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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL, DRUGS ADVISORY COMMITTEE

Tuesday, November 16, 1999

9:00 a.m.

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COMMITTEE MEMBERS PRESENT:

STEPHEN D. HANAUER, M.D., Chairman

ROSEMARY BERARDI, Pharm. D.

GEORGE D. FERRY, M.D.

NANCY L. GELLER, Ph.D.

LOREN LAINE, M.D.

JOANNE A. WILSON, M.D.

C O N T E N T S

P R O C E E D I N G S

CHAIRMAN HANAUER: I'd like to welcome you to this morning's meeting. It's obviously going to be an important Advisory Committee meeting, probably precedent-setting, depending upon the--well, in any event, on the outcome of the Committee's thinking process regarding this.

My name is Steve Hanauer. I'm from the University of Chicago, and I'm the Chairman of the GI Drugs Advisory Committee. To begin with, I'd like to have an introduction of those of us at the table. Perhaps we'll start on this end with Dr. Senior, introducing ourselves to the audience.

DR. SENIOR: I'm John Senior. I'm a GI medical reviewer at the FDA.

DR. HOUN: I'm Florence Houn. I'm the Office Director for the Office of Drug Evaluation III at FDA.

DR. TALARICO: I'm Lilia Talarico. I'm the Director of the Division of GI and Coagulation Drug Products.

DR. WALD: I'm Arnold Wald. I'm from the University of Pittsburgh Medical Center.

DR. BERARDI: I'm Rosemary Berardi and I'm from the College of Pharmacy at the University of Michigan, and I'm the consumer representative to this Committee.

DR. LAINE: I'm Loren Laine and I'm from USC Medical School, in Los Angeles, gastroenterology.

DR. WILSON: I'm Joanne Wilson. I'm at Duke University Medical Center, gastroenterology.

MS. STANDAERT: I'm Joan Standaert, the Executive Secretary of the Committee.

DR. FERRY: I'm George Ferry, pediatric gastroenterology, from Baylor College of Medicine, in Houston.

DR. GELLER: I'm Nancy Geller. I'm Director of the Office of Biostatistics Research at the National Heart, Lung, and Blood Institute, in Bethesda.

DR. RACZKOWSKI: To my left will be Dr. Robert Prizont, who is a medical reviewer from the Division of Gastrointestinal Drug Products. I am Dr. Victor Raczkowski, the Deputy Office Director in the Office of Drug Evaluation III.

DR. GALLO-TORRES: I'm Dr. Hugo Gallo-Torres. I am the Medical Team Leader of the reviewing division, the Division of Gastrointestinal and Coagulation Drug Products.

CHAIRMAN HANAUER: And at this point, Joan Altandaert is going to read a statement regarding conflict of interest.

MS. STANDAERT: 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 is has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S.C. 208(b), full waivers have been granted to Dr. Loren A. Laine and Dr. George D. Ferry which permit them to participate in all official matters concerning Lotronex. A copy of these waivers may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A-30 of the Parklawn Building. We would also like to disclose for the record that Dr. William M. Steinberg will be excluded from participating in all matters pertaining to Glaxo Wellcome's Lotronex.

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 his comments. Dr. Arnold Wald would like to disclose for the record that he was an investigator on alosetron, but not the principal investigator. He also has a grant from Glaxo on a matter unrelated to alosetron.

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 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.

That concludes the statement for this meeting.

CHAIRMAN HANAUER: Anyone else want to comment regarding that?

[No response.]

CHAIRMAN HANAUER: Okay. For each of these Committee meetings, there is an opportunity for the public to make any comments, and at this point we've been notified that there are two individuals who represent the International Foundation for Functional Gastrointestinal Disorders who would like to speak.

I would like to invite Nancy Norton to make the initial comments.

MS. NORTON: Thank you. Good morning, Members of the Committee. Thank you for the opportunity to appear before you today. I am the founder and President of the International Foundation for Functional Gastrointestinal Disorders and the current Chairman of the Digestive Disease

National Coalition. The IFFGD addresses the needs of individuals with functional gastrointestinal disorders, irritable bowel syndrome being the most predominant one.

As the founder of IFFGD, I began the organization in 1991, when there was little educational information or support available to patients and no specific medical treatment offered to patients living with irritable bowel syndrome. It wasn't until the mid-1990s that we saw a stronger interest in the functional GI disorders, and IBS in particular.

Irritable bowel syndrome is a chronic complex of symptoms affecting as much as 20 percent of the population. Symptoms include abdominal pain, bloating, constipation, diarrhea, and fecal soiling. These common dysfunctions strike people from all walks of life and result in a significant toll of human suffering and disability.

Irritable bowel syndrome represents one of the most common conditions encountered by gastroenterologists and general internists. It accounts for 20 to 50 percent of referrals to gastroenterology clinics. Approximately 70 percent of individuals with IBS in the community are female, with the incidence being reported as high as 90 percent in medical centers.

In the U.S. Household Survey of Functional gastrointestinal Disorders, Prevalence, Socio-Demography,

and Health Impacts, draftsmen reported that individuals with IBS will miss 13.4 days of work annually, as opposed to the 4.9 national average. IBS alone has recently been called a multi-billion-dollar problem by the gastroenterology community.

Survey data by Tally reflects that patients with IBS incurred an annual health care bill of $742, in 1992 dollars, compared to $429 for those without the condition. Data also reveals that there is an increased risk of unnecessary abdominal surgery correlated by IBS patients. Hysterectomy or ovarian surgery has been reported in female patients with IBS as high as 47 to 55 percent, and has been performed more often in the IBS patient than in comparison groups.

One of our goals has been to move the research field forward to provide a better understanding of the pathophysiology of IBS and the underlying mechanisms, with the hope that one day better medical treatments will be available for patients with irritable bowel syndrome. It appears we may be approaching that day.

We are seeing the development of drugs designed specifically for the treatment of irritable bowel syndrome. If these drugs are found to be safe and effective, I would urge you to make them available to patients who so desperately need them. "Desperate" is not a word that I use

lightly. The toll of IBS is on the individual's quality of life and discomfort, affecting almost every aspect of their life. There remains a quiet desperation among IBS sufferers. As many people have said to me, it has become too much.

The world Health Organization has defined quality of life as being not only the absence of disease and infirmity, but also the presence of physical, mental, and social well-being. Quality of life may also be defined as an individual's overall satisfaction with life and one's general sense of personal well-being. It also includes their functional capacity and their own perception of disease.

Health-related quality of life includes physical function, somatic sensation, psychological state, and the social interactions that are affected by one's health status. Health-related quality of life indicators are subjective. Their validation lies primarily with the patient.

Eisen, Locke and Provenzal report gastroenterologists spend 50 percent of their time caring for patients with functional bowel disorders. These disorders do not have mortality or physiological endpoints. Thus, the evaluation of health-related quality of life becomes critically important. Patrick Drosman and

colleagues developed the IBS quality of life measures that distinguishes symptoms, functional state, perceived quality of life, and social disability components. Their results confirm that IBS has a broad and significant impact on persons' quality of life, in addition to the disease activity and symptom impact.

Just what is that impact? At IFFGD, we talk to tens of thousands of individuals who live with irritable bowel syndrome and there's a constant theme that we hear from women and men. They consistently confirm the isolation that many IBS sufferers experience. Partly, this is because IBS is very difficult for most people to discuss. Many patients believe it would help if they could talk about their condition and share their experiences, but the reality for them is that even mild symptoms can be very embarrassing. More severe symptoms, like unpredictable pain, urgency, and bowel incontinence are close to unmentionable for many sufferers.

Interviews with IBS patients consistently reveal that few talk about their symptoms with anyone else. Indeed, many patients go to great lengths to hide from others their condition and their own distress. Imagine for a moment how difficult that is. Imagine what your life would be like if everyday, or even several times a week, you woke up and within an hour's time you have severe symptoms

of a GI flu. You have severe abdominal cramping to the point of being doubled over in pain. You are nauseous and you have diarrhea. You are unable to leave the bathroom for an hour or more. You are now exhausted from what you have just been through.

It is difficult to get yourself to work, but you arrive on time because you have allowed yourself an extra hour or two in the morning just in case you needed it. You plan your day around the availability of restrooms. You are hesitant to eat lunch or dinner because you fear the symptoms might start all over again. Sometimes, you miss work or must cancel appointments because of your problems.

IBS affects not only your professional life, but your personal life as well. It is difficult to plan trips, to eat in restaurants, or even to go shopping. Your friendships and your most intimate relationships and your sex life are affected by it. There's a quiet anxiety, an anticipatory response to what will be next. You may be depressed at times, feeling your life is out of control, or at the very least your life is controlled by your bowel. You live life from the edge of the room, never willing to truly participate to the fullest for fear of having to find the quickest way out. You feel a loss; there is loss potential.

Your disease is invisible to others, but it

affects every aspect of your life. Who would know your pain and the shame you feel, except those who are closest to you? Even those we are most intimate with may not understand. You feel as if you are the only one.

It has been said that the greatest fear is that of uncertainty. For people living with IBS, uncertainty is a 24-hour challenge; it does not go away. That challenge is net by millions of women and men everyday. They are to be credited for their enormous personal strength of meeting the challenge of the day and continuing to put their faith and lope in the medical community to provide the best answers.

Today, you are here to make recommendations on a potential new drug treatment for IBS. There should be no debate over the need for a drug treatment that has been developed specifically to treat multiple symptoms of irritable bowel syndrome. To date, we have had no drug treatment that treats multiple symptoms of irritable bowel. Our options have been limited to treating single, acute, predominant symptoms, with very little success. If Lotronex is shown to be safe and effective, it will fulfill an unmet need and represent a significant step forward in providing treatment for sufferers of irritable bowel syndrome.

Thank you.

CHAIRMAN HANAUER: Thank you.

I'd now like to invite Sue Eggle to provide

comments.

MS. EGGLE: Good morning. Members of the Committee, I certainly appreciate the opportunity you have given me to appear here today. I have been a sufferer of IBS since 1974, which is, of course, 25 years.

In 1974, I had a serious miscarriage, and as I look back today, that was the beginning of the mind/gut reaction. For three months, I was afraid to leave the house for fear of having the miscarriage. It was severe cramps and bleeding, and a pattern developed which has remained with me for 25 years.

For some years after 1974, I had numerous colon, small intestine, and stomach x-rays. IBS was never diagnosed. In fact, nothing ever seemed to be wrong. After a while, I just said forget it. I was so distressed in the 1980s that I sought out a GI doctor. He spent one hour just listening to me and I felt so good about our talk. He felt I had lactose intolerance, even though he never took any tests to prove it. So I followed that diet and things improved slightly.

So when I had these bouts of diarrhea and cramping, I thought it was all due to lactose intolerance. I also received some biofeedback, but my HMO would not pay for any of it and I could not afford it at $80 an hour. I felt it could have done great things for me, but the

treatment was not long enough.

None of the doctors I have had since the late '80s have given me time to talk or dialogued with me about my health issues concerning IBS. I really have not received adequate treatment over the years. The prescription of choice or because there was nothing else was Donnatal or Lomotil. They seemed to help a lot, but were very drying to my eyes, my mouth, and my skin. I have taken them on a limited basis for years.

Now, my physician has been prescribing Aprolozam, which has been doing the greatest job of altering the thought patterns between the mind and the gut. But I am not too fond of being drugged or feeling sleepy. One month ago, I had a car accident because I feel asleep at the wheel perhaps only for a few seconds. Now, I am a little skeptical about that medication. I am waiting with anticipation for this new drug.

I recommended to my physician some time ago that she subscribe to the IFFGD publication and purchase the book that Dr. William Solt wrote entitled Irritable Bowel Syndrome. She didn't give much response to this, didn't offer to read it, didn't make any moves to address the issue, which was very discouraging.

Because of lack of proper medications, there is another issue that I will soon face unless the medication is

approved. For many years, the one product that I relied on to travel on vacations and to carry on my window treatment business was Kimberly Clark's Depends Shields, which were always with me and upon which I relied heavily, and they have been taken off the market several months ago. They have enabled me to leave the house with a sense of security and saved me from many accidents concerning fecal soiling. I feel it is necessary to push this drug through as soon as possible to spare sufferers this huge embarrassment.

So you are thinking or saying to yourself, so what? Well, consider for a moment having an important meeting or appointment, like all of the rest of you do. But instead of being able to attend, you are doing word puzzles in the bathroom, and repeating this four to six times in a row, or lying down on your stomach on the edge of the bed to perhaps relieve the cramps, which I can only liken to giving birth, or having to stop about six blocks from home in the filling station and realize you didn't quite make it and turn around and go back home, or wondering what to do with your little grandchildren at the zoo or the museum or the movies while you are in the bathroom. Most people can do these things with peace of mind. I cannot count on that peace.

