Uprima and ethanol resulted in significantly higher incidence of abnormally low blood pressure values for both systolic and diastolic values when compared to Uprima and ethanol alone.

To recap the effects of Uprima with alcohol at a higher dose, .6 gram per kilogram, there were greater drops in systolic and diastolic blood pressure values with the combination, a higher drop in blood pressure at the time of peak Uprima and ethanol concentration, and there was also an increased sedative effect with the combination. Again, the results of these two bullet points are not shown here but were included in the briefing package for the committee. And there was an increased incidence of adverse events with the combination, as was shown with the lower dose of alcohol.

To summarize my comments, the bioavailability is higher in patients with renal or hepatic impairment.

Pharmacokinetic variability is too high to distinguish among Uprima doses that are so close to one another.

There is a pharmacodynamic interaction between Uprima and ethanol.

Uprima is associated with higher incidence of adverse events when dosed with moderate -- that is, 2 ounces of alcohol -- and higher amounts -- that is, 4

ounces of alcohol.

Thank you very much.

DR. HIRSCH: Good morning. My name is Mark Hirsch and I'm the primary reviewing medical officer for Uprima. For those of you who are new to the drug regulatory process, the role of the medical officer is to conduct the initial assessment of the clinical data in a new drug application. Then working with a team of scientists, an overall assessment of the safety and efficacy of the drug is made. Our team is fortunate to have access to experts like those on this panel who can offer their advice and opinions as we deliberate.

In a relatively brief period, I'd like to review quite a bit of material. First, we will look carefully at the efficacy and safety of the 2 milligram and 4 milligram doses individually. Then I'll touch briefly on the 2 milligram to 4 milligram dose titration regimen. Then we'll look at the results from the diabetic trial. Finally, I believe it is essential to understand the safety concerns associated with the 5 milligram and 6 milligram doses, doses which the sponsor chose to discontinue during phase III.

The clinical data set for Uprima consisted of the results from six controlled phase III trials and six open-label safety trials. I believe that the most

substantial clinical evidence comes from the three crossover trials. These three studies tested single p.r.n. doses of 2 milligrams, 4 milligrams, 5 milligrams, and 6 milligrams in randomized, placebo-controlled, crossover designs. Each crossover study included a 4-week no-treatment baseline period, followed by two 4-week treatment periods, separated by a brief washout.

So, starting with the 2 milligram dose, was the 2 milligram dose shown to be effective in the three crossover trials? The results shown on this slide are in agreement with the analysis conducted by the sponsor. The division has no major differences in this regard. However, we ask that you look carefully at these results and then provide your interpretation of these data and comment on whether you believe they demonstrated clinically meaningful efficaciousness.

The primary endpoint for all these trials was the proportion of attempts per individual which resulted in an erection sufficient for intercourse. Approximately 130 patients were randomized to the 2 milligram dose in each of these three studies. Here you see the results for the primary endpoint for each of the three crossover studies.

Here you see the combined results for a responder analysis. A responder, or treatment success, was defined as an individual who had at least 50 percent

successful attempts during a treatment period. In this secondary endpoint, there is an absolute difference of 12 percent. We have presented this secondary endpoint to offer you an additional perspective on this data.

Was the 2 milligram shown to be safe in the placebo-controlled crossover trials? Here I've listed the incidence rates of adverse events as reported in each of the three crossover trials. Although the overall adverse event profile appears relatively benign when compared to placebo, I'd like to turn your attention to two very important adverse event terms, hypotension and syncope. Hypotension was reported in a range of 0 to 1.2 percent of 2 milligram patients, and syncope in a range of 0 to 0.7 percent of 2 milligram patients. Please be aware that these are reported adverse events.

Of all patients who received 2 milligrams in the entire new drug application database, exactly how many reported syncope or hypotension as an adverse event and what ultimately happened to them? The answer is a total of exactly 7 out of 964 patients, or 0.7 percent, experienced hypotension or syncope as an adverse event. You should understand that these were individual and unduplicated adverse event reports and no patient was counted twice. Specifically, if a patient was reported as having both syncope and hypotension, he was counted only once as

syncope.

Three brief narratives from this group of 7 may help you better understand what actually happened during these events. One patient experienced nausea and syncope after taking two 2 milligram tablets within 4 hours. He was reported to be unconscious for approximately 4 minutes. I should highlight that this patient actually did take two 2 milligram tablets within 4 hours.

One patient experienced nausea, diaphoresis, vomiting, and syncope 30 minutes after an in-office dose of 2 milligrams. His syncopal event was reported to last approximately 3 minutes.

In addition to the cases of syncope, there were five adverse event reports of hypotension. I'd like to present one of these narratives here. A 50-year-old patient experienced hypotension, bradycardia, and sweating approximately 40 minutes after his first dose of 2 milligrams. The hypotension and bradycardia lasted for 5 and 10 minutes respectively.

I believe that the most important question regarding the 2 milligram dose is this. How many patients will actually use it? Well, in the long-term, open-label, flexible-dose studies, only approximately 6 to 11 percent of all patients remained on 2 milligrams when they were offered the opportunity to use higher doses. This table

also demonstrates that most patients titrated to the maximally allowed dose. Therefore, if patients tend not to remain on 2 milligrams when offered higher doses, the more important question is, what is the safety and efficacy at higher doses?

What was the efficacy demonstrated with the 4 milligram dose in the three crossover studies? Again, the division has no substantial disagreement with the sponsor in terms of the absolute efficacy data. We ask, however, that you assess these results in light of the safety concerns that I will try to delineate. Before we leave this slide, I again would like to point out that these are the results for the primary endpoint from the crossover trials and that approximately 120 patients were randomized to the 4 milligram dose per trial. Again, we agree with the sponsor's analysis of these figures.

Here you see the results of a responder analysis for the three crossover trials combined. There is an absolute difference between placebo and Uprima of 24 percent.

In my opinion the truly critical question to answer is now before us, and that is, is the 4 milligram dose safe? In order to answer this question, we should look first at the overall adverse events reports for the 4 milligram fixed dose in the three placebo-controlled

crossover trials. Here we see incidence rates of nausea of approximately 20 percent, dizziness of approximately 14 percent, somnolence or sleepiness of approximately 10 percent, sweating of about 10 percent, and vomiting around 1 to 4 percent. But I'd ask you to please focus on the incidence rates of hypotension of 3.1 to 6 percent and incidence rates of syncope of 0.9 to 2 percent. Again, please recall that these are investigator reported adverse events.

We think it is important for you to know exactly how many 4 milligram patients in the entire NDA database experienced syncope or hypotension as reported as an adverse event and what actually happened to these folks. By our count, 42 patients out of 1,279 dosed with 4 milligrams, or 3.3 percent of the entire population, reported one of these events. I'd like you to focus on that rate, approximately 1 in 30 patients, as you listen to these case narratives.

A 33-year-old man received 4 milligrams and was observed for 30 minutes in the office. While driving home -- and he was the driver in this case -- he became nauseated, fatigued, flushed, and sweaty. He attempted to stop his car, but he lost consciousness, lost control of his vehicle, and crashed into a fence.

A 36-year-old experienced pallor, sweatiness,

and syncope approximately 30 minutes after his first in-office dose. He lost consciousness for only a few seconds, but he remained tired, weak, and flushed for 8 hours.

A 50-year-old man experienced nausea after his in-office dose of 4 milligrams. He requested Compazine from the nurse. He had previously tolerated 2 milligrams without any incident. Upon her return, the nurse found him unconscious, apneic, unresponsive, diaphoretic, and incontinent of urine. He awoke spontaneously and began to breathe. His heart rate was 42 beats per minute. He was administered IV saline, oxygen, and Compazine. His bradycardia persisted for over 1 hour, requiring hospitalization.

A 60-year-old man experienced syncope 35 minutes after an in-office dose of 4 milligrams. He was unconscious for several seconds. It was necessary for the nurse to "adjust his head and rouse him." He was pale, hot, diaphoretic, and vomiting. He was placed supine, and he improved over 1 hour.

A 69-year-old man complained of diaphoresis 38 minutes after his first dose of 4 milligrams. His blood pressure at that time was 117/50 and his heart rate was 60. He then fainted and was unresponsive for 2 minutes. He was treated with oxygen and intravenous fluids.

It is notable that there were twice as many

adverse event reports of hypotension as compared to reports of syncope, and again these are unduplicated. Our assessment reveals that many of the hypotension cases were of no less significance. As evidence, I'll present a few narratives reflecting these events.

A 60-year-old male experienced hypotension with a blood pressure of 70/41, bradycardia with a heart rate of 45 beats per minute, pallor, fatigue, and sweating, 35 minutes after dosing. These symptoms abated within 2 hours of dosing.

A 56-year-old received 4 milligrams of Uprima despite presenting to the clinic with a complaint of diarrhea and abdominal cramping. After the dose, he experienced severe hypotension and he became unconscious for 15 to 20 minutes. He woke up, vomited, and was then transported to the emergency room where he again lost consciousness. His blood pressure was 60 millimeters palpable in the emergency room. His EKG revealed nonspecific ST-T wave changes and he required admission to the intensive care unit and intravenous fluids. This case is particularly concerning since it might signal problems in patients with low baseline volume status or low borderline blood pressure.

Finally, a 59-year-old patient experienced hypotension, dizziness, nausea, and sweating 25 minutes

after his first dose of 4 milligrams. His blood pressure was 72/50 and his hypotension persisted for 105 minutes.

The sponsor conducted a single controlled trial designed specifically to assess the impact of dose titration versus fixed dose regimens. Although patients in the study were allowed to titrate up to 6 milligrams, we do have data specific to the use of the 2 through 4 milligram doses. In this trial, you should be aware that patients were randomized to a 5 or 6 milligrams fixed dose arm, placebo, or a dose titration arm of 2 to 6 milligrams in which all patients were started on 2 milligrams and allowed the opportunity to dose upward as desired.

The data was analyzed for both the use of 2 through 4 milligrams and 2 through 6 milligrams. Was the 2 through 4 milligram dosing regimen effective in this trial? In regard to these actual figures, we have no major disagreement with the sponsor. We ask you to assess whether these results are clinically meaningful on their own and whether the benefits of these efficacy results outweigh the known risks.

Did dose titration actually limit the incidence of syncope and hypotension in this study? If we look at the incidence of adverse event reports for the term "hypotension" and the term "syncope," the incidence for these events was actually highest in the dose titration

group compared to the 5 milligram, 6 milligram, and placebo fixed dose arms.

We know that diabetes is a major risk factor for erectile dysfunction. The sponsor conducted a single controlled phase III study in well-controlled, relatively healthy diabetics. Was Uprima effective in this study? Here we see the results of the primary endpoint for the 4 milligram dose, that is, percentage of successful attempts per individual.

Here we see the results of the secondary endpoint, percentage of successful responders. Again, we ask you to consider these results and decide for yourself whether these differences from placebo are meaningful, whether efficaciousness was demonstrated in diabetics, and whether these results outweigh the known risks of the product.

What was the incidence of hypotension and syncope reported as adverse events in the diabetic trial? The combined incidence was 4 percent in the 4 milligram Uprima group versus 1 percent for 4 milligram placebo and 3.8 percent in the 5 milligram group compared with 0 for the 5 milligram placebo group.

Finally, we have extensive phase III trial data concerning 5 milligrams and 6 milligrams. The sponsor voluntarily decided not to request approval of these doses,

but we believe that an understanding of the risks of 5 and 6 milligrams is critical to the understanding of the 2 milligram and 4 milligram dose. The overall adverse events, as reported in the three crossover trials, reveal incidence rates of nausea of approximately 30 percent for 5 percent and 40 percent for 6 milligrams, rates of dizziness of approximately 20 percent for both doses, rates of sweating of approximately 15 percent for 5 milligrams and 20 percent for 6 milligrams, rates of somnolence of approximately 10 percent for both doses, and rates of vomiting of about 10 percent for both doses.

But I ask you to pay particular attention again to the incidence rates of hypotension and syncope. For the 5 milligram dose, these rates were 2.3 to 6.5 percent for hypotension and 2.3 to 3.5 percent for syncope. For the 6 milligram dose, these rates were 4.3 to 4.8 for hypotension and 2.1 to 2.3 for syncope.

