy of alosetron.

Thus, in women with diarrhea-predominant IBS and moderate or severe symptoms, alosetron produces robust and consistent improvement on

multiple symptom-based endpoints and important function-based endpoints.

I would like now to ask my colleague, Dr. Eric Carter, to come and discuss the safety assessment.

Safety Assessment and Benefit-Risk Overview

Eric Carter, Ph.D., M.D.

DR. CARTER: Good morning, ladies and gentlemen.

[Slide.]

I am Eric Carter. I am Vice President for Clinical Development and Medical Affairs with responsibility for gastroenterology.

I will present a summary of the safety data, as well as an overview of the benefit-risk balance for alosetron. The briefing document, the GSK briefing document provides these data in greater detail, and I will endeavor to refer you to specific sections for guidance.

[Slide.]

The safety focus is on events of special interest, namely, constipation and complications of constipation, as well as ischemic colitis. Special attention will also be given to related outcomes of hospitalization, surgery, and death.

[Slide.]

I will follow the general approach proposed by the CIOMS IV working group for evaluating safety signals and benefit-risk balance for marketed drugs. I will therefore review the weight of evidence for the dominant risks - complications of constipation and ischemic colitis, and related outcomes, hospitalization, surgery, and death.

Our safety database is extensive. It is comprised of data from clinical trials, which is recognized as the most complete and reliable, and therefore used for calculating risk estimates.

We also have a spontaneous safety database obtained from the postmarketing period. Exposure of a large number of patients may enable the identification of infrequent safety events, however, the interpretation of individual cases is often limited by lack of detail.

Early results on the background frequency of complications of constipation and ischemic colitis in IBS from the epidemiology studies were presented by Dr. Traber. Conclusions drawn from these studies will be used for context.

[Slide.]

The approach then has been to review, analyze, and interpret the databases, so as to draw conclusions on risk factors, and from this, on steps that can be taken to mitigate risks, as well as severe outcomes.

Taken together with information on the burden of illness, on therapeutic alternatives and on benefits afforded by alosetron, conclusions on the overall benefit-risk balance of alosetron will be presented as we understand it today.

[Slide.]

This table represents a summary of the events of ischemic colitis and serious constipation, as well as outcomes of hospitalization, surgery, and death related to these events, data from the clinical trials and approval in February 2000, and from the clinical trials and the spontaneous databases for today's Advisory Committee meeting.

You will note that as the clinical trial populations increased significantly from the time of approval until alosetron was withdrawn, the frequency of ischemic colitis has remained essentially unchanged. I will describe these cases, as well as the cases of serious

complications of constipation, in more detail in a moment.

At the time, alosetron was withdrawn in November of 2000, approximately 534,000 prescriptions had been written for approximately 275,000 patients. This is the population for the spontaneous adverse event report.

It is relevant to recognize that the spontaneous safety database has continued to change over time. Indeed, extensive publicity and claims presented by plaintiff attorneys continue to generate new reports or additional information in an ongoing manner. The exact numerator, therefore, will depend on cutoff dates. For our briefing document, we agreed with FDA to a February the 18th, 2002, cutoff date.

You may have noted that the FDA uses a cutoff date of March the 8th, 2002. This was to allow time to process information. The numerator will also depend on how individual cases are classified. Many of the individual cases of special interest, especially in the spontaneous database, are medically complex or contain very little information.

We have discussed these with FDA in order

to decide how best to classify them. We agreed with the Agency in a great majority of these cases. In some cases, after medical consultation with our experts, we reached different medical opinions as to the exact nature of the disease process leading to the outcomes of hospitalization, surgery, or death, and the role played by alosetron.

This may explain some of the differences in our totals, for instance, most notably in the number of deaths that we associate with the use of the drug.

Regardless of the exact numbers, we agree that there are serious risks, and this is what we are here to discuss today.

[Slide.]

Starting then with the constipation data.

[Slide.]

An adverse event of constipation in a clinical trial was recorded when a patient reported having constipation or if four consecutive days passed without a bowel movement.

Serious adverse events of constipation were defined according to the regulatory criteria, which is described in a footnote to page 60 of the briefing document.

Complications of constipation included cases of bowel obstruction, ileus, toxic megacolon, and perforation regardless as to whether these met the serious definition of constipation. Complications of constipation also included cases of impaction when this was a serious adverse event.

[Slide.]

This is a summary of Table 3, which can be found on page 59 of the briefing document, showing the reports of constipation in clinical trial subjects. Constipation was the most frequently reported adverse event. It was reported in a dose-dependent way, 29 percent of subjects on the 1 mg BID dose compared to 11 percent of subjects on the 0.5 mg BID dose.

Withdrawal due to constipation also increased with increasing dose. Note, however, that only about 2 percent of all patients treated with alosetron received the 0.5 mg BID dose. Note also that in most trials, laxative use was not allowed.

[Slide.]

This is a graph of all reports of constipation from Month 1 through to Month 3. As you can see, most of the reports of constipation

occurred in the first month, and indeed, patients that remained in the trials on the whole did not report further constipation.

Seventy-five percent of patients reporting constipation did so in the first month regardless as to whether or not they withdrew. Again, most patients reported constipation only once.

[Slide.]

Turning now to reports of serious complications of constipation. Eleven reports came from patients receiving alosetron in the repeat dose clinical trials. The time to onset varied greatly and most subjects were withdrawn from the trials. Ten out of 11 were hospitalized.

For 9 out of 11 subjects, constipation resolved with conservative therapy. One patient developed a toxic megacolon and underwent a colectomy. One patient developed a small bowel ileus and Crohn's disease was diagnosed at surgery to correct an ileal stenosis.

There were three reports in the placebo group involving obstruction. All resolved, but one underwent lysis of adhesions. One subject in the mebeverine arm of the comparative trial developed severe abdominal pain and constipation and was

withdrawn.

In contrast to the previous slide, this slide demonstrates that the differential rate in all events of constipation between alosetron and placebo is not translated into a similar differential rate of serious complications. Indeed, only approximately 1 percent of patients withdrawing due to constipation did so because of a complication.

Additional details are provided on Tables 4 to 7 in Attachment 2 of your briefing document.

[Slide.]

The cumulative risk calculations, shown on this table, as well as the incidence rates at Month 1 and Month 12. As we saw, most of the adverse events of constipation occurred in the first month of therapy. Cases of serious complications tended to occur more sporadically.

Based on the way serious complications of constipation were defined for the clinical trials, the risk estimates were not treatment related. Also, the incidence rate did not appear to increase over time.

[Slide.]

So, interrogation of the clinical trial

safety database reveals that constipation was the most frequent adverse event reported. It occurred in a dose-dependent manner, mostly in the first month, and mostly once. It was typically managed by withdrawing therapy and instituting routine care including laxatives.

There were reports of serious complications of constipation primarily obstructions and impactions, but also one colectomy and one laparotomy in a patient diagnosed with Crohn's disease.

The events of serious complications of constipation appeared to occur somewhat intermittently.

[Slide.]

Turning now to the marketing experience. Serious constipation and complications of constipation were defined slightly differently for the spontaneous safety database. Firstly, constipation was defined by the reporter.

Cases assessed as having a serious event according to the regulation were then identified. Cases with an event of constipation or related term were then individually evaluated to identify those in which constipation was the event leading to the

assessment of "serious."

Serious constipation associated with complications of constipation were then identified, i.e., perforation, toxic megacolon, obstruction, ileus, and impaction.

[Slide.]

From about 275,000 patients treated with alosetron, we have 100 spontaneous reports of a serious adverse event of constipation with the characteristics that are shown on the table. As was seen in the clinical trials, the time to onset varied, but occurred in the first month in 67 percent of cases.

In 58 of these 100 cases, the serious adverse event of constipation was associated with complications ranging from fecal impaction to perforation. These cases are described in Tables 8 and 9 on pages 69 and 70 of the briefing document.

[Slide.]

Outcomes of special interest associated with the serious constipation are shown in this table. These are listed in order of severity and not duplicated.

There were two deaths. One was an 82-year-old patient prescribed alosetron for

diarrhea-predominant IBS, who was hospitalized for constipation, and died following surgery for a ruptured diverticulum. The patient was concurrently receiving hydrocordone and belladonna, and reported a five-day history of constipation.

The second patient was a 62-year-old woman in a nursing home with Alzheimer's disease and receiving alosetron for the treatment of chronic diarrhea. She underwent surgery to correct Ogilvie syndrome, and was not resuscitated when she developed ARDS.

Intestinal surgeries included partial and total colectomy. Anorectal surgeries involved hemorrhoidectomies and rectal fissure repairs. Other patients were treated conservatively with withdrawal of therapy and the institution of routine care.

Dr. Mark Koruda, Professor of Gastrointestinal Surgery, is with us. He has reviewed these cases and is ready to answer any questions you may have.

[Slide.]

In summary, the clinical presentation of spontaneous constipation reports is similar to that seen for clinical trials. The great majority of

reports were not serious, and managed conservatively. However, there were cases of complications of constipation with serious sequelae and two deaths.

[Slide.]

Risk factors for constipation have been derived from interrogation of the databases and, in particular, by careful analysis of the integrated safety data from the clinical trials.

The United Healthcare Epidemiology Study proposes that patients may be at risk of developing complications of constipation and bowel surgery in association with IBS. Whether or not this applies equally to all subtypes of IBS is not known.

Constipation resulting from alosetron exposure is not unexpected. 5HT3 receptor antagonists slow GI transit and increase saltwater reabsorption from the gut as a class effect.

Constipation appears to occur in a dose-dependent manner with most cases occurring in the first month following initiation of therapy and occurring only once. It also increases with age.

Serious complications of constipation may occur more intermittently. Review of the serious constipation spontaneous cases suggests that

patients with preexisting constipation or co-morbidities that may aggravate the effects of constipation have worse outcomes.

These include patients who have had prior complications of constipation or intestinal obstruction, perforation, diverticulitis, and so on. Likewise, many patients developing complications of constipation were using constipating drugs in addition to alosetron.

[Slide.]

Moving now to ischemic colitis, the second dominant risk.

[Slide.]

Intestinal ischemia represents a broad spectrum of diseases. Ischemic colitis, more properly termed colonic ischemia, acute mesenteric ischemia, and chronic mesenteric ischemia, represent the main types. These are frequently confused.

Actually, each differs in terms of pathophysiology, clinical presentation, natural history, and prognosis, as outlined on the slide. Much more is known about acute and chronic mesenteric ischemia than is known about colonic ischemia at present.

Having said this, we believe that the spontaneous cases described as ischemic colitis in the safety databases represent ischemic colitis, and not acute or chronic mesenteric ischemia. The spontaneous database does contain a number of reports of acute and chronic mesenteric ischemia, which are distinct from ischemic colitis. These cases will also be discussed later.

Dr. Larry Brandt, who is with us, is an expert on intestinal ischemia. He authored the AGA Technical Review and Guidelines on this topic. He is familiar with the data and is available to answer questions as needed.

Dr. Kay Washington is also with us. She is an Associate Professor of GI Pathology, and she is also familiar with the cases and prepared to answer any questions you may have.

[Slide.]

The size of the clinical trial safety database has increased 4-fold since the time of approval in February 2000 until the time of the sNDA, so approximately 12,000 patients. The number of reports of ischemic colitis has also increased from 4 to 17. Thus, the frequency of reports has remained essentially unchanged during this period

at approximately 1 in 700, as reflected in the approved label.

[Slide.]

We have 17 reports of ischemic colitis from the clinical trials, and 12 met the definition of a serious adverse event. Most occurred in subjects less than 50 years of age. There was no apparent dose effect although numbers in doses other than the 1 mg BID are small.

The time to onset was varied, but mostly occurred in the first month. Sixteen out of 17 patients withdrew from the trials. Details of each of these cases can be found in Table 10 in Attachment 3 of the briefing document.

[Slide.]

The clinical presentation was similar in all cases with acute onset abdominal pain and hematochezia. Fifty-three percent of patients were hospitalized for a median duration of three days. Treatment consisted in all but one instance of withdrawal of drug and providing supportive care.

Constipation was reported in 18 percent of cases and estrogen use in 50 percent of cases. These are proportions corresponding to those of the overall clinical trial population.

[Slide.]

In this slide are cumulative risk and incidence rate estimates for the totality of treatment exposures in all trials pooled together. You will note that FDA, in their briefing document, provided several complementary estimates also derived from studies.

FDA also presents a study-specific approach directed at identifying a representative estimate in female IBS patients and in female IBS patients in the U.S.

Our results show that there is a 5-fold increase in the risk of developing ischemic colitis in alosetron-treated subjects compared to placebo-treated control in terms of events per 10,000 patients. This is also reflected in the incidence rates at 12 months expressed in terms of events per 1,000 patient years.

[Slide.]

From the marketing experience, 80 spontaneous reports of ischemic colitis have been received. For a clear interpretation, these were further classified as probable, possible, or insufficient evidence based on the extent of supporting clinical, endoscopic, and pathological

information.

[Slide.]

Only 58 cases met the probable, possible criteria, but summary characteristics are presented on this slide based on available data from all 80 cases. The clinical presentation was similar to that seen in clinical trials with early onset. Most patients were less than 65 years old and 60 percent were hospitalized.

Six spontaneous cases included a report of intestinal surgery. These included two right hemicolectomies and a partial colectomy site unspecified. Brief case summaries are described on page 85 and 86 of the briefing document for these three surgeries. The other three reports did not contain sufficient information.

[Slide.]

In addition to the cases of ischemic colitis, 12 spontaneous serious adverse event reports of mesenteric ischemia, occlusion, or infarction were received. The clinical presentation varied greatly, and interpretation in all cases is confounded by predisposing conditions including intestinal vascular insufficiency, hypercoagulable states, and thrombotic disease.

Given these circumstances, no meaningful signal can be derived regarding a role played by alosetron. Case summaries are shown on page 87 to 90 of the briefing document.

[Slide.]

In summary, then, ischemic colitis generally occurred early in therapy, presenting acutely. It occurred in subjects with a spectrum of baseline symptoms. It was typically transient and resolved without sequelae, and was managed by withdrawing therapy and supportive care. Six spontaneous cases did report surgery. There were no deaths.

[Slide.]

Ischemic colitis appears to be idiosyncratic and so unpredictable. The epidemiological data proposes that having a diagnosis of IBS carries a baseline risk. The risk observed in clinical trials has remained unchanged over the period of the clinical trial program during which the number of exposed subjects has increased approximately 4-fold.

Most of the cases occurred in the first month, although it is recognized that a small number of patients were exposed for more than six

months, however. Despite a concerted analytical effort, no specific risk factors including constipation or other medications have been identified. In other words, there is no evidence that constipation predisposes IBS patients to ischemic colitis.

[Slide.]

What do we conclude then with respect to the benefit-risk balance? Patients with their physician must balance the benefits against the risks when making an informed decision to initiate any new therapy. This will depend on the burden of illness for the patient and what alternative therapies have to offer also in terms of balance between benefits and risks.

As presented by Dr. Traber, IBS is associated with a significant burden of illness that requires treatment for many patients. He also indicated that today, therapeutic options remain limited. IBS, therefore, continues to represent a significant unmet medical need.

[Slide.]

As was also summarized by Dr. Traber, alosetron provides substantial benefits for women with diarrhea-predominant IBS with a spectrum of

chronic and debilitating symptoms.

[Slide.]

The most favorable benefit-risk balance would be achieved by restricting alosetron to women who have failed conventional therapy, and so have no therapeutic alternatives. Conversely, women with episodic or non-debilitating symptoms may not benefit from alosetron and may have an unfavorable benefit-risk balance. These patients would typically be managed with conventional therapy.

[Slide.]

In conclusion, then, the benefit-risk balance for alosetron is positive for diarrhea-predominant women with IBS who have failed conventional therapy. Implementation of the Risk Management Plan including changes to the label will focus on the population most in need, and will mitigate risks. This will provide the most favorable risk-balance for alosetron.

Dr. Wheadon will now take us through the Risk Management Plan. Thank you.

Risk Management Plan

David Wheadon, M.D.

DR. WHEADON: Thank you, Eric.

[Slide.]

I am David Wheadon, Senior Vice President of U.S. Regulatory Affairs at GlaxoSmithKline. I would like to thank the committee for the opportunity to present the risk management framework for the proposed reintroduction of Lotronex.

[Slide.]

Before going specifically into the Risk Management Plan, I would to very briefly revisit the issues of benefit-risk calculations and particularly the benefits and associated risk of Lotronex use.

As you see here, at the beginning of the determination of benefit-risk by the sponsor and the FDA, the sponsor and the FDA, as a joint team, evaluate the assess the benefits and the potential risk for the pharmaceutical treatment under discussion, and communicate such via labeling and other mechanisms to the prescribing community.

The prescribers then are key in determining the benefits and managing the risk for the individual patient for whom the drug is intended. Last, but not least, the patient once informed is the ultimate decisionmaker concerning the balance.

[Slide.]

As we have heard this morning, IBS carries a significant burden of illness, has a significant quality of life impact. It has reduced productivity particularly in the domains of work and school, and perhaps underlying the reason why we are here today, there continues to be limited treatment options.

[Slide.]

As Dr. Traber has outlined this morning, Lotronex has been shown to evidence improvement in moderate and severe IBS symptoms, particularly concerning urgency, frequency, and pain. It has also been shown to have global improvement in IBS symptoms, to have an effect on quality of life particularly around such things as sleep and physical and social functioning, and also has been shown to have a beneficial effect on productivity.

[Slide.]

As Dr. Carter has outlined, there are dominant risks associated with the use of Lotronex particularly constipation, which is an expected outcome given the mechanism of action of Lotronex.

The complications of constipation is an event that is potentially avoidable. Severe

outcomes can be mitigated by early recognition of signs and symptoms and timely intervention.

In terms of ischemic colitis, as best as we know today, this event is idiosyncratic, however, we believe careful monitoring of signs and symptoms is warranted with the overarching goal of mitigating severe outcomes.

[Slide.]

In terms of the Risk Management Plan that we have put before the committee, the overarching goals are as follow:

To restrict use to patients with the most favorable benefit-risk balance. As Dr. Carter has outlined, that continues to be women with diarrhea-predominant IBS who have failed to respond to conventional therapy. Beyond that, as is always true with the use of drugs in treating serious illness, informed patient use is key.

Additionally, with the appropriate adherence to the tenets of the Risk Management Plan, we hope to mitigate serious outcomes of constipation and to mitigate the serious outcomes of ischemic colitis.

[Slide.]

In general, there are certain common core

activities associated with risk management plans.

The evaluation of the benefits and assessment of risk, which we have all heard this morning, but additionally, balancing the benefits versus the risks particularly in identifying the appropriate target population.

Beyond that, the risk must be communicated both in terms of labeling, as well as other mechanisms of communication. The risks should be managed with informed patient use and appropriate prescribing.

Ongoing safety evaluation is key, as is true for the safe use of all pharmaceutical products, and ongoing program evaluation to assess the effectiveness of the plan that has been put in place.

[Slide.]

This schematic is intended to give you in one sort of fell swoop, the overarching goals and tenets of the Risk Management Plan of Lotronex. The physician will serve as the key in determine, first, the appropriate patient for use, that being women with diarrhea-predominant IBS that have failed to respond to conventional therapy, but beyond that, the physician will then sign a form

indicating, one, his or her knowledge and experience in treating IBS and in managing the potential complications of treating IBS, but also sign the form indicating that the patient has been appropriately counseled concerning risk and benefits.

Additionally, an initial titration period is being proposed based on prudent clinical care, that is, a half dose, 1 mg a day, initiation treatment for 30 days. A prescription will be written by their physician with a sticker affixed to the prescription indicating that the appropriate discussions and counseling has occurred.

The patient, once informed, will sign the agreement, as well, indicating that they have been counseled around the benefits and the risks, and the signs the symptoms to be perfect cognizant of.

The patient will then take a copy of the signed agreement form along with the prescription with the affixed sticker to the pharmacy. The pharmacist will serve as a real-time check, checking for the sticker, dispensing the prescription with a Medication Guide.

Following the initial 30-day treatment period, the patient will return to report any

adverse effects and to receive a new prescription, and this is a correction I want you to pay particular attention to - each new prescription will require a new sticker affixed to the prescription. There will be no refills.

Underlying this ongoing process will be the FDA and the company evaluating both the efficiency and effectiveness of the program, but also modifying the program as indicated depending on the outcome of the evaluations.

[Slide.]

Now, to go more specifically into the various responsibilities of the core components of this Risk Management Plan. There is a joint responsibility between ourselves and the FDA particularly around revised labeling.

The labeling has been revised, at least proposed to be revised, with a concise box warning that carries the key safety information particularly that serious gastrointestinal events, some fatal, have been reported in association with Lotronex use, these events including ischemic colitis and serious complications of constipation have resulted in hospitalization, blood transfusion, and/or surgery.

Physicians who are knowledgeable and experienced in treating IBS and in managing the complications should only prescribe the drug.

The indication is limited to women with diarrhea-predominant IBS who have not responded to conventional therapy. Patients will be instructed to discontinue use immediately if symptoms of constipation or ischemic colitis should occur and these occurrences should be reported to the treating physician.

As I mentioned, there is also a modification in terms of the initial titration period starting off at a half dose, 1 mg a day for 30 days to assess patient tolerance to the treatment.

A Medication Guide will be given to the patient both by the treating physician and the pharmacist that will include this key safety information.

Beyond this, we propose to meet jointly with the FDA on a regular basis, for example, quarterly to review the evolving safety information.

[Slide.]

In terms of specific GSK responsibilities,

we are proposing to establish an external expert medical review board to review events of special interest. We will also voluntarily expedite reports of events of special interest regardless of the seriousness or the expectedness.

We will, as well, provide a Dear Physician and Dear Pharmacist letter conveying the key elements of the Risk Management Plan and the labeling changes.

The physician-patient agreement kit will also be provided either via a 1-800 number, described in the Dear Physician letter, or provided via our sales representatives during the introductory period.

[Slide.]

Additional responsibilities that the Company will carry include providing Lotronex and IBS disease information to physicians via sales representatives, and an Internet web site will also be maintained where all the important information will be collated, as well as the ability for physicians to download the patient agreement forms.

[Slide.]

In terms of program evaluation, three studies will be proposed or have been proposed to

look at the safe use of Lotronex. One will target the utilization of Lotronex in a large managed health care research database, the United Healthcare Research database.

This database encompasses 5 million covered lives, and we will look at the appropriateness for therapy for patients that are prescribed Lotronex within this database, specifically focusing on demographic characteristics, IBS history and other GI history, and drugs dispensed in six months prior to Lotronex use or during Lotronex use, specifically to assess whether or not the intended indication and the contraindications have been adhered to.

[Slide.]

A second study will look at the compliance with the Risk Management Plan. This will be a pharmacy-based postmarketing study in association with the Slone Epidemiology Unit of the Boston University School of Medicine.

This study will be conducted in association with a large national retail pharmacy chain. Roughly 2,600 retail pharmacies will participate. Patients that are dispensed Lotronex will be contacted within one week of dispensation

of the drug, and questionnaire will be carried out, again focusing on IBS history, receipt of appropriate counseling regarding benefit and risk of Lotronex use, as well as the receipt of a copy of the agreement form and the Medication Guide.

A follow-up contact will occur 30 to 45 days after the prescription has been filled to assess further patient experience on the drug.

[Slide.]

A third study will focus specifically on Lotronex safety. The occurrence of events of special interest in relation to Lotronex use will be assessed, again using the United Healthcare Research Database.

The incidence of these events in patients receiving Lotronex will be ascertained, as well as the incidence of these events in IBS patients who do not receive Lotronex, in an attempt to further elucidate the possibility of risk factors for these events will be carried out. The target number of Lotronex users will be 10,000 patients.

[Slide.]

Focusing now on prescriber responsibilities. First and foremost, the prescriber will be responsible for appropriate

patient selection based on the modified revised label.

Specifically, in addition to the indicating treatment population, that being women with IBS of diarrhea predominance that have failed to respond to conventional therapy, contraindications will be key, as well.

So, patients with a history of chronic or severe constipation, that with a history of intestinal obstruction, stricture, toxic megacolon, GI perforation, and/or adhesions, a history of ischemic colitis current or a history of Crohn's disease or ulcerative colitis, active diverticulitis or a history of diverticulitis, those patients that are unable or unwilling to comply or understand the patient-physician agreement, and, as always, those patients with a know hypersensitivity to a component of the drug are clearly contraindicated.

[Slide.]

The prescriber will sign the agreement form confirming several things: one, that he or she is appropriate in terms of experience in treating IBS and in managing the potential complications of IBS. The physician will also

counsel the patient on the benefit-risk associated with the use of Lotronex.

[Slide.]

The prescriber will also educate the patients on signs and symptoms that require prompt action, obtain patient's signature on the agreement form, and provide a copy of the agreement form to the patient and place a copy in the patient's medical record.

[Slide.]

Again, these requirements of the prescriber are clearly outlined in the proposed modified label.

[Slide.]

Once this is carried out, the special sticker will be affixed to the prescription. No verbal orders or prescription orders by facsimile will be allowed. No refills will be allowed. Every prescription, both the initiating prescription, as well as follow-on prescriptions, will require the special sticker. As always, the prescriber will be responsible for active patient follow-up to assess patient response to the drug.

[Slide.]

In terms of the pharmacist, the pharmacist

will only accept written prescriptions with an affixed sticker. The pharmacist will, as well, dispense the Medication Guide, which is reflective of the key information associated with safe Lotronex use, and the pharmacist will, as well, serve as an additional resource for product information.

[Slide.]

Moving now to patient responsibilities, perhaps the most important. It is incumbent upon the patient to understand the benefits and the risks associated with Lotronex use. Once informed, the patient will make an informed decision regarding treatment and sign the agreement form.

The patient will be responsible for following the physician and Medication Guide instructions, and perhaps most importantly, the patient will need to be very able to recognize important signs and symptoms requiring prompt action including discontinuing treatment and seeking medical attention.

[Slide.]

Again, the modified label and the Medication Guide will clearly elucidate the responsibilities of the patient in terms of reading

the Medication Guide, not starting Lotronex if they are constipated, discontinuing the drug and contacting physician if certain key symptoms occur during the course of treatment, particularly constipation, worsening abdominal pain, bloody diarrhea, or blood in the stool, and perhaps also, importantly, to stop taking Lotronex and contact their physician if the drug does not adequately control IBS symptoms after four weeks of taking one tablet twice a day, which is the indicated dosage for treatment.

[Slide.]

So, as I have described for you this morning, the Lotronex Risk Management Plan is a thorough plan calling for the active engagement of key participants, namely, the physician, who must attest to their experience in treating IBS and managing its complications, the patient, who must be counseled and clearly sign that they understand the incumbent benefits and risks of Lotronex use, the pharmacist, who will serve as a real-time check in terms of the prescriptions and appropriate stickers applied to it, and counseling the patient and providing Medication Guides, and the Agency and the Company, who will be responsible for evaluating

the effectiveness of the program and modifying the program as might be indicated with experience.

[Slide.]

So, we believe the Risk Management Program put before you is designed to address the benefit and mitigate the risk associated with Lotronex use. The modified conditions of use favorably enhance the benefit-risk by restricting access to women with diarrhea-predominant IBS that have not responded to other conventional therapies.

The communication plan includes messages to prescribers, pharmacists, and patients, the modified package insert and Medication Guide will carry key safety information that is important for the prescriber and the patient to be fully aware of.

The patient-physician agreement process ensures that the appropriate discussion and counseling occurs prior to dispensation of the prescription.

The real-time double check at the pharmacy level provides an additional safety measure to ensure that only the appropriate patients are receiving the drug, and the ongoing program evaluation allows for assessment of effectiveness

of the program.

[Slide.]

This plan, we believe allows for informed patient use, should reduce the occurrence of complications of constipation, should mitigate the serious outcomes associated with complications of constipation and ischemic colitis, and perhaps most importantly, should strike a balance between mitigating risk without creating extraordinary barriers to patient access.

It is pleasure to introduce Dr. Robert Sandler, who will give us a clinician's perspective on Lotronex use.

Clinician's Perspective

Robert S. Sandler, M.D.

DR. SANDLER: Good morning.

[Slide.]

I am Robert Sandler. I am Professor of Medicine and Epidemiology at the University of North Carolina at Chapel Hill.

I am a gastroenterologists and although I don't specialize in IBS, like most gastroenterologists, patients with IBS comprise the largest group of people that I see in my practice.

I am also an epidemiologist and I have

done some research on the epidemiology of IBS. I have authored the Burden of Disease Report from the American Gastroenterological Association, and I have had a chance to read some of the epidemiology background papers that are pertinent for the discussion today.

So, I am here today as a clinician, as a clinical investigator, as an epidemiologist, and what I would like to do in the next 14 minutes or so is to share with you my impressions after reading the briefing documents from the Company and from the FDA.

[Slide.]

So, the topics I am going to cover are listed here. I am going to talk about the economic and social burden of IBS, our treatment options, the benefits and potential risks of alosetron, and I will give you my impressions of the risk management program that has been proposed.

[Slide.]

IBS is a common digestive complaint. The information that we obtained in the Burden of GI Disease Report suggests that there are 15.4 million prevalent cases, 3.6 million office visits, 150,000 hospital outpatient visits, and 87,000 emergency

room visits.

[Slide.]

As you might anticipate with that many health care encounters, the economic costs of IBS are considerable. On this slide, I have graphed the total direct costs from 1998 in millions of dollars. Somewhat unexpectedly, the largest component of those costs are hospital costs. Patients with IBS aren't usually admitted to the hospital, and this reflects secondary diagnosis codes for patients with IBS who were admitted to the hospital for some other reason.

Now, the other costs on here, I think ware more accurate - outpatient hospital costs, emergency room visits, and office visits, and it is somewhat surprising to note that $80 million was spent on drugs. This is surprising because the drugs that we have currently for IBS are not very effective.

So, if we total those direct costs, we come up with about $1.7 billion. We also tried to estimate the indirect costs. These are the costs from people missing work as a consequence of their IBS. That is almost $20 million.

In addition, there are these unmeasured

collateral costs. We know that patients with IBS are more likely to go to physicians for both GI and non-GI conditions.

Although you may quibble with the specific dollar figures, I think that the unmistakable conclusion is that IBS is a very expensive condition.

[Slide.]

The economic analyses ignore social and emotional costs of IBS that are unmeasured and immeasurable. Physicians, policymakers and critics typically pay insufficient attention to conditions that cause symptoms, but aren't fatal.

Let's face it, IBS doesn't commonly kill people, but this lack of appreciation for symptomatic conditions in insensitive and insulting to patients who are suffering.

People who say that IBS is not a bad disease have never taken care of patients with IBS. So, given the high prevalence and high impact, we need therapeutic agents that are effective.

[Slide.]

Unfortunately, there are currently no FDA-approved drugs for IBS that have been proven to be effective in randomized, controlled trials. The

drugs that we commonly use are fiber, smooth muscle relaxants, antidepressants, and anxiolytics. These medications are incompletely effective in the patients who are most severely affected, and they don't work for diarrhea.

[Slide.]

The pharmacologic treatment of IBS was the subject of a systematic review of randomized, controlled trials that was published in the Annals of Internal Medicine in the year 2000. The randomized, controlled trials that were part of that review demonstrated that the only drugs that were effective for IBS were smooth muscle relaxants. They are not available in the United States.

In addition, these randomized, controlled trials did not look at the impact on disability or patients' satisfaction with care.

[Slide.]

In contrast, I think you have seen today there is abundant evidence that alosetron works. This is a graphic that I ran across in the Company's briefing document, and I scanned it in, which accounts for the somewhat uneven quality, but what it does is it look at weekly adequate relief

for women with diarrhea-predominant IBS.

The reason I selected this particular graph is it shows that the duration of effect was 48 weeks, and as a clinician, I am impressed with the durability of the effectiveness of the drug.

[Slide.]

I am also impressed with the wide range of symptoms for which this drug is effective. You have heard this morning about a large number of studies that have looked at a wide range of different symptoms that our patients with IBS bring to the clinic. Again, as a clinician, I am impressed with the wide range of symptoms for which the drug is effective. So, I think there is no doubt that the drug is effective.

[Slide.]

Well, what about risks? Our information about risks comes from several different sources. First of all, it comes from controlled clinical trials, and this is really the best evidence on risk. It is the best evidence because there is a comparison group.

It is also the best evidence because in randomized, controlled trials, patients are monitored very carefully by their physicians, and I

think that, if anything, the adverse events in randomized trials are likely to be overestimated rather than underestimated.

Now, we can also find out about risks from spontaneous reports. The limitation of spontaneous reports is that they may be factually uncertain, incomplete, or imprecise. Importantly, the spontaneous reports are unable to account for cases that are not related to the drug. These are cases that occur as part of the background.

Now, that is not to say that spontaneous reports aren't important. Spontaneous reports can provide a signal for rare events that we could not determine from randomized, controlled trials, even large randomized, controlled trials. So, I don't want to give you the impression that I don't think spontaneous reports are important, but we need to recognize their limitations.

Finally, we can find out about risk from the epidemiology studies. The problem with epidemiology studies is that they can be susceptible to problems of misclassification of disease or exposure, however, they have important strengths.

The large epidemiology studies can rival

the spontaneous reports in their ability to detect rare events. In addition, and very importantly, the population-based epidemiology studies can provide insight into the background rate of disease in the general population that we can use to place the spontaneous reports in context.

[Slide.]

Let's turn to the complications of alosetron. The first is constipation, and based on reading the evidence, there is little doubt in my mind that the drug cause constipation. This is a predictable side effect based on the pharmacologic action of the drug. It's a 5HT3 antagonist that may result in constipation.

However, it appears that the constipation is dose related, it is more common at higher dose, and importantly, in randomized trials with nearly 12,000 patients, so-called complications of constipation were not more frequent in alosetron than in placebo-treated groups.

In the epidemiology study, none of these people got alosetron. In the epidemiology study, IBS patients were more than twice as likely to be hospitalized with these constipation complications than non-IBS patients, suggesting that these

complications may be a part of the disease, and not a consequence of the therapy.

[Slide.]

Now, ischemic colitis is potentially more serious. The collection of randomized, controlled trials suggests that people that take alosetron are about 5 to 6 times more likely to develop ischemic colitis.

All of the cases in clinical trials were self-limited and they did not result in sequelae, and in the epidemiology study, there was about a 4-fold increase in colonic ischemia in IBS patients compared to the non-IBS patients, and I would like to illustrate that with a graphic because I think it is important.

[Slide.]

So, this is the adjusted relative risk, 95 percent confidence interval, of colonic ischemia in 5 million members of the United Healthcare Database. None of these people took alosetron.

The way the slide works, this is relative risk in a log scale. Compared to the non-IBS patients, individuals who had an IBS diagnosis, within three weeks, were almost 50 times more likely to have a diagnosis of ischemic colitis.

Now, how do we interpret that? My interpretation is that these people within three weeks probably didn't have IBS in the first place. They probably had ischemic colitis and within three weeks, the diagnosis was apparent.

However, it is also interesting to note that as long as one year after diagnosis, the patients with IBS were still about 3 to 4 times more likely to have a diagnosis of ischemic colitis compared to the non-IBS patients.

Well, how do we interpret that? I think there is two possible interpretations. The first interpretation would be that patients with IBS are more likely to develop ischemic colitis. A second interpretation is that there is a group of people who have a poorly defined entity that resembles irritable bowel syndrome, but is, in fact, ischemic colitis, and that diagnosis becomes apparent over time.

I think the take-home message from this study is, first of all, we don't understand the entity of ischemic colitis very well, and, secondly, I think that this kind of epidemiology study can provide a context for helping us understand the spontaneous reports, particularly

when we see such a high relative risk within three weeks of diagnosis, suggesting that some of those spontaneous reports may, in fact, not have been due to the drug.

[Slide.]

So, what are my conclusions about risk? With respect to constipation, I think that constipation should be straightforward to manage. Primary care physicians, internists, and gastroenterologists can manage constipation.

The complications of constipation are not more common than placebo in randomized, controlled trials, and constipation may be less frequent with a lower starting dose.

With respect to ischemic colitis, I think that heightened awareness should provide for early detection, and colonic ischemia is almost always self-limited.

I would like to make a couple of comments about risk estimates, because there is lots of risk estimates in those FDA briefing documents, and I would make the following points.

With respect to the risk of ischemic colitis in people who take alosetron, the estimate from the collection of randomized, controlled

trials is 5.4. That means that people that take alosetron are 5.4 times more likely to get ischemic colitis.

But I call your attention to the confidence interval, which is incredibly wide. As a consequence of small numbers, it reflects the imprecision of that estimate.

Now, in the FDA briefing document, you also saw mention of something that many people call the etiologic fraction. This is the proportion of cases that are caused by the drug.

