FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BONE, REPRODUCTIVE, AND UROLOGIC DRUGS ADVISORY COMMITTEE (BRUDAC)

Wednesday, October 19, 2016

8:15 a.m. to 4:26 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kalyani Bhatt, BS, MS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

BONE, REPRODUCTIVE, AND UROLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Douglas C. Bauer, MD

Professor of Medicine and Epidemiology & Biostatistics

University of California, San Francisco

San Francisco, California

Matthew T. Drake, MD, PhD

Associate Professor of Medicine

Chair, Metabolic Bone Disease Core Group

Division of Endocrinology

Mayo Clinic College of Medicine

Rochester, Minnesota

Stuart S. Howards, MD

Professor of Urology

Department of Urology

University of Virginia

Charlottesville, Virginia

Vivian Lewis, MD

(Chairperson)

Vice Provost for Faculty Development & Diversity

Professor, Obstetrics and Gynecology

University of Rochester

Rochester, New York

Sarah Sorscher, JD, MPH

(Consumer Representative)

Researcher

Public Citizen's Health Research Group

Washington, District of Columbia

BONE, REPRODUCTIVE, AND UROLOGIC DRUGS ADVISORY COMMITTEE MEMBER (NonVoting)

Gerard G. Nahum, MD, FACOG

(Industry Representative)

Vice President of Global Development, General Medicine Women's Healthcare, Long-Acting Contraception, Medical Devices, and Special Projects Bayer HealthCare Pharmaceuticals, Inc.

Parsippany, New Jersey

TEMPORARY MEMBERS (Voting)

G Caleb Alexander, MD, MS

Co-Director, Johns Hopkins Center for Drug Safety and Effectiveness

Johns Hopkins Bloomberg School of Public Health

Baltimore, Maryland

Barbara Berney

(Patient Representative)

Rockford, Illinois

David Cella, PhD

Chair, Department of Medical Social Sciences

Director, Institute for Public Health and Medicine

Center for Patient-Centered Outcomes

Chicago, Illinois

Michael B Chancellor, MD

Professor of Urology and Director of the Aikens Research Center

Beaumont Health System

Oakland University William Beaumont School of Medicine

Royal Oak, Michigan

Daniel W. Coyne MD

Professor of Medicine

Division of Nephrology

Washington University School of Medicine

St. Louis, Missouri

Brian L. Erstad, PharmD

Professor and Head

The University of Arizona College of Pharmacy

Department of Pharmacy Practice & Science

Tucson, Arizona

Walid F. Gellad, MD, MPH

Associate Professor of Medicine and Health Policy

University of Pittsburgh

Pittsburgh, Pennsylvania

Philip Hanno MD, MPH

Clinical Professor of Urology

Stanford University School of Medicine

Palo Alto, California

Theodore Johnson, MD, MPH

Paul W. Seavey Chair in Medicine

Atlanta Site Director

Birmingham/Atlanta VA GRECC

Department of Vet Affairs

Professor of Medicine & Epidemiology

Emory University

Atlanta, Georgia

Kevin McBryde, MD

Program Director

Office of Minority Health Research Coordination

National Institute of Diabetes and Digestive and Kidney Diseases

National Institutes of Health (NIH)

Bethesda, Maryland

James D. Neaton, PhD

Professor of Biostatistics

University of Minnesota

Minneapolis, Minnesota

Christian P. Pavlovich, MD

Professor of Urology and Oncology

Johns Hopkins Medical Institutions

Director, Urologic Oncology

Johns Hopkins Bayview Medical Center

Director, Urologic Oncology Fellowship

Baltimore, Maryland

Ashley Wilder Smith, PhD, MPH

Chief, Outcomes Research Branch

National Cancer Institute (NCI), NIH

Rockville, Maryland

Robert J. Smith, MD

Professor of Medicine, The Warren Alpert School of Medicine

Professor of Health Services, Policy and Practice

School of Public Health

Brown University

Providence, Rhode Island

FDA PARTICIPANTS (Non-Voting)

Hylton V. Joffe, MD, MMSc

Director

Division of Bone, Reproductive and Urologic Products

(DBRUP)

Office of Drug Evaluation III (ODE III)

Office of New Drugs (OND), CDER, FDA

Martin Kaufman, DPM, MBA

Clinical Analyst

DBRUP, ODE III, OND, CDER, FDA

Suresh Kaul, MD

Team Leader

DBRUP, ODE III, OND, CDER, FDA

Olivia Easley, MD

Medical Officer

DBRUP, ODE III, OND, CDER, FDA

Jia Guo, PhD

Biostatistician

Division of Biometrics III

Office of Biostatistics

OND, CDER, FDA

Sarrit Kovacs, PhD

Reviewer

Clinical Outcome Assessments (COA)

OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. LEWIS: Good morning, everyone. I'd like to call the meeting to order. I'd like to first remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I would also like to identify the FDA press contact, Sarah Peddicord. If you're present, please stand. Oh, there you are, waving in the back. Got it.

Now, I'd like to ask the panelists to please introduce themselves. We'll start with Dr. Nahum

DR. NAHUM: My name is Dr. Nahum. I am with Bayer Pharmaceuticals. I'm the designated industry representative, and I am an MD trained in obstetrics and gynecology. And I'm in charge of clinical development for Bayer general medicine.

DR. ALEXANDER: Good morning. I'm Caleb Alexander. I'm an epidemiologist and internist at Hopkins, and I co-direct the Center for Drug Safety

and Effectiveness, and I also chair the FDA's Peripheral and Central Nervous System Advisory Committee.

DR. GELLAD: Good morning. Walid Gellad from the University of Pittsburgh, internist, and I lead the Center for Pharmaceutical Pharmacy and Prescribing.

DR. CELLA: David Cella from Northwestern University, Department of Medical Social Sciences, outcomes researcher.

DR. A. SMITH: Ashley Wilder Smith. I'm at the National Cancer Institute, chief of the outcomes research branch.

DR. JOHNSON: I'm Ted Johnson. I'm a VA investigator in the Birmingham/Atlanta VA GRECC, and I'm professor of medicine at Emory University.

DR. PAVLOVICH: Christian Pavlovich. I'm a urologist at Johns Hopkins, where I'm a professor of urology and oncology.

DR. HANNO: Philip Hanno. I'm a urologist at Stanford.

MS. BERNEY: I'm Barbara Berney, and I am

sort of the catch-all patient rep for FDA.

MS. SORSCHER: My name is Sarah Sorscher. I'm the consumer representative, and I work at Public Citizen as a researcher.

DR. R. SMITH: I'm Robert Smith. I'm an endocrinologist. I'm professor in the medical school and also in the School of Public Health at Brown University.

DR. DRAKE: My name is Matthew Drake. I'm an endocrinologist at the Mayo Clinic in Rochester, Minnesota.

DR. LEWIS: And I'm Vivian Lewis, and I'm a reproductive endocrinologist at the University of Rochester and chair of the committee.

MS. BHATT: Good morning. My name is Kalyani Bhatt. I'm the designated federal officer for the Bone, Reproductive, and Urologic Advisory Committee.

DR. BAUER: Hi. Good morning. My name is Doug Bauer. I'm an internist and clinical epidemiologist, professor of medicine, epidemiology, and biostatistics at UCSF.

DR. HOWARDS: I am Stuart Howards. I'm a urologist at the University of Virginia and Wake Forest Medical School.

DR. CHANCELLOR: I'm Michael Chancellor. I'm professor of urology and director of research at the Beaumont Health System and the medical school, Michigan.

DR. NEATON: Jim Neaton, biostatistician at the University of Minnesota.

DR. ERSTAD: Brian Erstad, professor and head, University of Arizona, College of Pharmacy.

DR. COYNE: Daniel Coyne. I'm a nephrologist at Washington University in Saint Louis.

DR. McBRYDE: I'm Kevin McBryde. I'm a pediatric nephrologist, and I'm a medical officer and medical monitor with the National Institutes of Dental and Craniofacial Research.

DR. KAUFMAN: Martin Kaufman. I'm with the Division of Bone, Reproductive, and Urologic Products, FDA.

DR. KOVACS: Sarrit Kovacs, a reviewer with

the clinical outcomes assessment staff in the Office of New Drugs, FDA.

DR. GUO: I'm Jia Guo, statistical reviewer at FDA.

DR. EASLEY: Olivia Easley, medical officer in the Division of Bone, Reproductive, and Urologic Products at FDA.

DR. JOFFE: And I'm Hylton Joffe. I'm the director of FDA's Division of Bone, Reproductive, and Urologic Products.

DR. LEWIS: All right. Thank you all, and welcome again.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that those individuals can express their opinions without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place only in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during break or lunch. Thank you.

Now, I'd like to pass it to Kalyani Bhatt, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. BHATT: Good morning. The Food and Drug Administration is convening today's meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the

committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of regular federal employees is not so substantial to be deemed likely to affect the

integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. Their interest may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of the efficacy and safety of new drug application, NDA 201656, desmopressin, a nasal spray submitted by Serenity Pharmaceuticals, LLC, for the proposed treatment of adult onset nocturia. This is particular matters meeting during which specific matters related to Serenity's NDA will be discussed.

Based on the agenda for today's meeting and

all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we'd would like to disclose that Dr. Gerard Nahum is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Nahum's role at this meeting is to represent industry in general and not any particular company. Dr. Nahum is employed by Bayer Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such

involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationship that they may have with the firm at issue. Before we start the meeting, I'd like to introduce and turn the mic over to Sarah Sorscher.

MS. SORSCHER: The director of Public Citizen's Health Research Group, Dr. Mike Carome, previously testified at an advisory committee meeting related to a different desmopressin product for treatment of nocturia due to nocturnal polyuria, and he testified against approval based on that product's safety effectiveness profile.

So I just wanted to declare that to the committee. My statements today will be my own. I'm not representing Dr. Carome or Public Citizen. I'm here to represent consumers and plan to do so.

DR. LEWIS: Thank you. I'd like to now introduce Dr. Joffe to help us get the meeting started.

FDA Opening Remarks

DR. JOFFE: Good morning, everybody. I'd

like to welcome you all to today's advisory committee. We'll be talking about desmopressin nasal pray for the treatment of nocturia. I'm Hylton Joffe. I'm the director of FDA's Division of Bone, Reproductive, and Urologic Products.

What I'd like to do over the next 15 minutes is give an overview of this proposed drug and also the proposed indication, treatment of nocturia. We'll then briefly discuss some of the issues with the applicant's proposed indication, some of the efficacy and safety issues, and then we'll end with the questions that we're asking the committee to discuss and vote upon.

The product is desmopressin nasal spray. In some of our slides, you'll see it referred to as SER 120. The applicant is proposing this for the treatment of nocturia in adults who awaken at least 2 times per night to urinate. The proposed regimen is a starting dose of 0.75 micrograms per night, which can be increased if needed, after 2 to 4 weeks, to 1.5 micrograms per night.

Desmopressin is a synthetic analogue of

vasopressin. It stimulates water reabsorption in the kidneys leading to more concentrated urine and less water excretion. There are other FDA-approved formulations of desmopressin: tablet, injectable, and intranasal formulations. None of these are approved for nocturia. They're approved for one or more of the following indications: central diabetes insipidus, primary noctural enuresis in children, and hemostasis in von Willebrand disease, and hemophilia A. The most important risk with these products is hyponatremia, and this led to removal of the primary noctural enuresis indication for the approved intranasal formulations.

Nocturia is defined as awakening at night to urinate with each voiding episode preceded and followed by sleep. It's typically considered clinically meaningful when there are at least 2 episodes per night. Prevalence increases with advancing age. It's associated with sleep disruption, decreased quality of life, and, particularly in older patients, falls and fracture. There are no drugs that are FDA-approved to treat

nocturia, so if this drug is approved, it would be the first one. But some drugs are used off label for nocturia, including some of the desmopressin formulations.

Outside the United States, there are other desmopressin formulations that are approved for nocturia, and these formulations are specifically approved for nocturia associated with nocturnal polyuria. Nocturnal polyuria refers to an excess of urine production at night. Typically, these other products are not recommended for initiation in adults who are over 65 years of age because of the risk of hyponatremia.

It's important to note that nocturia is a symptom of one or more underlying conditions. For example, just like chest pain is a symptom of a variety of conditions such as myocardial infarction, pulmonary embolism, pneumonia, gastroesophageal reflux disease, musculoskeletal pain, and so on and so forth, so too is nocturia a symptom of one or more underlying conditions, some but not all of which are shown on this slide.

For example, bladder abnormalities such as overactive bladder or bladder outlet obstruction from benign prostatic hyperplasia could lead to nocturia, as can edema associated states such as heart failure, nephrotic syndrome, as can neurodegenerative conditions such as Parkinson's and Alzheimer's. There's also a variety of endocrine and metabolic abnormalities that can lead to hyponatremia; same where there's a variety of medications, including diuretics, as well as caffeine and alcohol, and then also excessive fluid intake.

This brings us to issues with the proposed indication. As I mentioned previously, the applicant is proposing a broad indication, treatment of nocturia in adults who awaken at least 2 times per night to urinate without consideration of the underlying etiology. And as I just mentioned, nocturia is a symptom of one or more underlying conditions.

You'll also hear from FDA staff that the trials had numerous exclusion criteria. And also,

the trials did not systematically assess whether an improvement in nocturia could lead to worsening of other aspects of the underlying conditions. For example, if you shift urine output from the night to the day, could that lead to worsening of urgency or frequency in patients who have underlying overactive bladder or BPH. So these raise complicated issues, and this is one area where we will be seeking advice from the advisory committee panel.

I'd now like to turn to some of the issues with the designs of the pivotal phase 3 trials. There were two, DB3 and DB4. When these trials were under development, this application was within a different division at FDA. It was transferred to our division as the phase 3 trials were nearing completion. So during the design phase, FDA agreed with limiting enrollment in these trials to adults who are at least 50 years of age.

The intent here was to enrich the trial population with all the patients because all the patients have a higher risk of hyponatremia, and so

you could get a good sense of that safety issue in the older population. But the flip side is that we now have no efficacy or safety data in adults less than 50 years of age. And this is at odds with the applicant's proposed indication, which is treatment of all adults, regardless of age, for nocturia.

The trials also did not restrict fluid intake. For example, there were no instructions asking patients close to bedtime to restrict the amount of fluid they're taking in. As I mentioned previously, there were numerous exclusion criteria. Also, the trials did not test the proposed titration regimen. So as I mentioned, the applicant is proposing starting with a 0.75 microgram dose, titrating after 2 to 4 weeks, if needed, to 1.5 micrograms. But the trials tested these doses in parallel treatment arms, not in a titration regimen.

Lastly, FDA agreed during the trial design phase to focus the primary efficacy analyses on an modified intent-to-treat population made of placebo nonresponders. So as you will hear, these trials

had a screening phase, a 2-week lead-in phase, and then randomized patients to drug or placebo. After the trial was completed, the applicant then went back and figured out who was a placebo responder or non-responder in the lead-in period based on prespecified criteria. They then limited the key efficacy analyses to the placebo nonresponders.

When the application was transferred to our division and after results were known, we thought more about this, and we informed the applicant that we intend to focus on the intent-to-treat population, which includes placebo nonresponders and placebo responders. That represents a greater proportion of the randomized patients. And we view the placebo non-responder modified intent-to-treat population really as a subgroup analysis because in the end, the applicant randomized all patients to drug or placebo without taking into account whether they were a responder or not.

So results were similar, but for our analysis, we'll be focusing on the intent-to-treat population, which is the standard population when

looking at efficacy for not just drugs for nocturia, but across a broad range of indications.

The key efficacy endpoints, there were two co-primary efficacy endpoints. The first was the change from baseline in mean number of nocturia episodes per night, and the second was a responder analysis, the percentage of patients with at least a 50 percent reduction from baseline in mean number of nocturia episodes per night.

There were also several secondary efficacy endpoints, some of which are shown on this slide. In study DB4 alone, the first secondary efficacy endpoint was a patient-reported outcome known as INTU or impact of nighttime urination. This was developed with advice from FDA and was designed to assess the impacts of nocturia on patients' lives. And you'll hear from FDA staff about some of the strengths and limitations of this instrument. Other secondary endpoints included the percentage of nights with no nocturia episodes, and at most, one nocturia episode.

The next two slides go over some of the

efficacy issues. The first trial, DB3, studied 3 desmopressin doses against placebo -- 0.75 micrograms, 1 microgram, and a 1.5 microgram dose, and DB4 studied 2 desmopressin doses at 0.75 micrograms and 1.5 micrograms. In both of these trials, only the 1.5 microgram dose met both prespecified co-primary efficacy endpoints.

This slide shows some of the key efficacy findings with this 1.5 microgram dose. For example, in the first row, the first co-primary endpoint, the reduction from baseline in mean number of nocturia episodes, you can see at baseline, there were about 3 episodes per night across treatment groups, and the drug led to a 0.3 to 0.4 improvement per night in episodes compared to placebo, on average.

With regard to the second co-primary endpoint, the percentage of patients with at least 50 percent reduction in nocturia, you can see that the drug led to about an 18 or 19 percent absolute treatment difference compared to placebo, with about a third of placebo patients having at least

50 percent reduction in nocturia.

With regard to that patient-reported outcome, the INTU, which has a range of scores from zero to 100, the higher the score, the more severe the impacts, you can see at baseline, the score was about 30 across treatment groups. The 1.5 microgram dose in DB4 reduced the overall impact score by about 14 points on average, but placebo improved that score by about 12 points on average.

So the difference between drug and placebo was an average of only 2.6 points. All the findings on this slide are statistically significant, but our question is what's the clinical relevance of all these findings, another area where we'll be needing input from the committee.

Safety issues I've already mentioned, that hyponatremia is the most important risk. Hyponatremia can lead to seizures, coma, and death, particularly if it's severe and acute. You'll hear about the hyponatremia findings in the applicant's database. Basically, there was a higher incidence

with the 1.5 microgram dose compared to the 0.75 microgram dose, and there was also higher incidence among those who were over 65 years of age compared to those who were under 65.

So lastly, I'll turn to the discussion and voting questions, and this will help frame the issues for the panel as you hear the presentations from the applicant and from FDA. There are four discussion questions and two voting questions. The first discussion question reads as follows:

The applicant's trial's limited enrollment to adults at least 50 years of age had numerous exclusion criteria and had no restrictions on fluid intake. So we'd like the committee to discuss whether the applicant studied desmopressin is the appropriate patient population.

The second discussion questions asks the committee to discuss the clinical significance of the observed treatment effects of desmopressin or nocturia compared to placebo. So this gets at the clinical meaningfulness of the efficacy findings.

The third question asks the committee to

discuss whether the safety of desmopressin is being adequately characterized and whether additional safety data are needed. And the last discussion question gets at the indication. So it states that nocturia is a system that can be caused many conditions, some of which may co-exist in the same patient. And we ask the committee to discuss whether the applicant's proposed indication for the treatment of nocturia, that does not specify the underlying etiology, makes clinical sense, is it clinically appropriate.

If it is, then we'd like you to discuss the adequacy of the applicant's data to support such a proposed indication or whether additional data are needed. And if additional data are necessary, discuss what data would be needed to support the broad indication.

The first voting question asks whether there is sufficient evidence to conclude that at least one of the desmopressin doses is effective. We would like the committee to provide rationale for your answer. If you vote yes, we'd specifically

like you to comment on which dose or doses is effective and whether the data support the proposed regimen of starting with the 0.75 micrograms and titrating to 1.5 micrograms, if needed, after 2 to 4 weeks.

Then the last question asks whether the benefits of desmopressin outweigh the risks and support approval. Again, we'll be interested in hearing the rationale for your answer. If you vote yes, we'd like you to specify the indication that you believe is supported by your benefit-risk assessment, and if you vote no, we'd like to hear recommendations for additional data that you think might support a favorable benefit-risk assessment.

With that, I'd like to thank the committee in advance for all the input you'll be providing over today, and I'll turn it back to our chair.

DR. LEWIS: Thank you, Dr. Joffe.

We'll now proceed with the sponsor presentations.

Both the Food and Drug Administration and the public believe in a transparent process for

information-gathering and decision-making. FDA believes it is important to understand the context of an individual's presentation to ensure that such transparency occurs at the advisory committee meeting.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We'll now proceed with sponsor presentations.

Applicant Presentation - Seymour Fein

DR. FEIN: Thank you, Dr. Lewis.

Good morning, ladies and gentlemen. My name is Dr. Seymour Fein. I'm the chief medical officer of Serenity Pharmaceuticals, and today we'll be presenting information about our SER 120 new drug application for the treatment of adult onset nocturia. I'll begin with some introductory slides to provide background and overview of our presentation, and I would add that I think Dr. Joffe did an excellent job presenting some of my introductory slides, so I apologize in advance for any redundancy.

Nocturia is a multi-factorial medical condition with documented associated morbidity and mortality. The majority of patients with nocturia have noctural polyuria, but many also have overactive bladder or benign prostatic hypertrophy, and it's an unmet medical need, which impacts the activities of daily living.

Currently, there is no FDA-approved products specifically for the treatment of nocturia. The

many drugs that are used to treat OAD and BPH have been shown in the published literature to be relatively ineffective for the treatment of nocturia. Antidiuretic drug therapy has shown the most potential for treating nocturia and filling this gap.

So let's turn for a moment to desmopressin. It's a well characterized drug. It's a synthetic peptide analogue of vasopressin, the natural human antidiuretic hormone. It has antidiuretic pharmacology, which can reduce nocturnal urine production, and desmopressin is a highly selective V2 agonist with minimal hemodynamic effects when used at therapeutic doses, which traditionally have been much higher with previously approved desmopressin products than we're using with SER 120.

Published in vitro studies suggest no significant liver metabolism. Its elimination depends largely on intracellular proteolytic degradation with significant amounts of desmopressin, roughly 30 to 45 percent, excreted

unchanged in the urine. Desmopressin was first approved by FDA way back in 1979 in a variety of dose forms for such conditions as central diabetes insipidus and primary noctural enuresis, bedwetting in children.

What about using desmopressin to treat nocturia? Well, the current problem with desmopressin for nocturia is an unwanted prolongation of the antidiuretic effect beyond the hours of sleep, creating the risk of water retention and consequent hyponatremia. The solution is low-dose desmopressin, but not just low-dose desmopressin, a product with a predictable and consistent pharmacokinetic profile, which reliably controls the pharmacodynamic duration of the antidiuretic effect, and we think SER 120 provides this solution.

SER 120 is a novel, very low-dose desmopressin formulation specifically engineered for the treatment of nocturia. It's preservative-free. It is administered as a metered-dose nasal spray with 100 microliter

volume, and it's manufactured aseptically. It contains cyclopentadecanolide, CPD, a cyclic fatty acid, as a permeation enhancer to facilitate systemic absorption through the nasal mucosa.

So what is our proposed indication? Dr. Joffe alluded to this. We proposed that SER 120 is indicated for the treatment of nocturia in adults who wake up 2 or more times per night to void. Why 2 or more voids per night instead of the International Continence Society definition of 1 or more? Well, as Dr. Wein will shortly describe, there are numerous studies demonstrating that 2 voids is a threshold for clinical bothersomeness and significant comorbidities.

In terms of the indication being nocturia rather than other wording, such as noctural polyuria, approximately two-thirds of patients have more than one etiology contributing to their nocturia. Nocturnal polyuria is certainly the most common, but it is not often seen in isolation.

This last slide in my introduction just presents the rest of the agenda for Serenity's core

presentation. I'll now turn the floor over to Dr. Alan Wein, who will present nocturia as an unmet medical need.

Dr. Wein?

Applicant Presentation - Alan Wein

DR. WEIN: Thank you, Dr. Fein, and good morning.

My name is Alan Wein. As a consultant and advisor to the sponsor, I do have a financial interest in the outcome of this meeting. I was asked to talk about nocturia as an unmet medical need.

Nocturia is an underrecognized medical need. Many patients do not list this as their primary complaint simply because they do not believe that there's a specific resolution for this. It's not really simply due to overactive bladder in either women or men, and it's not simply due to benign prostatic hypertrophy in men either. It does have significant adverse consequences, and it does negatively impact the quality of life when it gets over a certain number.

This is the prevalence of nocturia in men and women based on multiple studies but showing those that have nocturia 2 or more times a night. The reason that's chosen is because you'll see shortly that it's really 2 episodes a night and more that the bothersomeness begins to come in. As you can see, there's a fairly sharp upswing after the age of 60, so that depending on the group, the prevalence is somewhere between 30 and 60 percent.

This is a simple cartoon that I made up a number of years ago just showing the various contributing factors to nocturia. Sleep disturbances and psychological factors are really indirect causes and are not really affected by any of the medications proposed to treat the type of nocturia that we're speaking of. The primary contributing factors are bladder storage problems and polyuria, notably nocturnal polyuria. Most cases involve some kind of mixture, and as you'll see shortly, nocturnal polyuria is involved in almost all of them.

This is a simply pie chart that shows

regardless of the demographic and geographic considerations, when you look at nocturia patients as a whole, those with nocturnal polyuria far outnumber those that do not have nocturnal polyuria.

Bear with me with this build slide that shows basically the effect of varying degrees of nocturia on various quality-of-life activities listed on the horizontal axis. This is no nocturia. This is 1 episode per night, this is 2 episodes per night, and this is 3 or more episodes a night. And as you can see, the most affected functions really are vitality, distress, discomfort, sleeping. Activities such as eating and speech are not affected, and you would not really expect them to be.

This is the slide that I referred to before that looks at when nocturia becomes a moderate or a major bother. It begins at 2 episodes a night, at 3 episodes a night, and it's approximately 56 percent, and at 4 or more, it's somewhere around 80 percent.

This looks at nocturia in a slightly different dimension. Instead of looking at the number of episodes per night, this looks at the number of nights per week that people have nocturia and relates this to the phenomena of daytime sleepiness, naps per week, and sick leave. So as you can see, less than 3 nights per week doesn't affect anything, but for over 3 nights in varying proportions, 3 to 4, 5 to 6, or every night, this does statistically significantly affect the occurrence of daytime sleepiness, naps per week, and also sick leave.

Falls were mentioned in Dr. Joffe's presentation as well as fractures. This looks at over 5800 -- this is community dwelling, not nursing home residents -- age 65 or older, and looks at the cumulative incidence of falls with moderate and severe versus mild, low, or urinary tract symptoms at baseline, and basically looks specifically at the episodes of nocturia. So these are nocturic episodes per night.

So you can see that the relative risk of at

least 1 fall and the relative risk of at least 2 falls significantly increased in 4 to 5 episodes per night and increased somewhat in those with 2 to 3 episodes per night.

For current nocturia therapy, behavioral modification has been shown to be effective in the short term. Now, what does that consist of? Well, it consists of fluid restriction in the late afternoon; if you have peripheral edema, leg wrappings and also elevating your legs in the afternoon for about an hour. Most clinicians have not found this to be fairly durable in terms of long-term clinical practice.

The drugs for overactive bladder, the antimuscarinics and the beta-3 agonists, don't really have much efficacy for nocturia specifically. And likewise, the alpha blockers and the 5-alpha reductase inhibitors for benign prostatic hypertrophy similarly have marginal effectiveness. Desmopressin has shown consistent and sustained efficacy for nocturia.

In summary, nocturia is a significant

medical condition associated with significant morbidity. It does disrupt normal sleep. It does cause daytime fatigue. It does cause loss of productivity, and it does impair the ability to perform daily activities. It does increase the risk of falls and associated sequelae. At the present time, there's no FDA-approved treatment that's specifically for nocturia. Thank you.

Applicant Presentation - Seymour Fein

DR. FEIN: Thank you very much, Dr. Wein.

I'll now present the clinical program of SER 120, focusing first on the clinical pharmacology, pharmacokinetics, and efficacy. To give you an overview of the program, it's a large program evaluating over 2300 patients. It consisted of two phase 1 studies and water-loaded volunteers and in subjects with chronic renal impairment, followed by a small phase 2 study in the target patient population. That was followed by an initial two phase 3 studies that were actually dose titration studies going from 0.5 to 0.75 micrograms, then the two phase 3 pivotal

efficacy studies, DB3 and DB4, which will be the focus of this presentation.

The program also included three open-label studies, a small study in the elderly, in the very elderly, 75 and older, with pharmacokinetic evaluation; the OL1 long-term study, which derived from DB1 and DB2 and treated patients for up to 43 weeks; and then the largest and longest of our open-label studies, DB3-A2, which rolled over patients from the DB3 study and treated them mostly at the highest dose that we're proposing in the label for periods of up to 2 years.

Turning first to the first phase 1 study and water-loaded subjects, these subjects were younger subjects, age 18 to 40. There was a 4-period cross-over with 48-hour washout between doses. It evaluated 3 different dose levels of SER 120 from 0.5 to 2 micrograms compared to a bolus injection, either subQ or intradermally, of desmopressin at a dose of 120 nanograms.

It shows several things. It shows a rapid onset of action. It shows a nice dose response

both in terms of the magnitude of antidiuretic effect and the duration, with the lowest dose giving an antidiuretic effect in the continuing water-loaded state for 2 to 3 hours, the intermediate dose for 4 to 5 hours, and the highest dose of 2 micrograms intranasally for 6-plus hours. Then if we look at the flip side of the pharmacodynamics in this study, the urine output, we can see a similar dose response, with the highest dose of 2 micrograms, essentially shutting off urine production for about 2 to 2 and a half hours.

We did pharmacokinetic evaluation in these subjects, and this is summarized for the 2 microgram SER 120 dose and the desmopressin 120 nanogram bolus subcutaneous injection dose. As you can see, the Cmax peak plasma level is much higher for the SER 120 2 microgram dose. The Tmax, time to peak plasma level, is much shorter. It's about 20 minutes compared to over 50 minutes for the bolus injection. The AUC infinity, however, is very similar for the 2 doses, so eventually a

similar amount of drug gets absorbed into the systemic circulation.

The terminal half-life is 90 minutes for the SER 120 dose, which is comparable to an IV bolus injection of desmopressin and over 2 hours for the desmopressin bolus subcutaneous injection. Putting all of this together, we can characterize SER 120 as having a very bolus-like PK profile with rapid absorption and no depo. And the rapid absorption and no depo contributes both to the efficacy and safety of the product.

We did pharmacokinetic analyses in five additional studies. These are summarized on this slide. Essentially, Cmax and AUC were unaffected in our pharmacokinetic analyses by age, gender, BMI, or renal function. However, terminal half-life, although unaffected by age, gender, or BMI, showed a relationship to renal function. Renal function showed statistically significant prolongation of the terminal half-life in patients with estimated GFRs less than 50 mL per minute.

I'll now turn to the two phase 3 pivotal

studies, DB3 and DB4. These studies had essentially identical design and methodology. There were only three key differences between them. The DB3 study had a pharmacokinetic substudy population and kinetics. It also had an additional dose of SER 120 at the 1 microgram dose level, which was eliminated from the DB4 study.

The DB3 study used a different PRO. It used the Abraham N-Q of L, which is a published validated instrument for males with BPH, but did not have same-day recall and did not meet all FDA guidelines for a PRO. In the DB4 study, we developed and validated a new quality-of-life questionnaire called the INTU, the impact of nighttime urination, and this was incorporated into the DB4 study as the first of the secondary efficacy endpoints.

This next slide shows a schematic representation of both studies. There was an initial 2-week screening period followed by a 2-week double-blind placebo lead-in period, as Dr. Joffe alluded to. All patients who went

through the double-blind placebo lead-in were randomized. We did know right at that time who was a placebo lead-in responder and who wasn't, and they were stratified across the dosage groups during the actual randomization on day 15.