Is there evidence of risk due to syncope or hypotension in this NDA? One case clearly demonstrates the risk potential. A 42-year-old man received a 5 milligram dose in office. He had previously tolerated doses of 2 and 4 milligrams. 1 hour after dosing, he felt nauseated. He stood up to find someone. He was found unconscious, bleeding from a tongue laceration and from a head abrasion. After smelling salts, he awoke. Within 15 minutes, he felt

better and went home.

5 days later he complained of a headache. CT scan revealed a left occipital skull fracture with a cortical contusion of the frontal lobe. MRI confirmed a left-sided nondepressed skull fracture and also reviewed a contra-coup injury of the right frontal lobe.

An additional 63-year-old patient was given a dose of 5 milligrams in the office. He had previously tolerated doses of 2 and 4. Shortly after dosing, he felt nauseated, lightheaded, and clammy. He last recalled going to the door for assistance. He was later found by the nurse with a head laceration. It was assumed he struck his head on a nearby table.

Finally, I believe that the bottom line is this. How many patients actually remained on any dose of Uprima for an extended period of time? Well, results from the long-term trials reveals that approximately 60 percent of patients prematurely terminate use before 6 months and about half of these discontinuations are due to lack of efficacy.

Since I've presented quite a bit of information in a short period of time, I'd like to present several summary comments that I hope you will consider in your deliberations.

First, in terms of the 2 milligram dose, we

agree with the sponsor's analysis of efficacy. However, we would encourage you to consider whether the benefits demonstrated over placebo are truly meaningful benefits. As an example, please consider whether a difference in the proportion of treatment responders from 36 percent with placebo to 48 percent with Uprima is a meaningful difference.

Second, the overall incidence rates of syncope and hypotension, as reported as adverse events by the individual investigators, was 0.7 percent.

Finally, it appears likely that few patients will actually remain on the dose of 2 milligrams when offered the opportunity to take higher doses.

In terms of the 4 milligram dose, we wish to emphasize that the combined rate of syncope and hypotension was 3.3 percent, or 1 in 30 patients. Some of the case narratives for these patients describe concerning events, including persistently low heart rate, prolonged hypotension, serious injury, and the need for urgent medical intervention to prevent serious injury.

It is important to note that the majority of syncopal events at 4 milligrams occurred in the confines of a physician's office and were generally, but not always, limited to the first dose or first increase in dose.

In terms of the dose titration regimen, we ask

that you look at the efficacy results from the titration study and seriously consider whether the 2 to 4 milligram dose titration regimen provides a real clinical benefit to erectile dysfunction patients. In addition, we wish for you to understand that dose titration itself did not limit the incidence of the combined report of syncope and hypotension.

In terms of the results in diabetics, we ask that you look at this efficacy data and seriously consider whether the 4 milligram dose provided a real clinical benefit to diabetic patients with organic erectile dysfunction. Here it is important to recall that the diabetic trial was the only well-controlled study in which the entrance criteria did not require patients to have at least one normal or nocturnal erection greater than 55 percent rigidity. These results in diabetics may cast some doubt on whether Uprima was demonstrated to be effective in the larger population of erectile dysfunction patients without evidence of normal nocturnal tumescence.

Finally, we believe that you cannot understand the potential safety issues with Uprima unless you aware of the safety results at doses of 5 and 6 milligrams. At these doses, all Uprima-related adverse events were reported at higher incidences. The incidence rates of hypotension and syncope in the crossover trials were

actually higher at doses of 5 and 6 milligrams. If the sponsor has decided not to request approval of these doses, why then are we presenting the results to you? You might recall that the serum blood levels or pharmacokinetics of Uprima are variable and pharmacologically doses of 4 milligrams, 5 milligrams, and 6 milligrams may be indistinguishable in any given patient.

I thank you for your attention, and I'd like to introduce our Deputy Director, Dr. Mann.

DR. MANN: Finally, the last speaker of the morning. Thank you for your patience and endurance in going through all of these multiple presentations with us.

I want to briefly review the drug-antihypertensive interaction study that was performed by the sponsor, and in doing so, I'd like to compliment them on doing a very nice job of extensively looking at the potential for drug interactions with Uprima in a wide variety of antihypertensive agents.

You've heard about the study design and some of the results this morning from TAP, so I will go through these slides somewhat quickly.

The study design was geared to look at the tolerability of a single 5 milligram dose of Uprima versus a single dose of placebo in patients taking a wide variety of antihypertensive therapies as shown on this slide.

24 males were geared to be enrolled in each group, and they were to be on at least 4 weeks of single agent antihypertensive therapy and be stable on that regimen. It was a double-blind, crossover study design with a 24-hour washout period between placebo and Uprima dosing. The patients were randomized in a randomized fashion to receive either Uprima 5 milligrams followed 24 hours later by placebo or placebo followed 24 hours later by a dose of Uprima 5 milligrams.

As part of the study, blood pressure and pulse measurements were obtained in every patient, and both standing and supine measurements were obtained. Several measurements were done prior to dosing and multiple measurements were done post-dosing as shown.

In addition, adverse events were recorded for each patient. An ECG and Holter monitoring were performed in each patient.

Of note, however, no pharmacokinetic sampling for either Uprima or antihypertensive drug levels were done in this trial.

As the sponsor presented this morning, I don't believe the FDA has any disagreement that the mean blood pressure results showed no significant effects for the non-nitrate groups or for the short-acting nitrate group. The long-acting nitrate group did show some statistically

significant changes in blood pressure, but again, we agree with the sponsor that on average those changes were under 10 millimeters of mercury and were not highly clinically meaningful.

As Dr. Jarugula presented earlier this morning with the alcohol interaction study, though, sometimes mean blood pressure changes don't give you the whole picture. So, the FDA also performed a per-patient analysis. In this analysis, adverse events for each patient were examined. Significant adverse events were considered to be nausea, vomiting, diaphoresis, hypotension, syncope, and there was one case of palpitations that was considered significant. The reason these were considered significant is, as you can recognize by now, these are the recognized adverse events attributable to Uprima.

There were occasional if not rare patients who presented with other adverse events. Those included headache, upper respiratory infection, fever, shortness of breath, tinnitus, rash, and asthenia. Since these were not attributable to study drug, they were not considered very relevant in this analysis.

Blood pressure results were also observed. The standing blood pressure results in particular were observed carefully in this analysis done per patient. Any patient who had an absolute systolic blood pressure reading less

than 85 or a diastolic blood pressure reading less than 45 after receiving study drug was considered notable. In addition, any patient who experienced a fall in systolic blood pressure by 30 or diastolic blood pressure by 20 was considered potentially meaningful.

Overall, this analysis done per patient for the 162 subjects enrolled in the entire trial, all antihypertensive groups combined, showed that there were 26 subjects who had an adverse event of concern. In 24 of those patients, they were noted to have suffered both an adverse event and one of those clinically relevant blood pressure findings I mentioned in the previous slide. 2 subjects had solely an adverse event. One was a Uprima patient and one was a patient. Both of those patients had experienced nausea as their adverse event.

Breaking it down by group, the non-nitrate therapies are shown on this slide with the adverse event results shown per patient. For example, there were 25 patients enrolled into the ACE inhibitor arm of this study. 1 of those 25 patients reacted to placebo versus 2 who reacted to Uprima. The results for the other non-nitrate therapy arms are shown on this slide, and as you scan across, you can observe that in general there were more adverse events associated with Uprima versus placebo, so that for the sum total of non-nitrate therapy patients, 1.6

percent of patients had an adverse reaction following placebo dosing versus 9 percent of patients who had an adverse event following Uprima dosing.

There was one syncopal event of note in the non-nitrate therapy arms which I'd like to mention briefly. This was a patient in the beta blocker group. His baseline blood pressure of 105/75 fell to 71/30 about 20 minutes after receiving Uprima. He had associated dizziness, nausea, and diaphoresis as well. He was placed supine, given IV fluids, and was later hospitalized for 24 hours of observation.

In summary, for the non-nitrate therapies, adverse events of concern were noted in 1.6 of subjects who had taken placebo versus 9 percent of subjects who had taken Uprima. There was one serious adverse event, a syncopal event, in a beta blocker subject who had taken Uprima.

We can conclude from this that patients did not tolerate Uprima as well as placebo. It is difficult to conclude that there is a drug-drug interaction between Uprima and antihypertensive therapies because the question arises could these events possibly just relate to adverse events associated with a 5 milligram dose of Uprima.

What about the nitrate therapy arms? There were 20 patients enrolled in each arm, and there were 6

Uprima reactions for the short-acting nitrate arm versus 0 placebo reactions. For the long-acting nitrate arm, there were 5 Uprima reactions versus 2 placebo reactions. Overall, 28 percent of patients had an adverse reaction following a single dose of Uprima versus 5 percent who had an adverse reaction of note following a dose of placebo.

That is summarized on this slide in the top bullet. Again, we feel that patients did not tolerate Uprima as well as placebo when they were receiving concomitant nitrate therapies. I think the fact that we did notice a somewhat higher percentage of reactions overall to Uprima in the nitrate therapy arm versus the non-nitrate therapy arm may in fact suggest somewhat of a potential for a drug-drug interaction between nitrates and Uprima.

I'm going to switch gears and do a brief summary of the summary comments you've already heard. I apologize if we seem somewhat redundant here, but before we lead into the questions for the panel, I did want to just recap briefly our summary of concerns.

The first concern that the FDA has raised on several occasions was that the patient population selected for controlled trials was somewhat selective in that patients with organic erectile dysfunction were excluded as part of the exclusion criteria, and moreover patients in

all three of the randomized, controlled crossover trials that we went over this morning were required to have a normal Nocturnal Penile Tumescence test as part of their inclusion criteria. As Victor Raczkowski presented, we do not care to present comparisons to other drugs, but I will state for the record that in all other drugs approved for erectile dysfunction, these particular inclusion and exclusion criteria did not exist in the pivotal trials.

We feel that this selective patient population has relevance to potential efficacy concerns and safety concerns that we've raised for you today.

With regards to efficacy, I think it's possible that Uprima could work better than placebo in patients with organic ED, and we may see a more dramatic effect in this population of more severe patients possibly if they are, indeed, more severe. Uprima may not work as well in patients with organic ED. That's the other possibility.

With relevance to safety, our major concern is that we feel that patients with more organic causes of erectile dysfunction may, in fact, be predisposed to more underlying cardiovascular disease and that in such patients Uprima may pose more serious safety concerns.

What kind of data do we have in patients with organic erectile dysfunction? There are two trials in this application that look at patients with organic ED

specifically. One of those trials was done in a limited number of patients who were status post-prostatectomy. I believe the number was 44, something like that. That trial was neither powered to show efficacy and the safety data was relatively limited. So, we have, instead, focused on the diabetic trial of patients to look at organic ED patients and how they responded to Uprima.

In this population, as Dr. Hirsch presented, there was a 25 percent successful attempt rate of the primary endpoint in the Uprima arm versus a 15 percent successful attempt rate in the placebo arm. We ask that you carefully consider this primary efficacy result in light of the safety data that we have presented for 4 milligrams of Uprima. That safety data focuses on an overall syndrome of vasovagal events with particular emphasis on a 4 percent overall rate of hypotension and syncope noted in this particular trial.

The 2 milligram dose of Uprima. I think we have gone over some safety issues, but our primary concern there is also efficacy. We've noted that overall success rates of 44 to 47 percent were noted in the three randomized, controlled clinical trials, the crossover trials, versus a placebo response rate of 32 to 38 percent. We ask that you carefully consider this efficacy in terms of safety.

Few patients, about 10 percent, remain on a 2 milligram dose of Uprima long term when given the option to titrate upwards. We again feel that this fact needs to be considered carefully in terms of the efficacy of this dose.

For the 4 milligram Uprima dose, we've laid out mostly safety concerns. Nausea and dizziness occurred in about 20 percent of patients overall, sweating and somnolence in about 10 percent, and vomiting in anywhere from 1.5 to 4 percent of patients. Overall, there was a 3.3 percent rate of syncope and hypotension in the clinical trials.

I'd like to note briefly that the FDA feels that the hypotensive events, when they are recorded as an adverse event, are potentially relevant and important to mention here. We understand that when clinicians code these terms, they have the possibility to record dizziness as just that, dizziness. We feel the term hypotension connotes perhaps a more serious concern.

