FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

UROLOGY SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

9:03 a.m.

Monday, April 10, 2000

Versailles Ballroom
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

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P R O C E E D I N G S

(9:03 a.m.)

DR. AZZIZ: Good morning. Let us begin our meeting of the Urology Subcommittee for the Advisory Committee for Reproductive Health Drugs. The topic today will be the safety and efficacy of Uprima, which is NDA 21-118, presented by TAP Holdings.

I would like to introduce a few people or at least discuss how we are going to outline today's meeting. You may have the agenda. We will have a little bit of a change in the agenda this morning. The presentations by TAP Holdings, which will begin at 9:10, will be extended to 11 o'clock, another 30 minutes. We will have an additional question and answer period in the middle of the presentations, and I will make sure that we don't run over.

I wanted to make sure that we understood that today we need to stay on time. I will make sure that we do so by simply interrupting the speaker and asking him to finish. Hopefully that won't be necessary.

Before I ask all the FDA staff and committee members to introduce themselves, I wanted to thank Dr. Marianne Mann for very good work in presenting the data, which is quite complex, in a legible fashion, which is something that we committee members really do need.

Another point is during the comments in the

session, I would ask you to please identify yourself before making your comment. This is obviously being transcribed, and it is very difficult to figure out who is talking if you do not do so.

So, without further ado, I would like to have introductions beginning in that corner.

DR. RACZKOWSKI: Good morning. I'm Victor Raczkowski with the FDA. I'm the Deputy Director in the Office of Drug Evaluation III, and that's the office that oversees the Division of Reproductive and Urological Drugs.

DR. MANN: I'm Marianne Mann, and I'm the Deputy Director of the Division of Reproductive and Urologic Drugs.

DR. SHAMES: I'm Dan Shames. I'm the team leader for Urologic Drugs.

DR. HIRSCH: Mark Hirsch, medical officer.

DR. JARUGULA: Venkateswar Jarugula, pharmacokinetics reviewer.

DR. AZZIZ: Dr. Jacobs will be here.

DR. O'LEARY: I'm Michael O'Leary. I'm on the faculty of the Harvard Medical School and a urologist at Brigham and Women's Hospital in Boston.

DR. DONATUCCI: Craig Donatucci. I'm a urologist from Duke University.

DR. LIPPERT: Marguerite Lippert. I'm a

urologist at the University of Virginia.

MS. PETERSON: I'm Jayne Peterson. I'm the Executive Secretary of the subcommittee with FDA.

DR. AZZIZ: Ricardo Azziz. I'm a professor of obstetrics and gynecology and medicine at the University of Alabama at Birmingham, and I'm chairing the committee.

DR. KOWEY: Peter Kowey. I'm a professor of medicine at Jefferson Medical College in Philadelphia and a cardiology consultant to the committee.

DR. GRABOYS: Tom Graboys. I'm a cardiologist at the Brigham and Women's Hospital and Director of the Lown Cardiovascular Center.

DR. D'AGOSTINO: Ralph D'Agostino, Boston University, biostatistician.

MS. SCOTT: Julia Scott, registered nurse, and I'm the consumer representative on the panel.

DR. TIEFER: Leonore Tiefer. I'm a clinical psychologist in the Department of Psychiatry at New York University Medical Center and Albert Einstein College of Medicine and a sex therapist and sex researcher.

DR. GREENE: I'm Mike Greene. I'm an obstetrician/gynecologist at Massachusetts General Hospital and Harvard Medical School.

DR. HANNO: Phil Hanno. I'm a urologist at the University of Pennsylvania in Philadelphia.

DR. AZZIZ: I would like to have Jayne Peterson, Executive Secretary of the committee, present the conflict of interest statement please.

MS. PETERSON: 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 participants, it 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 a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208, full waivers have been granted to Dr. Lippert, Dr. Jacobs, Dr. D'Agostino, Dr. Kowey, and to Julia Scott. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Further, we would like to disclose that Drs. Califf, Kowey, and Donatucci have involvements which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208, but which may create the appearance of a conflict. The agency has determined,

notwithstanding these interests, that the interest of the government in the participation of Drs. Califf, Kowey, and Donatucci outweighs the appearance of the conflict. Therefore, they may participate fully in all matters concerning Uprima.

In the event that the discussions involve any other products or firms not already on the agenda for which a 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 involvement with any firm whose products they may wish to comment upon.

DR. AZZIZ: Without further ado, to stay on time -- it is 9:10 -- I would like to have TAP begin their presentation, if you would please. As I noted before, we have extended the time allotted to them by 30 minutes, till 11 o'clock. After the presentation by Dr. Heaton on erectile dysfunction treatments and summary of efficacy, we will take 10 minutes for questions and answers, and then we will proceed.

Thank you.

DR. FRESTON: Mr. Chairman, ladies and

gentlemen, good morning. I'm Dr. Jim Freston from the University of Connecticut Health Center. I serve as a scientific advisor to TAP in the development of Uprima and for other drugs in their pipeline, and I am pleased to be able to moderate their presentations today and to present some of the data.

Others who will join me in presenting are shown on this slide. They include Dr. Barbara Bopp of the Drug Metabolism and Pharmacology Division, Dr. Jeremy Heaton, Professor of Urology at Queens in Kingston, Ontario; and Dr. Timothy Fagan, Professor of Medicine and Associate Professor of Pharmacology at the University of Arizona. Dr. Heaton is an expert in erectile dysfunction, and Dr. Fagan is a specialist in cardiovascular clinical pharmacology.

A number of TAP officials and scientists are here to support this presentation and can be called upon if needed, and they are listed here. We will introduce them, as needed, along the way.

We also have some other ED experts who are serving as consultants and have done so over the course of time in developing this compound. They are shown here. It includes Drs. Carson, Dula, Lewis, and Melman, as well as Dr. Ray Rosen in the Department of Psychiatry at Robert Wood Johnson. His presence is important to us because he

helped developed the IIEF, a survey instrument for sexual function, which we'll be referring to today. Dr. Addison Taylor is another professor of medicine, a specialist in cardiovascular and clinical pharmacology from Baylor, and Dr. Joel Morganroth from Philadelphia is a cardiologist and a specialist in electrophysiology and the interpretation of EKGs and something called Holter monitors that we will be discussing today. And finally, Dr. Gary Koch is a senior statistician from Chapel Hill.

Our proposed agenda is set out here. After my introductory remarks, we will turn to the pharmacokinetics and metabolism of the compound, and then we'll get right into the state of the art of ED treatments and the efficacy data. As Dr. Azziz mentioned, we'll take a 10-minute break there and then pursue the safety assessment, and then I'll try to summarize on time.

The FDA briefing document highlighted a number of areas for your focus and concentration, and we have tried to list them here. Some comparisons were drawn in the FDA briefing document to other approved ED therapies, and we found that that worked very well. It does provide a context for Uprima on both the safety and efficacy side and a point of reference as well. So, we'll be bringing in some of those comparisons too to assist in your deliberations.

You were asked to answer the question are the Uprima ED patients representative of those with ED in the general population, and we will address that comprehensively along the way.

The question was raised about the extent of pharmacokinetic variability. We will deal with that as well as the clinical relevance of the 2 milligram dose.

The efficacy in diabetes is of interest to all of us and we'll address that head on.

Also, a question was raised about why the patients dropped out of the long-term safety despite continuation of efficacy in most instances, a very important question. We'll deal with that.

But the main event today, if you will, obviously is in the area of hemodynamics. We're all aware that in recent years there has been quite a lot of interest in cardiovascular events, including deaths in patients with erectile dysfunction who have had increased sexual activity in the context of using ED drugs. So, we'll be spending a lot of time discussing that and its relationship to nitrate usage in this population and specifically in those who take Uprima.

And we will round out by discussing the nature of the experience when patients take Uprima at the same time as they consume alcohol.

Let us begin with the definition of erectile dysfunction. This is the one that we have used. It is the NIH definition and it highlights that ED is the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance. In recent years, WHO has also incorporated these features and added the concept of chronicity up to 3 months and variability. ED can come and go.

A bit about the epidemiology and demographics of ED. We have two major surveys that we can draw on for help in this regard. One is the U.S. National Health and Social Life Survey which was conducted in 1992 in 1,410 men and women between ages 18 and 49. I'm sorry. It's 1,410 men in this study of men and women, and they correlated ED to other diagnoses -- I will come to that in a moment -- and projected that ED was probably present in about 10 percent of men in this age bracket.

The other major study was the so-called Massachusetts Male Aging Study, MMAS, which actually antedated the previous study but was recently updated as well. This was a cross-sectional study of 1,300 men, a slightly older group. They found an ED rate of 52 percent. 10 percent of ED was complete, but most of it was moderate, with some minimal. They extrapolated to the U.S. population and concluded that probably 30 million men in

the U.S. suffer from ED, and they correlated ED with age, health status, and emotional status as well.

This shows the relationship of ED to age from the MMAS, and you can see that the incidence certainly does march up into the elder years. The increase is mostly in the moderate severity and the complete severity, with minimal remaining stable.

Now, although we all associate ED with age, it's important to point out that the incidence starts to tick up additionally because of the co-morbidities that creep in in the elder years. And the other point to be made is that, yes, even though it is more common in elders, there is plenty of it in middle age.

These are the associated diseases: hypertension, diabetes, heart disease, concomitant use of medications, depression, and psychological factors.

This shows the distribution of patients in some of these subgroups in the Uprima studies. The duration of ED was 4.5 years. We'll come back to that important duration.

Hypertension. 31 percent of our patients were hypertensives versus 33 percent in MMAS.

Coronary artery disease, 16 and 16. We defined coronary artery disease as patients who had previous angina, previous myocardial infarction, or a

revascularization procedure in the past, either angioplasty, placement of a stint, or bypass surgery.

So, you can see that our populations are looking very much like the general population in MMAS with ED.

Turning now to apomorphine itself. This is a drug, a USP drug. It has been around for quite a while. In fact, it was first used as a pharmacologic agent in 1869, and there are now over 1,100 literature citations using doses all the way from 0.2 milligrams to 1,500 milligrams, and approximately 8,000 patients have been studied in clinical trials around the world, in addition to the 3,000 in the Uprima trials.

It's approved in 12 countries for various indications, but mostly for Parkinson's disease which requires daily administration. The usual doses are 3 to 30 milligrams subcutaneously. Why Parkinson's disease? Because apomorphine has dopaminergic properties and they were recognized as long ago as 1967. In fact, the mechanism of its erectogenic effect is directly related to this property. Specifically, apomorphine activates dopamine receptors in the hypothalamus and limbic neural pathways, and that's how it works in erections.

Now, what about Uprima itself? It's reformulated apomorphine. It has been put into a

sublingual preparation. It, of course, has a unique central mechanism of action and, because of its sublingual formulation, a rapid and quite predictable onset of action. And we'll show you data to support the fact that it's effective for ED in a wide spectrum of organic and nonorganic etiologies and severities.

There's good news on the safety side. Again, we are all aware of the heightened interest in cardiovascular events in this population of patients. We're pleased to report that in extensive Uprima trials, there have been no deaths, nor have there been any myocardial infarctions or cerebrovascular accidents related to the drug, and no priapisms. Nausea was the most frequent adverse event, and syncope was the most significant. And we'll spend time on both of these.

The proposed indication for Uprima is for the treatment of erectile dysfunction in these doses, 2, 3 and 4 milligrams. The agency has asked us to present data at higher doses above the recommended dose, and we're pleased to do so today.

Above 4 milligrams, there's very little gain in efficacy, but there are more side effects. Therefore, we're recommending the doses 2 to 4.