Following day 15, there were 12 weeks of randomized treatment with study visits every 2 weeks and collection of serum sodium at every study visit. As Dr. Joffe mentioned, there was no fluid restriction. Patients in fact were instructed to maintain normal eating and drinking and behavioral patterns as they had before entering the study.

In terms of patient demographics, DB3 and DB4 had almost identical demographics, so I'll present them as the pooled ITT population. The mean age was about 66 years. Fifty-five percent of the population was 65 or older. We had been told both by DBRUP and by DMEP, respectively, in written minutes, to only enroll over the age of 50 in order to enrich the safety population, and we followed that instruction. Males represented 58 percent of the population, females, 42 percent, and the racial

composition represented a typical cross-section of the American population with regard to a percentage of Caucasians and African Americans.

Concerning nocturia etiology by history, this was by the patient's verbal medical history, but also by medical records, which all patients were required to produce. About 80 percent of the population had nocturnal polyuria, and this was verified on fractionated 24-hour urines during the screening period. About 35 to 40 percent of the population had BPH and 25 to 30 percent of the population had OAB. These were not mutually exclusive etiologies. Sixty-five percent of this population had more than one etiology contributing to their nocturia.

Dr. Joffe has mentioned the co-primary efficacy variables. They were the reduction in the mean number of nocturic voids and a responder analysis based on a 50 percent or greater decrease in the mean number of nocturic voids. And these were selected right at the start of our phase 1 program and were carried through uniformally in DB1

and 2, as well as DB3 and 4, in collaboration with the FDA.

I will present the co-primary efficacy endpoints individually by each of the pivotal studies, and then we'll go into a description based on a pooled analysis for further endpoints. As you can see, the mean number of nocturic voids at baseline varied from about 3.2 to 3.4, so moderate to moderately severe nocturia on average.

All dose groups, including placebo, experienced a significant numerical reduction from baseline to the randomized treatment period. However, in each of the studies, all of the active SER 120 dose groups had a much larger numerical decrease from baseline, and each of the dose groups showed statistically significant results relative to placebo in the DB3 study for all three dose groups and the DB4 study for the 1.5 microgram and 0.75 microgram dose levels.

If we turn to the second co-primary efficacy endpoint, this was the responder analysis. I would like to add that the greater than or equal to

50 percent reduction response definition was specifically chosen because we felt it was rigorous, that it was associated with clinically meaningful benefit, and would probably produce a better separation with placebo. Other nocturia development programs used less rigorous definitions such as 33 percent. And I believe these judgments were validated by the results of the DB3 and DB4 studies.

As you can see here, the 1.5 microgram dose group had a 52 percent response rate versus 32.8 for placebo. In the DB4 study, it was 46.5 versus 28.5, similar deltas in each of the studies and highly statistically significant results. The 0.75 microgram dose group for the second co-primary efficacy endpoint had p-values of 0.08 for both studies.

Now I'll present the integrated summary of efficacy for the phase 3 pivotal studies, DB3 and DB4. The results of the planned subpopulation analyses for primary efficacy endpoints and all of the secondary efficacy endpoints by individual

pivotal study are available in your briefing document.

Looking just to retrace and go back to the co-primary efficacy endpoints as a starting point, if we look at the pooled results for the first of the co-primary endpoints, we see similar results to the individual studies, as you would expect, starting at around 3.3 or 3.4 reductions in each dose group, including placebo, statistically significant results for both the 1.5 and 0.75 microgram doses of SER 120 relative to placebo.

If we look at the second co-primary, the responder analysis, for the pooled ITT population of DB3, DB4, again, similar results, 48.7 percent response rate in the 1.5 microgram group versus 30.3 percent for placebo in a dose-response fashion; 37.9 percent for the lower SER 120 dose versus 30.3 percent for placebo. And in the pooled analysis, both of these doses showed statistically significant results relative to placebo.

This next slide is a forest plot that looks at the pooled results for the co-primary efficacy

endpoints, the first one, by the various subpopulations that either we prospectively planned or were asked to analyze by the agency. And you can see that all subpopulations showed consistent statistically significant results for both dose groups, both the 1.5 and 0.75. And these are placebo -- the data are presented as placebo subtracted LS mean changes from screening.

So both the 1.5 and the 0.75 microgram groups showed statistically significant results for all of these subpopulations, by gender, by age, younger and older, and by all of the etiologies of nocturia, with one exception, and that was the small group with no nocturnal polyuria. That represented about 20 percent of the population, as I'll show later, had a sample size of under 100 patients per group, and even there, there was a strong numerical trend.

If we look at the responder analysis based on subpopulations by gender and age, you can see that the males showed statistically significant results for both doses. The males were the

somewhat larger sample size. The females showed statistically significant results for the 1.5, not for the 0.75. In terms of age, the younger patients and the older patients showed statistically significant results for the higher dose, the 1.5, and the older age group, which was the larger sample size, showed significant results for the lower dose, the 0.75 microgram dose.

Then looking at the responder analysis by nocturia etiology, patients with OAB, representing about 25 or 30 percent of the population, showed significant results for both doses. BPH showed significant results for the higher dose and a p-value of 0.054 for the lower dose. And nocturnal polyuria was of course the largest subpopulation and showed highly significant results for both doses.

The no nocturnal polyuria, which I alluded to before on the forest plot slide, had such a small sample size that statistical significance was unlikely, but the p-value was 0.08 for the higher dose, even in the no nocturnal polyuria group.

Turning to secondary efficacy endpoints, there were five secondary efficacy endpoints. They were selected for clinical relevance. And for each of the individual studies, they were analyzed in an hierarchical order for preservation of alpha. The PRO of the INTU was the first of the secondary efficacy endpoints in the DB4 study.

I'll not present those results right now. In order to present the INTU results in full context, based on its development and validation, Dr. Khalaf, who will present following me, will include the results of the INTU analysis in her presentation. But I'll present the results for the other four secondary efficacy endpoints in order.

The first of these was the time from going to bed, with the intention of falling asleep, to the first nocturic void or the first morning void in the absence of a nocturic void; in other words, the first period of uninterrupted sleep. In the literature and I think among clinicians, it's widely believed that 4 hours of uninterrupted sleep to begin is associated with a more restful night

sleep, better quality of life. There are published papers supporting that.

If you turn your attention first to the lower three bars, you'll see that in terms of the actual analytical metric, the change in time of this first period of uninterrupted sleep, both dose groups in the pooled analysis showed significant results relative to placebo, and on the upper three bars, the absolute time of first period of uninterrupted sleep was 4 or more hours for each of the SER 120 dose groups.

The second of the secondary efficacy endpoints was the percentage of nights on a per patient basis with zero nocturic episodes, essentially dry nights. And you can see that both SER dose groups produced statistically significant results relative to placebo in terms of the percentage of nights, with one or fewer nocturic episodes.

Again, both dose groups produced statistically significant results in the pooled integrated summary of efficacy analysis, and the

percentage of nights overall in the 1.5 microgram dose group was close to 50 percent. One or fewer nocturic voids per night is generally considered to be not associated with clinical bothersomeness or significant comorbidities.

Finally, the fourth and last of our secondary efficacy endpoints was a pharmacologic correlate, the reduction in the nocturnal urine volume. And as you can see here, both doses produced statistically significant greater reductions in noctural urine volume than placebo. The mean was about 125 mL greater reduction versus placebo for the 1.5 microgram dose group and about 70 mL for the 0.75 microgram dose group, so a nice pharmacologic dose response to support the therapeutic effect dose response that we observed in the previous parameters that I've described.

So I think we've established that SER 120 has substantial statistical efficacy and produces a much larger numerical responder rate than placebo. But what does it mean to be a responder? What magnitude of change could a responder expect in

these various efficacy parameters? This shows what an average responder could expect in the 1.5 microgram treatment group with a sample size of 214 patients representing the responders across the DB3 and DB4 study in that dose group.

There was a mean reduction from baseline of 2.1 nocturic voids per night, and that translates to 15 fewer nocturic voids per week. In terms of the graph on the upper right, the first period of uninterrupted sleep, responders had a 3-hour increment in the first period of uninterrupted sleep relative to baseline and in absolute terms enjoyed more than 5 hours of an initial period of uninterrupted sleep.

The change in percent of nights with zero or 1 or fewer nocturic episodes is represented in the lower left graph, and 20 percent of nights were dry nights among responders in the 1.5 microgram treatment group, and over 75 percent of nights had one or fewer nocturic voids in this responder population. In terms of the reduction in nocturnal urine volume, there was a mean reduction of 330 mL.

Finally, I'd like to address the other characteristics, which might be clinically important with regard to SER 120's effects. This graph shows the week-by-week, visit-by-visit mean nocturic episodes in the combined DB3, DB4 studies. Baseline here represents the start of true randomization, not the placebo lead-in, so there are 12 weeks of randomized treatment reflected in this graph.

You can see that most of the reduction occurs rapidly, and most of it occurs within the first 2 weeks. And the first 2 weeks are captured by two 3-day voiding diaries. One is given week 1, the other is given week 2. And the first of these voiding diaries starts within 2 or 3 days of the initiation of treatment.

So the onset of therapeutic effect is almost immediate, very rapid with SER 120. In addition, once you have the onset, it seems to be durable and sustained throughout the 12-week randomized treatment period at least in terms of the -- very consistent at least in terms of the delta between

the active groups and placebo. I would also add that 90 percent of patients in the DB3 and DB4 studies completed the study. So sustained and consistent efficacy is not the result of patients who are doing well staying in the study and patients who are doing poorly dropping out.

The last slide that I'll show you is a similar longitudinal view of the efficacy for the DB3-A2 study, which treated most patients on the 1.5 microgram dose group for periods of up to 2 years. This initial decrease is not incremental to what we saw in the randomized studies. It is a recapitulation of that.

However, you can see that once it occurs, it is well sustained throughout the 2-year treatment period. And the sample sizes, which are reflected on the top of the graph, are robust right through the 78-week time point, which is 1 and a half years of treatment.

With that, I will turn the podium over to Dr. Kristin Khalaf to talk about patient treatment benefit and the results of our INTU.

Applicant Presentation - Kristin Khalaf

DR. KHALAF: Thank you, Dr. Fein. I'd also like to thank Dr. Lewis, the advisory committee, and the agency for the opportunity to speak with you today. My name is Kristin Khalaf, and I have experience analyzing and interpreting PRO data. I am consulting for the sponsor and have no financial interest in the outcome of this meeting.

Today I'll be speaking to you about the patient treatment benefit of SER 120. The objective of this presentation is to give you an overview of the INTU questionnaire and to discuss the results from the DB4 study and our interpretation. To provide a little bit of context behind the development of the INTU, patient-reported outcomes are an important component of assessing treatment benefit, and this is especially the case for symptom-based conditions, where patient perspective provides key insight into how their health status impacts them.

Prior to the initiation of the DB4 study, the agency emphasized the importance of including a

PRO measure of the direct impacts associated with nocturia as a secondary outcome measure in evaluating a treatment response. Thus, in consultation with the FDA, the INTU was developed and validated to assess the impact of nocturia in order for it to be able to be used in the DB4 study. The methods utilized to develop the INTU were consistent with the FDA PRO guidance. Its development and validation was conducted in a nocturia-specific population with input from both men and women, and it has a 24-hour recall period.

Next, I'm going to provide a very high-level overview of the research that was conducted to produce the final version of the instrument. The development and validation of the INTU consisted of three steps. First, a literature review was conducted to identify whether there were any available or published nocturia-specific measures that met the FDA PRO guidance. The measures that were identified fell short of the guidance standards, so this confirmed the need to develop a new instrument that we later called the INTU.

To develop this measure, both qualitative and quantitative research methods were applied to ensure that there was relevant patient input into the questionnaire as well as sound psychometric properties. Through this process and in consultation with the FDA, the INTU emerged demonstrating strong reliability and validity in our population of interest.

The final INTU contains 10 items, the concepts of which are listed here. Some examples of the concepts covered in the INTU include things like feeling tired or not getting enough sleep due to nocturia. These 10 items can be summarized into two domains: daytime impact and nighttime impact. These two domains can be further summarized into the overall impact score, and it's the overall impact score that was the key secondary endpoint in the DB4 study.

All the scores ranged from zero or no impact to 100 or greatest impact. In other words, zero represents the best health status versus 100, which represents the worst health status with respect to

nocturia impacts. This version of the INTU is subsequently incorporated into the DB4 study. As previously stated, the mean change in INTU overall impact score was the first of five secondary endpoints in the DB4 trial.

The daytime and nighttime impact scores were also evaluated as prespecified exploratory endpoints. Additional key supportive analyses were also conducted to first understand the impact of SER 120 on item-level scores; second, to understand the proportion of responders on the Treatment Benefit Scale, which was another key outcome used in this study that I'll describe a little bit later; and third, to understand the INTU results in the context of those who reported improvement on the Treatment Benefit Scale. I'll first go into the results of the prespecified analyses.

The results for screening and mean change between screening and treatment for all the INTU summary scores are shown here. During screening, no significant differences were noted between groups for any of the summary scores. INTU summary

scores improved, that is decreased, in all three groups during the treatment period. Significant differences and changed scores between the 1.5 group and placebo were observed for both the overall and nighttime impact scores.

Specifically, for the overall impact score, we see a 14.1 point improvement for the 1.5 group versus an 11.5 point improvement for placebo, and for the nighttime impact score, we see an 18 point improvement versus a 14 and a half point improvement. The daytime impact score showed the same trends as for the overall and nighttime score, however, the improvements were of somewhat lower magnitude and statistical significance between changed scores was not achieved.

In addition to the prespecified trial endpoints shown here, key supportive analyses were also conducted to better interpret the INTU results, the first of which focused on item-level analyses. This forest plot shows the placebo subtracted mean absolute change between screening and treatment period by both item and domain.

Point estimates to the left of the vertical line indicate that SER 120 is favored while those to the right favor placebo.

In the case of 1.5 micrograms, all 10 items show a numerical benefit. We also see a numerical benefit for 9 of the 10 items in the 0.75 dose. This reflects the collected collaboration of all items to the INTU summary scores. And another way to visualize this net effect is through the use of a spider chart.

A spider chart is an alternative way to observe the between-group differences for all the INTU items. The axes represent the mean ranks for the items. Improvements in item-level scores between the screening and the treatment periods, which are denoted by the greater distance from the center of the chart, are shown here for both placebo, denoted here in gray, and the 1.5 dose, here in blue.

The diagram shows consistent separation between the 1.5 dose and placebo across all 10 INTU items. This once again speaks to the collective

collaboration of all the items and contributing to the INTU summary scores. The remaining supportive INTU analyses that I'll present today consider another important PRO that was also included in the DB4 study, the Treatment Benefit Scale.

The Treatment Benefit Scale or TBS is a single-item global assessment of change, which was administered at the end of the study. This single item evaluates the patient's perception of treatment benefit compared to their condition at baseline to determine whether they felt that their symptoms had improved, worsened, or stayed the same. The TBS is a useful tool for helping to understand to what extent clinical benefits translate to patient perceived benefit. Thus, the TBS can be used in tandem with the INTU to help ascertain clinically meaningful changes in the PRO.

The proportion of patients who selected each response option in each treatment group for the TBS are shown here. Of note, all the patients indicated that their condition either stayed the same or improved to some degree. The response

options of the TBS can be stratified or characterized into responders and non-responders. Patients who report that their symptoms are much or somewhat better are classified as responders, while those who respond that their symptoms are not changed or worsened to some degree are classified as non-responders.

When we compare responders in the 1.5 group versus placebo, we see a significantly greater proportion of TBS responders in the 1.5 group. In addition to comparing the proportion of responders to non-responders, we can also look at the relationship between each TBS response option and other outcomes collected in the study.

A cumulative distribution function, or CDF plot, is shown here to demonstrate the relationship between TBS responses, which are denoted by the three lines plotted here on the chart, and the primary endpoint of nocturic voids, shown on the X-axis at the bottom. CDF plots represent the cumulative percentage of patients, shown on the Y-axis, who achieve a response at different

response levels. And in this case, response is defined as the change in nocturic voids.

Anything to the right of zero indicates that patients experience more voids per night, and anything to the left indicate that patients experience less voids per night. This tells us that any point on the X-axis what is the cumulative percentage of patients that are selecting each response option on the TBS that achieve a certain level of reduction in nocturic voids.

So what this CDF tells us is that patients that perceive the greatest symptom improvement as per their response on the TBS do in fact experience the greatest reduction in nocturic voids. This establishes the legitimacy of the TBS in relationship to the primary endpoint.

We can also look at the relationship of TBS with the key secondary endpoint, the INTU. This CDF is very similar to the previous one, except that in this case, the response, shown here on the X-axis, is the change in the INTU overall impact score is from baseline. Once again, we see that

patients that perceive the greatest symptom improvement as per their response on the TBS do in fact experience the greatest improvements in INTU scores. These analyses collectively demonstrate that the TBS is able to differentiate well among patients who achieve improvements in key study outcomes.

To more clearly illustrate the clinical benefit of SER 120, we can compare CDF plots across treatment arms with respect to changes in INTU scores. In this CDF, each line now represents each of the three treatment arms in DB4. As with the previous slide, response is defined as change from baseline and INTU overall impact scores. Here, we see differentiation in the proportion of patients with improved INTU scores between the 1.5 group compared to placebo. This separation between treatment arms is indicative of treatment benefit.

In order to determine if the change was meaningful to patients, we can leverage patient response on the TBS. Thus, the TBS is used as an indicator of clinically meaningful change. The

mean value for the INTU total score for the group responding somewhat improved on the TBS was 10.38 points; that is, for subjects who reported being somewhat improved in the DB4 trial, their INTU total score decreased by an average of about 10 points.

This falls well within the region where clinical benefit is noted for the 1.5 microgram dose. Specifically, we see that approximately 14 percent more patients in the 1.5 group achieved this level of INTU improvement compared to placebo, or 55.1 versus 41.4 percent.

The CDF plot for the INTU nighttime impact score, shown here, is consistent with that of the overall impact score shown previously. Once again, the proportion of patients reaching a certain threshold of improvement was consistently higher for the 1.5 group, indicating clinical benefit. Here, the mean improvement among patients responding somewhat better on the TBS was 13.85 points. Approximately 16 percent more patients receiving the 1.5 microgram dose achieved

this level of improvement on the INTU compared to placebo, or 57.6 versus 42.2 percent.

For the INTU daytime impact score, shown here, we can see modest differentiation between patients receiving 1.5 micrograms compared to placebo. The mean change among patients responding somewhat better on the TBS was 6.91 points. 7.3 percent more patients in the 1.5 group achieved this threshold or 51.9 versus 44.6 percent.

In summary, the DB4 study met its key secondary endpoints. Statistically significant changes were observed in the 1.5 microgram group for the INTU overall impact score. The same finding was noted for the nighttime impact score. There was also a greater proportion of TBS responders for patients who received SER 120 1.5 micrograms versus placebo. A larger proportion of patients improved with respect to their INTU scores in the 1.5 group compared to placebo among patients perceiving improvement on the TBS.

These data collectively demonstrate that SER 120 resulted in a clinically meaningful improvement

in the patient-reported impacts of nocturia on daily living. Thank you. I'll turn it back to Dr. Fein.

Applicant Presentation - Seymour Fein

DR. FEIN: Thank you, Dr. Khalaf.

I'll now present the integrated summary of safety for SER 120. Desmopressin is a well characterized drug, which has been used for almost 40 years in patients ranging from infants to the very elderly. In that broad experience, the only safety issue of real concern has been water retention causing hyponatremia, so let's address that front and center.

This slide shows the incidence of patients with nadir serum sodiums post-baseline, and it does so by serum sodium range: mild decreases, 130 to 134; intermediate decreases 126 to 129; and more severe decreases representing frank hyponatremia of 125 or below. In our protocols, we define hyponatremia as the serum sodium between 126 and 129 with clinical symptoms suggestive of hyponatremia or any value of 125 or below with or

without symptoms.

As you can see, there is a higher incidence of mild decreases on the 130 to 134 range of serum sodium in the SER 120 groups versus placebo. In the 126 to 129 range, there are a few patients that had nadir serum sodiums less than 130. There were modest increases of these in the SER 120 groups versus placebo, but none of these patients had clinical symptoms.

For patients with serum sodium of 125 or below, the incidence was 0.1 percent in the placebo group, 1.1 percent in the 1.5 microgram group, and importantly, in the 0.75 microgram dose group, no patients had frank hyponatremia.

If we look at the incidence of nadir serum sodiums by gender for the DB1, DB2, DB3, DB4 safety population, we can see that there was really no difference between the genders in the incidence of low serum sodiums in any of these categories, and this might be a bit of a surprise. It might have been anticipated that females would have a slightly higher incidence of low serum sodium, but that was

not the case in these randomized phase 3 studies.

In terms of looking at nadir serum sodium incidence by subpopulation based on age, this divides it up between the younger patients, age 50 to 65, patients 65 years and older, and then a subgroup of the total patient population age 65 and older of age 75 and older. And we can see that the older patients in the 65-plus age group did show a modest increase in serum sodiums less than 130, but that there was no difference between the overall older age group and the very elderly, 75 years and older, in the randomized phase 3 study database.

Another important question is what is the onset of the low serum sodium? What's the first occurrence of serum sodiums below 130? And this slide addresses that question. You can see that in the placebo group, 1 of 2 of the patients would have had their first occurrence within the first 2 to 4 weeks of treatment.

In the 1.5 microgram dose group, 8 of 14 patients had the first occurrence in the first 2 to 4 weeks of treatment. In the 1 microgram dose

group, it was 5 of 9, and in the 0.75 microgram dose group, it was 6 of 9. So overall, 60 percent of first occurrences of serum sodium below 130 occurred in the first 2 to 4 weeks of treatment.

Then if we apply the proposed label recommendation, which is that any patient who is on treatment that has a serum sodium below the normal range at all, 12 of 14 of the 1.5 microgram patients who eventually had serum sodium of less than 130 would have been detected in the first 2 to 4 weeks of treatment, and 7 of 9 patients in the 1 microgram group, and 7 of 9 in the 0.75 microgram group, where over 80 percent of these patients would have been detected in the first 2 to 4 weeks of treatment.

This slide then shows the incidence of nadir serum sodiums for the open-label safety extension studies. And keep in mind that the 1.5 microgram dose group went to two years of treatment and observation, so it has a much longer period of time in which occasional sporadic serum sodium values just below the normal range could occur. So the

0.75 microgram dose group, which was not followed beyond 43 weeks, has a 5.5 percent incidence, and the 1.5 microgram group has a 12.5 percent incidence of any occurrence during the two-year treatment period in that range.

However, importantly, only one patient in the 1.5 microgram group had a nadir serum sodium less than 130 throughout the entire study, and that patient was in the 126 to 129 range and was asymptomatic. No patients in the 1.5 group or the 0.75 group had serum sodiums of 125 or below, and in the 0.75 microgram, which is a substantial sample size for up to 43 weeks of treatment, no patients had a serum sodium below 130.

The three patients in the 1 microgram dose group, who had serum sodiums of 125 or below, are reflective of the fact that all patients in the A2 studies started during the first 2 weeks of treatment on the 1 microgram dose group. So this is an indication that if the serum sodium in a particular patient is going to fall, it tends to fall early on in the treatment period and can be

detected early on.

Now, if we turn to treatment emergent adverse events, the take-home message here is that there isn't really much to say. The incidence of these events, the type of events, and the severity of these events were almost identical across the treatment groups, including placebo. And the only group or cluster of these adverse events, which was generally considered to be treatment related, were the local topical irritant effects related to the use of a nasal spray, including nasal discomfort, nasal pharyngitis, nasal congestion, and rhinorrhea.

We also did, and can show you later, a cluster analysis for adverse events associated with hyponatremia across the treatment groups for the randomized phase 3 studies and found absolutely no difference in the incidence of those adverse events that might be associated with signs of hyponatremia.

The next slide shows the serious adverse events, which occurred in the double-blind,

randomized phase 3 studies. It's important to note that the incidence of these was the same across the treatment groups, including placebo. And there were 3 deaths; none of them were believed related. The first two were in hospital with autopsies and were well explained.

I'll focus on the third one, the sudden death, because that occurred outside of a hospital in an 80-year-old Asian male. This patient had a history of myocardial infarction, hypertension, diabetes, and hyperlipidemia, had a normal serum sodium on day 15, and took only 2 or 3 subsequent doses of SER 120 before the event.

There were 3 serious AEs that were judged by investigators to be possibly or probably related. One of these was the hyponatremia in a placebo patient. This patient had recurrent episodes of severe hyponatremia below 120 with symptoms and had multiple hospitalizations. The medical causes were never explained, but we did audit his study drug, and we confirmed that he was on placebo.

The patient 42S033 was a patient in the

1.5 microgram SER 120 dose group, and this patient was found after the fact to be taking Dulera, an inhaled steroid, which was actually an exclusion criterion for the study, and also developed a concomitant GI illness with nausea, vomiting, and diarrhea, which should have resulted in her discontinuation of the study medication, but it did occur in the 1.5 microgram group. The patient with hypertension in the DB3 study had a prior history of hypertension and actually developed the worsening of hypertension during the placebo lead-in period with a blood pressure of 160 over 85.

Finally, if we look at the serious AEs, which occurred in the open-label safety extension studies, we see, again, similar incidence across the treatment groups. There were 2 deaths. Neither was related. The peritonitis with cecal perforation was in the hospital. The myocardial infarction was outside the hospital. This was a 79-year-old white male. He had a normal serum sodium of 139 on day 15, took 2 or 3 additional doses of drug, and the event occurred on day 19.

The patient with a possibly or probably related serious adverse event, thrombocytopenia, actually was a long-term patient on the OL1 study that had an uneventful treatment course on that study; then was screened for the A2 study a couple of years later, had a borderline normal platelet count of 150,000 at screening, developed an intercurrent illness with petechia during the 2-week screening period, and took 1 dose of study drug, and 12 to 14 hours later was found on a lab result to have a low platelet count.

That concludes the review of safety for SER 120, and I will now turn the podium over to Dr. Annette Stemhagen to talk about benefit-risk assessment and our proposed REMS plan, which we included in the new drug application. Dr. Stemhagen?

Applicant Presentation - Annette Stemhagen

DR. STEMHAGEN: Thank you, Dr. Fein.

I'm Annette Stemhagen, an epidemiologic consultant to Serenity. I have no financial interest in the outcome of this meeting. I've

worked on more than 100 risk management programs over the last 15 years, and I'll be discussing benefit-risk and the REMS.

When reviewing the totality of safety data included in a regulatory filing for product approval, it's important to ensure that the product's benefits outweigh the risks. The data have shown patient benefit of decreased number of nocturic episodes, increased hours of first uninterrupted sleep, an increased number of nights with one or fewer nocturic episodes per night, and improved daily living in patients with nocturia. The rapid absorption with no depo and low peak plasma concentration limit the antidiuretic effect of 4 to 6 hours while patients are asleep, thereby mitigating the risk of fluid retention.

The risk of hyponatremia is low, 1.1 percent at the 1.5 microgram dose with no cases at the 0.75 microgram dose in over 2300 treated in clinical trials. The rapid onset of efficacy and the effect on sodium enables benefit-risk assessment for an individual patient early in the treatment course.

To enhance the favorable benefit-risk balance, the sponsor in collaboration with its marketing partner, Allergan, proposed further actions to address the remaining risks with a risk evaluation and mitigation strategy or REMS. The REMS will be administered and evaluated by Allergan.

The messages that are important in risk mitigation, outside of a label or in addition to the label, are certainly aligned with the label. The first key risk message relates to appropriate patient selection prior to prescribing. Serum sodium should be within normal limits, and GFR should be measured as per the label. Patients should not be taking systemic corticosteroids, and dosing should begin at the lower dose with dose increase if treatment is not effective and SER 120 is well tolerated.

Additional risk mitigation messages are that serum sodium should be monitored within 14 days after initiating treatment or when a dose is changed. SER 120 should be temporarily

discontinued if the patient requires corticosteroid treatment or develops an illness that affects electrolyte balance. Risk mitigation must also be directed to patients. Healthcare professionals should counsel patients to recognize the symptoms of hyponatremia and to seek medical attention if those symptoms occur.

The goal of the risk evaluation and mitigation strategy, or REMS, is to minimize the risk to patients of developing hyponatremia by imparting the educational messages that I just reviewed. The proposed REMS is a comprehensive program of education and outreach with clear implementable messages.

The REMS will include a medication guide for patients and a communication plan directed to healthcare professionals. There will be continual assessment and feedback to be sure it's effective in its messaging. Allergan will submit REMS assessment reports to the FDA following the timetable of assessments of 18 months, 3 years, and 7 years.

In terms of the REMS components, the medication guide provides information for patients. It describes the risk of hyponatremia and its signs and symptoms. The key risk messages I outlined earlier are included in patient-friendly language, and the medication guide will be provided with each dispensing in unit-of-use packaging.

The communication plan for healthcare providers includes a letter to prescribers emphasizing the key risk messages. The letter will be sent to a wide variety of medical specialists and will also include a copy of the product label and the medication guide. A letter with similar content will be sent to the relevant professional organizations with a request to share the information with their members.

The proposed REMS has these features of an effective program. The messages are clear and comprehensible for both patients and healthcare providers. They're targeted and straightforward, focusing on hyponatremia and the importance of minimizing the potential risk. The REMS is

practical and implementable within routine clinical practice, and the messages directly inform healthcare providers about identifying patients who are at risk of hyponatremia early in the course of treatment.

Without adding burden to the healthcare system, the REMS is an important way to deliver education on the key risk messages to complement the product labeling. Thank you.

Applicant Presentation – Steven Kaplan

DR. KAPLAN: Good morning. It's a pleasure and privilege to present to the advisory panel, members, and guests. My name is Steve Kaplan. I'm a urologist at the Icahn School of Medicine at Mount Sinai, and I serve on the advisory board for Serenity and do have a financial interest in the outcome of this meeting.

I come to you wearing two hats. One of them is as someone who has spent his career in research for benign urologic conditions, BPH, OAB, having had five NIH grants in that pursuit. I'm also an active clinician who takes care of these patients

every day. And by far, the most difficult and challenging medical condition that I have to deal with is nocturia and patients as well. It is really a significant and unmet medical condition. In addition, the downstream consequences of nocturia are also very important: fractures, head injury, and even mortality. And these are the things we deal with as well.

Of concern as well is this is empirically treated. Often these patients are treated for either OAB and BPH, many of them unsuccessfully, many of them with side effects of these medications, and often leaving a patient very unhappy and coming back for trying to treat this problem. So there is a need, and I think physicians, healthcare providers, and patients are clamoring for a solution to this very important and underrecognized medical condition.

When we look at a product that comes to market, the things that we ask for are, one, does it work? And I think the data here shows that SER 120 has been effective, as you've seen from the

two pivotal studies. But more importantly, is it clinically meaningful? And for those patients who have that problem -- and I suspect there may be some folks here in the audience who do -- for the healthcare providers who have to take care of this problem, and for those who love those patients and want to help them with dealing with this important problem, I think the results are very clinically meaningful.

Is the drug safe? And I think you've heard this morning that the drug has been shown to be safe and well tolerated. And finally, does it work in a long duration? Is this a one-off and s short-stay study? And here, the data demonstrates that this is a durable and important response for these patients.