I decided that to have a fulfilling life living with IBS, I needed to let my family and friends know what

was going on in my life and name the demons. That diffuses a lot of anxiety and allows me to do my work as a window specialist, and travel. Most of my customers immediately discovered that I might be late for the appointment or installation, and that I might need to use their bathroom. No one ever asked to use my bathroom.

I love to travel, and do so frequently, such as coming here. On vacations, my husband and family know they will have to stop when I get frantic, and that leaving a motel or hopping on a bus at the crack of dawn is just not possible. I have traveled abroad with various medications. I stay around my room until I am ready to leave, which could be two or three hours after everyone else leaves, and checked out all the bathrooms. I have had many close calls on these trips.

In Greece, the toilets were in the floors. In Norway, the top of the mountains were far from a bathroom. In Germany, I was always looking around for the nearest facility. That is a terrible way to live, continually searching for a bathroom. And it is not something that can wait for one-half hour, but immediately. When the cramping begins, there had better be a bathroom. And the accidents, how upsetting. This chronic condition without much diagnosis has been treated very lightly by the medical profession and the drug companies, and I am very pleased and

happy that this is receiving national attention and research.

Thank you for listening today from the bottom of my heart.

CHAIRMAN HANAUER: Thank you.

Are there any other comments from the public? Anyone else want to make a statement?

[No response.]

CHAIRMAN HANAUER: Okay, thank you.

At this point, Dr. Houn, who is Director of the Office of Drug Research and Review, needs to make an opening introduction before our formal proceedings begin.

DR. HOUN: Thank you, Dr. Hanauer. I want to welcome the members of the Advisory Committee, the public, Glaxo Wellcome, and others to this very important meeting about the safety and efficacy of alosetron for relief of specific types of irritable bowel symptoms in women. It's an important meeting because the disease, as you just heard, has affected so many men and women, and the drugs that need to be developed should be safe and effective.

The company is to be commended for its work in bringing this application forward. I want to also thank the FDA review team who was involved in this project--Paul Levine, Paul Flyer, David Hoberman, Hugo Gallo-Torres, Robert Prizont, John Senior, Justie Chowdhury, Ku Jong,

Liong Jo, Maria Izar, David Lee, and Ron Cavanaugh--for their work on this application.

I'd like to call your attention to one issue. In the safety assessment as presented by Glaxo Wellcome, there were three cases with a diagnosis of ischemic colitis. On Friday, the company informed FDA of an additional case of ischemic colitis and an alternative diagnosis of the original three cases as infectious colitis from E. coli 3157.

The company requested permission for this new data to be presented to you, and we felt this was important to provide the Committee with this opportunity to hear the new data. However, this new data has not been reviewed by FDA and we will not be able to comment on it. The final resolution of the cases and diagnoses will involve additional review of the data by FDA and our independent consultants. Nonetheless, we do believe the Committee comments that you have today will be valuable for us as part of our evaluation of these cases.

Thank you.

CHAIRMAN HANAUER: Thank you.

All right, we're ready to go. I'd like to invite Dr. John Wood to open up the proceedings from Glaxo Wellcome's standpoint.

DR. WOOD: Dr. Hanauer, Members of the Committee,

Ladies and Gentlemen, good morning. My name is John Wood. As Director of Therapeutic Development and Product Strategy at Glaxo Wellcome, I have worldwide responsibility for development of new agents to treat gastrointestinal diseases and metabolic diseases.

On behalf of Glaxo Wellcome, I'd like to thank you for the opportunity this morning to review alosetron, also known by its trade name Lotronex, in some detail with you. Lotronex is the first medicine to be developed to treat multiple symptoms of irritable bowel syndrome.

The specific indication for which we're seeking approval from the FDA is the treatment of irritable bowel syndrome in female patients whose predominant bowel symptom is diarrhea either alone or part of an alternating stool pattern. This description reflects the precise study group in our key pivotal trials.

Before discussing alosetron, I'd like to review briefly with you some aspects of irritable bowel syndrome. Irritable bowel syndrome is a chronic conditions whose primary features are recurrent abdominal pain and altered bowel function. It has been estimated to affect up to 15 to 20 percent of people here in the United States, and as such is one of the most common diagnosed conditions both by family practitioners and also by gastroenterologists. The condition is more common, as we heard earlier this morning,

in women than men, with an approximate female-to-male ratio of about two to one.

We've already had an eloquent description this morning of the devastating impact that this can have on patients' quality of life, so I won't elaborate on that any further. Despite this high prevalence of the condition, there is little in the way of current specific treatment for this syndrome, and thus there is a substantial unmet medical need in terms of the development of new agents to treat both diarrhea-predominant disease or, for that matter, constipation-predominant disease.

We tend to classify patients with irritable bowel syndrome as either diarrhea-predominant, constipation-predominant, or alternators, patients who alternate between the two extremes. I wouldn't like my simplistic diagram here to mislead you. This is really a spectrum of activity rather than three discreet trunks, if you will, which is simply a way that we use to classify this. The studies which form the part of our application really represent patients who are diarrhea-predominant and alternators, and in the design of our clinical trials we sought to exclude patients with constipation-predominant disease.

Members of the Committee, you will be aware from your briefing documents that alosetron is a new chemical entity. Pharmacologically, it's a selective and potent 5

hydroxytryptamine type 3 receptor antagonist. In animal models of visceral pain, it inhibits the visceral pain reflexes. In irritable bowel syndrome patients, it delays colonic transit by an effect on the distal colon. And in addition to this, it increases compliance in the colon. A study in healthy volunteers has shown that it also increases intestinal water and electrolyte absorption.

Our new drug application comprises two placebo-controlled pivotal studies and, in addition, supplementary information on two dose-ranging studies. This provides the body of data in support of efficacy outlined in your briefing document. In addition to this, we've submitted data from a 12-month ongoing safety study in support of additional safety data with respect to alosetron.

In the Phase III program, alosetron was found to improve irritable bowel syndrome pain and discomfort in both of the key pivotal studies, and also to lessen urgency of defecation, to reduce the frequency of defecation, and to improve stool consistency. Reviewing the entire safety database, it was found to be well tolerated. In support of these statements, Dr. Mange1 later this morning will provide detailed evidence in support of each of these statements.

This morning, we will address a series of presentations in the three initial presentations by external consultants, the first by Dr. Michael Gershon, Professor of

Anatomy and Cell Biology at the College of Physicians and Surgeons at Columbia University, in New York. He will talk to us on serotonin 5HT3 receptors and signaling in the gut.

Following that, Dr. Michael Camilleri, Professor of Medicine and Physiology at the Mayo Clinic, will talk about the pharmacologic rationale for the use of 5HT3 antagonism in the treatment of irritable bowel syndrome.

We'll then proceed to a presentation from Dr. Lin Chang, Co-Director of the Neurenteric Disease Program at UCLA, in Los Angeles. She'll talk on gender differences in GI physiology and disease.

And then Dr. Mangel, Director of Gastroenterology from our Research Division in Research Triangle Park, North Carolina, will talk about alosetron efficacy and safety. And Dr. Kay Washington will address specifically the four cases that were labeled as having ischemic colitis from a pathological perspective. Finally, I will summarize briefly the conclusions of our presentation.

Thank you, and I'll call upon Dr. Gershon.

CHAIRMAN HANAUER: Just for the Committee's--from our standpoint, the sponsors asked if we would hold questions until after these next three presentations, unless you have a really burning, specific issue, Dr. Laine.

DR. GERSHON: I thought I'd begin by telling you about the special nature of the enteric nervous system and

just review that with you, and to give you some idea of how serotonin is important in signaling within the system and how 5HT3 receptors affect that and how alosetron acts on that, and to give you a rationale for the use of alosetron in IBS.

So the enteric nervous system is unlike any other part of the peripheral nervous system because it is a complex and independent division of the autonomic nervous system. It's the only part of the peripheral nervous system that can mediate reflex activity even in the absence of input from the brain or spinal cord. Many of the enteric neurons receive no innervation, in fact, at all from the central nervous system, and it contains intrinsic primary afferent neurons, motor neurons and interneurons that let it do this job.

It has many neurotransmitters in over 40 different types of neuron within the system, making it, in complex, something that has been called by me, among other people, a second brain. The structure, in fact, resembles the central nervous system more than peripheral nerve, so that I like to think of it as the brain gone south. It has, in fact, no collagen, and it contains glia instead of Schwann cells, as does the brain. To make matters a little more complicated, there's yet another cell, the interstitial cell of Cajal, which is a mesodermal cell which is pacemaker cell that

interacts with the nerves and is important in innervating smooth muscle.

Now, to do the job of controlling what goes on within the bowel, the enteric nervous system must have information of what's going on in the lumen of the gut, and yet none of the nerves of the bowel actually penetrate into the lumen. A system has therefore evolved in order to detect what's in the lumen, and one of the most prominent cells of that system, which is a mucosal epithelial cell, is the EC cell, which is thought to be a pressure-sensitive sensory receptor.

The idea is that deformation or pressure causes ions to enters the cell. The depolarization leads to calcium entry and serotonin is released, not into the lumen of the gut but into the wall of the gut, where it can activate both intrinsic and extrinsic sensory nerve fibers or primary afferent fibers to initiate signaling, so that serotonin can initiate both secretory and peristaltic reflexes through this mechanism, and serotonin can also send signals to the brain.

Now, three receptor subtypes of serotonin--and there are up to 20 of them--have been shown to contribute to neuronal responses to serotonin within the gut. The 5HT3 receptor mediates a very fast response, during which the electrical conductance increases because it opens an ion

channel. The 5HT1A receptor response is often masked, but that's this decreasing response here which is hyperpolarizing. And then there's the 5HT1P receptor, which has not yet been cloned, which mediates this slow depolarization which has the opposite effect of the 5HT3, in that conductance decreases so that these responses to electrogenic stimulation become larger.

This slide shows you the difference in receptors that the gut uses to activate intrinsic and extrinsic primary afferent nerves, and for simplification the system is spread out in these two cartoons. So the enderochromaphin [ph] cell, as I've mentioned, releases serotonin. That activates intrinsic primary afferent neurons using 5HT1P or 5HT4 receptors. The primary afferent neuron is cholinergic and uses osteocoline or the peptide, calcitone and gene-related peptide, CGRP, to trigger reflexes in follower, second-order neurons. This is intrinsic signaling which initiates secretary and peristaltic reflexes within the gut.

The same serotonin released from the same set of cells can differentially activate extrinsic neurons, and on the cartoon this shows a dorsal root ganglia neuron projecting to the spinal cord, but equal number of fibers, or more, in fact, go up the vagus nerves to the brain. This signaling pathway sends noxious information from gut to the

central nervous system. I like to say the gut is an organ from which one never hopes to get a progress report.

In this slide--and it would help if the lights could be turned down a bit--you can see where the serotonin 5HT3 receptors are actually located. This is an immunocytochemical preparation, and you can see that the receptors are located in nerves that surround the crypts and villi of the gut. So this is a preparation in which you're looking down on the wall of the gut. The villi are coming out toward you and they are surrounded by the 5HT3 receptors on these nerves.

Let me draw your attention to the fact that the receptors are located only on the nerves around the villi, and that the vasculature within the villi and its smooth muscle and within the gut has no 5HT3 receptors on it at all. So the 5HT3 receptor is a ligand-gated ion channel, so that the ligand is 5HT. As it opens the channel, ions can flow across the receptor. That leads to depolarization very rapidly.

Now, the responses can be seen to 5HT here, and this is the 5HT3-mediated fast response as recorded from enteric submucosal neurons with a microelectrode. As you can see here, the electrogenic response is less because the ion current is flowing through the channel. It's a high conductance channel. Notice as alosetron is given, it

selectively and completely blocks that response, the 5HT3-mediated response, and the effect of alosetron is completely reversible. Those were responses to serotonin.

And so you can see with patch electrodes, also, that serotonin causes the flow of an inward current which has a rapid phase and then a fall-off, and that alosetron, concentration-dependently and reversibly, blocks that current flow. And you see that the response is nicely concentration-dependent.