I would simply point out that because of the wide confidence interval around this risk estimate, and because of the questionable assumptions that go into calculating etiologic fraction, I think that that number may be potentially misleading.

Now, perhaps the most useful measure would be attributable risk. This is the excess cases as a consequence of the drug, and our calculations are that there are 3.9 cases per 1,000 per year. The reason this is a useful measure is that we can tell our patients that of every thousand patients who take the drug for a year, 3.9 of them will develop this outcome.

[Slide.]

I would like to end with my impressions of the risk management program. Now, the risk management program is designed to provide the medication to appropriate patients, specifically, women with diarrhea-predominant IBS who have failed traditional therapy.

It is also designed to target appropriate providers, that is, physicians who are experienced and knowledgeable in the management of both IBS and ischemic colitis, who have signed an agreement form, who have counseled patients about risks, safety monitoring, and benefits, who have signed an agreement and placed it in the medical record, and, finally, who have placed a sticker on the prescription and sent it to the pharmacy. This is a lot to ask for busy physicians.

Finally, I don't think we should underestimate the value of the Phase IV studies, the studies that have been proposed by the Company, will monitor whether appropriate patients are receiving the medication, and some of the studies can provide new insights about the risks of the drug and about ischemic colitis.

[Slide.]

So, what are my impressions of the potential impact of the risk management program? It is very clear to me that this risk management program will discourage casual use of this drug. This risk management program is not anemic, it is very onerous, and I think that, if anything, the risk management program might prevent some deserving patients from getting the drug.

The management program will alert physicians and patients to potential side effects and will lead to early termination and evaluation for adverse events.

Now, physicians deal with risk-benefit issues every day. They do that when they prescribe steroids or NSAIDs or immunosuppressors or biologics, and I think in this case of prescribing alosetron is no different.

[Slide.]

So, in conclusion, I would make the following observations.

IBS is a significant economic and social problem. Our therapeutic options are currently limited. Alosetron has demonstrated consistent benefits in rigorous studies and offers advantages to selected patients, specifically, women with

diarrhea-predominant IBS.

The risk management program would limit use to knowledgeable physicians and appropriate patients, and, finally, physicians and patients want the option to use an effective drug. As a clinician, I would use this drug in my patients with IBS.

Thank you.

Summary and Conclusions

James B.D. Palmer, M.D.

DR. PALMER: Let me just make some brief closing remarks.

[Slide.]

I think we have heard in the presentations to date that the reintroduction of Lotronex to patients without suitable therapeutic alternatives is supported by a substantial body of new data, a lot more spontaneous data, and we have nearly 12,000 patients in our clinical trial database.

The proposed Risk Management Plan strikes an appropriate balance between the need to mitigate risk without creating extraordinary barriers to product access.

The last thing I would like to mention, which I think is important, is GlaxoSmithKline's

expectations. If reintroduction is approved, it is our intention to be extremely cautious with this medicine. I think that is a very important point.

We hope we can work with the Advisory Committee and the Agency to achieve a positive outcome and, most of all, help patients with IBS for whom this drug may be effective.

Thank you.

DR. WOLFE: Thank you, Dr. Palmer. I thank you and your colleagues for your presentations.

We are scheduled for a break now, but what I would like to do right before we break is offer the panelists the opportunity to ask for clarification only of any of the presentations by GlaxoSmithKline, not to go deep into depth regarding questions, regarding the drug, rather, clarifications of the presentations.

Are there any questions from the panelists?

[No response.]

DR. WOLFE: If not, we will take a break. We will reconvene at 10:05.

[Break.]

DR. WOLFE: I would like to call on Dr.

Victor Raczkowski from the FDA to start the presentation.

FDA Presentation

Victor Raczkowski, M.D.

DR. RACZKOWSKI: Dr. Wolfe, Dr. Gross, members of the Joint Advisory Committee, invited guests, ladies and gentlemen.

[Slide.]

My name is Dr. Victor Raczkowski. I am the Acting Director of the Division of Gastrointestinal and Coagulation Drug Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

We have consolidated some of our presentations today, so the order will not be exactly as described in the paper copy that was handed to you.

Our presentations will focus primarily on those areas not covered by GlaxoSmithKline or where there are differences in interpretation of the data.

[Slide.]

We will have four FDA presentations. The first presentation will be the clinical trial experience that will be given by Dr. Thomas

Permutt.

The second presentation will be the postmarketing experience with Lotronex that will be given by Ms. Ann Corken Mackey.

Then, Dr. Tony Piazza-Hepp will discuss the Risk Management Program for Lotronex.

I will conclude with a discussion of risk-benefits, as well as some conclusions.

I will now introduce Dr. Thomas Permutt, who will talk about clinical trial issues.

Lotronex, Clinical Trial Experience

Thomas Permutt, Ph.D.

[Slide.]

DR. PERMUTT: I will be talking about some of the safety data from clinical trials of alosetron. Later, you will hear some discussion on the same issues with reference to the postmarketing data. I also have a few words to say about effectiveness, collaborative work with David Hoberman and Zili Li.

[Slide.]

The most basic question is how we quantify the risk of adverse events, so they can properly be weighed against the benefit. I will have part of the answer to that, and an important question in

itself is how the risk varies with the time of exposure.

Once we have some estimate of the risk in the overall population, we have to ask how the risk varies within the population, can we distinguish subpopulations at greater or lesser risk, in other words, can we identify risk factors.

The question of subpopulations is also important on the benefit side. If there are serious risks to be borne, they may, nevertheless, be tolerable in patients for whom the benefit is big. Similarly, if we find subgroups less likely to benefit, we would want to avoid exposing them to the risk.

[Slide.]

The risks that we are most concerned about are serious complications of constipation and ischemic colitis. Let's take complications of constipation first.

As you have heard, there are 11 cases among roughly 11,000 patients treated with alosetron in controlled trials, accrued rate of 1 per thousand. Most required hospitalization, one required surgery. There are also 3 cases in 3,000 placebo patients, as you heard, a nearly identical

rate, and the times of exposure are also comparable, 3 months in most cases.

So, a statistician might stop there except for a feature of the design of the controlled trials. Patients were, of course, monitored closely in the trials, and there were rules requiring discontinuation of certain patients with constipation.

For example, in a single trial which accounted for more than half the cases of serious complications of constipation, 37 percent of alosetron patients experienced constipation, and 12 percent of alosetron patients withdrew for that reason compared to 4 percent incidence and less than 1 percent withdrawals on placebo.

So, the risk of developing complications in a trial was limited by discontinuation in a way that does not necessarily reflect the risk in clinical practice. For this reason, we think the postmarketing experience is particularly relevant for the complications of constipation, as you will hear later.

The other potentially life-threatening risk is ischemic colitis.

[Slide.]

Excluding some studies with fewer than a hundred patients on alosetron, there are 20 controlled trials in our database for alosetron. Among them, as you have heard, they account for 11,000 patients treated with alosetron mostly for three months. Ischemic colitis occurred on alosetron in 8 of these studies. There was also a single case of ischemic colitis in a placebo patient.

What I have plotted here is Kaplan-Meier estimates of cumulative incidents at three months with 95 percent confidence intervals from the 8 studies that had cases on alosetron.

Considering all 20 studies, including the 12 with no cases, the pooled cumulative incidence is 2 per thousand at three months, and I have marked that with this horizontal line.

Now, there is some indication of heterogeneity among the studies. I have to call your attention especially to Study 20, this one here. More than half the cases occurred in this study. It was of six months duration, but again for comparison, what I have plotted here is the three-month cumulative incidence.

The confidence interval here barely

touches the pooled rate. So, there is some reason to think this study is really different. Of course, it comes to our attention after the fact precisely because the rate is different, so the difference may not be as remarkable as it would seem, but if it really is different, one reason to consider is the possibility of better ascertainment of ischemic colitis in this large study that took place relatively late in the course of development, after the investigators were already sensitive and especially looking for ischemic colitis.

Anyway, if you look at this study alone, you get an estimated three-month incidence of 5 per thousand compared to the pooled rate of 2 per thousand.

[Slide.]

What do we know about the risk over time? I have borrowed a figure from the applicant's background package to illustrate this. They have used a slightly larger pool of studies with about 12,000 patients, but it makes very little difference here.

The first thing I want to say is there is a lot of useful information in this picture, but hardly any of it is in the right half, that is, the

time after six months. Only 700 patients were exposed to alosetron for more than six months in these trials compared to 12,000 in the first month.

This here is one case of ischemic colitis after six months, which happened to be in a placebo patient. So no, there is no real reason to think what seems to show in the picture. There is no real reason to think the risk with alosetron levels off here, nor is there a real reason I think to think that the placebo rate catches up to it.

[Slide.]

That is better. This is the left half of the same graph. Over the first six months, and especially the first three months, we do have information. Now, what is plotted here is the cumulative risk, that is, if a patient takes the drug for three months, say, what is her risk of getting ischemic colitis at some time during those three months.

Well, it is about two-tenths of 1 percent of 2 in a thousand, as I said before. Now, this risk continues to rise of over six months, well, it can't get down. The longer I observe you, the more likely you are to have had the event, but the point is it doesn't really flatten out either.

The slope of this curve, what is called the hazard, does seem to be bigger in the first month than in the second through six months, maybe as much as double, but not statistically significantly bigger because we are still looking at small numbers of events with a lot of uncertainty.

In any case, although the cumulative risk may rise less steeply later on than in the first month, there is every reason to think that it continues to rise. How high it might rise after more than six months, I am not in a position to say, and I don't think anyone else is either. Unfortunately, this is what you really want to know if you are a patient contemplating alosetron over a long period.

I heard Dr. Carter say that most cases of ischemic colitis were in the first month, and this is true. It is not as impressive as it might sound because most of the studies were three months long, so you would expect to see a third of the cases in the first month. In fact, we saw somewhat more, but not dramatically more than that.

So, it is not as if you are out of the woods after a month or three months. Rather, it is

partly that most of the cases were where most of the treated patients were. If we watched people for a year or more, many people, or even for six months rather than only for three months, we might not expect most of the cases to be in the first month.

[Slide.]

What about risk factors? Well, a number of risk factors for ischemic colitis are known in general populations, but here, in the trial data with alosetron, we have been unable to identify subgroups more or less likely to develop ischemic colitis. That doesn't mean there aren't any. What it means is with 18 cases of ischemic colitis, we haven't been able to figure out what distinguishes the cases from the non-cases.

What that means is so far as we can tell, everybody who takes alosetron shares the risk of developing ischemic colitis.

[Slide.]

If the risk is unavoidable, are there patients in whom it is tolerable in relation to a large benefit? In this connection, I would like to discuss some of the data on urgency and also comment briefly on some of the productivity data

that Dr. Traber showed you.

[Slide.]

Four studies focused on an urgent need to go to the bathroom. I have pooled together two relatively early studies and also separately two later studies in which the patients were worse off at baseline. Looked at a subset of patients who began the study, reporting urgency more than five days a week, and counted how many of them finished the three-month study reporting urgency less than two days a week. There are other ways to cut it with similar results.

In the first two studies, it was 32 percent compared to 19 percent with placebo, and in the two later studies, it was 50 percent compared to 29 percent for placebo. So, in this group of patients with a lot of room to improve, substantial numbers of them did improve a lot.

[Slide.]

Now, we have heard about the burden of irritable bowel syndrome in terms of time lost from work among other things. This would also be a natural place to look for big benefits. The sponsored show these data in a slightly different form, and again I have cribbed a graph from their

background package.

There are unquestionably statistically significant differences between alosetron and placebo in the hours of work lost, but I want to call your attention to the scale here, if you can see it.

The differences between treatments are on the order of an hour a week or a day every couple of months, and they are less than this spontaneous improvement that you see with placebo.

[Slide.]

So, we have some evidence of a big benefit in urgency, not so much in productivity. We should also look for groups less likely to benefit, so as to avoid needless risk for those patients. The sponsor has been able to identify a few such risk factors for lack of efficacy, as you heard, in particular patients with hard or very hard stools, or fewer than two stools per day were less likely to be successfully treated than others.

You might also suspect that such patients could be at higher risk for complications of constipation although we don't know that.

[Slide.]

I posed a number of questions at the

beginning, and here is what I think we know about the answer. What is the risk? Well, for complications of constipation, we don't see any excess risk compared to placebo in the controlled trials, but this may be partly because many patients with constipation were discontinued from the controlled trials before they might have developed complications.

For ischemic colitis, there is an excess risk, as you have heard, of 2, maybe as much as 5 per thousand over three months. How does it change over time? Well, the cumulative risk continues to rise over six months although perhaps less steeply after the first month.

After six months, we have too little information to know, and it is something a patient should want to know.

Risk factors for ischemic colitis in patients treated with alosetron have not been identified. As far as we know, everyone who takes alosetron shares the risk.

Some patients with a lot of room for improvement did improve a lot. In contrast, patients with harder, less frequent stools at baseline did not benefit much.

Thank you for your attention. You are going to hear next from Ann Mackey of the Office of Drug Safety about the postmarketing experience.

Postmarketing Experience with Lotronex

Ann Corken Mackey, R.Ph, M.P.H.

MS. MACKEY: Hello. I am going to talk about the postmarketing experience with Lotronex.

[Slide.]

This presentation is a collaboration between Dr. Allen Brinker, Dr. Zili Li, and myself.

[Slide.]

This is an outline of my presentation.

[Slide.]

First, I want to talk a little bit about the Adverse Event Reporting System commonly known as AERS. It is a spontaneous, voluntary surveillance system. It is voluntary reporting by health care professionals and consumers, and mandatory reporting by manufacturers. To date, we have over 2 million reports in the database.

[Slide.]

Some of the strengths of AERS. It provides for early detection of signals, it identifies rarely occurring adverse events, and it captures information that clinical trials are not

able to capture, such as off-label use, use in patient populations other than those studied, drug combinations, and use in contraindicated conditions.

[Slide.]

Some of the limitations of AERS. It cannot reliably estimate true incidence rates of events because the number is underestimated, and the denominator can only be projected. It is subject to under-reporting. We have evidence that only 1 to 10 percent of adverse events get reported to FDA.

There is no certainty that the drug caused the event. It may have been due to underlying disease, concomitant medications, or any other number of factors.

[Slide.]

In our case series, we looked at ischemic colitis, small bowel ischemia, and serious complications of constipation. The ischemic colitis and serious complications of constipation cases are mutually exclusive. If the co-exist, then, the case was linked to ischemic colitis. All small bowel cases were discussed separately.

We captured reports received through March

8th, 2002. You heard the sponsor say their cutoff date was February 18th, 2002. This would allow for reports to be received and processed by the FDA.

[Slide.]

Reports received after the market suspension of Lotronex have come primarily from consumers and available clinical data are not comprehensive. More recently, reports have come from class action lawsuits, and again available clinical data are not comprehensive.

Reporter follow-up was intensive prior to the market suspension.

[Slide.]

First, we will talk about ischemic colitis. Our case definition was based on any or a combination of the following: the term "ischemic colitis" is explicitly used in the AERS report as a possible diagnosis; any endoscopic or histologic evidence of ischemic change or necrosis; or any radiologic evidence of ischemic colitis.

[Slide.]

We identified 84 cases of ischemic colitis associated with Lotronex; 33 cases were confirmed by biopsy, 17 cases were confirmed by colonoscopy without biopsy, and 33 cases were diagnosis only.

These were mutually exclusive.

[Slide.]

Eighty-one of these patients were female, one was male, and two the gender was unknown. The median and mean age of these patients was 55 years. The range was 25 to 80 years. The time to onset, median was 14 days, the mean was 39 days, and the range was 101 to 200 days.

We had time-to-onset information in 66.

[Slide.]

Presenting symptoms, these are not mutually exclusive. Fifty-four patients reported bloody stool diarrhea, 16 patients reported constipation, and 63 patients reported abdominal pain, 22 patients were using estrogen concomitantly.

[Slide.]

The outcomes of these cases, and these are not mutually exclusive, 54 patients required hospitalization, 11 patients required surgery. That is 10 resections and one unknown surgery. Two patients required transfusions, and there were 2 deaths.

Now, the sponsor stated that there were no deaths due to ischemic colitis. This is a

difference in assigning the cause of death. Per previous communications with the sponsor, we have agreed to disagree on assigning the cause of death in these two cases.

I am presenting the next two slides on behalf of Dr. Allen Brinker.

[Slide.]

This is information described in his review, which can be found in Appendix 4 of the FDA background package.

Epidemiologic studies submitted by Glaxo suggest potential for misdiagnosis of selected conditions as IBS. Examples are inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, and ischemic colitis.

By "misdiagnosis," we mean that patients originally given a diagnosis of IBS were later found to have other diagnoses, such as IBD or ischemic colitis.

[Slide.]

Given the risk of ischemic colitis due Lotronex and the potential for a background rate of ischemic colitis in the IBS population, we can calculate attributable risk.

Attributable risk permits attribution of

the percentage of spontaneous reports of ischemic colitis in association with Lotronex expected to be due to Lotronex.

Based on relative risk of 5.9 for ischemic colitis with Lotronex versus placebo--this is from the initial NDA--the attributable risk is 83 percent. Thus, we expect 83 percent of reports of ischemic colitis reported in association with Lotronex to be attributable to Lotronex, the remainder as background cases of ischemic colitis misdiagnosed as IBS.

[Slide.]

Now, we will talk a little bit about small bowel ischemia. Our case definition was any ischemic change of the small bowel documented by endoscopic, surgical, or pathologic evidence.

[Slide.]

We identified 6 cases associated with Lotronex. These cases reported ischemia, infarction, or necrosis of the small bowel. They were all female and ranged in age from 33 to 81 years.

Time to onset was a mean of 10 days for 4 of the patients, 120 days for 1 patient, and unknown for 1 patient. There were 5 surgeries and 3

deaths. The sponsor's case definition was much broader, and this is why they have identified 12 cases.

While each of these 6 cases may have an alternative explanation for the small bowel ischemia, because of an association between Lotronex and ischemic colitis, we believe that an association between the drug and small bowel ischemia could not be excluded.

[Slide.]

Now, we will talk about serious complications of constipation. Our case definition was constipation or suspected constipation that was associated with an ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis, or rupture.

[Slide.]

We identified 113 cases associated with Lotronex, 103 were female, and 10 were male. The median age was 57 years, the mean age was 54 years, and the range was 24 to 82 years.

The time to onset, a median of 14 days, a mean of 35 days, and a range of 1 to 180 days. We had time-to-onset information in 79 of the cases.

The presenting symptoms, these are not

mutually exclusive, 84 patients reported constipation, 28 patients reported bloody stool, and 74 patients reported abdominal pain. Nineteen patients were using estrogen concomitantly.

Some of the reports may not have mentioned constipation, but their adverse events led us to believe that they had constipation, and that is why these patients were placed in this category.

[Slide.]

The outcomes, these are not mutually exclusive, 83 patients required hospitalization, 34 patients required surgery, that is 25 intestinal surgeries and 9 anorectal surgeries, 2 patients required transfusions, and there were 2 deaths.

[Slide.]

There are a total of 14 deaths in patients receiving Lotronex. Association with Lotronex cannot be reasonably excluded in 7 cases - 2 cases of ischemic colitis, 3 cases of small bowel ischemia, 2 cases of serious complications of constipation.

[Slide.]

Once a drug is introduced into the marketplace, unstudied populations are exposed. This leads to detection of additional and more

serious adverse events. When looking at these data, keep in mind that the clinical trials have a denominator of approximately 12,000 patients, and the denominator is unknown for postmarketing data.

We look at the first event, ischemic colitis. In clinical trials, there were 18 cases with 1 surgery and no deaths. Postmarketing, there were 84 cases, 10 surgeries and 2 deaths.

If we look at small bowel ischemia, there were no cases in clinical trials. Postmarketing, we had 6 cases with 5 surgeries and 3 deaths.

If we look at serious complications of constipation, in clinical trials, there were 11 cases, 1 surgery, and no deaths. Postmarketing, we had 113 cases, 34 surgeries, and 2 deaths. I should say, though, in the clinical trials, if a patient was constipated for 3 to 4 days, they were taken off the drug and restarted and when constipation abated. If they were constipated for 7 days, then, the patient was out of the trial.

Clinical trials have strict entry criteria. Use in the real world is less stringent. In this subset of Lotronex adverse effects, we see the following: There were no men in pivotal clinical trials. Among the reporters who reported

this information in our case series of 203 patients, there were 11 men who received Lotronex.

There was no off-label use in clinical trials. Of the reporters who provided indication for use information in our case series, there were 22 patients who received Lotronex off-label. Some of the uses, as reported, included diarrhea, constipation-predominant IBS, alternating IBS, and abdominal pain.

The potential for use in contraindicated conditions is minimized in clinical trials. Of reporters who provided this information, there were 18 patients with apparent clinical contraindications, primarily history of constipation. Others included history of ischemic colitis, history of bowel obstruction, history of inflammatory bowel disease.

[Slide.]

Conclusions. In review of the IBS literature and studies submitted by Glaxo, we believe there is a real potential for misdiagnosis of selected conditions, such as inflammatory bowel disease and ischemic colitis diagnosed as IBS.

We expect that most, 80 plus percent of ischemic colitis cases reported in association with

Lotronex can be attributed to Lotronex.

[Slide.]

Presenting symptoms did not necessarily predict the severity of the outcome. These data do not reveal any potential risk factors for these events. We recognized a potential for unknown risk factors as yet identified.

Managing risk in the general population differs form managing risk in clinical trials.

Now, Toni Piazza-Hepp will present the Risk Management Program.

Lotronex Risk Management Program

Toni Piazza-Hepp, Pharm D.

DR. PIAZZA-HEPP: Before I begin, I would like to thank my colleagues in the Office of Drug Safety who provided me with valuable input for this presentation.

[Slide.]

I will be presenting the goals of a Lotronex Risk Management Program. I will also be including a discussion of options that can be considered when designing a plan to meet these goals.

[Slide.]

In 1999, the FDA Task Force on Risk

Management issued a Report to the Commissioner.

One of the key recommendations was that the FDA needed to apply a systems framework to medical product risk management.

This slide displays a proposed risk management model which is designed to encourage the integration of risk management efforts.

First, issues need to be identified and put into context. Earlier this morning we learned about the history and the risks related to Lotronex. We have also heard discussions surrounding the assessment of risks and benefits of Lotronex.

In my presentation, I will be identifying goals and risk management options for Lotronex. Following today's meeting, the FDA and GlaxoSmithKline will discuss a selection of a strategy for potential management of Lotronex.

If a strategy is selected, it will then be implemented. There will be phase in evaluation of results and a cycle to start all over again. We are involving stakeholders in this process, and today's meeting is one such example of that.

[Slide.]

We are considering the full range of

options for drug access. These include, first, no patient access, for example, the drug is not approved by the FDA or marketing is suspended.

Investigational New Drug or IND access allows availability only under a study protocol. For example, cisapride is a drug previously marketed that was withdrawn for safety reasons. It is currently available through a limited access program under an IND.

The topic of my presentation will be marketing under restricted distribution, which is the plan proposed by GSK.

Finally, there are normal marketing conditions where there are no special restrictions to drug access.

[Slide.]

There are risk management plans currently in effect that involve restricted distribution. This slide list some of the components common to most plans, and I will be addressing each in more detail. These are education, registrations, prescribing and dispensing restrictions, patient monitoring, and assessment of compliance with program elements and/or ability of program to manage drug risks.

[Slide.]

The purpose of education is to provide a description of the program, communicate risks and benefits of treatment, and can be used for other purposes, such as encouraging participation in plan assessment activities such as surveys, and encouraging reporting of adverse events.

Education is really a critical feature of all risk management programs. Considerations are potential burdens, such as expense and time and investments associated with creating and receiving this education.

[Slide.]

Some plans include registration of prescribers, patients and/or pharmacists. The purpose is to create a target population for education, monitoring, and conduction of follow-up surveys.

Registration also provides mechanisms to measure plan success, such as provision of a patient denominator. You would know the actual number of patients receiving the drug, you wouldn't have to guess or estimate, and linking mandatory surveys to these registrations also can occur.

Again, there are considerations along with

the additional consideration of patient privacy.

[Slide.]

The purpose of prescribing and dispensing restrictions are: to limit drug access to targeted patients; to allow pharmacists to verify that prescriptions are written only by authorized prescribers; no refills ensures patients return for follow-up; drug distribution in special packaging can limit drug supply. You can use it for others things like inclusion of a Med Guide, inclusion of surveys, you can have reinforcing messages on packaging, and so on.

Again, there are considerations, and one may be patient access issues for patients who may not be able to afford drug, patients who are remotely located, and also it is a concern that these programs may encourage alternate sourcing, such as importing drugs from other countries, going through underground drug networks, and trying to get drugs through the Internet.

[Slide.]

The purpose of patient monitoring at regular intervals is to assure patient follow-up for both benefit and safety. It provides an opportunity for reinforcing safety messages and an

opportunity for obtaining and evaluating adverse event information.

Again, you are going to hear there are burdens including the possibility of additional office visits, addition lab tests, and so on.

[Slide.]

The purpose of assessment of compliance with program elements is to provide data to be able to measure the success of the plan. This can include surveys or patients, prescribers, and/or pharmacists.

If the plan includes voluntary surveys, the level of participation may not be adequate and there is a question whether respondents will be representative really of all patients receiving the drug.

[Slide.]

Some, but not all, of the risk management plans currently in effect are approved under the Subpart H Regulation, which provides a requirement for postmarketing restrictions.

[Slide.]

I have reproduced some of the regulation, and I will just be hitting on a few of the salient points that is relevant to our discussion today.

21CFR314 Subpart H is the regulation covering accelerated approval for serious and life-threatening illnesses. Many of you may be more familiar with it in regard to its use for efficacy based on surrogate endpoints, but there is another piece of this regulation which relates to approval with restrictions to assure safe use.

If FDA concludes that a drug product can be safely used only if distribution or use is restricted, the FDA will require such postmarketing restrictions, such as distribution restrictions to certain facilities or physicians with special training or experience, or conditioned on the performance of specified medical procedures, and the limitations are consistent with specific concerns presented by the drug product.

[Slide.]

The FDA may withdraw approval, following a hearing, if the use after marketing demonstrates that these restrictions are inadequate to assure safe use or if there is failure of the applicant to adhere to the postmarketing restrictions, and there is a few other conditions in that regulation.

Also, promotional materials must be submitted to the Agency prior to the time of

dissemination.

[Slide.]

There are advantages to approving restriction programs under Subpart H. Subpart H gives the FDA tighter regulatory control and rapid withdrawal is possible if restrictions are not met or the plan fails to accomplish safe use. Auditing is needed to assess this.

Also, the review and pre-approval of all promotional material or advertising material is mandatory.

[Slide.]

Dr. Houn already mentioned that we do have four drugs currently approved under the Subpart H regulation, and I don't plan on going into the details of these plans any further during my talk, but there were plan details included in the background package.

[Slide.]

What are the potential options for the design of a Lotronex risk management plan?

[Slide.]

The GlaxoSmithKline proposal is to reintroduce Lotronex to the market and restrict access under the provisions of Subpart H.

[Slide.]

The program does have strengths. It has an educational component, enhanced labeling, a Medication Guide, special packaging which provides for a limited supply and includes a Med Guide, a dose titration phase that was discussed by the firm.

[Slide.]

Expedited reporting of the targeted adverse events of ischemic colitis and serious complications of constipation, pre-approval of promotional materials, a program evaluation component which was described by GSK, further continued study, and Dr. Wheadon had mentioned, although not part of this admitted plan, GSK has updated us that they intend to allow no refills without a new prescription.

[Slide.]

There are some weaknesses in the GSK-proposed plan. For patient selection, "failed conventional therapy" may not be adequate to describe severe forms of IBS, and this is a topic that we have asked the Advisory Committee to consider today.

In regard to qualified prescribers,

attestation of qualifications only is proposed. In the current plan, prescribers do not receive education, certification, or registration with GSK prior to receiving a kit with stickers.

The program does not limit prescribing to gastroenterologists. This is another area where we are seeking the opinion of the Committee.

Monitoring of patients by prescribers on a regular basis is not included in the description of the current plan. Instead, it is the patient that agrees to identify problems relating to benefits and risks, and then initiate contact with their doctor.

[Slide.]

Dr. Wheadon again already mentioned that the submitted program has been now changed. It originally did not include the concept of stickers on every prescription, but they are planning on adding this concept to their plan.

The utility of stickers as an authorized prescriber mechanism is really an untested method. We are not sure how well that is going to work. Also, the program assessment is not designed to measure compliance with the use of stickers.

[Slide.]

The program assessment includes a voluntary survey--and by "voluntary survey," I mean patients are invited to participate in the survey, but they are not required to do so--using a chain pharmacy, Eckerd Pharmacy patients.

There is no assurance that the survey will be representative of all Lotronex patients, and the program does not include other means to more widely distribute the survey, such as via the prescriber or in the special packaging, or require a mandatory survey, and by "mandatory survey," I mean that participation in the survey may very well be a condition of receiving the drug. This may be accomplished via registration of all patients.

[Slide.]

There are various considerations that were taken into account when creating proposed goals for a Lotronex risk management plan. A letter regarding Lotronex from CDER to IBS patients was posed on the FDA web site in the weeks following marketing suspension.

Goals stated in this letter included safer use of Lotronex in appropriately informed patients, continued access to Lotronex by severely affected IBS patients under closely monitored conditions,

and continued clinical studies of the benefits and risks and safe use of Lotronex.

[Slide.]

Now, over a year later, we needed to take additional considerations into account. First, even with continued study, the risk factors for ischemic colitis are still not known, and we should expect that these events will still occur regardless of any risk management program.

Complications of constipation may be prevented by recognizing constipation, but some patients did not report constipation before complications occurred.

In regard to Subpart H, in addition to the requirement for restricted distribution, there is the issue of IBS is a serious disease, and there should be the ability to determine the success of the plan.

[Slide.]

The proposed FDA goals for a Lotronex risk management plan are:

1. To provide access to severely affected IBS patients, in other words, to better reflect serious forms of IBS and to maximize the benefit portion of the benefit-risk ratio.

2. To limit prescribers to qualified physicians.

3. To identify ischemic colitis and serious complications of constipation symptoms early through close medical monitoring, in other words follow-up. Regular follow-up would also be needed to assess and initial and continued benefits.

4. Measure success of the plan, in other words auditing, where the collection of data would be needed.

[Slide.]

This slide displays some of the components that I presented earlier, along with the goals that I have just described. A red check mark represents a newly added feature, and the firm has decided to add the "no refill" concept, as I mentioned earlier.

So, in this plan, we have education, an authorized prescriber check mechanism, no refills, special packaging, and an auditing mechanism.

The submitted plan, however, does not achieve our current goals. In regard to Goal 1, it is uncertain if failed conventional therapy will be adequate to describe severe IBS.

For Goal 2, the current plan allows wide, uncontrolled availability of kits with stickers, and does not precertify prescribers or limit prescribing to gastroenterologists prior to allowing them to receive these kits.

For Goal 3, follow-up by physicians is not specifically addressed in the current plan.

For Goal 4, there is an auditing plan, but it does involve a voluntary survey, so there is a question about the ability to measure plan success.

[Slide.]

Well, if the GSK plan does not appear to meet the FDA goals, then, alternate plan design should be considered to better meet these goals. We considered how components from other risk management programs might be incorporated into a Lotronex plan in order to better meet these FDA goals, and we have also posed questions to the Advisory Committee seeking input on a number of these components.

[Slide.]

This slide again displays the components I described earlier and lists the FDA goals. The purpose here is not to vote on one plan or another, but rather to illustrate a process that can be used

when considering the value of adding each of these components.

As we move from right to left, a red check mark will indicate a newly added feature. Plan D is a GSK plan which I have already reviewed. Plan C adds physician registration prior to receiving kits with stickers, also adds limitation to severe IBS and regular patient follow-up.

In doing this, we now achieve Goal 1, that means the severe IBS, and Goal 3 for follow-up. Goal 2 may be met, but there is still a question as to what constitutes a qualified physician.

In Plan B, patient registration and limitation to gastroenterologists is added. In doing this, we now achieve all four goals.

In Plan A, we also considered the impact of limiting distribution to registered pharmacies only, and although this step would add additional checks and balances, it did not appear essential in the case of Lotronex to meet the four FDA goals. However, education of pharmacists should be stressed as essential to the plan's success.

[Slide.]

In conclusion, the full range of drug access options needs to be considered in regard to

Lotronex. If the approach is to market under Subpart H, begin with a more restrictive plan than that proposed by GSK in order to meet the proposed FDA goals, and to re-evaluate the program at a specified time, for example, at one year or some other specified interval for compliance with program elements and the ability of the program to manage risks, and the modify the program at that time if appropriate.

I would now like to introduce Victor Raczkowski who will speak on risks and benefit issues and provide a summary and conclusion for the FDA talks.

Thank you.

Summary and Conclusions

Victor F.C. Raczkowski, M.D.

DR. RACZKOWSKI: Good morning.

[Slide.]

This morning I will address risk-benefit issues related to the use of Lotronex. I will also allude to questions that FDA will be posing to the Advisory Committees, so you may wish to keep your hardcopies at hand.

At the end of my talk, I will provide a brief summary of some of the main conclusions

reached by the FDA speakers.

One goal for a risk management plan for Lotronex is to enhance and ideally to optimize the benefit-risk balance for its use.

[Slide.]

In my presentation this morning, I will describe, in turn, each of three approaches for modifying the benefit-risk balance for Lotronex. I will focus particularly on appropriate patient selection, trying to answer the question who are the right patients to take Lotronex.

The first approach is to limit the use of Lotronex to patients with the most disabling symptoms. The second approach is to establish conditions under which the benefits of Lotronex are increased. The third approach is to establish conditions under which the risks of Lotronex are decreased.

Note that the use of one approach does not necessarily exclude the use of another approach. In fact, all three approaches overlap to a great extent, and the approaches can be used together in enhancing the risk-benefit balance of Lotronex.

[Slide.]

Let's consider the first approach,

limiting the use of Lotronex to patients with the most disabling symptoms of IBS. The burden of the illness of IBS varies from patient to patient. Some patients have mild symptoms, whereas, others have moderate or severe symptoms.

As has been described earlier today by Dr. Traber of GlaxoSmithKline, approximately 70 percent of patients with IBS have mild symptoms, 25 percent have moderate symptoms, and 5 percent have severe symptoms.

Stated differently, symptoms of IBS can vary from being relatively mild to disabling. It stands to reason, then, that patients with IBS with the most disabling symptoms stand to benefit the most from drug therapy and may accept greater risks of drug therapy.

We commonly see this principle applied in other therapeutic areas. For example, patients with cancer often accept treatment with highly toxic drugs. Why do patients do this? Because the burden of illness of cancer can be quite high and patients are willing to significant drug toxicities in the hope of a remission or a cure.

This approach is also consistent with statements in the 1999 Report to the FDA

Commissioner from the Task Force on Risk Management, and I quote, "Medical products are required to be safe, but safety does not mean zero risk. A safe product is one that has reasonable risks given the magnitude of the benefit expected and the alternatives available."

Indeed, the first question that we will be posing today to the members of the Advisory Committee asks whether a patient population can be described for which the benefits of Lotronex exceed the risks.

This first question indirectly asks whether the use of Lotronex should be limited to patients with the most disabling or most severe symptoms.

[Slide.]

The second approach to modifying the benefit-risk balance of Lotronex is to question whether it might be possible to enhance the benefits of the drug. We know, for example, that Lotronex has beneficial effects on several symptoms in patient with diarrhea-predominant IBS. These include improving the symptoms of diarrhea, urgency, and abdominal pain and discomfort, and has been described earlier by Dr. Permutt of FDA, FDA

has performed analyses that demonstrate that some patients with diarrhea-predominant IBS, who have severe urgency, can have large benefits and substantial relief of their urgency.

On the other hand, FDA has also performed analyses that demonstrate that patients with harder stools and stool frequency of less than two times per day appear to have less benefit than those with softer stools or more frequent bowel movements.

So, another point for the Advisory Committee to consider today in its answer to Question No. 1 is whether Lotronex should be used exclusively or primarily by patients with severe symptoms, such as urgency, and whether its use should be prohibited or avoided by patients with relatively hard stools and a stool frequency of less two per day.

[Slide.]

GlaxoSmithKline has presented quality of life data today that suggest that Lotronex improves functional performance, however, as has been summarized by Dr. Permutt, the average gain in productivity, as assessed by hours not lost in the workplace in patients taking Lotronex, was about an hour more per week compared to patients taking

placebo.

However, another way to assess whether patients taking Lotronex have marked improvement in functional performance could be by prospectively conducting a randomized withdrawal study of irritable bowel symptom patients who have disabling symptoms, and the Advisory Committee will have an opportunity to comment on this possible approach when it answers Question No. 8. That question asks the committee for additional comments about a Lotronex risk management plan including suggestions for additional studies.

[Slide.]