Finally, we feel there is a narrow margin of safety provided with the 4 milligram dose of Uprima, and this is based on the safety data we reviewed for you with 5 and 6 milligram doses.

What about going from 2 to 4 milligrams in a titration fashion? Does that alleviate some of these safety concerns? And does it still provide substantial

evidence of efficacy?

There is one study -- this is the parallel arm study -- that compared placebo, 5 milligrams of Uprima, 6 milligrams of Uprima, and 2 going up to 6 milligrams of Uprima for both efficacy and safety. In this study, there was a 48 percent successful attempt rate in the 2 to 4 milligram level of titration versus a 35 percent successful attempt rate with placebo. We again ask that you look at this gain of 13 percent for the primary endpoint carefully in light of safety concerns.

And what about safety? Was the dose titration approach successful in ameliorating our safety concerns or at least reducing them somewhat?

We have safety results for the 2 to 6 milligram titration arm that show a 5.4 percent rate of hypotension and syncope. Compared to either the 5 or 6 milligram doses of Uprima arms in this controlled trial, the 5.4 percent rate was actually the highest. So, we did not feel that titration reduced our concern in this regard.

We have also raised concerns about interactions with other drugs. Dr. Jarugula presented his data on the alcohol interaction studies performed. We believe concerns are raised with the equivalent of approximately 2 ounces of vodka and go up higher as increasing alcohol doses are administered.

Is there a nitrate interaction? I believe it's possible, and that would be supported by the increased reporting of adverse events of nausea, vomiting, diaphoresis, dizziness, and hypotension noted with patients on nitrates versus the similar results of these adverse events reported with patients on non-nitrate therapies, but it is difficult to tell for sure.

As we address our questions for the committee, again keep in mind these points that we've brought up. I wanted to also bring up the uses in real life as the bottom bullet.

The sponsor has presented this morning an assessment of adverse events that were done using the total number of doses taken in the denominator and further projecting out an event rate per year for an individual patient. We ask that in real life you look more at the adverse event data done per patient in these clinical trials. We feel it gives the most realistic approach to safety and that the other approach possibly could underestimate event rates as the denominator is inflated with the number of doses taken per patient. It's obvious that patients who do not tolerate study drug are going to drop out from that denominator over time, thus giving you a perhaps inflated denominator that would underestimate safety concerns. So, we wanted to address that briefly.

Moving on to our questions, the first question for the panel doesn't deal so much with safety and efficacy profiles and risk-benefit assessments. We merely ask that you address does the patient population that has been studied support the proposed indication statement for the treatment of erectile dysfunction. If you believe so, please elaborate, and if not, please describe your concerns.

The second question: Do the data presented support an acceptable risk-benefit profile for the 2 milligram dose of Uprima? Again, we ask you to elaborate if you feel this is so, and if not, please describe your concern or concerns and include additional descriptions of a study or studies that might address these concerns.

And finally, the question for the 4 milligram dose is identical to that for the 2, so I won't put you through the pain of reading it thoroughly again.

Those are our questions for you, and now we are ready to take your questions for us. Thank you very much.

DR. AZZIZ: In order to stay on time, as I said earlier, let us go ahead and go to a break now. We will return to the questions for the FDA staff following lunch, and then the open forum.

It is now 12:30. Let us reconvene at 1:15. Thank you.

(Whereupon, at 12:30 p.m., the subcommittee was recessed, to reconvene at 1:15 p.m., this same day.)

AFTERNOON SESSION

(1:18 p.m.)

DR. AZZIZ: We'll reconvene if all the members can please sit down.

What I'd like to do this afternoon is, one, stay on time. Two, I'd like to begin with the public hearing portion of today, and then go ahead and go a session where we can just simply ask questions of both the sponsor and the FDA staff because we obviously have not had much time to ask questions. But we would like to make sure that we don't extend that question and answer period forever because we do need to answer the questions that have been posed to the committee.

Just one speaker and one person to respond? Is that right? We have only one speaker and that is Donald Vieth, I think. If I said that incorrectly, I'm sorry. If you would please state your relationship to the sponsor, any potential conflict of interest, and so on. Thank you.

MR. VIETH: My name is Donald L. Vieth. I'm 59 years of age. I want to thank you for the opportunity to recount my experience with the drug Uprima. TAP Pharmaceuticals invited me to testify today, and they are reimbursing me for my travel expenses.

In late 1997, I began to realize a decline in my sexual capabilities. The decline in capability was

manifested in a slowness in the ability to achieve an erection and the inability to maintain it over a reasonable period of time once attained. With this condition, a successful attempt at sexual intercourse was becoming more tenuous. To put the situation in proper perspective, let me say I went from a condition of erection on demand with a significant orgasm to a point where it was possible to have an ejaculation without benefit of erection or orgasm. So, that is just the sense of where I was. In essence, sexual enjoyment as I had known it had completely disappeared. For a man who had been married for 37 years and enjoyed a robust, imaginative, and intense sex life with his wife, the impact of this emerging condition was very troublesome. Although a marriage is based upon far more than sexual activity, the conscious realization that the erotic pursuit of the industrial strength, multiple orgasm was no longer an option constituted a devastating blow for both my wife and myself.

Considering the enormity of the situation, I consulted a urologist. I was diagnosed as having erectile dysfunction. Viagra was prescribed to determine if it was possible to mitigate my condition. There was no improvement in my condition or performance with the use of Viagra.

The urologist also indicated that they were

conducting evaluations of new drugs to mitigate the factors causing erectile dysfunction and wanted to know if I would be interested in participating in the evaluation of these drugs as they became available. I indicated that I would and my wife strongly supported my involvement.

I've been involved in phase III of clinical testing of Uprima since September of 1999. I want to note that my experience with Uprima has been remarkable. When taking Uprima, 30 to 60 minutes before the initiation of sexual interaction, I was always able to achieve an erection in a relatively short period of time after the initiation of physical stimulation, that is, within a few minutes. I have always been able to have sustained intercourse without difficulty and realize a quality level of orgasm. The use of Uprima has restored my ability to perform competently and achieve sexual satisfaction. I have been able to enjoy a significant turnaround in my sex life without experiencing any identifiable side effects. The use of Uprima has restored my sense of confidence that I can perform in a manner that satisfies both my wife and myself.

Based upon my personal experience, I would strongly support the approval of the drug Uprima.

If there are any questions about my situation, I'd be happy to address them.

DR. AZZIZ: Thank you very much for your comments. We generally don't have questions. But your comments will be taken in consideration. Thank you.

Without further ado, I don't think we have any other public speakers, so anybody in the audience who wants to take the opportunity, this is an open forum.

(No response.)

DR. AZZIZ: Thank you.

Let us go ahead and go to questions from the committee to both the FDA staff and the sponsor regarding the extensive data that was presented this morning. Again, please identify yourself before you speak.

DR. HANNO: I just have a question regarding whether the FDA has any policy with regard to drugs that might affect libido and whether the sponsor has data on the effects of Uprima on libido.

DR. MANN: I'll take the FDA portion of that question, if you don't mind. We don't have a specific policy on drugs for libido per se. I believe we look at all drugs in terms of their efficacy and their safety profiles, and if there's meaningful clinical benefit obtained, we will look at that, including potentially drugs for libido, as well as we have many other examples of drugs for quality of life type endpoints that are like that. I think each is taken on a case-by-case basis and look at

safety and efficacy.

DR. HEATON: Jeremy Heaton in response. Any drug that works on the central nervous system has to raise that possibility. This is a slide that demonstrates the change in sexual desire domain of the International Index of Erectile Function, a score which you've seen several times today. There are no clinical changes and, indeed, only one very slightly statistical change in the sexual desire domain in these patients as a result of the treatments given.

DR. AZZIZ: Dr. Greene.

DR. GREENE: I have four specific questions of clarification I'd like to address to the sponsor. Do you want me to do all four of them right now?

DR. AZZIZ: If they're quick. If they're not, we'll cut you off.

DR. GREENE: Okay, fine.

The first question was on three slides you mentioned vasodilatation as an adverse event, but I wasn't sure exactly what the definition of vasodilatation was.

DR. FRESTON: It was in the eye of the beholder. If the investigator thought he saw flushing or something like that, he would call it vasodilatation.

DR. GREENE: Okay. So, that presumably did not overlap then with other things like sweating or dizziness?

DR. FRESTON: These symptoms commonly track together as that prodrome that I mentioned. I should also re-mention in this regard that frequent mention has been made today of hypotension. I would emphasize that also was in the eye of the investigator. It was not documented by blood pressure recordings.

DR. GREENE: That was another question.

Another question, quickly, is in the patients that were Holter monitored, why was the Holter monitoring done? Was that done because there was an a priori concern about dysrhythmias or because of experience with the drug?

DR. FAGAN: It was not done on account of experience with the drug. Because there had been some syncope, TAP was very anxious to establish what the mechanism was, and to be certain that in fact it wasn't inducing serious arrhythmias. Therefore, prospectively this was included in a number of the studies so that that could be evaluated.

DR. GREENE: So, it was done in response to the experience with the drug, specifically syncope.

DR. FAGAN: Yes, the early experience with syncope and then these studies were designed. It was not done in response to any experience of any significant arrhythmias.

DR. GREENE: Okay.

DR. FRESTON: Could I just add to that for clarification? These syncope cases, these anecdotes that we heard about today, occurred, for the most part, very early when the investigators were using this drug for the very first time. The spontaneity of all this caught everyone by surprise, and in many cases there was quite an alarming, what turns out in retrospect to be, an overreaction.

Subsequently, we got on top of this, and part of the way we got on top of it was to decide whether or not these were cardiogenic syncopal attacks or noncardiogenic, i.e., vasovagal. So, the Holter monitoring and other measures were put in place to study that prospectively.

DR. GREENE: A question came up this morning with regard to the blinding and the efficacy of blinding in the study in the placebo. One of the ways of addressing the issue of blinding is simply to ask subjects during a placebo-controlled blinded trial whether they thought they were taking drug or placebo and then seeing if they were correct. Was that done in these trials?

DR. FAGAN: That was not done in these trials, but as you saw, there were analyses of the first period only and analyses in patients without symptoms.

DR. GREENE: And the final question that I had was with respect to the durability of the effectiveness of

the drug, was there data to suggest that the efficacy of the drug was the same, let's say, in the first month that it was taken and the last months that it was taken and over how long a period of time?

DR. HEATON: The answer is yes, there are data that will show that. The other issue is the long-term data. The patients who were responding respond at an 80 to 90 percent sustained response rate, which means that 80 to 90 percent of attempts continue to be successful.

DR. GREENE: Thank you.

DR. GRABOYS: Yes. I have concerns about the hemodynamic issues referable to the syncopal issue. As folks get older, they increase vagal tone anyway, so we see a lot of folks in their 70s and 80s who have vasodepressive syncope in the setting of increased vagotonia. The question really is, number one, how are you going to address this with tutoring physicians to prescribe this agent, and will there be a trial in the physician's office? How do you anticipate tutoring? I think that's really the bottom line on this. In an event that is very difficult to predict that may increase because of increased vagal tone and you don't have data on an elderly population that we're trying to address the specific issue to.

DR. FAGAN: There's a couple of answers to that. It's true that there isn't data on very many

patients over the age of 65. However, as you recall, we did show adverse events in those over 65 versus those -- actually, we probably didn't show that. Could we show that? And in fact, the adverse events are not greater in that group.

The other thing, you remember, is that this is vasovagal, so it's not just the vagal tone, but it's a withdrawal of sympathetic tone. Our sicker patients, which you might say were physiologically older, the ones with coronary disease, the ones with diabetes, had numerically less adverse events than the younger patients.

DR. FRESTON: I would also add that we want to capitalize on what we have learned in this regard, elders who are taking drugs that might cause them to have syncope from other examples. You remember in the early days of prazosin, the elders were getting syncopal events, and we'd say take this medication at nighttime. That's basically what we're saying should be done with this.

Likewise with Hytrin which reduces the frequency of urination overnight by just one micturition. We ask those patients to take it at nighttime and to lie down.

So, we want to incorporate some of these features into the patient information package.

DR. FAGAN: On the slide here, we have the

older patients. The ones over 65 basically have the same nausea rate, same dizziness rate, similar sweating rates as the younger patients.