The response is also selective. So you see the response to serotonin, the inward flow of current, is mimicked by nicotine, so that serotonin and nicotine, nicotine acting through an asteocholine [ph] nicotinic receptor, have similar responses. Hexamethonium completely blocks the effect of nicotine, but alosetron does not affect it. In contrast, alosetron inhibits the response to serotonin, but hexamethonium, which is a nicotinic antagonist, does not affect it.

So as a result, when we look with sharp electrodes, alosetron does not block the fast-depolarizing responses to nicotine at all, so that alosetron would be unlikely to affect cholinergic neurotransmission or signaling within the gut, and is therefore safe to administer to patients without fear of paralyzing the bowel.

And you see here, as predicted, alosetron, in

fact, does not affect the cholinergic fast EPSPs. The response can be seen here. This is the fast EPSP. That's a stimulus artifact, and you see that increasing concentrations even up to this massive concentration of alosetron has no effect on fast DPSPs. But since they are cholinergic, you see they are readily blocked by hexamethonium.

Now, to see how alosetron works in intact tissue, we've used this propulsion of a synthetic pellet in vitro to assay the peristaltic reflex. This propulsion of an artificial fecal pellet, colored appropriately brown, simply goes on for hours. And this is, you see, reproduction of ten trials, and you see that it moves at a constant rate reproducibly. That is abolished by tetrodotoxin and is nerve-dependent.

Now, alosetron completely fails to affect the peristaltic reflex in the guinea pig distal colon in concentrations up to 3 micromolar, so that as predicted, it's safe and does not block the intrinsic signaling pathway within the gut. However, if you artificially speed up the gut by adding 2-methyl-serotonin, which is a 5HT3 agonist, the pellet moves faster, and that is abolished by alosetron. So here you see the pellet moving faster because of 2-methyl-5HT, then settles down at that rate. And alosetron immediately brings it down to control levels.

So, in summary, what I've told you is that 5HT3 receptors are present on the terminals of extrinsic primary afferent nerves. Serotonin released from EC cells can activate those terminals and lead to signaling either through dorsal root ganglia to the spinal cord or to the brain via the vagus nerve. And these are noxious signals, Leading to nausea, bloating, or pain.

5HT, if it overflows, can also affect 5HT3 receptors which are present on motor neurons in the gut. These 5HT3 receptors are not innervated, so that no neurotransmission within the gut depends on those 5HT3 receptors. However, if serotonin overflows to reach those receptors, it can trigger painful evacuative contractions of the colon, and these can be blocked by alosetron which blocks that overflow stimulus.

5HT4 receptors and 5HT1P receptors are involved in intrinsic signaling by 5HT on the primary afferent neurons within the bowel. These are these red neurons here. Therefore, alosetron or 5HT3 antagonists can be given without fear of blocking the critical intrinsic signaling because it uses other receptors and can be used without fear of blocking neurotransmission in the gut because 5HT3 receptors are not involved in that. They are only involved in this emergency overflow mechanism.

Thank you.

CHAIRMAN HANAUER: The next speaker is Dr. Camilleri, from the Mayo Clinic.

DR. CAMILLERI: Good morning, Dr. Hanauer, Members of the Committee, Ladies and Gentlemen. My task this morning is to review for you the rationale for treatment of 'IBS with alosetron, a 5HT3 antagonist. The specific objectives which I hope to cover are the role of serotonin in disease, and I shall give examples of the role of serotonin in irritable bowel syndrome and in carcinoid diarrhea; and, secondly, to review the pharmacodynamic studies that provide the rationale for these 5HT3 antagonists in IBS, specifically the effects on motility, secretion, and sensation.

In a recently published study from Mike Farthing's group in Britain, it was demonstrated that patients with irritable bowel syndrome have post-prandial 5HT levels which are higher than those of healthy controls. Now, the prototype disease that is associated with high pre- and post-prandial levels of 5HT in the circulation is carcinoid diarrhea. This is a severe diarrhea that is associated with a neuroendocrine tumor in which the tumor produces a large amount of serotonin, among other transmitters, and this serotonin spills over into the peripheral plasma and has effect on the way in which the bowel functions.

Indeed, in order to study these patients, we had

to develop some novel methodology that allows us to objectively quantify the changes in motor function in the gastrointestinal tract. These novel methodologies are summarized in this slide. Using a gamma camera, and therefore a non-invasive technique, we are able to radio-label a meal and watch and quantitate the rate of emptying from the stomach and from the small intestine of that radio-labeled meal.

At the same time, we provide a different isotope delivered to the distal small intestine in a special methacrylate-coated polymer which dissolves in the distal small intestine, thereby liberating isotope, which then gives us an image of the content moving through the different segments of the colon. And on the next slide you will see that we have illustrated on an actual scan the proportion of isotope in different segments of the colon.

So here's an example of a patient who has carcinoid diarrhea, and we're seeing the isotope located in the different sections of the colon. This isotope is located in the descending colon about one hour after the meal was ingested. Two hours later, most of that isotope has not reached the rectum and is ready for expulsion because of a significant diarrhea.

Now, this is a process that would normally would take between 25 and 35 hours, and I would emphasize the

point that this has occurred in about 3 hours. Therefore, carcinoid diarrhea is associated with rapid emptying of the proximal colon. Quantitative data show that this rate of emptying is about six times that of healthy controls. We also see on this slide that the small bowel transit time is reduced partly as a result of a stimulation of motor function and partly because of the hyper secretion of fluid and electrolytes into the intestine as a result of the serotonin stimulation in the small intestine of these patients.

I would like now to review briefly the pharmacodynamic studies in humans that suggest that the 5HT3 approach would relieve diarrhea and pain, specifically through changes in motor function, fluid and electrolyte absorption, and changes in sensation. Let's first concentrate on the effects of alosetron on motility.

In a study performed by Whorwell and his colleagues in Manchester, United Kingdom, alosetron effect on colonic transit was evaluated in 12 patients with irritable bowel syndrome. This was a randomized double-blind placebo-controlled crossover study in which the dose of 2 milligrams twice a day of alosetron was evaluated. The method used to evaluate transit involved a common and well-validated system, which is the radiopaque marker transit method. Note here that the alosetron treatment was

associated with an increase in the colonic transit time, and that this was predominantly an effect on the left side of the colon.

In studies that we have performed at Mayo Clinic on the effect of alosetron on colonic transit and other parameters in carcinoid diarrhea, we have noted that an increase in the dosage of alosetron, .5 milligrams twice a day to 2 milligrams twice a day, results in a significant three-fold to four-fold reduction in the rate of emptying of the proximal colon. This is associated with a trend in the reduction of 24-hour stool weight in the patients with carcinoid diarrhea.

One of the secondary parameters that we evaluated in that clinical study which consisted of three weeks of treatment with alosetron was to determined the number of tablets of Loperamide that were required as rescue for the control of diarrhea. In patients with carcinoid diarrhea, diarrhea so severe that the patients need to carry an anti-diarrheal with them--and we quantified the number of Loperamide tablets used in this three-week period of time.

Notice in this graph that we have tabulated the cumulative percentage of patients who required equal to or more than five tablets of Loperamide over this three-week period. Notice also that the proportion of patients requiring rescue with Loperamide decreases with increasing

dosage of alosetron in this three-week trial.

What about fluid and electrolyte secretion? In a classical methodology study, Farthing's group has performed triple lumen profusion studies using a 30-centimeter isolated jejunal segment with occluding balloons at each end and the classical marker 14carbon-PEG 4000 as a marker of fluid and electrolyte flux.

Notice that absorption is above the zero line and secretion is below the zero line for both fluid flux and sodium flux. Normally, the small intestine is in a state of absorption for both sodium and for water, as shown by the boar and whisker plot in yellow. Alosetron resulted in an increase in the fluid flux and sodium flux in the absorptive sense, therefore suggesting that alosetron would have an effect in facilitating greater absorption of water and salts in the small intestine in humans.

Finally, let us review briefly some of the studies Looking at the effect of alosetron on sensation. In this study by Michel Delvaux and his colleagues, in Toulouse, France, the colon sensation was evaluated by means of a balloon which was placed inside the left part of the colon. Now, in these experiments the volume in order to induce perception of this distension stimulus and the volume to induce a sensation of pain in response to distension is being recorded and monitored to evaluate the threshold for

sensation.

Note that alosetron at these two dosages studied resulted in an increase in the volume to reach perception and an increase in the volume to reach pain threshold, suggesting that the sensitivity of the bowel was being reduced by that treatment. This study, incidentally, was performed in patients with irritable bowel syndrome.

Part of the effect of that change in threshold, that increase in threshold in response to alosetron can be explained by a change in the compliance of the colon. Here, there's an increase in pressure imposed on that segment of colon that is being evaluated. The volume of that segment of colon measured by means of this intracolonic balloon is increased, suggesting that the colon is more compliant; it is able to accommodate a greater volume, for instance, from gas in this case, but presumably also from more solid or liquid components of colonic residue or content.

So, in summary, you've heard that 5HT3 receptors are involved in visceral sensory, secretory, and motor processes in the gastrointestinal tract. Alosetron, which is a selective and potent 5HT3 receptor antagonist, decreases sensitivity to colonic distension, enhances jejunal water and sodium absorption, and slows colonic transit.

I thank you for your attention.

CHAIRMAN HANAUER: Thank you.

The last of the first series of speakers on behalf of Glaxo is Dr. Lin Chang, from UCLA.

DR. CHANG: Good morning. I'm going to speak today about gender differences in gastrointestinal physiology and disease, and particularly focus on irritable bowel syndrome, or IBS.

As you heard earlier from Dr. Wood, irritable bowel syndrome is predominantly seen in females. And there are other chronic pain disorders that are also seen in females more often than in males, and these include chronic constipation, fibromyalgia, chronic fatigue syndrome, interstitial cystitis, migraine headaches, and temporal mandibular joint disorder. These pain disorders share common clinical characteristics and can typically overlap in the same patient, and it has been hypothesized that these chronic pain disorders share a common etiology.

Before I review the gender differences in physiology, I wanted just to review the dimensions of the response to a painful or noxious stimulus. These dimensions include sensory ratings which measure the intensity of a stimulus, affective ratings which measure unpleasantness of a stimulus. There's cognitive, evaluative, physiological and behavioral responses that all contribute to the pain experience.

What I'm going to do today is review gender differences in various physiologic studies. That's going to include visceral distension studies in IBS patients, as well as healthy controls, and the responses to this visceral distention mainly by rectal discomfort thresholds, subjective perceptual ratings at the sensoral and affective ratings, autonomic responses to visceral distension, and brain activation using a neural imaging technique called positron emission tomography, or PET. I'm also going to review gender differences in colon transit times, as well as serotonin synthesis in the brain.

This is a study that we conducted at UCLA where we measured rectal perception to phasal rectal distention using a barostat device, which is a computerized distention device which measures volume pressure simultaneously. And what you can see on the y axis is discomfort thresholds, which is the pressure in the rectum at which point the patient feels discomfort. And we measured rectal perceptual thresholds in normal individuals, as well as in patients with IBS, and what you can see is that the mean discomfort threshold for IBS subjects is significantly lower as compared to healthy control subjects. In general, discomfort thresholds under 10 millimeters of mercury are considered hypersensitive.

Now, when we compared the rectal discomfort thresholds in IBS males and IBS females, even though the IBS

group was lower than the healthy controls, we found that the IBS females had a significantly lower discomfort threshold, mean discomfort threshold, compared to IBS males.

When we evaluated gender differences of rectal perception by unpleasantness and intensity ratings in IBS males and females using a visual analog scale, we found that IBS males and females rated the rectal distention similarly as far as intensity, but the IBS females rated the stimulus as more unpleasant than the IBS males.

We also, in addition to looking at perceptual responses, evaluated autonomic responses to rectal distention. This is a measure of heart rate variability area ratio, which is a measure of cardiosympathetic/parasympathetic ratio, and we compared males and IBS females. We performed this at three time points, one at baseline before any intervention is performed. The green lines show following balloon placement and the yellow line shows the heart rate variability in response to a rectal distention, which we call the tracking paradigm. And as you can see, the males in IBS have a significantly higher cardiosympathetic, parasympathetic balance compared to the IBS females.

Another measurement of autonomic response is skin conductance, which is the measurement of sympathetic arousal. We compared IBS males and females, again at the

three same time points as shown in the previous slide, and we found that IBS males have a significantly higher sympathetic arousal than IBS females.

Now, in addition to these perceptual differences, as well as autonomic responses, we wanted to look at superspinal processes and determine if there were gender differences in brain activation patterns in response to a rectal distention stimulus. What you see here is brain activation in yellow for the IBS males and in pink for the females. These areas are superimposed on an MRI at the same level, and here on the third panel you can see a combined Eigure.