The third approach to modifying the benefit-risk balance of Lotronex is to question whether it might be possible to decrease the risks of the drug. In this approach, the goal is to avoid adverse events, if possible. I say "if possible," because some serious adverse events associated with Lotronex may largely be avoidable, such as complications of constipation.

On the other hand, other adverse events associated with Lotronex may not be avoidable, or they may be avoidable, but we don't yet know how to avoid them. Examples of these adverse events

include ischemic colitis and mesenteric ischemia.

I will be going through these sub-bullets in the following slides, but way of overview, there are several ways to avoid adverse events, and these include the following four strategies.

[Slide.]

One way to avoid adverse events if through appropriate patient selection and education, for example, advising patients t discontinue Lotronex when they get constipated.

A second way to avoid adverse events is through appropriate physician selection and education, for example, advising physicians not to prescribe Lotronex to patients with constipation.

A third way to avoid adverse events is through modifying drug exposure, for example, Lotronex should be discontinued in patients who don't appear to be benefiting from the drug after four weeks of therapy at a dose of 1 mg twice a day.

A fourth way to avoid adverse events is to consider relevant a IBS factors, for example, Lotronex may be used as a continuous therapy even though the symptoms of IBS have a waxing and waning course. There may be room here to study whether

other dosage regimens, such as intermittent dosing during flares, might be a better way to administer Lotronex.

Of course, adverse events can't always be avoided, so the goal then is to manage these adverse events, and the goal here is early detection of warning symptoms and rapid intervention when warning symptoms occur. The idea is to mitigate the seriousness of adverse events by catching them early.

An example here with Lotronex would be for patients to detect and react to warning symptoms, such as blood in the stool, which might be a harbinger of ischemic colitis. In these circumstances, the patient should stop taking Lotronex immediately and should contact her doctor right away.

This is the overview slide. Let's walk through each of the points and some of their other implications.

[Slide.]

Let's start with patient selection because appropriate patient selection is one of the principal issues to be discussed today, and it is related to the first question that FDA is asking of

the Advisory Committee. I will spend a fair amount of time on this point given its importance.

Lotronex should be prescribed only to patients in whom the benefits exceed the risks, and this can be accomplished by appropriate inclusion criteria. By that I mean, giving Lotronex only to patients who stand to benefit.

This can also accomplished by appropriate exclusion criteria, and that is, not giving Lotronex to patients who are likely to be harmed by it.

So, giving thought as to whether, in special populations, such as men, the evidence supports its widespread use.

Another goal of patient selection is to prescribe Lotronex to patients who have been adequately informed of its risks and benefits.

[Slide.]

How do we best describe the patients in whom the benefits of Lotronex exceed the risks? If one look at how the indication for Lotronex has changed over time, one gets an idea of FDA's and GlaxoSmithKline's thinking on the subject. I will summarize three indications.

The indication for Lotronex when it was

approved in February 2000, the indication as it was revised in August 2000 after some of its serious postmarketing adverse effects had been reported to FDA, and, third, the revised indication proposed here today by GlaxoSmithKline.

GlaxoSmithKline had FDA's input in crafting this current indication, but it is not yet approved.

[Slide.]

When Lotronex was first approved in February 2000, it had the indication for the treatment of irritable bowel syndrome in women whose predominant bowel symptom is diarrhea. It also had a statement that the safety and effectiveness of Lotronex in men have not been established.

These statements came largely from an analysis of two randomized, double-blind, placebo-controlled Phase III efficacy studies, as well as some Phase II dose ranging studies submitted with the original New Drug Application.

It is worth noting that Glaxo Wellcome only studied women in those two, Phase III efficacy studies, and to be enrolled, women had to meet the ROME criteria for IBS and were excluded from the

study if they had hard stools.

Women also underwent lower endoscopic procedures within five years in order to be enrolled in the study. For example, women less than 50 years of age underwent flexible sigmoidoscopy, and patients more than 50 years underwent a full colonoscopy.

As it turned out, although efficacy was seen overall in the Lotronex group compared to the placebo group, it was limited to the subgroup of women with diarrhea-predominant IBS, not in women with alternating IBS or constipation-predominant IBS.

Therefore, the original indication reflected those findings, and the ROME criteria were summarized in the appendix of the original labeling. Endoscopy, however, was not described in the labeling.

Moreover, because men were not studied in the Phase III efficacy studies, the statement that safety and effectiveness in men have not been established was included in the indication.

[Slide.]

After the indication in June 2000, at which concerns over Lotronex's emerging

risk-benefit profile were discussed because of postmarketing reports of serious complications of constipation, and additional postmarketing report of ischemic colitis, FDA worked with Glaxo Wellcome to tighten the indication.

The indication at that time was that Lotronex is indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome. Diarrhea-predominant irritable bowel syndrome is characterized by at least three months of recurrent or continuous symptoms of abdominal pain or discomfort with either urgency, an increase in frequency of stool or diarrhea not attributable to organic disease, and there was a reference to see the appendix. The use in men had similar language to the original labeling.

This tightening of the indication reflected a sense that a woman should be given a firm diagnosis of diarrhea-predominant IBS in order to be prescribed Lotronex. In other words, the indication was intended to limit or decrease prescribing the Lotronex to women who had a casual or an interim diagnosis of diarrhea-predominant IBS.

Moreover, in contrast to the previously

approved labeling, the indications suggested that organic etiologies of symptoms, such as diarrhea, should be excluded before prescribing Lotronex, such as through endoscopy.

[Slide.]

In the appendix, the ROME criteria were adapted to diarrhea-predominant IBS and to make them more user friendly for clinicians.

[Slide.]

Now, here, in April 2002, we are looking at another possibility of an indication. As mentioned previously, this version of the indication proposed by GlaxoSmithKline had FDA input. Lotronex is indicated only for women with diarrhea-predominant irritable bowel syndrome who have failed to respond to conventional therapy and who have signed the patient-physician agreement.

The goal here in part is to delegate Lotronex to second-line status as a treatment for diarrhea-predominant IBS because of some of the risks associated with the use of the drug. The goal in part, as before, is to limit the casual prescribing of Lotronex to patients with symptoms suggestive of diarrhea-predominant IBS.

It is worth noting that the ROME criteria

are not in the label in any form. One of the down sides of this proposed indication is that Lotronex hasn't really been prospectively studied to see if it is effective in patients who have failed conventional therapies. For example, these patients may be resistant, not just to conventional therapies, but also to Lotronex.

[Slide.]

Another question is whether this adequately describes the population in whom the benefits of Lotronex exceed the risk. Therefore, more recently, questions have arisen about whether other terms besides "failing conventional therapy" would be appropriate to include in the indication either in place of or in addition to this phrase.

For example, patients could be described in terms of the degree of their disability or the degree of the severity of their condition. Again, the first question we pose to the Advisory Committee gets to this point indirectly.

[Slide.]

Does the proposed plan and the labeling adequately describe appropriate patients? Does it describe appropriate inclusion criteria in terms of the severity of irritable bowel syndrome symptoms,

degree of disability from IBS, the chronicity of IBS, the failure of conventional IBS therapies and what those therapies might be, or other important characteristics?

[Slide.]

An additional point for the Advisory Committee to consider is whether the patient should self-attest to whatever criteria are established to define the population. In other words, the plan proposed by GlaxoSmithKline has a physician self-attest to his or her knowledge of IBS, knowledge of Lotronex, and knowledge of complications associated with Lotronex. Should patients be asked to self-attest to the severity of their IBS symptoms, their degree of disability, the length of time they have had irritable bowel syndrome, et cetera?

[Slide.]

In terms of informing patients, GlaxoSmithKline's proposed risk management plan has several elements in it, and these have already been discussed and I won't discuss them further here. I will simply note that Question 4 to the Advisory Committee members asks about how to assess whether appropriate patients are receiving Lotronex, and

the same question asks whether patient's knowledge is being adequately assessed in the sponsor's risk management plan.

[Slide.]

I have spent a lot of time focusing on patient selection because appropriate patient selection is likely to be at the heart of any successful risk management plan for Lotronex, but let's move on.

Physician selection and education is also an important component of a risk management plan because the presence of these elements could improve the benefit-risk profile of Lotronex by helping to ensure competent and knowledgeable prescribing.

Our goal would be to have physicians who are knowledgeable and experienced in the diagnosis and treatment of IBS, who are able to diagnose and manage ischemic colitis and complications of constipation and who are knowledgeable about Lotronex.

[Slide.]

So, if Lotronex is marketed, should the prescribing of Lotronex be limited only to certain types of physicians, such as physicians with

certain knowledge, certain experience, of certain specialties or with important characteristics? This is Question 3 that we will be asking to the Advisory Committee members.

[Slide.]

Toni Piazza-Hepp has already covered the items in this slide, so next slide, please.

[Slide.]

So, we have talked about the importance of appropriate selection and education of patients and appropriate selection and education of physicians to improve the benefit-risk of Lotronex. Let's now talk about Lotronex-associated adverse events and how they might be decreased by decreasing exposure to Lotronex.

These adverse events include constipation, which is dose related we know, ischemic colitis, and small bowel ischemia, which appear to be idiosyncratic, however, it is not known.

[Slide.]

The risk of these adverse events will likely be decreased by modifying drug exposure, in other words, not treating patients with Lotronex at doses higher than needed, for longer than needed, or if they don't appear to be responding to the

drug.

For example, one possibility would be to limit dosage to decrease dosage-related side effects. In the sponsor's proposal, therapy is initiated with an upper titration, and when patients achieve the desired therapeutic effect, they remain at that dose and they do not go to a dose of 1 mg twice a day unless they do not achieve a desired effect at 1 mg once daily.

However, unanswered questions are whether it is appropriate to adjust the dose during maintenance therapy or whether drug holidays might be appropriate. Another component of GlaxoSmithKline's plan is to discontinue therapy in non-responders.

Ideally, we would be able to continue therapy only in true responders not only to continue therapy in apparent responders, in other words, patients who may be spontaneously improving, and not improving because of a consequence of taking Lotronex.

[Slide.]

So, we have talked about how patient and physician selection and education and drug usage could improve the benefit-risk of profiled

Lotronex. Next, the risk management plan could also consider relevant IBS factors to improve the risk-benefit profile of Lotronex.

A few facts have already been discussed. Lotronex is indicated only for diarrhea-predominant IBS, and not for alternating IBS, however, other IBS factors could be considered or evaluated.

Symptoms of IBS typically wax and wane, and yet Lotronex is given continuously. Studies could be performed to assess whether intermittent dosing, such as during flares of symptoms, is effective, and if so, how best to dose Lotronex under such conditions. Also, there may be greater risks of serious adverse events during particular phases of the condition. It is also clear that Lotronex should not be used in patients with constipation-predominant IBS.

[Slide.]

Lastly, if adverse events are not prevented, then, perhaps they can be managed to limit the seriousness of their outcomes. Again, these items have all been discussed.

[Slide.]

So, in conclusion, the burden of illness is variable in patients with IBS, and Lotronex has

beneficial effects on several symptoms of IBS. Patients with the most disabling symptoms stand to benefit the most from Lotronex, and the risk-benefit balance is likely most favorable in patients with the most disabling symptoms.

[Slide.]

Lotronex is associated with serious, or potentially serious, adverse events, such as complications of constipation, ischemic colitis, mesenteric ischemia, and death.

Outcomes of ischemic colitis and constipation, however, vary in seriousness. They range from mild and self-limiting and reversible upon discontinuation of therapy to those that require hospitalization, surgery, or sometimes are associated with death. Presenting symptoms do not necessarily predict the severity of some of these clinical outcomes.

[Slide.]

Risk factors for ischemic colitis or mesenteric ischemia have not been identified, so as has been stated, potentially everyone who takes Lotronex is at risk. The cumulative risk of ischemic colitis increases over time, and is about 2 to 5 per 1,000 patients at 3 months. The risk

may decrease after 1 month, but there is little information after 6 months. It possibly continues to rise.

[Slide.]

Constipation is a frequent dose-related side effect associated with Lotronex, and the numbers that I will quote here are already corrected for placebo.

Approximately 25 to 30 percent of patients experience constipation with Lotronex at 1 mg twice per day. Ten percent approximately withdrew from clinical trials because of constipation at 1 mg twice a day.

This can be viewed as a safety surrogate marker for potentially more serious outcomes, and, as we have heard, some serious outcomes of constipation are serious, requiring surgery, and have been associated with death.

[Slide.]

The full range of drug access options should be considered at today's Advisory Committee. One possibility is to begin with a more restrictive plan that could be loosened later and program monitoring should occur at the level of the patient, the level of the physician, and the level

of the pharmacist.

[Slide.]

The success of the plan should be evaluated through process controls and evaluation of outcomes.

Thank you.

DR. WOLFE: Thank you, Dr. Raczkowski, and thank you to the FDA for your presentation.

I am trying to keep on schedule here because we have a very busy schedule and we are behind quite a bit. What I would like to do now is to open up the floor to the panelists for questions for both FDA and for GlaxoSmithKline. Keep in mind these are questions regarding the presentations, not questions which will be subsequently discussed in the afternoon after the questions are posed to us that we need to discuss.

Questions on Presentations

DR. WOLFE: I know this definition is a little bit vague, but I am going to start off with one question and maybe you will get the gist of what I am getting at. The question I have is actually for both Drs. Piazza-Hepp and for Dr. Carter. This is a question actually I posed back in June 2000 about the risk of, and again, I think

the correct term is colonic ischemia, not ischemic colitis. I think it is a better term because, by definition, it is ischemia.

But the question comes up about estrogens, and there is a discrepancy in the risk factor--it is a risk factor of estrogens--with the FDA saying about 1 in 4 women were taking estrogens, and GlaxoSmithKline saying about one-half are taking estrogens.

Obviously, we all know estrogens can be a risk, and along those same lines, how many of those patients were smokers with or without estrogens?

DR. CARTER: Perhaps I can start and answer the GSK part of that question. As far as our fairly intensive, extensive investigation into risk factors of ischemic colitis, we obviously considered the possibility of estrogen because of the anecdotal primarily reports in the literature, and so forth.

Again, we could not find estrogen to be a specific risk factor. With respect to the apparent discrepancy in terms of our reporting estrogen use with that of the Agency, I don't have an answer for that.

With respect to smoking as an additional

risk here, I do remember, Dr. Wolfe, you raising this as a potential combined issue, and again at that time, I think the discussions were that there probably was not as we know a specific risk factor for colon ischemia, but let me defer that perhaps to Dr. Brandt with respect to smoking as a risk factor for colon ischemia.

Do you want to come and answer that, Larry?

DR. BRANDT: I would say a very brief answer. There are no randomized, placebo-controlled trials to evaluate estrogens, nor are there any type 1 data to show that smoking is a specific risk factor for colon ischemia although it is accepted as a general risk factor for atherosclerotic disease.

MS. MACKEY: I am just going to say that--I am talking about postmarketing data--for ischemic colitis cases, we had 22 patients using concomitant estrogen, that is 26 percent, and for the serious complications of constipation, we had 19 patients using estrogen concomitantly. That was 17 percent.

We don't have any smoking data. That is not typically information that we get on

spontaneous reports.

DR. WOLFE: It is an unresolved discrepancy still because for ischemia, you have still a difference in the numbers, but that is okay. Both of you are saying the same thing. You haven't identified it as a significant risk factor.

MS. MACKEY: Correct.

DR. WOLFE: Dr. Gross.

DR. GROSS: I have a few questions, one also on estrogens. Is it known in the UHC population, what percent of women not on this drug were taking estrogens is one question. The other question is there seems to be conflicting data on whether the complication is dose-dependent or not. Can someone resolve that for us?

Thirdly, is there any information at all on what the incidence of inflammatory bowel disease is in patients who initially present with a diagnosis of irritable bowel syndrome?

DR. WOLFE: For that last question for the afternoon regarding IBD versus IBS.

DR. WALKER: I am Alec Walker from Engenics. For the first question on replacement estrogens, we did do a case-controlled comparison of colonic ischemia in randomly selected control

women, and found actually no elevation in risk at all associated with replacement estrogen use. I don't have at hand the percentages that were the same in the two groups, but I can easily get them for you.

DR. CARTER: With respect to the question regarding IBD, we don't have that information. I am not familiar with that information.

The middle question?

DR. GROSS: Dose dependence.

DR. CARTER: Dose dependence. It seems to be a feature at least from the clinical trial population where the great majority of patients were exposed to the 1 mg BID dose, that, first of all, we can't really make a comment with respect to dose dependence in terms of complications of constipation.

We can make a comment perhaps with respect to patients withdrawing from trials as a result of constipation, but one of the features I think that we have seen is that the adverse event of constipation does not necessarily translate into a complication of constipation.

Again, we clearly saw a lack of relationship between the proportion of patients who

developed adverse events of constipation with respect to placebo and the proportion of patients that developed complications of constipation with respect to placebo.

DR. RICHTER: I have got a couple of questions. First, for Larry Brandt, I am struck by the fact that the age on onset for these patients with whatever you want to call it, ischemic colitis or colonic ischemia, it seemed somewhat young at 55 to 52. At least in my clinical experience, these tend to be older patients.

Also, I am interested in the normal person presenting with colonic ischemia that we see with abdominal pain and bloody diarrhea, the prevalence of men versus women. Maybe Dr. Brandt can answer that question, and then I have got a second question I would like to follow up with.

Is the age, Larry, younger than you would normally see, or does this fit into the normal picture of colonic ischemia?

DR. BRANDT: Let's stop there. We will do one at a time. I can't keep track of all these questions.

The first question in terms of the age, it is true that in large series of colon ischemia

patients, the disease seems to be more common after the age of 50 or 55, however, in recent series that are being reported, there is an increasing percentage of patients that varies anywhere from 10 to approximately 20 percent of patients that are under the age of 50 at the time of diagnosis, and most of these are under the age of 35.

There is a higher percentage of patients in the younger age group in which an etiology is found, and the majority of these patients, not in this experience but in the literature, are found to either be on medications that may cause that problem or to have underlying coagulation defects. That seems to favor a younger age population.

In the literature, there tends not to be in the older age population a gender difference. In the younger age population, there tends to be a female predominance.

DR. WOLFE: We are locked into a certain time slot for lunch. That is our limiting factor in the way we are locked into reserving spots. As a result, we are not locked into asking questions, and there are a lot of questions here. I am looking around here, there is at least eight people more who have questions, and we are not going to be

able to get to the public forum, which is very important.

What I am going to do now, as chair at this meeting, I am going to defer the questions to the Company, I am sure you will be here in the afternoon, I know the FDA will be here in the afternoon, so we will defer questions until the afternoon, and we will move on to the public forum.

A meeting like this, it is tough to say no break, but there is going to be no break right now, we just don't have the time to take a break.

There will be a short stretch break to get everything all ready for the public forum, so you have about three or four minutes to run out or stretch.

[Break.]

Open Public Hearing

DR. WOLFE: In most instances, one hour only is allowed for the public forum, but because of the nature of this discussion, we are allowing a greater period of time, however, all the speakers who have registered prior to the meeting know that they have a time limitation.

I am asking that they please keep to the time limit and actually, there will be a timekeeper

with a very loud alarm going off at the end of the time that is allotted.

I am going to announce the speaker and then who is on deck. We are starting with Dr. Sidney Wolfe, who will be followed by Ms. Nancy Norton.

Dr. Wolfe. No relative of mine.

DR. S. WOLFE: We are not sure about that.

In a review of 27 randomized, placebo-controlled studies, which a chart is on the first page, one dot represents one study, testing various treatments for irritable bowel syndrome, the median placebo response rate was 47 percent, measured as a percent, improved with rates as high as 84 percent, and in 11 studies, the placebo response rate was 60 percent or greater.

The study concluded that the placebo response rate was approximately three times larger than the difference between placebo and drug, the median of which was 16 percent. This is part of the difficulty of finding something that is really effective or irritable bowel.

This also applies to alosetron as seen in the second figure there, which is a re-analysis we did of Glaxo data, which we published in the

Lancet. What you can see is that over a three-month period, the mean pain and discomfort scores were quite similar. The analysis done by the Company showed a statistically significant difference, but really, the lines are very, very close.

The dose that was used in this study, 2 mg a day, 1 mg BID, is twice as much as what the Company is proposing as the starting dose in their attempt to get the drug back on the market, which is a total of 1 mg a day.

An FDA review of the use of this lower dose, which was done in dose ranging studies, found that there is no adequate evidence that the 1 mg per day dose, 0.5 twice a day, was significantly better than a placebo.

However, there was evidence in the same study of an increased risk at the 1 mg dose, a 4-fold increase in constipation severe enough to cause patients to withdraw from the study, compared with placebo.

Thus, Glaxo's proposal for remarketing Lotronex has a starting dose of 1 mg a day, which lacks proper evidence of efficacy required by the 1962 drug efficacy laws, but causes a significantly

greater incidence of severe constipation.

From our analysis of adverse event data and FDA briefing documents which were made available yesterday, as of the end of 2001--we don't have more recent data--there were 352 hospitalizations associated with the use of alosetron, the majority of which were associated with gastrointestinal adverse reactions including ischemic colitis and severe complications of constipation.

Eighty-five cases in the whole database were ischemic colitis, and there were 13 deaths, 7 of which according to the FDA show a "strong association with alosetron." Twenty-three patients required surgery because of complications from alosetron. That number is larger than what was presented this morning, it was over 30.

That these reported cases are about the tip of the iceberg can be seen from an important clinical trial included in an FDA memo by epidemiologist, Dr. Zili Li, who found that in one large trial, 10 out of 1,819 women being treated with alosetron for diarrhea-predominant irritable bowel syndrome developed ischemic colitis over a 24-week duration of the trial. In contrast, there

were no cases in the 899 patients in that trial treated with traditional therapy.

Again, for those who say that there is some underlying incidence of ischemic colitis in irritable bowel syndrome patients who don't have a drug, I think that may be true, but it is a very small incidence, if any.

Since there are 275,000 people who have used the drug, the 85 reported cases of ischemic colitis after approval certainly represent the well-known under-reporting of hundreds of cases of ischemic colitis which may actually have occurred.

Glaxo has stated that ischemic colitis mainly occurs because the drug was not used properly, but according to FDA, the first 70 cases that were reported, 80 percent of them, the drug was prescribed as labeled. It is interesting that 12 percent of those first 70 cases, the patient was using the 1 mg per day dose being proposed for the new marketing plan.

On the next page, there is a table just looking at the changing estimates, the incidence estimates for ischemic colitis, and it goes back to the FDA medical officer, Dr. Senior, back before the drug is approved, finding a risk estimate of 1

in 300 over 12 weeks, which would translate into a risk of 14.7 cases per 1,000 years, and finally, the study that was felt by Dr. Zili Li of the FDA to be most representative because the patients were really looked at carefully in terms of the occurrence of ischemic colitis, the trial I just mentioned. It was one case of ischemic colitis per 182 patients or a risk of 16.9 per 1,000 patient years.

The regulatory options, which you have heard about this morning, include, and the discussion hopefully will include, an IND, because I think it is the only reasonable option compared with some of these Subpart H options that have been described.

As mentioned earlier, there has been, with cisapride, another GI drug, according to Johnson & Johnson, the spokesperson told me about 1,000 patients had that drug available under their INDs.

The necessary combination of safeguards that I think we need to protect people adequately just can't be done in any marketed version. In an FDA slide presentation in an internal meeting a couple weeks ago, the very criteria which I have listed there, life-threatening disease, disease not

prevalent, which would make an ideal Subpart H drug, are just not met in this case.

The FDA has pointed out in the presentation that you just heard this morning by Dr. Piazza-Hepp, that a number of elements for even a stricter marketing version of the drug are missing in what the Company has proposed, and these would include restriction, as you heard, to gastroenterologists, and most importantly, regular monitoring by physicians.

We just don't believe that all these restrictions are realistic for a marketed drug, and if the drug is to be made available, it needs to be under an IND.

The conclusion is that with the exception of some drugs used to treat cancer, the frequency and severity of a life-threatening adverse reaction in this case, ischemic colitis, in patients using alosetron is among the highest I have seen for any other drug.

This risk, coupled with the marginal benefit, beyond that seen with a placebo alone, results in a risk benefit ratio clearly unfavorable to patients. The reintroduction of Lotronex into the market, even with the restrictions proposed by

Glaxo, would be a serious public health mistake likely, if not certain, to result in the need to be on the drug again.

I would just like to point that at the end of the public section, Dr. Paul Stolley, who was an epidemiologist at FDA, who worked on this drug, will make a statement.

Thank you with 12 seconds to spare.

DR. WOLFE: Thank you, Dr. Wolfe, for the succinct presentation. Dr. Wolfe, by the way, is Director of the Public Citizen's Health Research Group, and I ask all speakers, in fairness to everyone, that they state their current --

DR. S. WOLFE: No conflict of interest. Sorry.

DR. WOLFE: Again, that they state their current or previous financial involvement with any firm whose products they may wish to comment upon.

Our next speaker is Ms. Norton, and Mr. Roberts should be on deck.

MS. NORTON: I would like to indicate that my expenses have been paid by the International Foundation for Functional Gastrointestinal Disorders.

Mr. Chairman, I would like to thank the

Advisory Committee for the opportunity to appear before you today. I ask you to consider two issues that are key components of determining benefit and risk in IBS, what are the consequences of alternative therapies or no treatment for chronic multiple symptoms of IBS, and what is the level of disability, morbidity, and mortality associated with IBS.

Data reveals that for many people, there are severe consequences and a distressing level of disability, morbidity, and mortality that results from the search for effective treatment for unrelieved chronic symptoms of IBS.

The newly signed Veteran Education and Benefits Expansion Act of 2001, H.R. 1291, recognizes IBS as a chronic disability with an associated burden of illness that warrants compensation and disability under covered veterans, for Gulf War veterans.

The Expansion Act prompted us to look into the possible IBS mortality in the U.S. Vital Statistics data from the CDC. Remarkably, we found that between 1979 and 1999, 1,031 deaths were attributed to IBS. Where did the presumptions come from IBS does not lead to surgery, does not shorten

the life span, and does not cause death? The data says otherwise.

We asked several epidemiologists what they thought about the mortality coding associated with IBS. Among the responses were it may or may not represent miscoding, there may be under-reporting of deaths related to medical interventions that were never correctly attributed to the diagnosis of IBS, and finally, we don't know what it means. I think it is time we find out.

Let me elaborate on some of the things we do know. People die from procedure-related complications including from diagnostic tests and surgical interventions that are unnecessary, and people with unrelieved chronic symptoms of IBS are at risk for these procedures.

In January 2002, I was a panel member at the NIH State of the Science Conference on endoscopic retrograde cholangiopancreatography for diagnosis and therapy. The differential diagnosis of abdominal pain or possible pancreatic or biliary origin includes, in part, clinical apparent entities such as IBS.

Diagnostic ERCP has no role in the assessment of these patients. Yet, among those at

highest risk for diagnostic ERCP and ERCP-induced pancreatitis and even death are young, otherwise healthy females reporting recurrent abdominal pain.

There is a risk of cholecystectomy associated with unrelieved symptoms of IBS. A recent article in the British Journal of Surgery reported that cholecystectomy was common in patients with IBS, most often women. Symptoms of IBS may cause diagnostic confusion and lead to inappropriate surgery.

Longstress [ph] cites that the incorrect attribution of IBS symptoms to gynecological pathology can lead to unnecessary surgery. As many as 47 percent of women with IBS have undergone hysterectomy and 55 percent ovarian surgery.

Both radical and simple hysterectomy have shown to give rise to changes in urinary function including incontinence and to disturbances of bowel function associated with surgical trauma.

There is mortality data in relationship to incontinence. Nokenesian [ph] College reported that incontinence in elderly people living at home has appreciable effects on mortality.

Consider that IBS patients run the risk of incontinence not only due to surgical intervention,

but also as a result of the inability of the anal sphincter muscle to compensate for repeated bouts of loose stool or diarrhea, and many constipated patients experience fecal incontinence due to seepage around impacted stool.

In an IFFGD survey, 25 percent of individuals with IBS reported loss of bowel control, a disability that has enormous impact on a person's life and well-being.

I will conclude with the results from the IFFGD survey, IBS in the Real World, a quantitative research study conducted from February to March of 2002 among adults drawn from our database. While this information may not generalize all IBS, it clearly represents those at IFFGD that we talked to.

In the telephone survey, 350 respondents were interviewed who reported having a diagnosis of IBS. Almost half were diagnosed 10 or more years ago. Symptoms were reported as severe by 43 percent, moderate by 40 percent, and mild by 17 percent. Nearly half reported daily episodes of IBS symptoms and 70 percent more than weekly episodes.

Duration of the IBS episodes was reported

on an ongoing or continuous occurring every day of the year by nearly one-quarter of these respondents. Thirty-nine percent rated the pain of their IBS symptoms as extreme or very severe.

Symptoms in terms of interfering with daily life were described as extremely or very bothersome by two-thirds of sufferers. Five percent of respondents reported being on disability due to IBS. More than two-thirds reported visiting a physician or health care provider during the past six months for their IBS, with 15 percent of the total sample reporting six or more visits.

These IBS sufferers, seeking to control their symptoms, reported using 143 prescription drugs, 71 over-the-counter medications plus 67 herbal remedies, a total of 281 different preparations. Yet, overall, fewer than one-third of these IBS sufferers reported satisfaction from the drugs and remedies they used to treat their IBS symptoms.

Prescription drugs were more often considered to be effective by those with milder cases of IBS, less frequent episodes, or symptoms that do not interfere with daily activity.

Over-the-counter medications were rated as

either not effective or only somewhat effective by nearly three-quarters of those currently using them.

Significantly, 62 percent report side effects from the prescription drugs being taken. Almost half reported the side effects as severe or moderate. Twelve percent visited the ER, 7 percent were hospitalized, 24 percent had to visit their health care provider, 22 percent had to stop driving, and 18 percent reported missing work or school.

In summary, these IBS sufferers face the challenge of living with their disease day-in and day-out for years. Most suffer severe and painful symptoms that seriously impact their daily life.

They frequently utilize health care providers due to IBS symptoms, they take a plethora of drugs finding little or no relief. They are dissatisfied with existing medications prescribed for IBS symptoms from which they suffer frequent and sometimes severe side effects.

Mr. Chairman and members of the Committee, IBS is a serious disease. For the significant number of people whose symptoms are frequent and often debilitating, treatments are needed to

provide symptom relief. Unrelieved symptoms of IBS can lead to disability, morbidity, and even mortality.

In this context, a safe and effective drug to relieve the multiple symptoms of IBS would be a significant step forward.

Thank you.

DR. WOLFE: Thank you, Ms. Norton. You took Dr. Wolfe's extra 15 seconds.

Next, we have Mr. Jeffrey Roberts of the IBS Self-Help Group, and Mr. Corey Miller will be on deck.

MR. ROBERTS: I am here today representing patients and sufferers, and I have paid all of 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 Group.

The 11,000-member Irritable Bowel Syndrome Self-Help Group has endeavored since 1987 to educate and provide support for people who have IBS and to encourage both medical and pharmaceutical research to make our lives easier vis successful Internet web site for sufferers.

I have been a sufferer of diarrhea-predominant irritable bowel syndrome for over 25 years. There are challenges that I face each and every day in order to cope with the symptoms of irritable bowel syndrome.

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 members of the Lotronex Action Group, Irritable Bowel Syndrome Self-Help Group, and Irritable Bowel Syndrome Association. I would like to now invite the members of these groups to stand and be acknowledge for their efforts to date and to represent those members who were too ill to travel here today.

Thank you.

[Slide.]

While taking Lotronex, IBS sufferers reported a complete cessation of their symptoms. It dramatically changed their lives for the better. Following the withdrawal of Lotronex from the market in November 2000, the IBS Self-Help Group was flooded by messages from former Lotronex users

who were desperate for access to the medication.

Within a month, the Lotronex Action Group was established to bring about access to the medication. In the spring of 2001, the Lotronex Action Group submitted a 1,000-name petition to the FDA asking it to immediately work with the manufacturer GlaxoSmithKline to permanently provide the drug to those diagnosed with diarrhea-predominant irritable bowel syndrome.

The petition used data from an electronic survey conducted by the Irritable Bowel Syndrome that identified the side effects from taking Lotronex. Fifty-nine percent of those surveyed indicated they had no side effects at all.

[Slide.]

Through the months of March through April 2002, the IBS Self-Help Group surveyed irritable bowel syndrome sufferers about what type of restrictions, if any, they would be willing to accept for access to IBS medications.

Fifty-nine percent of those surveyed responded that medicine specific to IBS should be accessible to a sufferer diagnosed by a family physician or gastroenterologist, and not only a gastroenterologist.

It is important that family physicians, and not just gastroenterologists, be able to prescribe Lotronex because many sufferers do not have access to a specialist either because they do not live in a community supported by one or because their medical coverage does not provide access to one.

If a decision was made to allow only gastroenterologists to prescribe Lotronex, then many IBS sufferers would have difficulty getting access to it.

Furthermore, respondents want prescriptions to cover a 90-day supply. The survey also said that 63 percent are willing to agree to participate in a survey about use and side effects while taking Lotronex sponsored by the pharmaceutical and/or FDA agency.

Finally, 96 percent or respondents say that they would sign an informed consent form in order to gain access to a medication.

[Slide.]

Our survey showed that IBS sufferers are prepared to accept risks related to the use of Lotronex and other effective treatments for IBS. They are also prepared to participate in programs

to better characterize risks related to the use of Lotronex and other treatments and to work with the FDA to reduce those risks as much as possible.

The IBS Self-Help Group and IBS Association are prepared to place specific risk management information about Lotronex on their web sites in order to reach out to the IBS community. With close to 4 million monthly visitor hits, the highly active web sites can be vehicles to educate and provide signs and symptoms about Lotronex.

[Slide.]

In conclusion, IBS sufferers' quality of life was dramatically improved with access to Lotronex. IBS sufferers are prepared to accept the risks associated with its use and to work with the FDA to reduce those risks.

Adverse events should not deter either the pharmaceutical or FDA from maintaining the drug's availability. Lotronex has a place as an effective treatment for both female and male diarrhea-predominant IBS sufferers. Those who would limit access have obviously never walked a day in our shoes.

Thank you.

DR. WOLFE: Thank you, Mr. Roberts.

Next, we have Corey Miller; on deck, Dr. Stein.

Mr. Miller is with the Lotronex Action Group.

MR. MILLER: Members of the Committee, my name is Corey Miller and I am here today to speak on behalf of the Lotronex Action Group, for which I am co-founder.

[Slide.]

The Lotronex Action Group was founded in January 2001 with the help of the IBS Self-Help Group shortly after the removal of Lotronex from the market.

The LAG represents approximately 350 people that used Lotronex while available. I would like to emphasize that we are a patient group, and we receive no funding from any pharmaceutical company whatsoever. Our goal is to regain access to the medicine Lotronex for both women and men, which we feel is a miracle medicine that substantially improved the quality of our lives.

Moreover, the LAG believes strongly that the medicine is safe when prescribed and taken appropriately, and that the benefits far outweigh the potential risks for adverse side effects.

[Slide.]

The LAG, as mentioned by Mr. Roberts, submitted a petition to the former interim Commissioner, Bernard Schwetz, containing over 1,100 signatures of those wanting access to the medicine.

I am speaking here today as a patient in great need of a medicine that has, in my opinion, been pulled from the market due to lack of understanding of the debilitating nature that diarrhea-predominant irritable bowel syndrome or IBSD can have.

[Slide.]

For almost all the members of our group, this medicine was the only effective treatment for our illness. As stated in an open letter from the LAG to the FDA in the summer of 2001, the typical sufferer of IBSD is a 40-year-old female with primary symptoms including multiple and daily explosive diarrhea attacks and severe daily abdominal discomfort.

The most common secondary side effects include panic attacks, depression, withdrawal from social and family activities, severe disruption of daily activities, and malnutrition. The typical

IBSD patient has suffered from the illness since their early teenage years.

The adverse impact of IBSD on patient quality of life is dramatic, causing the typical sufferer to forego many aspects of life that others take for granted. For example, some of our members have been forced to relinquish their social lives, others have given up their careers and live as captives in their own homes.

People fortunate enough to have met an understanding partner and to have children often are not able to attend functions with their kids or participate in common daily activities. In many cases, the inability to lead a "normal" life causes severe depression and suicidal thoughts.

When IBSD patients try to take part in daily activities, they are often subject to panic attacks when confronted by situations in which a restroom is not nearby or suffer embarrassing accidents of defecation.

The Lotronex Action Group is comprised of women and men suffering from the most severe and debilitating symptoms of IBS. Many of us have found Lotronex to be the only effective treatment for IBSD, enabling many patients to assume normal

adult lives for the first time.

Please believe me when I tell you that all the existing treatments for IBS, ranging from fiber therapy to antispasmodals to antidepressants, do little, if nothing, to provide relief from the pain and discomfort of this illness for the most severe cases.