Now, what's the rationale for proposing approval of Uprima at this time? That is set out on this

and the following slide. As I pointed out, ED is associated with a number of diseases and conditions. Drugs with different mechanisms of action are particularly useful in diseases that have multiple pathogenic pathways. Think of hypertension, think of depression, Hypertension is a particularly good example. Multiple pathogenic mechanisms. In the beginning we had reserpine, hydrochlorothiazide. Then we got methyldopa. Then we added alpha-1 antagonists and beta blockers, and then calcium channel blockers, ACE inhibitors, and more recently the AT-2 inhibitors. Each class of drugs in its time advanced the field and more patients were able to have their hypertension controlled. Today, as you know, we can treat effectively hypertension in any patient, and in fact, with this array of different drugs, we can even tease out the etiologies of hypertension in some patients.

In contrast, the field of ED therapy is in its infancy. We've only got three drugs that are approved. One requires injections into the penis. One requires insertion of a pellet into the urethra. There's only one that's available orally. All of them work by a peripheral mechanism, and all have a unique set of adverse events. And there's no one drug that's effective for all patients. Treatment, moreover, is strongly influenced by couple and physician choice. So, a new drug with a different

mechanism of action ought to have considerable potential in this setting.

Uprima has a unique central mechanism of action, a novel delivery system, and a rapid onset. And we've studied it in 27 clinical trials, and we'll show you data to support our contention and conclusion that it's safe and effective treatment for ED in patients with and without organic disease.

This shows the scope of the 27 trials divided by classical FDA development phases, I, II, and III, and we've lumped I, II, and III down here. We've looked at the pharmacokinetics and metabolic rate, including in elders and those with renal and hepatic impairment. We've also looked at interactions with two antiemetics. We have done careful prospective studies in populations with these conditions: patients taking anti-hypertensives, five different classes, as well as short and long-acting nitrates.

We have looked prospectively in diabetics, in those who have consumed substantial amounts of alcohol quickly in conjunction with larger than recommended doses of Uprima, and we have a small group of patients with prostatectomy and spinal cord injury in whom we have just addressed safety issues, not efficacy issues.

The efficacy conclusions are based primarily on

three well-controlled cross-over studies that are unique in that they allow the patient to serve as his own control. In addition, there's a dose optimization parallel study in which patients participate in two phases. They adjusted the dose until they found the dose that was effective for them, and then they continued for the second phase, the so-called maintenance phase, at that dose, and we've drawn valuable information from that trial.

In addition, there are five long-term open-label studies and there are two first dose administered at home studies: one we'll be discussing today; the other, a larger study has just only recently been filed with the agency. We'll not be discussing that today because the agency has not had the opportunity to review those data.

I'd now like to turn the podium over to my colleague, Dr. Barbara Bopp, to go over the pharmacokinetics and metabolism.

DR. BOPP: Although apomorphine is synthesized from morphine by an acid catalyzed rearrangement process, the final chemical structure of apomorphine bears little resemblance to that of its precursor morphine. Apomorphine is not scheduled by the DEA. It was, indeed, specifically excluded from the list of opiate substances in the schedule 2.

Apomorphine is a relatively plainer molecule,

and if you examine its structure, it contains the dihydroxyphenethyl amine moiety that is common to dopamine and the other catecholamines.

Apomorphine was formulated as a sublingual tablet for use in the treatment of erectile dysfunction. This formulation was selected because it provided a means to obtain rapid absorption of the compound into the systemic circulation, thereby avoiding the first pass metabolism that had limited the usefulness of orally administered apomorphine for many, many years. Another potential advantage of the sublingual formulation is that it would minimize any possible effect of food on the absorption of apomorphine.

Depicted on this slide are the mean plasma concentration time profiles from the 2, 4, 5, and 6 milligram Uprima tablets that were administered to a group of 24 healthy young males in a crossover study, and you can see that the goal of rapid absorption of the compound into the systemic circulation was indeed achieved. Initially there is a very short lag time of about 5 to 7 minutes, which corresponds to the time necessary for the tablet to disintegrate and dissolve in the subject's mouth. Thereafter the plasma concentrations increase very rapidly and after Tmax, the apomorphine concentrations in the plasma also decrease very rapidly and fall to approximately

10 to 20 percent of their maximal levels by 4 to 6 hours after dosing. Thereafter, there is a somewhat slower terminal elimination phase which only occurs at very low apomorphine concentrations.

This slide summarizes the pharmacokinetic parameters obtained in the study I was just describing and also include those from a 1 milligram subcutaneous dose, which was included as a reference. Tmax, the time of peak plasma concentrations, averaged about 40 to 45 minutes with all of the sublingual doses compared to 20 minutes with the subcutaneous dose.

The peak plasma concentration, Cmax, averaged .7 nanogram per ml in the 2 milligram dose and increased to 1.9 nanograms per ml in the 6 milligram dose. Coefficients of variation, inter-subject variation for Cmax ranged from about 50 to 80 percent.

AUC also increased with the dose, with somewhat smaller coefficients of variation, about 40 to 50 percent.

Half-life was about 2 to 3 hours and was 2 to 3 hours and was similar with both routes of administration.

The next slide further illustrates the dose proportionality in the pharmacokinetics of Uprima. You can see that both Cmax and AUC increase in a linear and dose proportional manner. Compared to the subcutaneous dose, the bioavailability of apomorphine from Uprima was

estimated to be 16 to 18 percent across all doses. The 3 milligram dose, which is proposed for marketing, was not included in this study but does fall within the range for which dose proportionality has been established.

Some concern has been expressed about the variability in the pharmacokinetics of apomorphine. This slide attempts to give a little different perspective on that variability and presents a frequency distribution of the log normalized Cmax values from almost 250 subjects who received the 6 milligram dose of Uprima in our phase I studies. The higher dose is used in this presentation because that was the dose used in many of the phase I studies which were conducted early in the development of Uprima when we were evaluating the higher doses. A similar picture of variability could be found for the lower doses as well.

Mean Cmax in this population was 1.6 nanograms per ml. The median was 1.5 nanograms per ml. Approximately 65 percent of the subjects in this group had Cmax falling in these two bars between 1 and 2.7 nanograms per ml. You can also see that more of the variability in the Cmax values was associated with the low concentrations rather than the high concentrations.

Since the elderly are an important subgroup of patients with erectile dysfunction, we compared the

pharmacokinetics of Uprima in a group of 48 healthy elderly subjects, 64 to 82 years of age, compared to a group of younger male subjects 19 to 40 years of age. As you can see, the mean plasma concentration time curves in the two groups were reasonably similar. However, there were some minor changes.

Tmax was increased from about 45 minutes in the young subjects to 60 minutes in the elderly subjects, and Cmax was decreased by about 20 percent. Both of those changes were statistically significant. AUC, the area under the plasma concentration time curve, was increased about 10 percent in the elderly. That difference was not statistically significant. The upper bound of the 95 percent confidence intervals for the relative bioavailability suggested that a 30 percent increase in AUC was possible in the elderly. Half-lives were not different in the two groups. Since all of these changes in the pharmacokinetics of apomorphine are relatively small, no dosage adjustment should be needed for Uprima in elderly subjects.

The next slide summarizes some of the other aspects of the pharmacokinetics of apomorphine. It has a relatively large volume of distribution, suggesting extensive distribution into the tissues. This is consistent with its physical chemical properties as a

lipophilic basic compound.

Apomorphine is approximately 85 to 90 percent bound to the plasma proteins. This is true over a wide concentration range, far exceeding the therapeutic concentrations. It is primarily bound to albumin, with relatively little binding to alpha-1 acid glycoprotein.

There is minimal renal excretion of the parent drug and the compound is rapidly cleared by hepatic metabolism.

This slide illustrates the metabolic pathways for apomorphine. The compound, after sublingual administration, is predominantly metabolized by conjugation with either glucuronic acid or sulfate. Together these two pathways account for approximately 75 percent of the dose. Sulfation appears to predominate over glucuronidation, and apomorphine sulfate is the major metabolite found in the plasma and in the urine. It is not expected that either of these conjugates would have any pharmacological activity.

Apomorphine can also undergo N-demethylation, leading to the formation of norapomorphine which can then be conjugated with glucuronic acid or sulfation in a manner analogous to apomorphine. In vitro binding studies have suggested that norapomorphine has much lower affinity at the dopamine receptors than apomorphine itself. Unlike the catecholamines, methylation at the hydroxy groups is not a

significant pathway for apomorphine.

As you would expect, the formation of norapomorphine is mediated by the cytochrome P450 system. However, we must keep in mind that this is a relatively minor metabolic pathway and accounts for only about 20 percent of the dose.

We did a series of in vitro studies to characterize which of the cytochrome P450 isoforms were involved in the metabolism of apomorphine. Several isoforms can N-demethylate apomorphine, and the in vitro studies suggested that 1A2, 3A, and 2C19 were probably the principal isoforms involved in the N-demethylation of apomorphine.

We also did studies to evaluate the potential of apomorphine to inhibit the cytochrome P450 system, and indeed apomorphine can inhibit 1A2, 3A, and 2D6, but this inhibition was only seen at concentrations that were 1,000-fold higher than the Cmax from Uprima. Overall, the results of these in vitro studies combined with the extensive conjugation of apomorphine would suggest that it would be a very low potential for interactions of apomorphine with the cytochrome P450 enzyme system.

We also did a couple of specific drug interaction studies that Dr. Freston mentioned. Neither of the two antiemetics studied, Zofran or Compazine, had any

effect on the pharmacokinetics of apomorphine. The ethanol interaction studies will be discussed later by Dr. Fagan.

Finally, a very brief conclusion. After the administration of Uprima, apomorphine is rapidly absorbed and is also rapidly cleared from the plasma.

There is variability in the pharmacokinetics of apomorphine, but the clinical relevance of that variability can only be assessed through the safety and efficacy studies, which will be discussed later in this presentation.

No dosage adjustment is needed for the administration of apomorphine in the elderly.

Apomorphine is primarily metabolized by conjugation and has a relatively low potential for any interactions with the cytochrome P450 system.

Thank you. Dr. Heaton will now continue our discussion

DR. HEATON: Thank you. Good morning.

The current basis of management of erectile dysfunction stresses the importance of individualization in diagnosis and treatment. There is a significant imperative to make consideration of the partner and the environment in which the sexual interaction takes place. Management includes, first of all, the importance of lifestyle modification and education, and current treatment

emphasizes non-invasive therapies first -- and there is only one oral agent available -- and also the importance of patient and partner choice of therapy.

Uprima works by a central mechanism. It works through known pathways. It is a dopaminergic agent affecting serotonin and oxytocin, as well as nitric oxide pathways, starting in the hypothalamus and, importantly, progressing down the spinal cord where it induces normal response in the peripheral mechanisms.

In a summary of efficacy, the major issue is clinical considerations, and this extends further than mere rigidity and erection. It extends to the necessity to enable intercourse, to have a reasonable timing and onset of action, and to comply with the requirement that this must suit the choice of the couple and the physician.

Measurement of erectile dysfunction in clinical trials is difficult because there is no standard physical measurement. There is no accepted means of determining etiology in most cases of patients. In the past we have had the use of duplex ultrasound, pharmacotesting, and Nocturnal Penile Tumescence, but these are not used currently and routinely in clinical practice. We have, however, in this series of studies made good use of Nocturnal Penile Tumescence on recommendation of the agency.

In the later studies here, we have employed the International Index of Erectile Function, which you will see as an acronym IIEF several times, and the Brief Sexual Function Inventory, BSFI, which are validated clinical trial instruments that were introduced after the beginning of the Uprima program.