DR. GRABOYS: Someone said -- I'm not sure who -- in the discussion they would advise physicians to use their "clinical judgment." And this is in regard to the alcohol and in regard to nitrates. Again, whose clinical judgment are you talking about? Urologists, cardiologists, primary care physicians? I think this needs really to be fleshed out.

DR. FAGAN: Well, obviously it's whoever is prescribing the drug. We know that the majority of these drugs are provided by primary care providers, internists, family practitioners, nurse practitioners, so that's who we're going to be talking about.

Again, the general instructions pretty well cover everything. If they are supine, with one of the prodromal symptoms which are in 85 percent of the syncopes and 98 percent of the episodes of hypotension, then they shouldn't have any problem. And that's a fairly simple instruction.

As far as who you aren't going to give it to, I think you're probably more comfortable giving it to patients with more cardiovascular disease than most of the primary care practitioners will be.

DR. FRESTON: I would like to add that one expert actually portrayed the prodrome as perhaps an advantage and he likened it to tinnitus that occurs in patients who take aspirin. If they start to get the dose too high, you get tinnitus, and then you stop doing that. In many ways the symptom of nausea can be viewed in that fashion.

DR. AZZIZ: Dr. Califf.

DR. CALIFF: Rob Califf from Duke. I had two questions.

One is I want to make sure that I'm understanding the basic math on the efficacy side here in terms of intention to treat with regard to the subjective questionnaires. Did 100 percent of the patients return their questionnaires? And if not, what was the count given to a patient who didn't return the questionnaire?

DR. FRESTON: That's a good question, and I'd like to ask Susan Buttler. The issue is, how are the patients counted when don't fill out their questionnaire? Are they counted as treatment failures as in an ITT analysis? Anthony Edmonds will help us with that.

MR. EDMONDS: Actually we did an analysis in which we imputed the answer of no for patients who did not complete a questionnaire. In most of the analyses you've seen, we didn't include those data or those lack of data.

But as you can see here for the analysis, the very conservative analysis, where we impute no for patients who did not fill out a questionnaire, you can see similar efficacy results for the 2 milligrams, 4 milligrams, all highly statistically significant.

DR. CALIFF: So, it must have just been a few people who didn't return the questionnaires.

MR. EDMONDS: Correct.

DR. CALIFF: The second one is a little bit hard to get at specifically, but I think one of the really critical issues is trying to understand what the likelihood is -- the patients, for example, with coronary disease who got into the trials were like most people with coronary disease that you see in a clinic.

Maybe one way of getting at this would be -- this is a rough thing I usually use -- how many exclusion criteria did you have for your typical protocol? Was it 10, 20, 30, more than one page?

DR. FAGAN: Well, let's look at it another way. Let's look at it from the standpoint that these patients were enrolled in the studies by physicians who treat a large amount of erectile dysfunction, that they were not difficult to recruit, that very few people didn't meet the criteria, and there are the exclusion criteria.

DR. FRESTON: In this regard, we continue to be

puzzled about the statement that these patients don't represent the larger population. Basically the only patients we excluded were those with unstable medical disease. We described that in the case of the hypertensives, as shown there, and the diabetics. They couldn't have had any ketoacidosis in the antecedent months, and they had to have their blood sugars not very well regulated. And we excluded patients with spinal injury and total prostatectomy, and we excluded patients who had 0 erectile function.

Now, according to MMAS, only 10 percent of the ED population had complete ED. So, we might have missed 10, but we're puzzled about what this larger population is because we had them all in the study just like Viagra did.

DR. AZZIZ: Dr. O'Leary.

DR. O'LEARY: O'Leary from Boston.

With regard to the nausea situation, do I understand it correctly that there's a learning effect, if you will? In other words, with increased use of the drug -- or is it simply that they -- because they're staying on the drug, presumably it's efficacious and they ignore the nausea or they tolerate it.

DR. FRESTON: It may be all of those considerations plus one other consideration. We don't believe there's any evidence for pharmacologic tolerance.

This is a short-acting drug that's given intermittently, after all. We think, understanding the accommodation is better understood in the context of what happens to people when they experience a vasovagal episode with syncope -- think of yourself the first time you saw an operation. You may have fainted. You didn't do it again. People adjust to that first episode, and we think that's taking place in these patients.

DR. O'LEARY: So, it's a learning effect.

DR. FRESTON: Yes, we think so.

DR. FAGAN: Here where people took at least 8 doses so that it wasn't an effect of people dropping out, clearly it decreases very rapidly and after the fourth dose, it's below 3 percent.

DR. AZZIZ: Dr. Kowey?

DR. KOWEY: I have just a few questions related to the vasovagal syncope. I think what we're seeing here is a drug which has a cholinergic effect producing vasovagal syncope. 85 percent of them have prodrome. Am I to understand that 15 percent of the people who had syncope did not have a prodrome? Is that correct? You said 85 percent of patients had prodromal symptoms.

DR. FAGAN: That's true. In the 2 and 4 milligrams, 11 of 13 did have prodromal symptoms. I think cholinergic, though -- we've never said cholinergic. It's

not direct cholinergic, but it's --

DR. KOWEY: It's provoking the response which I think we probably can net out even though it may not have a direct cholinergic action.

The question I have is do patients who had vasovagal syncope -- you had some actually in the placebo group as well as in the treated group. Did you make any effort to screen out patients with a prior history of vasovagal syncope in the exclusion criteria, or do you know how many people had it before they got the drug or got placebo?

DR. FAGAN: We don't know and they were not screened out.

DR. KOWEY: Would you like to make that part of your labeling perhaps, that people who have a history of vasovagal syncope might not be good candidates for this drug?

DR. FAGAN: I think someone who's a frequent fainter with multiple repeated episodes probably would not be a good candidate. I don't think you should eliminate people who have had only one episode because that may have been entirely -- yes, you'd exclude 40 percent of the population, and it wouldn't really help.

But the other question is whether this should be given in the office. Given the very uncommon occurrence

of the syncope, you'd be putting roughly -- by my previous calculation, which I'd have to go through again, about 500 patients would have to come into the office and sit there --

DR. KOWEY: Well, you're not only screening for syncope in the office, you're looking for severe hypotension, which brings me to my next question, which was, did you prospectively define hypotension in the protocols, or was that left to the investigator to tell you when he thought somebody had hypotension?

DR. FAGAN: This is the standard sort of drug study, COSTART term, and that's the --

DR. KOWEY: So, you didn't prospectively say to the investigators this many millimeters of mercury you should report hypotension, or percentage drop in blood pressure.

DR. FAGAN: No, it was not. In fact, most of the studies, blood pressures weren't measured.

DR. KOWEY: And my last question is we're making a presumption here based on data that you've presented that what we're seeing is a response which is autonomically mediated. You saw some pauses on the Holters that were pretty prodigious. As I recollect, there were some that were stretching out close to 20 seconds of asystole.

DR. FAGAN: The 20 seconds was related to a blood draw on a patient who did not receive Uprima.

DR. KOWEY: I'm just saying that in people who got the drug and some people who didn't get the drug.

DR. FAGAN: Right.

DR. KOWEY: Okay. But clearly, for some people who got the drug, you had a concern about bradycardia because that's why you got the Holters put into the protocol. You knew that there was an incidence of this. From any other piece of data, ECGs or any other kind of information you may have extracted, how can we convince ourselves, especially given Tom's problem with older individuals and having a gross under-representation of the very elderly, that this drug does not have a direct electrophysiologic effect on the conduction system, in addition to an indirect effect?

In other words, how do we know -- and maybe Joel can answer this question, maybe he can't -- that the drug, in addition to having what appears to be an effect to cause vasovagal syncope, how do we know it also doesn't have a direct effect to cause sinus slowing for example? Do we have any piece of information that would tell us that?

DR. FAGAN: Yes. Let me say one thing and maybe Dr. Morganroth can respond.

The 20-second pause was in a patient who had his blood drawn and did not receive Uprima. There were 10- and 11-second pauses seen in 2 patients who did receive Uprima.

And the other piece is that we know that this drug has been given worldwide and in clinical trials to thousands and thousands of patients at doses manifold higher, orders of magnitude higher, than we're talking about giving to these patients when they're treated for Parkinson's --

DR. KOWEY: No. That doesn't answer the question because I don't care about that, you see? I don't care how many times it has been given at what doses.

What I'm asking is if you give this drug to somebody that has a conduction system disease and you do not have those patients represented in your database because you don't have a lot of old people in your database, are we sure that we're not going to also, in addition to having a vagomimetic effect, have a direct effect on the conduction system?

For example, do you have paired ECG analyses showing changes in PR interval or in heart rates in people that got the drug that did not become vagal? Do you or don't you? Do you have that information? That's what I want to know.

DR. FRESTON: Yes, we have a lot more information. Dr. Morganroth.

DR. MORGANROTH: I believe in every one of the trials, ECGs were obtained for and on drug, and in the analysis that you're requesting, there was no change in heart rate or in PR interval, which would suggest there is not a direct effect.

DR. FRESTON: Let me also add because this is a very important issue. There undoubtedly some additional subsets of patients that we haven't looked at, like those who had preexisting conduction disorders. We don't know those. My suggestion would be in the label it will need to be discussed what patients were included and, by implication, all those others were not, and maybe they can be specified and then investigated later in a prospective way.

DR. AZZIZ: Dr. Jacobs, Dr. Califf, and Dr. D'Agostino.

DR. JACOBS: I have two questions.

The design of the study included only people who were NPT, Nocturnal Penile Tumescence, positive. I didn't see anybody coming up with NPT negative on here. NPT could be negative for both a central reason and a peripheral reason. Have you got any collection of data on NPT negative people?

DR. FRESTON: Well, the NPT issue -- everyone has been confused about this today, and I suggested to Dr. Azziz that we have Dr. Ron Lewis come up and answer this question and put this in perspective for us. He doesn't like to admit it, but he's the father of the RigiScan.

DR. LEWIS: Not really. I won't take credit for that.

I appreciate the opportunity. Ron Lewis, and I have been a consultant to TAP and am currently President of the International Society of Impotence Research.

We've got to go back to the history of NPT. NPT has clearly been stated in our literature -- and it's clearly stated in all erectile dysfunction literature -- it does not distinguish between organic and non-organic disease. NPT does not make that distinction, and that's clearly established in our literature. So, to use this as a criteria for selecting patients to be either organic or non-organic, it is not in our literature. It's not supported by that.

There are three types of erections. There are erections that occur nocturnally, at night. There are erections that occur with sexual stimulation, and there are erections that occur with sex-stimulating visual-related erections.

In the literature, it is clearly established

that these are all different. So, a man can have impotence in a sexual situation and still have normal NPT. So, I think that's extremely important.

What is happening in impotence is that we are finding that probably questionnaires -- it's much like BPH. We thought we had everything as urologists figured out by BPH by using flow rates and everything else, and then we started using a symptom score. And we found out that the symptom score was actually more predictive of the degree of disease in the patient and the response to medication.

Similarly, we're finding this out with the questionnaires, the IIEF. We have shown in this study and TAP has shown I think this morning, that 75 percent of the patients either had moderate or severe erectile dysfunction that is more likely to indicate organic disease. These are patients that we are seeing in our office.

Finally, I want to remind why this selection of NPT was really put into the study in the first place and why it was not used with Muse, why it wasn't used with Viagra. This is a new agent. It is an opportunity to have an agent that acts centrally.

Now, to understand if this is going to have any relevance for the patients that we see, we didn't want to have severe end-organ disease. What the NPT does by using the criteria of only one episode of greater than 55 percent

base rigidity for no longer than 10 minutes on two successful nights, this indicated that there at least is some functional tissue in the end organ where a central agent might have effect. That was the only reason that the NPT was selected. And by all criteria which determines whether NPT is normal or abnormal, this clearly, by using only one episode of 55 percent less than 10 minutes, lies at the lower range of being considered normal NPT. By most people, it is not considered normal NPT.

So, I've heard that NPT has been used to sort out. It really can't be used in this situation. It was simply used as a tool to select those patients who have still an acceptable end-organ tissue response to an agent that's going to work centrally.

So, I've heard that this doesn't represent real patients. It does represent real patients. The urologists who participated in the studies -- and I was the central NPT reader and actually only recently participated in a study of patients that isn't even considered at this time, but basically what I found out from the people who were sending in to me as an NPT reader is that they had a very, very easy job of recruiting these patients from their practice. And I think that that's what we should be left with.