I don't have the privilege of treating diagnostic buckets. I have to treat a patient who comes into my office with symptoms, and many of these patients, the typical patient with nocturia, has something else going on. And the population that was studied here is the typical population

that you will see. They can have OAB and BPH and multiple medical conditions. Only 20 percent of the patients had a single diagnosis. This is the world that we have to kind of deal with.

I think both of the doses here have demonstrated efficacy, and from my perspective, I like having the ability to start with a lower dose, see if that patient is going to respond, and then have the ability to titrate upwards.

Now, desmopressin has been around for a long time. We've heard it this morning. It's been around. But there are some concerns about safety. And I think that the improved dosage formulation of SER 120 with its sustained efficacy and minimal side effects can be an important addition to our armamentarium to treat this very important medical condition.

I also think it's very important in today's world that there be an interface between patients and healthcare providers, and that an empowered patient with knowledge and information about managing the expectations of what a drug can

provide, and from the healthcare perspective and provider, what it can provide will be very important. I think the REMS plan provides that education, and I think hopefully sets the bar, at least initially, for what to expect and what not to expect, and what should be the future with using this medication.

In summary, SER 120 I think fills an important an unmet medical need that is effective and safe, and most importantly clinically meaningful. Thank you.

DR. LEWIS: Thank you.

At this point, I'd like -- I'm sorry.

DR FEIN: I just wanted to mention to the committee that we have additional experts who did not present, but are available here today to answer questions if need arises: Dr. Tomas Berl, a nephrologist and expert in electrolytes; Dr. James Longstreth, our pharmacokineticist; and Dr. Richard Trout, our biostatistician. There were also, hard copy errata, a few typographical errors, which appeared in our briefing document. Hard copy

corrections have been provided to you with your hard copy set of slides.

Clarifying Questions to Applicant

DR. LEWIS: Thank you. Sorry.

At this point, I'd like to entertain questions from the committee. Are there any clarifying questions for Serenity Pharmaceuticals? And please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter. Dr. Smith?

DR. R. SMITH: Yes. Thank you. Robert Smith. I have a couple of clarifying questions. The first is in regard to the placebo effect, which is striking both in its magnitude and its durability. So I wonder if the sponsor could help us to understand that a little better. If that placebo effect deteriorated over time and the drug effect were sustained, we could be seeing an underestimation of the drug effect.

So the question is whether you have any data on placebo that extend beyond the 12-week period.

I saw your time course over the 12-week period, and I see no decrease in placebo effect over that time. So the first question is whether you have any data on placebo effect that go beyond that period, whether you have any data on fluid intake changes or fluid intake logs from baseline, or other data that might provide some insight into the placebo effect. And then I have a second question, but I'll wait for the answer for that.

DR. FEIN: Thank you for that question. We do not have data, did not do studies, beyond the 12 weeks, which were placebo controlled. However, the phenomenon of high placebo response rates is well known across all of the voiding disorder studies, not just nocturia, but studies involving OAB and BPH as well. The reasons for this are unclear. There's speculation that they may be contributed to by subtle behavioral changes even when patients are instructed to maintain normal eating, drinking, and other behavioral and lifestyle patterns. But we do not have placebo controlled data beyond the 12-week time period.

With regard to fluid intake, we did not do -- we do have 24-hour fractionated urines at the end of the study and at the beginning of the study. I can tell you that in addition to the decrease in the nighttime urine volume, there was only a very small and not statistically significant increase in the daytime urine volume, 50 to 70 mL. It was not significantly different across the treatment groups, and the number of daytime voids did not significantly changed. It went up fractionally in the placebo group. It went down fractionally in the two SER 120 groups.

DR. R. SMITH: Thank you. And then just one other quick question. In regard to the patient with thrombocytopenia, I'm afraid I didn't follow the whole description of all that. But my question was, had that patient had a prior exposure to the drug, and then a window of non-exposure, and then a return to the drug? I remember something about participation in a prior study, but I didn't follow it well. And if there was prior exposure, the question is whether that was to the same

preparation with the same vehicle.

DR. FEIN: There was prior exposure. The patient was in the OL1 safety extension study from the DB1, DB2 phase 3 studies; did not get screened for the A2 safety extension study until a couple of years, 1 and a half to 2 years after the completion of the first experience. And the patient, as I said, joined the 2-week screening period, developed an intercurrent illness, did not feel well, and then developed the clinical petechia. He only took a single nasal spray of SER 120. It was the same preparation that he had used in the OL1 study, and then had a blood test for his petechia about 14 hours later, and then on that test was found to have a low platelet count. He entered the screening with a marginally low platelet count of 150,000.

DR. R. SMITH: And just quickly to follow up the evolution of that, there was full recovery? Any information --

DR. FEIN: There was full recovery.

DR. R. SMITH: Thank you.

DR. LEWIS: Dr. Gellad?

DR. GELLAD: Thank you. I have two questions. The first is, are there known interactions with other nasal products, many which are used over the counter; oxymetazoline, Afrin, or saline, or Flonase, nasal steroids? So I guess that would be my first question.

The second question just goes back to the placebo effect. Specifically, slide 40 I have to say struck me. The responder -- I don't know if you want to look at that. But 40 percent of those with no nocturnal polyuria in the placebo group had more than a 50 percent reduction in nocturic episodes, which I know it's a small sample, but that's part of the problem. But I wonder if you could just talk about that a little bit, the issue around placebo and especially in that group with no nocturnal polyuria.

DR. FEIN: With regard to your first question, there was no restriction of using other nasal sprays as long as they were administered in temporal separation by a few hours with our nasal

spray, which is administered in the evening, ideally about 30 minutes before bedtime.

So if a patient needed to take or routinely took a nasal spray during the morning or the afternoon, that was fine, and many, many patients in our study were on nasal sprays for seasonal or perennial allergic rhinitis, including steroid-containing nasal sprays. The restriction with regard to corticosteroids was for systemic oral, parenteral, and inhalant because of the higher bioavailability of inhaled steroids or at least the potential for higher bioavailability and the larger dose used in inhaled steroids.

With regard to the placebo response rate, yes, keep in mind that the placebo response rate across the entire population for the pooled DB3, DB4 analysis was 30 percent. So in patients without the volume component, whatever is happening and whatever is contributing to the placebo response rate, perhaps subtle behavioral changes and adjustments that are not even contained in the protocol, it's a little bit higher in the known

nocturnal polyuria group.

DR. GELLAD: And the only reason I mention that is I think this is the one instance where the 0.75 microgram dose did not have a numerically higher impact.

DR. FEIN: That's correct.

DR. LEWIS: Thank you. Dr. Neaton?

DR. NEATON: Thanks. A couple of clarifying questions. Just definition-wise, on slide 46, you made the point you were measuring the changes from baseline. Are you defining baseline here as the beginning of the screening period?

DR. FEIN: No. Thank you for that question. As I mentioned, this baseline in this slide -- and I apologize for any confusion because we do define baseline differently. Baseline from this slide represents the start of randomized treatment.

DR. NEATON: So it's the end of the screening period.

DR. FEIN: It's the end of the screening period after the placebo lead-in. It's formally day 15 of the study, and it then goes for the full

12 weeks of randomized treatment.

DR. NEATON: And then just two other questions. One, how often did you measure sodium in the long-term follow-up study?

DR. FEIN: Sodium was measured at every study visit, which started out at 2-week intervals, went to 1-month intervals, and finally over longer periods of time, 2-month intervals.

DR. NEATON: So at 2-month intervals, for everybody that stayed in the study -- and your incidence measurements that you reported in terms of hyponatremia took into account those interval estimates.

DR. FEIN: Yes. Display slide 2, please. This is the visit schedule for the DB3-A2 study, and you can see there's a gradual prolongation from 2 weeks to 4 weeks to 8 weeks.

DR. NEATON: Dr. Smith asked a question about the placebo responders, and I was curious that you have a 12-week -- or no, actually a -- I forget the length of it, maybe 8-week screening period -- or 2-week screening period --

DR. FEIN: Yes.

DR. NEATON: -- where you basically originally had planned to eliminate placebo responders.

DR. FEIN: No, no --

DR. NEATON: Or to include them as the primary analysis.

DR. FEIN: The reason -- yes. The reason, there was a screening period in all studies, DB1, DB2, DB3, DB4, 2 weeks. That was to objectively document the number of nocturic episodes to make sure that the patient actually had nocturia to a severity qualifying for the study. And the 2-week placebo lead-in was incorporated into the design of the DB3, DB4 studies in collaboration with discussions with the FDA because the sponsor and the agency were interested in characterizing the nature of the placebo effect and seeing whether we could identify a way to tease out some of the placebo effect.

So all patients went through the placebo lead-in, and they thought they were randomized at

that point. The investigators thought they were randomized at that point. But everyone who went through that was stratified and randomized appropriately. And in the end, it turned out that the analyses with the ITT population and then with the mITT population with the placebo lead-in responders eliminated were almost identical.

DR. NEATON: Maybe we can come back to that. But you mentioned in your presentation that you stratified on the responders, but in the book, you indicated only age and gender.

DR. FEIN: I will direct that question to Dick Trout. I know it was stratified by age and gender, but I believe that the placebo lead-in responders were stratified as well.

DR. NEATON: And your analyses are just carried out stratified by age and gender, right?

DR. FEIN: Dr. Trout, would you like to comment?

DR. TROUT: Good morning. My name is Richard Trout. I'm professor emeritus from Rutgers in the statistics department, a consultant for

Serenity but have no financial interest in the outcome of this meeting.

The randomization schedule, as was pointed out, was based on age and gender. In addition to that, separate randomization schedules were established for the patients who were classified as placebo responders from those who were classified as non-placebo responders.

We wanted to ensure -- again, not knowing how the placebo responders were going to perform during the rest of the study, it turned out we really didn't need to worry about it, but not knowing that ahead of time, we wanted to ensure that we had a balance among the treatment groups within the subset of patients which were felt to be placebo responders as we did with the age and gender.

DR. NEATON: That makes sense. So your intention-to-treat analysis essentially stratified on three factors.

DR. TROUT: Exactly, correct.

DR. NEATON: But your analyses only

stratified on age and gender. Was there some reason for that?

DR. TROUT: Again, we were concerned -- not concerned, but interested in the possible effect of that. As you saw, we had a number of slides that performed, so we just wanted to incorporate those. There were predetermined factors, and we just wanted to see whether there was anything going on with them; that's all.

DR. NEATON: Thank you.

DR. LEWIS: Thank you. Dr. Cella?

DR. FEIN: Could we show the backup slide with the results of the placebo lead-in responders? I just wanted to point out an interesting additional finding that we noticed. Display slide 2, please.

We did an analysis of the response of placebo lead-in responders, and we found that in the pooled DB3, DB4 ITT population, the placebo lead-in responders did numerically and statistically significantly better in the two SER 120 treatment groups than in the placebo group.

So there was an incremental effect of the active treatment even in the placebo lead-in responders.

DR. LEWIS: Thank you. I'm going to call on Dr. Cella, and then I'm going to hold on further questions. I will come back to those later so that we can have a break.

DR. CELLA: Thank you. I have two questions, one for Dr. Fein and one probably for Dr. Khalaf. And actually, the slide just shown and a previous comment you made, Dr. Fein, starts to answer my question.

I understand now that randomization occurred after the lead-in period, which is to say that even the sponsor didn't know the treatment assignment during the lead-in period. And patients thought that they were either getting placebo or active drug. So when they switched from the lead-in period to the post-randomization period, what were they told?

DR. FEIN: I would also add that the study site personnel, including the investigator, had no knowledge of the placebo lead-in period. It was

mark randomization on study day 1 after the screening, and patients exchanged bottles of nasal spray at every visit. Every visit, the dispense bottle was weighed on a scientific balance, and then it was weighed on return as an objective measure of compliance. But they just got a standard new bottle at day 15 versus day 1, and the randomization was handled by the electronic data capture system.

DR. CELLA: Did you get any feedback from patients that switched into an active drug that there was a different experience after 2 weeks, different sensation, different smell, different anything?

DR. FEIN: No, because the active component of the nasal spray is present in .0001 percent or less. Any fragrance or aromaticity of the nasal spray is produced by the formulation, including the CPD and the medical grade cottonseed oil. And there was no difference in the topical local effects. As you can see, placebo was identical in those regards to the active SER 120 groups.

DR. CELLA: And then for Dr. Khalaf, just very quickly, if not now, maybe at lunch, could you provide standard deviations for the baseline sample for the N-QoL for DB3 and for the newer questionnaire for DB4?

DR. KHALAF: Sure. If we can get the backup slide that has the N-QoL results? Show slide 2. This actually has the standard errors. You mentioned the standard deviations. Would you like to see the standard deviations?

DR. CELLA: Yes, but it's --

DR. KHALAF: Okay. That's something that I think we can provide at a later time today. We'll look into that and see if we can provide that.

I can't recall actually if there is a backup slide that has any variability measure for the INTU. No? Okay. So we'll look into that and provide those for you hopefully at some point.

DR. LEWIS: Actually, I got a correction about the time. I think we can take a question from Dr. Johnson.

DR. JOHNSON: Thank you. I had a question

about slide 23, and it's for Dr. Fein. I know that you were under advisement from the FDA to limit the lower age to 50, but I was wondering about the decision in the elderly patients group to limit the upper age to 85. And I was wondering if you could provide age ranges for longitudinal follow-up. I was worried that the elderly subjects, there was a low number and the lowest length of follow-up, and I was looking for data that you had for folks who were over 85 in some of the longitudinal follow-ups.

DR. FEIN: Well, 55 percent of the population was over the age of 65. About 22 percent was 75 years of age or older. And the rollover into the long-term safety extension study, the A2 study, was done independent of age. And in fact, we did an analysis in which we showed that there was virtually an identical allocation from each of the treatment groups in DB3, each of the four treatment groups. Placebo and the three active groups each contributed about 44 to 45 percent of their respective populations to the A2

study. There was no age restriction.

DR. JOHNSON: So just as a follow-up, with regards to the elderly patients, you capped the upper enrollment to 85. I was wondering about folks who were 86 through 90, 90 through 95. At some point, you just --

DR. FEIN: For my benefit, where are you getting the 85-year-old?

DR. JOHNSON: On your slide in the lower left-hand corner.

DR. FEIN: Oh. That was a small study just to get -- it was 56-day study to get pharmacokinetics.

DR. JOHNSON: My question was, why was there a restriction at the age of 85?

DR. FEIN: I can't give you a definite answer, but I believe it was just because the study required pharmacokinetic evaluation. One moment, please.

(Brief pause.)

DR. FEIN: I've been reminded that the protocol eligibility criteria did not have any age

restrictions. That reflects just the ages of the roughly 32 patients that were actually enrolled.

DR. JOHNSON: So I couldn't really tell the age range in other studies, and I would just be interested in that information.

DR. FEIN: We can get that for you, but there were very elderly patients, including patients in the early 90s.

DR. LEWIS: Thank you. Dr. Nahum?

DR. NAHUM: Thank you. I just have one clarifying question. In the briefing document from Serenity, you provided a definition of what a placebo responder was. And the first criterion is actually very transparent because it's consistent with the primary outcome variable, which is greater than 50 percent reduction in the number of voids per night.

But I wonder if you can clarify what the rationale for the second criterion is because it's basically or less than 1.8 episodes per night, which is somewhat different than the criteria that have been promulgated previously as being

clinically significant, being a threshold of 2, for instance, voids per night. So where did the 1.8 come from?

DR. FEIN: Thank you for that question. We were just trying to leave some room for improvement. In order for any patient to meet the 50 percent -- the responder criterion, which required a 50 percent decrease, if they had less fewer than 1.8 nocturic voids, they would have to go down between zero and 1 nocturic voids per night to even qualify, potentially qualify, as a responder. Even a single night with 2 would have mathematically eliminated them.

So there was some effort to be as liberal as we could, but to maintain some starting point, which had a sufficient number of nocturic voids to be valuable during the randomized treatment period.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: I thought the REMS plan was appropriate and clearly presented. My question -- or perhaps it's more of a request than a question, and I realize it's not practical. But

is there any actual training of the providers? Because that in my view would be very critical, and I didn't hear anything about that. And is there any enforcement of non-compliant providers?

DR. FEIN: I'm very glad you asked that question. Serenity tried to be proactive and prospective in submitting a proposed REMS as part of the new drug application. But clearly, this is not the final form, and if the FDA determines that the drug is to be approved or is approvable, then clearly there will be further discussion, including involving our marketing partner, Allergan, with the exact features and characteristics of the REMS and exactly how it will be executed.

So it's a very good point, and that would be determined during discussions with the agency and worked out collaboratively.

DR. HOWARDS: Thank you.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: Thank you. I think this is for Dr. Fein. I actually just had a comment and two quick questions. The comment is that during the

presentation and in your materials, you repeatedly referred to the impact of nocturia on falls and fracture. And I do want to point out that there's an updated analysis from that same study that Dr. Parsons published on looking at the incidence of fractures with nocturia that showed no effect. And I think that was just recently published in Journal of Urology. But I think it's important to show -- to add that to your background materials.

DR. FEIN: That's an excellent point, and I'm glad you made that point. Dr. Wein actually focused on falls because we understand that the relationship of fractures to the falls and to nocturia is a little bit more controversial. So we, Dr. Wein and I, did not specify that.

There are other publications. I know that the Parsons paper that you're referring to did adjust for bone density. That is a single publication and it has to be taken seriously. There are of course others, large epidemiologic studies which come to different conclusions. I think the jury is still out, but I'd like Dr. Wein

to also comment.

DR. WEIN: Thank you. There are a few studies in the literature that do quote an increased incidence of fractures presumably due to falls. In the study cited, you're quite right. But I think that study was men, correct, in the Journal of Urology, only men, not women. And they did relate it to the degree of bone demineralization.

So I think that has to be confirmed. I think the data by falls, I think they're irrefutable. The data by fractures, the reason that I didn't mention it and concentrate on it was because of that one study. I think that's arguable. Thank you.

DR. HOWARDS: And I had two quick questions. One actually had -- there was no discussion about actually where the participants in the 3 and 4 were recruited from. I think they were primarily from subspecialty clinics, but could you clarify that? And then the second quick question had to do with when did you decide about the co-primary outcomes?

I noticed from clinical trials.gov in 2011 and 2013, actually just only mentions the average number of voiding.

DR. FEIN: Each of the pivotal studies, DB3, DB4, involves 70 to 80 study centers spread all across the United States and Canada. It was a North American study. And they were a mixture of some specialty clinics and also the general physician's offices, geriatricians and the like, and a few academic centers, and a few centers geared to clinical research, but mostly subspecialty practices and multi-specialty practices.

With regard to the co-primary efficacy endpoints, we tend to be coy with clinicaltrials.gov, but the two co-primary efficacy endpoints were identical in DB1, 2, 3 and 4, and were in fact discussed and agreed to with the FDA at the end of phase 2 meeting before even DB1 was started.

DR. LEWIS: Thank you.

I know that some of you still have

questions, but I think it is now time to take a break. We'll try to find some time a little later.

We'll now take a 15-minute break. Panel members, please remember no discussion of the meeting topic during the break among yourselves or with any member of the audience. We'll return at 10:31.

(Whereupon, at 10:18 p.m., a recess was taken.)

DR. LEWIS: We'll now proceed with the FDA presentations.

FDA Presentations - Olivia Easley

DR. EASLEY: Good morning. My name is Olivia Easley, and I will be presenting the efficacy for SER 120. As we've heard already, SER 120 is a desmopressin nasal spray that is proposed for the treatment of nocturia in adults who awaken 2 or more times per night to urinate. There's no consideration of the underlying etiology of nocturia. The proposed dose is 0.75 micrograms before bedtime, which can be increased to 1.5 micrograms nightly depending on the patient's

response and tolerability.

The efficacy database in support of the marketing application consisted of two phase 3, randomized, double-blind, placebo-controlled trials involving a 12-week treatment period. These trials were entitled DB3 and DB4. Approximately 450 subjects were randomized to one of the 2 doses of SER 120 that are proposed for marketing or to placebo. Trial DB3 also included an intermediate 1 microgram dose, which is not being proposed for marketing and which will not be discussed further.

So again, you've heard about the design of the trials. I'll go over them again quickly. Each of the two trials involved a 2-week screening period during which subjects recorded the number of nighttime voids in a 3-day voiding diary collected each week, and study DB4, subjects also completed the INTU questionnaire.

Following screening, there was a 2-week double-blind placebo run-in phase during which all subjects were assigned to placebo, and they were unaware of this. And again, in each week, they

completed the voiding diary and the INTU, which was only in study DB4. And finally, after the placebo run-in phase, all subjects were then randomized to one of the doses of SER 120 or to placebo taken nightly. There were no restrictions on fluid intake during the trial, and they completed the voiding diary every 2 weeks during the 12-week treatment period, and in study DB4 the INTU at week 6 and 12.

There were two analysis populations, the intent-to-treat population, which consisted of all randomized subjects with at least 3 days of post-randomization efficacy data and a modified intent-to-treat population, which included only the placebo non-responders. Placebo non-responders were subjects who did not experience a greater than 50 percent reduction in the mean number of nocturic episodes per night compared to screening or had greater than 1.8 nocturic episodes per night during this placebo lead-in.

The sponsor had prespecified the modified intent-to-treat population as their primary

efficacy analysis population, but as Dr. Joffe explained earlier, FDA considers the ITT to be more scientifically valid because it includes all randomized patients and not a subgroup. Therefore, we will only be presenting the results for the ITT population.

The primary efficacy endpoints were the change from the 2-week screening period to the 12-week treatment period in the mean number of nocturia episodes per night and the percentage of patients with a greater than 50 percent reduction in the mean number of nocturia episodes per night. Selected prespecified secondary efficacy endpoints were the change from screening to treatment in the INTU overall impact score -- that was only in trial DB3 -- and the percent of nights with zero nocturia episodes or 1 or fewer nocturia episodes.

The trials enrolled men and women who were at least 50 years of age who reported a minimum 6-month history of nocturia with at least, on average, 2 nocturia episodes per night. In addition, they had to have documented nocturia by

voiding diary, at least 13 nocturia episodes over the 6 days in which they recorded during the 2-week screening period. A 24-hour urine collection was performed at screening, and the requirement was that the total volume be less than 4500 milliliters over 24 hours. And patients were also required to have a normal serum sodium concentration.

Exclusion criteria were numerous, as shown on this slide, and they included conditions that could cause or exacerbate nocturia or that could increase the risk of hyponatremia. And these included urologic conditions such as neurogenic detrusor overactivity; signs and symptoms of bladder dysfunction, for example, significant daytime urinary frequency; sleep disorders like obstructive sleep apnea; edematous states, including nephrotic syndrome or significant congestive heart failure; disorders of free-water intake or excretion like SIADH or diabetes insipidus; and then other significant medical conditions like unstable diabetes mellitus or uncontrolled hypertension.

Only loop diuretics and systemic corticosteroids were prohibited medications. The restricted medications that are shown on this slide were allowed, but only if the patient had been on a stable dose for at least 2 months prior to study entry, and those included alpha blockers, 5-alpha reductase inhibitors, anticholinergic medications, and SSRIs.

This slide displays the disposition of subjects in the two phase 3 trials. This is the intent-to-treat population. Close to 90 percent of subjects across treatment groups in both studies completed the trials. The discontinuation rate was a little higher in the SER 120 high-dose group compared to placebo. The most common reason for premature discontinuation was an adverse event.

The median age of subjects was 66 years old. The majority of subjects were white males, although 40 percent were women, and you did have representation from African Americans, Hispanics, and Asians, although significantly smaller.

The nocturia etiology, when subjects

enrolled in the trials, the investigator is assigned a probable etiology of nocturia for each subject based on the interview and review of medical records. Close to 80 percent of subjects across groups had more than one probable etiology. Usually it was nocturnal polyuria with something else, for example, BPH or overactive bladder. Only close to 20 percent of subjects were considered to have nocturnal polyuria alone as the cause of their nocturia.

In addition to the investigator assessment, as I mentioned, there was a 24-hour urine collection performed at screening, and patients who were greater than 33 percent of the urine was produced at night over the 24 hours. So more than a third of the urine produced for the entire 24 hours was produced at night; those patients were considered to have nocturnal polyuria. And again, close to 80 percent of subjects met that criterion for nocturnal polyuria, and the representation was similar across treatment groups.

Going on to the efficacy findings, the first

co-primary endpoint was the change in the nightly nocturia episode frequency. As you can see in this slide, at baseline, subjects across groups had a little more than 3 nocturia episodes per night. In the high-dose SER 120 group, subjects experienced approximately 1 and a half fewer episodes per night compared to placebo. The reduction was about 1.2 episodes per night, and the placebo-corrected reduction was 0.3 episodes per night in trial DB4 and 0.4 in DB3. So this was a statistically significant difference.

The lower dose SER 120, statistical testing was not performed in study DB3 because the intermediate dose, the 1 microgram dose, was not statistically significantly better than placebo. So according to the statistical analysis plan, which called for hierarchical testing, we did not test the 0.75 microgram dose. However, in trial DB4, you can see that the placebo-corrected difference for the low dose was 0.2 fewer episodes per night, and this was statistically significant compared to placebo.

This slide displays the second co-primary endpoint, the percentage of subjects with a greater than or equal to 50 percent reduction in nightly nocturia episode frequency. Again, for the high dose, which is shown in the blue bars, almost 50 percent of subjects experienced this response rate in both trials compared to about a third of placebo subjects; that's the green bars. And this difference between high dose and placebo was significant in both trials.

In DB3, again, because the 1 microgram dose failed, we did not do statistical significance testing for the low dose; and then in DB4, which only included 2 SER 120 doses, the difference was not statistically significant. So 36 percent of patients had that response rate compared to 29 percent with placebo, and again, not a statistically significant difference. So the net response rate for the high SER 120 group was about 18 to 19 percent. That was the placebo subtracted response rate.

The first ranked secondary efficacy endpoint

in trial DB4 was the INTU overall impact score. That scale ranges from zero to 100 with higher points signifying more significant impact to patients. At baseline, subjects had approximately 30 points on the INTU, and in the high-dose SER 120 group, the change to the treatment period, they dropped about 14 points; for placebo, a 11 and a half point reduction was observed.

So the placebo-corrected difference for the high-dose group was 2.6 points. This was statistically significantly different. And Dr. Sarrit Kovacs will be explaining the clinical significance of that 2.6 difference later this morning.

Secondary endpoints that were prespecified that FDA considers important and meaningful are with the percent of nights with no nocturia episodes during treatment. As you can see in this slide, the high-dose SER 120 -- so at baseline across groups, basically no one has no nocturia episodes. And then during treatment, in the high-dose group, between 10 and 11 percent of

nights, patients have on average no nocturia episodes. And compared to placebo, they're at 5 percent of nights with no nocturia episodes.

So the placebo-corrected difference is about 5 percent more nights that patients are nocturia-episode free, and this was statistically significant in both trials for the high-dose group.

Similarly important, the percentage of nights with one or less nocturia episode was another endpoint. And again, at baseline, only 1 percent of patients had a night with -- I'm sorry, only 1 percent of nights did patients report 1 or less episode. On treatment, though, with SER 120, 45 percent of nights, subjects experienced one or less episodes compared to 33 percent of nights on placebo. So with drug, 9 to 10 percent more nights with one or fewer episodes was observed, and this was statistically significant.

Now, I will turn the podium over to Dr. Jia Guo, who will discuss the clinical meaningfulness of the change in nocturia-episode frequency.

DR. LEWIS: Thank you. Dr. Guo, before you

take the podium, I'd like to recognize one other member of the FDA.

Dr. Kaul, could you please introduce yourself?

DR. JOFFE: Sorry. Can you repeat the question?

DR. LEWIS: I'd like Dr. Kaul to please introduce himself. He's joined the panel, and we haven't met him.

DR. KAUL: I'm Suresh Kaul. I'm the medical team leader for the Division of Bone, Reproductive, and Urologic Products.

DR. LEWIS: Thank you. Dr. Guo?

FDA Presentation - Jia Guo

DR. GUO: Good morning. My name is Jia Guo. I'm the statistical reviewer at FDA, and I'm going to present the results of the exploratory analysis conducted by FDA for 1 co-primary efficacy endpoint, the change from baseline in nocturia episodes per night. I'd like to point out, this analysis was neither prespecified in the study protocol nor requested by FDA prior to submission.

As you have seen from Dr. Olivia Easley's presentation, the 1.5 microgram dose achieved statistical significance on both co-primary efficacy endpoints, and the mean reduction in nocturia episodes were about 1.5 to 1.6 episodes per night versus 1.2 episodes in the placebo group. To evaluate if the reductions of this magnitude are potentially meaningful to patients and help interpret efficacy results, FDA conducted additional analyses. For this exploratory analysis, FDA used an anchor-based approach.

In study DB4, the sponsor collected additional information on the patients' self-reported treatment benefit using a single-item questionnaire. This questionnaire asked patients nighttime urination condition at the end of study compared to before starting the treatment.

The question had five possible responses, from much better to much worse, and the response represented a patient's perspective of the treatment benefit only. This questionnaire had a 3-month recall period and may have potential recall

bias. We then mapped the change in nocturia episodes to this treatment benefit scale as an anchor.

First, we looked at the TBS and the nocturia episodes reduction data. This bar graph shows the rates of each response to TBS in the two treatment groups. At the end of study, the response rate of much better was 43 percent in the 1.5 microgram group, which was 8 percent higher than that in the placebo group.

For the somewhat better group, the response rates were very similar, 37 versus 38 percent in the two treatment arms. For the not changed, the response rate was 20 percent in the 1.5 microgram group, which was 7 percent lower than that in the placebo group. No patient in the study reported feeling somewhat worse or much worse. Overall, more than 70 percent of patients reported some benefit.

This table shows summary statistics for change in nocturia episodes per night by TBS response categories. Negative values represent

reduction in episodes. The smaller the negative value is, the more reduction was in nocturia episodes. For the much better category, the population mean reduction was 1.9 episodes and went down to 1.2 episodes in the somewhat better category and 0.5 episodes in not changed category.

It appears patients who had more positive response on treatment benefit showed a greater reduction in episodes. Think back to the mean nocturia episodes reduction in treatment groups. The 1.5 episodes reduction in the 1.5 microgram group was between the much better and somewhat better categories, and the 1.2 episodes reduction in the placebo group is in line with the somewhat better category.

In addition to the summary statistics on the previous slides, we also look at a cumulative distribution function for change from baseline in nocturia episodes per night by TBS response categories. This CDF plot pooled all patients across treatment arms in study DB4. The X-axis represents the change in nocturia episodes per

night, and negative value means reduction. The smaller the negative value is, the more reduction there was in nocturia episodes. The Y-axis is the cumulative percentage ranging from zero to 100 percent.

This blue curve is the CDF curve for the patients who reported much better to TBS. For each value on the X-axis, the corresponding value on the Y-axis represents the cumulative percentage of patients who had at least that much reduction in nocturia episodes. The red curve is for patients in the somewhat better category, and the green one is for the not changed category.

First, we look at a median line on the Y-axis. Half of the patients had at least 1.7 episodes reduction in the much better category, 1.2 episodes reduction in the somewhat better category, and 0.5 episodes reduction in the not changed category. The top 10 percent of patients of each response category had at least 2.8, 2.1, and 1.4 episodes reduction.

For the bottom 10 percent of patients in

each response category, they had at least 1 and 0.4 episodes reduction in the much better and somewhat better categories, and 0.2 episodes increase in the not changed category. In this CDF plot, we see that for a fixed cumulative percentage, there's consistent separation between the three response categories with respect to nocturia episodes reduction.