There were different areas of activation in response to a 45-millimeter rectal stimulus. In particular, CBS males had a significantly greater activation in the insula compared to IBS females, and the insula is thought to play a role in antinociceptive and autonomic responses.

Now, gender differences have also been evaluated in colon transit studies. There's been multiple studies and three of these studies found that mean colon transit times measures by radiopaque sitz [ph] markers were shorter in men than in women, particularly in the right colon. However, there were two other studies that found no difference in transit times, although they tended to be shorter in the males than in females, similar to these three studies.

The effect of menstrual cycle was also evaluated in colon transit studies in healthy males and females, and they found that colon transit times were slightly shorter in the follicular phase compared to the luteal phase, but that it was not significantly different.

So the possible neurobiological mechanisms that may underlie these gender differences include female sex hormone-dependent differences in central opioid systems and gender differences in central serotonergic systems. Now, for this presentation I was just going to review gender differences in central serotonergic systems.

Raphe nuclei in the brain stem are a major source of ascending and descending serotonergic projections. The ascending serotonergic projections play a role in regulation of prefrontal and anterior singular cortex, central autonomic regulation, and mood. Descending serotonergic systems play a central role in descending pain and modulation systems.

There was a study that showed gender differences in serotonin synthesis rates in healthy males and females. They measured serotonin synthesis in the brain before and after tryptophan depletion. And tryptophan is a precursor of serotonin, and it is thought that if you fed a subject a tryptophan-depleted amino acid diet, serotonin synthesis rates would decline in the brain.

They found at baseline males had a 50-percent higher serotonin synthesis compared to females. Now, following tryptophan depletion, males had only a 9-fold decline in serotonin synthesis, compared to a 40-fold decline in females.

This figures shows the rates of serotonin synthesis in a male subject and a female subject. They are taking it at the same level. These are PET images, and the MRI shows the level at which these PET images were taken. And you can see the color-coded bar. The red and yellow areas show a higher rate of serotonin synthesis as compared to the blue areas. And you can see that, at baseline, the males have a greater rate of serotonin synthesis compared to females, and again the same finding after tryptophan depletion.

Now, the serotonin synthesis rates are easier to measure in the brain than in the periphery because of the higher levels, and these gender differences in serotonin synthesis rates in the brain may reflect gender differences in serotonin in the periphery.

Potential mechanisms of gender differences in visceral perception, as has been summarized in this presentation, include differences in CNS networks that integrate and process nociceptive information, specifically regional brain activation in insular and perhaps the

anterior singular cortex and periaqueductal gray, and rates of serotonin synthesis.

So, in summary, IBS and other associated conditions are more common in women. There are gender differences in rectal discomfort thresholds and in unpleasantness ratings. There may also be gender differences in colon transit. And there also appears to be gender differences in CNS networks which play a role in antinociception and autonomic responses.

Thank you.

CHAIRMAN HANAUER: Thank you.

Can we have the lights up, please?

And I'd like to open up this phase of the discussion to the panel for questions. I'm going to begin, actually, in that case.

Dr. Gershon, what has been presented as far as the effects of alosetron have been primarily motility and decreases in compliance. Yet, Dr. Camilleri discusses aspects of secretion that seem to not be accounted for by your description of the effect of 5HT3. Can you comment on that?

DR. GERSHON: Yes, I'd be happy to. Serotonin is involved in signaling both for secretory and peristaltic reflexes. If motility increases in the gut, then secretion will increase because there will be less time for fluid to

be absorbed from the gut. There is no evidence that 5HT3 receptors are involved in the intrinsic pathways that lead to secretion directly, so that the effects are likely to be due on secretion as the secretion absorption balance due to the effects on motility.

CHAIRMAN HANAUER: And while you're up there, a follow-up is that we are presented with data on the segmental nature of alosetron's effect, primarily in the left colon. Would you explain why it's regional?

DR. GERSHON: 5HT3 receptors are not in any way distributed preferentially as far as anyone has been able to tell. So there is not a basic distributional difference that would underlie that. On the other hand, the left side of the colon has a much more extensive afferent innervation than does the right side of the colon, and therefore because of the innervation might be expected to be more affected by 5HT and by 5HT3 antagonists.

There's actually quite a surprising difference if you look at the total number of afferent neurons in the colon regionally. The large intestine, for reasons that have not been clear physiologically, has almost as many neurons in it as the small bowel, and most of those are on the left side.

CHAIRMAN HANAUER: Other questions from the Committee?

Dr. Wald?

DR. WALD: This is addressed to Dr. Chang, who I think has convinced me that there are important differences between men and women with her data. Are the studies which have shown visceral hyperalgesia in irritable bowel really a gender-related issue? In other words, according to the data that you may be presenting here, it appears that there are not important differences between the male IBS and the control subjects. Has that been your experience or am I misreading the data?

DR. CHANG: Well, the greatest difference that you see is between IBS subjects, in general, and the healthy controls, and you see smaller differences between the IBS males and IBS females. Now, part of that might have to do with bowel habit because you see more constipated females than constipated males. So we're still evaluating if part of that difference has to do with bowel habit as opposed to just completely gender. But you do see gender differences, but it is--the greatest difference is just between the IBS group and the healthy controls. There is differences between IBS males and healthy males, but there's greater differences between the females.

CHAIRMAN HANAUER: Dr. Houn?

DR. HOUN: Could you tell us how many people were in those studies of rectal perception, as well as the

serotonin synthesis rate?

DR. CHANG: Yes. Our perception is about 90-some subjects for IBS and about in the 40s for the healthy control subjects. For the serotonin synthesis study, that was eight healthy males and seven females.

CHAIRMAN HANAUER: Could one of you comment on the potential interaction of cigarette smoking because of the effect of nicotinic receptors with alosetron? Michael?

DR. GERSHON: The data that we have indicates that the 5HT3 receptor and the nicotinic asteocholine receptor are completely different, so that nicotine, which can not only stimulate the cholinergic nicotinic receptor but also desensitize it, has no effect at all on 5HT3 receptors. And alosetron has no effect on the nicotinic asteocholine receptors, so that my prediction would be that whereas the effects of cigarette smoking would necessarily be bad, they are not bad for this reason.

CHAIRMAN HANAUER: Dr. Wald?

DR. WALD: This is a general question either for Dr. Camilleri or Dr. Chang. An issue has been raised in terms of the mechanisms by which visceral hyperalgesia occurs in people. And broadly speaking, there's been an issue of whether it's a biologic phenomenon or whether it's a psychological phenomenon, and I think Whitehead and Paulson recently summarized that quite nicely in an article

about a year ago, Michael, that you probably reviewed.

How do the data reconcile in terms of gender differences as well as irritable bowel, and is there evidence of different responses, for example, hypervigilance and such, as a gender-related phenomenon?

DR. CHANG: I would say that as far as the pain perception in IBS subjects, there's a contribution from hypersensitivity of afferents and the inactivation of pain inhibition systems or accentuation of pain facilitation systems. But I think there's definitely a contribution of hypervigilance, and we've looked at those some of those factors in males and females with IBS and we found that the IBS females tend to have a lot more extraintestinal symptoms and may have more adverse reactions or sensitivity to medications and other types of symptoms that may suggest that they have hypervigilance.

But I think it probably is seen in both IBS males and females, but there may be a suggestion that it's a little more predominant in females. But I definitely think that there's a physiologic component to IBS, but there's also contributions on psychological factors because it has been shown that physical and psychological stressors can influence IBS symptoms, probably specifically by acting on the emotional motor system and then contributing to the physiologic output of the antinociceptive system, the

neuroendocrine system, and the autonomic system.

DR. CAMILLERI: I would just add a minor comment, and I think that the role of hypervigilance is not one that should be underemphasized. Experimental studies demonstrate that in the presence of mental stress, the sensation of distention stimuli in the bowel is increased. On the other hand, in experiments that were performed with relaxation of the individual, the same sensation scores were again tested and they were dramatically decreased.

And I think some of the elegant imaging studies of the brain during rectal distention stimuli particularly from the UCLA cure group demonstrates this activation the dorsal lateral prefrontal cortex, which I think is a preeminent center pertaining to vigilance. So I think that there is an important supertentorial [ph] component to the hypersensitivity, as you suggest in your question.

DR. GERSHON: Can I just add one point?

CHAIRMAN HANAUER: Sure, Dr. Gershon, please.

DR. GERSHON: I think it also should be pointed out that if you continually stimulate a pain pathway, it's possible to induce hypersensitivity to pain, so that if you can interrupt that at the source of stimulation, you can dehypersensitize the pain pathway, so that both through a peripheral mechanism and through central mechanisms you can lead to visceral hypersensitivity. And it might be helpful

to get at the cause of the pain in the first place and reduce the symptoms in that way.

CHAIRMAN HANAUER: Dr. Wilson?

DR. WILSON: I have a question for Dr. Chang. You mentioned other disorders with a female prevalence, pain disorders. Do you have any brief commentary on serotonin studies and the potential for serotonin antagonism in these disorders?

DR. CHANG: I know there's a study where they had., I think--they had lower levels of serotonin in the CSF and Eibermyalgia. I don't think that extended to chronic Eatigue, but they've measured, I think, increased substance p and another factor which I can't recall at this point in the fibermyalgia subjects. But they haven't measured serotonin synthesis rates or other of these studies in these other groups.

DR. WILSON: Any PET scan data?

DR. CHANG: The only one that I know on chronic Eatigue is a spec scan and that was just done at baseline. It wasn't in response to any stimulus.

DR. WILSON: Thank you.

CHAIRMAN HANAUER: The question to that last answer was is there any PET scan data.

Dr. Ferry?

DR. FERRY: My question is related to any

differences in age, and I'm thinking specifically in really younger-age patients in these receptors or the responses, or anything known at all?

DR. GERSHON: We've actually looked in animals at the development of 5HT receptors of different types in the gut, and the 5HT3 receptor is relatively late in terms of its development and it is not present in the fetal gut, for example, in mice and rats. It develops after birth, so that responses to alosetron would not be expected during development.

DR. RACZKOWSKI: My question has to do with what is known about the effects of any of the 5HT3 antagonists on the vasculature of the gut, whether there might be an effect on blood flow or basal constriction or basal dilation.

DR. GERSHON: 5HT3 receptors are not present on the smooth muscle of the vasculature of the gut. Studies have been done by Dr. Sanders, who is here, which have shown that 5HT3 antagonists and 5HT3 receptors don't affect the vascular smooth muscle in the gut. There's no reason to believe that they would. The receptors simply are not there.

DR. GALLO-TORRES: A question for Dr. Camilleri. You concentrated your remarks on the colon. After all, the disease is to be called irritable colon. Could you briefly summarize data on motility of the whole intestinal tract and

stomach, the esophageal areas, and so on, please?

DR. CAMILLERI: Yes, thank you, Dr. Gallo-Torres. There have been some studies that have looked at the effects of 5HT3 antagonists in different regions of the gastrointestinal tract. From my recollection, there are no effects on esophageal or lower esophageal sphincter function. Some 5HT antagonists change the gastric compliance, making gastric compliance greater, just like the colon was shown on that slide.

There was one study performed by Mike Kamm [ph] in London, England, that did not find such an effect of alosetron on the compliance of the stomach. I am not aware of studies looking at motor function or transit in the stomach or small intestine, although some of those studies are ongoing at the present time.

In the slide that I showed you from Dr. Whorwell's laboratory in England, there was an attempt to assess the orosecal [ph] transit time using a baked bean substrait and hydrogen excretion in the breast, which is a standard, pretty well-established technique to measure orosecal transit time, and alosetron in those IBS patients had no significant effect on orosecal transit. It was for those reasons that I focused my comments on the colon in view of the fact that the data to date do not suggest that there is any motor effect on stomach or small intestine.

DR. GALLO-TORRES: Thank you.

DR. HOUN: Can you describe if there are any active metabolites that may affect vasculature in the colonic system?

CHAIRMAN HANAUER: Obviously, everyone is because of the potential of ischemia, whether or not it's eventually defined as ischemia, and we're all asking very specific questions focusing on primary effects on the smooth muscle. But we've seen that this is a very complicated organ system with secondary effects along the lines of secretion and motility. Can you consider any secondary effects that may affect any predisposition to reduced blood flow?

DR. KOCH: If I could, before we get to that, I just wanted to add there is an active metabolite in alosetron 6 hydroxy, but--

CHAIRMAN HANAUER: Introduce yourself.