It's important to recognize that Uprima endpoints were determined after each dose administration, in other words, on every attempt, and these were evaluated from the home-use questionnaires. Primarily the data points looked at were the erection firm enough for intercourse based on the patient response, the erection firm enough for intercourse based on the partner response, and the intercourse rate based on patient and/or partner responses.

There's a significant advantage in using home-use questionnaires versus a retrospective questionnaire, in that this makes a direct assessment of efficacy at each dosing attempt. It does not require the patient to recall attempts after a 4-week period. It also does not involve averaging the function over a 4-week period.

The issue of how representative this patient population is can be examined by means of looking at the inclusion criteria into the studies. Heterosexual males aged 18 to 70 were admitted. An essential ingredient was

the patient's partner consent and agreement to go through with the study, and the partner herself was studied in addition.

The presence of erectile dysfunction was confirmed by the principal investigator and also was pinned by the ability to attain and maintain an erection firm enough for intercourse in more than 50 percent of attempts in the 3 months prior to study.

There should be some documentation that a patient was physically capable of attaining some sort of erection, as documented by an ability to attain an erection sufficient for intercourse on some occasion during 3 months whether by masturbation, morning erection, or nocturnal erection.

Nocturnal erections were tested with NPT testing, Nocturnal Penile Tumescence testing, having a threshold of only 55 percent rigidity on 1 of 2 nights for 10 minutes, which is significantly below that required for normal NPT performance.

Patients were excluded if they had uncontrolled diseases.

They should have clinically acceptable pre-study laboratory values, including hormonal values.

Diabetic patients were explicitly included, but they should not have had diabetic instability as evidenced

by serum glucoses above 250 or recent episodes of ketoacidosis.

Similarly, hypertensive patients explicitly were included, as long as they had not had blood pressures over 180 or diastolics over 100.

Smokers were included but only at a low rate of smoking because of the potential for smoking to mask the nausea adverse event.

Patients were excluded with a history of allergic reaction to morphine, and they were also excluded if they had any history of pharmacotherapy concurrently or within 3 months prior to the study.

The term "no major organic component" may be confusing, but this is what was used in the mid-1990's. We're more knowledgeable now, but explicitly this term was coined to exclude prostatectomies, spinal cord injury, Parkinson's disease, multiple sclerosis, where you know there's no chance of pharmacotherapy having a reasonable effect. And penile prothesis and penile deformity for the same reason. Also, it is logical not to treat patients with end-stage and unstable disease, so these two were excluded from the trials.

So, what kind of patient was admitted with these inclusion criteria? The patients were 55 years old. They had a weight of about 200 pounds, and they had had a

duration of erectile dysfunction of an average of 4.8 years. The racial split is shown for you there.

This is a representative patient population, and we'll demonstrate, by looking at subgroups with organic disease, baseline erectile dysfunction severity, RigiScan values, and the duration of ED.

The major subgroups represented within these trial patients included hypertension in 31 percent; coronary artery disease, 16 percent; and diabetes and the other listed organic diseases that were found to be coexistent with the patient's erectile dysfunction.

If we look at the baseline severity based on a psychometric scale, the IIEF, and look at all the phase III studies and classify them according to a classification system that has been published, patients were found to have severe grades of ED in 39.3 percent, moderate in 35.4 percent, with a small minority having mild degrees of erectile dysfunction.

How does this population admitted to the studies compare with other studies both of drugs and in the general population? In fact, we see that the duration of erectile dysfunction is comparable to what has been seen in other clinical studies. We see that the medical conditions represented are almost exactly overlapping, whether you look at a population study, the MMAS, or previous well-

conducted clinical studies, the Viagra studies.

This is a bar graph of the NPT data on admission to the study. The RAU units is a measure of how much erectile activity occurred, and we're looking at tip rigidity units here. In the light blue, normal subjects are shown with their average degrees of RAUs, and in the yellow, the Uprima subjects are shown. The Uprima subjects never achieved the same degree of RAUs as the average patients in the normal population, and if we look at a second cut of the similar data from the RigiScans, we find again that the Uprima patients have a significantly different profile of their rigidities at the time they're admitted to these studies. These are two different populations, in other words. The Uprima patients have significantly less rigidity than the normal populations.

We would conclude, therefore, from looking at the patients admitted to these studies, that this is a representative population because it is reflective of the ED population as a whole. It includes both organic and non-organic co-morbidities. It's clearly defined and is relevant to clinical practice. It's consistent with well-conducted previous clinical studies. It's consistent with the MMAS. It included patients with varying degrees of severity. The RigiScans were clearly abnormal, and the patient population studied does support the proposed

indication.

Let's look at some of the efficacy endpoints. Remember, this is applied on every attempt. The primary endpoint is the answer to the question, did you attain and maintain an erection firm enough for intercourse? The major secondary endpoints include the percentage of partners who answered yes to the same question, the percent of patients and partners who respond yes to the question about whether they were able to achieve intercourse, and time to erection. Additional psychometric data is available from the patient Brief Sexual Function Inventory and the partner Brief Sexual Function Inventory, as well as the patient IIEF.

These endpoints, therefore, are consistently stated. They are clear, they are relevant to clinical practice and human use, and they are rigorously applied.

We'll first look at the crossover studies in regard to efficacy looking at the primary endpoint. Then we'll look at some subgroup analyses and the validated questionnaires.

This is a complex diagram, but it represents a schematic of the crossover studies that were utilized in the phase III Uprima studies. Patients were admitted at baseline. They were randomized to one of assigned doses. Within those assigned dose streams, halfway along they

would crossover and take placebo or conversely take the drug. Every patient, therefore, was exposed to drug. Every patient was exposed to placebo. And each line of drug has its own placebo for direct comparison.

This crossover design is important. It's a very rigorous design. It was suggested by the FDA and provides a very powerful tool. It allows patients to be their own control. All patients are exposed to study drug, and it's an appropriate design for stable chronic diseases.

This is the first of a series of equivalent bar graphs that you're going to see, and I'll walk you through this slowly. This is the combined data from the phase III crossover studies. The percentage of yes responses to the question, is the erection firm enough for intercourse, is found in the y axis. The yellow bars are baseline scores at around 25 to 27 percent. The white bars are placebo scores at around 33, 32 percent, and with statistical significance at the p .001 level at both 2 milligrams and 4 milligrams, 45.6 percent respond yes and 54.4 percent respond yes at 4 milligrams.

If we look at perhaps the most important outcome for a patient, did the attempt actually result in intercourse, the numbers are equivalent. The baseline levels are there for you to see. A small increase in placebo and the Uprima effect is visible with clinical and

statistical significance. We've not broken down these data into individual trials because the data are exactly representative across all the trials and correspond to the combined data.

If we compare what this means in terms of intercourse rates with available published data in the oral field, we find that the levels of placebo response in the Uprima trials compare very equivalently with that seen in the Viagra trials. We see at 2 milligrams, the lowest dose of Uprima, we have a very comparable figure with what has been seen in the phase III studies published with Viagra. Similarly, at the higher applied-for dose, 51 percent of patients were able to achieve intercourse on a per-attempt basis. That's 51 percent of attempts would result in successful intercourse.

What about the partner responses which were an essential and integral part of the Uprima studies from the very first? They are unique to the series of studies that have been done on Uprima. A particular scale was developed, the partner BSFI. This was utilized and validated within these studies. Obviously, partner consent and participation were required, and I've alluded to that. It stresses the point that all along this has been recognized as a couple's issue.

The partner responded to the first data point

exactly similarly to the patients themselves, with a baseline level that's flat across doses, a small increase for placebo, and a statistically and clinically significant improvement for both 2 and 4 milligrams.

If you ask about whether this attempt resulted in intercourse, the patients respond in exactly the same way. In fact, it is very important to note that there was 98 percent concordance between the patient's response and the partner's response. They all agreed about what was going on. Men did not lie about their response rates.

We can do many primary endpoint subgroup analyses and we have some analyses available comparing patients with substantial organic diseases as co-morbidities and non-organic co-morbidities, hypertensive patients, diabetic patients, patients with coronary artery disease, patients who had also got benign prostatic hyperplasia, patients who used alcohol, smokers, the older groups, and with all degrees of ED severity. I'll show you only a few of these because these data are substantially overlapping.

This is the documented organic disease subgroup, and if you will recall the numbers that I showed you on a previous bar graph -- and recognize that the baseline level is exactly equivalent -- the Uprima result is just slightly reduced numerically but still has full

statistical and clinical significance.

Similarly in the subgroup of the older patients, those over the age of 65 with a slightly reduced n, they come in with an equivalent baseline level and they are able to have significant improvement in erections firm enough for intercourse.

The severity of erectile dysfunction is an important issue, and analyses were performed in a number of ways to identify that Uprima does have good activity in all levels of severity. We studied severity cuts by IIEF criteria. We looked at patients who had had absolutely no success at having intercourse during baseline, and we also looked at the most severely abnormal RigiScans to see what their clinical responses were.

This is the definition of severity based on the IIEF, and if we look at the most severe subgroup of this, those who had severe erectile dysfunction, which was fully 39 percent of the patients, baseline levels are as you would expect, extremely low, a small increase for placebo, statistical and clinical significance of both 2 and 4 milligram levels with Uprima.

Every patient was assessed for their baseline response, and some patients had absolutely no erectile ability during their baseline period. These are the patients we're showing here. So, you'll see no yellow bars

because the number is 0. However, taking this most significantly incapable group, you can see that both 2 and 4 milligrams had a clinical and statistical improvement in erections.

Taking a maximum tip RAU units on the RigiScan, less than 9.5 is a published way of identifying those with most severe degrees of erectile dysfunction using the RigiScan measure. This group of patients actually looks very similar to what we've seen before with statistical significance and clinical significance of both 2 and 4 milligram levels for improvements with Uprima.

We, therefore, feel that Uprima is demonstrated to be effective in patients with severe erectile dysfunction as evaluated by IIEF or baseline success rates or with those with profoundly abnormal NPTs. We've also shown that Uprima is effective in patients with mild or moderate ED.

There are other endpoints and some of these are very important. We're going to look at some home-use endpoints and some validated questionnaires.

The timing of erection is a critical factor in patients' appreciation of the treatment they're receiving. In this figure, which you may take a little while to digest, you'll find that Uprima acts in the same time frame as does placebo. The important thing is the erection is

firm enough for intercourse only 33.8 percent of the time on placebo and it is effective 54.4 percent of the time on 4 milligrams of Uprima. This is a natural time course in the context of the clinical trial, and these numbers are not dose related.

The patients' assessment of the treatment success was based on having success in more than 50 percent of attempts, and by these criteria, both the 2 and 4 milligrams, as many as 60 percent of patients were deemed a treatment success.

If we look at the percent of patients with mean intercourse attempts achieving satisfaction over 3, which is mostly satisfied, on their home diaries on a per attempt basis and who had an improvement over baseline, we see again an improvement that is clinical and relevant at both 2 and 4 milligrams.

If we look at the partners' response in exactly the same context, the numbers are very similar.

And if we look at the 4-point improvement in erectile function domain of the IIEF, which has been regarded possibly as the most statistically evident way of proving clinical validity, we see that the numbers are exactly overlapping what we have seen almost in all other methods of measurement and to an appropriate statistical value.

So, the phase III crossover studies show clinical significance at all dose strengths and in all subgroups whether you look at patients with coexisting organic disease or no evidence of coexisting organic disease or the subgroups of hypertension and so on.

There is robustness of the Uprima efficacy results demonstrated by the fact that this persists across a variety of home-use efficacy endpoints and is confirmed by the results of validated questionnaires.

There was an issue potentially about the clinical relevance of 2 milligrams. This is statistically superior compared with placebo in all phase III crossover studies for the primary endpoint and virtually all secondary endpoints.