In the context of responder assessment, the Y-axis can also represent the proportion of patients who are considered responders at that threshold value on the X-axis. The CDF curve communicates the proportions of responders at every value along the change in nocturia episodes, so it allows all proposed responder definitions to be evaluated simultaneously.

Now, we examine two threshold values, minus 1.7 and minus 1.2, which are the medians of the change in nocturia episodes in the much better and somewhat better categories. Using 1.7 as a threshold, we define a patient as a responder if the mean reduction nocturia episodes per night was

at least 1.7, otherwise as a non-responder.

The responder rates were 50 percent, 20 percent, and 3 percent in the much better groups, somewhat better, and the no change group. Similarly, using 0.2 as a threshold to define responders, the responder rates were 81 percent, 50 percent, and 14 percent, respectively, for the three response categories.

In this CDF plot, we see that for a fixed threshold value, there's consistent separation between the three response categories with respect to the responder rate. This slide and the previous slide visually compared the separation of the three CDF curves along the X-axis and the Y-axis. It supported that the reduction in nocturia episodes was consistent with the difference seen between the anchor scale responses.

Based on this CDF plot, it appears that a mean reduction of approximately 1.5 episodes seen in the 1.5 microgram group and the 1.2 episodes in the placebo group fall between the somewhat better and much better categories and appear to be

meaningful to patients.

This slide shows the CDF curves of nocturia episodes reduction by treatment groups in study DB4. We examined the responder rates in both treatment groups using different threshold values. Using 1.7 episodes reduction at a threshold value to define responders, the responder rates were 36 percent versus 23 percent in the treatment group and placebo group. Using 1.2 episodes reduction as a threshold value, the responder rates were 58 percent versus 45 percent in the treatment and placebo groups.

Within the range between 1.2 and 1.7 episodes reduction, we find that the 1.5 microgram group had a consistent higher responder rate than placebo group using different threshold values to define responder, and the rate difference is approximately 13 percent.

This anchor-based exploratory analysis suggests that a mean reduction of at least 1.2 to 1.7 nocturia episodes per night may be potentially meaningful to patients. This CDF plot of mean

reduction in nocturia episodes showed separation between the 1.5 microgram dose versus placebo without overlapping or cross-over, and the 1.5 microgram group may benefit approximately 13 percent more subjects than placebo in reducing nocturia episodes.

Next, Dr. Sarrit Kovacs will present FDA's review on the impact of nighttime urination instrument.

FDA Presentation - Sarrit Kovacs

DR. KOVACS: Good morning. I'm Sarrit Kovacs, a reviewer with the clinical outcome assessments, or COA, staff in the Office of New Drugs at FDA, and I'll give a summary of available evidence on the impact of nighttime urination or INTU instrument's content validity, psychometric properties and performance, and an overview of the INTU related efficacy results and meaningfulness of the scores.

During clinical development of the SER 120 desmopressin treatment for adults with nocturia, the applicant included a patient-reported outcome,

or PRO instrument, in their phase 3 DB4 clinical trial. They included the INTU instrument as the first ranked secondary endpoint to support the efficacy assessment of SER 120 in decreasing the impact of nocturia on patients' daily lives.

Given that the INTU was the only PRO instrument prespecified as a secondary endpoint and type 1 error controlled, FDA review and my presentation are focused only on INTU and not on any of the other PRO instruments that may have been included as exploratory endpoints in the DB4 clinical trial.

The aim of the INTU was to assess the impacts of nocturia on daily living, including impact on restfulness, concentration, and level of emotional concern about needing to get out of the bed to urinate. The first four items have a 5-point scale ranging from not at all to all day, and the last six items have a 4-point scale ranging from not at all to very much.

All items were transformed to a scale ranging from zero to 100 points. The daytime

impact domain score includes items shown in dark purple-numbered circles, and the nighttime impact domain score includes items shown in light blue-numbered circles. The overall impact score was computed by taking the mean of the daytime and nighttime impact scores.

You may want to refer to section 3 table 1 in the supplemental INTU memo to the FDA backgrounder for a copy of the INTU instrument, as I may mention specific items and item numbers during my presentation.

The FDA examined the INTU's content validity specifically measuring impacts of nocturia on patients' daily lives. In line with recommendations from the FDA's PRO guidance for industry, the INTU was developed using a qualitative approach consisting of a systematic review of published literature and input from 28 English-speaking patients with nocturia. The qualitative sample appears to be representative of the DB4 clinical trial patient population.

The qualitative work appears to support the

assertion that nocturia affects multiple aspects of patients' lives, and the research identifies the key impacts associated with nocturia as shown in figure 1 on this slide. In general, the nighttime impact items appear to measure intensity or severity of sleep related impacts of nocturia and appear to be more likely to be sensitive to treatment effects. In addition, the daytime impact of tiredness appears to be highly endorsed by patients.

In general, the measured concepts and items included in the INTU appear to be relevant to and understood by patients. The most commonly reported impact of nocturia endorsed by patients in the 1 on 1 interviews was tiredness.

The applicant conducted a 2-week observational study to psychometrically evaluate the INTU instrument in 193 patients with clinically confirmed nocturia, and this quantitative study sample appears representative of the DB4 pivotal trial patient population.

The applicant examined the INTU instrument's

measurement properties and performance, and the results appear acceptable. The INTU's internal consistency reliability was tested to examine how well the INTU items all measure the same construct; in this case, impacts of nocturia.

For test/re-test reliability, the applicant examined the INTU's ability to have stable scores between administrations when no changes have occurred in the patient's nocturia status. Convergent validity was tested to examine whether the INTU scores moved in the expected direction with scores from other instruments measuring a similar concept. Known groups' validity tested how well the INTU scores could distinguish among mild, moderate, and severe nighttime urination groups.

The FDA has concerns regarding some of the INTU daytime impact items targeting more distal impacts of nocturia. Distal impacts are impacts that may be less directly related to nocturia, and therefore could be affected by factors other than nocturia such as comorbidities or psychosocial stressors, whereas in general, the nighttime impact

items appear to be more directly related to treatment effects.

In line with this FDA concern, the applicant observed high floor effects for 3 of the 6 INTU daytime items and 1 of the 4 nighttime impact items. Floor effects are when a high percentage of patients select the least severe response option, which in this case was the response of not at all, indicating that the item is not relevant to or not experienced by the patient.

The daytime impact items that showed the highest floor effects were items number 1, difficulty concentrating; number 2, difficulty getting things done; number 3, been irritable; and nighttime impact item number 7, starting your day earlier than you would have liked due to getting up out of bed to go to the bathroom this morning. These same four items also had high floor effects in the DB4 clinical trial data.

The applicant assessed the INTU's ability to detect change over time, examining whether the instrument was equally sensitive to improvement and

worsening in patients in the impacts of nocturia, meaning that the INTU scores change with actual change in patient's nocturia status. However, we noted that the applicant did not specify a threshold for a meaningful change in INTU overall impact score, which was the first-ranked secondary endpoint in the DB4 clinical trial.

In general, the results of the INTU's measurement property and performance analyses appear acceptable, however, there are some items that may not be relevant to or experienced by many of the patients. Interpretation of the DB4 clinical trial efficacy findings for the INTU overall impact score is challenging given that there was no prespecified threshold for a meaningful change for use in phase 3.

As was presented previously by Dr. Olivia Easley, the difference between the SER 120 arm's 14-point mean improvement or reduction in the INTU overall impact score from baseline and the 11.5 or 12-point mean improvement for the placebo arm was statistically significant, however, this difference

between treatment arms was numerically small.

The question before us is whether an improvement or reduction of 14 points in a zero to 100-point scale is meaningful to how patients are feeling and functioning in their daily lives and whether the mean improvement or reduction of 12 points achieved by the placebo arm is just as meaningful.

The FDA requested that the applicant conduct post hoc exploratory anchor-based analyses to aid in interpretation of the INTU efficacy results given that there was no prespecified threshold from clinically meaningful change. An anchor-based approach is the primary basis for how the FDA determines an instrument's ability to detect change and for defining a meaningful change in scores a responder definition.

Anchor scales are items or scales used to anchor the patient responder groups; in other words, improvement, no change, and worsening patient categories, which are used for evaluation of clinically meaningful change in scores.

The FDA requested that the applicant use two anchor scales for post hoc exploratory analysis. The first anchor was the Treatment Benefit Scale, or TBS, which was previously presented by Dr. Jia Guo, and the second anchor scale was reduction in number of nocturic episodes, based on results from the 1 on 1 qualitative interviews with the 28 patients with nocturia who reported, in general, that a reduction in 1 nocturic episode would be a meaningful change to them.

The FDA requested that the applicant use the DB4 data pooled across study arms for these analyses of the INTU's mean overall impact change scores. It appears that a mean reduction in INTU scores for patients reporting that they felt much better was 19 points out of the 100 possible points, whereas a mean reduction in INTU score for patients reporting that they felt somewhat better was 10 points.

When thinking back to the 14-point and 12-point mean improvements achieved by the SER 120 and placebo arms, respectively, we see that both a

14-point and 12-point mean improvement or reduction fall somewhere between the somewhat better and much better patient TBS categories.

A mean reduction in INTU scores for patients who had a reduction of at least 1 nocturic episode appears to be 16 points. Neither the 14-point nor the 12-point mean improvement achieved by the SER 120 and placebo arms met this threshold of reduction of at least 1 nocturic episode. A mean reduction in INTU scores for patients who had a 50 percent reduction in nocturia episodes appears to be 20 points. Again, neither the 14-point nor the 12-point mean improvement achieved by the SER 120 and placebo arms met this threshold.

In general, the TBS and nocturic episode anchors corresponded with improvements in INTU change scores, and the INTU's ability to detect change over time appears acceptable. Based on these anchor-based analyses, it appears that both a 14-point mean improvement achieved by the SER 120 arm and the 12-point mean improvement achieved by the placebo arm fall between somewhat better and

much better but do not correspond with the reduction of at least 1 nocturic episode or a 50 percent reduction in episodes.

As was presented by Dr. Khalaf, in order to explore what would be considered a meaningful change in INTU overall impact scores, the FDA requested cumulative distribution function, or CDF plots, pooled across the DB4 study arms. The CDF plot on this slide shows the distribution curves for each TBS patient category. Here the change in INTU overall impact scores from baseline are plotted on the X-axis, and the Y-axis represents the cumulative percentage of patients achieving a particular INTU change score or greater.

When exploring meaningful thresholds for change scores, we typically look at the median line on the Y-axis, or 50th percentile, with patients, and where that line hits each TBS curve. We then trace those intersection points down to the X-axis to see the corresponding change in the INTU overall impact score.

Looking at the median line, we see

50 percent of patients who reported that their nocturia symptoms were much better, the red curve, achieved about a 16-point or greater improvement or reduction in INTU overall impact score, and 50 percent of patients who reported that their nocturia symptoms were somewhat better, the green curve, achieved about an 8-point or greater improvement or reduction in the INTU overall impact score.

Based on this CDF plot, it appears that both the 14-point mean improvement achieved by the SER 120 arm and the 12-point mean improvement achieved by the placebo arm fall between somewhat better and much better and appear to be clinically meaningful to patients.

Because all of the exploratory analyses presented thus far were based on data pooled across study arms, we have not yet shown how SER 120 compares with placebo with regard to the change in the overall impact score. Therefore, this slide shows the CDF plot with separate curves for each of the treatment arms, and here we see that there is a

somewhat small but consistent separation between the SER 120 and placebo arms.

In summary, it appears that some of the daytime impact items in the INTU instrument measure more distal or less direct impacts of nocturia on patients' lives, which could be impacted by factors other than nocturia. The items measuring more distal impacts showed high floor effects and likely increased variability or noise in the INTU overall impact score. Therefore, inclusion of these items likely led to insensitivity of the INTU overall impact score endpoint in detecting treatment effects.

The nighttime impact items appear to measure more direct and relevant impacts of nocturia and appear to be more sensitive to treatment effects in the DB4 clinical trial data. Interpretation of the efficacy findings from the DB4 clinical trial is challenging given that there was no prespecified threshold for a meaningful change in INTU overall impact scores for use in phase 3, and it appears that both the 14-point mean improvement achieved by

the SER 120 arm and the 12-point mean improvement achieved by the placebo arm are meaningful with regard to how patients feel and function in their daily lives.

However, is the magnitude of a 2.6 point difference between SER 120 and placebo arms mean score adequate? Determination of the INTU overall impact score being fit for purpose and yielding meaningful results needs to be evaluated in the overall context of evidence given that the INTU is included only in a single pivotal trial.

Next, Dr. Olivia Easley will provide a summary of the efficacy findings.

FDA Presentation - Olivia Easley

DR. EASLEY: In summary, SER 120 1.5 microgram met both co-primary efficacy endpoints. Over 12 weeks of treatment compared to placebo, there was a mean reduction of 0.3 to 0.4 nocturia episodes per night, and 18 to 19 percent more subjects experienced a greater than or equal to 50 percent reduction in nocturia episode frequency.

SER 120 1.5 micrograms also reduced the INTU overall impact score from a baseline of approximately 30 points by 2.6 points more than placebo. The prespecified criteria for efficacy were not met for SER 120 0.75 micrograms. An exploratory analysis suggests that approximately 13 percent more subjects receiving SER 120 1.5 microgram experienced a clinically meaningful benefit in nightly nocturia episode frequency reduction compared to placebo.

The division's remaining concerns regarding the efficacy of SER 120 are the suitability of a treatment for nocturia without consideration of the underlying etiology: the clinical relevance of numerically small changes in nocturia episode frequency and in the INTU overall impact score for the SER 120 high dose; absence of efficacy data to support the proposed titration scheme; and finally, efficacy of the product in subjects younger than 50 years of age has not been assessed.

Now, Dr. Kaufman will present safety of SER 120.

FDA Presentation - Martin Kaufman

DR. KAUFMAN: Good morning. I'm Martin Kaufman, and I'm going to present the review of safety for SER 120. The safety database for SER 120 was comprised of over 1800 subjects with nocturia who received the drug for periods of time ranging from less than 1 month to more than 2 years. The duration and extent of exposure of SER 120 in nocturia patients was adequate.

For the 4 doses tested, over 600 subjects received the drug for 6 or more months, and about 350 subjects received the drug for a year or more. For the highest dose tested, over 300 subjects received the drug for 6 or more months, and over 200 subjects received the drug for a year or more.

The sponsor conducted four placebo-controlled trials and two open-label extension trials, which are summarized in this slide. The only trials that studied the 1.5 microgram dose of SER 120 were placebo-controlled trials DB3 and DB4, and open-label trial A2. Therefore, this presentation

primarily focuses on these data, though the data from all of the placebo-controlled trials were considered for the analysis of serious adverse events.

The designs of DB3 and DB4 were similar and were previously discussed by Dr. Easley during the efficacy presentation. Study A2 was the open-label safety extension of DB3. During the study, subjects started treatment at the 1 microgram dose of SER 120 and could be up-titrated to the 1.5 microgram dose if their serum sodium concentration remained normal. Similar to DB3 and DB4, there were no fluid restrictions during A2.

This slide provides a summary of the 5 deaths that were reported during the clinical trials for SER 120. All but one of the subjects were older than 75, and all were being treated with SER 120 at the time of their death. Three subjects died during the placebo-controlled trials. The role of the drug in two of these deaths is unlikely. One subject's death was attributed to coronary atherosclerosis and sarcoidosis, which was

confirmed by autopsy. The other was attributed to cardiac arrest and hypotension due to a bleeding abdominal aneurysm.

A role for the drug in the third death cannot be ruled out. This subject was an 80-year-old male with multiple cardiac risk factors, a history of myocardial infarction, chronic obstructive pulmonary disease, and asthma. Four days after starting the 0.75 microgram dose of the drug, he was found dead in his home. Neither his autopsy report nor death certificate was made available to the study site.

During the four placebo-controlled trials, 1413 subjects were randomized to treatment with SER 120 and 770 subjects were randomized to treatment with placebo, which equates to a randomization ratio of slightly less than 2 to 1. Therefore, the 3 deaths in SER 120 treated subjects, compared to none with placebo, could be consistent with the randomization scheme.

During the uncontrolled trials, 2 subjects died. The role of the drug in one of the deaths is

unlikely. This subject had a cecal perforation. He underwent surgery, but died 2 weeks later. The role of the drug in the other death cannot be ruled out. This subject was a 79-year-old male with a history of hypertension, hyperlipidemia, and previous myocardial infarction and transient ischemic attack. He started OL1 at the 0.5 microgram dose and was up-titrated to the 0.75 microgram dose at his day 15 visit. Four days later, he was found dead in his home. An autopsy was not performed. His death certificate listed the cause of death as probable myocardial infarction.

In the four placebo-controlled trials, the incidence of serious adverse events was low and similar for each of the 4 dose levels of SER 120 and for placebo. The only serious adverse event reported by more than one SER 120 treated subjects was basal cell carcinoma, which was reported by 3 subjects. For the cardiac disorders system organ class, the incidence of serious adverse events was also low, and none of the events occurred in the

1.5 microgram dose group.

The subject with congestive heart failure was a 56-year-old male who was diagnosed with congestive heart failure about 3 months after starting treatment with the 0.75 microgram dose of SER 120. At that time, he was found to have dilated cardiomyopathy, valvular abnormalities, left atrial enlargement, and pulmonary hypertension.

It is unlikely that SER 120 caused these abnormalities, but it's not possible to rule out an adverse effect of the drug on his underlying cardiac status due to fluid retention related to the pharmacologic effects of the drug. Hyponatremia was reported as a serious adverse event in 2 subjects, one in the 1.5 microgram treatment group and one in the placebo group.

The incidence of adverse events leading to discontinuation during DB3 and DB4 was slightly greater in SER 120 treated subjects than for placebo. The most common adverse events leading to discontinuation were nasal discomfort and

hyponatremia, however, the incidence of nasal discomfort was greater for placebo than for either dose of SER 120.

As you can see from this slide, the incidence of subjects with at least 1 treatment emergent adverse event was slightly greater for both SER 120 doses than for placebo. In general, the most common adverse events reported involved the nasocavity and nasopharynx, which is consistent with the route of administration of the drug.

Adverse events were most commonly reported in respiratory disorders system organ class and the infections and infestations system organ class. The most commonly reported preferred terms in the respiratory disorders system organ class were nasal discomfort, sneezing, and nasal congestion. The incidence of sneezing and nasal congestion were greater for both SER 120 doses than for placebo. Only the incidence of nasal congestion appear to be dose related.

The most commonly reported preferred terms in the infections and infestations system organ

class were nasopharyngitis and urinary tract infection. Only the incidence of nasopharyngitis was greater for both SER 120 doses than placebo and appear to be dose related.

Hyponatremia is a known risk associated with desmopressin and is consistent with the pharmacologic effect of the drug. During DB3 and DB4, there were no prespecified criteria for reporting adverse events of decreased serum sodium or hyponatremia. This slide summarizes the adverse events that were coded as either blood sodium decreased or hyponatremia. The incidence of events in the 1.5 microgram dose of SER 120 is greater than placebo for both preferred terms.

This slide focuses on serum sodium levels during DB3 and DB4. The table shows a categorical analysis of the lowest serum sodium values occurring in patients during the trials. There were three predefined serum sodium categories. The last category, serum sodium of 125 millimoles per liter or less, is consistent with severe hyponatremia. Five subjects treated with the

1.5 microgram dose of SER 120 were in this category. It is noteworthy that the lowest sodium values in one subject in the 1.5 microgram treatment group and one subject in the placebo group were assessed outside of the clinical trial, either at a doctor's office or an emergency room.

This slide shows the key characteristics of the SER 120 treated subjects in the 125 millimoles per liter or less serum sodium category. The last row of the table shows the characteristics of the SER 120 treated subject with hyponatremia reported as a serious adverse event.

This subject had two sodium values that were less than 125 millimoles per liter. The first occurred on study day 21. This assessment was done at an emergency room. The subject presented to the ER with a complaint of back pain. Routine labs were done and showed a serum sodium level of 122. Her back pain was treated, but the hyponatremia was not addressed.

She continued in the trial, and on study day 60, she had symptoms of hyponatremia and saw

her personal physician. Her sodium level at that time was 117. She was treated with normal saline intravenously, and per protocol, she was discontinued from the trial due to a hyponatremic event.

If you look at the characteristics of the subjects in this serum sodium category, all were older than 65 and 4 were 70 or older. All were being treated with the 1.5 microgram dose at the time of the event. Consistent with the protocol, all had baseline sodium concentrations within normal range. The hyponatremic events occurred throughout the study from day 21 to day 99, the final study visit. Only one subject had symptoms.

Four of the five subjects were being treated with corticosteroids. Of these 4 subjects, 3 were being treated with an inhaled corticosteroid, and one had been treated with a 4-day course of oral prednisone, 30 milligrams a day, starting 5 days before the hyponatremic event. One of the subjects being treated with an inhaled corticosteroid had also received an injection of 40 milligrams of

triamcinolone 8 days prior to the event. Three of the four subjects being treated with a corticosteroid were also being treated with a non-steroidal anti-inflammatory drug.

This slide compares characteristics of subjects in the 125 millimole per liter or less sodium category and the 126 to 129 millimole per liter category. For both groups, age was an important characteristic. Unlike the 125 millimole per liter or less category, SER 120 treated subjects in the 126 to 129 category were evenly distributed between the 1.5 and 0.75 microgram doses at the time of the event. While all subjects in the 125 or less category discontinued the study drug after the event, consistent with the protocol in the 126 to 129 category, all subjects, except for three, one in the 1.5 microgram dose group and two in the 0.75 microgram dose group, completed the study.

Based on the previous analyses showing that age may be an important characteristic of the subjects with decreased serum sodium, a subgroup

analysis of subjects less than 65 years of age and subjects 65 or older was done. For the 1.5 microgram dose group, the incidence of decreased serum sodium was less for the younger than for the older subgroup for each of the three serum sodium categories. Importantly, no cases of severe hyponatremia or serum sodium of 125 millimoles per liter or less were reported for the subgroup of younger subjects.

To address the risks of the drug, the applicant's proposed risk mitigation plan includes labeling and a risk evaluation and mitigation strategy or REMS. The proposed labeling includes contraindications for patients with hyponatremia or a history of hyponatremia, renal impairment, severe heart failure, syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus, polydipsia, and uncontrolled hypertension. There are also warnings and precautions for sodium losing conditions, heart failure, uncontrolled diabetes mellitus, and concomitant medications that could increase the risk of hyponatremia.

The proposed labeling also include recommendations to monitor serum sodium before and 14 days after initiating therapy or increasing dose and periodically as clinically appropriate. And if serum sodium decreases below normal range, to consider discontinuing treatment until sodium levels return to normal.

Labeling also provides the following instructions for initiating treatment. Serum sodium should be in the normal range before starting the drug, and patients should be started on the 0.75 microgram dose for 2 to 4 weeks with up-titration to the 1.5 microgram dose based on efficacy and tolerability.

The sponsor also voluntarily proposed a risk evaluation and mitigation strategy, or REMS, to mitigate the risk of hyponatremia. The elements of the REMS include a medication guide that informs patients about the risk of hyponatremia, describes its symptoms, and warns about its serious side effects. A communication plan consisting of a one time Dear Healthcare Provider letter with labeling

recommendations, and a timetable for submission of assessment of the REMS.

To summarize the safety findings for SER 120, there were 5 deaths in the controlled and uncontrolled trials. In the controlled trials, there were 3 deaths in SER 120 treated subjects and none in the placebo group. A role for the drug in two of the deaths is considered unlikely. A role cannot be ruled out for the other death. In the uncontrolled trials, there were 2 deaths. A role of the drug in one of the deaths is considered unlikely. A role cannot be ruled out for the other death.

Serious adverse events in the four placebo-controlled trials occurred with similar incidence for all dose levels of the drug and for placebo. There was one report of congestive heart failure at the 0.75 microgram dose and 2 reports of hyponatremia, one in the 1.5 microgram dose group and one in the placebo group.

In DB3 and DB4, the adverse events leading to discontinuation occurred at slightly greater

incidence in SER 120 treated subjects than in placebo. The most common events leading to discontinuation were nasal discomfort and hyponatremia. The incidence of nasal discomfort was greater for placebo than for either SER 120 dose group.

Common adverse events also occurred at slightly greater incidence in SER 120 treated subjects than in placebo. The events were most commonly reported in the respiratory disorders system organ class and the infections and infestations system organ class.

The most important risk of the drug is hyponatremia. In the 0.75 microgram dose, no subject had a nadir serum sodium value of 125 millimoles per liter or less, 2 percent had a value between 126 and 129, and 8.4 percent had a value between 130 and 134. In the 1.5 microgram dose, 1.1 percent had a nadir serum sodium value of 125 millimoles per liter or less, 2 percent had a value between 126 and 129, and 11.2 percent had a value between 130 and 134. Thank you.

Clarifying Questions to the FDA

DR. LEWIS: Thank you. Before I open it up to questions, I just want to let people know that we will have additional time for questions that may have gone unanswered, questions for the sponsor, after the open public hearing. So we do have a list of names, and if you still have those questions, we'll get to them later.

So at this time, I'd like to open it up for questions to the FDA, clarifying questions. Dr. Neaton first.

DR. NEATON: Thanks. I appreciate the efforts on both the sponsor and the FDA to try to get at the clinical relevance of the change, but I just wonder whether you can comment on using this treatment benefit scale, which as I understood it was only done once, at the end of the study.

It almost seems to me, by definition then, it's not too surprising you don't have too many people that are indicating that they are feeling worse or somewhat worse because they're at the end of the study, and you're relating it to things that

appear to be some correlation with the number of times people are getting up during the middle of the night and the other questionnaire. But it seems like it's not the best way to establish relevance. And related to that, why is there disagreement, from the FDA's point of view, on the second primary endpoint, a 50 percent reduction? That's my first question.

The second question is -- and this is again to both the sponsor and the FDA -- we keep calling these individuals that were identified during the placebo run-in period as placebo responders. However, if I understand things correctly, there was a screening period where people were identified as having meeting the eligibility criteria, enrolled, then were put on a placebo for 2 weeks, and then were put on randomized active treatment.

So in fact what's going on is a combination of both the placebo effect and just regression toward the mean because you caught some people high during the screening period, and on average, their true values were really lower. So I think it would

actually be useful, kind of thinking about it that way, to see the data for what you're calling placebo responders and non-responders because it may guide some discussion about who really should be put on this drug. I think you want to put people on the drug who really do have a problem with nocturia, and perhaps there's some misclassification going on here as well as, quote, "a placebo response."

So that's maybe a request to see some data after the break, but maybe the first question, the FDA can take.

DR. EASLEY: Sorry. Can you clarify what your first question --

DR. NEATON: What I heard the sponsor say is they came up with a secondary co-primary endpoint relating to a 50 percent response, which seems like it's -- you know, rather than looking at an average change in nocturia, it provides some measure of perhaps clinical relevance. And I think that's not unreasonable as well as some of the other secondary endpoints that were determined. And I have

misgivings about the analyses done by both the sponsor and the FDA relating that nocturia questionnaire to the Treatment Benefit Scale because it was only done at the end of the study and on a single occasion.

So I think there are limitations to those analyses, and I wonder if you agree.

DR. KOVACS: Typically, the FDA recommends including multiple anchor scales from the patient's perspective, like a patient global impression of severity, like a current state, point in time, mild, moderate, severe, let's say, nocturia impact, and a patient global impression of change from baseline just to try to incorporate the patient voice in what is clinically meaningful to them and how they're functioning and feeling in their daily lives.

So the Treatment Benefit Scale was as close as the FDA could find in getting the patient's voice to target that clinical meaningfulness of scores in the INTU and mapping that. So yes, there are limitations to the Treatment Benefit Scale.

There's a lengthy 99 recall period, which could potentially introduce recall error, but it was included as an exploratory endpoint, not a prespecified endpoint, suitable for labeling. So that was our attempt at trying to get at the clinical meaningfulness.

DR. NEATON: I don't have any problem with it as a secondary endpoint. I just have a problem interpreting the analyses and trying to gauge it, give it some clinical relevance to the change in the number of nights of nocturia because I think you're set up for, I think, having a very skewed data set because of where you collected it and the kind of responses you're going to get there. I don't know what was done to try to overcome that, but it seems like it's a major impediment to any interpretation of that analysis.

DR. LEWIS: Dr. Gellad?

DR. GELLAD: Thank you. I just wanted some clarification from the FDA on the efficacy issues around the 0.75 microgram dose, because I know I heard the sponsor say -- to talk about pooled

analysis where there wasn't effect. So I know that the dose was not tested in one of the trials and -- pardon? The dose was not tested because the 1 microgram didn't reach statistical significance. But I guess I just want to hear your thoughts about what is the significance of the pooled results in relation to the overall efficacy for that dose?

DR. JOFFE: I can start, and others can join in. This is Hylton Joffe. We don't typically pool data across trials for efficacy. It's not clear to me that that was even a prespecified plan. So from our viewpoint, we're looking at the data in each study according to the prespecified analysis, not this pooling, which we see more as an exploratory analysis.

There was a question that was just asked also about seeing data for placebo responders and non-responders. I don't believe we have a slide for that. I don't know if the sponsor has a slide that they could put up and walk through the data for the other question.

DR. NEATON: If you want to take your time

doing that, I think it would be useful to do a couple things, if I may, see it for the secondary endpoints and to look at your data on the number of nights during the 3 days that you did this, what is the average decline in your numbers from the original screening to the placebo run-in and then during follow-up, so that we actually can see the data that was collected at each of those 3-day diaries during those different time periods. I didn't see that anywhere in the report, and just having that information would be helpful I think.

DR. FEIN: If we could put up the backup slide concerning the placebo lead-in responders, that analysis, and display slide 2, please. Let me first say that the primary and prospective statistical analyses always used the 2-week screening as the baseline. The placebo lead-in was simply a device, a study design device, that was developed collaboratively with the agency to see if we could tease out the characteristics of placebo responders in advance of randomizing them.

I realize that may be confusing, but there

are two categories of placebo responders. The first, and the one that I think you are referring to, are the placebo lead-in responders. Those were still randomized in the study. And then the second is the randomized placebo responders, and that is relative to their screening baseline, not to any subsequent data from the 2-week placebo lead-in.

DR. NEATON: Yes. I'm just saying that what you're calling a placebo responder may not be a placebo responder. It's confounded with measurement error and regression to the mean.

DR. FEIN: Understood. Understood, but what the patients -- if we just say the patients who during the placebo lead-in met the prospective definition of a placebo lead-in responder, the slide on display shows the analysis of those patients. And perhaps surprisingly, even those patients had an incremental response after randomization relative to their original screening baseline on the 1.5 and the 0.75 microgram doses relative to placebo.

DR. NEATON: My question would be if you're

going to pursue this, you need to look at the other half of it. The question is, the treatment difference is protected by whether it's placebo response or whether it's regression toward the mean. Are they different between those you're calling responders versus not?

DR. FEIN: Well, I'm not sure that I understand that question. Let me first ask for slide 3 to be displayed. We also did the placebo lead-in responders based on the second co-primary, and you can see that, obviously, there's a high response rate based on the 50 percent reduction definition. But the SER 120 1.5 microgram group had a significant incremental responder rate relative to the placebo lead-in responders.

DR. LEWIS: Thank you. In the interest of time, we're going to have to try to get some other people in. We can return to this point if you still have questions. Dr. Alexander?