DR. KOCH: Sorry. Kevin Koch, from Glaxo Wellcome.

There is an active metabolite of alosetron 6 hydroxy metabolite, and it has about equal potency with the parent drug at the 5HT3 receptor. We don't see any appreciable levels of it in plasma when we dose the drug, if that answers the question.

DR. GALLO-TORRES: Since he's there, maybe I can

ısk a question. I think the question of interest is is :here a metabolite produced by the intestinal flora, either ı modification with the parent compound or the metabolite, a :olonic event, if you will.

DR. KOCH: We would not have data to address where :he metabolite is formed, no.

DR. CAMILLERI: I'll try to address to the best of ıy knowledge the question that Dr. Hanauer is posing, and :hat is is there another physiological effect, for instance, ›n compliance or motor function of the colon that could :onceivably change the vascular flow to the mucosa. And in ıy opinion, it will be very difficult to conceive of such, ›earing in mind the magnitude of the changes in compliance ınd tone that we see with alosetron and other 5HT3 tntagonists that are available for experimentation, so that :he change in compliance itself is unlikely to act as a leans to cut down the flow of blood to the mucosa which ›ould then be presumably one potential mechanism one would :onsider in relation to the so-called ischemic episodes,

CHAIRMAN HANAUER: Dr. Senior?

DR. SENIOR: Dr. Camilleri or Dr. Chang, you've nentioned that there are clearly some gender-specific ›sychological differences. Can you comment on whether you :hink these are nature or nurture? Is it because men are made differently than women or they are trained differently

in their upbringing to be more vigilant, as you say, to discomforts?

DR. CHANG: I think that's difficult to answer, and I'm sure that it's both nature and nurture. In somatic pain studies, they have shown that part of the reason there may be gender differences is because women are more likely to have an ability to report pain, as opposed to males. So I'm sure that extends to this pain as well. But I think as far as the contributing factors, I think it's for both, and I definitely think that there are different ways that males and females are raised and I'm sure that does contribute to part of the whole syndrome and the fact that these pain disorders are more prevalent in women.

CHAIRMAN HANAUER: Dr. Talarico, unless there are other--

DR. GERSHON: I wanted to just return briefly to the question that you posed before because I think it's an important one, and that is about whether the 5HT3 antagonist might in some way affect the vasculature. Every time I think about that issue, I come up thinking it might actually be protective against some of the phenomena that occur in IBS.

For example, these giant, massive migrating contractions of the colon which occur in IBS and can be induced, as Bill Chey [ph] has shown, in patients with IBS

with CCK administration, can be associated with occlusion of vessels because of the contraction. And those are completely abolished by alosetron, so I don't see how alosetron would be causing the problem, but it might be being given in a setting in which that problem exists.

CHAIRMANHANAUER: Dr. Talarico?

DR. TALARICO: As I understand, irritable bowel syndrome improves with age, and I would like to know how much of this is dependent on outside factors, cultural, environmental, under than changing in the physiology of the GI tract or drug.

DR. CAMILLERI: Dr. Talarico, the question of age and irritable bowel I think is still not completely settled. In fact, recent publications within the last couple of years suggest that the prevalence of irritable bowel syndrome among people over the age of 65 is similar, between 15 and 20 percent, to that which is documented in younger adults.

Whether individual patients over the years get less symptomatic when they go from younger adulthood to older adulthood is a question which I think has never been proven in a prospective follow-up. But I think one of the perceptions from more recent epidemiologic studies in the United States is that the prevalence actually continues to be the same over the age of 65 as it does under the age of 65.

Whether a reduction in sensation or muscle tone in some of the processes, for instance, in evacuation ameliorate with age or there is a reduced spasticity of the pelvic floor, resulting in less constipation, is hypothetical, but has never been proven.

DR. GERSHON: There is a major loss of enteric neurons with age, and so that might lead to a loss of symptoms simply because of the less of an effector organ able to respond.

CHAIRMAN HANAUER: Dr. Gershon, while you are up there, Dr. Camilleri suggested that other 5HT3 antagonists may have differential effects on the stomach and segmental portions of the digestive tract. Are we going to anticipate that we're going to see specific localized effects with other formulations?

DR. GERSHON: I think there are differences between the 5HT3 antagonists in terms of off rates from the receptors in terms of potency, but I don't think that you're going to, to answer your question, see differential effects along the GI tract.

CHAIRMAN HANAUER: They are all going to be confined primarily to the colon and not affect the stomach or small intestine?

DR. GERSHON: I didn't say that.

CHAIRMAN HANAUER: Can you explain that?

DR. GERSHON: Can I explain--

CHAIRMAN HANAUER: Why alosetron is primarily affecting the left colon by inhibiting 5HT3, whereas other products might affect the stomach or small intestine more.

DR. GERSHON: I don't think the other products affect the small intestine more. I don't think there's any evidence that other products affect the other parts of the GI tract more. I think that I tried to explain as best I could your question before on the basis of the intense innervation of the colon, saying that it would be more subject to problem and therefore affected by the drug in relieving the problem.

However, I don't know of any evidence that this-- unless Dr. Camilleri does.

DR. CAMILLERI: Well, I think we have to be aware that there has been opportunity to study other 5HT3 antagonists in different organs and different sites for a Longer period of time than we've had with alosetron. And so I did quote the one study that up to now has not been able to demonstrate an effect on tone or compliance in the stomach using alosetron. So the Chairperson's comment is absolutely right. On the basis of the current knowledge, it appears that one 5HT3 antagonist has an effect on the stomach, whereas another doesn't.

However, I do want to come back to correct a

misconception which seems to be going on, and that is that the transit effects of alosetron are restricted to the left side of the colon. If you'll notice in the experiments that I showed on carcinoid diarrhea, in fact, it was the right side of the colon, the proximal colon, the ascending and transverse, which appeared to be accelerated and which were normalized virtually by means of alosetron. So alosetron does have an effect on the emptying of the right side and the transverse colon.

I think that we are currently doing studies using the same more sensitive technique to evaluate proximal colonic emptying in patients with irritable bowel syndrome, and we are actually already noting that there is an effect in such patients when we use the scintigraphic technique rather than the perhaps less sensitive radio PEC marker technique in detecting proximal colonic emptying.

CHAIRMAN HANAUER: But I still want to know why there are going to be different effects on the stomach then.

DR. CAMILLERI: I'm not convinced there are going to be different effects. I think we just need to do more studies to determine whether it's a question of dose, means of administration, endpoint that is evaluated, et cetera. So I would keep an open mind as to whether there are different effects by the different 5HT3 antagonists.

CHAIRMAN HANAUER: Dr. Geller, then Dr. Wilson.

DR. GELLER: Dr. Chang, some of your slides addressed males versus females, and some males versus females with IBS. And I was interested in whether some of the studies which you quoted about IBS had also been done in normals, specifically heart rate variability, skin conductance, rectal distention. Do the results hold in normals as in IBS?

DR. CHANG: Yes. I showed actually for rectal distention studies in normals and they have a significantly higher discomfort threshold compared to IBS. That was my first figure slide. As far as the autonomic responses, we've looked at the heart rate variability as well as skin conductance in normals and the males and females are fairly similar, the healthy males and females. And the IBS females look a little closer to the normals. It's the IBS males that seem to be much more different, where they have greater cardiosympathetic and skin conductance, which is also a sympathetic arousal. But that's mainly in IBS males with alternating or diarrhea predominance.

DR. WILSON: For Dr. Camilleri, again, getting back to the question of gut versus blood flow, do you feel that there could be any distention of the right colon with increase in intracolonic pressures adequate to decrease gut mucosal blood flow as a mechanism similar to that sometimes seen in pseudo-obstruction of the colon?

MR. CAMILLERI: Yes. Dr. Wilson, the question is a very pertinent one. When one looks at the pressures achieved and the volumes achieved in the compliance curve, they are really quite artificial relative to the normal extant pressures and volumes of a non-dilated bowel. Your point is well taken that in the context of a large dilatation of the bowel such as many occur in mega colon, it is conceivable that those pressures then may be such that there would be a change in the mucosal blood which could have an effect.

And we know, in fact, even without any medication on board, some patients with mega colon can have mucosal necrosis. So I wonder whether the pathologist data would also address this question for you, but it is conceivable that in a massively dilated colon this needs to be examined, particularly to look at blood flow in response to 5HT3 antagonists.

CHAIRMAN HANAUER: Dr. Berardi?

DR. BERARDI: Dr. Chang, can you comment on any differences that might exist with regard to 5HT3 or serotonin in women with or without menses?

DR. CHANG: Actually, Dr. Mange1 will present the effect of the menses on the response to alosetron, so I'll let him do that. But there was no significance differences in colon transit in healthy women depending on their

menstrual cycle. So I'll let him comment on that.

CHAIRMAN HANAUER: Well, what about IBS patients according to their menstrual cycle?

DR. CHANG: There have been some reports that at the onset of menses IBS symptoms are worse. They have more pain, looser stools. So there are several studies that have shown that by patient report. I know that they have done--there's only one study that wasn't that well conducted as far as thresholds in IBS subjects at the different times of their menses and they didn't find really any differences.

But it's difficult to do that study because you have to make sure that you have the right phase, and every woman is different so you basically have to check their LH surge everyday. So those types of studies have not been well-conducted yet.

DR. BERARDI: What about pre- or post-menopausal women?

DR. CHANG: As far as the, what, alosetron or--

CHAIRMAN HANAUER: Changes in IBS, the motility changes or symptomatic changes.

DR. CHANG: As far as colon transit, which is the only measurement of motility that I know that they looked at pre- and post-menopausal--and Dr. Wald might know this better than me, but I don't think that there was any differences. And I don't think there's differences--and Dr.

Camilleri might correct me--in the symptoms of pre- and post-menopausal women.

DR. WALD: I just had a question for Dr. Camilleri. We talk about diarrhea-predominant, constipation-predominant, and mixed irritable bowel. Do you know of any studies in terms of either colonic transit or motility or visceral sensation that would allow us to distinguish among these groups from a physiological standpoint?

DR. CAMILLERI: The studies that have been done really haven't included enough of the people in the middle to really allow us to determine whether a physiological endpoint such as transit of visceral sensitivity parameters would constitute a sufficient surrogate marker to separate the two. I can quote data from patients with constipation-predominant irritable bowel or diarrhea-predominant irritable bowel that have been demonstrated to have effect on transit, and you are obviously very well aware of those.

We also know that among patients with rectal hypersensitivity, certainly there tends to be a greater proportion of patients with hypersensitivity who have rectal urgency or diarrhea. However, there are patients also in the constipation group that also have been shown to have lower thresholds.

DR. WALD: The reason I'm bringing this up is one

of the reviewers--I think Dr. Prizont--mentioned the issue of diarrhea and how we define diarrhea-predominant or are they simply non-constipated. And even in the diarrhea-predominant irritable bowel patients, you have periods of relative normalcy, sometimes even constipation.

Does this represent a shift in what's going on in the colon or the intestine, and would we expect to see physiologic changes in that group, and what is diarrhea-predominant irritable bowel?

DR. CAMILLERI: Which of those 15 questions would you like me to address first, Doctor?

DR. WALD: Oh, any one.

DR. CAMILLERI: I certainly believe that if we had a simple non-invasive surrogate measure for the transit in the bowel, for example, it would be possible to look at the fluctuations in motor function as evidenced by transit. The question is up to now there hasn't been such an easily available, repeatable, low-radio-isotope-exposure method to do so.

Certainly, the symptomatology of patients, as you say, does fluctuate, and I think as we will see when Dr. Mangel gives his presentation, in the context of this particular set of clinical trials there was some special attention given to identifying patients at the time when they have diarrhea predominance, or at least no

constipation, in order to make sure that there is no floor effect which would confound the clinical trials. So at the present time, the best surrogate we have is the assessment of the symptoms and that is what we'll use to facilitate the focusing of this particular study population.

CHAIRMAN HANAUER: Dr. Senior?

DR. SENIOR: Don't go away, Dr. Camilleri. You mentioned other drugs and, of course, we know ondansetron was the first drug of this class, and this alosetron is an analog really. Ondansetron is, of course, approved for nausea and vomiting of chemotherapy and post-operatively. Does ondansetron affect gastric emptying to slow it or increase it, and does ondansetron have any effect on the colon motility?

DR. CAMILLERI: That's very perceptive of you to ask that question, Dr. Senior, because I did the studies that showed ondansetron has an effect experimentally on the colonic response to feeding a meal. So after we eat a meal, the colon produces a major contractile response and this can be reduced in healthy people, and it can also be normalized in patients with carcinoid diarrhea. So, yes, other 5HT3 approaches are able to influence this reflex colonic response to the ingestion of a meal.