Thank you.

DR. JACOBS: Are you saying that an NPT negative patient is not a candidate for this?

DR. LEWIS: No. In fact, that was actually pulled out too. When we were going to address the NPT data, it was noticed on those two slides that were shown this morning that clearly the bell-shaped curve was far to the left of what has been described by Dr. Levine as normal studies. These were more likely patients who had severe disease. When we looked at the response of tip rigidity -- and that's rigidity area under the curve under two criteria, number one is less than a certain percentage. It was actually presented in two different rigidity measurements. But even when we look at the most severe, less than 9.6 area under the curve, still those patients had the same response. So, with very severe disease even by NPT, they too responded. So, both groups did have a response.

DR. JACOBS: My second question actually had to do with the drug most likely to be taken with this drug in the real world and that's Viagra. Are there any patients that have taken both drugs?

DR. FAGAN: There's been a pilot trial with the combination, and there's a combination trial which has been planned but not initiated.

DR. JACOBS: And there's no safety data to

report on that pilot trial?

DR. HEATON: There are no data from that trial available today.

DR. FRESTON: Mr. Chairman, could I follow up too on just one point that Dr. Lewis was alluding to?

There was confusion in one of the FDA slides today and I'd like to clear it up about whether or not these people really did have erectile dysfunction. This has to do with the 50 percent success rate at sexual stimulation. That was the cutoff beyond which we didn't want patients to participate. That's not to imply that most patients hit up against that 50 percent level. As a matter of fact, 39 percent of our patients had absolutely no sexual response at all in the preceding 1-month baseline period.

DR. AZZIZ: Thank you.

Dr. Califf?

DR. CALIFF: I'm sorry to keep coming back to this. What I'm really struggling with here is to try to get the best estimate of the treatment benefit and the treatment risk at the 4 milligram dose.

Twice you've said that people that had taken the treatment 8 times somehow gave us a better estimate of what the effect, in terms of inducing hypotension, was than other data, when I would have thought it just the opposite.

Usually if someone takes a treatment 8 times, we call it the healthy survivor effect. That is, if I got hypotension or got nauseated the first 3 times, I probably wouldn't take it the fourth time. So, I need to understand that point better. I would think that would be underestimating the risk if you had people that really took the treatment.

DR. FRESTON: Well, it's a very good point, and this is different from what we usually see. Again, we have the phenomenon of the adverse events diminishing over time, and that occurs, by the way, whether we look at the 2 milligram, 4, 5, or 6. Again, we think it's just a combination effect that we alluded to before, presumably related to learned behavior.

If I may, I'd like to also point out the agency in its presentation today pointed out that most patients, maybe upwards of 90 percent, gravitate up from 2 to 4 milligrams. The implication was that now they're going to have 4 milligram AE rates. That doesn't follow because of the accommodation. There's a balancing effect that takes place.

DR. CALIFF: I don't think you're answering my question. I mean, typically people who have adverse events drop out. Those who are left have a lower rate of adverse events. That's seen in almost every treatment. How do you account for that in your analysis?

DR. FRESTON: Dr. Jennings.

DR. JENNINGS: Dennis Jennings from TAP.

In the tables you see of our adverse events, they are as Dr. Mann suggested, presented as per patient. So, if somebody had an adverse event during their first two attempts, they are shown in those percentages. The nausea slide you saw put up trying to show the declining in the adverse events was just noting that if we did take the patients who stayed in for a while, we see that those are declining. In fact, nausea for example was not something that very many people were dropping out from because, if you notice, the adverse event rate on the first dose was pretty close to the total adverse event rate that we saw in that study.

DR. CALIFF: So, to be scientifically clear, we can't use these data to say that there's actually a diminution in nausea because you really haven't separated out the effect of dropout. It would be almost impossible to do so.

DR. JENNINGS: Well, I think the slide we put up does do that to some extent because what we're saying is there's a very small number that are dropping out due to nausea. But if you take the patients who had sufficient exposure so we can look at how their nausea rate changed over time, those ones are clearly declining. So, there's a

little mix in there, but I think it's helpful.

DR. FAGAN: Let me make one other point, and that is, of the 13 patients who had syncope on 2 or 4 milligrams, 7 continued in the trials, took a total of 150 doses, and nobody had syncope a second time.

DR. D'AGOSTINO: I have two questions. You have to forgive me if I don't have sort of the background to put this in for the particular condition, but we're talking about, from the sponsor's point of view, that in fact the patient population is representative and similar to other patient populations that have been used in these type of studies. Down the road when we start coming to the questions, we're going to be asked about the patient population with the implication that some of the FDA -- more than implication, the explicit writing that it's not typical. So, you have to forgive my ignorance that I don't have all the literature sitting in front of me, but I need some sense of why is this patient population that we used in the studies different.

DR. HIRSCH: To my knowledge, no other sponsor used the following two inclusion/exclusion criteria: the phrase "no major organic component." And frankly, I'm not sure how that was used. I'm not sure what an investigator did to decide that a patient had no major organic component. For example, if a person had bad diabetes and

that was what was thought to be causing his erectile dysfunction, did the investigator say, well, he had a major organic component and I can't include this person? I think that's what happened, but I could be wrong. I don't know how that was used.

The second this is I don't know of any other studies that used NPT at all as an inclusion or exclusion criteria.

DR. D'AGOSTINO: And what would be the problem with the NPT? Is that you would think you'd have a population that -- it slices the target population, obviously, but that somehow or other the effect from the efficacy or from the safety or from both would not be representative in these studies?

DR. HIRSCH: Well, I think it's fairly simplistic really in that a patient with one erection in two evenings, which is greater than 55 percent rigid compared to a hard plastic rod is a person who can get physiologically an erection greater than 55 percent of a rigid plastic rod, which means they can in the evening. Whether they can during sexual stimulation or they can during erotic arousal, I agree that might not be true, but they physiologically can get something of an erection.

DR. D'AGOSTINO: Let me ask the second question. Does anybody want to respond?

DR. HEATON: I'd like to take the opportunity to answer those two issues.

First of all, the expression, the phrase, "no organic component," was used based on discussions to give a general overall gestalt to the patients who were being admitted to the study as of the perspective of 1995-1996. This is a time when the whole issue of organicity and psychogenicity of erectile dysfunction was in a state of flux, and it was a point of interest. "No organic component" was meant to guide the investigators to the kind of patient who did not have a prostatectomy, who had not had spinal cord injury, who didn't have Parkinson's disease, who did not have MS, they had not had penile prostheses or penile surgery, and they did not have any end-stage or unstable diseases.

So, the actual expression itself was not a criterion of admission, and it resulted in, as I tried to demonstrate quite clearly earlier, that there is a very substantial proportion of patients with organic co-morbidities. Now, that's a cautious term because that does not imply that I know that the hypertension or the coronary artery disease is absolutely the cause of the ED in that patient. However, when you have the organic co-morbidity present and it's present at the same rate as in comparable clinical trials and in a patient population sample, such as

the MMAS, I'm reasonably well consoled that this is a representative population.

I really have to take up again the issue of the NPT. 55 percent on one occasion for 10 minutes is not a normal erection. These patients were chosen not to have normal erection. The RigiScan was introduced after extensive discussion with the agency with a desire to introduce some organic level of -- some objective level of measure, and in the early 1990s, this was a very good standard of objective measure. So, the purpose there was to, as Dr. Lewis stated, just avoid the appearance of people with no end-stage penis and, therefore, people who were basically inappropriate for a pharmaceutical trial.

This slide is another way of looking at that same idea. This is one we showed before where if you have absolutely no success during baseline, which by any standards would have to be a very robust measure of erectile dysfunction, these patients had fairly similar values compared with the group as a whole at a decent statistical level. We could again go through the IIEF criteria that also resulted from the application of this. So, we could look at the people who had the very low RigiScan scores, which is under 9.5, again showed a very substantial spectrum of efficacy.

So, it's a difficult issue, and NPT actually

has been something that urologists have been wrestling with for its utility.

DR. AZZIZ: I'd like to have Dr. O'Leary comment.

DR. O'LEARY: I'll actually be a little more blunt, Dr. Heaton. I don't think we should get too focused on the NPT. There are a lot of urologists who don't use it, who think it's of very little value. In fact, with all due respect to Dr. Lewis, there are some urologists who refer to it as the RigiScam rather than the RigiScan. So, I think it's important that we not get too focused on that.

DR. DONATUCCI: Craig Donatucci from Duke, urology.

I want to second that. In essence, I think first off people say RigiScan and I think the statement was made this morning it's a reflection of REM erection activity that makes -- it occurs during REM sleep and in fact it doesn't measure REM sleep. So, if the patient doesn't have REM sleep, it's not measuring anything. It's just too inaccurate to hang anything on.

DR. AZZIZ: Let me just ask a question of Dr. O'Leary and Dr. Donatucci because your comments were timely, but how does this impact? You just said that the NPT isn't really of much value. There seems to be an agreement with those of us who don't do NPTs. Does this

impact in any way --

DR. D'AGOSTINO: Yes. How does it help my question?

DR. AZZIZ: How does it help dissect this issue --

DR. O'LEARY: In some ways I don't think it really does, and I don't want to say that I've completely discounted it.

But the treatment -- and I thought I would wait till later, but I may as well just get this out now. The treatment of erectile dysfunction is largely goal oriented for those of us who specialize in it, who are interested in it, and take care of these patients on a daily basis. Certainly there are some patients that if we can, we like very much to have a precise diagnosis, to be able to use those objective parameters that are available to us, most of which, by the way, are invasive, to be able to precisely determine what the etiology of their ED is. But for the most part, when I see a 60-year-old man in the office who has hypertension, maybe he's on a diabetic medication, and he tells me he has erectile dysfunction, I believe he has erectile dysfunction and I go ahead and I treat him.

I don't routinely do NPT. The NPT monitor is sitting in my closet gathering dust. I will occasionally do penile doppler studies and so on, but I think that most

urologists who have an interest in this would agree with me that we're goal oriented. That's how we treat people. So, in evaluating the patients that are in this population, in this database, they look pretty much to me like the kind of people that I see every day.

DR. AZZIZ: So, the NPT doesn't add or detract.

Dr. Tiefer, please.

DR. TIEFER: Can I just speak to the NPT issue? Because I agree with Dr. Lewis that these patients don't have normal NPTs. But I think the presence of so many NPTs in so many patients is of interest to those of us who did collect thousands of NPTs of patients for a very long period of time, and my sense is that these are better NPTs than the patients who walk in the door. Patients who walked in the door with a variety of etiologies did not have 55 percent of maximum base for 10 minutes on at least one occasion when measured for two consecutive nights. This is just better.

So, if that's relevant then -- and I think in conjunction with the subjective question which was asked, namely have you had an erection sufficient for intercourse in the last 3 months, to which again the random selection of patients who walks in the door typically is very equivocal about that. And you press them and press them and then a lot of times, they say, no, they had an

erection, a partial erection, a floppy erection, but it wasn't sufficient for intercourse. So, those two pieces of information taken together do suggest to me that these patients are in better shape than the random assortment of patients walking in the door at the present time.

DR. O'LEARY: Well, I'm not so sure I agree, but I'm not sure that that's germane necessarily. I do not happen to believe that the RigiScan is of much value. Period. That's my opinion.

DR. TIEFER: Well, I think it's of no value when it shows no response because you have no idea why it's showing no response.

DR. O'LEARY: Right.

DR. TIEFER: But when it in fact shows a substantial and prolonged response, though not a perfect and normal response, that didn't happen by fairies through the air. Something produced that.

DR. O'LEARY: No, but it may very well be that that patient has -- I'm sorry to get into a debate about the RigiScan.

DR. AZZIZ: We're not going to debate too much longer, but I think we need to just go ahead and finish your statement. Go ahead.

(Laughter.)

DR. O'LEARY: It's possible that the patient

can have a positive RigiScan or negative RigiScan by having a good erection and not be able to perform at all. And we see this all the time.

DR. AZZIZ: Well, this is very unusual to have disagreement in the medical community.

(Laughter.)

DR. AZZIZ: Dr. Hanno.

DR. HANNO: Yes. I have a couple comments in terms of what Mike has been saying. I don't think issue of the RigiScan is related to how useful is it clinically. The point is, I think, that it enriches the patient population. The use of the criteria that the sponsors put out enriches the population they're looking at. I don't use the RigiScan clinically, but I think we're looking at an enriched patient population and that we have to keep that in mind.