It shows a 4-point improvement on the IIEF erectile function domain in 45 percent compared to only 27 percent of placebo.

It's statistically significant compared with placebo in patients with moderate to severe ED, as well as patients with a variety of organic diseases.

And intercourse rates, most importantly, increase from a placebo rate of 29 percent to 42 percent for Uprima at 2 milligram, which is a 13 percent increase, which compares favorably with the 16 percent increase seen with Viagra at its lowest dose.

Let's briefly look at the efficacy in diabetic patients. The diabetic patient subgroups were in a separate trial, crossover design, similar to that which you've seen previously, were studied at 4 and 5 milligrams. This was, as a whole, a more severely affected group than the previous combined studies, with 61 percent filling in the severe erectile dysfunction category.

If you look at the 4 milligram and the combined groups, both statistical and clinical significance is obtained with the effect of Uprima, and it's interesting to note that in this group of patients, the baseline level of function for the erections firm enough for intercourse is as you would expect, significantly lower.

If we look at the diabetics who took part in the phase III crossover studies and look at them as a subgroup, the efficacy of 2 milligrams and 4 milligrams is displayed here, again in a similar pattern to that which you've seen previously.

In conclusion, about efficacy in diabetic patients, this is similar to the results seen in other clinical studies where efficacy in diabetic patients is lower than that seen in the general population. The crossover study specifically suffered from a randomization imbalance, but statistically significant results were noted in the 4 milligram arm and both dosing groups combined from

the specific diabetes crossover study.

In the diabetic patients, who were naturally enrolled in the phase III crossover studies, efficacy improved approximately 10 to 20 percent over placebo in all dose strengths.

There was one parallel design study that I should report on here which is a slightly different structure from that we've seen previously. Obviously, the absence of crossover within each arm is there. So, there was a fixed dose at 5 milligrams, 6 milligrams, and a voluntary titration phase where patients were allowed to adjust their dose upwards.

These are the data from this study and obviously the subgroups will not have their own placebo group. But the placebo and baseline for the study as a whole is exactly as we have been seeing.

If we look at the dose optimization efficacy on the primary efficacy outcome, which is erections firm enough for intercourse, we see an overall of 53.9, and if we truncate it to the applied for doses of 2 and 4 milligrams, the efficacy is seen at 47.6 percent.

If we take the partners' view of exactly the same situation, the partners ratify that at 2 and 4 milligrams in the dose optimization structure, they're able to obtain erections at 48 percent.

And if we look at whether the attempt resulted in intercourse, this is inevitably a few percentage points lower, but nonetheless the statistical and clinical significance is fully maintained.

How about the long-term studies? An important issue of discontinuations. Obviously, the long-term studies were designed primarily to collect safety information, and within these studies, a number of factors clearly contributed to patient discontinuation such as lack of efficacy, which we would expect, adverse events, which we would expect. But there were the additional factors of the approval of new compounds, the arrival of new compounds on clinical prescription in the marketplace, and in particular Muse and Viagra both came out during this period.

These studies were long and had very stringent patient requirements because, you remember, all these data are acquired on a per-attempt diary completion, and there were, in addition, competing investigational studies.

Nonetheless, this is the complete data set for all doses for the 6-month progress, and you'll see that by the end of 6 months, 83.5 percent of the time patients had erections firm enough for intercourse. The n value has decreased from 1,000 to 426.

This shows that in short-term studies we know

that treatment success can be achieved in 50 to 60 percent of patients, and yet 80 percent of patients actually entered into long-term studies. So, we're going to expect a 20 to 30 percent dropout based on patients enrolled who had no efficacy.

Also, dropout rates were significantly influenced by adverse events, the approval of Viagra and other competing trials, and the burden of patient inconvenience associated with frequent visits. Despite this, over 42 percent of patients reached the 6-month time point in the long-term studies and demonstrated sustained and reliable efficacy.

So, if we look at all doses and look only at those patients arriving out at the last data point and project back, what their level of success was is demonstrated here. At the conclusion of the 6 months, they are achieving reliable per-attempt erections firm enough for intercourse at the 83.5 percent level. And if we limit this to 2 and 4 milligrams, which are the applied-for doses, this number shows that patients who are successful on 2 and 4 will maintain a very satisfactory level of function, around 88, 89 percent repeated attempts at intercourse, having erections firm enough for intercourse, on every occasion.

So, efficacy in the long-term studies

demonstrates that patients remain in long-term studies and will have sustained and reliable responses with erections in more than 80 percent of attempts.

Patients obtaining efficacy in long-term studies are similar to all Uprima patients if you look at their baseline success rates.

The overall efficacy conclusions can be stated thus. The clinical trials included patients who are representative of the general ED population. They were similar to those done in community studies and similar to those done in other clinical trials.

Uprima at 2 and 4 milligrams has been shown to be statistically and clinically significantly better than placebo in large scale controlled studies.

At 2 and 4 milligrams, Uprima has demonstrated a clinically relevant improvement in IIEF erectile function domain, which is a 4-point increase, in comparison with placebo.

The Uprima partner efficacy data has been shown to be almost identical to the patient efficacy data, with a 98 percent concordance.

And patients remaining in the long-term studies have substantial and reliable responses with erections in more than 80 percent of attempts.

It has been demonstrated that Uprima is

effective in all subsets of patients and they have been identified to you before.

Uprima efficacy has also been demonstrated in all severities of ED.

Uprima has been shown to have a rapid and natural onset of action.

And it has been demonstrated to have significance in all satisfaction and erectile function indices in the psychometric scales that you have listed.

Thank you for your attention.

DR. AZZIZ: Let's go ahead and take 10 minutes for questions.

DR. FRESTON: Mr. Chairman, I wonder if I could make an explanation to the committee about a change in plans. We have obviously deleted several slides from the projector that are before you. We wanted you to have a full set, but you can catch up to where the speaker is simply by flicking forward.

DR. AZZIZ: Thank you.

Questions from the panel, please. Dr. D'Agostino. And please identify yourself as you ask questions.

DR. D'AGOSTINO: Ralph D'Agostino.

Can I ask a question about the subsets of individuals, the diabetics, hypertensives, and so forth?

Given the entry criteria of the NPT scale, you do get these individuals but you get them -- for example, the diabetics. Do you get them at a more favorable position? You put the Viagra data up there. I'm just trying to see how I should evaluate it. It's not diabetics as one would necessarily recruit in a study, but it's diabetics who have a favorable NPT score. Can you say something about that potential confounder in terms of interpreting some of these results?

DR. FRESTON: I think the first point to make here is that we would not want you to compare our data against Viagra's in diabetics or anybody else. These are separate studies. That's just for your point of reference. We want you to compare the data versus placebo and baseline.

DR. D'AGOSTINO: Well, but still in terms of trying to understand what these rates mean, you unfortunately gave me the Viagra comparison. But forget the Viagra comparison. In terms of am I trying to evaluate what's going on in these subsets and trying to interpret them, given this added feature of the entry criteria. Can you tell me something about how I should look at that data?

DR. FRESTON: Yes. We'd like to call on Susan Buttler right there who can clarify that.

MS. BUTTLER: Hi. I'm Susan Buttler from TAP.

There might be some confusion that wasn't quite

conveyed to you in the 804 study which was our diabetes study. The specific study done in diabetics did not have NPT testing as a facet of it. It was not part of the inclusion/exclusion criteria. So, hopefully that addresses your concern.

DR. D'AGOSTINO: Well, I still have those subsets in the other studies, and I'm just trying to get a sense. I mean, it's going to lead, obviously, to the safety question also, what are these individuals like and what are you really measuring in terms of the ability of the drug.

DR. FAGAN: The exclusion criteria excluded people with systolics over 180 and diastolics over 100. The diabetics were excluded with fasting glucose, I think, over 240. So, only the most uncontrolled patients were excluded, ones that you wouldn't want to clinically treat with this drug anyway.

In addition, if you look at the 804 study at the baseline success rate of about 10 percent, you know that in fact you were getting patients with quite severe erectile dysfunction and severe diabetes.

DR. FRESTON: Our calculations indicate that our exclusion criteria excluded about 10 percent of patients with hypertension who failed to meet these entry criteria and about 5 percent of diabetics.

DR. GRABOYS: Yes, Graboys, Boston.

Two subsets that maybe you will be able to expand upon. One is the African American population because, as I saw the numbers, you're looking at a relatively small subset. And the second is the elderly patient population because in cardiology we're seeing a lot of these folks come in who are 76, 75, 80, 82, 83, and if you have any other information on that, I think it would be helpful.

DR. FRESTON: Well, it's been particularly difficult to recruit African Americans to ED studies. We're not the only ones who have had trouble. We don't understand it entirely, but it appears to be something cultural within that population. We can't get them in. We tried.

With respect to the elders, we had a cutoff because in keeping with the development of most drugs, one likes to span about 90 percent of the target population and then later go and focus on other minorities, be they children, not for this drug but for other drugs, or very elders.

Now, the data we do have above age 60, for example, shows enduring efficacy at that age and higher versus the younger.

DR. GRABOYS: 65 to 70, right? Because the

cutoff was 70.

DR. FRESTON: Yes.

DR. FAGAN: When we get some of the safety data in the specific interaction trials and patients on multiple cardiovascular drugs with a mean age of 67, that will probably be of some use.

DR. TIEFER: Dr. Tiefer.

Did you have any corroboration by the partner about these inclusion criteria? For example, when you required that a patient be able to have an erection sufficient for intercourse during the preceding 3 months, this was on the patient's report alone? And how often was it just a morning erection or a masturbatory erection?

DR. HEATON: This was on the patient's report and we noted in the studies, that there was extremely good corroboration in the patients and the partners in all of these studies. Susan Buttler has further information.

MS. BUTTLER: In all of our clinical trials, we involve patients and partners, and partners were required to come in not only for the informed consent process, but also to address the issue that you're talking about, whether or not the patient's data was corroborated. And it was in their medical histories and the information that was documented at the site.

In addition, if you look at the baseline

performance of patients, we knew what our patients were at baseline both on what the patient said at baseline and the partner's data. We probably did point out to you, but I'll mention it again. 98 percent of the patients' data and partner data correlated very well, so it was a high rate of correlation.

DR. TIEFER: Well, I understood that those were the data during the drug trial, but I wondered did you ask the partner about the preexisting situation and whether the patient was capable of erection, intercourse, masturbation, what, during the previous 3 months.

MS. BUTTLER: The primary information would have come from the patients, but the patients and partners were required to be at the visit to be assessed to be included in the trial. Whether or not partners would have disputed the patient's information in front of their partner, I can't really expand on, but we did make every effort we could to corroborate that data.

DR. KOWEY: I actually do not want to wander too far from my expertise, but I have a few questions about design.

One problem I have -- and the agency brought up in the briefing booklet -- was that patients should have naturally been unblinded from their therapy. The question is, when you're using a subjective questionnaire, can you

give us some idea of how much you thought there was unblinding in this study? I mean, from your perspective. There's no way to answer this question definitively, obviously, and I'm not sure there was unblinding. But it is an issue when you're using a drug that produces a fairly high incidence of nausea. So, could you answer?

DR. FRESTON: Let me start on that first. First, it was a very low incidence of nausea. 98 percent of the patients at 2 milligrams had no nausea at all, and I'll show you those figures. So, nausea was usually not present.

Moreover, we looked at the efficacy data in patients who experienced no nausea and it's the same as in those who experienced nausea. So, we don't think the presence of nausea, or any other effect, led to unblinding.

DR. KOWEY: That's 2 percent that didn't get nausea? That's not what that says.

DR. FRESTON: This excludes patients who had no nausea. So, we're just looking at the efficacy in patients who had no nausea, and you can see that it still stands up.