There are also data in the literature that suggest that ondansetron can affect the compliance of the stomach

and the tone after ingestion of a meal. And I think, as you're indicating, probably more studies can be done to further characterize the effect of alosetron.

CHAIRMAN HANAUER: For Dr. Gershon, regarding the gender differences, do you think that these are primarily central or are there peripheral, second-brain implications of gender?

DR. GERSHON: It's impossible for me to answer that question adequately because there have been to date no questions addressing gender differences in the second brain, in the enteric nervous system. There will be soon when I get back to the laboratory, but at the moment there have not been. But there is one thing that has been demonstrated, and that is one of the backup transporters that is up-regulated when the serotonin transporter is knocked out is sensitive to estradiol. And it's purely speculative to know whether that explains any of this, but I could go through a scenario with you, but it would be hypothetical.

CHAIRMAN HANAUER: Dr. Prizont?

DR. PRIZONT: A question to Dr. Camilleri. You mentioned the effect of alosetron on calcinoid diarrhea, which is an example of extreme serotonin production. Do you have any examples of other actions of alosetron on other types of specific or non-specific diarrhea?

DR. CAMILLERI: Well, the only other one that I

know has been studied is its relation to the irritable bowel, and we'll be hearing about that. So I'm afraid I have not studied it and I don't know of any other studies with alosetron in other diarrhea1 diseases, but perhaps somebody else knows the answer to that question.

DR. WOOD: I don't think we've studied it in-- [inaudible].

DR. PRIZONT: I was referring to more specific infections, like cholera diarrhea or E. coli diarrhea or Shigella diarrhea or salmonella diarrhea.

DR. MANGEL: We have not, Dr. Prizont. Dr. Prizont, the only other study, and the study is ongoing, is that we're evaluating alosetron with individuals with dumping syndrome, post-gastrectomy diarrhea, and that study is ongoing at present.

CHAIRMAN HANAUER: And that was Dr. Mange1 who just spoke.

Other questions from the Committee?

I think it would be most prudent if we took a ten-minute coffee break at this point before going into the more lengthy discussion of the clinical trials. So we'll resume in ten minutes, please.

[Recess.]

CHAIRMAN HANAUER: This process proves the point that there is no such thing as a ten-minute break, but I'd

like to get the proceedings moving and invite Dr. Mange1 up to begin his presentation.

Thank you.

Can I ask you to cease the discussion in the back even if you're not going to sit down? Thank you.

DR. MANGEL: Dr. Hanauer, Members of the Advisory Committee, Members of the Reviewing Division, Ladies and Gentlemen, thank you for the opportunity to present our results on alosetron in the treatment of irritable bowel syndrome with you today.

I would like to begin my presentation with a review of characteristics of irritable bowel syndrome patients, followed by a description of our Phase II and Phase III studies. I will then present our safety database and our conclusions on the alosetron development program.

Irritable bowel syndrome is characterized by abdominal pain and discomfort, with associated alterations in bowel function. The alterations in bowel function may include an increased sense of urgency, changes in stool consistency and frequency, increased sense of incomplete evacuation, the presence of mucous, and bloating. In an effort to determine which of these symptoms were most bothersome to the patients which we evaluated in our Phase III program, the following question was inserted into our Phase III database: when your irritable bowel syndrome is

active, which of the following symptoms bothers you the most? The three most frequent responses from the patients in our Phase III program were abdominal pain, urgency, and number of bowel movements or stool frequency.

Today, I will show you results for alosetron in the treatment of irritable bowel syndrome. I will show you that alosetron improves multiple IBS symptoms by providing adequate relief of IBS pain and discomfort, by reducing the percentage of days with urgency, by decreasing stool frequency, and by firming stool consistency.

The principal studies which I will report on are shown on this slide. We conducted two dose-ranging Phase II studies, S3BP12 and S3BA 2001. The P12 study randomized 467 patients from outside the United States. The 2001 study randomized 370 patients; 315 came from within the United States.

The Phase III confirmatory program consisted of two placebo-controlled efficacy and safety studies, S3BA 3001 and S3BA 3002. Each of these studies recruited over 600 patients exclusively from within the United States. We also conducted a 12-month-long safety study, S3BA 3003, which randomized 859 patients, also exclusively from within the United States.

I would now like to briefly review our Phase II program with you. Shown on this slide is the study design

for the two dose-ranging Phase II studies. Each of these studies recruited both male and female patients. The studies were randomized, double-blind, placebo-controlled.

In the P12 study, which is represented on the upper panel, all subtypes of IBS patients were enrolled, into a two-week screening period. Following completion of the screening, there was a 12-week treatment phase with either placebo, .1, . 5, or 2 milligrams BID alosetron. Following completion of treatment, there was a two-week follow-up period in which no treatment was given.

The second dose-ranging study, S3BA 2001, primarily recruited diarrhea-predominant IBS patients and those with an alternating bowel pattern. Once again, there was a 2-week screening period, followed by 12 weeks of treatment with either placebo, 1, 2, 4, or 8 milligram BID alosetron. Following completion of the treatment phase, there was a two-week follow-up period once again, and during the follow-up period there was no treatment given.

I would like to review with you briefly our key findings from our Phase II study which led to our Phase III study design. One of our goals in Phase II was to develop or identify an endpoint which would reflect multidimensional improvement in irritable bowel syndrome. In Phase II, we developed and validated the endpoint of adequate relief of IBS pain and discomfort. In our Phase II studies, we also

introduced electronic data capture to large, multi-center IBS trials, and we also identified gender-specific efficacy with alosetron.

I would now like to briefly describe each of these key features. The adequate relief of IBS pain and discomfort endpoint was piloted and validated in the 2001 study, and this became our primary efficacy measure in our Phase III program. Positive responses to the adequate relief question reflects improvement on multiple IBS-relevant domains.

The primary adequate relief measure was simply the question, in the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort? This question was asked of patients once every seven days, and patients would respond either yes or no to the question. We have validated the endpoint of adequate relief in the sense that we have shown that it is responsive to treatment, it is reproducible, and correlates with other meaningful measures to IBS patients. I would like now to show you some of these correlations or associations. They are also outlined in your briefing document.

The purple bars on this slide represent individuals who report adequate relief. The green bars represent individuals with no adequate relief. As you can see, those with adequate relief show benefit on multiple

IBS-relevant domains, including pain/discomfort severity scores, pain/discomfort-free days, percent days with urgency, changes in stool consistency, and changes in stool frequency. It's very important to realize that this slide is not evaluating the effects of alosetron versus placebo. This slide is evaluating what it means when a patient says they have adequate relief of IBS pain and discomfort.

Adequate relief of IBS pain and discomfort is an endpoint which reflects benefit on multiple IBS-relevant parameters. The validations of the adequate relief endpoint that we observed in our Phase II program were confirmed in both Phase III studies, as outlined in you briefing document. We also thought it was essential to develop a reliable method in which to capture data.

We believe that there are inherent problems associated with data collection by standard paper diary cards, such as uncertainty around the timing of when patients record data, as well as the potential for retrospective changes on the cards. We therefore developed an electronic data capture system in which patients would telephone in daily to a central database. Patients responded to automated questions by pressing appropriate keys on a touchtone telephone pad.

Once patients entered their symptom data, the data were timed and date-stamped by the system, and once the data

were entered, the database was secured and not accessible to modification. In our Phase II program, patients were asked questions about pain and discomfort, as well as bowel function. In Phase II, we observed the system to be operational 98 percent of the possible time, and patients completed 82 percent of possible phone calls. Our conclusion on the electronic data capture system is that this represents an advantage over traditional methods of data collection.

The next key feature which I would like to discuss with you which was alluded to earlier this morning was that of the identification of gender-specific efficacy with alosetron. Shown on this slide are results from our 2001 study. The endpoint evaluated here is the monthly adequate relief responders at month 3. Female IBS patients are shown on the upper panel, male IBS patients on the lower panel.

In female patients, all doses of alosetron produced improvement over that seen with placebo alone, with 1 milligram BID alosetron producing the most robust response. By contrast, in male IBS patients, no dose of alosetron produced substantial improvement over that noted with placebo.

In the other dose-ranging study, S3BP12, gender preferential efficacy with alosetron was noted. And in S3BP12, 2 milligram BID alosetron in female patients was

observed to be superior to either .1 or .5 milligram BID alosetron. As we just saw on the previous slide, in the 2001 study 1 milligram BID alosetron was superior to higher doses, including 2 milligrams. In each of the Phase II studies, efficacy was also observed to be preferential in female as compared to male IBS patients.

The overall findings from our Phase II program which impacted upon our Phase III design are as follows. We concluded that 1 milligram BID alosetron was our lowest most effective dose. The population of studies was females, as this represented the population with clear efficacy in our Phase II program. Females, as pointed out by Dr. Wood earlier this morning, also represent the population constituting 70 percent of IBS patients. Our primary endpoint for progression into our Phase III program was that of adequate relief of IBS pain and discomfort.

I would now like to review our Phase III program with you. We conducted two identical, simultaneous Phase III studies, S3BA 3001 and S3BA 3002. The primary population enrolled in these studies were diarrhea-predominant IBS patients and those with alternating bowel patterns, and all patients were female. There was a 2-week screening period, followed by 12 weeks of treatment with either placebo twice a day or 1 milligram BID alosetron. Following completion of the treatment phase, there was also

a follow-up period of our weeks duration without treatment.

For determining the sample size of the studies, 90 percent power at an alpha-equals-O.05 level was assigned for a 15-percent different on our primary endpoint, that of the monthly adequate relief responders. We assumed based on our Phase II program a 20-percent dropout rate and this yielded a sample size of 600, 300 patients on alosetron, 300 patients onplacebo.

The key inclusion criteria into our study were individuals, once again, needed to be female, have at least a six-month history of irritable bowel syndrome, be age at least 18 years. And if an evaluation of the patient's colon was not performed within five years of randomization, then one was done prior to enrollment into the study.

As noted earlier, there was a two-week screening period in the studies. During the two-week screening period, daily pain/discomfort scores were collected, as well as stool consistency scores were collected. At the conclusion of the screening period, the scores for abdominal pain and/or discomfort, as well as for stool consistency, were averaged. To be eligible for enrollment into the study, individuals' pain/discomfort scores needed to range between 1.0 and 3.3 inclusive on the scale shown below, where 1.0 represents mild pain.

It should be pointed out that the average score

needed to range between 1.0 and 3.3. On any given day, patients could have any degree of severity of abdominal pain and/or discomfort. The stool consistency score needed to be greater than or equal to 2.5 on average during the 2-week screening period, where a 2.5 is between hard and formed stool.

The primary exclusionary criteria for the studies were unstable medical condition, current evidence and/or history of other relevant gastrointestinal conditions, certain abnormal laboratory values, and concurrent use of specified medications, including but not limited to other 5HT3 receptor antagonists, analgesics or motility-acting agents.

In the 3001 study, we screened 1,470 patients, of which 626 were randomized, 309 to alosetron and 317 to placebo. 237 and 246 patients completed the respective arms. This represents a completion rate of approximately 75 to 80 percent, consistent with the anticipated dropout rate of 20 percent. A very similar pattern was also noted in the 3002 study.

At the time of entry into the study, the demographics for the patients randomized are shown on this and the next slide. Patients entered with an average age of approximately 45 to 46 years. The vast majority of the patients were white, and approximately 40 percent of the

patients reported still having their menstrual cycles. Forty-six percent of the patients reporting using fiber during the two-week screening period.

Patients reported approximately 10- to ll-year history of IBS symptoms at entry into the study, although I remind you once again only a 6-month history of IBS symptoms was required for enrollment into the program. The enrolling investigators characterized approximately 70 percent of the patients as diarrhea-predominant and approximately 27 to 28 percent of the patients as those with alternating bowel patterns.

During the two-week screening period,.the average pain/discomfort score was approximately a 2 on the 5-point scale reviewed earlier, and 2 represents moderate pain. Patients reported approximately 13 percent of the days as pain/discomfort-free, and approximately 70 percent of the days during the screening period with urgency. Patients reported a stool frequency of 2.7 bowel movements per day, and a stool consistency of approximately 3.4, also on the 5-point scale shown earlier where 3.4 represents between formed and loose stool.