DR. ALEXANDER: I have two questions for the FDA. So one is, what would be -- I just want to come back to Dr. Gellad's question. So what would

be the argument for approving the 0.75 microgram dose given that the prespecified endpoints for efficacy weren't met?

DR. EASLEY: That's our question to you all.

(Laughter.)

DR. JOFFE: The applicant is trying to make the case that numerically hyponatremia occurs at a lower incidence with the 0.75 micrograms compared to the 1.5. This is a symptomatic condition. You could start on the lower dose, see how folks respond, and then adjust. The problem there is patients may respond just because there's placebo effect built in there also.

So the applicant wants both doses approved with this titration regimen, and we're not sure, and that's why we've asked the AC panel to weigh in on this.

DR. ALEXANDER: Okay. So the second question is a point of clarification as well, which is you mentioned that the indication for primary nocturnal enuresis was removed from the label for intranasal desmopressin, suggesting a differential

risk of the intranasal and oral formulations, or whatever the alternative formulations are that are used to treat that condition.

So can you help us understand better -- I guess I'm unclear about two things. First of all, does the currently marketed formulation of the intranasal product differ in terms of PK and PD, pharmacokinetics and pharmacodynamics, from SER 120? And then secondly, if so, do we have direct comparisons of these two products?

In other words, there was enough concern about hyponatremia that the FDA rescinded a label indication, which is an uncommon and pretty serious step on the part of the FDA. So can you help us understand what the evidence base was and what the similarities or differences are with respect to the pharmacology of that product and the one that we've just considered?

DR. JOFFE: Let me see if our clin-pharm comments -- have any comments about PK. You know, the applicant didn't do a head-to-head study of their drug versus the intranasal formulation, is my

understanding. There is on the FDA's public website -- if you google, you can read the alert that we posted, and it also includes a summary of the data that supported this decision. There were cases of hyponatremia. They weren't only with the intranasal and nocturnal enuresis indication, but that's where the bulk data were, and I encourage folks to look at that alert as well.

We can see if clin-pharm has anything to add. And then also, we have our postmarketing folks. I don't know if they have anything they'd like to add as well. And that removed indication was for children, just to be clear.

DR. SHON: Jihong Shon, clinical pharmacology reviewer. I am going to provide a response regarding comparison between approved desmopressin nasal spray and the currently proposed nasal spray. As advisory note, [indiscernible] approved a dose higher than a [indiscernible] proposed dose, around the 10-fold. But there is no direct [indiscernible] compared to a PK study, and so we can't provide at this moment.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: Thank you. I have two quick questions for the FDA. One is, what is the experience reported in terms of side effects of people who have taken this off label, desmopressin for nocturia, in the elderly population? Do we have data on that? And second, why do you think patients with nocturnal polyuria didn't show a better response than the other diagnoses? Which puzzles me a lot, and that's going to be very important when we're looking at indications. So those are my two questions for FDA.

DR. JOFFE: Okay. Let's turn to our Division of Pharmacovigilance to address the first question.

DR. KAPOOR: Hi. My name is Rachna Kapoor. I'm in the Division of Pharmacovigilance, and I will begin by showing slide 7. Basically, we look at FAERS. FAERS is the FDA adverse event reporting system, which is a computerized database that reports spontaneous reports for drugs and biologics.

So basically, for desmopressin, we looked at the FAERS database for all reports of all adverse events, for all formulations of desmopressin, and we looked at the reason for use, and the data is, until September 30, 2016. So what we identified was that we broke it down by the different age groups of zero to 17 and 17 to 50, less than or equal to 50, and greater than 50 years.

What we identified was you can see the trend across the board, the majority of the reasons for use who are not reported on all the categories. However, for the different categories, you can see that nocturia enuresis, a related urinary indication, was the top reason for use that was reported for all three of the categories. Coming in second was diabetes, and third was the bleeding disorder or coagulopathy indications.

Any questions?

(No response.)

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: I have two questions related to cardiovascular risk and one brief labeling

question. The first two, this is a drug that's approved for treatment of hemophilia, as I understand it, because it releases certain clotting factors, so factor 8 and von Willebrand factor. And there are some case reports of MI and other thrombotic events with the IV formulation and also one with the oral formulation.

I'm wondering what thought was put into the potential risk there, especially in a population that has lots of cardiovascular comorbidities. And then also, I notice that the rates of hypertension and vascular disorders were doubled in the 1.5 microgram group versus placebo, which could be a fluke because I know that mean hypertension, mean blood pressure, didn't change. But I'm wondering if you had any thoughts on that as well. And then I'll save my labeling question for after the answer there.

DR. KAUFMAN: Could you just repeat that first question for me quickly?

MS. SORSCHER: So as I understand it, the reason this drug is used to treat hemophilia is

that in subjects without hemophilia and subjects with certain kinds of mild hemophilia, it causes the release of certain clotting factors, so factor 8 and von Willebrand factor. And there have been cases of thrombotic events in people taking this drug, usually the IV formulation but also one oral case. And we know this formulation has similar pharmacological properties to the IV formulation.

So I'm just curious about whether you've put any thought into whether this might cause cardiovascular risks, particularly because a lot of the deaths and serious side effects have involved MI and clotting events.

DR. KAUFMAN: Right. If you looked at the entire database, I believe there were two cases of DVT. One case, the patient had had foot surgery I believe 3 or 4 weeks before the incident, and the other patient, there was some confounding event, and I can't recall exactly what it was. But that was for DVT.

Can you put up the slide for serious adverse

events? Slide number 5. We saw the one cardiac arrest, but that was secondary to the bleeding aortic aneurysm. And arterial sclerosis of the coronary artery, that was extensive -- at autopsy, that was found to be extensive and probably wasn't a result of the drug. It's unlikely that it was a result of the drug over that period of time. Then for coronary artery disease, you just have one. There really weren't any other serious adverse events on the cardiac disorders.

MS. SORSCHER: There was a death caused by probable myocardial infarction.

DR. KAUFMAN: Right. And that patient --

MS. SORSCHER: You said it occurred 4 days after the patient was up-titrated to the 0.75 dose.

DR. KAUFMAN: Correct. And that one, we couldn't rule it out. That patient did not have an autopsy, and the information that we got was from the death certificate, which was -- I mean, it was what it was, probably myocardial infarction, and there really wasn't enough data to make a causality assessment.

MS. SORSCHER: So my last question was, with the labeling, has there been any suggestion, either from FDA or the sponsor, that they're seeking a black boxed warning, a boxed warning, related to hyponatremia?

DR. KAUFMAN: A boxed warning for hyponatremia?

MS. SORSCHER: Yes.

DR. KAUFMAN: We actually haven't gotten down to the actual labeling, specifics of the labeling yet. But this is something that we're considering basically in a risk-benefit, does the risk of the 1.1 percent of severe hyponatremia justify the benefit of the drug.

DR. LEWIS: Thank you. Dr. Johnson? Thank you. Dr. Nahum, and I think that will be our last question before lunch.

DR. NAHUM: Thank you. I have a comment, and I'd like to follow up on the efficacy issue. A lot of the FDA's presentations surrounded an analysis of the PRO instrument that was developed in the second phase 3 study. I have a general

comment, which is from industry's perspective -- I mean, PRO tool development is particularly difficult, lengthy, and somewhat costly.

In this particular case, the post hoc analysis with regard to relevance seems to have come to some conclusions, but it seems to have stopped short of doing some other things, and I'll mention that in a second. But in these particular trials, there were two co-primary endpoints, at least for the 1.5 microgram dose that were met, in both of the trials.

In the first prespecified secondary endpoint related to this PRO instrument, it would seem to me that with the negotiations that went on with the division, with the agency in general, to arrive at these co-primary endpoints and have them satisfied would probably be sufficient as long as the secondary endpoint, in this case, the first prespecified one being the PRO instrument, would be consistent with what was satisfied in the co-primary endpoints having been met. And it seems to me that that's the case here.

So the post hoc analysis now of trying to dissect apart the clinical relevance threshold of the PRO instrument seems to me to be going a little bit further than sponsor should be held accountable at this point. That's my first point.

And the second one is, the point was made with regard to the INTU that there were some of the questions that either were not seemingly relevant because it was a floor that was not penetrated or they weren't measuring something meaningful. If this was the case in the post hoc analysis, did you eliminate those questions and do the analysis with the remainder of the INTU? Which would seem fair under those circumstances.

DR. KOVACS: So there are two things. One is that something could be statistically significant but not necessarily clinically meaningful to patients, so we do take into account the patient input into whether or not it was clinically meaningful. And from our review, it looks like both the SER 120 and placebo arms' mean scores on the INTU overall impact score look

clinically meaningful to patients, and we'd like to have the AC look at whether they think that it's enough of a separation between the arms.

Then the other question that you asked about -- I'm sorry. What was your last point?

DR. NAHUM: Well, it was really my first question, which was, if this is the first prespecified secondary endpoint and both of the co-primary endpoints are met, and if the trend is consistent with the primary endpoints and statistically significant, shouldn't that be enough of a burden for the sponsor so that they don't then need to, post hoc, demonstrate some threshold for clinical meaningfulness? Haven't they already done what they've been asked to do?

DR. EASLEY: They have done what we've asked them to do, however, if there were no risks associated with this product, then that would be one question. But when we're considering risk of hyponatremia, then you have to think about, yes, there was a statistical difference, but the absolute change is so small and the placebo effect

is so great, you can't just check off the box that they won.

DR. NAHUM: That's actually a different question because I think that's benefit-risk ratio assessment at that point. I'm just talking about clinical efficacy in isolation. And then we get, of course, to the risk piece, which you've brought up, and I would agree that needs to be considered, absolutely. But when I look at the 18 to 19 percent delta in the greater than 50 percent reduction versus placebo, for instance, that means the number needed to treat is about 5. And if I look at the 9 to 10 percent nights with less than or equal to one episode per night being a threshold, then the number needed to treat is about 10.

So from an efficacy standpoint, this would seem to me to fall well within the sorts of criteria that are generally used by FDA to say that a drug is efficacious.

DR. EASLEY: Yes, I absolutely see what you're saying. I think one reason we did these

post hoc analyses, though, is to get a sense of what -- if you tell someone you're going to have 0.3 fewer episodes a night, what does that even mean? It was really more to help us understand the data so we could make a more informed decision. It's not ideal, obviously, but I think it is helpful.

DR. JOFFE: And I think at the end of the day, it's a totality of data situation because, sure, you could look at the responder analyses and say there's an 18 or 19 percent absolute treatment difference, but then you could look at the mean difference and say, oh, it's only 0.3 to 0.4. So how are you weighing all this data together to come up with an assessment of whether the drug is efficacious or not? So that's where we think it's useful getting input from the patients themselves, what do they think the impact of these improvements are on their lives because at the end, that's what we care about.

DR. LEWIS: Thank you.

DR. KOVACS: And then to --

DR. LEWIS: Oh, I'm sorry.

DR. KOVACS: Sorry. Just to respond to your last point where you asked if we did any analyses taking out the items that had the floor effect, we did not. There were other items that did show floor effects as well, but the ones that I mentioned in my presentation were the ones that were the highest, like 48 percent or 40 percent.

DR. LEWIS: Dr. Joffe?

DR. JOFFE: I just want to tie up some loose ends. First, with regard to myocardial infarction, we can dissect individual cases here, but at the end of the day there are very few events. They're unstable. It's very hard to say that there's a signal there. And then the other thing is we can't really use our postmarketing pharmacovigilance data because older patients, heart attacks are common. And so we're going to see a lot of those events, and FAERS doesn't really give us a denominator whereas to say is this a meaningful change from the background rate.

So it's difficult to tease that question

apart. So that was one thing I wanted to point out.

The second thing, there was a question from Dr. Hanno about the difference with nocturnal polyuria and those who don't have nocturnal polyuria. I don't think it's quite clear yet why there would be a difference between the two. Our table on page 17 of the efficacy background includes the results for nocturnal polyuria present versus absent. And you could see the results here, but I think that it does need some more discussion in terms of why are things different in patients who don't have nocturnal polyuria.

Lastly, there is the alert that I mentioned on FDA's website. I think we'll just have Dr. Easley quickly summarize those data about the withdrawn indication, and then we can break after that.

DR. EASLEY: So in 2007, the indication for primary nocturnal enuresis was withdrawn from the nasal spray formulation because of 61 postmarketing reports of hyponatremic related seizure. The

majority of these cases were in children under the age of 17. So that was what drove that. The dose is greater than the sponsor's dose. It's a different formulation, so it's hard to compare these findings with the sponsor's proposed formulation.

DR. LEWIS: Quickly, Dr. Joffe, you mentioned the efficacy document. Are you talking about this document?

DR. JOFFE: No, sorry. FDA's background --

DR. LEWIS: The background material.

DR. JOFFE: -- document. Page 17 of the efficacy has our descriptive analyses because this was an exploratory analysis based on baseline nocturnal polyuria, present or absent.

DR. LEWIS: Thank you.

Before we break for lunch, I just want to remind people there will be time for additional questions after the open public comment, and also that some of the comments that people have rather than questions, they will be able to get those across during the discussion period. We have

discussion time as well. So in terms of thinking of questions, if you still have questions, which are clarification items, then, yes, we'll be able to deal with some of those after the open public comment period, and that will be for both.

So at this point, we're going to break for lunch. We'll reconvene in this room. Let's take a little less than an hour because we're a little late getting started. Let's reconvene at 1:05, and then at that point, we'll begin open public hearing. Please take any personal belongings with you. Please remember, no discussion for panel members about the meeting topic either among yourselves or with members of the audience.

For those of you who may be new to the panel, pick up your lunch at the kiosk in the lobby, and then we have a meeting room reserved behind this room. Everything is in the meeting room. Don't go to the kiosk, just for the panel.

(Whereupon, at 12:12, a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:12 p.m.)

Open Public Hearing

DR. LEWIS: I'd like to reconvene in a few seconds, so if people could start to take their seats, please. We're going to be moving to the open public hearing part of our session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, it's direct competitors. For example, financial information may include sponsor's payment for your travel, lodging, or other expenses in

connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships, it will not preclude you from speaking.

FDA and this committee place great importance on the open public hearing process. The insights and comments can help the agency and this committee in their consideration of the issues at hand. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you.

So if we're ready, I'd like to invite speaker number 1 to step up to the podium and introduce yourself. Please state your name and any

organization you're representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings. I am a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data to provide objective health information to patients, providers, and policymakers. We do not accept funding from drug companies, so I do not have any conflicts of interest.

Nocturia symptoms are caused by a wide range of underlying conditions. It is not surprising that SER 120 does not create a clinically meaningful improvement when averaged across all of these conditions. It may be effective in a subset of people with the specific underlying conditions or other characteristics, but the sponsor has not identified that group of patients or their underlying conditions.

To justify FDA approval, a drug should have a clinically meaningful improvement over placebo for patients to whom it would be prescribed. A

general indication for patients with nocturia would not be appropriate because the drug clearly does not work well for a general population of nocturia patients.

You probably share my concern that the sponsor's studies excluded patients with diseases or treatments that could reduce the safety of SER 120, and yet these same patients would consider the drug if it were approved for all adults with nocturia. There are other safety concerns as well. The studies did not measure possible effects on underlying conditions. Further studies should determine that treatment with desmopressin does not worsen any of the conditions that cause nocturia or co-occur with it.

In addition, about 11 percent of patients experience mild hyponatremia and 1 percent experience severe hyponatremia, which requires careful monitoring. For approval, the benefit of SER 120 need to outweigh the risks for most patients, but to achieve that, we need data on which patients are most likely to be harmed, and

that information needs to be widely available and mentioned in any advertising or promotional materials.

Patients' age is also a concern. Most patients with nocturia are over 50 years old. There are also many patients under 50, and the safety and effectiveness of the drug could be very different for younger adults. This may be especially true for pre-menopausal women. Only a small number of pre-menopausal women were studied, and they were not analyzed as a separate subgroup, so it is impossible to know that the drug is appropriate for these women.

Since 78 percent of the patients were white, the risks and benefits may also differ for other racial groups. There are versions of desmopressin on the market already. It is not clear that this version has a better risk-benefit profile. Whether or not it is better, if approved, SER 120 will be much more expensive. While cost is not the FDA's concern, the skyrocketing cost of older pharmaceuticals that are re-purposed is a clear

threat to Medicare, the affordability of health insurance, and to public health.

For this reason, this advisory committee should make sure that it only approves a drug for an appropriate indication and that the indication includes ages and types of patients most likely to benefit. Unfortunately, information in labels has little impact on prescribing behavior, and DTC ads tend to minimize those details.

In conclusion, do not recommend this as the first drug approved for nocturia symptoms unless there's a clinically meaningful benefit and sufficient safety profile for a clearly indicated population. And overly broad indication does not help patients and could harm them. Thank you.

DR. LEWIS: Thank you. Would speaker 2 please approach the podium and introduce yourself?

DR. LAVINE: Thank you for the opportunity to share my perspective as a patient with nocturia. My name is Dr. Howard Lavine. I'm a professor of political science at the University of Minnesota, and I have suffered from nocturia for nearly

15 years. I come before you this afternoon to dispel any myths that you might have heard that nocturia is simply an inconvenience or only a symptom of another malady, poor health, or aging. While I have no financial interest in the outcome of this meeting, Serenity Pharmaceuticals supported my travel.

Since 1997, I've been unable to sleep through the night without experiencing the need to arise 2 to 4 times to void my bladder. The condition has been so burdensome that I have sought diagnosis and solutions from several physicians over the years, including a number of urologists, but they have been unable to find an exact cause for this condition, even after invasive procedures such as a cystoscopy and neurodynamics test to help me successfully treat it.

While trying to get some medical answers to my problem, I sought numerous home remedies, including reducing my liquid intake in the evenings, but nothing seemed to work. Each night, I went to bed knowing that I would not be able to

make it through the night without waking up several times to use the bathroom.

After being subjected to multiple tests, my bladder, prostate, and kidneys all checked out fine. I had no other medical conditions, and I'm otherwise in good health. And at the end of the day, my physicians concurred with the diagnosis of nocturia, a condition I knew very little about.

At the time, I remembered being relieved that I did not have any serious disease. I figured that now the problem was identifying some form of treatment that must be available to alleviate my condition, a treatment that would allow me to be able to sleep through the night without having to get up 2, 3, and even 4 times to urinate.

I was shocked to learn that while there were potential treatments that could address some of my condition, there was and continues to be no drug treatments specific for nocturia available here in the United States. As my condition worsened, my nocturia was not just the lost of a few hours of sleep with the inconvenience of having to get up

and disturb my sleeping wife to head to the bathroom, my sleep began and continues to be interrupted often by pain in my groin and a nausea that can only be alleviated by urinating. The pain can be so severe that it sometimes takes me a while for it to subside and for me to be able to fall back asleep.

For nearly 15 years, I've been unable to get a complete night's sleep, and the constant trips to the bathroom have led me to try some creative solutions out of desperation. The combination of exhaustion and frustration after dealing with years of nocturia led me to take inventive action to avoid getting out of bed so many times each evening. Without going into too much detail, let's just say that my wife put a quick end to my solution to find some reprieve from the torment of nocturia.

Despite all of my home remedy efforts, I remain resigned to several trips to the bathroom every night, and then trying to fall back asleep while my pain and nausea slowly recede. I mention

this because while nocturia might seem like just a nuisance, I can assure you that for me and the millions of my fellow sufferers, nocturia can cause pain, anxiety, and even depression. I'm also worried about how a lack of sleep might affect my life as I get older. I know that fatigue, reduction in cognitive skills, and chances of falling all increase with age and a lack of rest.

I also know that I'm not alone. Recently, the National Association of Continence stated that 1 in 3 adults over the age of 30 make at least two trips to the bathroom every night just as I do. And while the majority of those who are diagnosed with nocturia are usually over age 60, I can tell you from firsthand experience that it can happen at any age.

What I'd like to impress upon you today is an understanding that nocturia is not simply an inconvenience, but a serious medical condition that millions of people like me suffer from each night. The fact that this committee has come together gives me hope that a new treatment option may be on

the horizon. While I'm not a researcher and I can't offer input into the specifics of a particular treatment, I hope that that this committee will evaluate the potential treatment with an understanding of the negative clinical impact that nocturia has on patients.

Once nocturia is fully recognized as a serious medical condition that impacts the health of its sufferers, perhaps millions of us who experience this condition will be able to get the nocturia-specific treatments that we need, and then maybe I can finally get a good night sleep. Thank you again for the opportunity to speak to you.

DR. LEWIS: Thank you. Would speaker 3 please approach the podium?

DR. RUBENSTEIN: Good afternoon. I'm Laurence Rubenstein from the University of Oklahoma. Thank you for allowing me to testify today. I'm a physician specializing in internal medicine and geriatric medicine. I have spent much of my career studying falls in older adults and researching ways to prevent them.

Today, this committee is considering a new treatment for one of the leading causes of falls in the United States, nocturia. I have no financial interest in this meeting. I have not been paid to come here, although my travel across the country was supported by Serenity Pharmaceuticals.

I currently hold the Donald W. Reynolds chair and professorship in geriatric medicine at the University of Oklahoma College of Medicine. Previously, I was professor of geriatric medicine at UCLA College of Medicine and was co-chair of the Fall Prevention Center of Excellence in Los Angeles, which is affiliated with both UCLA and USC. Having published more than 350 peer-reviewed research papers, books, and textbook chapters, I am well credentialed in the study of fall causation and the lasting effects that a fall can have, especially on aged population.

Falling is a serious clinical problem that can lead to life-changing injuries and even death. In fact, falling is the leading cause of fatal, unintentional injuries in the older population, and

the sixth leading cause of all deaths among elders. Falls occur most often at certain predictable times of day. Falls are particularly common and lethal at night.

Nighttime is a high risk time for falls because of the confusion that a sleeping person often feels when awakening and getting up at night. One of the most common reasons for nighttime wakening is nocturia, and a very high percentage of serious falls occur when elders get up to urinate. This is especially so among older adults who are frail or who suffer from another medical condition such as dementia. Rising at night to urinate can be a dangerous experience.

Nocturia related fall risks in older adults have been especially well documented in hospital and nursing home settings, places where patients are less mobile than in the usual American home. Patients in an institutional setting are especially susceptible to falls because of their frailty and concurrent illnesses. About 1.3 million people live in U.S. nursing homes, and about 1.5 falls

occur per nursing home beds every year. Moreover, about 1800 fatal falls occur in U.S. nursing homes annually.

These astronomical numbers do not even take into account unreported falls. From these statistics, you can see that falls among older adults are a major source of healthcare utilization. Costs for inpatient and outpatient medical care related to falls have been shown to total more than $55 billion annually. In my judgment, nocturia related falls comprise over a third of all institutional falls.

Now, take a moment to consider the health and economic impacts of significantly lowering the fall incidence in nursing homes and community living populations by treating nocturia. I won't extrapolate a number, but I think we can all agree that the impact of fall reduction would be substantial. Nocturia sufferers should not have to risk their safety to rise multiple times in the evening to urinate. This condition dramatically compounds the risk of falling, a real clinical

danger and a leading cause of death.

Any medication that might reduce the incidence of rising at night will be a major step forward in fall prevention. The Centers for Disease Control and Prevention noted in 2012 that the reduction of medical risk factors is a key component of fall prevention. Nocturia should not be considered simply an inconvenience but rather a clinical condition that can lead to serious complications, falls being one of the most severe of these.

If we can reduce the need to rise at night, a time when fall incidence peaks, then the medical community will undoubtedly be taking a big step forward toward reducing falls in the United States for both the average American and the senior population. Thank you for this opportunity to testify.

DR. LEWIS: Thank you. Could we hear from speaker 4?

DR. NEWMAN: Good afternoon, members of the BRUDAC, and thank you for allowing me to speak

about a condition I encounter in my practice every day. My name is Diane Newman, and I'm a nurse practitioner with a doctorate in nursing practice, specializing in urology. I currently serve as adjunct professor of urology and surgery at the Perelman School of Medicine at the University of Pennsylvania, as well co-director of the Penn Center for Continence and Pelvic Health in the Division of Urology.

Nocturia is a symptom reported by patients way too often. I'm here today to talk about our need for specific treatments for a urologic condition that affects men and women from all walks of life. While I have no financial interest in the outcome of this meeting, I am disclosing that my travel from Philly has been supported by Serenity Pharmaceuticals.

As an expert in urology, I see the impact that nocturia has on men and women, many of whom have been seeking help for a long time. My practice is a tertiary specialized practice, and most of my patients have seen multiple providers

prior to being referred. In the case of nocturia, roughly 40 percent do not see an improvement in symptoms with current treatments, although these treatments improve other bladder related symptoms.

People arrive in my office desperately seeking relief from getting up in the middle of the night twice or more to urinate. These patients present tired and frustrated because getting up at night to urinate has a significant impact on the person's quality of life, especially on daily alertness and activity.

Nocturia can result in many problems: fatigue, sleepiness, falls, fractures, and traumatic injuries. Nocturia can also have an impact on spouses who complain that they awaken also, interfering with their sleep. Sadly, patients and partners report being unable to fall back asleep after getting up to go to the bathroom to pee.

In addition to being frustrated because of awakening multiple times nightly to void, nocturia is not being treated with the same urgency as other

serious conditions. But to a patient who has nocturia, nocturia is a serious condition, usually the most bothersome bladder symptom reported. And sadly, nocturia is sorely lacking in a specific treatment. If a person's nocturia is not caused by prostate conditions or overactive bladder, they have no treatment option and no choice but to live their lives with diminished quality.

Nocturia is an inconvenience and doesn't just cause my patients to feel a little sleepy; it affects their productivity and general well-being. Many patients suffer from depression from the constant lack of sleep, which in turn affects the relationships with their partners, with their children, and their friends. Partners are affected too, often waking up every time the person gets up to use the bathroom in the night. In many cases, it's the spouse or partner who has been driven to seek help because the problem is affecting both of them.

Those that are still in the workforce lose productive time during the days. In the United

States, sleep related issues cost society $13.6 billion with 76 percent of those costs directly related to absenteeism and lost productivity due to lack of sleep. It is not uncommon for a patient to claim that they fear falling asleep at the wheel while driving to and from work because of fatigue and not getting adequate sleep.

Nocturia has an impact on those who are retired as well. I have met with patients so sleep deprived because of their nocturia, they report significant daytime fatigue. Not getting enough sleep is not merely an inconvenience; it can be downright dangerous. As patients experience more and more episodes of nocturia per night, the comorbidities, lost productivity, depression, not to mention the increased risk of falls in the night because of going to the bathroom, may rise as well.

The greater number of voids per night, the more impact nocturia has on a patient's life. An elimination of the need to get up to urinate at night would be ideal, but a small reduction of even

one incidence per night can drastically improve the quality of life of numerous patients suffering from nocturia.

I close by asking the FDA BRUDAC to consider nocturia as a truly serious condition, one in need of its own treatment in order to provide relief and a higher quality of life to my patients and the millions of other Americans across the country suffering from nocturia. Thank you.

DR. LEWIS: Thank you. Could we hear from speaker 5, please?

DR. GREEN: Hello. My name is Dr. Eboni Green. I'm a registered nurse and a licensed long-term care administrator. I have dedicated my life to improving the circumstances of the elderly and their caregivers. I am also the co-founder for Caregiver Support Services, a 501(c)(3) non-profit organization that exists to improve the health and well-being of both family and professional caregivers.

I have no financial interest in the outcome of this meeting; rather my interest in being here

today is to advocate for family and professional caregivers who like me are caring for a loved one or client who suffers from nocturia. My travel from Nebraska has been supported by Serenity.

Having served as a nursing assistant and later as a registered nurse, I've witnessed the negative and lasting effects that nocturia has on both patients and caregivers. Now through Caregiver Support Services, I identify and resolve issues that contribute to caregiver distress and burnout. Nocturia is one of those issues.

I'm here today to provide you with some professional insights and to share a bit about my personal life as well. Not only is my career devoted to caregiving support, I am also the caregiver for my mother-in-law Emma as well. I call her Mom. Earlier this year, she was infected with a virulent strain of influenza, was placed on a ventilator, went into a medically induced coma, and suffered a stroke. We didn't know if she would survive. Mom has since transitioned to rehabilitation center to receive therapy, but our

goal is to bring her home.

One major barrier to Mom's transition is nocturia. Nocturia causes Mom to wake up three or more times each night to urinate, but she can't remember that she's unable to walk to the bathroom on her own, so that when she tries to stand from bed, she often falls. In fact, my husband and I receive several calls from the rehabilitation center once or twice a week reporting that Mom has fallen. This repetitive circumstance is heartbreaking.

From this experience, I can attest to the negative effects that nocturia has on both the sufferer and the caregiver. My husband and I need to be fully alert at our jobs, but the reduced sleep has caused both of us to struggle. The effects on Mom's life have been even worse. Waking up multiple times a night has led to decreased daytime functioning and even more concerning, anxiety and depression.

These additional issues have made her recovery hard. The exhaustion, depression, and

anxiety have made it extremely challenging to engage her in the recovery therapies necessary for her to return home. In fact, we meet regularly with the staff and doctors to modify her anxiety and depression medications to help her achieve her highest level of functioning.

The impacts of nocturia are compounded in nursing facilities. Patients are too frail or aged to rise regularly and wear adult diapers, which often leads to the patient's dignity being decreased and an increase in skin break down. Rashes and other infections sometimes ensue from the dampness. The caregiver or nurse must change the patient who is suffering from nocturia frequently each evening, putting both individuals at an increased risk for injury. For a caregiver tending to multiple patients, a reduction in even one trip to the bathroom or omitting one incontinent episode per evening would dramatically improve both a patient and caregiver health outcomes.

Those of us providing support and care to

nocturia patients are actually at a risk for some of the same mental and health complications as patients such as daytime exhaustion, anxiety, and depression. Our healthcare system cannot afford to lose a single caregiver because they are burned out. The ongoing support required for a person with nocturia is viewed as a never-ending commitment in the caregiving community because the condition is not recognized for its clinical impacts and is falsely addressed as a symptom rather than a medical condition.

My hope is that the perspective on nocturia changes today to acknowledge the real and lasting harm that this condition has on the health of both patients and their caregivers. Thank you for your time and for allowing me to share my personal and professional experiences with you today.

DR. LEWIS: Thank you. I'd like to hear from speaker 6, please.

DR. BRUCKER: Good afternoon. I wanted to thank the members of the Bone, Reproductive, and Urologic Drug Advisory Committee for allowing me to

participate in this important discussion on nocturia. My name is Dr. Benjamin Brucker. I'm a board certified urologist and assistant professor of urology and urogynecology at New York University. While I did receive reimbursement for my travel here today, I'm not being paid for my testimony, and I have no financial interest in Serenity Pharmaceuticals.

In my practice, I help patients manage nocturia, bladder problems, incontinence, and other conditions such as BPH. In doing so, I've seen firsthand the effects nocturia has on the health and well-being of this diverse patient population. In fact, nocturia is one of the leading reasons patients come in to see me, and that's why I felt compelled to speak here today.

Despite the common misconception that nocturia is a simple lifestyle issue that only affects those in failing health, it should be noted that roughly a third of adults over the age of 30 suffer from nocturia, a condition that forces a person to wake at least once, but usually 2 to 4

times a evening, to urinate. It is especially prevalent among older adults with a prevalence as high as 77 percent among elderly women, and 93 percent among elderly men.