DR. AZZIZ: Dr. D'Agostino?

DR. D'AGOSTINO: I had a similar question. In terms of looking at the data, given the way you presented the data, I'm presuming that there was no interaction between the first and second period of the crossover. I'm

asking this, though I'm saying it in an affirmative way. But then the results for the first period and second period would be the same. So, even if the blinding was broken, it didn't sort of carry itself into the second period from people thinking they were on treatment, or now thinking they might be on placebo. Is that all true?

DR. FRESTON: Anthony Edmonds, statistician, will answer that right behind us.

MR. EDMONDS: I'm Anthony Edmonds from TAP.

Yes, we looked at sequence effects, and there was no evidence of carryover effects in the studies.

We also did an analysis of the first period only, if you would like to pull that slide. The results from this analysis are very similar to what we've seen before, so that even if there were a concern about this, these data are very consistent with the data that we've already presented to you overall.

DR. AZZIZ: Let's go ahead and continue so that we can give the sponsor sufficient time to present. We will have plenty of opportunity to ask questions, of course, in our deliberation later on as well.

DR. FRESTON: Thank you, Mr. Chairman. Let me now continue with the safety assessment.

In this safety assessment, I would like to provide an overview of the treatment exposures, the

dimensions of the exposure, and then we'll go on to address the overview of adverse events. We'll then concentrate on syncope, and obviously we're going to spend the most time in this very important area of hemodynamic effects. We'll take up syncope as part of that and we'll show you the results from some specialized prospective studies in diabetics where we had them hooked up to monitors and stressed them, and similarly with patients on antihypertensives, nitrates, and those given Uprima with alcohol. Then I'll come back to nausea and close with some additional safety issues.

Now, let me remind you of the database from which the safety assessment has been drawn. We have information on over 3,000 patients at all doses. I'll show you data at the 2 and 4 milligram dose drawn from just under 2,000 patients. It's important to realize that in this kind of treatment, every dose administration is a separate treatment event with its own efficacy parameters and its own potential for adverse reactions. Thus, we're going to be talking about 75,000 treatment exposures at all doses and 35,531 at 2 and 4 milligrams.

We have 461 patients who have been treated for at least 6 months and 127 treated for at least a year.

This shows the age distribution, coming back to your concern. Yes, there are not as many elders in there

as we'd like, but we have quite a few between 61 and 70.

Now, with respect to this population, I'll remind you again that it's very similar to the Viagra population and quite relevant to the ED population at large.

Most of the patients in the Uprima trials were taking other medications. In fact, 90.6 were taking other medications, and I've shown the different classes, major classes here. You can see that they are mostly drugs for cardiovascular diseases.

This shows the list of the adverse events that occurred in more than 5 percent of patients, more than 5 percent of patients, not more than 5 percent of dosage administrations, which is another issue we'll come to. The AEs in order are shown here.

The first point to make is that there is a dose-response relationship. At the recommended doses, for example, nausea, 15.5 percent of patients experience that, and at higher than recommended doses, it was higher.

The second point I want to bring out is that I've highlighted certain of these AEs because they tend to track together. They, in fact, form a cluster of AEs which serve as a useful prodrome for heralding the potential of syncope, and we'll come back to that.

And we'll do it right now. Dr. Fagan.

DR. FAGAN: I'd like to address four of the points raised by the agency.

First is syncope. Syncope is a sudden, transient loss of consciousness with lost of postural tone associated with spontaneous recovery as soon as the patient is supine. Published estimates are that syncope may occur in up to 40 percent of the population during their lifetime from a variety of causes.

There are cardiogenic causes of syncope which are primarily due to arrhythmias. We're more interested here in non-cardiogenic. Most common to this is vasovagal. Published estimates range from 50 to 80 percent of all syncope. It's biphasic. There's an initial phase of apprehension, anxiety, and increased heart rate, followed by a vasodepressor phase, with decreased heart rate, blood pressure, cardiac output leading to a faint or syncope. There's usually prompt resolution when the patient is supine. It's self-limiting, and usually accommodation occurs so that a stimulus that may produce vasovagal syncope one time usually doesn't. 60 to 85 percent of people who have syncope never have another episode. There are other types of noncardiogenic syncope, but they represent a small percentage and aren't really relevant here today.

Why do we think that the syncope with Uprima is

noncardiogenic? There are a number of reasons. It appears to be vasovagal because of the timing and the pattern of the syncope. There's a typical prodrome. There's an absence of association with evidence of cardiovascular disease, and we have data from Holter monitors.

We did a total of 1,702 Holter recordings beginning before and continuing for several hours after the doses of Uprima. This was in a total of 344 subjects and patients. We included in this patients in the diabetic study, patients in the nitrate and antihypertensive interaction studies, and patients in the alcohol interaction studies. Basically what we saw was a similar incidence of arrhythmias in the patients when they received Uprima compared to when they received placebo or prior to receiving Uprima.

What's the overall syncope in the Uprima studies? I'll make two points here. One is that it's obviously dose related, going from .2 percent at 2 milligrams to 2.1 percent at 6 milligrams. There appears to be some reduction when the dose is optimized, although it certainly isn't eliminated.

We looked at a number of demographic characteristics to try and see who might have syncope and who might not. There were no associations with that long list of concurrent medications that Dr. Freston showed you.

There were prodromal symptoms. They're listed here, and any one or more of those is considered to represent the prodrome and would be things that you would warn the patient about, about possible impending syncope.

How well does it work? Well, whether you look at all doses or just 2 and 4 milligrams, 85 percent of the patients of the syncopal episodes were associated with the prodrome at that administration. Whereas, with 2 and 4 milligrams, less than 2 percent of administrations without syncope had the prodrome. So, about 85 percent had one or more prodromal symptoms and rarely did the prodromal symptoms come without syncope. So, it distinguishes quite well.

Of the nearly 2,000 patients who received 2 and 4 doses of Uprima, we had 13 episodes of syncope. That's about 1 per every 2,700 doses. What does that mean? Well, let's say the average couple who chooses to use Uprima uses it twice a week. That's 100 times a year. So, that couple can expect 1 episode of syncope in 27 years.

Now, if you go back to the development of this drug, the early syncopal events were unexpected, and because they were unexpected, there were some strong reactions on the part of the physicians. There were some interventions and there were two injuries associated with these syncopal episodes. However, since that time, with

education of the patients and the physicians basically telling them to lie down if they have any of the prodrome, there have been many fewer interventions and no serious injuries. And there were no sequelae in the two injuries that occurred early on.

The incidence of syncope is 0.6 percent of patients having syncope at some time if the dose is optimized to 4 milligrams. It's 1 in 2,700 doses at 2 or 4 milligrams. 85 percent of the patients will have the prodrome which will warn them of the possibility of syncope, and all of the syncopal episodes occurred within 1 hour of dosing. So, past that time, they should be relatively safe.

In the context of the usage and instructions to remain recumbent, we should have a further reduction in the risk of syncope, and that's been evaluated in a large study with nearly 1,000 patients that was submitted to the FDA but has not yet had a chance to be fully evaluated.

Now, in conclusion, the syncope question. The patients who have a syncopal event will have a vasovagal prodrome to warn them. Most of them will be recumbent, which means that they won't have syncope in the vast majority of circumstances. They will be accompanied by a sympathetic partner, and they're unlikely to be doing anything dangerous like driving a car or operating heavy

machinery.

For context, let's think about a few other marketed drugs that have the same or higher rates of associated syncope, drugs that are used for non-life-threatening situations: bupropion, used for depression and smoking cessation; alpha blockers for BPH; and Muse for erectile dysfunction.

How about hypotension? The mean maximum decrease may not be familiar to everyone here. Basically this is a way of looking at the worst case as far as decreases in blood pressure. You take each individual patient across multiple time points, find the one point where they had the greatest decrease in pressure. You do that for each patient and average those numbers. Obviously then the averaged maximum decreases are going to be much more than you'll see on the average at any point in time.

Placebo then will tell you what the random variation of blood pressure is in the absence of any pharmacologic intervention. Now, those of us who do a lot of ambulatory blood pressure monitoring or have patients who bring in lots of home blood pressures, know that there's a great deal of variability throughout the day in response to meals, anxiety, cold, smoking, and that this is something that is really not any problem for the patient, although many times they're surprised when they see how

much they vary.

This is the mean maximum decrease in blood pressure from the third phase III crossover study looking at supine and standing blood pressure and at the recommended doses of 2 and 4 milligrams. There are no statistically significant differences between placebo and Uprima, and in fact, there are totally clinically insignificant differences as well.

If we look over time with 2 milligrams, there's no difference.

If we look at 4 milligrams, there's no difference, supine or standing.

How does this look compared to Viagra? This is as good as a comparison as we can do, but there are some differences. The prime thing here is that we're looking at 2 hours spread out on this scale with Uprima, and the first 2 hours with Viagra just fall in here. Basically we see no statistically significant decrease in these 150 or so patients with 4 milligrams of Uprima, and numerically it's only about 4 millimeters of mercury, whereas we have about twice that decrease with the maximum recommended dose of sildenafil.

How often did hypotension occur? You're going to get a chance to see some of these episodes in detail. They're quite infrequent at 2 milligrams, and when the dose

was optimized as high as 5 milligrams, there were no events. When you optimize up to 6 milligrams, 2.5 percent of the time. None of these patients had injury. None had sequelae, and the only thing that they had to do was lie down for a period of time, which was variable.

In addition, these events are essentially all vasovagal. It's not that this drug is a direct vasodilator and decreases everybody's pressure. In most people, it does absolutely nothing, and only the ones who have this vasovagal effect have a decrease in pressure. In fact, 52 of the 53 who had hypotension had the prodrome. So, the prodrome predicts hypotension just as it predicts syncope.

In summary, we didn't see anything at 2. We didn't see anything at 4. I didn't show you 5 milligrams in the interest of time. There were statistically but not clinically significant mean decreases. The decreases you see with the highest marketed dose of Viagra is about twice what you see in the supine position, both supine, with the highest proposed dose of Uprima.

Less than 5 percent of patients reported hypotension overall, and 98 percent of them had a prodromal warning.

What about safety in diabetics? These are patients who have high incidence of cardiovascular disease. It's just as likely that you'll have a myocardial

infarction if you have diabetes and no known coronary disease as if you've already had a myocardial infarction. We also know that their autonomic nervous systems are not all that they might be in a younger, healthier patient, and therefore, conceivably these patients could be at higher risk.

But in point of fact, what do we see as far as the mean maximum decrease in blood pressure with Uprima compared to placebo? Absolutely no difference. As you'll see later, this and other higher risk subgroups actually have numerically less adverse events than younger, healthier patients, and you'll see that in detail a little bit later.

So, the adverse event profile, which I haven't shown you, was very similar to what we see in all the phase III trials in all the patients. Remember that this was done at 4 and 5 milligrams, so half the patients were higher than a recommended dose. When we looked at the Holter monitors, we saw no abnormalities that could be attributed to Uprima, and there were 3 of 205 patients who had syncope.

With regard to nitrates, well, we all know that in the field of ED that there is certainly concern with nitrates and with other hemodynamic interactions. Because of this, a trial was designed to look at pretty much the

worst possible case. We took patients with significant coronary disease -- I'll show you some of the other things -- and then subjected them to a much worse situation than they might otherwise be subjected to clinically. So, at 5 milligrams of Uprima, above the recommended dose, 162 patients. We did our pressures with a Dinamap so we wouldn't miss any, if anything exciting happened. We did Holter monitors in all these patients and recorded adverse events.