The disposition of the patients who were randomized into the 3001 and 3002 studies are shown on this slide. Once again, approximately 75 to 80 percent of the patients completed the study. For alosetron-treated

patients in both studies, the primary reason for withdrawal from the study was the development of constipation. Ten percent of patients randomized to alosetron withdrew from each of the respective studies. Constipation is a class effect of 5HT3 receptor antagonists.

The primary endpoint of our Phase III program which was prospectively defined in agreement with the FDA is that of the adequate relief of IBS pain and discomfort endpoint. Once again, the primary measure is the question, in the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort.

During the course of the Phase III program, we also collected other secondary and supportive endpoints. The key secondary endpoints were stool consistency, percent days with urgency, stool frequency, percent days with incomplete evacuation, and percent days with bloating. The other endpoints were pain severity scores, pain/discomfort-free days, and the symptom checklist 90R or SCL-90R, which represents a psychometric instrument.

As in the Phase II program, we employed electronic data capture in our Phase III program. Adequate relief data were collected weekly. Bowel function and pain and/or discomfort data were collected daily. In Phase III, we observed the system to be operational greater than 99 percent of the possible time, and patients completed 85

percent of possible daily phone calls.

For statistical analysis, missing data resulting from withdrawals or otherwise were handled by the last observation carried forward principle. As outlined in your briefing document, other methods for managing missing data were also applied. Findings were robust for the methods of managing missing data.

Treatment comparisons for adequate relief were by the Mantel-Haenszel test, and for bowel function by Van Elteran's test. All p values were two-tailed using a type 1 error rate of alpha equals 0.05. To help reduce the accumulation of the type 1 error rate for multiple endpoints, testing was done sequentially. In other words, we pre-specified the order for testing endpoints, and it was required that p be less than or equal to 0.05 for each endpoint before testing the next endpoint in sequence.

I would now like to review our Phase III efficacy results with you. The prospectively defined primary endpoint of our Phase III program was the monthly responder for adequate relief of irritable bowel syndrome pain and discomfort. The definition of a monthly responder for adequate relief were individuals who answered the weekly adequate relief question as a "yes" for at least two weeks in a four-week month. For months with incomplete data, or, in other words, for months in which some of the weeks but

not all of the weeks were answered, then the missing weeks were considered as no relief. For months in which all weeks were missing, then the last observation carried forward principle was employed on a monthly basis. Initially, we evaluated the number of months with adequate relief. This represented the first step of our multiple endpoint adjustment strategy. Patients on alosetron treatment reported significantly more months with adequate relief in both studies, as compared to those patients treated with placebo.

Having achieved significantly more months with adequate relief in alosetron-treated patients, we next focused on the individual months. Shown on this slide are data from the two pivotal Phase III studies 3001 and 3002, the 3001 study shown on your left, the 3002 study on your right. The y axis on the graph represents the percent of monthly responders. Alosetron-treated patients are represented by the yellow bars, placebo-treated patients by the green bars.

In the 3001 study, at each monthly interval there were significantly more monthly responders during alosetron treatment as compared to those patients treated with placebo. In the 3002 study, there were significantly more monthly responders at month 1 and month 3 during treatment with alosetron, and the value approached statistical

significance at month 2.

To try to obtain better clarity on the onset of action as well as the durability of the response, we also evaluated the responses to the weekly adequate relief question. Once again, the 3001 study is shown on the left, the 3002 study on the right. The y axis for this graph represents the percent of patients for each treatment group which answers the weekly adequate relief question, in the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort, as a "yes."

In the 3001 study, significantly more patients answered the question as a "yes." By the end of the fourth aeek of treatment, as you can see, once significance was achieved, benefit persisted throughout the remainder of the treatment phase. Following cessation of treatment with alosetron, benefit rapidly dissipated.

In the 3002 study, significantly more patients in the alosetron group answered the question as a "yes." By the end of the second week of treatment, benefit persisted throughout the remainder of the treatment phase. Following cessation of treatment, benefit once again rapidly dissipated.

In an attempt to visualize the high degree of consistency between these two studies, I would like to show you these two graphs overlaid on the same plot. Shown here

is the data from the 3001 study, and then when the 3002 study is superimposed upon that graph with the same axes, of course, you can see a remarkable degree of consistency for the alosetron treatment groups in the two studies.

As you may recall, in the 2001 study we also evaluated in female IBS patients the 1 milligram BID dose of alosetron. When we superimpose the results of that study once again on the graphs from the 3001 and 3002 study, we once again see a high degree of consistency with the alosetron treatment of IBS patients. Our summary of our primary efficacy data are that alosetron provides significant and sustained adequate relief of IBS pain and discomfort, and that benefit rapidly dissipates following cessation of alosetron treatment.

We next evaluated various secondary endpoints. I would like to initially discuss urgency. Urgency, as we know, is an unpleasant sensation, and therefore an improvement in urgency is represented by a decrease in the percent days with urgency. As shown on this graph, significant improvement occurred in alosetron-treated patients by the end of the first week of treatment in both the 3001 and 3002 study. Benefit in both studies persisted throughout all 12 weeks of treatment. Following cessation of treatment, benefit once again rapidly dissipated.

We next evaluated stool frequency and a virtually

identical pattern emerged--significant improvement by the end of the first week of treatment, significant improvement throughout all 12 weeks of treatment. Stop treatment, symptoms rapidly return. An identical picture once again for stool consistency--significant improvement by the end of the first week of treatment, significant improvement throughout the entire treatment period; stop drug, symptoms return.

We also evaluated other secondary endpoints. Alosetron produced significant at month 2 and 3 in 3001, and in month 3 in 3002 on percent days with incomplete evacuation. In neither the 3001 or 3002 study was there any significant improvement on percent days with bloating. Evaluation of the other supportive endpoints showed at month 3 and month 2 and 3 for 3001 and 3002 studies respectively, there was significant improvement on pain/discomfort daily scores. And in the 3001 study at month 3, there was significant improvement for pain/discomfort-free day responders. In neither the 3001 nor the 3002 study was there a significant improvement on any global indices for the SC-90R.

At the request of the FDA, at the end of Phase II meeting, we evaluated whether the occurrence of menses confounded, or represented a confounder for the effects of alosetron. Shown on this slides are patient which were able

to menstruate in the 3001 and the 3002 study. The data are represented as the proportion of weeks with adequate relief for weeks in which patients had menses versus weeks in which patients did not have menses. As can be seen, benefit of alosetron was present in both studies under either scenario, whether individuals who were able to menstruate were not or were having menses during those particular weeks.

Our overall summary of efficacy is as follows. Alosetron significantly improves multiple symptoms of IBS by providing adequate relief of IBS pain and discomfort, decreasing days with urgency, reducing stool frequency, and producing firmer stools.

I would now like to review our safety database with you. Our safety database was composed of preclinical evaluations, including acute, sub-chronic, and chronic animal studies. We also conducted mutagenicity, oncogenicity, and reproductive toxicology studies. In Phase I, ascending single and repeat-dose studies were done, as well as an extensive cardiac safety program.

In Phase II and Phase III, we collected adverse events, serious adverse events, and laboratory values. And in our 12-month, long-term safety study, we also collected adverse events, serious adverse events, laboratory values, and electrocardiograms. As cardiac conduction should be evaluated for all new chemical entities, we conducted an

extensive cardiac safety program.

Preclinical studies were composed of telemetry studies from dogs and guinea pigs, in vitro-recorded action potential duration, and other electrophysiologic parameters. From purkinje fibers and using patch clamp techniques, we recorded a delayed rectifying potassium current known as IKR from ventricular myocytes.

In Phase I, we targeted electrocardiograms at and around the time of Cmax, and also performed a cisapride co-administration study. In the long-term safety study, ECGs were collected at baseline and after two months of continuous dosing. The conclusion from these and other studies are that there were no effects of alosetron on cardiac conduction or any other cardiac-related parameter.

In our Phase II and III program, 1,263 patients received BID doses of alosetron for up to 12 weeks in duration. In the long-term safety study, 640 IBS patients received 1 milligram BID alosetron for periods up to 12 months in duration. In ongoing studies, approximately 1,250 patients are presently receiving treatment with alosetron. In healthy volunteers, maximum daily doses of alosetron up to 16 milligrams BID have been administered.

Shown on the next slide are the most frequent adverse events reported during the Phase II and Phase III program. During treatment with alosetron, the only adverse

event which occurred at a substantially greater frequency on alosetron treatment than that on placebo was constipation, a class effect of 5HT3 receptor antagonists.

With 1 milligram BID alosetron, constipation was reported in 27 percent of alosetron-treated patients, as compared to 5 percent of patients who received placebo treatment. Although constipation was reported with 1 milligram BID alosetron in 27 percent of the treated patients, it's important to note that most patients only had a single episode of constipation, and that only 10 percent of patients in the Phase II-Phase III withdrew secondary to constipation.

Specific parameters of constipation were as follows: a median onset of approximately 10 days, a median duration of 6 days. The enrolling physicians and the patients quoted a severity of constipation as mild and moderate, constituting 65 percent of the cases.

In an irritable bowel syndrome study, we view collection of bowel functions as important and relevant endpoints. Therefore, routine laxative use was not permitted in our studies. However, if individuals underwent four consecutive days without a bowel movement, a brief interruption of alosetron therapy was permitted. In the alosetron Phase III program, the interruption occurred in 9 percent of alosetron-treated patients who had constipation.

With interruption of alosetron therapy, only I percent of the patients failed to resume bowel movements within the 4-day drug holiday.

We also collected serious adverse events during the Phase II and Phase III program. An identical frequency of events occurred with 1 milligram BID alosetron as noted on placebo. However, as was referred to earlier today, four cases of ischemic colitis were reported during the alosetron development program. The proper denominator for these four cases is approximately 3,000 patients. We believe, of these four cases, only one case actually represents ischemic colitis. I will walk you through the data today, and we will also present by Dr. Kay Washington an evaluation of the specific histologic specimens.

In these four patients, the onset of symptoms occurred at times of 2 days, 7 days, 3 weeks, and 8 weeks after initiation of treatment with alosetron, all cases resolved with sequelae, and of pertinence to discussion earlier today, radiographic evaluation on all of the patients during the course of their illness showed no gross dilatation. Three of the cases are outlined in your briefing document by both us and Dr. Lawrence Brandt. We, as well as the FDA, became aware of the fourth case just recently, and I would like to walk you through that case now.

The individual was a 61-year-old female who, on the seventh day of treatment with 1 milligram BID alosetron, reported severe abdominal pain, bloody diarrhea. She was noted to have an elevated white count and a fever. A CT scan was done the following day, which was October 29th. The CT scan revealed mural thickening of the entire transverse colon, descending colon, and hepatic flexure.

Changes were read by the radiologist as consistent with colitis, but it was deemed by that radiologist that ischemic colitis was unlikely because of the large extent of vascular territories involved. A colonoscopy was done a few lays later, on November 2nd. The formal colonoscopy reports reads in distal transverse to the descending colon, there were patchy areas of edematous hyperemia adjacent to pale areas. I should note that we did receive an endoscopic photograph of this patient and we do not concur with that diagnosis, or with that endoscopic report. When we reviewed the photograph, we did see exudate, petechiae, and areas of erosions, and perhaps ulcerations.

The biopsy from this specimen was read by the pathologist at the local hospital as ischemic colitis, although no histologic details were given. The patient was discharged to home the following day and is reported to be doing well. The four reported cases, it's important to note, occurred in the 12-week studies. There have been no

reports of ischemic colitis in two ongoing 12-month studies, of which approximately 1,000 patients are receiving treatment with alosetron.

We know from the literature that serotonin may represent a vasoconstrictor. Serotonin agonists have also been reported to cause ischemic colitis. As 5HT agonists may induce ischemic colitis, we attempted to determined how a selective antagonist to the 5HT3 receptor could also induce ischemic colitis. We initially, as we discussed earlier this morning, looked at whether or not alosetron serves as a direct vasoconstrictor.

As was pointed out by Dr. Gershon, these studies were done by Dr. Kenton Sanders, who is in the audience and could provide additional details if the Committee has questions. Contractile activity were monitored from dog and guinea pig inferior mesenteric arterial smooth muscle. No increase in either spontaneous or nerve-induced contractions were noted with doses of alosetron up to 1,000-fold the KD dose. As Dr. Gershon had mentioned this morning, on the vascular from the gut, 5HT3 receptors are also not present.

We also went back and re-reviewed our long-term, high-dose animal studies in which animals received exposures for up to two years' duration of doses up to 800- to 1,000-fold the clinical dose. There was no increase in either colonic or small intestinal lesions with alosetron treatment

in these studies.