I have a couple of questions for the sponsor. One is that since about 90 percent of the patients are going to be taking the 4 milligram dosage based on what we've seen, in the label do you think that you should list the side effects of the 4 milligram dosage separately rather than combining it with the 2 milligram? Because I think the combination tends to make it look like the side effects would be less.

And then I have one other one about the label.

Would you put anything about eating? Some of the comments that you made with regard to the study and not eating a lot within 1 hour of taking the medicine, would you want to put those in the label as well?

DR. HEATON: We think those are both good ideas to consider for the label.

DR. FRESTON: We want to get the very best label that we can that capitalizes on the experience we have gained as these studies have unfolded, especially now that we've gone to the first dose at home studies and learned a lot from them. Some of those features I think could be helpful.

DR. AZZIZ: Again, labeling issues we'll bring up as we discuss a little bit further, but right now we need to concentrate on getting our data clear.

I have a question for the FDA staff. Maybe I am not understanding this, but there is a great variability which I think is demonstrated in the 4 milligram, 5 milligram dose, 2 milligram. In other words, great variability in the Cmax and the AUC. But I am unclear as to what does it matter because, yes, we know that there's great variability and that there's overlap in the Cmax, for example, up to 5 or 6 milligrams. But if you had never studied the 5 or 6 milligram, the population of 1,200 patients or so that apparently were started with 4

milligrams should have taken into account that variability.

So, in this case I'm not quite sure just because it overlaps with the 5 and the 6 milligram dose, I am unconvinced that this represents "the same dose." And so, I think I may need to have a little bit of clarification in that regard.

DR. MANN: I'll speak in general terms to your question. I do agree with you that the most germane data is the 4 milligram data compared to placebo and the 2 milligram data compared to placebo. As we delve into the 5 and 6 milligram data, I believe the only point we wanted to make there is that on an individual patient level at least, we cannot always distinguish what kind of pharmacokinetic profile a given patient is going to have. But you're absolutely right in that the main focus of safety should deal with the 4 milligram data in the clinical trials.

DR. FRESTON: Dr. Azziz, if I may on this issue of variability, it's one of the things that we wanted to bring up and we're glad you opened it. The clinicians around the table know very well that clinical data trump pharmacokinetic data. We have no looked at those different doses in 75,000 exposures, and we do see a dose response there even if we didn't in the kinetic data. So, the PK data are used to try to predict the future, but you still have to test it in patients versus subjects.

DR. AZZIZ: Since you brought that up, the clinical efficacy data is, of course, very important, and you have your diabetic data, which I am looking for right here in front of me. At the 4 milligram dose, we have a 16 percent success, which means 50 percent success, which really means that not everybody had erections every time, but 50 percent erections is probably satisfactory. 16 percent for placebo, 25 percent for Uprima in the diabetic population of n of 90. Is that correct?

And if that is correct, is the 25 percent, i.e., a 9 percent plus, really clinically relevant from a practitioner point of view? Because if I have a drug that's 25 percent successful, unless it was life-threatening, it would be very tough to sell.

DR. HEATON: That's certainly a good issue and there are two ways of looking at the diabetic data. This the diabetic patients from the crossover studies where you see the numbers are slightly different to those within the diabetic study itself. If I could have the previous slide.

In the 804 study, the numbers that you mentioned are, indeed, lower, but the baseline entry point of a patient is 5 percent of erections firm enough for intercourse. The achievement of 25 percent of erections represents a 5-fold gain for that individual.

The point that Dr. O'Leary referred to earlier

is extremely important in understanding what are the clinical measures of significance in this study. This is a goal oriented treatment, we are not in a position to sit in judgment of the diabetic patient to assess what he would consider an appropriate clinical gain. It's a difficult question. I can answer it more extensively if you wish.

DR. AZZIZ: No, no. Wait a minute. You said 5-fold. I'm not interested in baseline. I'm interested in placebo versus drug. There's not a 5-fold increase there. Maybe I just missed that as you zipped through there.

DR. HEATON: The 5-fold gain I stated was from baseline up to the response at 25 percent. The placebo response was 15 percent, and so if you take that as a sustained placebo response, there would be a therapeutic gain there of about 10 percent.

DR. AZZIZ: Right, but not 5-fold. Placebo to drug is really what we're interested in. Okay, thank you.

Dr. Donatucci.

DR. DONATUCCI: I just wanted to say that my experience treating patients for this condition is even a 25 percent chance is certainly satisfactory. Basically I've given patients options and they've selected a drug when I told them there's almost virtually no chance it would work, and they still select it. So, when you're talking about this particular condition, you just can't

count that out.

DR. AZZIZ: Thank you.

Dr. Califf?

DR. CALIFF: I just want to make sure that we have agreement between the FDA and the sponsor on just what the data are that we're discussing. I think the key data on page 6 and 7 of Dr. Hirsch's presentation, the 4 milligram dose -- from what I understand from the presentations, basically placebo is about a 35 percent response rate and treatment in the low 50s with some discounting below that because of these were only people who responded to the questionnaire, but not much discounting because almost everyone responded. So, about a 20 percent increase overall.

On the --

DR. AZZIZ: Before you continue, I'm sorry. Do you all have a copy of the FDA's presentation somewhere? No, no. The sponsor. Because I think they're looking for it.

DR. CALIFF: What I'm confused about is I felt some dissonance between the two presentations of the sponsor and the FDA. If we can at least agree on what the data show, then we can argue about how to interpret it.

DR. HEATON: Again, the page number, sir?

DR. CALIFF: Page 6 of Dr. Hirsch's.

DR. MANN: Could you clarify which slide, Dr. Califf, on page 6 you're speaking of and the data that you're asking about?

DR. CALIFF: Yes. We could look at both of them. I was initially just talking about the top slide, the primary efficacy endpoint.

DR. MANN: And this is for the 2 milligram dose of Uprima?

DR. CALIFF: 4 milligram.

DR. MANN: Okay.

DR. AZZIZ: Are you all ready to answer that question please? Page 6, the top, begin with the top slide.

DR. MANN: I'm sorry. You're looking at a different version of our slides than we are, so we're a little confused. If you could give the title of the slide and the data on that slide, that would help.

DR. CALIFF: It says Uprima efficacy of the 4 milligram dose, and the bullet says primary efficacy endpoint.

DR. MANN: Okay.

DR. CALIFF: I think that you would agree on that slide, the numbers are about a 20 to 25 percent improvement, and then on page 7, safety of the 4 milligram dose is the one that I'm really wondering whether you agree

on where it shows, for example, nausea, 20 percent; dizziness, 14 percent, hypotension between 3 and 6 percent, and syncope between 1 and 2 percent.

DR. MANN: Just for clarification for the sponsor, these ranges given on this slide come from the three controlled clinical trials, and I believe they were in agreement with your backgrounder package but you can clarify that if you wish.

DR. AZZIZ: Could we get a response from the sponsor?

DR. HEATON: We agree with the slide.

DR. MANN: Go ahead. You can describe your slide.

DR. FAGAN: This shows the syncope rates at different doses and with different regimens. At 4 milligrams, we see that overall it's 1.2 percent. When the patient started with 2 milligrams prior to 4 milligrams, it was 0.6 percent.

DR. CALIFF: And your hypotension rate at 4 milligrams?

DR. FAGAN: Well, the hypotension again is a subjective thing, and if we had a good definition, if we had measurements everywhere, we could probably --

DR. CALIFF: You know, in most clinical trials where it's been looked at, relying on sporadic reporting of

something hypotension grossly under-reports the phenomenon.

DR. FAGAN: That's why we did the prospective clinical trials in patients with significant cardiovascular disease and also the 491 trial where we did blood pressures sequentially after the first dose in about 450 patients.

DR. CALIFF: So, your estimate then of the rate of hypotension is --

DR. FAGAN: It's in the crossover studies at 2 milligrams, 0.7 percent, around 4 to 5 percent at the higher doses; with dose optimization up to 5 milligrams, 0 percent, 0 of 146 patients; and at 2 to 6 milligrams, 2.5 percent.

DR. CALIFF: Okay, thank you. That's helpful to frame the issue.

DR. AZZIZ: Well, that was nice to clarify.

DR. KOWEY: One of the things that I'd like to know, did you do a formal analysis of dose to response, a statistical measurement of incremental response past 4 milligrams? One of the things you guys have been saying all morning is that you didn't see any more benefit at 5 and 6 milligrams, but there are lots of times when there appeared to be some increment in benefit on some of the graphs.

For your primary endpoint, did you do an interaction study between dose and response and can you

show us what that statistical analysis looks like? When you have it.

DR. AZZIZ: Dr. Tiefer?

DR. TIEFER: Yes. I wanted to ask about the concurrent medication issue. You list on your slide that 18 percent of your patients were taking psychotherapeutic agents and then separately you list that 15 percent were taking anxiolytics, sedatives, and hypnotics. So, I wondered are the psychotherapeutic agents SSRIs or what was going on there?

DR. FRESTON: Yes. I think I'll need to ask Susan Buttler or the statisticians to help us with that. It's my impression that they were mostly SSRIs and tricyclics, and the anxiolytics were separate, but I'd like to get a precise answer for you. Susan, can you help us?

MS. BUTTLER: Some of the med classes that you've seen do overlap a little bit, and in fact, the percent of patients were taking Compazine also fell into the psychotherapeutic class. But it also did include patients who were on SSRIs as well as patients who were on anxiolytics, went into the anxiolytics group. So, it's a somewhat complex system of looking at the drug. So, it did include both of those.

DR. TIEFER: I just asked that because I think the question raised earlier, what is going to be the most

likely combination which I think we could all debate, but I think the drug-related erectile problems, drug-related libido problems, drug-related ejaculatory problems are a growing concern. So, any erection drug, particularly one that's supposedly acting centrally, we'd like to know as much about the conjunctive psychotherapeutic agents as possible.

MS. BUTTLER: If I could just add a point to that, I think you're concerned with something we noted when we designed our studies. Thus, we had appendices that included many of these medications with known side effects. SSRIs are one of them of which are several other medications. In fact, it's a very long laundry list. We required that patients that participated in our studies did not do alterations in their dosages so that we wouldn't know what we were measuring. In other words, patients with SSRIs were allowed into the study, but they were not allowed to be changing their dosage because the simple change in dosage could alter their erectile dysfunction ability. So, we did address your concern in that regard, so we really did measure efficacy of Uprima, not efficacy of changing the dose of a concurrent med.

DR. FRESTON: Anthony has additional clarification.

MR. EDMONDS: Anthony Edmonds with TAP.

Actually I was going to answer the previous question about comparisons among specific doses.

On this slide, we have a first period analysis of placebo, Uprima 2 milligrams, 4 milligrams, and 5 milligrams. Although the studies weren't powered to detect differences between doses, you can see that among the 4, 5, and 6 milligram doses, there aren't any statistically significant differences, but the 2 milligram dose is not as good as the 5 and 6 milligram doses.

DR. AZZIZ: Thank you.

I have a couple of questions that are addressing some of the FDA's concerns. One is the issue of the changing in definition of a serious adverse event. Again, go to Dr. Shames' handout that you have.

DR. FRESTON: Yes.

DR. AZZIZ: On page 5, that last phrase, "or events that require intervention to prevent impairment or damage." I want to make sure that this is correct, and if so, I'd like you to explain that.

DR. FRESTON: Yes. I'm pleased to have the opportunity to clarify this.

In the collection of SAEs and submission of such AEs to the agency, the complete definition in all of its elements was rigorously complied with. Thus, the agency has received all SAEs by their definition.

The problem that happened was inadvertently some of the summaries and intermittent reports that came to the agency didn't include all of those elements. It was an oversight, but all the protocols and case report forms contained the full definition and we complied with that. All the SAEs were reported.

DR. AZZIZ: The full definition meaning it includes that phrase, "or events that require intervention to prevent impairment or damage."

DR. FRESTON: Absolutely.

DR. AZZIZ: Dr. Hirsch, could you comment?

DR. HIRSCH: There is no question in my mind that there were cases that required intervention which were not defined as a serious AE.

DR. AZZIZ: And that is a difference again between the numbers of, say, 30 or so versus 15 or so.

DR. HIRSCH: I believe so.