I am telling you this from my personal experience and also have a stack of over 50 letters from some of our members that will attest to the same.

[Slide.]

It is apparent that IBS has been categorized by the FDA as an illness that does not cause death, therefore, a zero tolerance criteria for adverse side effects has been placed on medicines developed to treat IBS. Why else would we be there today? The percentages shown earlier, in my opinion, clearly show that Lotronex is not that dangerous of a medicine, not much more than any other prescription medicine on the market.

What that tells me as a patient is that any medicine ever developed to treat my debilitating illness has to be perfect, and you know as well as I do, and it was mentioned earlier,

that all medicines have some associated risks.

Current unavailability of Lotronex leaves many patients with no satisfactory treatment option. Some turn to other prescription medicines not suited for their illness, while others abuse over-the-counter medicines like Pepto Bismol and Imodium with serious potential adverse consequences.

The member of the Lotronex Action Group are prepared to accept risks related to the use of Lotronex and other effective treatments for IBSD. We are also prepared to participate in programs to better characterize risks related to the use of Lotronex and other treatments, and to work with the FDA and the pharmaceutical companies to reduce those risks to the extent possible.

We have requested that the FDA reexamine and redefine the severity of IBSD and the level of risk as tolerable for an effective treatment for this debilitating condition. IBSD, while not directly deadly, can be life threatening and causes severe damage to the quality of the lives of the sick and their families.

After taking Lotronex for almost two full years, with no side effects whatsoever, I am only

able to be here today because I am now taking prescription medicine Zofran. It's another 5HT3 receptor antagonist.

I am fortunate that my physicians understand my situation and I can afford the 30 dollar-plus price tag per pill. Many others are not so fortunate.

To my knowledge, no long-term studies have been done to determine if this medicine is safe for long-term treatment, so you see the FDA has merely shifted the problem. With Lotronex, there is a set of parameters established and the risk is known. It was a much more controllable situations.

Now, those 300,000 people that were taking Lotronex, or 275,000, which I saw this morning, are taking, like myself, whatever they can to stop or relieve their suffering.

If two people commit suicide due to severe IBS-related depression, which was a major factor in GSK's presentation earlier, that would match the number of probable deaths linked to Lotronex. Again, I quote "probable" because it hasn't been identified that those deaths were linked specifically to Lotronex.

Also, I want to add one other item. After

hearing of the proposed management proposal this morning by Glaxo, I wanted to address one item on that regarding prescription refills. This is just my personal feeling in general.

I am on a couple of medicines to treat IBS since Lotronex was pulled off the market. Being in a working profession, it is a burden, it is very much a burden to go see a doctor. If you are traveling during the week and whatnot, it is very difficult every month, if I am going to be on the medicine for the rest of my life, to go in every month and see a physician and have to get a prescription.

I would recommend to the Board to consider that maybe initially, for the first three months or six months that could happen, and then gradually, as a person's need for the medicine has been identified, that maybe that gets reduced and relaxed over time, as long as they are responding favorably to the medicine.

Thank you for your time.

DR. WOLFE: Thank you, Mr. Miller.

Dr. Gary Stein is next. He is representing the American Society of Health System Pharmacists, followed by Mr. Brown.

DR. STEIN: Thank you. My name is Gary Stein. I am the Director of Federal Regulatory Affairs for the American Society of Health-System Pharmacists.

ASHP is a 31,000-member national professional association representing pharmacists who practice in hospitals and other components of organized health care systems.

ASHP has a long-standing commitment to helping pharmacists manage the risks inherent in prescription and non-prescription medication use, and we recognize that the FDA has the same commitment, particularly in regard to new or higher risk drugs.

Unfortunately, many of the risk management plans that have been implemented in recent years involve restricted drug distribution systems. There has been a substantial increase in the number of new pharmaceuticals that are available only through limited distribution systems.

Increased reliance on restricted drug distribution systems is a growing concern among ASHP's members. These systems often exclude individual hospitals, as well as community pharmacies, from distributing medications and use

other means of distribution to deliver medications directly to patients.

While a number of drugs have been relegated to restricted drug distribution systems, we lack information on how well these systems work.

Pharmacists are responsible for ensuring that medications are readily available for patients who need them. Disruptions in non-standardized distribution processes are not trivial matters. They create procedural confusion for pharmacy and other hospital staff, and increase the potential for mistakes.

Any restrictive distribution or special handling procedure that disrupts that central oversight role of pharmacists represents in interruption in standard medication use policies and procedures in the health care system.

In November of 2000 and again in January of this year, ASHP drew FDA's attention to this issue. We have suggested that when a manufacturer implements a restricted distribution of a drug product, the FDA should obligate the company to ensure that a patient's usual pharmacist relationship is not disrupted.

ASHP also recommended that if a restricted distribution system is being considered by the Agency as a condition for marketing approval, practicing pharmacists, professional pharmacist societies, and patients should be consulted before any restricted distribution requirements are imposed on the product.

While restricted distribution systems for individual drugs may have a safety intent, they paradoxically also represent corresponding safety threats in complex health system settings. Any distribution process that bypasses pharmacists' control or requires exceptional procedures in such setting would be contrary to the best interests of patients.

ASHP members recognize that some exceptions will inevitably have to be made in a patient's best interests. An important point, however, is that these should truly be extraordinary exceptions.

The prospect of multiple unique restrictive drug distribution systems is a frightening picture for health system pharmacists. Deviations that are unique and that greatly differ from standard practice create obstacles in

delivering and administering medications safely.

The patient-pharmacist relationship should not be misinterpreted as merely a product distribution function. The pharmacist's minimum responsibility is to assess the overall appropriateness of all medications with regard to dose, drug interactions, compliance, and patient counseling.

Patient and pharmacist relationships in which this level of care is achieved depend on mutual trust, the pharmacist's thorough awareness of the patient's overall medication use, and the pharmacist's actions to ensure the timely supply of drug products.

Restricted distribution systems that limit the pharmacist's ability to develop these relationship are disruptive. Restricted drug distribution systems that involve physician-to-patient delivery prevent pharmacists from providing medication appropriateness, dosage, and interaction checks, patient education and counseling, monitoring and follow-up evaluation.

Thoughtful consideration needs to be given to the fact that some of these medications may be initiated or continued for hospitalized patients.

Hospital pharmacies may not be able to acquire these medications in a timely manner. This has an adverse effect on patient care and cost. The hospital setting is also where a sticker system fails miserably.

ASHP believes that rather than unique drug product distribution schemes, the FDA, in consultation with stakeholders including pharmacists, physicians, nurses, other health care professionals and patients, should develop models or managing patients for whom any high-risk drug product might be indicated and prescribed.

Manufacturers should be required to design distribution procedures and supporting patient care materials in conformance with these models.

Drug-specific requirements for a model should be developed during pre-approval demonstrations and adjusted over time based on postmarketing surveillance. Pre-approval demonstrations, perhaps through the Centers for Education and Research on Therapeutics, the CERTs, should focus on requirements for ensuring appropriate use and monitoring, such as patient work-up and selection, provider and patient education, and patient monitoring.

Such demonstration projects could answer a number of our concerns about important issues, such as uniformity of procedures for patient selection, what kind of distribution systems are most supportive of continuity of care, and what kind of approach is served best for provider and patient education.

Thank you very much.

DR. WOLFE: Thank you, Dr. Stein.

Mr. Brown, followed by Ms. Lisa Kenney.

MR. BROWN: Good afternoon, Dr. Wolfe, and members of the Committees. My name is Bill Brown. I am a practicing attorney in Columbus, Ohio. I don't sue doctors, I represent many of you. I have practiced for 42 years and had IBSD for over 40.

In 1999, after visiting a number of GI doctors in Columbus with no success, I wound up at the Mayo Clinic, and wound up on an open-label study for alosetron. It was truly my miracle pill.

I used it for 16 months until it ran out. I have never had any side effects to it. Nobody has paid me to be here, it's a six and a half hour drive from Columbus to speak for four minutes.

Previously, I have filed with you a more detailed statement including my personal experience

with IBSD, which I hope you will have time to read. It won't take you more than about five or six minutes.

But there are three basic issues that I really want to address, that I think are very important. I am a little appalled almost at Glaxo's comments this morning regarding the availability of this for men. As you can see, there are many of us that suffer with IBSD. It is not just women.

That issue needs to be addressed by the Committees, and I believe at least indicate that Glaxo have some sort of a continuing open-label study for us to participate in. I was almost totally cured with this.

The second thing, of course, other than gender discrimination, is age. There have been some comments that have said that it gets better with age, and I am here to tell you that IBS is 10 times worse than it was at 59, 10 years ago.

I have read the entire transcript, your 247-page transcript from last year's meeting, so I am familiar with what you have covered. Dr. Camilleri, which is a brother to most of you in this thing, addressed the issue of what he calls

this "exquisite dilemma" in last year's Gastroenterology Journal, and I quote him. "Unfortunately, withdrawing a drug while saving some individuals from a serious adverse effect, may deprive others of the only agent able to relieve their suffering."

There currently has been much thinking about compassionate use, about restricting dispensation, about waivers, warning labels, none of which seem to address the issue that you need to really address.

The biggest item I have seen that needs to be addressed is physician education. If you limit this to GI docs, there may not be one in Apple Valley, Montana, within 400 miles of somebody who needs a drug.

My family physician, my primary caregiver in Columbus, knows more about Lotronex and IBS than at least half a dozen GI doctors that I personally know in Columbus. Don't restrict it to just GI docs.

I have an older son who is a drug rep for Lilly. He doesn't work with Lotronex, of course, he works with diabetes. His biggest problem is getting in to educate the doctors, to detail them

on these drugs. Fortunately, it is no longer an entertainment thing for the doctors anymore. Eli Lilly and other companies have restricted the entertainment of the physicians, but that is the biggest problem.

You need to establish, like we have in the legal community, continuing legal education, serious medical education of the doctors who are going to prescribe, maybe set up a class having passed an educational requirement, but please do not eliminate Lotronex. People like Solvay, as you are well aware, interrupted their Cilansetron studies for a year because of what has happened to Lotronex.

We need the Lotronex. It is the only thing that is available, and if you stop it, there is going to be very little, if any, additional research on IBS, which we need to have. Consider that.

Thank you.

DR. WOLFE: Thank you. I am impressed. Four minutes for a lawyer is very, very good.

Ms. Kenney, followed by Maria Zargo.

MS. KENNEY: My name is Lisa Kenney. I am a member of the IBS Support Group, the Lotronex

Action Group, and I am also a long-term sufferer of IBS for over 10 years.

I made it here today, and the only reason why is because of my emergency ration of Lotronex given to me by my compassionate and supportive gastroenterologist.

I appreciate this opportunity to be heard on behalf of hundreds of thousands of IBS sufferers, many of whom are unable to attend today given the debilitating symptoms of severe intestinal pain and diarrhea.

Without Lotronex, our lives are once again severely compromised in ways no other person could possibly understand but the IBS patient, our family, our friends, and our doctors.

We are imploring the FDA and GlaxoSmithKline to please return our only hope in controlling IBS by restoring the single most effective and safe IBS drug Lotronex. Prior to Lotronex, living with IBS was a nightmare. By the time I was a senior in college, I knew that life would never be normal. Every normal event was met with trepidation and uncertainty, and every simple task was a major challenge.

Getting up in the morning, making it to

school, going to work, or even eating a simple meal was a victory in itself without being stuck in the bathroom fatigued and writhing in pain.

IBS impacts every aspect of my life - career, education, relationships, marriage, parenting, all had to be rearranged. I had given up a great dream to become a doctor due to this illness. While I have accepted my limitations and acquired a computer career for the many years that followed, the excruciating impact of IBS remains.

Then, in May of 2000, something magical happened, and I started Lotronex, and a small hope became a dream come true. I remember that joyful brief period very well. I remember all the youthful years I had missed, all the things I couldn't do, and even simpler still, all the things I couldn't eat or drink, all came back with safe invitation.

Even my skin and bones frame, I am fat again, and there was time for family and friends, and energy for work or play. After 10 long years of suffering, endless days and nights twisted in agonizing pain, I felt free for the first time, freedom from IBS.

Lotronex removes much of that anxiety and

the fear and the shame that we all carry, so there is no more hiding in the bathroom, and there will be no more hiding from the world. I thought life was just beginning.

Then, on November 28th, 2000, the unthinkable happened, and in one brief moment, Lotronex was gone. It was as if time had reversed and everything positive, painless and powerful, was taken away, and every day since Lotronex has been removed has been a huge step backwards.

They say that IBS is not life threatening, that it does not kill. Well, I disagree. IBS threatens my confidence and my will to survive every single day of my life. It had been increasingly difficult for me as it was before Lotronex, until Lotronex literally saved my life and my livelihood, but without Lotronex, I can no longer sustain a demanding work schedule, and I couldn't face life without it. Life without Lotronex was, for me, a life without quality of life.

I have come a long way since my crisis and I have dreams yet to fulfill, but I am unable to meet them without Lotronex. So, I am anxious to return to productive life, and I will continue to

be proactive in winning Lotronex back for myself and for countless other people, an undeniable need of this small miracle pill.

In closing, we have been informed of the serious side effects of Lotronex, and we acknowledge the potential risk in developing ischemic colitis and severe constipation. We understand that the benefits of Lotronex do not come risk-free, no medication on the market does.

We are not so overcome with desperation from our suffering that we would fail to consider these risks seriously, and we would certainly yield to close GI supervision under this medication just to ensure its safety.

No other drug has been able to treat IBS symptoms with unparalleled efficacy. Lotronex can save, and has saved, so many lives from further pain and suffering. It has helped to reunite patients with their families, friends, and forge an even closer doctor-patient relationship.

As educated consumers and IBS patients, we are more than prepared to accept the risks with the tremendous benefits of Lotronex. So, please don't take away the only hope we have for a much better life, a life with the quality of life.

Thank you.

DR. WOLFE: Thank you, Ms. Kenney. Maria Zargo is next, followed by Julia Alberino.

MS. ZARGO: My name is Maria Zargo. I am a LAG coordinator, but I am here representing myself and some who were unable to attend this meeting. No one has paid for me to speak.

I am a wife, mother, former career woman, and I suffer from severe IBS. Most recently I was forced to resign my position with a prestigious Fortune 500 company. I was no longer able to make the 45-minute commute to work every day without stopping at a supermarket to use the restroom. My work life, my family life, and my independence had been permanently compromised until Lotronex came along.

I had been on a reduced dosage of Lotronex for nearly two years without side effects. I am living proof that this drug is extremely effective and very safe when used correctly and at the proper dosage.

As with any other medication on the market, dosage administration should not be considered a "one-size-fits-all" scenario. Your risk management debacle could be solved if you

would only adhere to this advice, advice given by those who are the true experts - the users of Lotronex.

All drugs have side effects, and knowing what we know about the risk-benefit ratio of Lotronex, we are willing to accept those risks. The majority of us have expressed a willingness to sign a waiver if need be, as is currently being done with other drugs, but that was never even presented to us an option. Nor have we been given the option of a truly viable compassionate use type program that doctors would be willing to endorse.

With Zelnorm's rejection and Cilansetron's approval being questioned, one can only presume that this continues to be politics as usual, and not at all about science and patient needs.

It would be easier to have ailments like migraine headaches or IBD because there are effective treatments on the market, and public perception is one of understanding and sympathy. Today, IBS sufferers have no viable alternative medication that works. Lotronex continues to be the only drug ever prescribed that has significantly improved or completely eliminated the horrible, debilitating symptoms of

diarrhea-predominant IBS.

For those who continue to view IBS as nothing more than a "vexing inconvenience," we hope that the information we provide you with today will change that view. Being hospitalized for dehydration caused by IBS is more than an inconvenience. Stories of suicide attempts attributed to IBS suffering cannot be ignored.

Missing out on life's simple pleasures like attending your child's sporting events is downright depressing, and it affects everyone in the family. It goes beyond a quality of life issue. Being afraid to leave your home for extended periods of time for fear of embarrassing incontinence is humiliating and not a mere inconvenience.

The cramping and pain, the exhausting, numerous trips to the bathroom, the inability to eat healthy, nutritious foods can be intolerable, and not just an inconvenience. Job loss and family stress are undeniable and commonplace. So, I am hoping that you can understand why I take offense when someone refers to my condition as a mere inconvenience.

IBS continues to be poorly understood.

Even today, there are still some doctors who are truly misinformed, referring to it as "bathroom anxiety." Because of these misconceptions and lack of information, many patients are misdiagnosed with "mental health" problems and are given unfair labeling and treatment.

For this reason, the treatments and medications that have been prescribed over the years have fallen far short of success. I have attached a list of prescription drugs and herbal remedies that patients have tried over the years with little benefit, if at all. This list should have been distributed to you.

The bottom line is, sure, there are alternate IBS treatments on the market today. What some refuse to understand is they don't work. We are being subjected to experimenting with dangerous addictive drugs like codeine, Vicodin, and Oxycontin that have a much higher risk factor than Lotronex and do not contain the benefits that Lotronex provides.

The FDA worries about the risks associated with Lotronex? What about the side effects and toxicity we are exposed to by taking these other drugs? There is one other drug that I have

purposely not listed. That is ondansetron, which is Zofran. It has made it possible for me to travel to Bethesda and speak before you today.

It has proven significantly superior over the other remedies I have attached, and only because it is chemically related to Lotronex.

In this great country of ours, we often hear the words "freedom of choice." On November 28, 2000, that freedom of choice was taken away from us. For many on Lotronex, it was the first time in years in living a normal life was possible, a life that so many take for granted.

Finally, please return Lotronex to those of us who so desperately need it. We depend on it, our families depend on it. Please keep the patients' needs at the forefront and put money and politics aside. By continually denying us this right to Lotronex, the long-term repercussions will be catastrophic and future IBS drug research will be kept on the back burner. Our fate is in your hands.

Thank you.

DR. WOLFE: Thank you, Ms. Zargo.

Next, we have Julia Alberino, followed by Terry Olifiers.

MS. ALBERINO: Hi. I am Julia Alberino. I am a member of both the IBS Self-Help Group and the Lotronex Action Group, but I am not here today to represent either of them, I am here to represent myself and other patients who cannot travel here. No one has paid my expenses to be here, and I have no affiliations with GlaxoSmithKline, the FDA, or any other party to what is being decided here.

I have had IBS for more than 30 years, and I have tried in those 30 years not to let IBS control my life, but the fact is that it has and it does. Every time I have had to cancel a business meeting or a trip, every time I have been too sick to attend a social event, every time I have had to give up a job because the commute was too long and I couldn't commute to the job and be away from a bathroom for that long, IBS was controlling my life.

I am an intensely private person, so embarrassing accidents in public could send me into hiding for weeks. In the material that I submitted to you, I described some of those incidents that happened. As I have gotten older and my IBS has gotten worse, I have learned a few tricks.

I keep a change of clothes near at hand

wherever I am. I scope out the bathrooms every time I am in an unfamiliar place. I watch very carefully what I eat. I have learned to wear protection if I am going to be away from a bathroom for any length of time. I only travel by train because they have bathrooms.

That has had an impact on my professional life. I am required to travel as a part of my job. I have often had to rearrange schedules or ask someone else to do it for me.

But in all these years of suffering, I did have 22 months that were remarkable. These were the months that I was on Lotronex, and I won't go into how I got it past the time it was withdrawn from the market, but I did use it for nearly two years.

During that time, I could meet all of my work responsibilities, I took on new ones. I started graduate school, which I had to drop out of when Lotronex was withdrawn, and I ran out. I was able to stay in school until I ran out of Lotronex.

I knew there could be problems. My physician was candid with me before I started Lotronex. She explained the risks of colonic ischemia and severe constipation. She explained

the signs and symptoms to look for. She told me we had to stay in close touch during the time that I was on Lotronex, and I will admit on the third day of taking Lotronex, I had have an episode of constipation.

I called my doctor, she said skip today's dose. I did. The constipation resolved. So, I think risk management that involves physician-patient communication is crucial. I will grant that. I am not out for give it to us with no restrictions.

The night that I came home and found out that Lotronex had been withdrawn, I was devastated. However, I quickly got as much as I could lay my hands on, I cut my dosage down. One pill a day worked for me almost as well as true. Half a pill a day did not work as well, but I did stay on that dose for a while to stretch the supply.

I guess the point is no one size fits all. I would also like to stress that patients have responsibility. They have got to know their own bodies, they have got to be in contact with their doctors, and be in touch the minute something goes wrong.

My experience, my personal experience is

that if Lotronex is prescribed and used correctly and conscientiously, it is safe and effective. I believe this committee can come up with a risk management program that will work, and I would urge that that program involve stringent reporting requirements and patient experience, so that additional information on the safety and efficacy and long-term effects of Lotronex can be compiled and used to make it available to more people in the future.

Thank you for allowing me to speak.

DR. WOLFE: Thank you, Ms. Alberino.

Next, we have Terry Olifiers, followed by Diana Hoyt.

MS. OLIFIERS: My name is Terry Olifiers. I am a LAG member here at my own expense.

I have suffered with IBS since I was in my early 20s. I am now 55, and that is an awfully long time to have to go through painful intestinal attacks that are unbearable and urgency at inconvenient times.

I have tried a number of medications to no avail. At the same time, my IBS has become worse, often causing incontinence. I reviewed this with my doctor, and he prescribed Lotronex.

I was started on two pills a day. At first, I experienced constipation, so I stopped taking it and called my doctor. He recommended taking Metamucil and when I was ready, to cut the dose in half. I started taking one pill daily and Metamucil twice a day, and that did the trick.

I was skeptical that this medication would work because none had ever before, but I was willing to try anything. Well to my surprise, I suddenly was living a normal life. I could now leave my house without fear. I no longer had the embarrassment of having to change my clothes at work or running into restrooms and trying to figure out how I would leave. It was a miracle.

In late November, a friend of mine who was also having great success from Lotronex told me it was being removed from the market. I was devastated. I called the FDA, Glaxo Wellcome, and went to my congressman's office, which on my behalf wrote a letter to the FDA.

I was hysterical. I received the information that pharmacies could dispense the Lotronex they had. I am a medical assistant in a pediatric office. I was so desperate that on my day off, I sat with the Yellow Pages and started

calling every pharmacy. I had to fax the FDA report to a number of pharmacies to prove they could fill the prescriptions.

I called the doctors that I worked for to fill them. I spent over $500 and would gladly have spent more. IBS is extremely life altering, and nobody would go to the lengths that I did for an ineffective medication.

Every day I see advertisements for medications with risks that are far greater than Lotronex, and yet they are still on the market. Obviously, the dosage was an issue. Some need the two pills a day, while others need less. Well, I did fine with one pill today. To conserve, I broke pills in half. I found that a half a pill a day still worked for me.

The withdrawal of Lotronex was premature. There are thousands of people who have been put in a position since the withdrawal to try other, more dangerous drugs that are not as effective including antidepressants, and that is absurd.

Nothing works like Lotronex, and the FDA has admitted that. I have hoarded enough Lotronex that I still continue to take a half a pill a day. To stretch out my time with Lotronex, I skip pills

if I can stay home, not a great way to live, I am sure you would agree.

I would like to emphasize that after two years on Lotronex, I am healthy and living proof that Lotronex can be used safely and effectively. I am hoping that it will be back on the market before I run out and put into a position where I have to try other drugs that might be harmful to me.

Please let us not close our eyes to the need for IBSD patients to be able to have access to Lotronex, so they can live normal, productive lives, enjoy their families and friends, and go on vacations, as I am sure all of you do.

This is not too much to ask for, and Lotronex is the answer. To anyone who believes this medication should not be reintroduced, let them contend with IBSD for one week, and they surely would change their minds.

Thank you.

DR. WOLFE: Thank you.

Next, we have Diana Hoyt, followed by Kathleen Ghawi.

MS. HOYT: Hi. My name is Diana Hoyt. I want to thank you for giving me the opportunity to

speak to you today.

Let me begin by reassuring all of you that I have no connection to any drug company, I am not being paid to say this, and I have come here at my own time and expense in hopes that you will hear my plea--I will try not to be emotional--and bring Lotronex back.

I took Lotronex for 16 months, and they were the best 16 months of my life. I am a successful business woman, I am a wife, and I am a mother.

I have been a recruiter for 15 years, and I manage an award-winning sales office. I say this hopefully to give myself some credibility because I think I am going to be pretty emotional here.

Standing here right now is so far outside of my comfort zone. Just to be here, I have to take four Imodium in the morning, I have to not eat for 24 hours, and I am wearing a diaper, and that is pretty pathetic.

I take about 8 to 10 imodium a day just to get through the day, and I am sure that is wreaking havoc on my system.

Before Lotronex, I thought I had the worse IBS imaginable, and since taking Lotronex, and

since its removal, I have met many people that are sicker than I am, which I found hard to believe. They have had to quit their jobs, they can't work, they can't leave their homes, so maybe I should consider myself lucky.

I have been trying for months to think about what I would say to all of you, what can I possibly say that would make a difference. I have suffered from the debilitating effects of IBSD for almost 30 years. I am 43 now. I have spent most of my life rushing to a bathroom, sweating, in pain, heart pounding, praying that I would make it in time, and most of the times I don't.

I have had accidents by the side of the road, on a deserted street, in my car, at my desk at the office. I have thrown my soiled clothes in a dumpster and cried all the way home.

If I am asked to do anything, my first question is always is there a bathroom there and can I handle it. Anywhere I go, anything I do, the bathroom is the number one concern.

I am not even going to talk about my family because then I am really going to cry, but they have made such sacrifices for me. I have a 3-year-old son and I will never be able to give him

a normal life without Lotronex. I can't take him to the park, I can't drive a carpool, I can't do anything that a normal person takes for granted.

It is funny that I have kept this bottle for seven months, and it's empty, and it sits in my bathroom, and I think I keep it because it represents hope for me that someday I will be able to fill it back up and I can lead a normal life.

I guess I could be selfish and ask that you only allow Lotronex to be given to those of us that it has helped in the past. That would be the easy thing for me to do, but I ask that you find a way to get this life-altering medicine to everyone out there that can benefit from it, whether it be male or female.

Let's find reasonable ways to monitor the symptoms, put the responsibility where it belongs, with the doctor and the patient. I hate to think what would have happened to me if I had never had the opportunity to try Lotronex and know that it was out there. It is a miracle drug.

I know that it cured me, and it should give hope to everybody out there with IBS that there is something that will make a difference and help you to lead a normal life.

Although IBSD may not be life threatening, you can see from my story, and those from everybody out here, that a life without Lotronex is a miserable existence.

So, I think quality of life is the issue here. I beg you to bring Lotronex back to those of us who so desperately need it.

Thank you very much for listening.

DR. WOLFE: Thank you, Ms. Hoyt.

Ms. Ghawi is next. Could I ask is Terry Romeo here? If not, the next speaker will be Mike Schmidt.

Ms. Ghawi.

MS. GHAWI: I am Kathy Ghawi. I am from St. Charles, Illinois. I am also out of my comfort zone. I am a suburban homemaker. I was a soccer mom long before it became very popular.

I want to say that I think they should make speaking in front of this committee an olympic event, because condensing your entire adult life with IBSD in four minutes has to go for the gold medal. I will do so.

As a college history major, I was saddened to see how they would talk about the ravages of war for World War I and World War II and the Vietnam

War, and talk about man's inhumanity to man. Let me assure you the removal of Lotronex, the only effective treatment for IBSD, has to rank right up there with man's inhumanity to man.

It is enough my mother suffered, my sister suffered, and now my children. Enough is enough. We have to find some respect for this disorder.

It is interesting. We have several cases of IBSD, irritable bowel disease, in our family, and it is interesting how they say that a third of IBD sufferers also have IBS. Well, isn't that something that we have all these drugs to control the irritable bowel disease, and yet you could have the IBS going with no remission. It is very, very sad.

There are so few IBD sufferers, but they seem to get all the respect and all the attention. Now, I am not in a competition for pain and suffering. I think pain and suffering is terrible wherever it comes from, and it should be addressed equally.

I also wonder, since it is reported that mostly women suffer from IBS, is it possible that this is another gender inequity in terms of research and funding and taking it seriously

because it's women? I ask that. I don't have the answers, but I throw that out to the powers that be.

I have to tell you that I was insulted because early on in my 36 years of dealing with this condition, I was told it was all in my head amongst other things. Yet, when I was on Lotronex, I lived a normal life. I could eat anything, I could go anywhere. Stress, who doesn't have it every day of their life? Fiber, who needs it? When you had Lotronex, it was not an issue. Diet and exercise. I was even told to lose weight. Well, thank you.

Lotronex made me live a normal life. I would ask all of you who are members of the medical community, who told us year ago that it was all in our head, to acknowledge you made a mistake, but now we can correct it, because we have the research available to do something about it.

I don't want to see another generation of people to have to go through what I have to go through. I also want to say that I am only here today, not because of the medical community, but because of the support of my family and my friends and the Lotronex Action Group.

I want to single out my daughter for traveling all the way. I live in Illinois, she lives in North Carolina. We had a parade up here.

It is important that you know that when one person in the family has a chronic disorder, the entire family suffers. It is because of them that I am here today, and I will continue to go on, and the members of my group.

I have to tell you, you have got to find a way to resolve whatever goes on behind closed doors. It is not a matter of politics when you are in our shoes. You have got to find the answer. You can't look at the bottom line. It is the patient name at the top line that you have got to look at.

I am wearing today a floral lapel. It's the forget-me-not flower. When you are deciding what to do with our lives, take a look at the white forget-me-not. It represents the purity of the patient who wants the cure, and the blue stands for the blue pill Lotronex. Please return it and remember the patient.

Thank you.

DR. WOLFE: Thank you.

Mr. Schmidt, followed by Brenda and

Franklin Compton.

MR. MORRIS: Good morning. My name is Bob Morris. I will be speaking for Mr. Schmidt who could not be here today.

I am an attorney with the firm of Smith, Phillips, Mitchell & Scott in Batesville, Mississippi. We currently represent 20 individuals who could not be here, each of whom took the drug Lotronex and were injured as a result.

We have filed a class action in the Southern District, Federal Court, in Southern Mississippi seeking class certification of a nationwide class based on the type of injuries that we are seeing from the use of the drug Lotronex.

Our firm is also working in association with the Schmidt firm out of Dallas, Texas, who represents numerous individuals from Texas who also took the drug Lotronex and were injured.

I am here representing our clients today and the clients from the Schmidt firm to stand in opposition to the reintroduction of the drug Lotronex under the current proposed scenario.

It is our position that the risks outweigh the questionable benefits of Lotronex and that during the time Lotronex was on the market, it was

being overprescribed to individuals with IBS, which is, in itself, a poorly defined condition.

By the end of 2000, Lotronex was associated with at least five fatalities, 63 cases of ischemic colitis, 75 cases of severe constipation, and 3 cases of mesenteric occlusion.

Because of the rate of under-reporting adverse advents to the FDA, it is likely that there were many more adverse events than this, some say perhaps 10 times as many cases.

It is our position that this is not an efficacious drug and that there was only a 10 to 15 percent difference in the response between patients that received Lotronex and the patients that received placebo. In addition, on a discomfort scale of zero to 4, Lotronex only relieved patient symptoms 0.12 to 0.14 points more than placebo.

Furthermore, the endpoints in the studies that Glaxo Wellcome submitted to support this drug were based on self-reported subjective criteria.

We also have serious reservations about the proposal of Glaxo Wellcome as to the class of potential users of this drug if it is reintroduced. This is based in part on Glaxo's past marketing record, and also on the fact that a person who

fails to respond to conventional treatment may then have access to the drug.

We heard today from numerous persons that this is a problematic situation because there does not appear to be an effective treatment that is considered conventional to date. This means that the lack of effective treatment could allow every person with IBS to potentially receive this drug upon reapproval.

The prior Medication Guide submitted for Lotronex and required by the FDA shifted the responsibility of preventing adverse events from Glaxo Wellcome to the pharmacists and patients. It is obvious that this did not prevent serious gastrointestinal events.

Further, the proposal now set forth by Glaxo Wellcome where it is requiring individuals to diagnose themselves with having ischemic colitis is deemed to be inappropriate at this time.

Because there is no pattern with respect to predictive factors for what patients may develop ischemic colitis or severe constipation, even the use of Lotronex in a subpopulation of individuals may result in severe adverse events or fatalities.

It is very difficult to require physicians

to only prescribe a drug to a restricted patient population when dealing with an ill-defined condition such as IBS. There will be an extremely well-defined criteria necessary to evaluate and decide on which patients should receive Lotronex.

Gradually, over time, it is likely that the drug will be prescribed to all IBS patients, and there will be even more fatalities and serious adverse events.

An active monitoring program is proposed herein today for Lotronex. If it is reapproved, it is of questionable value since only about 10 percent of adverse events are ever reported to the FDA.

I would go on record on behalf of my clients from the State of Mississippi and the Schmidt firm's clients whom they represent from the State of Texas, and ask that this drug not be reapproved at this time.

Thank you.

DR. WOLFE: Thank you.

Next, we have Brenda Compton, followed by Dennis Larry.

MS. COMPTON: First of all, I just want to say I didn't catch your name, but have you ever

soiled your pants in public?

My name is Brenda Compton and I have diarrhea-predominant IBS. I don't represent anybody except myself. I paid for my own way up here, and the first thing I did as I came in for the meeting this morning was make sure I knew exactly where the bathroom was as I have always had to do for the last 30 years every time I leave my house.

Now, I want you to spend the day in life with me. I am not a statistic, I am a person. I went on a field trip with my son, his sixth grade class, to the Georgia State capital. We boarded a bus in Flowery Branch, and began the one-hour ride. Fifteen minutes into the trip, the cramp hits my gut, and the familiar panic begins. I am soiling my pants.

Because this is a common occurrence, I have on lined panties. I pray no one notices the odor. Our school bus arrived and pulls up to the capital steps. I have already made my way to the front, so that I can get to the restroom as quickly as possible.

I change panties, throw the ruined ones away, and cry. I try to regain my composure for my

son's sake. I go back out to join him and his group, and guess what. It all begins again.

This is a scene I have lived out virtually all my adult life, and just when I am convinced it can't get any worse, it does. On June 25th, 1998, I had emergency surgery, and in a matter of two hours, I went from no menopausal symptoms to postmenopausal, depression. The bouts of diarrhea came more often, they came every day now. I began to lose weight at an alarming pace. I dropped to 88 pounds.

My doctor performed every conceivable and invasive test, if you have never had them, to try to find a cause, but everything was fine, no physical reason. Her only conclusion is I have an incurable disease -- incurable disease called irritable bowel syndrome.

Meanwhile, over the coming weeks and months, I continued to lose weight. The doctor orders a bone density scan because I have now reached 77 pounds. My life is in jeopardy. She tells me this. I have lost 11 percent of my left hip because my body has lost every bit of its fat and it is now pulling bone density just for me to live. So, it was life threatening to me. I almost

died from it.

Then, on May 9th, 2000, I got to my doctor for another visit, but this time there is hope. She tells me a new drug called Lotronex has just been released, and she wants me to try it. I begin that afternoon, and in three days, the diarrhea is gone, a true miracle.

Over the coming days, I deal with the fear that it will return, but it doesn't. My weight gradually increases, and my life is a new experience, normal.

Then, I remember seeing the morning news on November 28th, 2000, but nothing else registered the rest of the day. I cried uncontrollably. The availability of the only medication that had allowed me to live a normal life for seven wonderful months was gone. Today, I take another drug that sometimes works, sometimes doesn't. Most of the time it doesn't.

Once again, the humiliation and fear is back. She sent me into psychotherapy because I was suicidal and severely depressed. I am begging you to bring this drug back. I am not asking you, I am begging you. I keep this as a remembrance of the miracle of my life, and only you can bring it back

to me. I have copies of my doctor's letters that my life was threatened, almost went to the hospital.

Thank you.

DR. WOLFE: Thank you, Ms. Compton.

Mr. Larry, to be followed by Dr. Stolley.

MR. LARRY: I bring to you an interview of my client, Gloria, from North Florida who suffered bowel perforation following severe constipation. She now is quadriplegic, lives on a PEG tube, lives on oxygen. Here is her story. She asked me to bring this to you because she is addressing her comments to you, the FDA Committee.

[Videotape shown. Experience of Gloria Lockett.]

DR. WOLFE: Dr. Stolley.

DR. STOLLEY: My name is Paul Stolley, and I was formerly the Chairman of the Department of Epidemiology and Preventive Medicine at the University of Maryland School of Medicine at Baltimore.

I am co-author of a Foundations of Epidemiology Textbook and currently work half-time at the Public Citizen Health Research Group.

During the academic year of 2000-2001, I

worked 80 percent time at the FDA as a consultant in epidemiology for the group that collects and evaluates adverse drug reactions.

I co-authored and signed the FDA Memo of November 16, 2000, that preceded the November 28th decision by Glaxo to withdraw Lotronex from the market. I am also a practicing physician.