As rectal bleeding may represent either undiagnosed or misdiagnosed ischemic colitis, we also reviewed our cases of rectal bleeding which were reported as an adverse event. A review of this database revealed no evidence of undiagnosed ischemic colitis.

As no mechanistic rationale has become obvious to us, we revisited the diagnosis of ischemic colitis. Dr. Kay Washington, a GI pathologist at Vanderbilt University, conducted a review of the histopathology of the previous specimens. Dr. Washington also evaluated immunohistochemistry for the possible presence of E. coli 0157:H7. E. coli 1057:H7 was specifically evaluated for, as this causes hemorrhagic colitis with both symptoms and-- well, with symptoms which very well may mimic ischemic colitis.

I would like to interrupt my presentation now for Dr. Washington to review the pathology.

DR. WASHINGTON: Thank you. First, I'll go over the list of material I received to review with you. We were able to review the H&E, the routine stain slides on each patient, and on three of the cases we received unstained slides that we could stain by immunohistochemistry for E. coli 0157:H7.

When I go through the cases individually, I'm

going to refer to them a little differently. They are in sequential order here and I'll show you the cases in that order. The first case is from 1996, and I'll refer to it as the '96 case. The second two cases are the '98 cases, and the fourth case is the '99 case. And then we'll summarize that as well.

I want to show you a couple of slides from my teaching collection just to get us started on what the histopathology of these lesions looks like. This is a case of culture-confirmed E. coli 0157:H7 colitis from my collection, and you can see that it's an intensely congested mucosa. There is a pseudomembrane composed of inflammatory cells, numerous neutrophils, acute inflammatory cells, in the surface, a lot of mucosal necrosis in the surface. And the crypts are preserved in a pattern very reminiscent of ischemic colitis.

When we look at these crypts, we see what pathologists refer to as micro crypts. The crypts are almost withering in an ischemic-type injury. But this is E. coli, and notice the laminapropria contains numerous inflammatory cells in this example of infectious colitis from E. coli. So it's a mixed pattern. It looks ischemic in that the crypts are preserved but relatively small, the so-called micro crypt appearance of ischemic colitis. But the laminapropria is very cellular, and that's an appearance

that goes along more with infectious colitis, so a combination pattern in recognizable cases of E. coli 0157 colitis.

Now, this, in contrast, is ischemic colitis, and notice again we have these very small crypts, the micro crypts of ischemic injury. The laminapropria out here in the area of injury is not nearly as cellular as in the example of E. coli 0157.

So now I want to take you through the histopathology of these four cases under discussion. This is the 1996 case, and this is the worst area of the mucosa right here. The changes in this biopsy were very minimal. Most of the colonic mucosa looks normal, but in this area we see a little bit of what pathologists call reactive change. There's a little bit of loss of goblet cell mucin here, but notice that the laminapropria really does not contain many inflammatory cells. I see no neutrophils infiltrating the crypts and the surface is pretty well preserved here. So this is a very minor, non-specific change and I cannot assign any particular diagnostic label to this biopsy.

And this was a biopsy from elsewhere in the colon, normal-appearing colonic mucosa taken at the same time, and you can see that this is indeed normal-appearing colonic mucosa, so very minor changes in this patient in 1996. She had a follow-up biopsy, which again was very normal in

appearance. The surface mucosa is preserved. There's no mucosal necrosis, no increase in inflammatory cells. We did see a slight increase in mucosal eosinophiles which is exquisitely non-specific in the GI tract, and so essentially normal colonic mucosa in the follow-up biopsy in the 1996 patient.

Now, the two 1998 cases have virtually identical histology and they are really the cases of interest here. This is from the first 1998 case, and notice we have this rather exuberant pseudomembrane sitting here composed of mucin with numerous inflammatory cells, mainly neutrophils, intermixed.

Now, deep to that mucin layer or necrosis is a bit of colonic mucosa that shows a pattern of ischemic injury, with the micro crypts and the dense cellularity of the laminapropria. And we can find other areas in that biopsy that that appears similar, with the exuberant pseudomembrane overlying an area that looks like ischemic injury.

The key to this biopsy is to look at the more intact mucosa, and when we look at this intact mucosa we see that the cellularity of the laminapropria is increased with inflammatory cells. And we also, of note, find neutrophils in this laminapropria and infiltrating crypts. This is the pattern of an infectious type colitis. So we have the combination pattern of infectious colitis and ischemic-

appearing injury, and that should prompt the pathologist to consider the possibility of E. coli 0157 infection in this patient.

This is a control slide of E. coli 0157 stained with the antibody that we use. This was provided to me by a colleague who cultured the organism, the specific serotype. And the large brown, pale-staining structures in the background are red cells. The bacteria are the smaller, darker-staining structures. And I think you can see within the mucin of this particular case, there are few clusters of organisms that are staining in this fibrinous exudate, and this is where we would expect to see the bacteria in E. coli hemorrhagic colitis.

Now, we're moving on to the second 1998 case, and the histopathology looks identical to the other 1998 case. We have the pseudomembrane formation, necrotic crypts intermixed with fibrin, mucin, and inflammatory cells overlying an area that looks like ischemic injury, with a dense laminapropria and the micro crypts.

And this biopsy demonstrates even more strikingly than the previous 1998 biopsy that in the intact mucosa, we do have this pattern of acute self-limited colitis going on. We have numerous neutrophils in the laminapropria, and they are also infiltrating crypt epithelium here. This looks like an infectious colitis to the pathologist.

And if we look at the laminapropria, we can see numerous neutrophils out in the laminapropria as well. And I'd like to point out on this slide that I really did not see structural abnormalities in the blood vessels of the laminapropria. We, of course, don't have larger vessels that were sampled, but no structural abnormalities of the vessels were noted in these slides. So both 1998 cases show a combined ischemic infectious-type pattern that is highly suggestive of E. coli infection, and I really would not Label those cases as pure ischemic colitis.

This is the 1999 biopsy, and I think you can appreciate some differences just on this lower power in this biopsy. We've got preserved crypts here, the ischemic, and that very dense pick laminapropria that we see in ischemic colitis, but very little in the way of inflammation here. And there is an exudate and one area of ulceration here, but it's qualitatively different from the exudate we saw in the cases that I consider to probably be E. coli colitis. It's more fiber and there are less inflammatory cells, very Little mucin mixed in.

And in the intact mucosa, we see a laminapropria that is normal in its cellularity. We do not see neutrophils infiltrating the laminapropria or in the crypts, so we do not have that superimposed pattern of infectious colitis in this case. So this I would be more willing to

classify as an ischemic colitis. And the immunostain for E. coli in this case was negative. I could not demonstrate organisms in this exudate in the 1999 case.

So just to summarize the histopathologic findings in these four cases, the 1996 case which we looked at first really is not diagnostic of either ischemia or E. coli colitis or any specific entity I can put a name on. The features are very mild and non-specific and had resolved on the follow-up biopsy.

The two 1998 cases, because of their combined pattern of ischemic and infectious colitis, I consider to be highly likely to represent E. coli 0157 colitis. I would not classify these as simple ischemic colitis. The 1999 case, I believe, does represent a case of ischemic colitis based on its histopathologic features.

Are there any--shall we take questions now or--

CHAIRMAN HANAUER: Now, don't we finish off and then we'll--

DR. MANGEL: Our conclusions on ischemic colitis are that the preclinical studies do not suggest an etiologic basis. We believe a single case was consistent with ischemic colitis, and that was in the 61-year-old female. We conclude there is no evidence for a causal relationship between the development of ischemic colitis and alosetron treatment.

I would next like to review with you our long-term 12-month safety study. This study evaluated both males and females receiving either placebo or alosetron treatment for periods up to 12 months. The randomization schedules was one to three in favor of alosetron. Forty-seven males and 163 females received placebo, while 167 males and 473 females received alosetron.

Although analysis is ongoing at the present time, or at least at the time of inclusion for the Advisory Committee, we have data on 415 patients who received at least six-month treatment with alosetron, and 187 patients who received alosetron treatment for a year. Evaluation of the adverse events of this population in the present study revealed an identical pattern as was noted in the 12-week Phase II and Phase III program.

The only adverse event to occur to a substantially greater frequency with alosetron treatment as compared to that observed with placebo was that of constipation, occurring at a rate of 31 percent on alosetron and 5 percent on placebo. Evaluation of the female patients in the long-term safety study, in particular, revealed a near identical pattern.

We also collected serious adverse events--I'm sorry. In the long-term safety study, we had anticipated a dropout rate of 40 percent, and we noted approximately 40

percent of the patients to withdraw from treatment during the study. As observed in the Phase II and Phase III program, for alosetron-treated patients the primary cause for withdrawal was the development of constipation, and constipation occurred at a similar rate as noted in the Phase II and Phase III program.

In the long-term safety study, we also collected serious adverse events. There was no increase in serious adverse events in the long-term safety study in either males or females. And I also remind you once again no cases of ischemic colitis were reported in the long-term safety study.

As part of our safety evaluation in both the 12-week study as well as the long-term safety study, we collected laboratory values, routine hematology, and chemistry panels. As for all new chemical entities, an in-depth review of liver function tests was undertaken. A similar frequency for elevations in liver function tests at the greater than two-fold level was observed for alosetron-treated patients at 1.4 percent as that seen with placebo-treated patients at 1.2 percent.

Individual cases were reviewed by myself and Dr. Hunt, and we concluded that no signal was apparent. No serious adverse events of hepatitis or elevated LFTs were reported. ALT elevations greater than three-fold normal

were also observed. Subjects with ALTs greater than three-fold normal during the treatment period and those who exceeded pre-treatment values occurred at a rate of .4 percent in the placebo group and .5 percent in the alosetron-treated patients. The range of ALT elevations were up to 9.6-fold normal in placebo-treated patients and up to 7.9-fold normal in alosetron-treated patients. We conclude that there is no evidence for alosetron-induced hepatotoxicity. Our overall conclusion for laboratory values are that there are no clinically relevant changes in any hematologic or chemistry parameter during alosetron treatment for up to 12 months.

Our overall conclusions from the alosetron development program are as follows. We believe alosetron provides adequate relief of IBS pain and discomfort. Alosetron improves urgency, stool frequency and consistency. Alosetron displays a favorable safety profile, with constipation representing the only adverse event of note.

We believe the data presented today strongly support our proposed indication that Lotronex, alosetron hydrochloride, is indicated for the treatment of irritable bowel syndrome in female patients whose predominant bowel symptom is diarrhea either alone or as part of an alternating stool pattern.

I would be glad to entertain questions now. I

would also like to mention that Dr. Michael Camilleri has reviewed the cases of ischemic colitis and would also be glad to entertain questions on that. Dr. Mitch Shiffman, from the Medical College of Virginia, an expert hepatologist, is also here to entertain any potential questions there may be with respect to the liver function tests.

Thank you.

CHAIRMAN HANAUER: Thank you very much, Doctor.

Dr. Laine, do you want to start?

DR. LAINE: Sure, since I've been so quiet. You know, whenever you do clinical trials, there's always the distinction between statistical significance and clinical significance. And when I looked at your hypothesis and sample size determination for your Phase III studies, it appeared that you chose 15 percent as a meaningful difference. When I look at your 1-, 2- and 3-month differences in your primary endpoints on the two studies, although you achieved statistical significance in five of those six time periods, you only achieved what apparently you were defining as clinically significant difference in one of those six time points.

Could you comment on that distinction?

DR. MANGEL: Yes. The study was powered to detect a 15-percent difference between alosetron-treated patients

versus placebo-treated patients on the primary endpoint of monthly adequate relief responders. That, we believe, is a different notion from the definition of clinical significance.

We do believe it's an important issue. What is clinically relevant, however, to the IBS patient--we believe this is the first agent shown in two large, multi-center, contemporary, placebo-controlled studies to show benefit for the treatment of irritable bowel syndrome. For the weekly adequate relief parameters, the range of benefit for alosetron versus placebo was on the order of 10 to 15 percent. We should also point out that adequate relief was only one endpoint in this study. And, of course, irritable bowel syndrome is a multidimensional condition.

Could I have the D folder, slide 11?

When we look at the relative improvement in other endpoints as well, we see that in addition to adequate relief, we are seeing improvement on urgency, consistency, and frequency. When represented as percent improvements, depending upon which endpoint you are evaluating, we see between 15 to 20 percent benefit with alosetron improvement as compared to placebo.

Could I have slide F-3, please?

We also believe that an important aspect of the robustness of our data are the virtual superimposability of