DR. FRESTON: Could we go back to the definition? Because to require to prevent impairment and damage is the full definition, not just requiring any sort of intervention. And a good illustration of the difference is in those early cases when patients had syncope and the investigators didn't know what they were dealing with, they put in a nasal catheter. That's an intervention. Is that an intervention to prevent permanent impairment or damage?

No. So, I think, Mr. Chairman, that may be the point of contention.

DR. AZZIZ: Well, certainly putting a nasal catheter may not be to prevent impairment, but the reality is I think this is where we're splitting hairs. That is a fairly aggressive intervention. Now, whether the investigator overreacted or not is a different point, but I mean, I think that certainly we'd like to hear that as adverse events.

The second issue has been brought up that perhaps the Cmax or the AUC has been related to side effects or adverse events. Was there any attempt to correlate Cmax or AUC in that the higher the Cmax, the more prone to adverse events? Is there any data in that regard? Yes, ma'am.

MS. BUTTLER: Actually I wanted to address the prior comments regarding the SAEs. I ran and I was overseeing all the clinical programs, and I just wanted to clarify a point about that required intervention to prevent permanent damage.

In fact, it was our investigators' opinion of that assessment. So, despite the fact we may or may not have felt that they overreacted to the situation, if an investigator felt that it required intervention to prevent permanent damage, it was considered an SAE. It always has

been a part of our protocols. It always has been a part of our case report forms.

And I sincerely apologize for our oversight in our clinical trial reports that have obviously caused this confusion, but I can assure you that all of those patients, regardless of what TAP or any of our consultants or anybody thought, if the investigator felt they required intervention, those went in as SAEs.

DR. AZZIZ: Thank you.

Can somebody answer my other question please? The correlation between Cmax or AUC and the incidence of adverse events.

DR. FRESTON: Dr. Bopp.

DR. BOPP: This slide will show the apomorphine Cmax in some of the subjects that experienced vasovagal events during phase I studies when we did have the opportunity to correlate Cmax with these events. This is the Cmax for the individual subject and that is the mean Cmax for the group from which that subject was derived. So, if you look down that list, you can see that many of the Cmax tended to be higher than the mean, but they were certainly not on the extreme side.

In a couple of instances, the event happened in conjunction with an ethanol interaction study, and the ethanol concentrations are shown in that second column

along with the mean for that. Occasionally some of them are lower. Many of them are around the mean or within 1 standard deviation. It is not occurring in subjects with very extreme Cmax.

DR. AZZIZ: Thank you.

Does the committee have further questions right now for the sponsor or the FDA staff?

DR. JARUGULA: Could I add one more point to that?

DR. AZZIZ: Dr. Jarugula.

DR. JARUGULA: I agree with the just submitted analysis, but I would like to clarify a little bit more on the relationship between the Cmax and the syncope or hypotension events. Looking at the table you just looked at, the most subjects had Cmax values that are higher than the group means. The subjects that did have lower than the group mean and had hypotension or syncope also had taken alcohol. So, you have to take the Cmax values of those subjects and also ethanol values in concentration when you are looking at the relationship between syncope and the Cmax.

DR. AZZIZ: Thank you.

Now we're going to go ahead and proceed to questions that the FDA has posed to the committee. Dr. Greene, did you have something?

DR. GREENE: Yes, just one question for Dr. Mann. Two questions actually.

DR. MANN: Sure

DR. GREENE: It's similar to the question I asked the sponsor, which is there are several tables where you include vasodilatation. Again, was that just from their report to you so there's not a precise definition for that?

DR. MANN: That's correct.

DR. GREENE: Then the other question was several places in your analysis where you state "there was patient reported hypotension," the patient doesn't report hypotension.

DR. MANN: Yes. When I wrote these down, I took them directly from the case reports of the patients. You're speaking, I assume, of the drug-drug interaction study where I gave individual case reports for those patients.

DR. GREENE: Well, for example, on page 77, it says, "Comment: It is noteworthy that 4 percent of patients reported hypotension at the 4 milligram dose."

DR. MANN: Oh, I apologize for that, and that's incorrect writing. You're absolutely right. I believe the hypotensive events were recorded by the investigator and it was their judgment. As the sponsor has pointed out, the

definition was not clear. Not every patient had a blood pressure reading. It was just the term they used to describe the event.

DR. GREENE: Okay.

DR. AZZIZ: Thank you very much.

Any other questions? We won't be muzzled after this, but I'd like to proceed on because we do need to come up with some conclusions.

Could I ask the FDA staff to please put the first question up on the screen? You're trying. A computer glitch.

Anyway, the first question is, does the patient population studied support the proposed indication "for the treatment of erectile dysfunction"? If yes, we need to elaborate, and if no, we need to describe our concerns.

Any comments regarding this question first from the committee? Dr. Califf?

DR. CALIFF: There are a lot of arguments I guess about the details of the patient population, but it seems to me they've got well-controlled studies that show statistically significant evidence of meeting the endpoint that was defined. I haven't heard anyone say that the population is totally unrepresentative of patients that might be seen in the clinic.

DR. AZZIZ: Dr. D'Agostino?

DR. D'AGOSTINO: The thing I was trying to flush out was is it an enriched sample and does that make a difference, and I didn't hear any negatives.

DR. JACOBS: In fairness to the question of enrichment, it could be enriched the other direction too.

DR. D'AGOSTINO: Well, enriched in the clinical trials sense of enriched.

DR. JACOBS: In the clinical trials sense, there are patients they eliminated that this drug might work very well in. For instance, I don't know what it does in MS. Maybe it's a great drug for the MS indication. I could see they're being enriched both directions.

DR. KOWEY: Can I ask the urologists on the committee, would you be able, as a urologist, to understand who you should treat with this drug if it were labeled the way it should be labeled?

DR. DONATUCCI: I would say several things about this. First off, the risk factors -- I know there's confusion about the question of no organic cause, but the percentage of risk factors present in the population of the patients, hypertension, cardiac disease, et cetera, actually mirrors the data that I have in my own practice when I went back and looked at the risk factors in my patient population.

Now, they admit that they have eliminated the

bottom 10 percent, the most severe, based upon the Male Massachusetts Aging Study. As far as the severity, they used the International Index of Erectile Function, and I believe the breakdown was about 39 to 40 percent with severe ED based upon that statistically valid parameter.

So, I think that the population in my opinion is representative of the great majority of patients with erectile dysfunction. It's not certainly 100 percent but I don't know that it needs to be.

DR. AZZIZ: I have a question. Organic versus inorganic or organic and non-organic. Is that an issue at this point? Certainly the fact that they had an ability to achieve an erection obviously tells us that it's not fully organic. So, is that something we should note here?

DR. DONATUCCI: I think traditionally this has been an issue. It dates back to the point when we really were pretty ignorant in the pathophysiology, and 90 percent of patients were thought to be psychogenic. Basically as we became educated, we realized that psychogenic erectile dysfunction is becoming less and less common, although obviously any patient with erectile dysfunction has a psychogenic factor. I think there are a lot of patients who we even today label as psychogenic who probably have some underlying pathophysiologic process we can't elaborate, perhaps at a cellular level. So, bearing that

in mind, in my own opinion I'm not sure that's a critical distinction.

DR. AZZIZ: Dr. Tiefer.

DR. TIEFER: I find that it's a difficult question to answer because of how these drugs are used in the real world. The official definition of erectile dysfunction is now relevant only for a certain proportion of people who are interested and who are using these drugs. I think in addition to those with official erectile dysfunction, we've now got people with erectile worries and erectile insecurities who are perhaps making up the lion's share of people who are going to obtain and use these drugs, which brings me to my particular concern which happens to be the alcohol one.

There's now growing evidence of the availability of Viagra at least in clubs and alcohol-available settings, not to mention the Internet is another problem. But if we're thinking about how these drugs are obtained, how they're used in the real world, we've been sort of discussing this in a very hermetic kind of a way as if patients who come into the urologist's office and have co-morbid disease and so on are actually the only population that's going to be addressed. I think that we're too smart to do that, and therefore I'm having just a little trouble with the way this question is phrased. It

seems almost dated and old-fashioned.

DR. AZZIZ: But just to clarify, we do need to answer some questions. Obviously, our function will be to determine if a population will be automatically treated if treat one, but we can't certainly regulate the illicit use of this drug on the Internet or in parties and so on. We really need to be very careful that we give an answer to this first question which is does the patient population studied support the proposed indication for the treatment of erectile dysfunction. So, I'd like to sort of just stay there, not to minimize that question, but --

DR. TIEFER: I agree to a certain point, but we're also interested in the labeling. We're also interested in the potential advertising of these kinds of drugs because it's something that our concern for patients must make us concerned about.

DR. AZZIZ: Absolutely. We're not going to get into labeling yet. We just need to answer the question yea or nay, and then we'll move in to elaborate our concerns.

Any other comments about yes or no? Dr. D'Agostino.

DR. D'AGOSTINO: Did we hear an answer to the question if a patient comes into an office, they would know who to treat?

DR. O'LEARY: Well, you heard from one

urologist. Dr. Donatucci commented on it. O'Leary. I'm another urologist. I don't think I have a particular problem with understanding what the indications for this medication would be. I still have some concerns about safety issues. We haven't gotten to that yet, but as far as does the population that was studied support the indication, I think I don't have any question that the answer is yes.

DR. AZZIZ: Dr. Hanno.

DR. HANNO: I just do have some concerns about the enrichment of the study. I would say that the indication should reflect the fact that the studies that support the drug were enriched. In other words, there's some loss of face validity if we don't say that this drug was tested in patients who did show erections in NPT and were able to get erections on their own, and that's how it was tested. So, when we put the indication forth, that's what it should be indicated for.

DR. AZZIZ: But, Dr. Hanno, let me ask you this. It says, "for the treatment of erectile dysfunction." Would you change that? Is there something you'd do to that wording?

DR. HANNO: I would change the wording to reflect the fact that it's indicated for treatment of erectile dysfunction in patients who have erectile activity

on NPT and/or are able to get erections on their own.

DR. AZZIZ: Well, let's get to the labeling first. Let's go ahead. We haven't heard from everybody that needs to comment. Let's go ahead and put that to a vote. Does the patient population studied -- each of you has to vote and speak into the microphone and get it recorded on the Federal Register so that they can find you at home.

(Laughter.)

DR. AZZIZ: Does the patient population studied support the proposed indication "for the treatment of erectile dysfunction"? Let's start out around the table here to my right, the voting members. Dr. Jacobs.

DR. JACOBS: Yes.

DR. AZZIZ: As far as I know, everybody can vote. That's what I was just told.

Dr. O'Leary.

DR. O'LEARY: O'Leary, yes.

DR. DONATUCCI: Donatucci, yes.

DR. LIPPERT: Lippert, yes.

DR. CALIFF: Califf, yes.

DR. AZZIZ: Azziz, yes.

DR. KOWEY: Before I say yes, which I'm going to --

(Laughter.)

DR. KOWEY: -- I know you don't want to talk about labeling here, but I do think that this is in part a labeling issue in that I think that they have studied a circumscribed, somewhat selected patient population. So, as I say yes, it is with the stipulation that we will discuss somehow in the labeling what that indication is, that it's not a blanket erectile dysfunction claim. It has some qualifiers. So, the answer is yes with qualification.

DR. AZZIZ: I just want to remind the committee before we continue. We're just an advisory committee. We're just putting in our vote and we will give as many recommendations to the FDA who will then shove them in the back drawer and never remember them again.

(Laughter.)

DR. AZZIZ: No, no. But the point is we're just advisory, so yes, we can give all the concerns we have. So, we will do it.

DR. KOWEY: And I just did. Thank you very much.

(Laughter.)

DR. GRABOYS: Graboys, yes.

DR. D'AGOSTINO: D'Agostino, yes.

MS. SCOTT: Scott, yes with reservations similarly talked about.

DR. TIEFER: I like this new option. Tiefer,

yes with reservation.

DR. GREENE: Greene, yes.

DR. HANNO: And I'll say yes with reservations that it's reflected in the label.

DR. AZZIZ: Thank you very much.

Let's go ahead. If the answer is yes, elaborate. At this point it seems to be unanimous yes, that the population studied supports the proposed indication. Now we are ready to bring up some concerns for potential labeling changes or changes in population.

Dr. Greene.