Nocturia has a profound impact on patients. The condition prevents them from getting a full night's sleep, leading to decreased alertness during the day. Imagine trying to sit here today if you had to get up, walk to the bathroom, use the bathroom, wash your hands, walk back from the bathroom, and try to fall back asleep 3 or 4 times before needing to get up this morning. More than that, nocturia leads to mental health issues, reduced daytime productivity, and an overall decline in quality of life.

Another concern as a clinician is the potentially devastating impact getting up to toilet in a dimly lit room while fatigued from lack of sleep has on my older patients. Studies have shown seniors with nocturia are two times more likely to fall at night. Most of us know falls sustained by senior citizens can be devastating and even

life-threatening. For example, the CDC estimates 2.6 falls occur per nursing home patient per year, and about 1800 older adults living in nursing homes die annually from fall related injuries. Those who survive frequently sustain injuries that result in permanent disability and reduced quality of life.

However, nocturia can strike people of all ages and all health levels. A patient of mine comes to mind, a 42-year-old healthy mother of three who has been battling incontinence issues and nocturia since the age of 27. She deals with fatigue, depression, and reduced productivity, and reduced quality of life from her condition. And yet, there is little that can be done for her due to the limited treatment options available.

Another group of patients that suffers disproportionally from this condition of nocturia are patients with limited mobility. This group has its own set of obstacles when dealing with nocturia. I have treated patients with multiple sclerosis and Parkinson's disease whose limited mobility coupled with nocturia has resulted in them

accepting the uncomfortable inhumane and unhygienic need to awake at night and make the conscious choice to void into a diaper, feel warm urine in their diaper, and then lay there trying to get back to bed at night. For those brave enough to attempt to get out of bed, they have an increased risk of falls as well.

Unfortunately, there are no approved monitored, regulated drugs specifically to treat nocturia for me practicing in the United States. My colleagues in other countries such as Canada and Japan have options for drug therapies. Drug treatments are available for BPH and overactive bladder, which may be comorbidities associated with nocturia.

These drugs treat daytime symptoms but are largely ineffective for nocturia. Remember that only half of the patients with nocturia may have a concomitant condition such as overactive bladder or BPH evidencing the need for nocturia-specific treatments. After a patient tries and fails conservative therapies like behavioral

modification, as a physician, I have to make the decision how to best offer and use off-label options, often with mixed results. In short, we need better treatments.

What I've come to understand that today the committee is here to discuss one particular drug, I would like to be clear that I'm not here to endorse any specific treatment. As a clinician, I need therapeutic options. Even an option with a modest improvement will have a tremendously positive impact on my patients.

I ask the FDA to consider the serious health impact of nocturia and its impact on patients and millions of Americans that suffer from this condition. These are patients that are looking to the research community and clinicians to help address their needs.

Time has come for treatment specifically for nocturia, and I hope this committee will provide physicians like me the necessary tools to continue to give patients the best treatment possible. Thank you for your time and consideration.

Clarifying Questions (continued)

DR. LEWIS: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will shortly turn its attention to address the question at hand -- the task at hand, which is the careful consideration of data as well as the public comments. Before we do that, I know that there were several people who had questions that weren't answered, and we have a list of those.

So we're going to take the next 20 minutes to do that, and I'll call on folks who are on the list. But again, I'd like to remind you to please reserve comments for the discussion time period because there are four different discussion items that we're going to be addressing. So if it's a comment, please try to place it within those comment areas rather than a question. And if the question's been asked by someone else, then out of respect to getting everyone a chance to have their say, please refrain from comment.

So let's start with the FDA questions.

DR. COYNE: I had a question related to falls. In addition to falls, as we've heard repeatedly, being associated with getting up at night, mild hyponatremia is associated with an increased risk of falls and an increased risk of fractures independent of osteoporosis, at least according to some observational studies. And yet, when we heard about the safety data, we didn't hear anything about anybody ever falling, which I find kind of amazing given the high number of elderly patients in this study.

Does the FDA have data on falls in this trial, or for that matter, the company? Or was this a matter of more that it wasn't really focused on in the data collection, and therefore this information wasn't really collected?

DR. KAUFMAN: Right. For treatment-emergent adverse events, they were less than -- they weren't common events, and they were less than 2 percent. Perhaps the company can give more detail on that.

DR. FEIN: Could we show the backup slide

with regard to -- please display slide 2. This slide shows the falls that were recorded in the DB3 and DB4 phase 3 studies. You can see in the placebo group, there were a total of 6 falls, in the 1.5 microgram group, a total of 2, and in the 0.75 microgram SER 120 groups, 4 falls in each of those dose categories.

For the pooled results, there were only a couple of fractures. One I think was in the placebo group and one in the 1.5 microgram group, but it wasn't clear that the fractures were related to the falls. These studies were not of a sample size, of the epidemiologic type sample size that could capture that information reliably, but these are the data that we did collect.

DR. COYNE: And the data you show here isn't adjusted for the time of monitoring, the number of months on therapy? Do you have some estimate of how many months of treatment each of these groups were? Or this is only from the 12-week?

DR. FEIN: Yes. Each of these groups were exposed for 12 weeks.

DR. COYNE: So in the open-label, 12-month plus treatment, you don't have data on falls?

DR. FEIN: I believe that there were a few falls recorded in the adverse event database, but we don't have -- we would have to try to get a slide for you.

DR. COYNE: So in the queries, when you met with the patients at the visits, there was no specific question, since the last visit, have you had any falls?

DR. FEIN: Adverse events were not elicited; they were spontaneously reported. There was not a question that was directed at patients other than how are you feeling and is everything -- has anything happened to you that's a problem.

DR. COYNE: Sure. I understand.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: Thank you. I think this is an FDA question. It kind of relates to what we talked about right before lunch, which I'm trying to identify who might benefit most from the drug. And we talked about this issue about the efficacy, to

my read, including that subanalysis that you did, looked like it was less effective in those that did not have nocturnal polyuria.

So the question is, were the analyses repeated when you excluded that 20 percent? And probably a more important question is, was there any attempt to look at a relationship between severity at nocturia at baseline and how effective the drug was? In other words, was there an interaction with the severity of the number of falls at baseline -- excuse me, the number of episodes of polyuria and how effective the drug worked both in terms of number episodes in the 50 percent responders?

DR. FEIN: Let's address the question of severity with the backup slide for less than 3 and more than 3. Please display slide 2. This divides up the patient population for the pivotal phase 3 studies, the ITT population, between that group that had 3 or fewer nighttime voids at baseline and those that had more than 3.

You can see it pretty much splits evenly,

the overall patient population for each of the dose groups. And both the patients with less severe nocturia and more severe nocturia had similar results. In this pooled analysis, both doses -- even with the smaller sample size, both doses produced -- well, the 1.5 microgram dose produced a statistically significant result. For the 3 or fewer episodes, the p-value for the 0.75 microgram was 0.07, and in the group that had more than 3 episodes, the more severe, both doses produced highly significant results.

Then there was a first part to your question, I believe.

DR. BAUER: The question had to do with repeating the analysis, excluding those that did not have nocturnal polyuria.

DR. FEIN: Well, only 20 percent of the population didn't have nocturnal polyuria. Most of those that did also had either OAB or BPH. We did all of those subpopulation analyses.

Show slide 2, please. This slide shows the percent of patients with more than one etiology,

and only one etiology. Roughly 65 percent of the population had more than one etiology, and the number with nocturnal polyuria only was under 20 percent. Even in those patients, there was, you might recall at the 1.5 microgram dose, a p-value of 0.08, but it was a very small sample size with under 100 patients per treatment group.

DR. BAUER: Okay. But the effect size is actually smaller. So is it fair to say that there was no conclusive evidence that it was effective in those who did not have nocturnal polyuria?

DR. FEIN: I wouldn't go that far because if one imputed a larger sample size, although the numerical differential with placebo was smaller, it actually would achieve a statistically significant result. So I would say that it appears to have somewhat a lower efficacy, but I would not say that it was not effective.

DR. LEWIS: Thank you. Dr. Cella?

DR. CELLA: I have a question for the FDA and one for the sponsor. Should I just do the FDA question now? Both? Okay.

The FDA question relates to something that Dr. Alexander raised, and I think Dr. Easley appropriately pushed back and said, "Well, that's what we're asking you," and that was regarding what's your sense of the evidence for the 0.75 microgram dose.

But then, Dr. Joffe, you mentioned -- you made a statement that I want to ask kind of a regulatory position on because it got me thinking. I think you said something to the effect of the placebo effect is a problem in evaluating the 0.75 dose or something like that. I was actually thinking one could craft a statement to say use the safe dose to allow a 2-week period for the placebo effect to join in with what may be a modest effect of a safe dose, and then raise the dose in the non-responders.

That could be a logical clinical practice, but is that an acceptable regulatory view?

DR. JOFFE: No. The drug wasn't studied that way. I think the point, what I was trying to get across, is when you give a drug to an

individual patient, and you see a response in that patient, part of that response is probably the placebo because it's hard to separate how much of that response is purely from the drug and how much of the response would have been just from a placebo effect. So I was trying to get that across.

I think what we have to do here is the first step, when we walk along the path towards approval, is there substantial evidence of effectiveness? So I think that's the question we have to face first. Is there substantial evidence of effectiveness for the 0.75 microgram dose and then also for the 1.5 microgram dose? Once you've reached that decision, then the next question becomes, well, how does the benefit-risk assessment weigh out?

Hopefully, as we've structured the questions, that will come out because we're asking folks to first vote on this evidence of effectiveness.

DR. CELLA: So to clarify, we should not consider the likelihood that in those first 2 weeks at a 0.75 dose, you'll be seeing both effects.

That troubled you, but on a clinical level, that might actually have some appeal. But we should not consider that. Is that what you're saying?

DR. JOFFE: I think you have to consider whether the 0.75 microgram dose versus placebo, whether that comparison shows evidence of effectiveness.

DR. CELLA: Okay. Thank you.

The question for the sponsor, and maybe the FDA, is did you look at the -- this is on that single question asked at the end of the treatment period. TBS I think is the acronym. Did you look at the correlation of that question with the current state? Because very often it's more correlated with current state than with the actual changed score, and that can render it as problematic in terms of interpreting it as an anchor.

DR. FEIN: I will direct that question to Dr. Khalaf.

DR. KHALAF: That is a very good point, that one of the key limitations of using something like

the TBS or something similar to the TBS, like the Patient Global Impression of Change or the Patient Global Assessment, is that patient's condition at that time, when you're asking them to retrospectively think about how they felt at baseline, will unduly be influenced by what they're feeling at present.

We did not look at the correlation between, for example, nocturic voids and their present condition. If that's something that you're interested in seeing, we can see if we can get that for you quickly enough before the day's over. But we didn't look at current. That's a good point.

DR. CELLA: More important to get would be those standard deviations. If you could only do one, those baseline standard deviations will be helpful.

DR. FEIN: Could you show RR-4, please? Display slide 3. If you need more statistical input, I will get Dr. Trout up. But this reports the standard deviations for the INTU DB4 study at baseline, for the N-QoL and the DB3 study, at day

57 and day 99. And the INTU is reported as a mean of the 2 times it was administered during the double-blind, randomized treatment period.

DR. LEWIS: Thank you. Dr. Johnson?

DR. JOHNSON: It was a comment [inaudible - off mic].

DR. LEWIS: Okay. We have about 10 more minutes and several questions that we might have for sponsor. Dr. Alexander?

DR. ALEXANDER: I have a question both for the FDA and the sponsor. For the FDA, it sounds like you guys raised lots of concerns about the trial design or things that you highlighted: numerous exclusion criteria; no restriction on fluid intake, which I note that DB1 and DB2 did have; no testing of the proposed dosing regimen that's being proposed for the label.

So why did you agree to these design features if they were felt to be important limitations of the current design?

DR. JOFFE: Good question. I think in any situation, FDA's advice is the best recommendations

we have at the time. Sometimes 20/20 vision makes us say we would have done things a little different. Here, we're a little complicated also by the fact that this application started in our division, then moved across to another FDA division, and them moved back to us, so there are some professional differences of opinion across the divisions as to how we would have designed the trials.

So I think those are all the factors. I think what we're left with is some uncertainties about some of these things, and we have to factor that into our final decision.

DR. ALEXANDER: Okay. Thank you. And then for the sponsor, it's pretty clear that hyponatremia is one of the really big concerns here. My understanding is that this is age related. And also in other countries where desmopressin is approved, it's contraindicated among the elderly. And if I understand correctly, the rates of clinically significant hyponatremia were about 3 to 5 percent for those over 65.

This is in a really, really controlled development setting where you had individuals getting labs every 2 weeks. There are plenty of reasons to be skeptical that patients are going to come anywhere close to that in the real world, and there are also plenty of examples of products being pulled or having multiple risk communications in generally relatively ineffective efforts to try to increase the rates of laboratory testing associated with specific products. So I'm talking about things like liver testing for glitazones, liver testing for pemoline, testing for atypical antipsychotics, looking at glycemic levels, and so on and so forth.

During one of your slides, you said if we apply the proposed label, 60 to 80 percent of subjects who would have experienced clinically significant hyponatremia would have done so, and would have been captured within the first 2 weeks.

So the question is, have you modeled or can you tell us what would be the rates of serious adverse events if, say, a third of patients had the

proposed laboratory testing, or say a half of patients had the proposed laboratory testing? Because I think in the real world, that's much more likely to be the types of numbers that you're going to see in many clinical settings with respect to patients successfully being observed through serologic monitoring.

DR. FEIN: Thank you for that question. Please display slide 2, please. Just putting this up as a reference. This shows the incidence of nadir serum sodiums by age group. We've seen this before, but I just put it up to refresh everyone's memory.

The incidence of nadir serum sodiums below 130 were modestly higher in patients above the age of 65, however, we have the fortunate experience of having a world-wide experience with other low-dose desmopressin products. We believe SER 120 is the lowest dose, the most precise pharmacokinetically, the most precise pharmacodynamically with regard to controlling peak blood levels and also having a low coefficient to variation from dose to dose and

patient to patient.

In many desmopressin dose forms, it's as much the coefficient to variation, and the fluctuation of absorption from dose to dose and patient to patient, that contributes to the risk of hyponatremia as the absolute dose itself.

Minirin Melt, for example, has been approved around the world in Europe at much higher doses, 60, 120, and 240 for nocturia. In Europe, it is limited in the label to patients less than 60, but there is basically a decade-long experience with that drug, and although we don't have precise pharmacovigilance data, it is not believed to have produced a public health problem.

More recently, even the lower dose version of the melt, Nocdurna, which is at dose of 25 micrograms and 50 micrograms, was approved specifically for nocturia in Canada in 2014 and did not have age restrictions, to the best of my knowledge. And within a few months, it was approved by the EMA for European use, and again without age restriction. And I don't believe it

had a REMS requirement for any laboratory monitoring.

So I think the experience with the other low-dose desmopressin products for nocturia, even though some have been labeled -- not all, but some have been labeled for just use in under 65-year-olds -- should give us some reassurance that these types of drugs can be used in widespread clinical practice safely, and apparently effectively because more and more patients are using them.

DR. ALEXANDER: So 21 out of the 23 people that experienced hyponatremia were over 65, if I'm correct. So I guess the question is, do you know what proportion of patients would have been captured if only half received the recommended laboratory testing?

That's the question that I asked, but I guess maybe another one would be, are you suggesting that these are what you think to be the upper limits of what we're going to see if this were to be approved and used in the real world?

You're saying it wouldn't be any more common than what we're seeing in the clinical trial? Is that what you're stating?

DR. FEIN: I believe it would actually be less common if the regimen, the treatment regimen, that is recommended in our proposed label and that is also reflected in the REMS plan, in the proposed REMS plan, would be put into effect because it would initially start everyone at the 0.75 microgram dose group. And only those patients both tolerating the drug and not responding adequately in terms of their own sense of clinical benefit would be dose adjusted to the 1.5 microgram dose.

DR. LEWIS: Thank you. Dr. Chancellor?

DR. CHANCELLOR: I have two questions. On one of the slides, it stated that a proposed risk mitigation labeling -- that if sodium decreases below normal range, consider discontinuing treatment until sodium returns to normal.

So that got me thinking, have you had patients with sodium drops that you can start the medicine safely and when?

DR. FEIN: Most of the patients that are represented in these slides reflecting nadir serum sodiums, particularly in the 130 to 134 range, remained in the study and continued to have serum sodium evaluations at every visit, and most often, this represented just an isolated excursion.

DR. CHANCELLOR: Okay. So my second question is in regard that one of the slides mentioned that more than three-quarters of the patients had an additional etiology beyond nocturnal polyuria for their nocturia. And in your exclusion criteria, there were a number of restricted drugs you can be on.

So do you have a table listing common urologic drugs, antimuscarinic, beta 3 agonists, alpha blockers, PDE5 inhibitors, like the number and percent? And is this correlating at all with AE? Because in the real world, patients may be on multiple drugs for urologic problems.

DR. FEIN: Those drugs were not excluded. In fact, many patients --

DR. CHANCELLOR: Right. So do you have a

table of them, like how many are on them, and what percentage of patients are on them, in correlation with the adverse events?

DR. FEIN: I will see if we have such a slide. I'll try to respond verbally in the meantime. And again, repeat your question.

DR. CHANCELLOR: How many patients and what percentage of patients are on the common urologic drugs, including antimuscarinic, beta 3 agonists, alpha blocker, and PDE5 inhibitors?

DR. FEIN: We'll try to get that exact number if there is a slide available. Many patients were on these restricted medications, as long as they were on stable doses. We did not want to chase a moving target during the study, which could confound the analysis of the efficacy of nocturia for obvious reasons.

So all we tried to do was to maintain stable doses of those drugs. I know that, for example, more than half of the patients in our studies had a history of hypertension; 250 to 300 of them were on thiazide diuretics or combinations. There were

numerous patients on OAB drugs and BPH drugs.

When we did a subpopulation analysis specifically of OAB and BPH patients who were -- and please display slide 2 -- who were on treatment, active but stable treatment for those conditions while on study, we found similar results to the overall population. In fact, there was a minus 1.4 decrease in the 1.5 microgram group versus minus 1 for placebo and minus 1.3 for the 0.75 microgram dose group. And despite the modest sample sizes of roughly a hundred per treatment group, the p-value was highly significant for the 1.5 microgram.

In addition, all patients with a history of OAB and BPH were analyzed separately whether they were on treatment or not, and they too responded very well similar to the nocturnal polyuria patients.

DR. LEWIS: Thank you. Dr. McBryde?

DR. McBRYDE: Thank you. I had a quick question for the sponsor, and I know the sample sizes are quite large -- or small, I should say. I

was curious. Looking at the literature, the prevalence of nocturia among black or African Americans is at least 50 percent higher than among whites, though looking at the percentage, there were only about 60 African Americans.

Do you have any data on the efficacy of SER 120 and the co-primary endpoints looking specifically at African Americans to see if in fact there is any evidence of racial differences in response? Or the other question is also the INTU, it looked like there were only 3 African Americans out of the 28. Do we know if it is more generalizable to a non-white, non-Hispanic population?

DR. FEIN: This was on the validation, you're talking about?

DR. McBRYDE: Yes.

DR. FEIN: I'll let Dr. Khalaf address the latter question. With regard to your first question, as we showed -- and if we could put back up the core presentation demographic slide -- the racial composition of the studies was very much in

line with the racial composition of the American population. There were 12 and a half to 13 and a half percent -- it's right here.

If you look under the race category, African Americans represented 13.5 percent of the placebo population, 13.7 percent of the 1.5 microgram population, and 9.2 percent of the 0.75 microgram population. Roughly, the African American percentage of the population was 12.5 percent, so it is exactly representative of the demographics of America.

DR. McBRYDE: Yes. But the demographics of nocturia is not the demographics of the U.S., though, so African Americans are disproportionately represented amongst individuals with nocturia. So I was curious do we know anything about how they respond to therapy.

DR. FEIN: We --

DR. McBRYDE: I mean, I know it's 40 to 60 subjects. I was just curious.

DR. FEIN: We did not do that subpopulation analysis. We'd be very happy to try.

DR. LEWIS: Thank you. Dr. --

DR. FEIN: Dr. Khalaf was going to answer --

DR. LEWIS: Oh, I'm sorry.

DR. FEIN: -- the second question.

DR. KHALAF: So regarding the stand-alone validation study, there were a couple of African American patients, and to the point you just made, that's also relevant. For your other question, we didn't have more African American patients, but I can say that the regions, we had three different states represented across the 28 patients that were interviewed, and those were the patients that were recruited.

So we attempted to get as diverse of a population as possible, and that included a certain threshold for quotas for different races. And we met all those quotas.

DR. LEWIS: Thank you. One last question. Dr. Erstad?

DR. ERSTAD: This question is for the sponsor. A few times now, we've heard about the

product formulation of it, and the elegance of the formulation, et cetera. It's my understanding that there were no absolute bioavailability studies with this product, correct? In other words, it being actually compared to an IV product. And similarly, I assume there were no studies comparing this to any of the other products that are out there, whether United States or other countries.

Just getting to the point, that we really don't know about some of the bioavailability issues of this specific product.

DR. FEIN: We did compare it, though, in the phase 1 water-loaded volunteer study, which had the detailed pharmacokinetic component to a subcutaneous bolus injection of desmopressin, and that is known to have close to a hundred percent bioavailability. So that was, we believed, a good stand-in for an IV infusion.

Actually, that brings to mind a point that I wanted to raise from this morning just in terms of clarifying what I may not have clearly stated. I think someone asked a question or made a comment

that I had said that the pharmacology of SER 120 was the same or similar to IV desmopressin.

If I said that, I apologize. What I meant to say, of course, the pharmacology of desmopressin is the same independent of the dosage form or the route of administration in terms of it being a selected V2 agonist. What I have tried to say was that an important pharmacokinetic parameter, the terminal half-life was similar for SER 120 and IV desmopressin because it is so rapidly absorbed. It has a very bolus-like PK profile.

So that's what I was comparing to IV desmopressin. It also brings to mind -- I'm a medical oncologist-hematologist by training, and desmopressin was originally developed to treat a coagulopathy, mile von Willebrand's disease, and mild classical hemophilia, perioperatively, to avoid the use of pooled biological products at the time. And it requires orders of magnitude, higher doses to achieve that limited coagulation effect.

Other than parenteral desmopressin marketed, oral, nasal spray, and melt [ph] products are still

much higher doses than we're using. The nasal spray used in children, for example that elicited the withdrawal of the PNE [ph] indication, is a 10 microgram metered nasal spray, and the dose range for children was 10 to 40 micrograms, with the average being 20 micrograms.

Even though the bioavailability is somewhat lower, by comparison, our dosage form is 0.75 micrograms and 1.5 micrograms. And more importantly, or as importantly, the coefficient to variation is much lower so that you don't get the fluctuations from dose to dose and patient to patient.

DR. LEWIS: Thank you. We'll take a couple more questions. Dr. Hanno?

DR. HANNO: Thank you, Dr. Lewis. I just have one question for the company.

On page 3 of the communication that you sent out, they quote an article by Ohayon in 2008, that patients with nocturia occurring 5 or more nights a week, independent of the number of voids per night, have more daytime sleepiness, naps per week, a

higher percentage taking sick leave than if your nocturia is on 3 or less nights per week.

So do you have the data from using this drug how many went from 5 times per week to 3 times per week, or did I miss that?

DR. FEIN: Virtually, all of our -- the incidence of having no nocturia overall was around 10-11 percent for the 1.5 microgram dose and 20 percent for responders. So there were relatively few nights of zero nocturia voids.

DR. HANNO: No, no. But how many started the treatment with 5 nights a week and dropped to 3 nights a week?

DR. FEIN: Everyone started the treatment with nocturia 7 nights per week, everyone.

DR. HANNO: So about 10 percent --

DR. FEIN: During the treatment, 10 percent -- in the 1.5 microgram group, 10 percent of nights had no nocturic episodes.

DR. HANNO: So 10 percent would be considered successful based on this criteria?

DR. FEIN: Well, that is simply one way to

look at --

DR. HANNO: Oh, I know.

DR. FEIN: -- one way to look at improvement. I would say the vast majority of our patients continue to have some nocturia most nights because they started with an average of 3.2 to 3.4 We did not do that analysis of looking at the number of nights per week, but I think it would have been a very small number of patients.

DR. LEWIS: Thank you. Just in the interest of time, we're going to have to cut the questioning short. I'm going to ask Dr. Drake, who I don't think we've heard from yet.

DR. DRAKE: Okay. We've heard a fair bit about hyponatremia here, and just sort of thinking how this medication works, it's given basically at bedtime, maybe 10:00 or so, and because of the pharmacokinetics, it should be worn off basically after about 6 to 8 hours.

The serum sodium diaries that were checked were typically morning values, I'm guessing, or early to mid morning. Is it of value to look for

hyponatremia that might be occurring overnight? Because total free body water will be -- it won't be excreting free water. So are we missing some hyponatremia I guess is my question.

DR. FEIN: That is an excellent question. That was not looked to. Of course, that would have disturbed sleep and confounded the ability to accurately count nocturia. And this was of course a home study, not a sleep study. But it is an intriguing question, and I would say that because the patients -- even though they were not instructed not to ingest fluids overnight, generally when one is sleeping, one doesn't ingest fluids or at least to any significant degree.

Even with the recruitment of third-space fluid into the intravascular space, keep in mind that urine production is not completely shut off. Urine production is lowered and deferred a little bit, so I wouldn't think that the accumulation of extracellular or extravascular fluid would accumulate significantly in the intravascular space to cause that.

We generally -- almost all of our serum sodiums were checked early to mid morning as you anticipated; you're absolutely correct about that. And I would think that that would give one overall the best chance to catch a hyponatremia or any lowering of sodium. But what you're proposing would be an interesting small study.

DR. LEWIS: Thank you.

DR. HANNO: Was it required in your study that you collected all the data early morning? I mean, you said overwhelmingly, so sometimes it wasn't?

DR. FEIN: Well, patients were asked to come in during the morning. Most patients came in first thing in the morning, but some patients came in mid morning or later in the morning. The majority came in early in the morning.

Questions to the Committee and Discussion

DR. LEWIS: Thank you. We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public

observation, public attendees may not participate except at the specific request of the panel.

We're going to move on to the questions, four for discussion, two for vote that are in your packet. Before we do that -- I assume you all have kind of perused those, but take a moment to do so -- I'm going to ask Dr. Cella if he has comments about the discussion items because I know you have to leave before we manage to get to the vote.

DR. CELLA: Thank you, Dr. Lewis, and I beg your forgiveness for my early departure.

So I asked the question I asked earlier about the 2 doses because I think without the kind of logic that I was applying in my question, I would have a hard time being convinced that the 0.75 microgram dose is any more effective than placebo across all of the endpoints. On occasion, there was statistical significance, but I didn't see any evidence of clinical significance.

Not so much with the 1.5 dose. And there, it seemed to me that the urine count, the times getting up at night, data were compelling and

probably meaningful. But I come down -- and this is why I was asking about standard deviation -- I come down on a position of not believing that the patient-reported data support the clinical meaningfulness of that 1.5 microgram dose.

The reason for that is these are powerful analyses that were applied to this study. And compliments to the sponsor. The data quality seemed good. There was not a lot of missing data. And when you use a powerful analytic approach like analysis of covariance in a trial like this with fairly good numbers, large sample size, you can get statistical significance without clinical meaningfulness, and I think that's a big part of why we're here.

The patient-reported data, the instrument itself appears to be good, and I think the FDA agreed with that as well, but it did not appear to me that it created a meaningful separation between the placebo arm and the 1.5 microgram arm. That 2.6 point difference in the FDA analysis did not emerge as one that would likely be considered

clinically meaningful. Although the FDA didn't say that, you could sort of see that in the background.

When you look at a zero to 100 scale like this, I'm familiar with a lot of different zero to 100 scales in a lot of clinical settings, and very often the standard deviation is somewhere between 15 and 20. It just happens to work out that way. So I was suspicious that it would be in that range. It's a little lower in the sponsor's dossier. When you look at the unchanged group, the standard deviation of that overall score was more in the 11 to 13 range.

Had that been the standard deviation at baseline, I might have shifted my weight a little bit toward a perhaps this is clinically -- this is a meaningful difference. But as it is, when you look at the effect size of a 2.6 difference between placebo benefit, if you will, and 1.5 microgram benefit, the difference is 2.6 points. That's well below 0.2 effect size, which is a very trivial effect size in terms of the group difference.

It does appear that both groups, the placebo

and the 1.5 groups, feel better, and report feeling better, and get up less at night. But I at the end of the day did not find myself convinced that the patient-reported data supported clinical meaningfulness of the difference between placebo and 1.5.

DR. LEWIS: Thank you. So we're now going to proceed with the discussion items, and I'll ask you to follow the same process of raising your hand, and we'll call on you one by -- I'll call on those who wish to make a comment for the discussion items before we vote.

The first discussion question is displayed there. The applicant's trials limited enrollment to adults at least 50 years of age, had numerous exclusion criteria, and no restrictions on fluid intake. Discuss whether the applicant studied desmopressin in the appropriate patient population. Comments? Dr. Johnson?

DR. JOHNSON: Thank you. I think that the enrollment of at least 50 was a request of the agency. I did ask a question earlier about the

notion of how many folks over 85 were in the study. I think that the no restrictions on fluid intake would have a bias away from finding a positive result.

The numerous exclusion criteria, I wonder in a real-life clinical practice whether or not you would need to reassess for exclusions that are incident during treatment. And I thought Dr. McBryde's point about African American populations having a larger prevalence of nocturia and that they were, relatively speaking, underrepresented in the sample was a consideration.

DR. LEWIS: Ms. Sorscher?

MS. SORSCHER: I know that we had a comment earlier that the incidence of hyponatremia would likely be less common outside the clinical trial setting. I have to disagree with that because these were clinical trials that had these extensive exclusion criteria, and a lot of the patients that were excluded were at greater risk for hyponatremia. They were also at greater risk for nocturia in many cases. These are people with

heart failure, diabetes, and renal problems.

So these are going to be a lot of the patients who are in the populations being targeted for this product, so I think there's a real concern that the actual rate could really be higher in practice.

My other comment was -- so yes, the FDA did work together to create the exclusion of adults under 50, but at this point, it's not really a question of whether it's the FDA's fault that that happened, but whether what's best for the public. So if in fact you need to go back and do more testing to see if it's effective in that population, then that's what you have to do regardless of what was agreed before.

One more comment on that is that I would not recommend changing the indication to be adults over 50 because it would basically skew prescribing. If it had any impact at all, it would skew prescribing towards the population for whom there's the highest safety risk. So you'd really have to go back and gather that data. An indication limitation

wouldn't help there.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: I guess my comment is it's a little bit of a funny question because they studied it in who they studied. The question is will it be used in those who they studied, and that's really I think the FDA's mandate for safety. I mean, it was studied in individuals over the age of 50 who don't have a lot of other comorbidities, have a GFR bigger than 50. I guess that would be my comment.

The one concern I would have is this issue about severe -- and this is what I was going to ask before, is what exactly constitutes severe BPH symptoms and what constitutes severe overactive bladder because those were excluded, and a lot of people with BPH were included.

So my inclination is that a lot of this will be used by individuals with very severe BPH in the clinical setting, and I don't really know what that means from the trial. So that would be the one population for which I would have a question.

The other is whether this is going to be

used completely and appropriately in nursing homes by individuals who are wetting their bed. In all honestly, there are risks of falls, but there are also other risks in nursing homes. And that would be the other population I'd be concerned about.

DR. LEWIS: Dr. Hanno?