In that memo, we argued that there were compelling reasons for withdrawal of Lotronex from the market. The main points we made in that memo were that the drug is minimally effective and for only the diarrhea-predominant form and only in women, and that the price paid for this gender-specific diarrhea-predominant efficacy is much too high - ischemic colitis that can result in surgery, colectomy, and death, severe constipation that can require hospitalization and surgery, mesenteric artery thromboses requiring surgery, and rarely causing death.

The rate of ischemic colitis associated with the drug is remarkably elevated and beyond dispute as there were 16 cases in the alosetron-treated arms of the clinical trials and only one case in the placebo arm.

While the drug is only approved for 12

weeks of use, in actual practice, this chronic condition may be treated indefinitely with the drug.

The rate of ischemic colitis associated with Lotronex may be as high as 1 per 300 users in just the 12-week period. While many of these colitis episodes have not led to serious damage, there have been perhaps 7 or more reported fatalities and numerous surgical interventions.

The questionable argument has been made that ischemic colitis is a feature of irritable bowel syndrome, however, when the FDA searched its own adverse drug reaction files for reports of ischemic colitis, no reports of ischemic colitis were found associated with loperamide or diphenoxylate.

I believe this drug should never have been approved and I urge you not to reintroduce it, as you will just create another mini-epidemic of ischemic colitis and other problems.

Thank you.

DR. WOLFE: Thank you, Dr. Stolley.

This concludes the public forum. I want to thank all those who spoke for a couple of reasons. First of all, I commend you all for

doing what physicians can't do very commonly, that is, keeping on time. You did a wonderful job. Many of us run meetings with continuing education, by the way, which includes IBS oftentimes, and our speakers tend to run over. You were wonderful in keeping right to the point and keeping on time.

I want to editorialize here to some extent. I want to thank those of you who are the patients, who traveled here great distances, on your own money, and on your own time, to make public what should be a private matter between you, your family, and your physicians, and I thank you all for coming here.

We will reconvene at exactly 1:45.

[Whereupon, at 12:55 p.m., the proceedings were recessed, to be resumed at 1:45 p.m.]

AFTERNOON PROCEEDINGS

[1:45 p.m.]

DR. WOLFE: Before we start the questions, I would like to offer the opportunity for members of the panels to ask FDA and GlaxoSmithKline the questions from before. What I am going to do, instead of just going to individuals, I am going to go right in order around, and if you don't have a question, say pass. I will start again with Dr. Richter, if you want to continue your line of questioning to either FDA of GlaxoSmithKline.

Let's try to keep the questions succinct and the answers succinct, as well.

More Questions on Presentations

DR. RICHTER: The question I have is really for Victor and maybe other people at the FDA. Surely, there must be, I am sure there has been other drugs that have come through the FDA for an IBS indication with diarrhea being a major symptom, and have they had the opportunity to go back and look through those studies to see if there is this unusual instance of ischemic colitis, particularly in the background, because I have to say I find that background data in the normal population of IBD a little surprising from my own

clinical experience.

DR. RACZKOWSKI: I am going to ask Dr. Hugo Gallotorres to answer the question, but just in general terms, many of the drugs that were developed for IBS or that have any sort of indication for IBS are old drugs, and we certainly are looking at some of the newcomers in this field as to whether this might be a class effect or not.

DR. GALLOTORRES: Yes, indeed, we have several applications for diarrhea-prone IBS, but these are INDs and we cannot comment on this, but there are several. I hope that answers your question.

DR. RACZKOWSKI: Just one more comment. Some of the other drugs that had been developed in this area, some of the older drugs were the anticholinergics, and they basically failed in terms of being able to demonstrate efficacy for IBS.

DR. WOLFE: Dr. Cryer.

DR. CRYER: This is a question for the sponsor. So, given that IBS is not infrequently an episodic disease, what can the sponsor tell us about the timing or the incidence of ischemic colitis as it relates to the phase of IBS, which

the patients in the clinical trials were in?

DR. CARTER: Most likely because of the small number of cases that we saw in the clinical trials, we really don't have that data. Most of the patients I believe, at least based on the baseline characteristics, which on the whole were two weeks in duration, were in the same chronic phase. We don't have any evidence of any change in their baseline presentation. So, I can't answer that question.

DR. WOLFE: Dr. Anderson, any questions?

DR. ANDERSON: No.

DR. WOLFE: Dr. Venitz?

DR. VENITZ: Yes, I have a question for Glaxo, as well. I am looking at your background material where you justify your dose, which is right now 1 mg BID. I am on page 22, looking at the results of your Phase IIA studies, and I am wondering whether you have really found the optimal dose, because obviously, one of the things that you are proposing as part of a risk management plan is a dose titration strategy, implying that the dose right now may not be the optimal dose for every patient.

So, what is the evidence for you to have

started in the first place with a 1 mg BID dose?

DR. TRABER: Well, you are quite right that a decision to choose a dose is a very important one in the clinical trial setting. There was a lot of discussion around what dose to choose at the end of the Phase IIA studies.

The dose of 1 mg BID was chosen, though, and therefore, all of the Phase III clinical trials were done with that dose. So, therefore, the vast majority of evidence we have is with 1 mg BID.

The dose titration issue gets at the fact that the physiological effect or the pharmacological effect of the drug is to cause constipation in a reasonable percentage of patients, and often in drugs that have a predictable type of side effect, clinical practice often dictates some titration up of the dose.

Furthermore, when used in the market, there is lots of testimony from patient's physicians that a lower dose works, so we feel the titration that we propose is prudent medical care although the vast majority of our data is based on 1 mg BID.

DR. VENITZ: I am very much in favor of dose titration, don't misunderstand me. It is just

I am looking at your dose titration studies, and it appears that the doses higher than 1 mg, you actually have less of a benefit or less of at least short-term benefit.

So, I am not sure whether the 1 mg dose is already at the plateau of your dose response curve or you could even go lower than 0.5, which is what you are proposing right now as your starting dose.

[Slide.]

DR. CARTER: This was the first of the two, Phase II dose ranging programs in female patients where the 2 mg dose was seen to be more efficacious, at least for the female population there than the lower doses.

If we go to the next one, E12.

[Slide.]

This is the second dose-ranging study where if I can just look at the males first, we see the dose is seemingly no benefit with respect to the placebo for the male, whereas, in the female study, the adequate relief endpoint was clearly beneficial, more beneficial at the 1 mg dose.

DR. VENITZ: But as you go higher, at least pharmacology would dictate that you would see more of an effect, and you actually have a

reduction as you go to higher and higher doses. I guess that is what I am pointing out to you.

DR. CARTER: Right. I mean that is a feature of what we saw in this particular trial.

DR. VENITZ: Let me rephrase my question then. Do you see any benefit in going actually lower than the 0.5 as a starting dose and starting maybe at 0.25, or do you think that that is going to be completely futile?

DR. CARTER: It may be that this is something that we have to consider, but I suspect that we probably are going to reach a point where the efficacy would just not be shown at that point.

DR. VENITZ: The second question that I had, did you actually break this down by the severity of the symptoms and baseline conditions?

DR. CARTER: I don't believe we did.

Dave, do you know whether we broke this down by severity of symptoms at all?

DR. VENITZ: It may be worthwhile doing to see whether a different starting dose, depending on the baseline severity, would benefit.

DR. McSORLEY: In the Phase II studies that we did, the first study that was done in Europe had all IBS subtypes and both genders, and

what we saw was a beneficial effect primarily in females who had the more diarrhea-like bowel habits, looser stools, more frequent stools.

In the 8-2001 study that is shown here, also enrolled both genders, that was done in the U.S., and because of the results we saw by the severity of bowel functions in the previous study, this study was limited to look at just the higher stool consistencies.

So, we had evidence from earlier on that it was more beneficial in those with more diarrhea-like symptoms and less beneficial for those with firmer and less frequent stools.

DR. VENITZ: Is there any way that you can tease out if there is a different starting dose possibly required for the different subpopulations?

DR. McSORLEY: Well, at this point, you can see the numbers are getting pretty small, and that n equal 197 is across all five of the dose groups, so it is probably a little bit difficult to tease that out additionally with so few patients.

DR. VENITZ: Okay.

DR. WOLFE: There is another. Efficacy is one thing. The other reason is to start at a lower dose. For those of us, let's jog our memories a

little bit. When we used sulfasalizine, we started with a 5 mg dose knowing full well it didn't really work, but we did it for safety purposes, and you have shown that constipation is dose-dependent.

I can tell you know--this is anecdotal--but some of my patients did well on 1 mg every other day, as did other patients in the audience, and some of the records that I did read. So, mostly for safety purposes, sometimes it is prudent to start at a lower dose to see its tolerance, especially in dose-dependent constipation.

So, I would actually ask that you would consider if we go forward with this, starting at a lower dose for that reason.

DR. LaMONT: For Dr. Raczkowski, your final slide said that the success of the plan could be evaluated through process controls or evaluation of outcomes, and I just wonder what you had in mind for that and what criteria might be used to finally withdraw the drug.

Would it be the same toxicity, worse toxicity--I assume worse toxicity would be one reason, but would similar or identical toxicity be reason to finally withdraw?

DR. RACZKOWSKI: These are actually questions that we are posing to the Advisory Committee, Questions 4, 5, and 6 are largely focused on process controls, and Question No. 7 is focused on outcome and whether or not the Advisory Committee feels that those are appropriate.

DR. LEVINE: A question for Glaxo and a question afterwards for Dr. Krist. I wondered, it is apparent that during the clinical trials, there was much more attention paid to constipation, both the observation of it and the withdrawal, the statistics are higher for those people who, during the clinical trials, were stopped because of constipation.

As it opened into the market, there was less available about the complications. Toward the ends of your studies, when you were still having clinical trials, can you pick out any particular trials in which the incidence of constipation was higher as the public and as the physicians were more aware of it toward the end of your trials or trials that are still under progress, and not analyzed well yet from a chronological point of view?

DR. CARTER: No, I can answer that in two

ways. First of all, the trials where attention was placed on constipation, and there were two, one trial was the open-label trial that we have referred to before where patients knew that they were on a drug that was potentially constipating, we tended to see more constipation there.

In two other trials, the urgency trials that Dr. Traber showed this morning, one of the secondary objectives was to look at the impact of an intervention, withdrawing drug or drug holiday, or instituting laxative use, and we instructed the investigators to make sure that the subjects in these trials proactively reported any event of constipation.

What we saw there is that we saw a rise in the reports of adverse events of constipation, a rise in the alosetron-treated group, and a rise in the adverse event reports of constipation in the placebo group, so that the delta was about the same.

DR. LEVINE: I will pass on the next one to Dr. Krist because we will probably discuss it, unless you want me to go ahead. Actually, what I was going to ask Dr. Krist is, as a family practitioner, it is apparent on one of the possible

routes of approval of this product, is to consider the burden that the physician has to do to take care of it, the interaction, the time involved, gastroenterologists versus family practitioners.

I wondered, in your experience using some other drugs where you are, in fact, committed to do--

DR. WOLFE: Time out. This is questions to the Company.

DR. LEVINE: Just to the company?

DR. WOLFE: Yes, Company and FDA.

DR. LEVINE: That is what I thought, I don't think this is the time.

DR. WOLFE: This is clarification now for presentations. We will get that later on. Actually, we will have some time for that.

Dr. Fleming.

DR. FLEMING: Several questions. Let me try to highlight two related key questions and just see how time allows.

Dr. Raczkowski made a very key point in his presentation, noting that patient selection is at the heart of a risk management plan as we go from here and think how can we either treat or evaluate a patient population in the optimal way,

identifying as best we can who those people are that seem to have the greatest chance of a favorable benefit to risk.

There are two key aspects of that. One is identifying the population at lowest risk and the population at highest benefit. So, taking things one at a time, where ischemic colitis is a key focus here with incidence rates projected at 2 to 5 per 1,000 at three months.

We heard several discussions today, and they seem to repeatedly make the same point. Dr. Carter, Dr. Permutt, Dr. Mackey all said data do not reveal any potential risk factors for ischemic colitis, and Dr. Mackey went beyond that to say presenting symptoms do not necessarily predict severity of outcome.

So, my first question is, is it proper, am I missing anything, is it proper to conclude at this point, as it relates to ischemic colitis, that we really don't have insights as to who we would identify as that cohort that would be at a lower risk?

The second aspect of benefit to risk is benefit, is efficacy, and a similar question arises there, what insights do we have? I know Dr.

Raczkowski speculated that patients that have the most disabling symptoms stand to benefit the most.

Are there direct data that the FDA or the sponsor can put before us that provides insights about potential effect modifiers? The only thing I could find from this morning's presentation was slide A32 by Dr. Traber that basically looks at potential effect modifiers for efficacy based on baseline level of severity for baseline pain, urgency, and frequency, and it doesn't show any effect modification. It shows the same magnitude of effect that either is not greater effect in any specific subcohort.

So, two related questions. Are we missing anything that you folks know that we haven't seen, that would assist us in identifying the subgroup that has the greatest likelihood of achieving favorable benefit to risk?

DR. TRABER: Let me speak to the efficacy question first. I also mentioned around that trial, looking at the data, separating it out, that indeed individuals with harder stools, fewer bowel movements, fewer than two bowel movements per day did not have an efficacious response to alosetron. So, there is a subpopulation of individuals that

identified themselves as diarrhea-predominant, but did not have an effect.

However, the data that I did show, by separating out the information, shows that those with moderate or severe symptoms, as defined by both urgency, numbers of stools, and pain, had similar benefit.

In looking at the information with more severe patients, and that would be those patients that had urgency more than 80 percent of the time, more than 80 percent of the days, there was a marked efficacy improvement there, so we did look at more severe groups.

But in the post-hoc analysis of the studies, both moderate and severe patients had the same, had effect.

DR. FLEMING: Could you show us those data that basically separate out the most severe patients from lesser severe patients to give us a direct data presentation of what that effect modification is?

While you are getting that, a second question, you have specifically stated that your proposed target population would be diarrhea-predominant IBS who failed to respond to

conventional treatment. Do you have any specific evidence, when we target that group who had failed to respond, to show us that we, in fact, have direct evidence of efficacy in that subcohort? Two additional questions, I guess.

DR. TRABER: The direct answer to that is no, we don't have a clinical trial taking patients who have failed a defined conventional therapy and placed them alosetron. What we were looking for in the labeling was a straightforward way to identify individuals that would have more severe debilitating disease, those individuals who have been evaluated to have diarrhea-predominant IBS, who had been treated by a physician and failed conventional therapy, which would be education, reassurance, diet, anticholinergics, and antidiarrheals, and that that subpopulation would be an effective way for physicians to identify a subgroup.

The other thing is we did evaluate in comparison alosetron to traditional therapy, so a selected group of individual who were selected for all the same characteristics, and although, on an open-label trial, randomized to either traditional therapy or to alosetron, and saw marked

differences.

DR. FLEMING: But that would be, of course, a different--I mean those who would be people who hadn't failed obviously.

DR. TRABER: It answers a different question.

DR. FLEMING: So, essentially, what is really critical if we are looking at a proposed indication, is to, at a minimum, have direct evidence that in that proposed indication, i.e., those that have failed conventional therapy, that we have confidence of efficacy, but I am eve looking for more than that, the evidence that you would have to confirm what we would hope to be the case, but nevertheless, isn't always true, and that is those with more severe baseline disease, in fact, are those who benefit the most.

I think you were going to present something on that?

DR. CARTER: If you can put up L-35.

[Slide.]

This was again post-hoc analysis here, looking at the pooled data from five placebo-controlled trials, looking at symptoms on a daily basis with adequate relief of pain and

discomfort as stratified for the most severe symptoms at baseline, and then followed over the duration of the trial here. Weekly adequate relief with the pain severity of greater than 2.5, which was in the moderate to severe category.

DR. TRABER: You want a comparison of the less severe patients to the more severe patients.

DR. FLEMING: Indeed, as you presented in slide A32. This just seems to be more confirming that you have roughly the same magnitude of effect across all subcohorts.

DR. TRABER: Could you put up A32 then.

[Slide.]

Here, the point is you are correct. We did stratify to what we call moderate and severe pain, urgency, frequency, and so forth. What we don't have on this slide, and I wonder if somebody could find this slide, is those individuals that had harder stools or less than two stools per day, and their effect by alosetron, which is the question you are asking.

This is 3 to 4, and this is 4, but there is also a subgroup less than that.

Maybe what we can do is find the specific slide for you and come back to that. I think the

FDA also concluded from their analysis of the data that the individuals with less than two stools per day also had less efficacy than the moderate to severe.

Your other question, which I think was your first one, was about ischemic colitis, and, indeed, you are correct. We found no evidence of a predictor for individuals who might develop ischemic colitis.

DR. RACZKOWSKI: Some of the analyses that were done independently by the FDA statistician showed that patients with less severe urgency at baseline tended to respond roughly with the same order of magnitude of a treatment effect as those with more severe urgency.

I don't know the details of exactly how the data were cut, but that observation was confirmed. In addition, patients who did have the harder stools or stools less than twice per day also tended to have less benefit.

DR. FLEMING: So, in summary, for this critical point that you put before us, at least the data that we have right here either doesn't allow us to identify the risk groups that have the greatest risk or lesser risk, or efficacy, those

that have the greatest benefit or lesser benefit at least relative to the analyses that have been done to date?

DR. RACZKOWSKI: Well, I think we would be interested in any qualitative advice you might have in that regard.

DR. WOLFE: I hate to be a drill sergeant, but we allotted 20 minutes initially for this, so let's again keep these questions succinct, try not to repeat the same question, and answers also succinct.

DR. METZ: I have a couple of quick questions.

First of all, regarding the colonic ischemia question, I found it interesting it was mentioned earlier that some of the effect of this agent may be to reduce pain sensation, and some patients become so constipated and had a lot of pain, got sick because they didn't know that things were happening.

On the other hand, I find that all the patients who presented with colonic ischemia, presented with pain, and that was 75 percent of the time. Colonic ischemia, to my understanding, generally does not present with pain.

The next point that comes up is that there were these five cases that were discovered by the FDA, perhaps in dispute by Glaxo, of mesenteric ischemia, which does present with pain and which in itself for me is a real life-threatening condition, and I am wondering if we can clear up the dichotomy between those two. That would be Question No. 1.

DR. BRANDT: I think that I can answer that for you. You are correct when you say that patients with colonic ischemia have a pain that is different from pain in patients with acute mesenteric ischemia. I am not going to answer a question that hasn't been asked yet, which speaks to the difference between acute mesenteric ischemia and colon ischemia, but I think it is crucial that at some point in this discussion we do that.

To answer your question, patients with colon ischemia frequently have abdominal pain in their presentation, but it is usually a mild pain, an inconsequential pain, and one that the patient might even forget that he or she had it unless prompted and reminded of it.

The predominant symptom is almost always rectal bleeding and bloody diarrhea. So, if you have a patient who has what you believe to be colon

ischemia, and has severe abdominal pain, then, they either have severe colon ischemia with transmural disease and are close to perforating, who have transmural gangrene, or they have colon ischemia and acute mesenteric ischemia, or they have acute mesenteric ischemia with GI bleeding, and maybe they have elements of both, and perhaps you were a little bit confused, or it is their underlying background disease of abdominal pain.

But you are right, the presence of significant pain should make one think significantly about the accuracy of the diagnosis.

DR. METZ: Thanks. The other point was in terms of this titration issue and the efficacy at the lower doses. I understand very few patients have been treated 0.5 BID. Our of interest, I would like to know if Glaxo has data on the 0.5 BID, number of patients, and how well they responded, female predominant group. It is probably a small number.

In practice, I think what will happen is this drug is really going to be used on an as-needed basis. It will be used briefly and then stopped, and depending on how the disease is going. So, do you have any data on using this agent as it

may well be used clinically, which is more of a prn use?

DR. CARTER: We don't have any data on the prn use at all. As far as the data on the 0.5 mg BID, I think we have shown you, and what you see in your briefing document is the data that we have there. We don't have any additional data in diarrhea-predominant women.

DR. TRABER: I just thought I would quickly follow up on the question that I said I would get back to some data on. We have found some of that.

If you could just show the first slide there.

[Slide.]

We have these cuts for a variety of data. This happens to be the baseline consistency of the stool. This is the most mild group in terms of consistency, and there was no statistical difference between the two groups in terms of consistency in this mild group.

[Slide.]

However, if you get to the baseline consistency where it was rated 4 to 5, there was a highly significant response from week 2, all the

way through the 12 weeks.

So, we have these cuts of data showing that the lowest level of symptoms didn't have statistically significant responses.

DR. WOLFE: Dr. Gross.

DR. GROSS: I am getting the sense that there wasn't a significant effort to try to rule out inflammatory bowel disease in these patients with irritable bowel syndrome.

Were the patients that had perforation and death, or other complications, screened at all for Crohn's disease or ulcerative colitis?

DR. CARTER: Although we did see some very rare number of cases where the patient was subsequently diagnosed with inflammatory bowel disease that originally been on irritable bowel, most of the patients, at least in the clinical trials, on average, carried a diagnosis, a single diagnosis of IBS for at least 10 years, so these were chronic IBS patients, these were not typically new IBS patients.

With respect to the postmarketing surveillance data, we see somewhere in the region of 5 to 20 percent of off-label use, if you will, and some of those will possibly be patients with

inflammatory bowel disease.

Do we have enough cases to be able to make a statement with respect to a differential impact on complications of constipation or ischemic colitis in inflammatory bowel disease, the answer is no.

DR. STROM: Three questions. The first is we are seeing a pretty consistent pattern of on the order of a 30 percent placebo response, perhaps a 50 percent response on the drug, very consistently statistically significant, but very modest in magnitude, and yet we are hearing very dramatic response from individual patients that is clearly very convincing.

Could we be having here a problem of law of averages, that your 30 to 50 percent is mixing together some people who are having very large effects and other people who are having no response, and so the net effect is a modest response only, but if you, instead of dichotomizing of just response, non-response, you looked at degree of response, you might have a bimodal response, and might be able to pull out a small subgroup of people who should use the drug, and, in fact, will benefit dramatically from it?

DR. TRABER: I think this is a very good point. I think the one consistent thing that we have seen in all the trials is the fact that multiple symptoms of IBS are affected by that 20 percent differential between the placebo response, and therefore, the global effect in some of the other quality of life effects are pretty pronounced.

However, I am going to ask if we have information about the spread of the data for the responders. Dave, do you have any comments on that?

DR. McSORLEY: I think that we have shown you, we have tried to retrospectively go back and look at response in different severities of subjects.

DR. STROM: Let me try to be clear. I am not asking now severity of how the patient started. I am asking, rather than the response or not response, which is what you average together, look at the degree of response.

Was this small, average response that we are seeing, in fact, everybody responded a little bit, or a few people responded a lot, and most people didn't respond at all?

DR. McSORLEY: Some of the analyses we have done, in the urgency study we have tried to look at that. I mean I think you still are asking a question of separating out who is responding the most. I think you have to be a severe patient, you would have a greater response than those who would not. If we could show slide N165.

[Slide.]

This was an analysis that we worked on with the Agency at identifying patients who had urgency control on less than 30 percent of days at baseline, and then identifying responders who had been satisfactorily controlled on at least 75 percent of days at months 1, 2, 3, and then overall months.

So, what this does is it attempts to identify those who would be making the larger changes from an improvement rather than little changes for people who are not that severe. This was replicated pretty much in both of those urgency studies.

If we could go to N166.

[Slide.]

Further restriction. Again, having less than or equal to 30 percent of days with control at

baseline, to then having greater than 85 percent, you see again there is a suggestion of a pretty good difference in the proportion of patients who actually moved quite far.

In addition, we did some of these analyses at the request of the Agency to look at some of the quality of life endpoints, again trying to identify those who would show dramatic changes. If I could show slide L14.

[Slide.]

We have a quality of life instrument, the IBS Quality of Life questionnaire was done in five placebo-controlled studies, and here, we looked at some of the individual questions. This happens to be four questions with respect to the social activities score.

What we are showing here is the proportion of patients who changed from rating themselves as "severe" at baseline to having none or mild symptoms at the end of 12 weeks. What this shows is a pretty nice improvement from a more severe state to a very much improved state.

If we can look at L15.

[Slide.]

These are activity function questions, and

we see a similar thing.

L16.

[Slide.]

These are two energy questions. I don't know if that actually addresses your question fully, but that is the extent at which we have attempted to identify those patients who would be making large improvements.

DR. STROM: This certainly begins to get at it. I guess what I am trying to get a sense, and I think I am hearing the answer to be yes, although if I am hearing you right, I am not totally sure, that there is a subgroup of people who are responding a lot. We have heard that in the testimony. We have seen that in these data.

Can you differentiate for us those who were responding a lot from the rest of the people who don't respond as much, if that is true?

DR. McSORLEY: We haven't actually done that other side of the equation. What we focused on, again in anticipation of some of these questions, was to try to identify those subsets of patients who were severe, who may derive the most benefit.

The clinical trials program was halted

when the drug was withdrawn, so we couldn't prospectively identify these kinds of subgroups. We had to retrospectively go back, and all of our focus has been on the more severe patients, and we haven't actually done the complementary side looking at the less severe other than to look at the adequate relief endpoint with respect to those patients who again have lower stool consistency, meaning firmer stools, less stools, less urgency. Those patients we know do not derive as much benefit, in fact, there are at higher odds for a lack of efficacious response.

DR. STROM: I will try one more time just to be clear. It is among people who start out severe. I am not asking about the people who start out mild. Among people who start out severe, there is a subset of people who have a major response is what you are saying.

I assume there is a complementary subset of people therefore who don't respond much.

Have you looked at retrospectively, not as a prospective study, within your clinical trial data, can you differentiate for us, of those people who start out with severe disease, those people who are going to have a large improvement versus those

people who are not going to respond at all, because they are being mixed together in the efficacy data we are seeing?

DR. WOLFE: Dr. Hoberman from the FDA wants to say something about this, too.

DR. HOBERMAN: When I originally reviewed the Lotronex NDA, I noticed an interesting pattern. I think this will get to Dr. Strom's question.

If you look at the distribution of response, it turns out that it is highly bimodal. You respond to this drug or you don't respond to this drug. If you break it out by the number of months, consecutive months in which you respond, there is a big spike in the beginning where you don't respond at all, and there is a big spike for people who respond for all three months.

In the middle, there is random garbage. So, that is one reason why it was clear to me that if you don't respond to this drug in the first month, you are probably not going to respond. The chances of responding for all three months, if you do respond in the first month, it is about 85 percent.

Also, getting to this question of yes, we have heard these dramatic responses from the people

who have come to testify. That doesn't surprise me. I think it is a small percentage. One of the things I think you have in your packet that I did do was I looked at a very tough threshold for response, that a person had to start with at least 70 percent of baseline urgency and had to fall to some threshold for every single week of the 12 weeks.

So, those are the people I think we have heard from. That happens in the order of 10 to 20 percent of the time, around 10 percent, so there really is--it is an absolute 10 percent. I am not talking about a treatment difference, but I think that it may be fair to say that since this drug works, that there is a small number of people who are going to get dramatic effects from it.

DR. STROM: That is exactly the group I am looking for. Can you compare, did you do analyses that would compare that 10 percent who would have dramatic responses to the other 90 percent, so that we can try to differentiate them, because if this drug can be steered to the people who are going to dramatically benefit from it, then, obviously, the risk-benefit of the drug dramatically improves?

DR. HOBERMAN: I am sorry to disappoint

you. I didn't get much further than the Company did. My sense is that is going to be hard to tease out. I took this data from the two urgency trials. I am not sure the numbers are going to be there to really make anything definitive, because I think I agree with the Company that there isn't a whole lot of data here to say that somebody is going to respond, and somebody not respond, unless they have formed stools or something like that when they take the drug.

The last thing I might point out is--I don't know whether the Company pointed out--but the baseline urgency of the so-called urgency trials, 3011 and 30031, actually was quite a bit higher than the original trials.

What at least I found, I don't know about the Company, was that the actual responder rate was higher in the so-called urgency trials with the more severe baseline urgency, both in the drug group and the placebo group, and I wasn't expecting that.

I don't know what to make of it, but there is certainly an indication that more severe patients in that general sense might get a little more effect.

DR. CARTER: Dr. Wolfe, may I make just one comment? We have talked a lot about the therapeutic gains seen vis-a-vis individual symptoms here, and there have been some comments about that this gain is possibly modest in some instances. I think we all need to remember that IBS is a multi-dimensional syndrome, and what really matters to the patients is not necessarily whether any one or other symptom is improving.

So, when we asked the patients, using our global improvement score to integrate the sum of their symptoms, we actually saw therapeutic gains in the order of 30-plus percent, and I would say that that is not a modest effect if we benchmark it across the therapeutic gains of other drugs.

DR. WOLFE: I want to move the discussion along, however, this is very valuable because the more we clarify here, the less time it will be necessary, then, to answer the questions later on.

I want to make one comment about symptoms in general as opposed to structural lesions. This has nothing to do with IBS, but I think the best example here is when we talk about reflux disease. It is very easy to show healing of esophagitis, but it is much more difficult to show an improvement in

pain symptoms.

So, when we talk about pain, there is a lot of subjectivity involved, and an improvement is an improvement, and I think we have to keep that in mind.

DR. STROM: One comment there and then my other two questions. When you study pain, though, you usually have a bimodal population. You usually have responders and non-responders. In order to maximize the risk-benefit of the drug, we need to identify those responders, so instead of being used in the whole population who are at risk, identify the responders.

Let me move to the second question. What is clear is we don't have any information on risk factors for ischemic colitis. In the population that was treated with the drug, there are only 18 cases, you are not going to have enough power, it is not a surprise.

How about risk factors for ischemic colitis in general, because you would expect that the people who are at higher risk for ischemic colitis in the general population would also be at even higher risk of ischemic colitis when placed on this drug. Those would be logical people to

contraindicate use in.

DR. BRANDT: There are many risk factors that have been identified for colon ischemia although in the vast majority of cases, even in the older people, the classic population, you don't find anything other than general atherosclerosis in the population.

Having said that, the minority of people are well accounted for by medications, of which there are more than 80 that have done this, among which are NSAIDs and sumatriptan, and estrogens, et cetera, coagulation disturbances probably the most common being factor V Leiden, parasitic disorders, and a variety of other factors.

DR. STROM: Last question. We have heard a lot about the definition, Dr. Traber talked about, formal definitions of irritable bowel syndrome as a difficult thing to initially define, and a lot has been developed out of this research. Dr. Carter talked about formal definitions for the outcomes and the detailed medical record review needed to achieve that.

Dr. Walker's data has been referred to a number of times, suggesting a background rate of serious complications in people who had a diagnosis

of irritable bowel syndrome.

Was that with or without access to medical records, were those claims diagnoses only or was that with medical records, and what level of medical record review comparable to the clinical trial review were you able to do?

DR. WALKER: The complications of constipation that we reported was based on claims data that were structured to be similar to those used in the postmarketing definition, so it was obstruction ileus without surgery, impaction, and the like.

When we reviewed the medical records, and we have done that for 80 or so cases, what we are finding is that there is actually very good confirmation of that, but the attribution to constipation is infrequent, maybe 30 percent with your constipation attributable.

DR. DAY: I have a number of questions for Dr. Wheadon concerning the risk management plan, however, since so many of the questions this afternoon are going to be devoted to that, I will wait until the appropriate time, but I will be interested in particular in comprehension of the materials prepared, the Medication Guide, the

labeling, the physician-patient agreement letter, and so forth, and how they are going to assess comprehension by all of the parties involved, the patients, the physicians, and the pharmacists. So, I will wait until then.

DR. WOLFE: Dr. Gardner.

DR. GARDNER: Dr. Strom has taken care of two of my three questions, so I will ask the third.

For Dr. Walker, when you looked at the United Healthcare databases, specifically, the prescription database, out of which you gave us one finding related to the characteristics of the prescribers, did you get a feeling for the continuation rate, the dispensing patterns there. I am specifically interested because we have heard repeatedly that in the months on market, approximately half a million prescriptions were written for approximately 275,000 people, and for chronic medication, we are now somewhere under two scripts a person in a period of time.

I wonder if the pattern or prn use is evident in the prescription data at United Healthcare. Can we get any enlightenment about this?

DR. WALKER: There were about 2 1/2

prescriptions per patient who received Lotronex during the marketing time. The date of first prescription, of course, extended right up until the end, so that there wasn't an opportunity for everybody to even have a repeat prescription.

DR. GARDNER: Sorry, I guess I mean for those that started right out, and I assume it took some time to get on the formulary and all those caveats relating to finding a market, were you able to identify whether, in fact, there is a subgroup of people who are actually using this product chronically and filling every 30 days?

DR. WALKER: No, I only have the 2 1/2 over the average.

DR. HOUN: FDA did some analysis on use. Dr. Zili Li?

DR. LI: Yes, we did some additional analysis based on the HMO data. At this time, we have not got final approval about source of data, so I just let you know on the nature of the data. Basically, we did analysis based on about 1 percent of all the prescriptions in the United States, on one HMO network.

Another one is from HMO network, which I will say has 20,000 patients, women, used Lotronex

during nine-month period. So, it roughly covered 10 percent of the patients who have used Lotronex in the United States.

So, what we did, what we received from HMO is all the detailed prescriptions, prescription for each members during the nine-month period. Then, we applied the lifetime table analysis to try to estimate, for the patient when they started with the drug, how long they remained in the treatment.

The result, the bottom line we got is for all the patients start from day one with Lotronex, by the day 30, about 60 percent of patients would drop from the prescription, so they would not continue their prescription, they would not continue their treatment anymore beyond 30 days. Sixty percent dropped just on their own, whether interaction with the physician, we don't know, for whatever reason, but from the pharmacy data, they do not renew this prescription beyond 30 days, 60 percent.

About 20 percent of patients, they used up to three months, and roughly, about 10 percent used the drug continuously if we just observe the pattern of prescription, for six months, 10 percent for six months.

Since the drug only in the nine months on the market, and the patient beginning very small, so roughly by the month 7 or 8, we got down to 6 or 8 percent of population remained on the treatment by the seven or eight months, so we are thinking that is the data you wanted.

DR. METZ: You say 60 percent of the people stopped. That meant they didn't renew their prescription.

DR. LI: They do not renew it.

DR. METZ: But that doesn't necessarily mean they didn't like the drug, and they stopped it because it didn't work, because this could just as well mean that the person was using it prn, and didn't get around to the next prescription because they didn't need it anymore, they hadn't run out.

DR. LI: I think you ask a very good question. I could not answer to you at this point why, the reason patient stopped the prescription. Maybe they think they are cured, but at the time, I just let you know intention, our analysis of time is we heard a lot of patients think they have great benefit. We assume those people who demonstrate a great benefit will be the patients who stay on the drug for a long time. So, that is our objective at

that time, to try to identify those people, what percent of people were likely to stay on the drug for more than six months or longer, who were likely to benefit from this drug.

DR. WOLFE: I think it is multifactorial. Some didn't continue because it didn't work. We know it doesn't work in everybody, and also some take it prn, and some people just stop taking medication. We know that.

DR. LI: Thank you.

DR. STROM: But it is interesting, it is the same 10 percent figure we heard before of the people who get dramatic responses.

DR. CARTER: Can I just add one comment here, and that is, that surrounding all of the publicity in June, we started to see a fairly dramatic drop in the prescription of alosetron, so from the time of the publicity around the adcom in June until it was withdrawn at the end of November, we basically have a bell-shaped curve with peak at just before that time.

So, I think that the actual time that we have, of length of time of treatment, it becomes very limited as time goes by.

DR. WOLFE: As I said, multifactorial.

DR. CAMPBELL: Perhaps I could ask for two clarifications on the risk management program. I believe in the background material, in the evaluation of program effect, a comparator group was identified to be used to compare effect of the program with the actual users.

In the presentation, I didn't hear, nor did I see in the materials, a comparator group would be part of that evaluation. First, is that group present or are there issues of privacy here that I would like you to respond to?

DR. WHEADON: There was mention of a comparator group in terms of the study focusing on occurrence of events of special interest where you look at patients that were prescribed Lotronex. You would also look at patients with IBS who had not been prescribed Lotronex.

Now, there will be some issues in terms of trying to have exact similarities in terms of that cohort, but there will be an attempt as best one can to look at issues around the occurrence of the events of special interest.

DR. CAMPBELL: And do you believe you will be able to get the information from the IBS patients who are not part of the risk management

program, they will not have signed--

DR. WHEADON: Well, again, this is a standard research paradigm in the United Healthcare database with the ability to collect information in an appropriate manner in respect to patient privacy, but I will let Dr. Allen Walker add more specifics around that.

DR. WALKER: The matching would be done in terms of health care utilization patterns. The use of claims data, which is clearly deeply encrypted when we use it, would fit under expedited review in the usual epidemiologic application, so I don't anticipate a problem.