How was this tougher than the normal situation? It's a higher than recommended dose of Uprima. There were multiple concurrent drugs. 18 of the 20 patients on short-acting nitrates were on at least one other drug that could lower blood pressure and about 16 or 17 were on two or more drugs that could also lower blood pressure. In the long-acting nitrate group, it was similar. And then we made them stand up and down and stand up and down and up and down, which as we know being in the standing position is where you get the blood pressure drops, it's where you get the symptoms. And the treatment is to stay lying down. So, we did exactly what you should tell your patients not to do just to see how bad we could make it.

They were an older group, average 67 years, a variety of other agents. Some of the short-acting patients were on not only antihypertensives but long-acting nitrates

at the same time, and they had just a few other things wrong with them: hypertension, previous myocardial infarctions, previous revascularization, stroke, diabetes, congestive heart failure, and atrial fibrillation. So, I would submit that these are about as sick a patient as you want to prescribe a drug for ED.

Mean maximum decrease in pressure. Basically the only place we see a statistically significant difference is in the standing position with either the short- or long-acting nitrates.

When we look at the time course, we of course see this very nice response to sublingual nitroglycerin, which is very obvious. There's no statistically greater decrease in the combination of nitroglycerin and Uprima which is shown in the magenta here. The nitroglycerin was dosed at this point in time; Uprima was dosed here. So that we could see the maximum pharmacodynamic effects based on when we knew that the Cmax would coincide.

When we look at the long-acting nitrates, we see that there is in fact some statistically significant difference. If you remember how much variation we saw just with placebo, about plus or minus 9 millimeters of mercury from baseline in healthier patients, then you see that that's about how much of a decrease, although obviously this is systematic and not random, but it's within the

range that we often see clinically. There was a significant decrease in diastolic, but it's a matter of about 3 or 4 millimeters of mercury. And there's no statistical or clinical decrease in blood pressure past 1 hour.

Now, how does that compare to Viagra? These are obviously two different studies, and there are some differences. In fact, this comparison is loaded in favor of Viagra. How so? We have higher than a recommended dose of Uprima. We have a mean middle recommended dose of Viagra. These patients are standing. The Viagra patients were sitting. The timing is a little bit different. You just saw this. And we know that out here is where Uprima was dosed, nitroglycerin here, and there's the decrease. Viagra was dosed here, sublingual nitroglycerin here. You see that the decrease due to nitroglycerin is pretty much identical in the two studies, but there's a much greater decrease in systolic pressure of about 27, 28, 30 millimeters of mercury with the combination of sublingual nitroglycerin and Viagra.

The other thing you'll notice is that by 1 hour, the pressure with sublingual nitroglycerin -- this is actually an hour and a half after Uprima -- that it's back to baseline, whereas here we're still very much below baseline and don't really seem to be increasing very fast,

although we don't really have that data.

If we look at diastolic blood pressure, we see exactly the same thing. No difference from placebo with Uprima. Big difference with Viagra. And a decrease about as 6 times as large with the combination there as with this combination.

If we look at the long-acting nitrates -- again, you've seen this graph before -- you know that a few of these points are statistically significant but they're not very large. You see that there's a much larger -- nearly 45 millimeter mercury -- decrease when Viagra is given to patients receiving a long-acting nitrate. Here again, we're using a higher than recommended dose of Uprima and a median dose of Viagra. The doses of long-acting nitrates were not identical, but they were quite similar overall.

If we look at diastolic blood pressure, we see exactly the same thing: 3 or 4 millimeters of mercury here, gone in an hour and a half; 23 millimeters of mercury here and still persisting after a couple hours.

So, in conclusion, as far as nitrate and Uprima interaction, we had no syncopal events. We had no Holter changes that we could attribute to Uprima. We saw them on nitroglycerin alone. We saw them before Uprima, but nothing that was specifically with Uprima and not at other

times.

The blood pressure decreases with Viagra were considerably larger and longer in duration than those with Uprima.

The patients who did have clinically significant decreases in blood pressure also had prodromal symptoms. So, again, they would have been warned and, in fact, had no syncope.

We believe that with adequate patient instruction, basically reinforcing what you tell everyone, that Uprima can be administered to patients taking nitrates given some degree of clinical judgment.

Now, fully 30 percent of the ED population can be expected to be taking antihypertensive drugs, and we can think of certainly pharmacodynamic interactions. Drugs that lower blood pressure, given together, usually lower it further. So, the same trial included five different classes of antihypertensives. I'm not going to show you the time course because nothing happened. There's no statistically or clinically significant differences here except this statistically significant difference which is because on placebo there was abnormally low variation in that group.

So, in conclusion regrading the antihypertensives, there's no clinically significant mean

changes from baseline in blood pressure or heart rate with the five different classes. The adverse events, which I haven't shown you, were similar to other Uprima I, II, and III studies. There were no Holter monitor changes which we could attribute to Uprima except some that were attributable to a vasovagal effect, sinus pauses, rare instance, secondary heart block. Those were occasionally associated with adverse symptoms and sometimes were totally asymptomatic.

Only 1 of the 122 patients had syncope. That patient was on a beta blocker. Again, that's not a higher incidence than we see with 5 milligrams in the other trials.

What about alcohol? In an early phase III trial, there was a syncopal event in a patient who drank a whole lot. He liked lots of things, different kinds of hard liquor, beer, all at once, and because of this syncopal event, it was thought that it would be appropriate to conduct some alcohol interaction studies.

In the first study, we used a relatively high dose of Uprima, 5 milligrams, and a relatively high dose of ethanol. This corresponds to about 4 to 6 ounces of 80 proof hard liquor depending on body weight of the person.

There were two serious adverse events. They were serious adverse events by virtue of being admitted to

the hospital. They were not serious because they had infarctions or strokes or any sequelae, but they made that definition because they were hospitalized.

But because of this, it was decided to start out with a little lower dose of ethanol. So, 6 milligrams Uprima, 0.1 gram per kilogram of ethanol. No SAEs. There were 4 patients who had nausea and pallor and were given oxygen as a precaution, but they were not hypoxemic.

Further trials were then conducted with 6 milligrams of Uprima and .3 and .6 grams of ethanol. I'm going to skip the .3. But the design was exactly the same, double-blind, randomized, all the good things. There were three periods. In each period, the patient on all 3 days got Uprima or a placebo tablet, and on the last day they got either ethanol beverage or a placebo beverage.

Now, the other thing that's different about this third day is that only on the third day, when they got the combination, they also stood up and down, stood up and down, and had bloods drawn. That didn't happen on days 1 and 2 when we were looking at Uprima alone. So, when we see some increased adverse events, there's really a confounder here.

Again, we wanted to see what was the worst thing that could happen. So, we had a higher than recommended dose of Uprima. We had a high dose of ethanol.

It was consumed within a short period of time. We stood them up and laid them down and stood them up. We drew blood frequently. Also we confirmed that the time of peak alcohol concentration was also the time of peak apomorphine concentration.

What do we see? We see that only in the standing position do we see any differences between ethanol alone and ethanol plus Uprima. Those of us who have dealt with this know that ethanol in fact is a vasodilator and does lower blood pressure to some extent.

This is the low dose study and I won't bother with it.

With the higher dose study, we do have during the first hour some decreases in blood pressure on Uprima plus ethanol that are greater than ethanol alone or Uprima alone. But again, this only extends out to the first hour. It's relatively small decreases in pressure. Again, the ones that really cause this decrease are the ones that have vasovagal events and hypotension related to that. The ones that don't have those events don't really decrease, except of course, you can see that ethanol -- because this is the two ethanol groups -- does lower blood pressure and that does persist for some period of time.

If we look at diastolic blood pressures, we see exactly the same thing. Supine we see nothing. Standing

we do see a few millimeters of mercury difference.

Adverse events. We could go into a lot of detail here and you'll hear more in the FDA presentation. It's true that the adverse events were higher with the combination, but this was also the day that they didn't get to just lie supine the whole time. They had to be stood up frequently and they got needles stuck in their arms frequently.

So, what were the instructions to the patients in the clinical trials? The instructions were what you see here. They should limit themselves -- it says minimal. I'm not sure that is minimal, but this is the amount they were told to limit themselves to during the 6 hours prior to study medication, not prior to 6 hours, but during that 6 hours.

What do we see if we look at patients in the crossover trials who have 1 or more drinks a day versus people who don't drink at all? Is there a difference in adverse events? No.

So, in conclusion, the subjects were stressed with high doses of Uprima, high doses of alcohol, standing up and down, and getting stuck with needles. There were mean decreases in standing blood pressure greater with Uprima plus ethanol than ethanol alone during the first 60 minutes, but not beyond that. There was an increased

incidence of adverse events. There were some probably clinically insignificant changes in pharmacokinetic parameters, and when we look at the phase II and III trials, we don't see any differences in adverse events, including syncope.

There were no Holter monitor changes due to Uprima except some that were due to vasovagal effects. They went along with the symptoms, and there were no increased vasovagal changes with the combination compared to Uprima alone. So, that didn't appear to be enhanced by adding the alcohol at all.

Now, Dr. Freston is going to wrap it up.

DR. FRESTON: Thank you, Dr. Fagan. We're just going to discuss a few extra AE considerations, adverse event considerations, and then summarize.

This shows the frequency of AEs shown along the left again as a function of dose, 2, 4, 5, and 6 milligrams. Again, I'll draw your attention to the fact that nausea was the most common AE and there was a dose response for it and virtually all of the other AEs, which of course is the main reason why we're recommending 2 and 4 milligrams, particularly with dose titration.

About nausea, we had the opportunity, after each dosing, to ask patients if they experienced nausea and we did. If they did, we asked them to grade it mild,

moderate, or severe.

We draw your attention to the 2 milligram dosing. Nausea was very uncommon, occurring in only about 2 percent of all patients treated at that dose. If we look at the patients who experienced severe nausea, there were none in the 2 milligram dose.

Let's look now at the 4 milligram dose. Again, 80 percent of the patients had no nausea at all. If we concentrate on those having severe nausea, it turns out to be 0.2 percent.

If we analyze the data with respect to what are the chances of having nausea with any given treatment episode, I remind you that there are about 35,000 treatment episodes at the 2 and 4 milligrams. The incidence of nausea per administration was 2.2. Using the theme that Dr. Fagan just sounded about what does this mean in the real world of 2 treatments per week for a year, that means that there would be about 2 episodes of nausea in a year at the 2 and 4 milligram dose and they would be mild. Incidentally, we did the same analysis for vomiting. The incidence there is .2 percent. In other words, there might be 1 episode of vomiting in 5 years.

Now, the effect of nausea also wore off with the repeated administrations. We can see that here and in other ways. This shows the incidence of nausea with the

first dose and with successive doses. We've included only those patients who took at least 8 doses or had at least 8 treatment episodes. So, you can see after the first couple of episodes, the chance of having nausea on any successive dose is well under 3 percent.

So, to summarize the nausea, there was no impact on efficacy. We looked at the data in patients with nausea and those without. It was the same. We showed you those data earlier. It was mostly mild. There was infrequent antiemetic use. I've provided that in your handout. It's not in the slide to save time. Very few patients were discontinued because of this, and the incidence declines with continued use.

Now, the FDA briefing document addressed patients and described them in detail who had suffered adverse events, and they were described whether or not they related to the drug, unrelated, or due in fact to placebo. They were all described there. For the most part, they involve syncope and hypotension, and Dr. Fagan has already dealt with those.

I would like now to briefly address the serious adverse events, the SAEs, and the reasons for premature termination.

I'd like to clear up a misunderstanding. In your briefing document and I believe on one of the slides

that I saw from the agency this morning, it says that the definition of SAEs was changed during the trials. That's not in fact true, and we apologize for that misunderstanding. This is the definition of AEs that was used by TAP throughout all of the Uprima trials. It includes all of these facets and conforms to the FDA and ICH SAE definition.