DR. GREENE: If I understand the comments of some of the urologists, may I interpret what you said to suggest that the sensitivity and specificity of this NPT testing is sufficiently poor that you wouldn't consider it very helpful one way or another in enriching or not enriching the population?

DR. O'LEARY: Yes.

(Laughter.)

DR. AZZIZ: Dr. Kowey? You better restate that, though.

DR. KOWEY: I am probably the least competent person to do this, and I'll defer to my urology colleagues. It sounded like that there were some restrictions put on patient enrollment which could potentially have an impact

on the patients who were entered in the trial. And the FDA has said this. I mean, we heard it clearly from the staff.

So, the question is in the labeling what should be said -- and I don't know what should be said -- about the kinds of patients that were enrolled in the trial and how a clinician who's going to prescribe the drug may be able, in their clinical practice, to select those patients to optimize the chances that the drug is going to work.

And the reason why I'm being so persnickety about this is this is not an innocuous drug, and therefore I would like to see people who are not going gain benefit not be exposed to it. It doesn't make any sense. So, the risk-benefit, which we're going to come to is directly proportional to this question. And if we can't define the population, then I'm not going to be terribly excited about letting the drug on the market, voting for approval. If you can tell me that, yes, we can tell you who the population is with a reasonable degree of certainty, then that's very important to me. So, that's up to you guys.

DR. DONATUCCI: Clearly there's a spectrum of disease, and I think it has been stated earlier that based upon the way the study was designed, those patients who had total erectile failure were eliminated from consideration in the study. Based on clinical experience with other therapeutic alternatives, we know that the more severe and

the long lasting the disease process is, the more risk factors, et cetera, the less likely. In fact, there have been studies in the literature you can -- this is somewhat drastic -- biopsy the penis and quantitate the degree of smooth muscle present. And as that percentage drops, responsivity and degree of erectile function drops.

So, clearly people at the end of the spectrum are not going to be great candidates for any drug therapy. For those of us who do it every day, that's pretty obvious to us, but perhaps that should be spelled out in the labeling.

DR. AZZIZ: Dr. O'Leary?

DR. O'LEARY: I think one of the reasons why, as I'm reading through this data set, NPT was used to begin with was because it was the only thing that was "objective." In an attempt to try to include as much objective data as possible, it was the only thing that was really available on a large scale. In fact, most of us don't, as I think you've heard, use NPT very much. It has very limited value in day-to-day practice.

So, while I understand what the goal of the study was, I've basically discounted it. To me it's not a particularly important part of the data set or the inclusion criteria, for that matter. The inclusion criteria, to my mind, reflect what we see in daily

practice, as I said before.

DR. AZZIZ: Dr. Jacobs.

DR. JACOBS: I know we're going to talk about labeling eventually, but this sort of fits into it too. I think a sentence that says there is no evidence that this drug helps people with total erectile failure, spinal cord injury, multiple sclerosis, Parkinson's disease, would be the sort of sentence we would want to see in a label. Not that it's forbidden. There is no evidence that this helps those people.

DR. AZZIZ: In a second, we will be dealing with risk-benefit. We have just simply decided that the population studied seemed to represent the population that you all see.

So, any other comments about the population studied?

(No response.)

DR. AZZIZ: Let us move on to the second question. Do the data presented support an acceptable risk-benefit profile for the 2 milligram dose of Uprima? If yes, please elaborate. If no, please describe your concerns, including additional studies that might address these concerns.

I'd like to hear comments about this.

DR. GRABOYS: There is a population of folks

out there that all of us in clinical medicine see every day and that's the coronary artery disease population. In this population, these folks are biting at the bit for an alternative. So, there is a huge market -- obviously you all know that -- for this agent or for any agent, anything that can help their erections.

So, what we are kind of trying to deal with is the issue of polypharmacy. Since we are pushing in cardiology nitrates and at the same time we're trying to deal with folks who have got erectile dysfunction, well, this is fine in terms of the Viagra. I think the message is out. But in terms of your drug, the jury is out as far as nitrates. I didn't hear anything about the dosing, about the long-acting. I didn't know exactly what that was. But we have folks that we are increasing their dose 20, 40, 60, 100, 180 milligrams of nitrates, while simultaneously they may be on your drug.

So, I don't know. Do you feel sanguine about this in terms of how we're going to be educating physicians to prescribe the drug? What about the patient population?

I think that the polypharmacy issue is a significant one and the nitrate issue is a significant one. And I couldn't vote on this until it's resolved.

DR. FAGAN: Would you like us to respond?

DR. AZZIZ: If there is direct data to answer

that question, go ahead. We'll take a short second or two.

DR. FAGAN: In the long-acting interaction trial, the doses of Imdur ranged from 30 to 120 milligrams a day in several patients. It was dosed 4 hours before they got their drug. Isosorbide was 40 b.i.d. in a couple of patients. ISMO was I believe 20 b.i.d. in several patients, and there were several patients on various levels of patch therapy. So, there were a few that were toward the upper end of the spectrum, and I think most of them were respectable doses.

DR. AZZIZ: Other concerns, questions? Dr. Califf.

DR. CALIFF: Specifically with regard to the 2 milligram dose, it seems to me that as a specific question, it's kind of like old-fashioned medicine: It's not much good, but it probably won't do much harm either. It really seems almost not important relative to the 4 milligram issue. The answer to the 4 milligram issue is if the risk-benefit ratio is adequate, then it seems like the 2 milligram, although it wouldn't stand on its own in my opinion, needs to be in because of the dose escalation issue and the likelihood that some patients may benefit.

DR. AZZIZ: A question for the sponsor again. Just to bring up Dr. Califf's point, the vast majority of patients didn't seem to stay on 2 milligrams. 2 milligrams

didn't seem to be very effective. I mean, you have a few percentages above what it was before. The only reason you are asking for approval is because of the titrated regimen. Is that correct? I'm unclear as to what the reason for that would be otherwise.

DR. HEATON: There are several points here. Some patients do respond very satisfactorily and will stay on 2 milligram. On the basis that patients should remain on the least drug that is effective, those patients should have the opportunity of a 2 milligram tablet.

The other thing is that the dose escalation is a logical thing to do and has been shown here.

DR. KOWEY: Maybe I can do my Ray Lipicky impersonation and bring up a point about that. I think you're right, by the way, that there clearly are people who respond to 2 milligrams. There might be people who respond to 1 milligram. Perhaps, Rob, the risk-benefit equation there -- even though you would argue, gee, you're not really getting much of an effect at all, some people might respond at a milligram and get no hypotension.

DR. CALIFF: Maybe it would be best to start with placebo.

DR. KOWEY: You get a nice little rise with placebo. Excuse the pun.

(Laughter.)

DR. KOWEY: But I agree with Rob. I think that the 2 milligram is easy in terms of risk-benefit because there's not much risk. But I do think there is some benefit, and I would not want to see the 2 milligram not get approved if the 4 milligram were approved because there were responders to 2 milligrams.

DR. AZZIZ: But again, the majority of the use with 2 milligrams is part of a titrated regimen.

DR. HEATON: The majority is, yes.

There is a factor that has not been identified in discussion today about dopaminergic agents, which points out that there is a characteristic of this class of agents which means to say they are better prescribed in the appropriate dose than simply going up to the max. This is characteristic of dopaminergic agents. Otherwise, patients with ED will always migrate to the max.

DR. AZZIZ: Thank you.

Dr. O'Leary.

DR. O'LEARY: In response to the question, I'm looking at the data that say that somewhere between 40 and 46, 44, 47 percent of patients respond. Now, I realize scientifically we're comparing this to placebo, but clinically I'm comparing it to somebody who doesn't respond at all. So, if I've got a 2 milligram dose of this drug, I know that's not what we're supposed to do, but that's what

happens in clinical practice. And if I give this to somebody -- I wish the FDA would approve placebo, but they haven't approved it.

(Laughter.)

DR. O'LEARY: Because I would definitely give that. In all ED trials, it about a 30 percent response and it's the same, by the way, for lower urinary tract symptoms with BPH. It's about a 30 percent response to placebo. Now, maybe urologists are just luckier than other practitioners in terms of giving a pill to a patient.

But to me a 2 milligram dose makes -- that's where I would start based on the data that I've been presented.

DR. AZZIZ: You're primarily treating men who are highly susceptible to the placebo.

(Laughter.)

DR. AZZIZ: Dr. Tiefer?

DR. TIEFER: Let me just say that I think what happens is that in the real world most patients with erectile problems have very poor sex education, poor verging on none, no formal sex education, no opportunity to talk openly about erotic technique, and that the opportunity to talk with a physician often with the partner present is the first time certainly since the problem began and maybe in the person's entire life -- we've heard this a

million times. Right? I've never talked to anybody about this before. I think that's the active agent in the placebo effect, that the person is actually talking about with their partner the fact that they want certain things, they feel certain things, and so on.

I would really like to see trials of sex education before we start throwing drugs at people. We live in a country where there's no government approval for sex education, but tremendous institutional support for drugs. So, when I see here, do the data presented support an acceptable profile for this drug, to me it's not acceptable because of the absence of any sort of formal sex education to the patients with this problem. It's as if we were discussing a diabetes drug and the food pyramid was a federal secret and you weren't allowed to talk about these things with anybody because it just wasn't part of the medical model.

So, again, I feel like the question kind of is not in the real world where the patients need information about sexual technique, age-related changes, and so on.

DR. AZZIZ: Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: I just wanted to say if you travel from one field of medicine to another, these differences, placebo versus the drug effect, aren't trivial

effects. You may say they're trivial in your mind, that they don't look big, but getting a 33 percent increase over placebo is substantial. And we have three studies that did it.

DR. CALIFF: You're talking about the 4 milligram dose.

DR. D'AGOSTINO: No, no, even the 2. We have those three crossovers, didn't we?

DR. CALIFF: They weren't significant, were they?

DR. D'AGOSTINO: Yes.

DR. CALIFF: All were?

DR. TIEFER: Statistically significant.

DR. D'AGOSTINO: Well, and clinically I don't think that this is a trivial margin. It could be overwhelmed by safety, but I think on the basis here it's not trivial.

DR. AZZIZ: Thank you.

Dr. Donatucci.

DR. DONATUCCI: Yes. I just want to make one comment that addresses one of the FDA questions that came up earlier in the context of what we're discussing now. This is a very variable condition, and it changes over time. Patients are very motivated initially and they may lose their motivation with time. There was a question I

believe about long-term dropout. My experience with every agent that I've used is that they all experience long-term dropout regardless of what we're using.

Michael O'Leary mentioned BPH earlier. A senior urologist once said that's an unevaluable condition because all the tests we use to evaluate you can argue till the cows come whether they're reflective of the condition or not. In a sense this is also similar. So, it's a very difficult condition to pin down, particularly for any individual, but we have to do something and we have to make a decision. I understand what you were saying earlier about sex therapy and just discussing the problem, but that doesn't help you make a decision that you have to make today.

So, I think again that this 2 milligram dose has been shown to be statistically effective. The clinical significance may not be apparent to someone who doesn't take care of these patients, but again I've had patients, I have literally told them this drug will not work for your condition, and they'll say I want to try it anyway, given the other alternatives.

DR. AZZIZ: I have a question maybe for the committee, but also for the sponsor. Risk-benefit. We've talked a lot about benefits. I have to agree with Dr. Tiefer that I wish we could really have a study of sexual

counseling. That is an extremely important area that is underfunded and understudied. But today we're here to study a drug.

But the risk issue has not been addressed, and I have a couple of concerns. That is the alcohol use. I can tell you some individuals will have responsible sex and not have a drink before they have sex, but most people will have more than a couple of vodkas. I am unclear as to how safe it is in the face of a couple of vodkas. You had one fellow there who had a rye, a bourbon, a vodka, and a beer, but that's pretty standard for a lot of the patients.

(Laughter.)

DR. AZZIZ: No sex education either.

(Laughter.)

DR. AZZIZ: But that is an issue I think I'd like to -- if you could just look at that alcohol adverse events please and review that because that is a concern, particularly because your proposed labeling does not have sufficiently explicit the potential for alcohol interaction. You asked the patients not to take it before they use the drug, and then your alcohol studies were relatively modest because, in fact, you got scared when you used a good dose.

DR. FAGAN: Well, there's a couple of things. First, the instructions were don't take more than two