DR. CAMPBELL: Second question. The proposed relabeling carries a statement "not proven effective in men." Is it your intent that that would disqualify men from participation in the risk management program by the sponsor, or does it mean that the prescribing physician could include the physician, but do that by taking increased liability?

DR. WHEADON: Recall that the risk management program is intended to assess the use of the drug in the real world. So, as such, while the indication clearly is earmarked for women with

diarrhea-predominant IBS that haven't responded to conventional therapy, if an individual physician chooses to prescribe the drug to a male patient with IBS, that would be a component in looking at patient demographics of those patients that received the drug, that would be assessed under the auspices of the risk management plan.

DR. CRAWFORD: My questions also deal with the proposed risk management plans if the product were to be reintroduced. I have one for Dr. Piazza-Hepp and three for Dr. Wheadon or any representative of the sponsor.

For the FDA, several times during the presentation of the proposed aspects of different programs, you were talking about pharmacist registration or pharmacy registration. I would like to get it clarified which one is the intent for our consideration for today's advice.

For the sponsor, I would like clarifications, please, about patient supply. It was clear that in the proposed risk management plan, you propose a 30-day supply for the first month, and also it was clear that there would be a new prescription required after that, but what is to keep the prescriber, if anything, from writing

for a 90-day supply or a 6-month supply? Are there any proposed days supplies limitations?

The second question, I would like to hear a little bit more about these stickers. It appears that the physician can make an attestation statement about knowledge and experience, and if I am interpreting it correctly, at that point, any willing physician could get the stickers through an 800 number of the sales representatives.

Is that correct, and if so, what is the purpose of it?

DR. WOLFE: We will discuss that question.

DR. CRAWFORD: We will discuss that question? Thank you.

Lastly, just a few more remarks, please, about explicitly, does the proposed risk management plan have anything to do with hospitalized or institutionalized patients? I did hear the statement that gastroenterologist in the hospital could write it without a sticker, but will the proposed plan have explicit language about the role of the prescriber, the patient, and the pharmacist for institutionalized patients?

DR. PIAZZA-HEPP: I believe the first question was addressed to me, and that was, yes,

were you saying registered pharmacists, individual pharmacists, or pharmacies? Just based on the plans that are in effect and do that, it is usually the pharmacies, either a retail pharmacy or some plans actually use a central pharmacy that is registered, and it is limited to that central pharmacy, also some institutions, the pharmacies are registered, and they get training and education. Individual pharmacists, that has not happened to my knowledge.

DR. WHEADON: To answer the two that I am allowed to answer right now, focusing initially on the issue of subsequent prescriptions beyond the first 30-day initiation period, the intent is that the desire would be for, as I indicated, active physician follow-up. However, after the first 30 days, we are not mandating, in terms of the risk management plan, specifically, that prescription can be limited only to 30 days after the initial treatment period.

However, the way we are proposing for the drug to be packaged, in terms of unit of dose sort of packaging, the easiest way of dispensing the drug and the easiest way for the patient to receive the drug, would be in a 30-day framework, but there

is nothing that would prevent a physician from deciding to prescribe for longer than 30 days after that initiation period.

In terms of hospitalized patients, the risk management plan does not specifically address patients that are hospitalized beyond the standard requirements of the appropriate patients, the agreement form which would be extant, as well, for hospitalized patients, but we haven't addressed specifically how a hospital pharmacy beyond a physician indicating appropriately that the right patient was being prescribed the drug, would adhere to the risk management plan. We were focusing more on outpatient use.

DR. COHEN: A quick question regarding also the risk management plan. There is a growing trend to use computerized prescribing and recently with that Accutane Smart program, we learned that the military, the Department of Veterans Affairs, and some other sites, as well, use a system for computerized prescribing that actually communicates directly with the pharmacy systems.

So, is thought being given to use that as an alternative to the sticker program? I am not sure whether that has been discussed or not.

The second thing is with regards to the pharmacy-based postmarketing study that was being done with Eckerd and the Slone Epidemiology Unit, was there a thought given to expanding it beyond that one pharmacy chain? Was there thought, for example, involving independent pharmacists and survey process of some type?

DR. WHEADON: Starting with the first question, we had not intended to include the computer-generated prescription for the allowance of dispensing of the drug. The intent was, at least in the initiation of the program, was to do the paper-dependent process with the sticker applied to the prescription. You might want to discuss that further when we go into dealing with the questions.

The second question concerning the Slone Epidemiology Unit and the participation of Eckerd's retail pharmacies, my understanding is--and Dr. Louik, who is here from the Slone Unit, can add beyond this--but we wanted to start with a free-standing chain and sort of, if you will, test the process of the evaluation of the program with Eckerd, and this procedure is already set up with Eckerd, however, I don't know that there is any reason it can't be expanded beyond the Eckerd chain

if numbers indicate we need to do that.

Dr. Louik, would you like to respond beyond that?

DR. LOUIK: Yes, I would just like to add one comment with regard to the independent pharmacists. I think it is important to emphasize that this is a pharmacy chain and a centralized database that will be defining the patient population, and it doesn't depend on any action on the part of an individual pharmacist. I think that is an advantage of the program, as well as the fact that we will have information on both respondents and non-respondents to the program because of the way of identifying Lotronex prescriptions rather than using a pharmacist.

MR. LEVIN: In your briefing material, you indicate that you have "no plans" for drug sampling or direct consumer advertising, and I was wondering whether you consider that part of a risk management program, that is, you were sort of saying you are not going to do that, and what are your plans as regards IBS infomercial kind of advertising, non-brand specific, but trying to sort of raise awareness of the disease?

DR. WHEADON: I think as I think Dr. Houn

and Dr. Piazza-Hepp both referred to, the issues of restricted access under Subpart H, as defined in the Code of Federal Regulations, and as such, such direct-to-consumer advertising would be not allowed, if I recall the restrictions of Subpart H, under those restrictions.

DR. HOUN: Subpart H just requires pre-approval, and it does not disallow DTC. I think, though, that at this time, nobody is proposing DTC.

DR. WHEADON: Absolutely. The Company is not proposing DTC. In terms of infomercials, if your indication or your question is concerning provisions of information around IBS, as we have indicated, there would be a web site that would provide information on irritable bowel syndrome, that would provide information on the appropriate use of Lotronex for physicians, but obviously, in terms of how web sites are maintained, there could potentially be patient access to that, as well. The intention really is to provide the information concerning safe use of the product as contained in the Medication Guide and in the modified proposed labeling.

DR. KRIST: I will ask a pretty quick

question here, and I apologize for stepping back, but it is dealing with the postmarketing data. One of the first things we are going to be talking about is are there certain patients that might have a greater benefit-to-risk ratio.

One of the things we have been talking about was limiting this to more severely affected patients, and that in the randomized, controlled trials, there are not necessarily any subgroups with higher risks.

One of the things that I am interested in is that often when medications are extended to the real world setting, the more severely affected patients might be at a higher risk because they might be more likely to have other comorbidities, and they might be on other additional medications, or since IBS is more of a diagnosis of exclusion, there might be the risk of a more severely or a patient with more severe symptoms having some other underlying pathology.

So, what I am interested in is in the postmarketing data, is there anything to suggest that there were more complications in patients who had more severe symptoms.

DR. CARTER: Obviously, again, we have to

qualify the postmarketing data as being incomplete very often and devoid of information at other times, so it is difficult to draw firm conclusions, but we certainly saw, in looking at individual cases, that patients that, indeed, had comorbidities or were on other medications that might impact, for instance, colon motility, were at higher risk of developing complications. I mean this is a qualitative analysis here, not a quantitative analysis.

DR. WOLFE: Ms. Mackey.

MS. MACKEY: Yes, we had no information to suggest that based on postmarketing reports.

DR. GOLDSTEIN: I would like to come at this from a different direction. Earlier today, we heard the FDA state, someone, and I quote, "There is a real possibility of misdiagnosis of IBS when it was really IBD."

We know that there are 15 million sufferers of IBS, many of them who reside in rural areas, and at the conclusion of his summary, Dr. Raczkowski said, "We must avoid adverse events by enhancing chances of a correct diagnosis," all of which leads me to ask the sponsor whether, in fact, they have any plans for materials to make the

distinction between IBS and IBD, and/or to recommend any diagnostic procedures that would exclude one.

In concluding, I would point out Ms. Norton's rather eloquent plea for the importance of an accurate diagnosis.

DR. WOLFE: We are going to actually discuss this indirectly, because this deals with one of the questions regarding who should be the principal persons involved with prescribing this drug, and should it be limited. That is going to be the question discussed because among gastroenterologists, we don't generally confuse IBS with IBD.

DR. SULLIVAN: I have a couple of quick questions. I noticed in the briefing package that this is a high clearance drug with a lot of metabolites, and it was unclear to me whether these metabolites have been characterized, whether they are active.

Specifically, why I ask the question is, has the sponsor looked to see whether there is any inference on coagulation or anything like that with the major metabolites.

DR. KOCH: Kevin Koch, GlaxoSmithKline,

Clinical Pharmacology.

Yes, we have. The major metabolite that we see, that has activity is 6-hydroxy. It is about equipotent with the parent drug in terms of 5HT3 binding activity, but we only see about 1 percent.

DR. SULLIVAN: What is its duration of action?

DR. KOCH: I don't know, we haven't measured that. This is in vitro receptor binding activity for potency. In the serum, we see only 1 percent relative to parent of that metabolite, so it is probably not contributing very much in terms of actual activity in vivo.

Your second question?

DR. SULLIVAN: Whether the metabolites--

DR. KOCH: Coagulate?

DR. SULLIVAN: If it not important, then it probably doesn't matter. I had some follow-up questions, particularly with respect to the drug-response relationship or I think it is probably fair to say that the sponsor hasn't done a stellar job in clearly figuring out what the minimal efficacious dose is.

I am interested to know whether the

sponsor has ongoing or plans to look more carefully at the PK-PD relationship. Most small molecules, there is a very good relationship between concentration and response. For example, one would wonder whether the sponsor would ask patients with IBS to take the drug one hour before a meal because Tmax is about an hour.

You would expect the maximum pharmacodynamic response to possibly coincide with Tmax. Have you looked at AUC? Have you looked at trough levels? Have you characterized this relationship? I would opine that, had this been done early on in the program, possibly we wouldn't be in the pickle we are now with having gone to market with probably too high a dose.

I should also, perhaps, ask Dr. Wheadon to clarify. He said, on his risk-management plan, half the dose. I believe it is the same dose but it is half the exposure. It is the same dose but given less frequently. Once a day was the proposal.

DR. KOCH: Just to address your first question on pharmacodynamics. We would have loved to have done that kind of analyses, but we are still searching for a good pharmacodynamic

surrogate. As you saw, the effect measures are symptomatic. We don't really have a good dynamic measure.

DR. SULLIVAN: I think you have published data on visceral pain. There is, at least in the package insert, one study at the dose of 4 milligrams looking at salt and water retention. These are not easy studies to do, but I think they are doable.

DR. TRABER: Maybe I could just comment and answer. First of all, you asked if there were ongoing studies. All studies were stopped at the time of withdrawal and clinical trials were orderly shut down. So there are no ongoing clinical trials.

The other thing is that the physiological measurements, either balloon distention, colonic motility, other pain sensation and those types of things, there is not, as yet, a good correlation between those and the symptoms for patients with IBS.

Indeed, should this come back to market in a restricted-access format, and should we continue to do clinical trials with this compound, we would look at those PK/PD relationships.

DR. WOLFE: Could I follow up on that question? How is the drug metabolized? I forget. By which route?

DR. KOCH: There are several P450 enzymes involved, 2C9, 1A2, 3A4.

DR. WOLFE: Not 19? That is not involved?

DR. KOCH: Not 19; no. Or 2D6.

DR. SULLIVAN: I think I would agree with the sponsor that there are not likely to be any interactions based on the P450.

DR. WOLFE: The question I was getting at was 19. There are a lot of differences with different ethnic populations. If we have got a metabolism but it is not 19, we are not going to see much of a difference, at least that we know of yet. But we may see that in the future.

Ms. Blackman, do you have any questions?

MS. BLACKMAN: I do have one question. It was indicated by GlaxoSmithKline and seemed to be disputed by the FDA that most of the risk involved in taking Lotronex was within the first month and that we don't have data after six months. However, there was a slide shown that, for 48 weeks, there was efficacy. So what happened to those patients? Were there surgeries, hospitalizations, deaths, for

those folks who were on for the long-term safety and efficacy studies?

DR. CARTER: Yes. Of course, the number of patients that extended beyond six months was relatively small. But we saw, for instance, one of the ischemic colitis in the placebo patient was in the second six-month period. But there was no--we couldn't tell whether or not there was any differential, if you like, between the two time points in terms of the events of special interest.

MS. BLACKMAN: What was the sample size for the people who went 48 weeks?

DR. CARTER: The sample size, I believe, was 600, thereabouts.

MS. BLACKMAN: I also wonder--I mean, there have been several comments about patients who take NSAIDS, who take other drugs that have serious side effects. Has the FDA done any sort of analysis on how they are comparing this drug, this disorder, compared to other non-life-threatening disorders such as sexual dysfunction and things like that that have had deaths and serious side effects associated with medications that have been approved?

DR. HOUN: Yes. Every drug that is

approved gets adverse events and we look at them the way we have looked at Lotronex. There are medical officers assigned from the Review Division and Drug Safety Division. There are team meetings over these adverse events.

More recently, over the last five years, drug adverse events are being discussed publicly. Resolin was discussed publicly. PPA was discussed publicly. Thalidomide was discussed publicly. Every drug, when we ask for a vote on should it be approved or not, we talk about safety data.

So, in terms of all drugs, the look at safety is uniform in the sense that this is something we care about. We look at efficacy. We look at that very carefully, too. But, again, a lot of situations we are put in is that we are looking at apples and oranges. Is ischemic colitis and then adequate relief of IBS symptoms--how do you measure them? That is where we need advice from all stakeholders. That is why you are here today.

DR. WOLFE: We will now move on to the questions for us. Dr. Raczkowski will now introduce the questions and then we will answer them, as best we can.

Introduction to Questions and Charge to the Committee

DR. RACZKOWSKI: This afternoon we have eight questions for the advisory committee's discussion. What I will do, then, is read them into the record.

[Slide.]

No. 1; Can a patient population with diarrhea-predominant irritable bowel syndrome be described for which the benefits of Lotronex outweigh the risks and, if not, why not? If so, describe the population in terms of the following characteristics: severity of symptoms, degree of disability, chronicity of IBS, failure of conventional IBS therapies and any other important characteristics.

[Slide.]

No, 2; At this time, should Lotronex be a) available to patients with diarrhea-predominant IBS without marketing restrictions, b) available to IBS patients with appropriate marketing restrictions, to be defined, or c) withheld from the market. Explain.

[Slide.]

No. 3; If Lotronex is marketed, should the

ability to prescribe Lotronex be limited to certain types of physicians. If so, describe the physicians in terms of the following qualifications: knowledge, experience, specialty and any other important characteristics.

[Slide.]

Question 4 regard patients. 4a; GlaxoSmithKline proposes to restrict use of Lotronex to patients who sign a Patient-Physician agreement. This agreement is then filed in the patient's medical record. Is this adequate to insure that only patients with the most favorably benefit-risk balance receive Lotronex? Is auditing of this agreement needed?

b; GlaxoSmithKline proposes a utilization study of United Healthcare Research Database as a mechanism to audit whether appropriate patients are being prescribed Lotronex. Is this auditing mechanism adequate to achieve this goal? If not, describe an adequate auditing mechanism.

[Slide.]

c; GlaxoSmithKline proposes a pharmacy-based study using the Slone epidemiology unit and Eckerd Corporation to audit patients' knowledge and awareness of the risks and benefits

of Lotronex. Is this auditing mechanism adequate to achieve this goal? If not, describe an adequate auditing mechanism. Define adequate performance on either GlaxoSmithKline's or another knowledge audit.

d; Should patient enrollment, for example, registration, be part of the risk-management plan?

[Slide.]

5; Regarding physicians. GlaxoSmithKline proposes a plan in which physicians call a 1-800 number to receive a self-attestation kit, including stickers. The physicians self-attest to their qualifications by signing the "Section for the Physician on the Patient-Physician Agreement." This agreement is then filed in the patient's medical record. Is the sponsor's proposal adequate to allow for evaluation of physician adherence to the program; for example, the extent of Lotronex prescribing outside of the program. If not, describe an adequate auditing mechanism.

[Slide.]

b; Define an adequate level of adherence to the program by physicians. c; Should physician enrollment--for example, registration--be part of the risk-management plan?

[Slide.]

6; Regarding pharmacists. GlaxoSmithKline proposes the pharmacists accept only written prescriptions with an attached sticker. The goal is to verify in real time the patients being dispensed Lotronex are under the care of enrolled physicians. Also, pharmacists will provide medication guides to patients whenever Lotronex prescriptions are filled or refilled. The goal is to provide patients with written information about the safe and effective use of Lotronex.

a; Are the sponsor's proposals to meet each of these goals adequate? If not, describe adequate mechanisms.

b; Should pharmacists' adherence to the program be audited? If so, how?

[Slide.]

7; Regarding safety outcomes. a; Should clinical outcomes--for example, ischemic colitis, severe constipation and death--be used to assess the success of the risk-management program? For example, should the rates and/or degree of severity of ischemic colitis and constipation be monitored with the specific goal of evaluating the effectiveness of the program?

b; If so, specify the adverse events that should be assessed and when the assessments should be made. Describe acceptable rates for these adverse events and/or acceptable degrees of severity.

8; Please provide any additional comments that you may have about a Lotronex risk-management program; for example, suggestions for additional studies.

Thank you very much.

DR. WOLFE: Thank you, Dr. Raczkowski.

Discussion of Questions

DR. WOLFE: Before we get started, I want to point out to the panelists that we have a little less than two hours to accomplish what normally takes four hours. So, we are going to do it in the following way. We are going to go around the table for these questions. We are going to start right in order because, clearly, the first two questions are seminal because if we advise not to go on, there is probably very little reason to go on any further.

So we need to concentrate on the first two questions initially and then we will move on. I am also going to have an additional question to pose.

I can't say this to the public, but I can say it to you. If you make your comment, and it is your turn, and we will go in different orders, and somebody has already made your comment, don't repeat it. Just say, "I agree with Dr. Smith, Dr. Jones," whoever you agree with. And that's good enough.

You also have the right later on to realize, "You know something? Maybe I don't agree with what I said initially. Maybe I changed my mind." You will have time to change your mind because we are going to vote after we have the discussion on each question. So is that clear to everybody? So, again, please try to be succinct. We have less than two hours to discuss what takes four hours.

So we will start with question No. 1. I will repeat it again to you. Basically, what we are looking for, is there a patient population for which the benefits of Lotronex outweigh the risks. If not, why not? If so, describe the population in terms of the following characteristics; severity, degree of disability, chronicity, failure of conventional therapies and any other important characteristics.

We will start this time, since you went last, we will start with Ms. Blackman.

MS. BLACKMAN: I think a patient population can be defined. I think from the studies we have seen, it is a little difficult because they weren't stratified necessarily. But there are measures for severity. I think urgency and stool consistency and pain are the more severe characteristics that should be looked at for a patient population.

DR. SULLIVAN: I would certainly agree. I think that it is abundantly clear, at least from the patient representatives, that people that have diarrhea-dependent urgency, the pain is, perhaps--if it is associated with that, then, clearly, it is helpful. Pain, I think, is questionable from another point of view.

But I think, overall, the benefits far outweigh the risks for this population.

DR. GOLDSTEIN: I agree with my two colleagues with no reservations at present.

DR. KRIST: I think--you know, one of the things we have been talking about when trying to identify groups that are at greater benefit is that the randomized controlled trials don't show very

many specific characteristics. I think the ones we pointed out are diarrhea and at least two episodes of urgency per day, and then trying to think about which groups might have lower risks.

Once again looking at the severe adverse events, there are not specific subgroups at greater risk. But I do think you can--certainly restricting it more to patients have failed the conventional therapy will lower exposure to potential risks and that way decrease the gross number of adverse events.

DR. LEVIN: I guess I have heard nothing yet that gives me comfort that we can identify that subset of patients clearly enough to make the statement that the benefit would outweigh the risk. But I am willing to be educated as we go around the room.

DR. COHEN: I would go along with previous colleagues other than Dr. Levin. I agree.

DR. CRAWFORD: I also concur with the previous comments. The only thing I would like to have added to this is to specify is are we talking about females only or males and females?

DR. WOLFE: Why don't you tell us?

DR. CRAWFORD: Certainly the data that

were presented were for females. But I was certainly also swayed by many of the patient representative comments. I defer to those with more clinical expertise.

DR. WOLFE: Remember, one of the questions at the end is are there further studies that you would recommend.

DR. CRAWFORD: Thank you. Then I would like to recommend more studies. Thank you.

DR. CAMPBELL: I, too, agree. It is possible to identify a patient population, if only, we, in fact, have done that--if, in fact, only through an IND mechanism. But there is a way to define that population. The challenge is how and my only comment is a very high threshold needs to be established.

DR. GARDNER: I agree with the comments so far. The one thing that we haven't discussed and maybe we need more data about, the comment was made that the people in the clinical trials all have long-term established disease and that helped to distinguish that, perhaps, from people who, in Dr. Walker's studies, had colonic ischemia within three weeks, or three months, of a diagnosis, something like that.

So, perhaps, rather than severity, maybe we could look at the possibility of some measure of chronicity or long-term duration of disease to help us understand this because that might also, then, carry with it the likelihood, perhaps, of having failed on other therapies or at least not getting adequate coverage on other therapies as well as having ruled out other things earlier on.

DR. WOLFE: By the way, it is called proper diagnosis.

DR. GARDNER: Yes; it may be called proper diagnosis which is a topic for later on, I assume.

DR. WOLFE: Dr. Day?

DR. DAY: I agree that a group of people can be identified who would benefit from this drug. I think very careful explication of what constitutes mild, moderate and severe situations needs to be made, perhaps even in the labeling because, depending upon what we say about who can prescribe such a drug, if it is reintroduced, if there are physicians out there who take patient complaints and so on, how are they going to interpret what is mild and what is severe.

We had some cutoffs today that indicated

that only 5 percent of people with this complaint are in the severe category. I am not sure that all of our patient representatives would agree that there are only 5 percent of people with this complaint who should be so treated. So I would like to make sure that the communication is adequate and clear and forceful about what constitutes these categories of severity.

DR. STROM: I also agree. I would add three substantial restrictions in terms of defining the group I think is at sufficiently high benefit to be worth the risk. I do not think the risk-benefit is warranted for the up to 20 percent of the population that we have heard has IBS. I think one definition would be severity and I would be much more comfortable with a 5 percent severe--the top 5 percent than the large numbers, given the whole population is at risk.

Second, I would want excluded from the population people who we know, a priori, are at high risk of ischemic colitis based on other data. So I would want to see formal risk-factor studies of ischemic colitis and a predictive model for who is at high risk of ischemic colitis, and the people who have those risk factors should be

contraindicated.

The third is I would like to see a formal predictive model to get at this 10 percent that we have now heard twice seem to be responders. Both within the clinical-trial data and within the HMO data, we have heard the same thing and both of those are rich data sources that could be used to get us predictive models to try to say, so instead of saying there is 20 percent of the population using it, or 15 million people, you take the 5 percent who are severe, you take the 10 percent of those who are likely to be responders, and we are talking now about 0.5 percent who would be exposed to the risk, and, in the process, making it available to virtually everybody, hopefully, who really would benefit from it.

DR. GROSS: I think definitions are the problem we keep bumping up against here. I can't define what is severe. I think I have to leave that up to our gastroenterology colleagues, but I would feel more comfortable if I had a chance to review those definitions once they are determined. I haven't heard the definitions yet.

I think we also need to add some criteria for what is irritable bowel syndrome and some

determination, if we are going to treat the people with this drug, do we need to do screening procedures such as colonoscopy. Certainly, a flex-sig is clearly not enough. And do we also want to work them up for clotting disorders.

DR. HOUN: Could you answer that?

DR. WOLFE: Could we answer that?

DR. HOUN: As part of severity, Dr. Gross is saying--he is asking about should there be, should there be.

DR. WOLFE: I am going to say something. I will get to that.

DR. HOUN: I am wondering if he has his opinion.

DR. GROSS: I can't define severity. I am not a gastroenterologist. I would like to see what definitions they come up with before I would say yes.

DR. WOLFE: I must be getting old because I go back to history sometimes. But, on Day 1 of medical school, we learned, in pharmacology, that all drugs have an LD50 which varies from drug to drug. Actually I forget who mentioned this before, but someone mentioned this before, we use drugs every day that have a significant risk, not only

for conditions.

I will give you one just striking example. For osteoarthritis, which my rheumatology colleague consider a nondeforming disease, consider it inflammation. They don't consider it arthritis. We use NSAIDs which carry a definable risk which includes death. We use them every day. I doubt if there is one person in this room who hasn't used these drugs.

We all know they work. We all know they have a risk. We all know we are rolling the dice sometimes taking them, but we still take them.

In this situation, we are entering a new era. I point out that--my specialty is acid secretion. We have been there, we have done that, and we know the answer. We have got the final pathway. It is already taken care of. But this is a new frontier. Neuroscience is a new frontier. The enteric nervous system is even newer.

That is really why we are not sure what we are doing is yet complete. And we are not going to know for decades. But this is a first attempt to try to understand what we are doing with regard to treating a very debilitating disease which has a very big impact on quality of life. It isn't

necessarily lethal, by itself, but can lead to lethal consequences.

So I think we do have a definition. As a gastroenterologist, we know how to diagnose IBS. That is what we do for three years of a fellowship. The diagnosis--I think it is fairly clear here. If a person has to be referred to gastroenterologist, that is severe IBS. That is severe enough to warrant the use because the person referring to the gastroenterologist has tried the other remedies that are standard therapy which really haven't proven to work.

So that, by itself, someone who wants--I think we all agree, it has to be diarrhea-dominant IBS. I don't think there is any doubt at all. We can't include anybody with constipation in there. So it has to be someone with IBS who has diarrhea-dominant--I would call it IBS-DD, not IBS-D. Right now, all we have is evidence in randomized controlled trials that it really works for women.

Now, having said that, that doesn't mean a physician can't use it for a man by law, as far as I know. But I think it warrants further studies to show that it does, indeed, work for men if it is

going to work at all, or it doesn't work for men for the average person.

The other thing, I agree completely with Dr. Strom. Anybody with a hypercoagulable state, until proved otherwise, should be excluded. It should be a contraindication using this drug until we know for sure that it is safe. That seems to be a risk factor for any kind of ischemic disease.

We don't know for sure here, but it makes sense. Ischemia is caused by hypercoagulation in other instances. So I think we define the population fairly easily for us, for gastroenterologists; it is someone with IBS who is diarrhea-dominant, who has failed other remedies and has a definite--the diagnosis by our definition of the ROME criteria.

DR. METZ: Far be it from me to disagree with the chairman after such an eloquent speech, but I would like to just add a couple of points. I think the global assessment on how your patient is doing is probably the most important indication for trying this agent and that, by me, defines a group of patients that have tried other therapies beforehand, who have been referred on to a gastroenterologist. It is not a specific symptom.

I think the urgency seems to me to be helpful in that it shows a group of patients who do get benefit. I am particularly concerned about missing diagnoses and whether you do that by forcing every patient to have the appropriate exclusion endoscopic procedure or not is something we need to discuss, whether you look at chronicity before they actually get onto this agent, how long you have had the disease beforehand so we are excluding those who have active IBD or something else as well that might be getting in the way.

Patients who don't respond to a first trial or a first month of therapy I think should not be allowed to continue with the drug which is one issue I would add onto what Dr. Wolfe said beforehand.

DR. FLEMING: Can we define a patient population in which benefits outweigh the risks. Let me try to answer that first globally in terms of the entire dataset. We actually haven't talked in length today about benefits. With time limited, we have, understandably, really been focusing on risks.

If we look at the benefits data that was presented to us, particularly in the pivotal

studies of the 3001, 3002, 30013 and 06 trials presented by the sponsor on Pages 24 to 26, we certainly see evidence of benefit relative to urgency. We see about a 10 percent improvement in the fraction who had urgency today. Stool frequency is reduced by about 25 percent.

The primary endpoint was adequate relief in the past seven days of pain and discomfort. The percent that are successful on that measure seem to be 12 to 15 percent higher. That seems to be the main signal of effect.

Interestingly, and the sponsor put this slide up--it is Slide A112. It is also on Page 26--if you look at Study 3006, the overall percent that improve here, as the percent of people who do have adequate relief in the past seven days of pain discomfort, which was the primary, No.1 symptom, it is improved by about 12 percent, from 40 to 45 percent, up to 55 percent. That is the treatment signal. When these patients, then, go off the placebo control, the success rate drops from 44 percent in half.

So, more or less, the placebo effect seems to be as large as the treatment effect. The treatment effect added on to the placebo effect,

but the placebo effect is substantial and the waxing and waning of the disease process leads to over and above the placebo effect, about a 20, 25 percent overall success rate in the control arm.

My overall sense of this, then, is I believe there is real effect but, in the global population, as studied in this trial, it is modest. It is at the level that we have to worry about whether they are offsetting AEs.

Obviously, as we have spent a great amount of time today, we have concerns about the ischemic colitis and serious constipation and, in my own sense, it is complicated in the entire dataset to say, does this provide a favorable benefit to risk. So I think the questions of the FDA here, which is to say, all right, if it is really complicated in the global dataset, can we find subgroups in which it is less complicated, in which benefit to risk more clearly emerges in a favorable way.

The data that we have seen is very limited here. It might be that there are subgroups that have more favorable benefit to risk but, as Dr. Strom said, with the nineteen people having ischemic colitis, no wonder it is not a surprise we

have had difficulty discerning who are those people that are at risk.

I worries me that even early symptoms, though, make it difficult to know who are those people that are going to have subsequent significant events. In addition to that, from what we have seen, there is little evidence to say where is the efficacy going to be greatest. I think it is reasonable to speculate that those that have the most disabling symptoms at the beginning have the most room to gain.

So at least it is reasonable to speculate that those people might well be those that would have a more favorable benefit to risk and yet it is still somewhat speculation because the data show at least just very modest evidence that those that start with a more severe baseline have a better opportunity for benefit.

So, based on the data, I struggle being able to say I can see a subgroup in which there is clear evidence of more favorable benefit to risk although I could speculate that, plausibly, if we had a lot more data, it could be those people that start with more serious conditions at baseline.

One of the issues that has been raised is

can we make modifications to this dose regimen in order to maximize benefit to risk. The difficulty here is I don't even know for sure what the question is because I don't know for sure what the sponsor is proposing the schedule to be. Is it BID or is it QD? If, in fact, it is 1 milligram QD, then we don't have--we have got limited data on efficacy, is Point 1.

Point 2 is if the sponsor is planning to go forward, as is written here, and those that have failed to respond to conventional treatment, we have minimal data there as well. Thirdly, and the final point, is that Dr. Raczkowski has put forward some very logical criteria that we might think about in the ways of refining dosing based not only on possibly having the 1 milligram per day dose schedule but titrations, adjusting for maintenance, drug holidays, discontinuing once you are in response, managing AEs more effectively to discontinue more rapidly.

All of those things may help on safety but I don't have a clue how that is going to effect efficacy. So if we make these modifications, including dose changes, and we select patient populations such as those for whom no other therapy

is effective, we have got very limited understanding of what actual efficacy is.

The bottom line is I can't look at all these data and say, clearly, there are subgroups that could be benefitted here where there is clear evidence they may well be, but the data here, at this point, don't allow me to conclude clearly benefit to risk is especially favorable in any specific subgroup with any specific schedule that we have proposed.

DR. LEVINE: I think there is evidence that many of us in gastroenterology see patients who are referred to us with IBS and they really haven't had conventional therapy. They have had short courses of fiber. They have had inadequate courses. And it goes on and on with all the drugs that we see.

So the first problem is this is the fact that the definition of chronicity is easy but the definition of conventional therapy, even in a gastroenterologist's office, is not always adequate. I think, given that, there is also, as we have heard today from the public, a very small and dramatic group which probably we can identify. I would doubt it is more than 5 or 10 percent of

all patients with IBS. I think that is the group that would be targeted.

I think, since originally, when it was available on the market, it was grossly overused and it was not 5 or 10 percent of the market. I would dare say it was almost anybody, occasionally, because of the demands of the patient for diarrhea-producing IBS.

So I would say it would be important to look at other drugs. It would be important to be very strict about admission to the type of severity. I don't think that will be too difficult. I think we can talk about the number of bowel movements, accidents, et cetera, and we can identify the group that really would need this.

I also think, in deference to the chairman, I am a little hesitant about gender differences. I think they are true. It is true Dr. Camileri is not here but he has alluded to evidence that, even in males and females, neurotransmitters, estrogens--there may be hormonal differences in the normal state which are exaggerated even further in IBS when a balloon in put into the rectum and people measuring tolerance or intolerance.

So I think there probably are distinct gender differences that we know very little about so I am a little hesitant to go full-head with males at this point.

DR. WOLFE: (Comments off mike)

DR. FLEMING: I agree with you. I misspoke. I agree with you.

DR. LaMONT: I think we have to be careful to define the features of this first statement as was raised by several previous speakers, particularly what is conventional therapy and primarily who would be patients that would be excluded.

What we are coming up with here is actually another clinical trial. We are asking physicians in their offices and pharmacists to actually do another clinical trial and see if we can improve outcomes. It doesn't seem to me that anything that has been said today is going to help us predict who is going to get ischemic colitis but we can probably exclude patients that would get severe complications of constipation by adding exclusion for patients with previous impaction, for example, or patients that have had other problems related to constipation.

DR. HOLMBOE: I would just want to agree with some of the things that Dr. Fleming said earlier. What we are really doing by trying to define this population is not necessarily define those characteristics but by characteristics that predict a better benefit to risk ratio. What we are really doing by picking these characteristics is reducing the exposure. We are simply reducing the population that would be exposed to this drug as a risk-management strategy, not that we can necessarily stratify.

I think we have heard clearly today, we can't predict who is going to have ischemic colitis, as has been brought up, or colonic ischemia. So I think that, regardless of the population chosen.

The second thing is magnitude of benefit actually was fairly similar between those with moderate symptoms and severe. So I think trying to do it on that basis also doesn't make any sense. If you think in numbers of needed to treat, quite frankly, it is not terrible. It is anywhere from eight to twelve patients have to be treated for one patient to benefit. The number needed to harm is around 700 for colonic ischemia.

So if you look at it in that terms, not a terrible risk-benefit ratio. It is just that disease under consideration makes it much more difficult because of the severity of the ischemic colitis as a complication. So I agree with the things said by Dr. Fleming and Dr. LaMont previously, if you could be very careful about some of the definitions we come up with regard to conventional therapy, et cetera.

DR. VENITZ: I do believe that we have a population that benefits, I am not sure whether we can identify, based on the data. It sounds reasonable to me to assume that people that have a more severe stage of the disease have a better potential for benefit. I would concur with what is said before. Proper diagnosis, to me, is about as important as looking at the severity of the disease.

DR. WOLFE: Dr. Anderson?

DR. ANDERSON: I take the first question. I believe that a patient population can be identified. For the second part of it, in describing that population, I am going to go with the chair and follow his directions.

I do have a concern, however, in the sense

that there seem to be a lot of gaps in the data which we have. It may very well be that it would be to our advantage to begin to look at where those gaps are and try to fill them in. Secondly, I think it might be important in the future for the researchers to take a look at those thirteen metabolites that the sponsor said are generated when Lotronex is used.

I am a chemist and I am always concerned about the chemicals and what happens in that process. So, even though that is not a part of this question, it was raised earlier and I think that is a good thing to look at.

DR. CRYER: With respect to the question of can a patient population potentially be described who might benefit, the answer is yes. But I agree with Dr. Fleming. I don't think that, based on the data that we have seen, that that specific patient population has yet been described.

We have guessed, we have assumed, what those characteristics might be. We have assumed that it might be 5 to 10 percent of the population who has diarrhea-predominant IBS, but we don't understand. We don't know who they are. So, in whatever direction we move forward, I would propose

that, in that mechanism, we have a very well-defined orderly process, whether it be in a very well-designed registry or if it be in the process of random sampling, as has been proposed by the sponsor, or has not been extensively discussed, whether it be in the form of a clinical trial, continuing clinical trials with access, we need to better define this population in a very orderly fashion.

But I don't yet believe that that population which will be has yet been defined.

DR. RICHTER: I think we can define this group but it is not going to be as simple as how many bowel movements you have because you tell a patient, "How many bowel movements did you have?" and they know that, to get in the study, you have to have eight a day, they will tell you eight a day.