What happened was in some of the reports and summaries, certain parts of this definition were not mentioned, but I can assure you that all of the SAEs were, in fact, reported to the agency.

Now, what were they? Well, the agency briefing document described 49 patients with SAEs. However, a number of these were described twice and even three times. If we back those out of the calculation, we find that there were 30 patients who may have had SAEs. The agency felt that 21 of these were possibly related to the drug. The investigators themselves thought just 15 were, leaving 6 unresolved, and I'd like to just run through those very briefly so that you can understand the nature of these disputed cases.

The first is a 59-year-old man who had taken 4 doses at 2 milligrams. One day after taking his fourth dose, he suffered an MI for which he was hospitalized. The investigator felt that since this drug was long gone from

his body and he had an MI a day later, that that was unrelated to the drug. We agree.

The next case was a 68-year-old man who had taken 10 doses of 2 milligrams. 12 to 18 hours later, he developed unstable angina, was hospitalized, worked up, treated appropriately. He had had angina for some time, and in fact had had an MI 8 months before. He completed the study and in fact took another dose. The investigator felt that that was unrelated. We agree.

The next case is a 59-year-old who, after his second dose -- and we're not sure when he took his second dose. It seemed to have been sometime within the previous 3 days or so, but we're not positive. In any case, the patient was a passenger in an automobile that was involved in an accident, and he was banged up by the accident and discontinued from the study because of the disability related to the accident, not of course to Uprima.

A 56-year-old person had a 4 milligram dose, 4 days later developed a classical case of viral gastroenteritis. It was treated appropriately.

A 51-year-old person after the ninth dose, 4 and a half hours, developed lightheadedness, nausea in the context of a febrile illness and an episode of bigeminy. That patient was hospitalized. He had previous episodes of bigeminy before, and the febrile illness resolved. And the

investigator felt that that was unrelated to the drug.

And finally, a 49-year-old person who had taken 15 milligrams at the 5 milligram dose had diaphoresis, dizziness, nausea, and syncope 90 minutes after taking the dose. He was taken to the hospital, in fact had hypoglycemia for completely inexplicable reasons. Haven't seen it before, haven't seen it since.

Now, these are the cases then that we described in the NDA. There are 15 cases of serious adverse events conforming to that specific definition that I set out. Three of those occurred at the 2 and 4 milligram dose, and all of those were the syncope cases. You can see that the remaining 12 occurred at the above recommended doses.

Incidentally, for your reference, there were also a lot more SAEs that were reported that were not associated with the drug.

Turning now to the final issue of premature terminations from the study, this shows the reasons why patients discontinued prematurely. The reasons are listed along the left. You can see that there was no single overwhelming reason for discontinuing. In fact, the cases were distributed among all of these different reasons, including adverse events, noncompliance, lack of efficacy, patient request, and partner request, and so on.

Let me draw your attention here. There was one

discontinuation due to an adverse event at the 2 milligram dose, that is 1 percent. There are four cases. And 5 percent of the whole were discontinued because of an adverse event in the 4 milligram dose. So, these were unusual at the recommended doses.

We're now looking at the discontinuations for adverse events specifically to see what the causes were. Nausea was the most common AE, obviously. You can see that very few patients were discontinued because of nausea. Obviously, very few in addition were discontinued because of syncope.

Now, we looked at subsets of all the patients, the special populations with respect to their AE profile, and we found no differences between them.

We also looked at subgroups in detail particularly hypertension, diabetes, and patients with coronary artery disease. Now, this is a little bit complicated, but it's a very important slide so I'd like to walk you through it.

We show the AEs down the left. Here we show the patients with hypertension and compared against those without hypertension. So, let's just focus on that for a moment. We show the n's and the percentages. You can see that those with hypertension didn't have more nausea than those without. And that holds as we go right down the

column.

Going now to diabetes, those with diabetes had 11.7 percent nausea. Those without had 15.9 percent.

Coronary artery disease. Those with CAD, 15 percent had nausea, 15.4 percent did not.

In other words, we consistently don't see any more AEs in these special groups and numerically sometimes less.

Now, we have tried our best to address the issues raised by the agency in which they requested your special attention. I am now going to skip forward. I've provided in your slide booklet a summary of each issue. We have covered all of them, but they're there for your reference so you can get to them quickly during your discussion period. They are set out like this. Each issue is followed by a one-page summary of what we've presented to you today, and it goes right on through the efficacy in diabetics, the key points, why patients were discontinued in long-term studies. The hemodynamic data are summarized for you there for your convenience. The nitrate interaction data, the summaries are there for you, and finally the information you need about the alcohol interaction story.

So, Mr. Chairman, ladies and gentlemen, I'd just like to summarize.

Erectile dysfunction is a common condition with multiple etiologies and important health consequences according to the NIH. It's associated with a number of diseases and conditions, as we have described.

Drugs with different modes of action are useful in this situation to deal with different mechanisms of action. Current therapies are obviously limited. There's no single drug that works for all patients. Each drug has its own unique adverse event profile and there's no ideal treatment for any patient. And all of the drugs work by a peripheral mechanism.

Treatment is strongly influenced by couple and physician choices.

So, new drugs with a different mechanism of action ought to be of potential benefit in this setting. Uprima does, in fact, act through a unique central mechanism. Its efficacy has been evaluated using consistent and relevant endpoints after each attempt, plus unique supporting partner data and utilization of RigiScan data.

The Uprima trials represent, therefore, a significant advance in the state of the art of ED clinical trials. The efficacy of Uprima 2 and 4 milligrams was demonstrated in all the studies with all endpoints in patients with all of those different concomitant diseases

and in patients with no known organic disease.

Both patient population and successful intercourse rates were similar to those seen in the Viagra trials.

The safety of Uprima has been evaluated in 27 studies involving over 3,000 patients and over 75,000 doses. The duration of treatment has exceeded 1 year in 127 patients, and 461 have been treated beyond 6 months at the time of the NDA. Of course, we have much more data now.

The AE profile was similar in patients with all of these concomitant diseases.

Uprima can be taken with alcohol, provided patients don't exceed the recommended levels. Uprima can be taken with nitrates, using the recommended patient instructions.

There were no pharmacologic interactions between Uprima and five different classes of antihypertensive drugs.

There were no deaths or major illnesses like MIs or CVAs.

Nausea was the most frequent adverse event occurring in 15.5 percent of patients at the 2 and 4 milligram dose and in just 2.2 percent of treatment administrations. Accommodation occurred to nausea.

Syncope occurred in 0.8 percent of patients at 2 and 4 milligrams and only 0.4 percent of treatment administrations and was minimized by titration of dose. The syncope was nearly always associated with a prodrome or early warning system.

In conclusion, Mr. Chairman, ladies and gentlemen, Uprima is a safe and effective treatment for ED in patients with and without known organic disease.

With respect to risk-benefit, at the 2 milligram dose adverse events were in fact rare and efficacy was demonstrated in all phase III studies. At the 4 milligram dose, also there were few adverse events, and the efficacy was particularly robust. And there were no deaths, MIs, CVAs. Therefore, the risk-benefit is clearly in favor of Uprima.

Uprima is a useful and needed addition to the treatment of ED because it has a unique central mechanism of action, a novel delivery system, given sublingually, which allows it to work rapidly and consistently in about a half an hour.

Patients, couples, and physicians will have another choice of a safe and effective noninvasive drug with a different mechanism of action.

Thank you.

DR. AZZIZ: Thank you very much.

Since we are a little bit past time, I'd like to hold questions until we return, and then we'll have the FDA staff presentation. Let's take a break. Thank you. Let's just make it 15 minutes.

(Recess.)

DR. AZZIZ: I'd like to restart.

A point of information. We're simply going to move up the lunch time by 30 minutes, meaning we'll have lunch starting at 12:30 or as soon as there's time, and then reconvene at 1:30. So, we'll still have one hour for lunch.

Before we begin, Dr. Raczkowski would like to make a few comments.

DR. RACZKOWSKI: Good afternoon. I'm Dr. Victor Raczkowski from the FDA.

Both Dr. Freston and Dr. Fagan in their presentations made a number of direct comparisons of Uprima with other agents for erectile dysfunction. They made these comparisons numerically in terms of both safety and efficacy.

FDA believes that such data are very difficult to interpret because no direct comparison trials have been performed between Uprima and other agents. There's the potential that different patient populations have been studied, and oftentimes these were based on small studies.

So, what we are asking the advisory committee to do today is to focus on the safety and efficacy data that is before you for Uprima on its own merits. You will notice that none of the FDA slides or any of the FDA questions have references to comparisons with other treatments for erectile dysfunction.

DR. AZZIZ: Thank you.

I think we're going to start out with Dr. Shames.

DR. SHAMES: Welcome to the first meeting of the Urologic Subcommittee. Thank you for the work you have already done and perhaps the more difficult work you're about to do.

My name is Dan Shames. I'm the team leader for Urologic Drugs in the Division of Reproductive and Urologic Drug Products.

During my brief presentation, I will mention the FDA presentations you will hear this morning. I will make a few remarks regarding the etiology, diagnosis, and treatment of ED, and I will then offer you six points to consider while listening to the FDA presentations.

The FDA presentations and presenters are Dr. Jarugula, who will discuss pharmacokinetics and drug alcohol interactions. He is from the Clinical Pharmaceutics and Clinical Pharmacology Section.

Dr. Hirsch, who is a urologic medical officer, will discuss clinical safety and efficacy.

Dr. Mann will discuss drug-antihypertensive interactions and also summarize.

Historically the etiology of erectile dysfunction has been classified as either psychogenic or organic. We now recognize that this classification system is oversimplified and that many patients have a combination of psychogenic and organic factors to explain their erectile dysfunction.

The Nocturnal Penile Tumescence test, or NPT, evaluates erections that occur during REM sleep. This test, although somewhat controversial, has been used to assure that no major end organ or penile pathology exists which may prevent development of a normal erection. It is thought that men who have erectile dysfunction from a variety of causes, such as peripheral vascular disease, will have diminished nocturnal penile tumescence activity.

In the majorities of the studies submitted by the study sponsor, a normal NPT or at least erectile activity and therefore the potential for normal erections was required for study entry. The men with erectile dysfunction entering into the study were thought by the study sponsor to have no major end organ disease and no major organic etiologic component of their erectile

dysfunction. This subpopulation of ED patients with normal NPTs does not represent the general ED population.

Dr. Heaton did an excellent job of reviewing ED in general. I just would like to reiterate at this point, we have two products on the market, intracorporeal, intraurethral treatment, and in 1998 an oral treatment was approved.

I would now like to place for your consideration six points to use while you're reviewing our presentations.

The first point to consider relates to the select population studied in these trials. Patients with no major organic component who were in generally good health were included. Patients were excluded from the trials if they had any significant medical conditions that could adversely affect their health. These patients in most of the trials had NPTs which demonstrated erections. They must have had erections within the last 3 months, and they must have had up to 50 percent successes during the baseline period.

You should next consider the interaction with alcohol and apomorphine. Apomorphine has been used as a behavior altering agent in alcoholics most likely due to its emetic properties. Patients in these trials were cautioned to limit alcohol intake "to a minimum" for the 6

hours prior to dosing. In addition, you should pay attention to the alcohol interaction remarks that will be made by Dr. Jarugula.

The next point we would like you to consider is, are these trials appropriate to predict real-life simulation? We know that clinical trials never simulate real life, but we believe that the design of the trials here performed may have resulted in an underestimation of the adverse events that would be observed in the general ED population.