DR. HANNO: I'm just wondering, this really depends on what the drug -- who it's meant for and what is the indication. Because there were so many exclusions, I think they did remove a lot of patients. And if they get an indication for nocturia as a whole, and you have 20 exclusions with LUTS and several other things, then you haven't really diagnosed -- nocturia's not a good diagnosis for this.

It's a symptom, and I would tend toward nocturnal polyuria as the diagnosis for the drug rather than the symptom nocturia because they've kind of enriched the population by already removing a lot of these other people who are going to end up on the drug just because they have the symptom nocturia.

DR. LEWIS: Dr. Smith?

DR. R. SMITH: Yes. I guess I would just make a follow-up to that. I'll just say I agree with a lot of the discussion I've heard. As a follow-up to that, I think that in my understanding of the term, nocturnal polyuria would not exclude some of the conditions that we might be concerned about that were excluded from the study.

For example, congestive heart failure may be characterized by nocturnal polyuria as elevation of edematous extremities mobilizes fluid so that I don't think that would resolve the problem for us. It would change the situation, but I don't think that would be a workable way of addressing that problem.

Another comment I would just sort of add -- and I'm not going to repeat what others have said in terms of the age group that's been targeted. I agree that we only have data about the age groups that are represented in the database, and everything else is supposition. At some level of reassurance, patients who are younger than 50

years of age I would anticipate -- if restricted to the same set of exclusions that have characterized the population under study, I would anticipate that we would see no more, and probably less, of a problem of hyponatremia.

So if we try to make some extrapolations about the consequences of a broader application just now focusing on age in adult patient groups, I would feel some confidence in terms of extrapolating the adverse event data in a younger group.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: My main concern on this topic is that in the practice of medicine, this will be used in all kinds of patients with the contraindications. And therefore, I don't know how the company could have handled this, but by all these contraindications, they're leaving open lots of people who will get this medicine who they didn't give it to.

DR. LEWIS: Thank you. Dr. McBryde?

DR. McBRYDE: I wanted to follow up a little

on what Dr. Smith had said. As I was thinking about it, I originally thought nocturnal polyuria as well, and then saw that there was some data looking at them both. And perhaps it's a bit of a nomenclature issue.

I looked, and I can't find that the International Continence Society or anybody else has a primary nocturia versus secondary nocturia diagnosis. But as a pediatric nephrologist, we think of primary nocturnal enuresis. So we sort of put it out there that you've excluded all those other things that were exclusion criteria that are populations that are at higher risk for hyponatremia and adverse events from this. But that gets missed with just saying nocturia.

I think that's kind of a problem for me. I'm not terribly bothered by the 50-year-old age limit. I think a lot of the exclusions were appropriate. Some of them I think reflect the drug development. I've been thinking -- other drugs that I think probably should have been on the exclusion list -- I hate to say it, but SGL2

inhibitors that induce both sodium and water loss, and then treating somebody with an antidiuretic therapy could retain water at a time when they're inappropriately losing sodium. That could exacerbate hyponatremia, certainly in the heart failure population. And folks with kidney disease but not meeting the GFR measurement, there might be tovactam, which was a V2 aquaporin channel antagonist, which would directly interact with this drug.

So there are other things that aren't envisioned in this that I think would be populations that probably should be excluded and I think might be captured a primary versus secondary nocturia definition; though, unfortunately, I don't see that there's any consensus on that in the literature.

DR. LEWIS: Okay. Thank you. So on this first -- oh, I'm sorry. There's one more? Dr. Neaton?

DR. NEATON: I just was going to maybe add the comment, the exclusions worry me most

concerning the safety. But one other thing I just want to bring up is that, on average, people came in at screening with a little over 3 times getting up per night. And post, 30 percent of the people dropped to a level that was called a non-responder before randomization.

When we saw the introductory data this morning, I guess I was impressed with the quality-of-life data and the bothersome symptoms associated with nocturia, and would have drawn the line more at 3 as opposed to 2. So I think there's some argument for ensuring that people who get the drug really have persistent nocturia defined as something higher than 2 per night.

DR. LEWIS: More comments. Dr. Ashley Smith.

DR. A. SMITH: Thank you. Just to put a little bit of a finer point on the younger age group and the need to look more carefully at potential adverse events, particularly since conditions may be different for young people, on the one group that we haven't thought about or

considered is pregnant women. And certainly there are a number of other conditions that may be more relevant for younger people, and if we haven't characterized well, I think that shouldn't be considered.

DR. LEWIS: Dr. Gellad? Sorry?

MS. BHATT: Was it Dr. Alexander, that you had your hand up?

DR. ALEXANDER: Sure. I think it's a tough question because the question is relative to what. But the exclusion criteria obviously limited the generalizability, but they increased the homogeneity of the sample. There was a comment about the fluid restriction, and I think that a fluid restriction would have made it harder rather than easier to show a difference between the groups. But maybe I'm wrong or maybe I misunderstood the comment.

I think the fact that 4 out of 5 of the group that experienced the severe hyponatremia, whatever on inhaled corticosteroids, or maybe 3 were on inhaled and 1 was on oral, is a cautionary

tale and sort of a reminder about the potential for drug-drug interactions, which others have alluded to already.

The final thing I'll say -- and I'm a country doc. I mean, I see patients for bread and butter clinical medicine. My experience with people with nocturia is a little different than some of what I've heard. And I appreciate that there are many places that people go for care and also patients may manage this very differently. But in fact, in my own practice, the majority of patients that I see with nocturia are elderly men who, frankly, say that it's okay, and they decline -- in many cases I'm offering them a potential treatment or often treatment for BPH, which is the cause for many of them, and many of them manage.

I'm not suggesting that this isn't a really serious problem and symptom for many, many men, but I do think it's important also to recognize that in many of these cases, these are individuals that say, you know what, I'd rather not have another

medicine, and I just get up and use the john, and then go back to bed.

DR. LEWIS: Thank you. Dr. Nahum, and then Dr. Smith.

DR. NAHUM: Thank you. I just want to focus in on the last part of what's said on the slide here, the question. It says, "Discuss whether the applicant studied desmopressin, the appropriate population." And I think Dr. Gellad said, well, it's a funny question because they studied who they studied. But it's a little bit more than that because they got input from the agency in a formal way, multiple times, and they had a special protocol assessment performed, which was agreed to I believe in 2011, if I'm not mistaken.

Perhaps I can ask the FDA to comment about that. But at least in the applicant's briefing document, it says that they did get feedback from a special protocol assessment. So there were multiple degrees of communication with the agency about the patient population to be studied, and the question appropriate to me means appropriate vis a

vis what?

I guess what I've heard the discussion here to be is not about the internal validity of what's been studied here. It's about the external validity of who might use it in the general population once it gets approved. And to me that's kind of a labeling issue and risk management issue, and sort of an education issue. It's not an approval issue. In other words, they studied who they studied, they proved what they proved in that population. It was agreed to by the FDA. And ultimately, it comes down to the FDA's labeling in risk management to decide that it's used in the proper population once it's approved.

So I think it's a funny question because the appropriateness of the population that was studied was established a long time ago, many years ago, and it's been carried through in the phase 3 studies.

DR. LEWIS: Dr. Smith?

DR. R. SMITH: So I wasn't going to respond to that; I was going to respond to the earlier one.

But I guess my feeling is about this committee, at least my personal feeling about this, is that history of how we got here aside, our job is to try to evaluate efficacy and risk as applied to a real patient population.

So somehow, it's perhaps useful, and important, and one can appreciate how we got into this circumstance, but we're trying to offer advice I think in a real-world setting about what we anticipate as real-world use of these drugs. And again, how the FDA then manages that opinion, I think the FDA will do what they need to do. But I don't see how I could approach that any other way. It's really looking at patient benefit and patient safety, not who said what and what got done under what historical setting.

I feel like I'm just responding, and so it's the last thing I'll say. But I wanted to respond to the issue about the significance of non-receptiveness of patients to taking medications for nocturia. It would require more understanding perhaps about what is behind that. But there are

reasons why patients might not want to take some of the medications, for example, those used for BPH. And some of that, we might argue, well, they wouldn't know, for example, that they might experience postural symptoms with an alpha blocker until they tried it unless they're in medicine.

But there is a bit of folk knowledge about things like 5-alpha reductase inhibitors, anti-androgens, and there are consequences for patients. So people who even not medically informed I think may be adverse to the notion of taking medications that may be associated with changes such as impotence, or as has been written in a lot of newspapers, potentially things that result in depression. So I think it's hard to apply that to another medication. It is an operative, but I don't quite know how to weight that.

DR. LEWIS: Thank you. Dr. Pavlovich?

DR. PAVLOVICH: I don't know who I agree with more, but in looking at this question of the appropriate patient population, I think what the

sponsor did was kind of what a clinician would do in any case, and that is this is not going to be an over-the-counter medicine. It has to be prescribed by a healthcare provider. And it's our job to make sure patients who we just give a product like this to don't have some of the conditions that would make it dangerous.

I mean, there are loads of symptomatic states that we treat, and we know what not to prescribe when someone has a specific comorbidity or is on a certain medication. And in our era, it's actually hard to prescribe something when the electronic medical record you use has pop-ups that come up all the time and say, no, patient on an inhaled corticosteroid; are you sure you want to prescribe that? No. Patient over 85. No.

So again, I think this is completely an appropriate patient population to study this. I mean, why would you have people with diabetes insipidus in such a trial? The 50-year cut-off, well, if you didn't have that, you would have enrolled about 5 to 10 percent of people under 50

because age correlates with nocturia, and nocturnal polyuria, and BPH, and LUTS, and overactive bladder. So you wouldn't have your answer. You would had 8 percent of people in their 40's, and you wouldn't know in that subset if this is safe or not because it would be a tiny little subset.

So I think barring all the history with the FDA and the sponsor that crafted this specific population for this study, I think in reality, it would represent the kind of people that I would be able or would want to offer something like this to at the more effective dose.

It's a symptom. Many of these people will have pre-existing conditions that predispose to it. But if nocturia is the salient symptom, then it would be nice to have something in the armamentarium, and that's I think why this was done. But if there's a real concern about the safety in the other non-studied group, again, that's something that as clinicians, we do that all the time. That's not problematic to me.

DR. LEWIS: Thank you. One last comment,

Dr. Coyne?

DR. COYNE: I would bring up the point, going back to that sentence about the appropriate patient population, that the data from Europe would support that it's nocturnal polyuria that this is an indication for, and that's not what they studied. They added in a subgroup -- maybe they thought that was savvy -- of individuals who did not have nocturnal polyuria with the idea that maybe they could get a broader indication.

My concern is two-fold. One, that subgroup of no nocturnal polyuria didn't respond to the high dose, so no significant improvement. And second is to essentially, with approval for this indication, create a new disease of simply nocturia that doesn't require specific differential diagnosis to decide whether this therapy is appropriate.

We've gone through this with anemia in multiple disease states, and I think it would be a mistake to approve a very broad indication that now we have a disease called nocturia that's treatable by this product in all patients.

DR. LEWIS: Ms. Berney? And remember that some of these issues are interrelated, and we will have opportunity to talk about them with the other discussion points.

MS. BERNEY: There's a lot of information here for somebody who is not a medical professional or statistician. But I am a patient who lives with 5 times a night, every hour. And that's why today, I've been sort of nodding off because I was up every hour last night.

I would love to know that there is something that I could be treated with that would help me. However, I'm also diabetic. I have high blood pressure. I take two different water pills. I can tell you that my physician, who just retired, might prescribe this for me in the hope that it would help me, even knowing that I also regularly take steroids, corticosteroids.

I can't -- I don't mean to demean anyone, but I know that, at least in the environment where I live, medical care is you're in two minutes, and you're out. And doctors don't always have time to

assess all of those things. So it worries me that there are all these exclusions, and this is suggestive for the broad nocturia, which doesn't necessarily cover the people who actually really have a problem because they're excluded. So I personally would be afraid to take yet another medication.

DR. LEWIS: Thank you. So to summarize on the first question of the limited enrollment related to age exclusion criteria and fluid intake, it sounds as if most of the panel had more concerns about the numerous exclusion criteria than anything else. The age restrictions, most people did not have an issue with. And the fluid intake, similarly, very little comment on, but certainly a lot of concerns related to the multiple exclusion criteria and the overlap with both medications that would be used for that and other disease states.

So let's, with that, move to the second question, which we'll display now on the screen. Discuss the clinical significance of the observed treatment effects of desmopressin on nocturia

compared to placebo. So again, if you would just raise your hand, Kalyani will put you in the queue. Dr. Johnson?

DR. JOHNSON: As someone who does investigator initiated research in nocturia and was one of the co-authors of the Tikkinen article that was looking at the cut-point of 2 versus 3, I do think that there are several people with 2 episodes of nocturia who have major or moderate bother and would like some treatment. So I'd hate to see this go down to 2.

Nocturia does matter. I think if you look at package inserts in the lower urinary tract symptom portfolio, there is a robust placebo response for many agents that have been approved in the portfolio, and that the request for those drugs is to have statistical separation from placebo. And I think broadly in the context of what's out there in lower urinary tract symptoms, the types of effect reductions that we're seeing are rather robust for this agent.

DR. LEWIS: Dr. Gellad?

DR. GELLAD: I think this is not a new experience for the FDA or even this division, but the issue here is you have a drug that is, on average, of probably minimal benefit for most people. But for a certain percentage who really, really struggle, the drug may make a large difference in their life. And that's really the struggle, I think the regulatory struggle, about what you do with this drug.

I think the drug reached its primary endpoint. The 50 percent reduction in rate of nocturnal events is significant. The responder analysis was significant. I don't honestly know what to make of the patient-reported outcome, but that was just in one of the trials. So I would say, in totality, it seems like the clinical significance, on average, is important, and even more important it is for those small subsets who could really benefit, a very large clinically significant benefit.

I'll just say, personally, I have a lot of patients who do struggle with this issue, and it

really is -- to have a benefit where it's 2 or more fewer -- 1.7 I guess was the responder analysis, but to have 1 and a half to 2 fewer events per night is clinically significant and should not be ignored.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: Yes. I would say I guess I'd characterize them as modest but convincing at the 1.5 microgram level, but I would still underscore modest. It's unfortunate that the INTU patient-reported outcomes weren't more convincing. I think that's a much tougher sell.

I didn't have the statistical sophistication that David Cella did to consider the standard deviations and what not, but just about any scale you imagine, pain scores, physical function, blood pressure, any measure that's zero to 100, if you just told me we found reductions of 12 or 14, but the difference between the groups is only 2, I'd say, well, that's the same number, that both groups are the same number; I mean, if you look at this from afar.

That's not to say, of course, that they're not individual patients for which the effects are much more profound. But I think it's unfortunate that the INTU results aren't more compelling. And as David pointed out, you have substantial improvements in both groups, so there's a great effect from placebo, and there's a great effect plus a little bit more from the treatment.

The 0.7 [sic] microgram, I'd suppose we put this in the depends who you ask category. But what we're hearing -- what I heard from the agency is that the endpoints for efficacy for that weren't met, and what I see from the sponsor is a few different analyses that indicate either borderline statistical significance, or I think for one of the co-primary endpoints for one of the trials, statistical significance. But I think the 0.7 [sic] micrograms is a much tougher sell in terms of efficacy, which is what my comments were focused on here.

DR. LEWIS: Dr. Howards?

DR. HOWARDS: This is a little redundant,

but I think compared with placebo, the improvement is almost trivial. If I were a patient that got up 4 times a night, and I then had an advantage over placebo of getting up 3.8 times a night, I don't think it would be worth any risk, let alone the potential risks here.

DR. LEWIS: Thank you. Ms. Berney?

MS. BERNEY: I'm one of those people, unfortunately, who is, in a number of areas, statistically insignificant, but I can tell you that, for me, it's significant. If I get up 5 times a night, and I can take a drug that lets me get up only 4 times a night, to me that's a big difference.

As the patient, who is the one getting up all night long and never getting a night's sleep, it makes a difference. I personally have some issues with this particular drug, but for that group of people that it would help, I think it's an important -- it could be an important addition to treatment because even one fewer for me would make a difference.

DR. LEWIS: Dr. Bauer?

DR. BAUER: I just wanted to weigh in about the clinical significance because this is just such a fundamental issue about clinical trial design. And when you're designing a trial, you go back, and to set it up, you say, well, how big of a difference do I want to detect?

So when I read this question, the first thing I went looking for was what did the sponsors think was a meaningful difference in their power calculations? And if you go back and look, they posited a difference of 0.3, I think, and 0.35 in the two trials and the mean number of episodes per night, and a 15 percent difference between placebo and treatment as a meaningful effect.

Now, that doesn't sound meaningful to me as to what we've heard about, but in fact that's what they posited, and that's what they showed. And I think to hold them to a different standard now than to what they actually said, and for us to then say was this clinically meaningful or not I think is a little bit of a value judgment because I think they

actually have shown what they set out to do, which was demonstrated the effect side that they wanted to do in those two trials.

DR. LEWIS: Dr. Neaton?

DR. NEATON: I kind of like the idea that they had two co-primary endpoints. The fact that the second one, which was kind of binary, 50 percent response, kind of helped lend some clinical relevance to the average difference between the groups in the number of times people got up per night.

The other thing, actually which I think was good in this study, was they had a number of secondary endpoints, actually a couple of which I thought were more clinically relevant, in my mind, than the primary, and they hit them all with the 1.5 dose.

I didn't know this question is concerning the lower dose, but I actually regarded the pooled analysis as pretty important. When I looked at that and thought about what they were recommending, it made some sense to me to kind of deal, as best

as possible, with some of the potential safety issues by using a dose, which at least combined across the two studies, looked to have some efficacy. So I thought the answer is efficacy looked pretty good to me.

DR. LEWIS: Dr. Pavlovich?

DR. PAVLOVICH: Yes, I'd echo that. I was impressed with the co-primary endpoints. I also liked the second one, which was the less than -- or greater than and equal to 50 percent reduction in getting up at night.

I really think that can put -- it's hard to, like Dr. Howards said, appreciate a 0.3, 0.4 change in mean. That doesn't mean actually -- no one actually gets up 0.3 times. It's either 2 or 3, or 3 or 4. But if you spread it out over the week, that's 1 and 2 times less overall, and that goes to that second co-primary endpoint where you had probably, on average, 1, 2, or 3 times fewer getting up at night over that week, and as we heard from our patient representative, it's meaningful. As a clinician that would seem meaningful, again,

in the right patient population in whom other things may have been considered, tried, et cetera.

I think lastly, I'll just say that when one has these massive placebo effects in all urinary dysfunction studies, to show a signal beyond that is impressive, and that's where you saw that 5 to 10 to 15 percent improvement in fewer episodes in those cohorts over the week.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: Thank you. I think there is marginal efficacy for the 1.5 dose. At first, my thinking in the 0.75 was forget this; it's really like placebo. But you can make a case for starting -- with such a great placebo response, you can make a case for starting people on placebo, and less will have to go to the dose that has potential significant side effects. So I'm not totally against the 0.75, although initially I thought that should be thrown out.

DR. LEWIS: Thank you. So to summarize the clinical significance of the observed treatment effects compared to placebo, most people came down

on the side of feeling that this -- or perceiving this is a meaningful difference, though certainly modest, pretty much at the 1.5 microgram -- 1.2 microgram [sic] dose rather than the 0.75 microgram dose because it is essentially a quality-of-life issue, though not necessarily well reflected in the INTU studies, which were a little problematic, for some.

Question 3. Discuss whether the safety of desmopressin has been adequately characterized and whether additional safety data are needed.

DR. CHANCELLOR: Actually, a question for this section that may know more about the Beers classification on potentially inappropriate drug in the elderly than not. Desmopressin is listed there, and I was just wondering how that relates to what we should be considering.

DR. LEWIS: Could you repeat that? I'm sorry.

DR. CHANCELLOR: The Beers classification.

DR. LEWIS: Beers classification. Got it.

DR. JOHNSON: As a geriatrician, I can both

answer that question and reflect on a couple of things that I wrote down. So the new Beers categorization in 2015 did have the first appearance of DDAVP in the list of drugs. The tables are different, and I'd have to go back and look at which table it's in. There are drugs that are always inappropriate, drugs that are potentially inappropriate. But it is a listed drug, DDAVP, not SER 120 that we're talking about now, but DDAVP.

For my considerations on safety, I'm very worried about the very elderly, the folks who are over 85. I have done clinical trials with desmopressin in a nursing home setting. It is the wrong population for use. I worry about the lack of monitoring that we'll see in real-world settings without checking on low sodium.

I don't know whether or not checking within the first 7 days is appropriate. We did see a lot of fairly significant hyponatremia emerge by 2 weeks. I don't know when those folks became hyponatremic. If you follow elderly patients for

long enough, they will develop contraindications to the drug, and so I'm interested about reascertaining whether or not people have exclusions for safety reasons.

There is one situation where the patient -- one of the participants were seen in the emergency room, discharged with a sodium of 122 without treatment. The lack of knowledge about hyponatremia in the general medical community is unfortunately high.

DR. LEWIS: Dr. Gellad?

DR. GELLAD: I would say I also have the same concern about the use in a nursing home, but it gets at this issue of what is the population that actually fit the clinical trial. How many nursing home patients have a GFR over 50, or not on a loop diuretic, not an inhaled steroid, don't have sleep apnea, et cetera, et cetera? But that is a concern that it will be used there, even off label.

The other issue I didn't get a chance to ask about was this issue of NSAIDS. And I didn't know if the NSAIDS that were associated with the severe

hyponatremia was something to worry about or not, whether it was prescription-strength NSAIDS or over the counter. But it seemed like 4 of the 5 cases of severe hyponatremia were associated with both steroids and NSAIDS and something to consider. I would say, otherwise, I think that the sponsor has done a good job demonstrating the safety and dealing with the issue of hyponatremia.

DR. LEWIS: Thank you. Dr. Alexander?

DR. ALEXANDER: I'll say again what I said before, if my calculations are correct, which is that 91 percent of the rates of hyponatremia that were clinically significant occurred in people over 65. And I think it's highly unlikely, I'd fall out of my chair, if it really turns out to be the case that rates of monitoring in clinical practice come close to approximating rates in this clinical trial. I've never seen it in any clinical setting before.

With that said, I don't think there are a ton of outstanding questions. I mean, I'm a little bit curious about some of the vasoreactivity, and I

missed the fact that it may increase factor 8 levels or von Willebrand, and those were intriguing. But I don't have great concerns about that. I just have concerns about the rates of hyponatremia that we're likely to see among the population that's most likely to use this, which seems to me the elderly.

That was the majority of people that were enrolled in these trials, and I can only imagine in clinical practice, if the label were just kind of anybody over 50 for any cause of nocturia, I'd just be flabbergasted if there weren't much higher rates of people getting started on this medicine and failing to come back when recommended for labs. And of course, labs slip through the cracks as well. But even if they didn't --

I guess the other thing that I don't think has been stated explicitly but I think there's a proposal for, kind of this 14-day follow-up. So you check at baseline, you check at 14 days, and then as clinically indicated -- and who knows what that means. Of course, we entrust our clinicians

to have good heads on their shoulders, but a 73-year-old on a thiazide diuretic but stable, a little bit frail, normal sodium, and then I check it 14 days, and then -- I don't know. I don't know. So those are my thoughts.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: I just wanted to add that I am also worried about the indication creep, because the way this has been presented is that this would be widely prescribed by generalists, in general practice. And I think that without requiring some sort of expertise, or even, as a matter of fact, knowing what conditions might be most appropriate for this -- for example, I would argue that this also ought to be in individuals that have nocturnal polyuria. And just actually going through the process of trying to figure out who that is and who isn't might sensitize people or get these people referred to experts who would know enough to actually also know who the drug might be dangerous in.

Again, I would argue in general practice,

drug interactions are really critical. And I think if you're talking about NSAIDS and inhaled corticosteroids, which are used ubiquitously in general practice, unless we have more safety data about that, I'd be concerned.

DR. ALEXANDER: But the labeling is going to affect who it's prescribed by as well. I mean, I agree that lots of generalists could use this, but I also think if there's -- if it were to be approved, I think there is labeling that would change that. And frankly, the marketing and promotion strategies and the manufacturer are also going to have a big influence on who uses it.

DR. LEWIS: Thank you. Dr. Smith?

DR. R. SMITH: So focusing on another point, rather than restating what I've already heard that I substantially agree with, I think that the size of the data set that we have available has given a limited opportunity to observe rare adverse events, and I remain uncomfortable with the numerical excess of deaths in the treatment group. And I understand they're very small numbers; they may

have no meaning. But I feel that that needs some further scrutiny perhaps if this is approved in a post-marketing context.

I understand -- I heard the comment from the FDA about how difficult or insensitive postmarketing surveys can be when it's on a high baseline. So an elderly group with a significant mortality and significant cardiovascular events is a high baseline, but I would still encourage that if the drug were improved. And I'd be a little more optimistic in that if these are events that are somehow induced by the drug, the time course may be one fairly early after introduction of drug. There's no data to support that here, but potentially it wouldn't be as grim a circumstance of being able to identify increased mortality or increased cardiovascular events.

I don't know what mechanism -- I can think of some mechanisms, but no compelling mechanism as to why that should occur in the patient group that was described. But I'm uncomfortable with the numerical excess and think it needs further

attention down the road.

DR. LEWIS: Thank you. Dr. Neaton?

DR. NEATON: Well actually, part of my point was the same point just made. But related to it, given this drug is going to be used over longer terms, I think there's more controlled data which is needed so we can interpret these serious adverse events in the context of the drug that's being given. I think while the open-label study was somewhat helpful, I think a more controlled data, to understand that, and other events is important to do.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: With regard to long-term use, I think the data we have go out to one or two years. And this is a drug that presumably will be used indefinitely, and the risk of hyponatremia and of developing comorbid conditions that could further that risk, increases over time. I don't know how long a study you can request, but I think it's troubling that we only have that one or two years of data.

Then with regard to the clotting risk, rare events, it's hard I know to study them, but I think I'd like to see just a little more attention from the FDA, analysis, the adverse events data, looking at timing, a literature review. Maybe it's possible to do a PK study. Anything that could inform that risk a little more I think would be helpful.

DR. LEWIS: Thank you. Dr. Erstad?

DR. ERSTAD: With regards to the relatively uncommon or rare adverse events, to expand on what Dr. Smith said, and I agreed with all the comments he made, the one thing that does give me comfort, if this was a brand new drug and we're basing all of our safety just on these two studies, that would be one thing. But in fact, desmopressin's been used worldwide for a lot of conditions for many years, and a lot of different formulations. And that gives me at least some, a modicum of allaying some of my concerns with regard to these uncommon rare but serious adverse effects that come up literally in every FDA meeting that I'm involved

with.

DR. LEWIS: Thank you. Any other questions? That's it? Okay.

On the question of whether desmopressin has been adequately characterized and additional safety data are needed, there were concerns consistently voiced by panel members about not just the increased death rate but some of the potential morbidities that can occur over longer term, especially in a population in which the drug will actually be used, even with strict labeling indications.

This is an elderly population, or will be an elderly population very likely, that has significant comorbidities; some panel members raising specific concerns about using the drug in a nursing home population, and of course that the monitoring that was present in the study under very controlled circumstances is not likely to take place in the real world.

Let's turn our attention to the next question, and then we'll have a break after this

last question. Nocturia is a symptom that can be caused by many conditions, some of which may co-exist in the same patient. Discuss whether the applicant's broad purpose indication for the treatment of nocturia that does not specify the underlying etiology is clinically appropriate.

If it is, discuss the adequacy of the applicant's data to support this proposed indication or whether additional data are necessary. If additional data are necessary, what data would be needed to support the broad indication? Dr. Hanno first.

DR. HANNO: Thank you. I think with a broad indication like nocturia, this drug is going to be used by general practitioners and just the vast realm of physicians, nurse practitioners, and I'm afraid that people won't be diagnosed with what's going on and be treated appropriately.

I mean, they could have BPH, overactive bladder, diabetes, stricture. Who knows what's causing it? And I think if you limited the diagnosis to something like nocturnal polyuria,

that automatically indicates -- and it's not a hard diagnosis to make, but you need to do some thinking and need to do some diagnostic studies. I think then you'd have a much more appropriate population. It would be overused. So I think the indication needs to be changed.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: Yes, I agree. I do not think it is appropriate to just have nocturia. It should require a diagnosis, not just a symptom. And I also favor the nocturnal polyuria, which would require a diagnosis and may in fact limit the use of the drug to just those who know what they're doing. So I do not think it would be appropriate to just have nocturia.

DR. LEWIS: Ms. Sorscher?

MS. SORSCHER: Yes. With regard to the population where nocturnal polyuria was absent, it was a small subset of the total population. But looking -- FDA did an analysis of the response in that population, and there was a trend towards reduced efficacy in every measure in that group.

And it actually did numerically worse than placebo on the second co-primary endpoint, which was the 50 percent responder rate. So I really don't think that that group should be part of the indication. So I guess I agree with the previous speakers on that point.

DR. LEWIS: Thank you. Dr. Chancellor?

DR. CHANCELLOR: I feel nocturia is broad. I like the European assessment of idiopathic nocturnal polyuria. So not only do you show there's too much urine production, but being idiopathic meaning they don't have heart failure, peripheral edema, sleep apnea, and other conditions.

DR. LEWIS: Thank you. Dr. Coyne?

DR. COYNE: I would go along those similar lines. I think that an indication for nocturnal polyuria is appropriate if it excludes the secondary causes, as we've discussed, which essentially reflect what many of their exclusion criteria are.

So in particular, identifying uncontrolled

diabetes, heart failure, use of loop and thiazide diuretics, and chronic kidney disease would probably be very high on the list of excluding them from use of this drug, where, in all likelihood, the patients are going to be at greater risk of side effects, and probably receiving a therapy that's not really ideal for their problem.

DR. LEWIS: Thank you. Dr. Johnson?

DR. JOHNSON: I wanted to echo what Dr. Coyne and Dr. Chancellor said. I think that nocturnal polyuria is the right pathway to go down. I want to compliment the sponsor on identifying that many of their participants had multiple causes, and I think that that's the real world.

I do want to alert folks that nocturnal polyuria is a definition that's being revisited in terms of standards with the International Continence Society and other groups because some people think that they've set that definition too low. So if we're going to hang our hook on nocturnal polyuria, we would probably want to fix the definition.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: I was just going to ask about this issue about idiopathic nocturnal polyuria. There are individuals in the trials who had BPH, and so would that -- I don't know enough about that specific -- I mean, it seems like individuals with BPH on medical treatment, who still have symptoms, may benefit, and that they're in the trial. I'm not sure that those necessarily should be excluded if they're maximally medically managed for BPH.

But that would be my only concern about limiting it to just idiopathic. It seemed like that in the trials, there were individuals who had other causes who you would not want to exclude.

DR. HANNO: You could have other causes. And once they're treated, if you're still having this problem and it's contributing, then that would make sense, everything you say.

DR. LEWIS: Thank you. So there was pretty much universal agreement that nocturia is a symptom and really a broad indication, and it's not really appropriate as a proposed indication. However,

nocturnal polyuria at least implies that an attempt has been made to diagnose serious conditions, which should be treated and recognized otherwise. And if those conditions have been addressed, then it may be appropriate to apply this drug.

With that, I'm going to say let's -- I think we've completed our discussion points. We'll take 15 minutes break, and come back and address the two questions on which we have to vote.

(Whereupon, at 3:15 p.m., a recess was taken.)