So it tends to be a gestalt. Really, I think the important things that have come out of this discussion that I really support is that there is a group, that this group probably needs to be defined in conjunction with the general physicians and the gastroenterologists working together so that everybody is on the same base, that they have

diarrhea-predominant, they have chronicity. Beware of the older person who suddenly presents with irritable bowel symptoms.

Each one of these testimonials from the patients are classic histories of that they have had irritable bowel symptoms for twenty or thirty or forty years. I wonder how many of these patients that have gotten these drugs and had bad situations were older and had symptoms that had been going on for four or five or six months. That is not the classical irritable bowel.

In light of the testimonials and the fact that this is an averaging of symptoms, I think, if you are going to open this up under some restriction, you ought to allow both genders to have access.

DR. WOLFE: Again, the FDA does need some guidance. Actually, what I would like to do here now is be a little simplistic. For Part a) of this question, I want a yes/no. We will go around the room to the voting members. Just a yes/no. We will start with Dr. Richter. Can a patient population be described for which the benefits of Lotronex outweigh the risks?

DR. RICHTER: Yes.

DR. CRYER: No.

DR. ANDERSON: Yes.

DR. VENITZ: Yes.

DR. HOLMBOE: No.

DR. LaMONT: Yes.

DR. LEVINE: Yes.

DR. FLEMING: No, not with current data

DR. METZ: Yes.

DR. WOLFE: Yes.

DR. GROSS: Yes.

DR. STROM: Yes, potentially.

DR. WOLFE: Please strike "potentially" from the record.

DR. DAY: Yes, carefully.

DR. GARDNER: Yes.

DR. CAMPBELL: Yes.

DR. CRAWFORD: Yes.

DR. COHEN: Yes.

DR. LEVIN: No.

DR. WOLFE: That allows us to move forward to the next question. This will be a little bit more difficult. Actually, there is no vote on this but if you could somehow record what are responses are. Is that good enough for you?

DR. HOUN: Tom, could you repeat the

numbers?

MR. PEREZ: 4 no, 14 yes.

DR. RACZKOWSKI: Tom, if you wanted to, you could have people just raise their hands to be sure. Maybe the no's could--

MR. PEREZ: I beg your pardon?

DR. WOLFE: A recount is demanded.

DR. RACZKOWSKI: You might ask people to raise their hands just to be sure.

DR. WOLFE: We will do this again real quickly. Those who are voting members, how many vote yes?

[Show of hands.]

MR. PEREZ: 14.

DR. WOLFE: How many vote no?

[Show of hands.]

MR. PEREZ: 4. Was there a problem?

DR. WOLFE: Democracy works. We still have the right number. What I am going to do here is we are going to try, please, just to be very brief. We will go around the room. Just try to get it in one sentence what population you would start with. Identify which population. Two sentences is fine.

DR. HOUN: To save time, we did collect

the information that people discussed.

DR. WOLFE: We will move on, then.

DR. HOUN: I would just ask if FDA has any other questions. My question is you did not discuss colonoscopy. There was some concern about misdiagnosis. Is that something that you are recommending?

DR. WOLFE: We will discuss this later when it comes to who should be--should this be restricted to gastroenterologists because, again, we spent three years working on how we diagnose IBS. I am not saying we are absolutely perfect in this, but we do a good job.

DR. HOUN: The other question is urgency. The descriptions from the testimonial was fecal incontinence. Is that something that you think, in terms of a description in the indications, would be helpful, people who experience this?

DR. WOLFE: So you are saying they have to have fecal incontinence before we would prescribe this drug?

DR. HOUN: I am asking. Every one of the testimonials described the anguish of that as a marker of their quality-of-life impact and is that something you would recommend, those of you--

DR. WOLFE: This is by a show of hands. Do you think it is necessary to have fecal incontinence to be prescribed this drug? How many feel it is necessary to have this, fecal incontinence? Please raise your hand high.

DR. LEVINE: Plus other--

DR. WOLFE: No, no; she is saying fecal incontinence.

DR. LEVINE: Solely?

DR. HOUN: As part of--people recommended--

DR. LEVINE: It is a part of a spectrum and other symptoms, not alone. Should it be an added indication?

DR. WOLFE: I think you are saying it should be so severe, that it is fecal incontinence associated with the symptoms is what you are saying?

DR. HOUN: Right.

DR. WOLFE: So how many feel there has to be fecal incontinence before you are prescribed the drug?

[Show of hands.]

DR. HOUN: That gives me an idea. We don't have to vote on that. I just wanted to

understand that.

DR. WOLFE: I am going to really go for it. How many think, at this point, it has to be diarrhea-dominant IBS?

[Show of hands.]

DR. WOLFE: So we all--let's attack the gender issues. Do you want the gender issues? Are there data sufficient, at this point, to recommend use of this drug in men? I think we all agreed, those who voted yes, in women there are data to suggest. Let's go to men now. Are the data sufficiently presented by the sponsor to allow recommendation of this drug for use in men? How many would say yes?

MS. BLACKMAN: Do you mean allow recommendation of or do you mean allow physicians to prescribe as they see fit because that is two different--

DR. WOLFE: No. They have to be recommending to the FDA that they go ahead and say, in the package insert, that it is okay to use it in men, too, based on the data. That is the question I am asking. Does anybody think there is sufficient data at the present time to warrant its approval for use in men?

[No response.]

DR. WOLFE: How many don't think there is data sufficient to recommend it?

[Show of hands.]

MR. PEREZ: I need to clarify something here. Are we going to taking votes on this?

DR. WOLFE: We just did.

MR. PEREZ: No. What I am saying is are we going to record official votes or are we just trying to figure out which direction to go in?

DR. WOLFE: I want the FDA to have a sense of what it is looking at.

DR. HOUN: No; I want voting just on the official questions. These are additional clarifications and we don't have to have formal votes. We got your overall sense that, in the labeling, men should not be part of the labeling.

MR. PEREZ: Thank you for the direction.

DR. WOLFE: I think Question 1 is done. What I would like to do is do Question 2 and then take a little bit of a break. How does that sound? So, let's go to Question 2 because this is a key question. At this time, should Lotronex be available to patients with diarrhea-predominant IBS without marketing restrictions, available to IBS

patients with appropriate marketing restrictions to be defined or withheld from the market?

It is a), b) or c). I think we can answer very quickly. If you want a little explanation, fine, but we have already gone through it to some extent. So, we started in this direction before. Let's start in this direction now. Joel?

DR. RICHTER: I could support it in a form of b) but not with this vague program, this risk management program. I am much more enthusiastic for an IND program similar to Cisipride in which gastroenterologists and generalists work together to make sure they have the disease and follow the patient closely and then, with maybe an extended period of time with it as an IND and we have a better issue on the safety thing, then maybe open it up to this restrictive--

DR. WOLFE: So you are saying b) with restrictions. Again, our job is to recommend the FDA will work with the sponsor to make--and we will discuss these questions later on as well, what restrictions we recommend.

DR. HOUN: Let me just clarify. IND access is the research protocol only. It is not marketing. If you believe that, then it is

withheld from the market at this time and you can offer an explanation.

DR. RICHTER: Whatever you did with cisipride. You didn't withdraw cisipride from the market.

DR. HOUN: No; cisipride is not a marketed drug. It is not a marketed drug. The sponsor has withdrawn it from marketing. It is available under IND only. It is a very onerous process to get cisipride because you have to fill out investigator forms. It is IND only.

DR. WOLFE: The other thing is I don't want to discuss other drugs. This is on its own. It stands on its own. Again, the question, is a), without restrictions. First of all, does anybody here feel it should be just without restrictions?

[No response.]

DR. WOLFE: So we will go to b) and c) now. Do you want this approved with restrictions which will be defined by the FDA or do you want it withheld from the market and make it an IND which the sponsor can then, basically, discuss that option later on?

But, right now, do you want it released with restriction or withheld entirely? Joel, do

you want to try again?

DR. RICHTER: Restrictions.

DR. CRYER: Restrictions.

DR. ANDERSON: b)

DR. VENITZ: b)

DR. HOLMBOE: b)

DR. LaMONT: b)

DR. LEVINE: b)

DR. FLEMING: c), although I would like a clarification and that is my understanding--what is the understanding of the time line for b) versus c) where c), in my view, and I will clarify in Question 8, will be--there will be a prompt randomized trial done that, hopefully, can get these answers in a very timely way.

DR. WOLFE: I want to ask GlaxoSmithKline. If the answer is c), what are you going to do? Are you going to basically--we vote for an IND only, are you going to go ahead and continue studies with this drug?

DR. FLEMING: And that question is for, b), what is the time frame to actually get it on the market if that is the strategy?

DR. PALMER: Let me answer for b), first of all, which is the approval with restrictions.

First of all, the steps to get to market are several. We would have to agree the labeling and agree the risk-management plan with the FDA. That would take some time.

I think everyone needs to get on the same page with where we are. We took the drug off the market in November, 2000. We took it off the market. So there is no material. There is no commercial stock available for the drug. There is drug substance that would have to be manufactured into tablets and packaged once the packaging had been agreed with the FDA.

So, unfortunately, this would take time. I don't want to be locked in on a time estimate right now, but what we would be looking at is in the order, from this moment, moving forward four to six months before actually drug availability.

Does that answer your question?

DR. WOLFE: It is very important that everybody in this room understands that. If today, the FDA decides they want it approved, there will be no drug on the market for four to six months. Do you all understand that?

That is another question that is going to be asked. Dr. Metz asked me very quietly, but I

was going to ask the question also. The drug isn't going to suddenly appear four to six months from now. You are going to have the drug all along. Are you going to have an IND available for those people who would like the drug because they have been on it in the past?

DR. PALMER: No. Our position has been constant on this. We withdrew the drug and we have said very consistently that we will not support and IND program moving forward really because we don't think that is the best way to serve the patients who are going to need the drug.

We estimate, if you look at women with diarrhea-predominant disease, if you look at consultors and you look at the number of people who might be wanting to access the drug, you are looking probably in excess of 100,000-plus. Frankly, when you get to that level, the logistics of running an IND problem are A, very significant and B, the nature of the IND program would mean, I think, for a lot of the patients that you have heard about speaking today, they would find access to that medicine actually very difficult. It would be very onerous, even more onerous, than the hurdles we have already put in front of the

physicians with the restricted access program for physicians who actually do this.

DR. WOLFE: Thank you. We are coming back to Dr. Fleming but, in the meantime, anybody who voted previously want to change their vote from b). Everybody has a b) up to Dr. Fleming. Are we all sticking with the b)?

Dr. Fleming, we are back to you.

DR. FLEMING: Then, just to repeat, recognizing that there is a significant time here to get to implementation under b) and recognizing, in my view, that there are serious unanswered questions about populations in which we have favorably benefit to risk where I believe there should be some prompt conducted randomized trials that, hopefully, could get us answers in a timely way, I vote for c) with the conduct of those trials that would be clarified in the answer to Point No. 8

DR. METZ: I am an enthusiastic b).

DR. WOLFE: b).

DR. GROSS: A question first. Thalidomide; is that under a b) type restriction or c)?

DR. HOUN: It is under b).

DR. GROSS: Okay. I will vote for b).

DR. STROM: I vote for b) although with restrictions much more severe than the proposal we heard about before.

DR. DAY: b)

DR. GARDNER: b), what he said.

DR. WOLFE: I like the perfect answer.

DR. CAMPBELL: b), what she said. But all of these are researchable questions and we are being asked to make a decision without the data on all of them. All of these should be taken as researchable questions rather than simply yes or no.

DR. CRAWFORD: A stricter version of b).

DR. COHEN: b), also, with improvements in the risk management program that is being proposed.

DR. LEVIN: I concur with Dr. Fleming, c).

DR. WOLFE: So we have two c)s and 14 b)s. What is the GPA on that? I think that gives you a sense.

Let's take a ten-minute break. It going to be eight-and-a-half minutes. We will start a 4 o'clock because we have a lot of questions to answer still.

[Break.]

DR. WOLFE: Question No. 3; If Lotronex is marketed, should the ability to prescribe Lotronex be limited to certain types of physicians? If so, describe the physicians in terms of the following qualifications; knowledge, experience, specialty and any other important characteristics.

We will start with Ms. Blackman. One second, before I go on. The first two questions were clearly very, very important. Not that the other ones aren't, but if you don't want to say anything, don't feel you have to say something. Again, if you feel that someone else has given your response, just say he said or she said.

MS. BLACKMAN: I do not think that it should be limited to only gastroenterologists. I feel that there are family practitioners who may have more knowledge about IBS than some of the gastroenterologists. I think that is true. I wonder if there should be some kind of CME program or registration for the physicians who prescribe Lotronex who are trained on diagnosis.

But I do want to iterate that misdiagnosis is malpractice. That is not something that the FDA should be regulating. So I would like to see doctors have to go through some kind of program

where they enroll, where they register and are able to prescribe.

DR. WOLFE: Can I summarize? You are saying anybody who has the proper education in this drug, basically?

MS. BLACKMAN: Right.

DR. SULLIVAN: I would say that, in an ideal world, it should be a board-certified gastroenterologist. However, we don't live in an ideal world and I think that creates issues for gastroenterologists who claim they are board-eligible, whatever that means.

I think that a physician who has some sort of background knowledge should be able to prescribe it and there are various strategies that you could come up with that would deal with that issue. For example, you could have a web-based system where a physician could answer a questionnaire and be registered. There are various strategies which could deal with that issue.

So I think that basically any physician who has the training.

DR. GOLDSTEIN: I would agree that any physician who has the training but two things. I would remind everyone at the table that this is, in

fact, a syndrome not a specific disease. In some iterations, gas and bloating. Other iterations, urgency, et cetera, et cetera. General practitioners, as well as gastroenterologists, see a substantial number of people, and particularly those people who live in the rural, semi-rural, areas without access to care, need it.

The second comment is that, as the father of three daughters, I don't want this to be viewed as chauvinistic, but I would urge the sponsor to consider studies in men. We did hear a patient representative, male, today. I think it is something that at least ought to be considered.

Finally, I have some sympathy for a suggestion from someone at the head of the table about the desirability in the diagnostic process of considering colonoscopy for a variety of reasons, mostly to get at an accurate diagnosis, exclude IBD and the like. In everyone? No. It would clearly be difficult, if not impossible, to require it. But I think it is something that was said at the head of the table and with which I have considerable sympathy.

Finally, the sponsor's program to educate the medical community, I think, is something that

needs to be emphasized. They have both the skill and the resources to do this and I think it would make an enormous difference.

DR. WOLFE: Dr. Krist, before we go any further, I forgot to say something that needs clarification that I discussed with FDA in the break regarding use in men. The way the label stood before was that it said that effectiveness has not been proven in men yet. So, with that kind of wording, it would allow this drug to be used in men without proven benefit until further studies were done before approval could be obtained. So that leaves the door open for use in men.

DR. GOLDSTEIN: I would agree with that and I am sure that the FDA can work out the appropriate language.

DR. KRIST: Just as I start to answer this question, clarifying my position here, I am a family physician, so that everyone knows that. I have a pretty strong opinion on No. 3.

I do have a lot of concerns, like Dr. Fleming was expressing, about whether the studies have shown the benefits and which groups this is the best for. But clarifying that, if it is decided that this medication--that there are groups

of patients who will benefit from this, I do believe that it probably shouldn't be reduced by specialty.

I think that the FDA's second goal of trying to ensure that qualified physicians are prescribing this medicine is a good goal and I think that that should be done. But I don't think that saying that only gastroenterologists prescribe it necessarily is going to ensure that that second goal happens. So you won't necessarily ensure the patient safety from that standpoint.

I think the other issue is that I think that all physicians will be affected by this even if you restrict it to just one specialty because what is going to happen is patients are going to have complications and they are going to see their primary-care physicians, or the primary-care physician is going to see a patient who is on Lotronex and I will be trying to decide whether to put them on hormone-replacement therapy or using other medications.

So it is going to cross specialties even if attempts are made to restrict it to just one specialty. And then, as has been mentioned, there are communities where there are not access to

gastroenterologists.

I think that one of the other important things to just understand about primary-care physicians, in general, is that--one of the things I teach our students and residents who come through is that primary-care physicians are experts. They are experts in common things. Irritable bowel syndrome is a very common illness.

The other thing that they are experts in is recognizing what they know and what they don't know. So there is going to be a lot of room for collaborative work between primary-care physicians and gastroenterologists, particularly with establishing diagnosis and with patients who are more complicated. But I don't think that, just by restricting it to a gastroenterologist, that that would make the difference or ensure a qualified physician for prescribing it.

I do like the model that has been mentioned of specific physician CME. A good example would be for institutional review boards or for being a primary investigator with research. There is on-line education through the Department of Health and Human Services to prove that a physician is qualified as opposed to just a

physician's statement that they are qualified.

The risk of a physician's statement that they are qualified is you have a risk of including physicians who are unconsciously incompetent, who think they are qualified but really aren't, particularly if we are going to ask physicians to go through and, with patients, ensure that an informed or a shared decision is being made.

We are asking for a different level of knowledge on this topic. We are asking for doctors to be able to say the risk of ischemic colitis is somewhere between 3 and 17 out of 1000 and specific numbers that many doctors might not normally know, but that a patient will need to know in making a decision on this medicine.

DR. LEVIN: The first thing is just a point of information. Is there any precedent for restriction by specialty?

DR. HOUN: There have been restrictions for doctors based on ability, like for mifepristone, to diagnose and manage pregnancy, ectopic pregnancy. You don't have to have surgical-intervention skills but we do, in that restricted system, say you have to have a referral system in place to handle surgical intervention.

For the other restricted drugs, the physician must register with the program and some of them have specific education that they have to go through to register, but it doesn't preclude multiple specialties from joining the program.

DR. LEVIN: I would support the model that was just described, registration but specialty is not enough.

DR. COHEN: Today we heard that the drug was clearly overused when it was available and was on the market. We heard that there has been misdiagnosis. To me, as a pharmacist, I would want to make sure, for patient safety reasons, that appropriate individuals were prescribing it. And I would want to restrict it to a gastroenterologist because when I get that prescription with a sticker, that will communicate something to me.

But I also, certainly, can see a certification process through CME, et cetera, for family physicians, general-practice physicians. But it would need a certification process of something.

DR. CRAWFORD: I concur with what Dr. Cohen just said.

DR. CAMPBELL: This is one of those

researchable questions. The truth is we don't know how to answer this question. There is no data to drive or inform our decision. As experimentalists in that situation we should say there is no difference until there is a proven difference. So, at this point, I believe it should not be restricted to just gastroenterologists.

However, I do believe the criteria for prescribing this medication should be a well-developed credentialing or certification program that would require the prescriber to not only demonstrate appropriate knowledge but to also be able to demonstrate that in practice.

DR. GARDNER: I agree with Dr. Campbell and have that documented in some way.

DR. DAY: I would like to mention that there is an intermediary plan. The FDA has proposed, in some of the briefing material, that there could be a start with a very conservative plan to be relaxed over time, say, after a period of a year. This would answer Dr. Campbell's concern if it were restricted to specialists for one year and we could look at the incidence and types of AEs, and then relaxed after a year, if that is a satisfactory profile. Then see what is

after that. Then we would know better if that has been contributory in the past, that people with insufficient knowledge and experience have been prescribing this drug.

I would like to support, in addition, the CME approach and that everyone go through the education and demonstration on line or another means

DR. STROM: I should clarify. In answering, I am not only an epidemiologist, I am also a primary-care physician. I think it should be restricted away from primary-care physicians toward gastroenterologists and, in fact, gastroenterologists who have gone through some special registration scheme.

I think there are two reasons to restrict it to gastroenterologists. One is the diagnostic certainty, diagnostic correctness thing that we have talked about all day, which I think is a major issue in differentiating inflammatory bowel disease from irritable bowel syndrome.

I think even in the group of letters that many of us got lobbying us before this meeting, there were patients who gave their clinical scenarios and it was clear that those patients

lobbying for this drug for irritable bowel syndrome really had inflammatory bowel disease and didn't seem to realize that.

I think that confusion is a major issue and is a reason why you need gastroenterologists to be the people using it. I think the other reason it should be restricted to gastroenterologists is a question of severity. This is an extraordinarily common condition which is severe in a small subset of people. It is very severe in the subset of people but one way of making sure you are getting it to the most severe people is by restricting the treatment to gastroenterologists.

If the irritable bowel syndrome is not sufficiently severe that they have gotten to a gastroenterologist, it is probably not severe enough to need the risk of this drug.

DR. GROSS: I am going to propose a middle ground and that is that if the general internist wants to use the drug, it must be done in consultation with a gastroenterologist, although the general internist can prescribe it after approval by the gastroenterologist.

The reason for this is a couple-fold. I, personally, know several cases of general

internists seeing the patient with IBS that turned out to be inflammatory bowel disease and the diagnosis was delayed not by a matter of a month or two but by a year or two.

Secondly, as far as certification is concerned, there is something called book knowledge and something called experience. I think certification would attest to book knowledge but not necessarily to experience.

DR. WOLFE: I really have mixed feelings listening to everybody speak but, in an ideal world, I think this would be best restricted, initially, to gastroenterologists. However, if someone is living in the middle of Montana and there is no one around for 400 or 500 miles, that makes it impractical. So you can't put in an insert, "If you live in Montana, you can use it. But, if you don't, you have to go to a gastroenterologist."

I think that proficiency--I think that you could word it in such a way that it would say proficiency in digestive diseases and the diagnosis and treatment of irritable bowel syndrome. It does bother me that the question has been raised about confusing this with IBD. Again, experienced

gastroenterologists, those who do three years of training, don't have that much difficulty.

I am not saying that they are perfect. But they do well. On the other hand, if there is confusion, I think a good primary-care physician will refer the patient on. So some wording can be somehow be put in that allows for consultation or proficiency.

The other thing that can be considered, and this comes from doing trials, is sort of five or six questions can be posed. For example, does the patient have blood in their stool. If it is yes, they don't get the drug. It should not be prescribed. Is this disease chronic, defined as more than--we are going to put the ROME criteria in there. Just quick questions, a check list to see if the person really should or should not be taking this drug.

So, again, I have mixed feelings but I think, in reality, it would be very difficult to restrict this drug to gastroenterologists only.

DR. METZ: I would focus on the fact that IBS is a diagnosis of exclusion and that it is a syndrome and that, in actual fact, to diagnosis this condition, you need to exclude IBD. I think

that requires an endoscopic evaluation. We can argue about whether a flex-sig is enough or you need a colonoscopy.

But I think one of the issues here is that you would need to go through a check list, as Dr. Wolfe suggested, and if you have had any blood in your stools, you don't count. If you haven't had an endoscopic evaluation to rule out IBD, I think you would be out.

That doesn't mean it has to be the gastroenterologist doing the prescribing. But I think they have to be in the loop in the evaluation and the diagnosis of the patient. Once that patient is then put onto a program, I think it would be totally appropriate for a well-trained, primary-care doctor who has gone through CME training, however it is evaluated, to continue prescribing for that patient.

But I would like to see a proper diagnosis up front. I think that is where all the issue came for the postmarketing data is I see that sudden jump in the first three months, I am attributing to misdiagnosis and I think you can prevent that.

DR. FLEMING: I pass.

DR. LEVINE: I would agree with Dr. Wolfe.

I do think there is an insurance policy here and I would like it clarified by Dr. Raczkowski. I think anybody who signs off on this in any way is probably liable legally. So if that is true, I think a family practitioner would be, and a gastroenterologist would be, loath to sign anything away if they felt uncomfortable that they didn't know how to manage this. I think that is an insurance policy.

Could you clarify that, Dr. Raczkowski? If someone signed off on this, they would be liable?

DR. HOUN: I think malpractice is governed by each state and how each state handles those issues. There is not an indemnity form that you would sign saying you accept the risks and will not sue for them. Wherever you practice, the norms, in terms of practice standards, apply to you.

DR. LEVINE: But my point is, if a doctor in Montana or in New York writes down and says, I am going to put this person and follow the educational program, et cetera, then he knows that if something happens to that patient, it probably may result in that state in legal problems.

So I think that is an issue that should be

kept in the back of the mind. In any event, I am with you, Mike. I go along with what you--I would say to everybody, you would have to do it even though I would prefer to see it solely in gastroenterologists.

DR. LaMONT: I like the hybrid model where an internist or a primary-care doctor working in conjunction with a specialist can ascertain and establish the diagnosis. So I vote for a hybrid model.

DR. HOLMBOE: As a general internist practicing in a city with a very poor population, it is often very difficult, even when there are gastroenterologists in the city, to get them to be seen by gastroenterologists. So I think that, with the model proposed by Dr. Wolfe, that is quite doable.

I think that there would have to be some sort of certification. You would have to document you had the knowledge to prescribe the medication. On top of that, I would build in the check list and exclusions into the patient agreement. I would make that part of the form so it becomes part of the records instead of making it separate. That will help remind the physician what to do.

Third, although we will get to this later, I think that, particularly for those outside of gastroenterologists who decide to do this, there should be some form of an audit, at least early in the course of their using it, to make sure they are using it properly. I think that would help.

DR. VENITZ: I don't think we need any restrictions according to subspecialties but I do think that certification and documentation of competency is required. I am sensitive to Dr. Gross' suggestion that there should be some referral system set up a priori to make sure that the diagnosis is not missed. But, from that point on, I don't see why anybody that understands the drug and the disease but is not an enterologist couldn't follow up and make whatever adjustments.

DR. ANDERSON: I agree.

DR. CRYER: So what we are trying to accomplish here is to reduce the risk to the patients who are going to be exposed to the drug. I think that is accomplished. I think the case has been well stated that it is accomplished by excluding other diseases which could mimic IBS and its presentation.

Also, to the extent that the patient

population who is ultimately prescribed this drug mimics or parallels the patient population which was studied in the clinical trial would be desirable. So, to achieve that, if we look back at the exclusion or inclusion criteria for the clinical trials, there were patients who were studied by either flex-sig or colonoscopy within five years of diagnosis.

So, to accomplish that in the clinical practice and clinical implementation of this drug, I do not think that prescribing needs to be done by a gastroenterologist. But I do think that this physician-patient agreement needs to reflect the fact that some sort of evaluation for other diseases has been done in a similar way that the clinical trials were actually conducted, possibly, even, to specifically state that evaluations for other processes such as Crohn's disease or ulcerative colitis have been done.

I think specifically that needs to be indicated and documented in the section for physicians, that acknowledgment. I also agree that there should be some sort of certification that is done by physicians and, by having that acknowledgment as part of this document, that helps

serve as an educational tool for physicians in that every time they go through the prescribing, this prescribing exercise for patients, they go over in their mind that, yes, this patient has been evaluated for Crohn's by someone; yes, he has been evaluated for ulcerative colitis, diverticulitis, and those conditions do not exist.

So, to summarize, I don't think it should be done, prescribing restricted to a gastroenterologist but there needs to be some component to document that that evaluation of other disease processes has happened.

DR. RICHTER: I see this as a multistep process and there are a lot of unknowns in Question 1 and Question 2. For this to be inserted back into the public, this is a place where I do think, in the beginning, we ought to have some restrictions. I think it ought to be restricted to gastroenterologists for the first year, first year and a half, allow the company to do more studies, really get an idea of the safety situation there, not because I think gastroenterologists want this drug restricted to themselves. I think they would prefer this be for everybody.

But, until we really have a handle on this

ischemic-colitis area, by restricting it to gastroenterologists to start with, with a careful monitoring, see how this restrictive system--everybody wins. The patient gets the drug. Hopefully, we have a better idea of the patients that have to, and then widen it with the goal to be that it will be widened after you have had an experience with the gastroenterologist-only drug.

DR. WOLFE: Before we go on, I want to state one thing to the audience. There is no conflict here. Dr. Richter stated this very, very clearly. This is actually a shortage of gastroenterologists. We are not looking, right now, for a horde of patients to come to us. So that is not the reason for restriction here at all.

There is a serious shortage in many, many places throughout the country. I actually have a question for the FDA and for the sponsor. I would assume--I see several gastroenterologists here work for GSK. I would assume that there will be people available in case there were questions by physicians, to call the 800 number, a consumer number to call. Would that be correct?

DR. TRABER: Yes. I think the company would provide, as was mentioned by Dr. Wheadon, a

website and 1-800 numbers and lots of information.

I would just put into the mix here a couple of comments. One of the most important things I heard from the patients and from a lot of people is to make sure that the people who have the proper risk-benefit have access to this drug.

Many of you know that I ran a GI training program. I will just say that there are gastroenterologists that are trained as gastroenterologists who have, then, never treated patients with IBS and they restrict their practice to hepatobiliary disease or whatever. They are no more qualified to, twenty years down the line, treat irritable bowel syndrome as other people, or they may not see patients.

Furthermore, there are lots of physicians who may focus in irritable bowel syndrome and see a lot of patients in that way that are not gastroenterologists. So I would just put that into the mix that I am as much for credentialing of gastroenterologists as anybody, but certifying in this particular area is, I think, important.

DR. WOLFE: So, to vote on this question, I think I can simplify to some extent. Is there anybody here who doesn't agree there should be some

kind of knowledge of IBS that is mandatory to treat? So we all agree there should be some kind of knowledge of IBS and knowledge regarding the use of this drug. I think everybody agrees with that.

I think the question could be basically boiled down to does one have to be a gastroenterologist. I think that is the restriction we are talking about. So I think just a simple yes/no right now would suffice because we have to move on. So, again, the question, right now, that we are going to take a vote on, should this drug be restricted to gastroenterologists from Day 1.

The specific model, I think you have seen--the FDA has seen a lot of opinions raised here. We can all agree that, in conjunction with someone with expertise in IBS would be desirable. But, right now, I think the question specifically being asked is should we restrict this drug. Let's first answer that, yes or no. Should it be restricted to gastroenterologists, yes/no.

DR. LEVIN: Yes; gastroenterologists.

DR. WOLFE: This is by hands. Okay. How many feel it should be restricted by gastroenterologists at this point?

[Show of hands.]

DR. WOLFE: How many feel that it can be restricted to others. There may be abstentions, too--it can be used by others as well.

[Show of hands.]

DR. WOLFE: With restrictions. We already talked about restrictions. That is understood

DR. METZ: Can I insert something? Is one of those restrictions that you have had a preestablished diagnosis including a look at the mucosa?

DR. WOLFE: I don't think that is necessary. ROME criteria are available. If you have a twenty-three-year-old woman who comes in with a ten-year history of diarrhea, I don't think--and it fits all the ROME criteria, I don't think it is necessary to do a colonoscopy or a sigmoid in every case. Sometimes I would. It is clinical judgment.

DR. GROSS: How about consult with a gastroenterologist who treats IBS and IBD.

DR. WOLFE: That is up to you as a primary-care physician. Primary-care physicians, I think if you are uncomfortable, that is why God created gastroenterologists. That is what we are

here for.

DR. CRYER: Dr. Wolfe, in the patient that you just described, this twenty-three-year-old woman who fits the criteria, it is still possible that she could have IBD. We have learned, we have heard, that IBD is one of those conditions in which there may be increased risk for ischemic-related problems.

I don't think that it should be restricted to a gastroenterologist, but I agree with Dr. Metz, there needs to be some sort of validation that we have excluded the possibility of those diseases.

DR. WOLFE: So you are saying that every single patient should have some kind of endoscopy of some sort. Let's vote on the gastroenterologists here.

DR. CRYER: I am not saying that. I am just saying that there needs to be some sort of confidence in the prescribing physician that those conditions have been evaluated and that confidence needs to be documented in the physician aspect of this form.

DR. WOLFE: I agree. We are just saying it different ways. We should be confident that the diagnosis, as confident as we possibly can be. We

are never going to be 100 percent confident of anything

DR. METZ: The one point that struck me that distinguished the premarketing data from the postmarketing data is that, in all those premarketing studies, there was a screening visit including a scope.

Actually, an issue that wasn't raised, I would be very interested in knowing in how many patients who were screened and failed because they had an abnormal endoscopy. I did ask that of Glaxo during the break and I was told very few. But I didn't get a specific answer.

DR. WOLFE: It is going to stay very few because we really have to move on. Unfortunately, as the chair, I have another question that I have added in here because the question has been raised by Dr. Fleming and a few others and that is there is really very little data to suggest a dose-dependent dose-response curve for efficacy.

But there are data at present to show a dose-response curve for constipation. So we know, for safety issues, there is a dose-response curve there. I would, personally, like to get some recommendations quickly regarding what dose we

would start at and for how long we would recommend that dose titration continue.

DR. HOUN: Before you begin that, before we leave the prescribers, the qualified prescribers, I understand there is some recommendation that the prescribers, some of them can be in consultation with GI. There is some consideration that this previous exclusion of organic disease should be considered.

What I heard different was about an education program prior to being called qualified. I got pretty much that most people would be in favor of that; is that correct?

DR. WOLFE: Yes.

DR. HOUN: So not just someone who self-attests, but you are saying an active education program. Some people have mentioned you test to show that--

DR. WOLFE: You need a quick list, too, before prescribing the medication. That could actually be a very quick education for the patient and for the physician.

Can we move on? Since we started at the ends, I am going to start in the middle here. What I would like to propose, and if we spend a lot of

time, we will have to cut it. We will just cancel the question. I would actually rather start with--suggest; we don't vote. We suggest to FDA and to the sponsor that the dose be a half milligram.

Again, the data show very clearly, starting at a half to 1 to 2, there was a difference in the incidence of constipation. So I propose starting with a half milligram and then going on from there.

DR. CRYER: As a point of clarification, do you mean a half milligram BID for a total 1 milligram daily dose?

DR. WOLFE: I will go back to the example I used before and that was sulfasalazine. We start at 5 milligrams a day on a drug that we used 1 gram four times a day. So I would start with a half milligram a day, go to a gram a day and then to 2 grams a day. Milligrams; excuse me. We are not treating elephants. We are treating humans here; yes.

So I would start with a half a milligram a day to a milligram a day to 2 milligrams a day.

DR. TRABER: I just wanted to remind the committee that what we have proposed is 1 milligram

once a day. That is kind of what was in the sNDA.

DR. WOLFE: What I am suggesting is maybe you may consider and start with a half a milligram a day

DR. METZ: Is there any data on that? In terms of the PK/PD, we heard there isn't any information in the trials--I think the information that you showed us was in BID dosing. So is it 1 milligram once a day or 0.5 milligrams twice a day?

DR. WHEADON: First of all, I need to clarify one thing. Remember, that we are discussing a supplemental NDA. The NDA that has been approved and was voluntarily withdrawn does not include a 0.5 milligram tablet. It only involves a 1 milligram tablet. So, if you make a recommendation concerning 0.5, you are adding on to the time frame that Dr. Palmer has referred to earlier.

So that is another consideration that needs to be kept very strongly in mind.

DR. WOLFE: Again, in consideration of safety, you showed data very clearly--in my view, you showed data very clearly showing that a half a milligram a day, total dose, there was, even in those patients, some constipation. When you went

to 1 milligram, there was a little more. Then, with 2 milligrams, it was even more, unless I misread the data.

So, again, if no one else feels that way, then we will just go to the 1-milligram dose.

DR. VENITZ: I am in agreement with what you are saying in terms of starting at a lower dose. I am not sure whether it should be done as part of the standard of care in terms of actually reapproving the drug. But I would encourage the sponsor to do a prospective study.

You have a study proposed right now in your risk-management plan. But you look at doses lower than 1 milligram a day; in other words, half a milligram a day, all the way from 0.5 to 2 milligrams per day.

And you look at safety and efficacy in a prospective trial because, personally, I am not convinced that, with the dose finding that you have done in phase 2A, that you have found the optimized dose. What you would probably find is that the dose, the optimal dose, is going to be different by patient.

But I don't think that I would recommend that as the dose that was used for the patient at

large, but it should be used as part of clinical trial where you can actually assess the dose response within a patient.

DR. PALMER: Can I just raise the issue here? I mean, I think this is a very important issue in terms of the availability of the drug moving forward. I think we all recognized, when we made the proposal for 1 milligram once a day, that this was a pragmatic solution to a safety issue.

If we accept the pragmatic solution, then the track, in terms of where everyone wants to be who is sitting out there, which is to have the drug available, is much shorter than the track which is being discussed which is to have a 0.5 milligram tablet, potentially run dose ranging in parallel.

We can go either way on these options, but we have to make some decisions. I would be absolutely clear, the 1 milligram once a day is a pragmatic decision based on data on just intuitive up titration, good medical practice and reducing the risk of constipation. I just wanted to make that clear.

DR. WOLFE: Is the pill scored? Is the tablet scored?

DR. PALMER: The tablet is not scored, as

I remember.

DR. VENITZ: That is exactly why I was in favor of what you are proposing right now for the standard of care as far as making it available to the public at large. But I also would encourage you, in your phase IV study commitment that you have in here, to add a lower dose, even if that means you are going to have to develop a new, a lower-strength dosage form.