The treatment periods were generally 1 month in duration, which is a relatively short period in which patients were exposed to the drug. The first dose and increases in doses were administered in the office. This meant that there was opportunity to treat adverse events, perhaps preventing more serious consequences. Remember, the sponsor proposes at-home dosing if Uprima is approved for marketing.

Food intake was restricted in the 1 hour right before dosing. No large meals were allowed during that period of time. This may have reduced the incidence of nausea and vomiting.

Alcohol intake was restricted, as mentioned, to a minimum within 6 hours of dosing.

Various inclusion and exclusion criteria may

have defined a healthier subpopulation compared to the general ED population. This might indicate that a larger proportion of adverse events would be expected from the post-marketing population compared to the clinical trial population.

3 milligrams was not studied in these trials. Therefore, you must conclude that both 2 and 4 milligrams are safe and effective to allow marketing of all three doses as proposed by the sponsor.

5 and 6 milligrams were dropped from development by the sponsor because of a "less acceptable risk-benefit profile." The highest dose that the sponsor wants to market is 4 milligrams, and as you will hear from Dr. Jarugula, Uprima has wide pharmacokinetic variability causing concern about the risk-benefit profile of 4 milligrams in some patients.

Please evaluate whether statistical differences expressed for efficacy parameters will translate into important meaningful differences for patients.

Please evaluate the clinical relevance of the effect size. For example, if the proportion of patients that reach an endpoint is 32 percent in the placebo arm and 46 percent in the Uprima arm, the effect size, or the improvement due to Uprima, is a difference between the two, or 12 percent.

How well do patients accept Uprima doses over longer-term periods? In longer trials, what proportion of patients remain at 2 milligrams when given the choice of dose? And how many patients discontinued treatment at higher doses?

The sponsor proposes to market this drug to all ED patients, yet study primarily patients with ED of nonorganic etiology. The sponsor, however, did a moderate sized trial in patients with diabetes. Please pay particular attention to the effect size in this trial.

This particular issue was mentioned by Dr. Freston, and I'm going to proceed to explain the issue because this is what had to deal with in the NDA and we can sort it out perhaps in the discussion period.

The definition of serious adverse events, it appeared, was changed in mid-development of the drug. The more inclusive definition was used for the first 20 percent of the patients and includes the phrase that is highlighted in yellow. To paraphrase, a serious adverse event is "any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in persistent disability and incapacity, or events that require intervention to prevent impairment or damage." The less inclusive definition, which removed the "intervention" phrase, was used, as far

as we can determine in 80 percent of the patients studied.

Because of the change, we believe there would be consequences as to how events were reported. For example, a patient that experienced hypotension and bradycardia in the physician's office required treatment with IV fluids and oxygen and then recovered was not considered to have experienced a serious adverse event if the yellow phrase was removed.

The FDA calculated both syncope and reports of hypotension as important adverse events, and for this reason, some figures regarding proportion of important adverse events in various trials and at various doses may differ between FDA and the sponsor.

Regarding reports of hypotension in the NDA, the FDA found that there were approximately 140 patients who had hypotension reported as adverse events in the total patient database of 3,035. Some were not included as serious adverse events. Some were not included in the main body of the report but were found in the appendices.

Regarding reports of hypotension in the sponsor's briefing document, which you received, the FDA calculated that only 2 of the 140 patients who had hypotension reported adverse events were mentioned in the sponsor's briefing document sent to the committee. These two cases were defined by the sponsor as serious adverse

events.

As mentioned, the FDA considers hypotension important in the evaluation of the risk-benefit profile of Uprima. Our analysis of syncope and hypotension will be shown to the committee during our presentations.

Finally, we would like to ask you to hold all questions until the end of all of our presentations. Now Dr. Jarugula will discuss the pharmacokinetics and alcohol interaction.

DR. JARUGULA: Thank you, Dr. Shames.

I'm Venkateswar Jarugula, pharmacokinetic reviewer with the Division of Reproductive and Urologic Drug Products.

Now I am going to present on pharmacokinetics and drug-alcohol interactions of Uprima. Over the next 20 minutes, I'm going to briefly discuss the general pharmacokinetic features of Uprima, the pharmacokinetics of Uprima in special populations, particularly in subjects with hepatic or renal impairment, and then I'll discuss a little bit about pharmacokinetic variability observed in one of the phase I trials for Uprima. Then I will discuss in detail the pharmacodynamic aspects of the drug-alcohol interaction studies that were submitted in the NDA. Finally, I will summarize my comments.

The general pharmacokinetics of the drug.

Apomorphine is rapidly absorbed from Uprima tablets following sublingual administration, with maximum plasma concentrations occurring in about 40 to 60 minutes, and it is rapidly cleared from the circulation with a terminal phase half-life of about 2 to 3 hours.

Apomorphine is extensively metabolized by liver mainly via glucuronidation and sulfation. Apomorphine sulfate is the major metabolite that is found in plasma. This metabolite is a conjugate and it is not believed to be pharmacologically active.

Following radiolabeled administration, apomorphine accounted for only less than 1 percent of the total radioactivity circulating in plasma, indicating again the extensive metabolism of this drug.

Pharmacokinetics of Uprima was investigated in subjects with hepatic impairment or renal impairment. The subjects were classified as mild, moderate, or severe hepatic impairment based on their scores, and subjects with renal impairment were classified as mild, moderate, or severe based on their serum creatinine clearance values.

As we can see here, in subjects with hepatic impairment, there was a significant increase in mean peak plasma levels, the Cmax, and also a significant increase in area under the plasma concentration curve, which is a measure of the systemic exposure of the drug.

In subjects with renal impairment, although there was no significant change in the Cmax, there was about 52 to 67 percent increase in the area under the plasma concentration curve in moderate to severely renally impaired patients.

This slide summarizes the PK variability noted for two PK parameters, the Cmax and the AUC, from a single-dose crossover PK study. This study looked at doses 2 milligrams, 4, 5, and 6 milligrams in a crossover fashion. Listed here are the range of values that are observed for Cmax and AUC. As one can note, the range of values for these PK parameters, particularly for Cmax, are quite overlapping at the higher doses, 4, 5, and 6 milligrams. As was mentioned before by the sponsor, the percent variability for Cmax ranged from 40 to 80 percent in this study. The range of variability that was noted for the Cmax here makes it particularly difficult to distinguish doses of Uprima that are so close together, 4, 5, and 6 milligrams.

The pharmacokinetic and pharmacodynamic correlation of Uprima. Based on the analysis of data from the phase I studies from which the data blood levels were available, no significant correlation between the Cmax, AUC, and blood pressure changes was noted. However, the significant adverse events, such as syncope and

hypotension, occurred in the phase I studies usually at the time of maximum plasma concentrations, and these events occurred in the subjects when they had Cmax values that were relatively higher than their group averages, indicating that the Cmax may be an important PK parameter.

The safety may be difficult to predict based on the dose of Uprima due to the variability that was noted in Cmax, as was shown in the previous slide.

Now I will turn my attention to the alcohol interaction studies. Four alcohol-drug interaction studies were conducted and were submitted in the NDA. These studies have looked at the interaction of Uprima at 5 or 6 milligram doses and alcohol doses ranging from .15 grams per kilogram to .6 grams per kilogram.

Among these studies, study M97-762 looked at the interaction of Uprima at a low dose of alcohol, .15 gram per kilogram, and this study did not reveal any significant pharmacodynamic or pharmacokinetic interaction.

In all of the studies, there was no significant pharmacokinetic interaction noted except for the fact that at the highest alcohol dose, there was about a 23 percent increase in mean Cmax values.

Let me briefly explain how Uprima and alcohol were dosed in these studies, except for the low-dose alcohol study. Just to give an idea, .15 gram per kilogram

alcohol dose is approximately equivalent to 1 ounce of vodka based on a 70 kilogram body weight. Alcohol was administered as vodka diluted in 450 ml orange juice and it was ingested over a 30-minute period, and then Uprima was administered 1 hour after start of the alcohol ingestion.

While this may be a feasible method of dosing of alcohol to look at the interaction, it should be noted that in real life the timing of Uprima dosing in relation to the alcohol consumption or the amount of alcohol consumed by the patients may be variable. It should also be noted that phase III clinical trials restricted alcohol intake to a minimum for 6 hours prior to drug administration.

Study M97-745 looked at the interaction between 5 milligram Uprima and .6 grams per kilogram alcohol dose, the highest alcohol dose studied in these studies. This study was terminated due to significant adverse events noted in two of the subjects that participated in the study. There were no definite conclusions because of the premature termination of the study and because none of the subjects received both alcohol and placebo beverage.

This slide summarizes the significant adverse events that led to the premature termination of the study. There were 2 subjects who experienced these events.

One subject, after experiencing significant

vomiting and diaphoresis, lost consciousness for 1 minute at approximately 40 minutes after dosing with 5 milligram Uprima. This subject did not receive any ethanol as per the protocol. He had hypotension. His blood pressure was 71/37 and his pulse was 41. He was administered with IV fluids, oxygen, and followed by .5 milligram atropine.

A second subject experienced hypotension. His blood pressure was 55/38 at 30 minutes following Uprima dosing. This subject also received ethanol prior to Uprima dosing. He was found to have the second highest Cmax of Uprima and also the highest ethanol level in his group, indicating that there could be a pharmacodynamic interaction between Uprima and alcohol.

Additionally, 2 other subjects also experienced prolonged hypotension in this study.

Study M98-838 looked at the interaction between 6 milligram Uprima and .3 gram per kilogram alcohol. .3 gram per kilogram alcohol dose is approximately equivalent to 2 ounces of vodka in this study.

Shown here are the mean maximum drop in blood pressure from baseline following each treatment, Uprima alone, ethanol alone, and Uprima plus ethanol combination. As can be noted here, the mean maximum drops in standing systolic and standing diastolic for the combination Uprima and ethanol were higher than either Uprima alone or ethanol

alone, with the difference with the ethanol arm being statistically significantly different from the combination arm.

Similarly, there were higher orthostatic changes both in systolic and diastolic for the combination, the difference with the ethanol being statistically significant here.

This slide summarizes the incidence of treatment emergent adverse events that are pharmacologically related to apomorphine. As can be noted here, the combination of Uprima and ethanol resulted in a higher incidence of adverse events when compared to Uprima alone or ethanol alone. Particularly the incidence of dizziness, vomiting, and hypotension are increased twofold in the combination when compared to the Uprima arm alone.

To summarize the effects of Uprima with alcohol at .3 gram per kilogram dose, which is equivalent to 2 shots, 2 ounces, of vodka, there is a trend toward a greater drop in blood pressure with the combination. There was also higher incidence of abnormally low blood pressure values and there was also a greater sedative effect with the combination. The results of these two bullets are not shown here. However, the results were included in the briefing package for the committee.

As mentioned earlier, an increase in the

incidence of adverse events was also noted for the combination at this dose of alcohol.

Study 98-891 looked at the interaction between 6 milligram Uprima and .6 gram per kilogram alcohol dose, which is equivalent to 4 ounces of vodka, again based on a 70 kilogram body weight.

The mean maximum drops in blood pressure from baseline are shown here. The mean maximum drops in standing diastolic and supine systolic are significantly different with standing diastolic being statistically significantly different from Uprima alone or ethanol alone. And that for supine systolic is only statistically significant from Uprima alone.

This slide summarizes the incidence of treatment emergent adverse events. Again, the combination of Uprima and ethanol resulted in a much higher incidence of adverse events compared to Uprima alone or ethanol alone. Particularly the incidence of dizziness, pallor, and hypotension are about two- to threefold higher in the combination arm.

Shown here is the incidence of abnormally low blood pressure values. Abnormally low blood pressure values are defined as less than 80 millimeters mercury for systolic and less than 40 millimeters mercury for diastolic. As can be seen here, the combination of the