DR. PALMER: Again, just to again set the scene of where we are, all work stopped in November, 2000 when we withdrew. If we are now in a mode where we are moving forward, then clearly we are into a different plan because then phase IV commitments, everything else, can come back on the table and we can look at what we need to do to fully characterize the drug.

A lot of the things that have been suggested round the table today were actually on the slate to do. Obviously, if we find a way forward, then those would be reactivated.

DR. DAY: Speaking of what is on the slate to do, I notice Dr. Hoberman presented data showing that individuals of lower weight had a higher incidence of adverse events. I was wondering if

you had given any consideration to titrating the dose as a function of the weight or height-weight considerations per patient.

DR. CARTER: I don't believe that we actually gave that as a consideration. But, perhaps, if I am speaking out of school here, one of my colleagues can then correct me. I don't believe that that was ever the case.

DR. PALMER: We were in the process of setting up some studies in the Asia-Pacific region looking at people of lighter body mass, smaller body mass. Obviously, they got put on hold at the time that we withdrew the drug.

DR. WOLFE: Dr. Goldstein?

DR. GOLDSTEIN: One other consideration. I don't know where, if at all, there are pediatric studies done or contemplated. In point of fact, Kline and Barbero, the late Julio Barbero, had done some studies in small children in St. Louis and there are others. But, in terms of an incentive to consider a 500 milligram dose form, or half the 1 milligram dose, let me put it that way, that is something that might add a bit of incentive to considering something like that.

DR. HOUN: Mr. Chair, I think we should

move on.

DR. WOLFE: I want a quick yes/no, a show of hands.

MR. CARTER: Mr. Chairman, I'm sorry. We do have one slide that shows the constipation data for the 0.5 milligram BID dose that might be pertinent before--

DR. WOLFE: That is 1 milligram a day.

DR. CARTER: That is 1 milligram a day but that is all that we have. So we don't have a 0.5 milligrams QD.

DR. WOLFE: Why don't you show it quickly, then.

DR. CARTER: E8, please.

[Slide.]

So we have seen the 11 percent adverse events. Obviously, the numbers are small, 14 percent in women, median time to onset, 8 days, and then the withdrawals due to constipation were as you see here. We did have that one subject reporting ischemic colitis, a male patient.

DR. WOLFE: You are reinforcing it is a lower incidence of constipation. It is much lower.

Let's move on. Just quickly, I want a show of hands. Is there any sentiment for starting

at lower than 1 milligram a day, starting at a half a milligram a day? By show of hands. Would anybody interested in a lower dose at the present time?

Right now, 1 milligram a day; correct? And then moving upwards. What I am proposing is a half milligram a day and moving upwards.

DR. STROM: As part of the study or as part of the initial marketing?

DR. WOLFE: As part of the release of the drug.

DR. CRYER: I would just like to make one comment. The data that we just saw here was for 0.5 milligrams BID. What is currently on the table is for 1 milligram total daily dose per day. To the extent that we can, I really would like to encourage us to make our decisions that are data driven. The data that we have are for 0.5 milligrams BID. So I would propose a compromise between the two; yes, 0.5 milligrams, but twice daily because that is the dosage form for which we have data.

DR. HOUN: Mr. Chair, I think we should move on.

DR. WOLFE: We are moving on.

DR. HOUN: It is clear that the company is not prepared at this point to manufacture 0.5. I think we can discuss with them where they would be with manufacturing 0.5 in the future. And I hear your concern that there might be some safety advantages to that and I also hear the concern there might need to be efficacy studies to elaborate more on that efficacy for that dose.

DR. WOLFE: We will move to Question 4. GSK proposes to restrict use of Lotronex to patients who sign a patient-physician agreement. This agreement is then filed in the patient's medical record. Is this adequate to ensure that only patients with the most favorable benefit-risk balance receive Lotronex. Is auditing of this agreement needed?

We have actually, in a way, discussed the first part of this question by--did we discuss this, do you think, the first part of the question? Everybody agree?

Okay. Is auditing of this agreement needed? Do we all think it needs to be audited? Is there anybody who thinks it shouldn't be audited? Okay.

We will go the next part, b. GSK proposes

a utilization study of UHC as a mechanism to audit whether appropriate patients are being prescribed Lotronex. Is this auditing mechanism adequate to achieve this goal? If not, describe an adequate auditing mechanism.

I would like to start with Dr. Gross.

DR. GROSS: I have one additional suggestion and that is most educational efforts, if they are didactic, don't work. If they are interactive, they are more likely to work. Therefore, I think, much as the Advisory Committee on Immunization Practices has done for vaccines, some kind of questionnaire should be developed for patients and a separate one for physicians that they need to answer and get correct in order to be prescribed the drug or to prescribe the drug.

DR. WOLFE: So you are saying that that, in itself, what they are proposing is not adequate, that more is needed?

DR. GROSS: Yes, along the lines I recommended.

DR. DAY: I would like to comment more thoroughly on this proposal. Everyone agrees here today that the patient plays a key role in identifying AEs in reporting and so forth. I think

that the sponsors put in place a number of good things that will help, the med guides, the patient-physician agreement form, and so on.

However, we can put all the appropriate information in all these documents, but if patients cannot find, understand, remember and use the information appropriately in an accurate and efficient way, then it is functionally absent. I think that the patients who are here today are very knowledgeable and very willing to consider all of these things and sign as appropriate.

However, there will be new people entering the pool if this drug is reintroduced. The plan, at least provided in the briefing materials by the sponsor, include some knowledge questions within a larger survey mechanism and that mechanism deals with a lot of other things. The only thing that is said about how the data will be analyzed, with respect to knowledge, is that knowledge will be looked at in terms of the other variables such as the demographic variables.

They do mention some of the appropriate things to test; a patient's knowledge of the benefits, of the risks and appropriate actions to take. However, it is a written survey and, as the

FDA has pointed out today, it is voluntary. If there were a patient registry, then it could be mandatory, they say.

Sure. But, still, a written survey that is taken on one's own in one's own residence or in the car or wherever has some inherent limitations. So, if, for example, someone does not answer one of the questions, does that mean that the person does not know or forgot or was interrupted.

So there are other mechanisms for this intention in addition to a written survey. There could be a phone survey. That would ensure whether the patient is looking at the medication guide while answering the survey or not. With just the self-take written one, the person could just be going through and ticking off the answers from the medication guide and, therefore, we would be evaluating the ability to read, not the ability to understand, remember and use the information.

So the phone survey would add some additional help on some of these matters. I think it would be useful to consider doing a laboratory study which could go into people's knowledge and understanding and ability to apply this information in more depth. Using various cognitive tasks

including free recall, recognition and scenario tests, you can probe the same information more and more deeply.

When you do this, you can find that, perhaps, when someone is just asked to recall or find information and say it, and if they can't, it doesn't necessarily mean they know nothing about it. Some of the more sensitive measures can be used to show they know something about it. You can also use this mechanism to find out what types of information are communicated well, no problems, versus one or two that people are misunderstanding. Then we could determine, are those one or two things likely to create safety issues.

As for what the level of acceptance on such surveys should be, or laboratory studies or whatever they are going to be, it is hard to set an a priori percent correct. It depends upon the nature of the task and the instrument that is being administered. In some of the work in my laboratory, I can find that there are some questions in some original materials, based on original materials, where people get 20, 30 percent correct.

That is clearly unacceptable. But, with

that information, we can modify the information in the label, in the medication guide, in the patient-physician agreement form and then see a dramatic increase up to over 90 percent. So I don't think we can set an a priori percent-correct level for some of these items but, clearly, something above 85 or something in the high range, given the possible bad outcomes that can come about from some of these types of information if they are not fully understood.

As to when this kind of program should be done, the sponsors propose it will be in post-market days. That is fine. I would suggest that a very quick study with a limited number of participants can be done before the drug would be reintroduced to find out exactly what types of information are well understood and see if any stand out that are not understood so that labeling issues and medication-guide issues could be addressed.

In my lab, I have compared just a small group, under 100, with thousands that are done in the usual kinds of label-comprehension studies, say when you go from prescription to OTC. Although the overall levels of percent correct may change, the

patterns are identical. What you have trouble with out in the real world is what you have trouble with in the lab. So a lab study can be done very quickly.

The final point here is that the sponsor would probably perceive this as a burden difficult to meet in the time plan that they would like to have and also that there would be various costs involve. I can just say that these are really relatively minimal given the usual kinds of comprehension studies that go on. As I say, these more limited ones mimic the outcomes of the big ones.

Finally, I would like to just mention that this kind of comprehension study could be considered with the physicians and with the pharmacists as well as the patients for the materials that they receive.

DR. WOLFE: To summarize, we have two no's so far. You have a lot of studies so far that have been suggested to you. I think that actually answers Question 8 to some extent as well as looking at lower doses.

We really have to go on, but does anybody--

DR. DAY: I would just point out, it did say, in this question, if the plan does not meet an acceptable level, what would be a plan that would.

DR. WOLFE: Oh, yes. That's great. Fine. You did a wonderful job at it. But we have to move on now. Does anybody here disagree with our two respondents so far saying no, everything is wonderful the way it is and leave it this way, the auditing that has been suggested is adequate?

So we all agree so far with our two colleagues that what has been planned so far is inadequate and more needs to be done. That is to say, that the drug is going to be delayed until it is--

DR. HOUN: Could I have a show of hands of who feels the plan is adequate?

[No response.]

DR. HOUN: Who feels that it is inadequate. Voting members only, please.

[Show of hands.]

DR. HOUN: Some abstentions; is that not correct? Who is abstaining? Raise your hand.

[One hand raised.]

DR. HOUN: Okay.

DR. GARDNER: May I just make a

clarification? It isn't that I think necessarily that more needs to be done but maybe some different things need to be done or substitutions need to be made because I don't think that this--I am certainly not voting to take everything they have proposed and say, "In addition, you need to do more."

DR. WOLFE: Okay. We are on c. GSK proposes the pharmacy-based study using the Slone epidemiology and Eckerd Corporation to audit patients' knowledge and awareness of the risks and benefits of Lotronex. Is this auditing mechanism adequate to achieve this goal? If not, describe an adequate auditing mechanism. We sort of just did that.

That's good. So we are saying that, yes, these things are okay, these are okay, but there are additional things that should be considered. You had suggested some already.

DR. STROM: Jackie didn't say that these are necessarily okay and other things should be added. There are a number of other suggestions you could make. Patient registration is one of them. Random audits of registered physicians. You can compare numbers of stickers given to sales in order

to look to see if, in fact, the numbers are the same.

There are a number of ways around it. Personally, I am more comfortable with UHC, not as sufficient, with other things added to it. I have more concerns about the Slone suggestion because of the issue of cooperation, that the people who will participate in that kind of voluntary survey are going to be biased people. They are going to be more likely to be knowledgeable and it is going to lead to misleading information. It is going to make it look better than it is.

So I would substitute some of these other things for that, not just simply add, as Jackie specified.

DR. GARDNER: I concur.

DR. WOLFE: FDA, are you happy with this answer so far?

DR. HOUN: Victor, is there any other further clarification? I think the only thing we would like further clarification is on patient enrollment. That is registering of all patients who will get this drug. Is that something the committee thinks should be done or should not be done?

DR. WOLFE: Does anybody have any comments on this?

DR. GARDNER: You have more information on how the Accutane registry worked, but I have to assume that, since we have now gone through several interactions of additional patient-protection mechanisms, that the patient registry was not meeting the goals that you had. So I don't know why this one would be any different at all.

DR. CRYER: I have some fairly strong thoughts about a registry. The point that came across very clear to me in the postmarketing experience is that the postmarketing dataset is incomplete. We have heard that presented by the sponsor. We have heard that presented by the FDA. We have heard it a number of times today.

What I really also feel strongly about is getting more data about the safety of this drug. One of the ways to accomplish that is through a registry in which patients, as a condition of receiving the drug, you register for the drug and all of these characteristics that we are trying to capture are then captured through the registry information.

So I, personally, would be very strongly

in favor of a registry as a condition of enrollment in this prescribing program.

DR. BEITZ: I just wanted to clarify a point on the Accutane program. That involves voluntary participation in the Slone survey. It always was voluntary and it continues to be voluntary even in the new program that we have implemented.

DR. HOUN: Under patient registration, there are programs such as clozapine requires patient registration as well as the thalidomide requires patient registration. But other programs do not. Some require physician registration only.

DR. WOLFE: I have a question. This registration, obviously, implies not forever and forever; at least for the time being. You are saying that you want it until some adequate data are available.

DR. HOUN: It sounds like that is why people would like registration here, is to help answer questions about patients, risk factors and identifying responders, perhaps. It sounds like it is an information-gathering tool at this point.

DR. WOLFE: There is no reason to attach a time limit to it. You can decide that later on.

So let's just vote. How many here would favor--

DR. LOUIK: Excuse me. Can I just clarify some differences between this program and the Accutane program, because I think there are some--

DR. WOLFE: If you can do it in fifteen seconds.

DR. LOUIK: There are some very important differences. First of all, in the Accutane program, which was a voluntary survey, there was no denominator data available. We never knew how many forms were out there or how many patients were approached. In the methodology that we are describing here, we will have denominator data. We will be able to calculate participation rates and we will be able to compare responders and nonresponders on a variety of demographic variables.

DR. WOLFE: Thank you. That was pretty good.

Let's try to vote at this time. How many favor patient registration?

[Show of hands.]

DR. CAMPBELL: It is very conditional, yes, until we have some data to describe the operation of it and so forth.

DR. WOLFE: How many do not favor patient registration at the present time?

[Show of hands.]

MR. PEREZ: So we have two abstaining.

DR. WOLFE: How many abstain? Somebody abstained. If you don't want to vote, that means you abstain. So how many are in favor of patient registration?

[Show of hands.]

DR. SELIGMAN: One member of the committee has left. Dr. Richter left.

DR. WOLFE: How many are against patient registration?

[Show of hands.]

MR. PEREZ: We have thirteen in favor, two abstained and three not in favor.

DR. WOLFE: Question No. 5 regarding physicians. GSK proposes a plan in which physicians call and 800 number to receive a self-attestation kit including stickers. Physicians self-attest to their qualifications by signing the section for the physician on the patient-physician agreement. This agreement is then filed in the patient's medical record. Is the sponsor's proposal adequate to allow for evaluation

of physician adherence to the program? If not, describe an adequate auditing mechanism; b. define an adequate level of adherence to the program by physicians and c. should physician enrollment--i.e., registration--be part of the risk-management plan?

DR. GARDNER: Mr. Chairman, didn't we start to address some of this when we dealt with--

DR. WOLFE: We sure did.

DR. GARDNER: So self-attestation may be out. Can we ask if whatever certification program goes in could be linked to some of these questions?

DR. GARDNER: We really had discussed this regarding restricting it. We discussed it fully. We feel some kind of self-attestation is necessary for prescribing this, some kind of evidence of proficiency in the disease, whether that is a learning process, a CME program, a form to fill out, a questionnaire. I think we all agree to that already.

DR. GROSS: So it could be tested and there won't be an attestation, there will be a test.

DR. CRAWFORD: Since we are considering the physicians as part of the risk management

program, at this point, I would like to ask the committee to address whether we should advise that it only be a 30-day supply which is not part of the sponsor's plan.

DR. WOLFE: You mean no refills, no automatic refills.

DR. CRAWFORD: I brought up earlier, even with a new prescription, it could be a 90-day supply, which effectively is refills, or six months. So, should we as a committee make advice that is more conservative?

DR. WOLFE: You actually brought up a very important point and that is a 90-day supply--my definition of a prescription is 30 days but, with some of the plans now, they are 90-day supplies. I am not sure that is what FDA had in mind was a 30-day supply. What did you have in mind?

DR. HOUN: The sponsor proposed a 30-day supply.

DR. WOLFE: So it is 30 days very specifically, then.

DR. HOUN: However, I don't think there is any proposal to ensure that 30 days is only being written for--it would allow other doctors to write as they wish. But I think they are

recommending--Dr. Wheadon, say what you are recommending.

DR. WHEADON: The recommendation is the initial treatment period would be for 30 days at the 1-milligram-a-day initiation paradigm. Following that, it would be up to the prescriber. The intention would be it would be a standard 30-day prescription, but there would be no restriction around that with the exception of the unit-dose packaging that would essentially encourage 30-day prescription but would not require it.

DR. WOLFE: This kind of has some issues because there are certain plans now that are 90-day plans. So you have to work with some of these companies like Merck-Medco and really discuss these because they are 90-day plans and you are going to get a 90-day prescription. It doesn't mean a person can't be reevaluated at 30 days and the prescription continue. So I think some wording will be required in that requirement.

DR. CRYER: I think there are three points which make Dr. Crawford's suggestion a tenable proposition. They are the three following observations. We were told earlier that patients

who did not respond after the first month were unlikely to subsequently respond.

Two, we know that the sponsor has suggested a titration phase of 1 milligram for one month and 1 milligram twice daily for the second month. Third, it is suggested that the patient attest to if the symptoms have not improved after four weeks of taking the 1 milligram twice daily that she will stop taking her Lotronex.

Because of those three observations, I think--I mean, there is no other suggestion other than to have a 30-day supply so that one can evaluate the initial titration phase and then subsequently one can evaluate the subsequent treatment phase on BID.

DR. WOLFE: Being in VA it is very different. We have patients who have 90-day plans. So I think what will have to be done is some kind of wording with the companies will have to be worked out before this can be implemented properly.

DR. WHEADON: One correction to your statement concerning the force to 1 milligram twice a day. The intention is to have the 1 milligram once a day for the first 30 days, the initiation treatment. There will then be a decision tree.

That decision tree is no adverse effects, no efficacy. You then would go to 1 milligram twice a day, which is the indicated efficacious dose.

If you have no adverse effects but, as we have heard in terms of some anecdotal experience, you did evidence efficacy, it would be the recommendation in the labeling that you maintain the 1 milligram once a day strategy.

DR. CRYER: That seems reasonable. The point that I was trying to get at is that, after 1 milligram twice a day for four weeks, the majority of the evidence that I have heard suggests that there really is not a compelling reason to continue after that and there needs to be some way to make that assessment.

DR. CAMPBELL: There is a little confusion around here, I think. But my understanding of what we are saying is, during the titration and dosage adjustment period, it will be a 30-day regimen. Beyond that, it is a more flexible regimen. 30 days is an arbitrary point in time to make this a locked-in time. I don't think we want to require all of the IBS patients to be seeing a physician every 30 days to get this new prescription.

DR. WOLFE: But it is not uncommon with

many drugs to reevaluate the new drug, the patient takes it for a month and you reassess. That is not uncommon at all. There are many drugs like that. Theoretically, when NSAIDs were out, you took it 30 days or less, two weeks, you drew LFTs. So that is not uncommon at all to see a patient again after 30 days of taking a drug for the first time.

DR. BALDWIN: No, but that is what I said, during the titration and dosage and developing--

DR. WOLFE: After that, every 30 days is not necessary, for sure.

The question is what is considered an adequate level of adherence to the program by physicians. Let's start on this side. What is an adequate level? Do you want 100 percent? 90 percent? 80 percent? 0 percent?

MS. BLACKMAN: I'm sorry; I couldn't understand the question. What was the full question?

DR. WOLFE: There is a program in place that physicians have to have the stickers and self-attestation and there is a regular process by which physicians will be prescribing the medication. So there has to be some kind of level of adherence with an auditing mechanism. Do we

want 100 percent? Are we demanding 100 percent level of adherence, which is, in my view, fairly unrealistic or will we accept 90 percent? Or do we want 80 percent? What number will we be looking at?

I don't have the expertise to really make that recommendation. I need some advice from people who deal with these kinds of things.

DR. LaMONT: Mike, the next question has been answered with stickers. So it sounds like it is going to be 100 percent under 6 regarding pharmacists. If Question 6 demands 100 percent, it sounds like, if you write a prescription without a sticker, it is not going to get filled. So it sounds like it has got to be 100 percent.

DR. WOLFE: So, people in the risk-management group, is that realistic, 100 percent?

DR. GARDNER: No; it isn't. And we haven't discussed the stickers yet.

DR. LaMONT: Maybe you should do 6 first.

DR. WOLFE: We can do them together because they are together because, generally, I am pretty sure pharmacists will only fill prescriptions from people who are qualified to

write prescriptions, generally. So it has to be in writing. It can't be by telephone. It can't be by fax. It has to be in writing with a sticker.

So are we saying, then, that physicians and pharmacists must adhere to this and 100 percent adherence is required?

DR. GARDNER: Are you opening the floor to the discussion of stickers?

DR. WOLFE: Sure.

DR. GARDNER: Okay. This is not something that makes pharmacists terribly happy. We have already heard earlier today that it doesn't apply. It is very, very difficult for inpatient pharmacy at all. In the outpatient setting, pharmacists are now looking at yellow stickers for Accutane and we may be looking at, I don't know, blue stickers for Lotronex until the next risk-management committee and then we will have some other kind of stickers.

We think that, perhaps, a bigger picture needs to be taken here. I know that pharmacy organizations have worked extensively with FDA risk managers to develop a plan for long-range networking of management for circumstances like this involving pharmacy. My recommendation would be that the agency and the sponsor work with the

pharmacy community to find an optimal mechanism for managing and adhering to the needs of the risk-management program without this committee dictating that some color stickers be put on outpatient scripts.

DR. WOLFE: Could I ask the FDA a question? Does the sticker program work for Accutane?

DR. HOUN: The sticker program just went into effect one month ago.

DR. GARDNER: April 10.

DR. WOLFE: Is it working? Or is it too early? Do you want a sticker program?

DR. HOUN: A sticker program is being proposed by GSK as a way to help with the control process.

DR. WOLFE: Do you want a sticker program?

DR. SELIGMAN: That is what we are asking you.

DR. WOLFE: I want to know what they want.

DR. HOUN: I think we want a program that works. So I appreciate the pharmacists' concern that one more program is going to put a level of complexity that maybe it is not going to work.

DR. WOLFE: Has any physician here ever

dealt with a sticker program? We are really shooting from the hip. We have no idea what this entails.

DR. GARDNER: Precisely.

DR. WOLFE: The pharmacists do know.

DR. GARDNER: Furthermore, the requirement of a hard copy with a sticker on it every time may not be optimal from the standpoint of pharmacy practice. We have already heard that in the VA, you have a different--and, perhaps from Michael Cohen, we have heard that in the VA there is a different system. So, I would rather that we not get prescriptive as a committee about what ought to happen with the prescribing logistics.

DR. DAY: I don't think Dr. Gardner is saying that it is too much of a burden on the pharmacist but that the pharmacy community should look and see what would be an appropriate way to meet the same goal.

DR. COHEN: I have to agree with Dr. Gardner. I have to agree 100 percent that we are just going to see additional programs in the future with stickers. There is a nonstandard program that we are proposing here. There are different facets for each one. It just doesn't make sense to keep

going on these sticker programs.

MS. CRAWFORD: Mr. Chair, very briefly, I have to catch a plane, if I might add, one aspect of the proposed risk-management program that I, personally, found quite inadequate, lacking and a bit disappointing was with the written part which limits the pharmacist's participation, at least in writing, to a very technical role that any clerk could do, to look at a sticker and to give out a medication guide.

I think I would like to ask, in a revised risk-management program, that the sponsor work with the agency in developing a more comprehensive one that looks at the pharmacist's cognitive and clinical skills as well as a member of the team and pharmaceutical care who would know largely of the prior therapy, concurrent therapy, the drug interactions, could educate and counsel patients, could do follow up and monitoring which I feel is neglected in the current plan.

DR. WOLFE: Dr. Cryer and then Dr. Holmboe.

DR. CRYER: Very briefly. We heard from the pharmacists, from the people who have the pharmacy perspective, that the stickers are

unlikely to work in an implemented program. The question states that the goal is to have a program in which dispensed Lotronex is under the care of an enrolled physician. I would suggest that if there were a registry of physicians who were certified for this program that that registry could be provided to the pharmacist to obtain this goal without a sticker.

DR. HOLMBOE: I would also point out that simply putting a sticker on the script is not going to attest to the physician's proper prescribing of Lotronex. So I don't see the sticker really helping in ensuring that physicians are using the drug properly. I would, again, go back to some of the things we were talking about earlier and consider some audit of physician practice. The sticker is not going to do that.

DR. WOLFE: Last comment from Dr. Strom.

DR. STROM: Let me suggest, as a way of trying to summarize, I think the sense you are getting from all of us, and I agree, is that the concept of the sticker, concept of assuring that you have a certified physician, we are in support of. The question is whether the sticker is the right way to do it or whether there is some better

way of registration of physicians that might well be much more efficient--a registry of physicians might well be a more efficient way to do it, but I think I am hearing support for some way of guaranteeing that it is being written by a certified physician by whatever mechanism that is.

DR. WOLFE: Do you have enough information for this question?

DR. HOUN: Yes. I think the remaining question I would have is then do you feel that physicians should be registered and, if you do feel they should be registered, the proposal is the check of registration be the real-time check, whether it be through stickers or some other, looking up at a database. That would be the two questions I have for you.

DR. WOLFE: Can I try to answer this for all of us. We talked about this before, about having some kind of proficiency in the diagnosis and treatment and IBS and if there were some kind of questionnaire, an educational process, and then--I had to use certification because it takes three years to be certified in GI, so certification, a process of some sort for the use of this agent, and then also with a check list for

the patients, the proper candidate. Is that adequate for you?

DR. HOUN: The certification would mean having gone through a hurdle of some type of educational interaction. If you pass, then you are able to prescribe Lotronex. Is that correct?

DR. WOLFE: Could that be, for example, faxed on to send to someone at the FDA? Is that possible--or e-mailed or something like that.

DR. HOUN: That is the question. Is the name of physician who has completed that hurdle, should that be centralized to be checked by the pharmacist that they, in fact, have been certified, have been qualified. Is that the trek you would prefer as opposed to stickers? Or are there more problems with that?

DR. WOLFE: I think that is what we said. The only thing that I have with it, personally, is that it becomes a registration issue and it is almost a privacy issue in a way. But that is a minor issue. I think we, more or less, said we have to do it that way. Does anybody feel differently that we should not register

DR. METZ: This seems to me to becoming an incredibly cumbersome system here where you are

just getting so many checks and balances all over the place that no one will be able to keep track of it.

Correct me if I am wrong. I get the feeling we want to register the patient so we can learn about the outcomes and make informed decisions for the next step. We want to register, one way or another, the physicians because we want to have some way of working out that they are competent to do what they do and, therefore, by virtue competent, they are going to be able to prescribe.

I think the pharmacists do their regular job. They have a look at a prescription when it comes by and they say, you know, you are getting a prescription for a drug that has some kind of bad side effects. Have you been aware of those? Let's look at what other drugs you are on. Maybe you are taking an opiate, et cetera.

I don't see why you need to have a sticker. I don't see why you need to register them. And I think the bottom line is when you are going to evaluate the outcome. You are going to look at the outcomes and you are going to look at the physicians and the pharmacists are going to do

their regular job.

Now, correct me if I am wrong, but that is sort of my assessment of it.

DR. WOLFE: If you have a patient registry, aren't you going to have a physician registry automatically?

DR. HOUN: We don't need to.

DR. STROM: Let me say just I think, again, we are asking operational details that probably we would, as a group, be comfortable with any of the various solutions. One solution would be a centralized physician registry. Another mechanism might be the physician has a document, a diploma, from his certification course and he gives a copy to the patient along with the prescription and the patient just takes that with them along with the prescription.

I think there are lots of different--I am not saying that is the best way, at all. All I am saying is the goal here is that the pharmacist needs to know--there needs to be communication with the pharmacist that the physician was certified in some way, by whatever mechanism, working it out jointly especially with the pharmacy community, whatever works best for the pharmacy community, to

be able to do that.

DR. CRAWFORD: Thank you. I agree with the last statement from Dr. Strom, but, Dr. Metz, I would like to add one thing to what you said. I agree that, as part of the regular pharmacy practice, the pharmacist should do the job. I am not saying it should be an extra program except I do think the risk-management program should also include an educational component for the pharmacists.

DR. WHEADON: Three very quick points. Number one, I think what Dr. Houn is sort of alluding to, and it is a question we also have, is ownership of these registries. Certainly, from our perspective, it is not the role of the pharmaceutical company to be a certified or a check, if you will, concerning these registries. So that is a problem that maybe the committee can't wrestle with but at some point we will have to wrestle with that.

Second of all, I think the point was very well taken that the number of requirements that are being built into this plan have become, to my mind, considerably onerous and I am really concerned that the barriers will be so high that the patients that

we heard from earlier today will probably not be able to get access to this drug. That is really a concern.

I think those two things just need to kept in mind.

DR. WOLFE: That answers your question, doesn't it?

DR. HOUN: Thank you.

DR. WOLFE: We knew this was going to be tough to answer all these questions. There is a lot of material we covered here today. I think, for Question 8, we have already discussed a lot of other ideas. That doesn't mean we have to stop today. If you have other ideas, you can communicate them to the FDA. I don't think there is any issue there, so we are not going to discuss this any further, just finish up with Question 7.

DR. FLEMING: Could I--

DR. WOLFE: Yes.

DR. FLEMING: Dissenting opinion. I think I would like to have two minutes, at least, for it. I think it is one of the most important issues to put on the table, but I am willing to wait.

DR. WOLFE: So you are not happy with the decision to wait, but you will wait.

DR. FLEMING: Oh, no. I'm happy to wait. I just want to skip--

DR. WOLFE: Oh, no; not skipping it. I am saying we will be able to send questions in and other ideas.

DR. FLEMING: No, no. I want to orally convey something today on 8.

DR. WOLFE: Go ahead.

DR. FLEMING: Now?

DR. WOLFE: Knock yourself out. Go ahead.

DR. FLEMING: Okay. Given the answer to 1, at least from my perspective, that there certainly is promise here but there certainly are, also, uncertainties about what is the population or subpopulation in which we can feel confident we would have a favorable benefit to risk, what I have been struggling with is what is a strategy that will get us a clean and timely answer and, if, in fact, is successful, would also allow us to reduce some of this onerous implementation we have been discussing about for the last hour.

We don't know, but there is a lot of reason to anticipate that those patients that have the most disabling symptoms could stand to benefit the most, and we have heard a lot from the

testimonials to give credence to that suspicion.

So how could we, in a very timely way, address whether or not we get substantial efficacy in that cohort?

My proposal would be that we could do from as rapidly as possible a randomized comparative trial that would either be dose arm or two dose arms, depending on the choice of the sponsor and the FDA.

It could be the 1 milligram QD and/or 1 milligram QD and 1 milligram BID against control. It would involve 500 to 750, max a thousand patients. These would be patients that would be enrolled who would be in this very high-risk category.

If this group, as Dr. Hoberman was speculating could be the case, does, in fact--and it follows also from Dr. Strom's earlier questions--if this group has a subcohort that experiences profound benefit, at the benefit that we heard testimonials about today, then that level of benefit, if it occurred in 10 percent of the patients, in my view, would allow much more liberty as to the level of risk that we could accept.

A cohort that would stand to gain a great deal would have a favorably benefit to risk even if

we were less certain about the exact level of the ischemic colitis. So, with 500 to 750 patients randomized as rapidly as possible, enrolled over, let's say, three months followed for an additional three months--i.e., six months from the time that that study was initiated--we would be in a position to be able to assess, as has been speculated here--that there is a subcohort that would experience a very significant level of clinical benefit, a response that could be obtained in a very rapid time frame and it would be, in fact, possible in this, if we chose to do so, to also answer the question about efficacy in those people who failed to respond conventional therapy.

If you, in fact, wish to enroll that cohort, we would actually, for the first time, get direct efficacy information in that cohort. It would also be possible, if we chose to refine the dosing, as has been discussed today, if you wish to titrate, if you wish to discontinue for early nonresponders or if you wish to manage effectively on AEs, all of these could be built into this study that could give us an answer in 12 to 18 months.

The second phase would be a separate randomized trial in a much broader cohort that

would be, in fact, a larger, longer-term study that would answer the much more difficult question in patients that are not as restricted to those that are the most serious in terms of initial baseline characteristics, can a dosing schedule be identified where we would receive, or we can identify, favorable benefit to risk.

So it would be a two-trial strategy where the first trial could be done in a very timely way and, if what we are hearing today in the testimonials is true, that subcohort could identify substantial benefit that would give us clear confidence that we would have favorable benefit to risk even though we would have small numbers in the trial.

DR. WOLFE: Dr. Traber has a brief response.

DR. TRABER: Just a brief response. I completely concur that there are many different ways that we can continue to study the efficacy and identify patient populations. But let me just say that obtaining drug substance, study start-up, patient enrollment, analysis, and so forth, you just described 18 months to two years of work after which it would have to be analyzed and reviewed.

We would be talking about three years hence approving the drug.

DR. FLEMING: It could definitely be shorter than that. One thing that has already been on the table is there is going to be six months time before even Option B that we discussed earlier could be implemented, that would allow the planning stage for this trial before it is available. So the planning stage of this trial could occur during this time that the drug wouldn't be available anyway.

The point is the drug to study would be available at the end of the planning stage so you wouldn't lose the planning-stage time frame that otherwise you would.

DR. WOLFE: We have already voted not to really go that route. We have already voted to have the drug made available when the sponsor can make the drug. That is what we are recommending. You don't have to take our recommendations. That is what we are recommending.

The study, I think, that GSK is fully committed to doing a lot of the studies that are being recommended. Am I correct?

GSK: That's correct.

DR. WOLFE: We have already all voted that--well, not all. Most voted that we would favor that scheme. Is everybody happy--unless you all want to sleep here tonight--is everybody happy, again, corresponding with FDA regarding Question 8 with further studies?

7a. Does anybody here think that we shouldn't worry about ischemic colitis, severe constipation and death as an endpoint? I think that is clear, through our discussions, we want to look at that. So, 7a., we all want to look at that unless I am way off base.

The question is, what are acceptable rates for adverse events and/or acceptable degrees of severity. Basically, what you are saying is we don't know at this point. I don't think we have the answer. Would you say that?

DR. FLEMING: For severe events?

DR. WOLFE: Do we know what the rate is, what is acceptable?

DR. FLEMING: Certainly, the problem is any time we are looking at what is an acceptable rate of severe events or safety events it is in the context of what is the magnitude of benefit we are going to achieve. So, indeed, we have some global

data on what the risks of ischemic colitis would be and what we see is evidence of benefit that is at a comparable level in a very subjective manner.

So the struggle here today is to try to find the subgroups or the refinements of the management program that will improve benefit to risk.

DR. WOLFE: Do you want a number from us? 15 percent? Dr. Strom.

DR. STROM: I think what is clear from the discussion today is the acceptable rate is somewhere very close to where it is now because, if the rate was lower, we wouldn't even have needed today's meeting. If the rate was higher, the vote would have been, no, don't have it on the market.

So, in terms of what is the acceptable rate, it is the rates we heard about today. If there is a way to identify subgroups who are more likely to benefit through the kinds of studies Tom is suggesting or long before that, through analysis of the existing clinical-trial data, as I talked about before, or analysis of the HMO data, as I had talked about before, which could be available potentially in weeks instead of in multiple months, then that could increase the likelihood of benefit

and would make the acceptable rate a lot better.

DR. WOLFE: Dr. Cryer.

DR. CRYER: Ten seconds. The only way for us to know exactly what that rate is going to be is if we capture the denominator data. The only way to have the denominator with confidence is to have a patient registry. That will allow us to understand what the actual rate is. It will also allow us to answer the question of does Lotronex benefit patients in whom conventional therapy has failed. We need the denominator for both of those questions.

DR. WOLFE: Can I summarize this by saying that we would accept, right now--oh, is there someone else who wants to speak? Go ahead.

DR. GARDNER: I just want to say that I am not comfortable with the agency or the company going away thinking that we believe we have designed a risk-management program by committee here today. I want them to understand that--I know that you have specific questions and that we have had votes but, please, from our perspective, if you would take our best advice and the sense of what our concerns are and, to the extent that any of us can help you, call on us individually, but this is

not a wholesale package we have voted out of here today.

DR. COHEN: Just a quick comment. It would be great to actually have a meeting on risk-management plans so that we could discuss it openly and maybe come up with some standard ways to approach these kinds of issues.

DR. WOLFE: I was going to attempt to summarize saying that we want to get as low as possible the complication rate which is what we are all saying, but we don't know what that is going to be at the present time. We don't want it to be any higher than we have seen. We would like it to be lower. But we are willing to accept right now what we have seen to date.

Is that fair? If that is the case, if there are no other comments, then--

DR. FLEMING: There are some dissenting votes to that.

DR. WOLFE: There are some dissention to what I have just said. But, having said that, we all know there is some dissention. We are not in full agreement, but I think, without spending another few hours really going into these questions, we really can't say much more.

Anyway, if that is the case and there are no other pressing comments, I would like to adjourn this meeting and thank everybody for their comments and for their participation.

[Whereupon, at 5:25, the meeting was adjourned.]

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