DR. LEWIS: Before we move to the final two questions, Dr. Joffe has a comment for us.

DR. JOFFE: Thank you, Dr. Lewis. I was interested in hearing what folks thought about the last part of the question. It sounds like we've heard a lot of discussion about not so much comfort about a broad indication. But is there any additional data that could be provided that could support this broad indication? Does anybody have any thoughts on that?

PANEL MEMBER: Well, with regard to

individuals who -- as was pointed out, about 80 percent of the patients had nocturnal polyuria, and many of them have comorbidities that also account for, in part, their nocturia. I don't really have a problem if you've got that plus something else that you can use this therapy.

So with regards to the individuals who didn't have nocturnal polyuria, their data, even in their combined data set, didn't reach statistical significance. So I think to get a broad indication, you'd have to do a separate study in individuals who don't have it, and demonstrate that in fact the 1.5 microgram dose is clinically significantly better than placebo.

If you're doing a long trial -- because although we talk about we have all this data on desmopressin, it's not really in 75-year-olds who are in early dementia. So I think there's both a plus and minus in doing a study that actively looks at the incidence of falls and fractures as there is some argument for equipoise in that the drug reduces frequency at night, but also may increase

the incidence of hyponatremia.

I would point out lastly, because there was no other opportunity, that while the sponsor has talked about the nadir sodium, we're checking them presumably a good 4 to 8 hours, or even 12 hours, after this drug has worn off. And indeed, their nadir may will have occurred at about the time they got out of bed in the morning. So the hyponatremia may be somewhat worse.

DR. LEWIS: Thank you. Dr. Johnson?

DR. JOHNSON: I wanted to offer a couple of thoughts about falls and fractures. I think this is epidemiologic association data, and it shows that maybe it's a nighttime mobility problem. Maybe it's a daytime sleepiness problem. Maybe it's because folks with nocturia are just frail.

I think that people were talking about falls and fractures, about making this an important condition, and I don't think that we're going to be able to drive any study that will show a reduction in falls and fractures. I think that perhaps for me, at least, that's a distraction.

I want to link risk and benefit just for a second. I know we're talking about benefit right now, but this notion of a 0.75 dose, several people developed hyponatremia at that dose, and so I'd hate to see us go with an efficacy-only argument because I think that those folks who developed hyponatremia at 0.75 would have much more significant or much more rapid development of hyponatremia if they started at that higher dose.

DR. LEWIS: Dr. Smith?

DR. A. SMITH: Just to underscore the comment earlier related to age, I think that it made sense to restrict the study to people over 50 because the target population was really people who were going to be more prevalent in terms of nocturia. But I don't think that that suggests that we should use that evidence alone to justify the use in younger people, and would need more evidence to determine whether it's both efficacious and also doesn't have adverse events.

DR. LEWIS: Dr. Alexander first. Sorry.

DR. ALEXANDER: I didn't fully understand

the comment, the one before the last one, but I don't know -- about the 0.75 microgram dose, but I think we're going to get back there with one of the next two questions.

I don't totally disagree with the concern about people that didn't have nocturnal polyuria, but it does seem a little odd to take a post hoc subset analysis of a group and identify that they're non-responders, and then to make a decision about who should ultimately -- the product should be labeled for based on that.

I mean, I'm not sure I have a suggestion about a great number of additional studies to perform. I will say in my, as I said, maybe very unusual clinical practice, that's not a diagnosis that I'm that fluent with and that I make that much. I mean, the vast majority of people that my colleagues and I see I think are primarily with nocturia that's bad are primarily women with overactive bladder or men with BPH, or both.

But I'm not sure there is a great deal of additional data that I think are really vital now.

And I guess I would just underscore again this question of whether it makes sense to say that we should do a post hoc analysis on a subset, and show that there's no response. I mean, what if we looked at some other patient characteristic and found that there wasn't a response among that subpopulation? Would we then say that it shouldn't be labeled for that group either?

DR. LEWIS: Thank you. Dr. Coyne? I'm sorry. Dr. Smith?

DR. SMITH: I was going to make a similar point. Rather, I saw Dr. Neaton's hand. Are you going to comment about the statistical issues related to this -- so I'd rather have a comment from you. That's what I was going to address.

DR. LEWIS: Dr. Neaton?

DR. NEATON: I was going to make the comment earlier. There are a number of subgroup analyses that were reported both by the sponsor and the FDA, and none of them that I could find were associated with any kind of test for interaction as to whether or not the differences we're seeing, the p-values

for the individual groups, were just a chance finding.

So I really think that you need to look at the totality of information, all of the outcomes, and try to kind of gauge what you decide about a subgroup based upon a test of interaction, at least between the subgroups and other measures, that would guide you as to whether you're just looking at a chance finding. And I didn't see that for any of the data that I saw presented in either the sponsor's or the FDA's book.

DR. LEWIS: Dr. Smith?

DR. SMITH: Yes. To follow back on that, I was going to bring the question from the FDA back to the FDA because the question is if additional data are necessary.

So the situation we have here is we have a study population that is being related to nocturia. Within that, we have a substantial percentage that we're describing as having nocturnal polyuria, and we're beginning to latch on to this notion that that might be a better definition for a patient

population for which this would be an appropriate treatment.

So then that comes back to a question of if we have these studies, and within them we have a subpopulation, and whether from an FDA -- so I'm kicking it back to the FDA -- whether from the FDA perspective how much discomfort there might be in making a decision -- in a way I'm restating what you said in layman's terms, in a way. But moving from within a study a subset within the study, and then using that to define a target group without viewing that as an invitation to study or a hypothesis-generating observation.

The reason I'm directing that back to the FDA is because your answer to that might influence how I would answer this question if we -- okay.

DR. EASLEY: Sorry. Is your question whether we would require additional study in a subpopulation or we could just use that data that they have and take that as -- well, I'm going to defer to my higher up.

(Laughter.)

DR. JOFFE: It's a difficult question because usually you design the studies how you want them done, and then you analyze as opposed to going back after the fact, and digging and trying to find a population that fits the data. So it's a difficult question to answer. I don't have a very good answer here.

What is the downside? I guess one downside is you could say there's an effect in a group when there isn't really an effect in the group or vice versa. You might say there's no effect in the group when there is an effect in the group. So those are the errors that might come about by making those kind of decisions.

I don't know. Do stats have anything they can add from a statistical standpoint? The preferred approach is always to study the population in the randomized patients because when you start doing subgroups, that's where you start to also lose some of this randomization issue.

DR. R. SMITH: Right. I would share that perspective. And then given that, I would just say

that there have been some very good arguments made about targeting a patient population with an appropriate definition for nocturnal polyuria, and appropriate exclusions might be in fact the best patient population based on the data we've seen.

I would simply say, I guess as an advisory committee member, that I do make the observation that there's actually no study that was designed, pre hoc, to look at the question of this nocturnal polyuria patient group, and then probe that. And I know that's a rough situation to be in, but that is in fact the reality that obviously you appreciate, but I would like to just state that as well, as a perspective.

DR. JOFFE: Like some of these other things, it raises some uncertainties with the data. And I think at the end of the day, you've got to take a totality of data view and see where your comfort level falls I guess in terms of what you think the data support. And we'll take that back and mull on that internally, but I think that's what you have to do in a situation like this.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: Yes, I think that's an important point about the clinical indication and this issue about nocturnal polyuria wasn't really studied. I guess the flip side, I will say my honest opinion is there is no data that anyone could produce that would, for me, support the benefit-to-risk ratio of an indication with nocturia. The potential of it being used way out of proportion to what it should be used if the indication is nocturia is just too high.

I guess for me, if I had to say what data would be great, it would be maybe a pragmatic trial where that is -- it is pragmatic rather than restricted in carefully chosen patients.

DR. LEWIS: Thank you. Dr. Pavlovich?

DR. PAVLOVICH: I guess as a clinician, I'll go on record saying that I'm completely comfortable treating symptoms rather than signs or diagnoses. I mean, I think we're all concerned that nocturia could mean anything.

Well, in urology, we treat erectile

dysfunction and lower urinary tract symptoms. Those are maybe the top two diagnoses outside of cancer. And we don't know what causes those. There are many diseases that affect them, many indications, many comorbid conditions, but we treat those and have drugs approved for them. We do diagnostic testing, much of it not even necessary or sanctioned by guidelines.

So nocturia, yes, it's a symptom, and it's what the company studied, and the vast majority of the patients also happen to have nocturnal polyuria. Whether that's causing this symptom or whether it's really the OAB, or the BPH, or another -- but it's not some of the more serious medical conditions like uncontrolled hypertension or diabetes.

So again, just putting that out there. I know a lot of people here have this huge reservation about a medication for nocturia because maybe that is just a symptom. But I would posit that we treat symptoms all the time because I for one don't know what causes most of the diseases

that I treat.

DR. LEWIS: Dr. Alexander, any additional data necessary, and what would that be? That's what we're talking about.

(Laughter.)

DR. ALEXANDER: Oh. Yes. I don't think so, nothing that comes to mind. And the second part of that, I guess what I would suggest, which is that maybe the presence of nocturnal polyuria or the frequency of nocturia and the amount of symptoms that the patient has is more important than the specific clinical indication.

I suppose nocturnal polyuria, that's defined as voiding more than 24-hour -- voiding more than a third of your 24-hour urine at night is a specific diagnosis. But I think that we saw evidence that the efficacy is greatest among those, essentially, who are most symptomatic, have the greatest frequency of nocturia. And here, we're seeing among those that have nocturnal polyuria, the formal diagnosis. So maybe that's more important than whether this is from heart failure or bladder

outlet obstruction, or the like.

DR. LEWIS: Thank you. Anyone else?

MS. BHATT: Do you have a question, Dr. Gellad?

DR. GELLAD: I just want to say one thing about that last point. I guess I would ask the urologists, what percentage of the individuals in this country with nocturia have nocturnal polyuria versus all the other causes?

That's the issue about nocturia, is this trial, 80 percent have nocturnal polyuria diagnosed based on urine. The question is, real life, is that also what we see if you took all-comers with nocturia? And I don't think so, but I don't know the definitive answer.

DR. COYNE: I think that gets at the core of all the exclusions. When I see nocturnal polyuria, it's because they have CKD, or they're on diuretics, and they're taking them late at night. But all of those were excluded, and therein lies the danger in saying this drug is approved for polyuria.

DR. HANNO: I'll agree with that. In everyone with LUTS, they excluded people with severe LUTS. Well, that's a huge cause of nocturia, whatever type of LUTS it is. So this is a very selected population to start with.

DR. LEWIS: So any additional data that we want sponsor to acquire or any suggested studies for the FDA?

(No response.)

DR. LEWIS: So we're going to move on question 5. We're going to be voting. We will be using an electronic voting system. Once we begin the vote, the buttons will start flashing, the buttons on your microphone stand, and continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote.

If you're not sure of your vote or you wish to change your vote, you may press the corresponding vote [sic] until the vote is closed. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed

on the screen, and Kalyani will read the vote from the screen into the record.

Next, we'll go around the room, and each person who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We'll continue in this same manner until all questions have been answered or discussed; that's until both question 5 and 6.

Question 5. Is there sufficient evidence to conclude that at least one desmopressin dose is effective? And provide a rationale for your answer. If you vote yes, when we go around the room, I'll ask you to specifically comment on which dose is effective and whether the data support the proposed regimen of starting with 75 [sic] micrograms, and then titrating upward, if needed, to 1.5 micrograms after 2 to 4 weeks.

The question is clear for everyone, so we'll now begin voting.

(Vote taken.)

MS. BHATT: The voting results, yes, 17; no,

1; abstain, zero; no voting, 1.

DR. LEWIS: Thank you. So we'll start with Dr. Alexander.

DR. ALEXANDER: Caleb Alexander. I voted yes. I felt that there was sufficient evidence for modest efficacy of the 1.5 microgram dose only. And that's simply based on its having met the prespecified endpoints in the two pivotal trials.

DR. LEWIS: And what about the question of titrating upward?

DR. ALEXANDER: I don't believe there was sufficient evidence to indicate the efficacy of the 0.75 microgram dose, so I couldn't propose that as a label because I don't think it was demonstrated to have been efficacious. So I guess the answer is no.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: Walid Gellad. I voted yes. I think the 1.5 microgram dose, there's sufficient evidence to conclude it's effective. I'm going to give you a very careful answer about the 0.75, about the titration issue.

I would say if we go back to the totality of evidence, I would say having seen all the evidence, the way that I would practice -- give the drug to myself, or a family member, or a patient -- would probably be to start with the 0.75 microgram dose. However, I do not know if that qualifies -- if the data support 0.75 independently as an effective dose that is clinically significant compared to placebo. However, it is the way I would practice, to be honest, given the strong placebo effect.

DR. LEWIS: Thank you. Dr. Smith?

DR. A. SMITH: So I voted yes. I thought that there was evidence for the 1.5 microgram dose, but not for the 0.75. I appreciate the previous comments about the placebo effect, but as I thought we had heard from Dr. Joffe earlier, we were really to look at the difference between placebo and the 0.75 effect.

I did want to make a comment about the PRO relative to the claim, and that is that I agreed with some of the discussion earlier that there is not evidence to endorse that there was a clinical

benefit based on the PRO. And in particular, when looking at the anchor relative to the reduction of nocturic episodes of greater than or equal to 1 per night, the score was 16. And with a 1.2 difference between placebo and the 1.5 dose, it didn't seem to me that having a 16-point difference would really rise to suggest that there is a clinical benefit based on the PRO. So I just wanted to add that.

DR. JOFFE: Thank you. So I missed it. Titrating upward or not?

DR. A. SMITH: No. I would say no.

DR. LEWIS: No. Got it. Sorry. Dr. Cella?

MS. BHATT: He's gone.

DR. LEWIS: Oh, I'm sorry. He's gone. Dr. Johnson?

DR. JOHNSON: I voted yes. I believe that there is sufficient evidence. I am also an advocate of starting at a lower dose and titrating up. That was not a tested strategy, so it's kind of hard to defend that in the labeling. But if 1.5 were approved in my practice, if I were to use it, I would use 0.75 starting.

DR. LEWIS: Thank you. Dr. Pavlovich?

DR. PAVLOVICH: I voted yes, same reasons as Dr. Johnson and Dr. Gellad. I agree with their comments. I think I too -- although there's not evidence to support the lower dose standing on its own, the totality, the dose-response curves, and the clinician's comfortableness with starting with a lower dose is something all would make me want to use it that way.

I think if you look at the data, there are also some indications that a lower dose might be efficacious in elderly patients as well. So it would be a good way to start, but overall I'm voting yes for the higher dose.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: Yes. I voted yes for the higher dose, the 1.5. And in terms of the 0.75, I didn't really see any efficacy, however, I probably want to give the clinician the opportunity to start with that lower dose, and I think that would be a safer way to do it. That's how I would feel.

DR. LEWIS: Thank you. Ms. Berney?

MS. BERNEY: I voted yes for the higher dose. And I'm sort of in a quandary about the lower dose, although I do sort of support the idea of starting with the lower dose to see how it's tolerated. In some patients, it's probably going to do the trick.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: I sort of had to fill in the blank with this question because it asks is it effective, but it doesn't say for what. So I filled in the blank with nocturia. And given all the concerns voiced here about that not being a distinguishable condition, and there could be subgroups within that for whom it's not effective, I voted no based on that. Also, I have concerns about the meaningfulness of the 1.5 dose. It's clearly statistically significant, but whether it's clinically meaningful is I think still an open question.

DR. LEWIS: Thank you. Dr. Smith?

DR. R. SMITH: Yes. Robert Smith. I voted yes. I felt that there was sufficient evidence

statistically to support the 1.5 microgram dose as being effective. And I also felt that the magnitude of that effect was clinically significant in my opinion.

I suspect that the 0.75 microgram dose is quite possibly effective, but I don't think there's adequate data to establish this. And I think this is a circumstance where perhaps a larger study might resolve that question. And if I had to guess, I would guess that we would find an effect.

I'm uncomfortable endorsing the idea of the 0.75 microgram dose in the absence of convincing evidence that it really has an effect. That's not doing evidence-based medicine. And I think the situation for the FDA, I presume, is the question of approving that dose preparation. This is a nasal medication, so it's going to require a specific formulation I believe.

I would be uncomfortable launching that without convincing evidence that it has an effect and is not just some placebo or a placebo with a little potentially harmful agent within it that

might have adverse effects but no benefit. So I feel that more data are required to support the 0.75 dose.

DR. LEWIS: Thank you. Dr. Drake?

DR. DRAKE: I also voted yes. I would specifically support the 1.5 micrograms. I didn't see much evidence for the 0.75, and I don't think they actually provided any data to support the proposal for starting at a lower dose and titrating up. I just, unfortunately, didn't see that data. I think clinically it probably makes sense, but in the absence of data that's what we have.

DR. LEWIS: Thank you. I voted yes on the 1.5 microgram dose. I agreed with both Dr. Drake and Dr. Smith, there's no data to support that the 75 [sic] microgram dose is going to be effective. And I share Dr. Smith's concern that making that available, you're really just going to release what is going to be a placebo effect for a lot of people, not that that's necessarily completely a bad thing, but it could also unleash a lot of untoward reactions that are iatrogenically induced.

So in the absence of data showing that the titration strategy is effective, I wasn't comfortable with endorsing that.

DR. BAUER: Doug Bauer. I voted yes for all the reasons that have been stated, 1.5, yes. And 7.5 [sic], I categorically say no. It did not meet the prespecified effect size that the investigators were hoping to find. And I think the whole notion of dose adjustment is really fraught with all sorts of questions about what's a responder, who is a responder or not. I just think that's not good medicine.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: I voted yes slightly reluctantly because I am not at all convinced that by my definition of clinically effective, this is clinically effective. However, I think to be fair to the sponsor, by the FDA's definition and by what I learned from the discussion, and what they were asked to do, I voted yes because of that, for 1.5

As far as 0.75, I would not support it because it's not statistically significant. And in

addition, it would add to the complexity for the treating doctor and the patient, as well as added expense. So that's my position.

DR. LEWIS: Thank you. Dr. Chancellor?

DR. CHANCELLOR: Yes. Mike Chancellor. Yes to the 1.5; no to the 0.75 or dose escalation, which was not studied. And given the short half-life, a couple hours, why wait 4 weeks? Why not escalate the next night?

DR. LEWIS: Thank you. Dr. Neaton?

DR. NEATON: I voted yes for the reasons that have been stated. I think the 1.5 was fairly clear-cut. I attach more weight to the pooled analysis for 0.75. It hit that for not only the primaries but all the secondaries.

So I think that should be looked at more carefully. We never saw an analysis here today that was generated for the group of people that were labeled, quote, "non-placebo responders." That's where I would expect to see a difference, which is greater. So perhaps when the sponsor and the FDA look at those analyses more closely, they

can sort that out.

DR. LEWIS: Thank you. Dr. Erstad?

DR. ERSTAD: I voted yes for the reasons stated, and I voted on 1.5. And on the 0.75, again, I don't think there's really any evidence. And I'll use that word to support this titration up to a 1.5 dose.

DR. LEWIS: Thank you. Dr. Coyne?

DR. COYNE: I voted yes for 1.5 for all the reasons that were stated before. With regard to the 0.75 and the titration issue, one, it was not demonstrated to be efficacious. But number two, by approving this dose as a step, many patients will not get titrated. So you're essentially granting approval to a drug at a non-efficacious dose that will capture a large market that is simply a placebo effect. So it will be very expensive, carry risks as we've seen in this study, and have no real benefit to the patient. And I think that that's a mistake.

DR. LEWIS: Thank you. Dr. McBryde?

DR. McBRYDE: Kevin McBryde. I voted yes.

I agree. I was struggling with some of the co-primary endpoints. I'm not sure that I think that 0.2 or 0.3 change in episodes per night between placebo and 1.5 was that dramatic. But what got me was really the secondary co-primary endpoint of the 15 percent higher rate of the 50 percent reduction. And I think even if the PROs didn't really -- say what you want to say about the PROs. I think reducing nocturnal awakenings to void by 50 percent in 15 percent of the subjects is a really good thing.

I agree with the same issues about the 0.75 micrograms. I'm not completely sold on that. I don't like the idea of putting it out there to titrate. As Dan said, I think it's a very expensive placebo, and I don't think that the evidence really supports that.

DR. LEWIS: Okay. Thank you.

At this point, I think we're ready to move on to the final question, do the benefits of desmopressin outweigh the risks and support approval? Provide a rationale for your answer. If

you vote yes, specify the indication that's supported for your benefit-risk assessment. If you vote no, include recommendations for additional data that might support a favorable benefit-risk assessment.

This time, I'd like to start on this side, so Dr. McBryde -- oh, I'm sorry -- you'll be the first to comment, but we're going to vote first.

(Laughter.)

DR. LEWIS: So you have a heads up.

DR. ALEXANDER: Can I ask a clarifying question?

DR. LEWIS: Sure.

DR. ALEXANDER: Are we take this question to mean under some guise? I take it, is there some circumstance, some label, some conditions under which we believe that the benefits outweigh the risks?

DR. LEWIS: Dr. Joffe?

DR. JOFFE: Yes. And you can comment on that when you provide your answer.

DR. LEWIS: Okay. We're going to vote.

MS. BHATT: You have to read the question.

DR. LEWIS: Read the question again? Okay. That's okay. We don't need to read it again; read it ourselves. There we go. So we get to vote now.

(Vote taken.)

MS. BHATT: The voting results for number 6, yes is 14; no is 4; abstain is zero; and then we have 1 no voting.

DR. LEWIS: Dr. McBryde?

DR. McBRYDE: I reluctantly voted yes. I think overall the incidence of hyponatremia was low. It clearly showed dose-response curve, which would be expected. Lots of caveats. It's a short-acting drug. We were checking levels probably 12-14 hours after they really would have nadired their serum sodium, based upon the kinetics and the urine studies that they demonstrated. But overall, I think it's relatively low. I think the difference of about 120 milliliters of urine output between the placebo and the 1.5 microgram group is enough that over the course of the night, it saves them some nocturnal awakenings.

I'm still a little bothered that in a highly prevalent population such as African Americans, I don't really know what this drug does and if the benefits are going to be shared equally amongst the population at risk. Certainly, all the caveats, the people that I would consider to be the highest risks for hyponatremia, fluid retention disorders, were excluded. And I think that's something that really needs to be carefully carried forward in any labeling decisions so that the wrong populations don't get treated and have adverse events that would be foreseeable given the mechanism of action of the agent.

DR. LEWIS: Thank you. Dr. Coyne?

DR. JOFFE: One question. Can folks please be sure to also comment on the indication that you think is supported --

DR. LEWIS: Indication. Sorry.

DR. JOFFE: -- by your benefit-risk assessment.

DR. McBRYDE: Dr. Coyne.

(Laughter.)

DR. McBRYDE: So like many others, I'm a little uncomfortable with -- I'm fine with the greater than 2 episodes per night. I think the sponsor did a very nice job, and I don't think FDA really questioned that greater than 2 episodes are disruptive to quality of life.

I do come back to -- I'm not particularly comfortable with a general indication for nocturia. Overall, I think the population that was studied is not really all-comers, and I think if it was a general all-nocturia, I worry that at-risk population for more serious adverse events or higher incidence rates of adverse events would be treated.

So I'm going to slyly avoid giving a recommendation of what kind of an indication I would support, but I'm going to say I don't particularly like the one that was proposed.

DR. LEWIS: Thank you. Dr. Coyne?

DR. COYNE: I voted yes. I think the indication should be for -- kind of repeating myself a little bit, on nocturnal polyuria, which

is more restrictive than the study was done. Sometimes the government's unfair. And I think it also needs a number of restrictions reflecting all of their exclusion criteria. I think these are important groups that were eliminated that do account for a lot of nocturia that occurs, and it's not at all clear that the risk-benefit in that population would be appropriate.

I also think that there probably should be a statement that institutionalized patients are not eligible for this and encourage the company to do further study in this population. I would view that as a group at great risk of getting treated with this, possibly even more than once a day, which is going to be a fiasco. And that population, as best I understand, is not reflected in this ambulatory study that was done.

DR. LEWIS: Thank you. Dr. Erstad?

DR. ERSTAD: I voted yes, and as I stated earlier, it's not only the evidence of these two trials, but the cumulative evidence of desmopressin used for other conditions that somewhat allays my

adverse effect concerns. I do lean towards the labeling indication of nocturnal polyuria, and I'd require close follow-up monitoring for the elderly, obviously, those at least 65 years of age, but especially patients 85 years of age and older, to assess for symptomatic hyponatremia.

Finally, I agree with the contraindications and the warnings proposed in the REMS.

DR. LEWIS: Thank you. Dr. Neaton?

DR. NEATON: I voted yes. It was a difficult decision largely because of the risk side of the equation for reasons stated earlier, a short-term study, really, for a drug which is going to be used potentially for very long periods of time, and limited controlled data after 12 weeks, or no controlled data after 12-weeks.

As I said before, there are many, many studies which are done that associate responses like we see here in the placebo group to a placebo response, that are not a placebo response, that are basically regression toward the mean and classifying people appropriately for the indication

that you're trying to treat.

So if you're going to use two, get two right by repeatedly measuring it over some duration of time to kind of make certain the person really has nocturia; otherwise, choose a higher level, would be my advice.

DR. LEWIS: Thank you. Dr. Chancellor?

DR. CHANCELLOR: Yes. I voted yes for the indication of idiopathic nocturnal polyuria. I'm not enamored with the word "idiopathic" but that it will restrict and focus on that you should not use it for conditions for nocturnal polyuria such as heart failure, peripheral edema, apnea, poorly controlled diabetes.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: I was very impressed with the safety of SER 120 in a carefully selected population with frequent controlled follow-up. And I was very impressed that not any of the patients required hospitalization for hyponatremia, but I voted no. Also, I used the non-nasal drug in many pediatric patients and never had a significant

hyponatremia problem. I do think nocturia times 2 is too low. I would raise it to 3, realizing that a sophisticated physician can use it for 2, where it's really a significant clinical problem for that patient, off label.

I like the indication of primary nocturnal polyuria, but my concerns are -- and I don't know if they're entirely appropriate in this discussion, but I'm going to articulate them. Once approved, this will be misused by non-specialized physicians in the, quote, "real world," especially after TV ads that say, quote, "Do you have to get up at night to urinate? Ask your doctor about SER 120?" quote.

I think many of these physicians most likely will not properly screen the patients for correctable causes and exclusion criteria, and will not confirm their clinical diagnosis, and will not first try behavioral therapy, which obviously would be better if effective, and I realize it's often not effective, for solving the problem or improving the situation for some of the patients.

I also, as I said after the previous question, think the clinical effect is pretty trivial. I think that makes the benefit-to-risk ratio unsatisfactory. And I also suspect that patients will take this medication, and then not have a satisfactory effect. We've seen that in the data. And then they will take an extra dose, and then we've got more hyponatremia than we had in this carefully controlled, very well done study. And that concerns me.

I also, as I expressed earlier, have concern about untrained providers, and I'm concerned about enforcement of people who violate the standards and the labeling. And I wish the FDA had a mechanism to limit the use of medications where it is necessary, which I think it is for this one, for people to take an online training course before they can prescribe the medication.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: So I also voted no, although I thought I was voting on the broad indication of nocturia. So I agree with what many of the yes

people said so far, but I also think Dr. Howards really articulated my position, which is I am struck that I think there are rare serious side effects that will be magnified greatly if this is used in non-specialist hands and applied to a very, very large number of patients, particularly those that are very elderly and are at highest risk. So I can't support that.

I do think that actually the sponsors can probably do a better job of convincing us that there is a high-risk population, not only those that receive more absolute benefit, but those that actually have a greater relative benefit.

I think the analysis showing that those that had the most nocturia did not have a greater relative risk for reduction probably needs to be analyzed a little bit more carefully because I suspect that there may be subgroups that could be identified that are at very high risk -- excuse me, that derive more benefit from the drug. And therefore, it might be worthy to treat them even though we acknowledge that some are going to

develop serious side effects. So I'll leave it at that.

DR. LEWIS: Thank you. I voted yes, pretty much agreeing with most of the others who voted yes. I did think that it should be approved only for the indication of nocturnal polyuria. And while that also may be a diagnosis that will be misused, at least it is a diagnosis. And for those who are attempting to have some better way to distinguish who should be treated, and more importantly, whose serious conditions should be pre-identified such as uncontrolled diabetes, it serves us some mechanism to see that that would happen. I think that it also allows for better labeling in terms of what kinds of issues might be exacerbated by using the drug. That's my vote.

Dr. Drake?

DR. DRAKE: I also voted yes. I looked at the question quite literally, do the benefits of desmopressin outweigh the risks and support approval? So based upon the totality of the data we saw here, I think that that does meet the case.

I think it needs to be in a very narrow indication, really fitting with all the exclusion criteria.

Patients need to be screened and looked at very carefully up front. But in that specific population at the dose of 1.5, there probably is benefit. But I share similar concerns with what will happen once this medication -- if it were to go forward and is approved, how broadly it will be applied and how indiscriminately it will be used by providers. So I share those concerns, but taking the question literally, I do think that the benefits do outweigh the risks.

DR. LEWIS: Thank you. Dr. Smith?

DR. R. SMITH: Robert Smith. I voted yes. I feel that the benefits of desmopressin in this preparation outweigh the risks, and they support approval. And in the process of that, that's a narrow enough view that I'm almost punting, I feel, back to the FDA because I feel that -- I conclude that for the 1.5 microgram dose, if in the FDA's resolution of a plan for this and further consideration and discussing with the sponsor, they

can assure -- first of all, I think for the patient population, as described by the sponsor, by the DB3 and DB4 studies.

But I think that that approval would be contingent on the FDA and the sponsor coming up with a program that would assure appropriate patient exclusions, and I won't go through the list, that can assure adequate education and informing of prescribers so it's appropriately used.

I think if the FDA feels that the dose escalation strategy as described by the sponsor is appropriate and, in fact, the best strategy, then I think there should be strong consideration given to requiring further study of the 0.75 microgram dose before granting approval.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: I voted no. I note that I think a lot of the respondents are voting on the indication of nocturnal polyuria and not nocturia, which is fine. But I'm not sure how the FDA can approve that indication without an additional

clinical trial because that wasn't actually the population that was tested.

I voted no because, specifically, I'm concerned about the potential for this hyponatremia adverse event, particularly when it's prescribed outside the narrow range of patients that were included in these trials. And I have specific concerns about the REMS not being sufficient to exclude the high-risk patients. First, there's no mention of a boxed warning, and I really urge the FDA to include that if this drug is approved.

The REMS seem to focus on letters to potential prescribers, which I think of as an advertising strategy. That's not something that's going to restrict meaningfully the use of the drug. Certainly having a limitation that it be prescribed by specialists who've taken courses and that there be some accountability would be useful there.

Also, this idea that the monitoring is going to rule out all the extreme cases, I agree with earlier comments that it's not realistic to expect that kind of strict monitoring to take place in

practice. We saw even in this clinical trial, there were patients using steroids. There was a patient who showed up at the ER twice with hyponatremia who wasn't withdrawn even though she met the criteria for that trial.

Close to 1 in 6 patients are going to be below the normal range; at least in this trial 1 in 6 was below the normal range. So you have a risk the physicians are going to become acclimated to seeing those values and not take patients off the drug. So I think it should not be approved based on the existing data.

DR. LEWIS: Thank you. Ms. Berney?

MS. BERNEY: I voted yes for all of the reasons that I've heard. I do have reservations about the target group for this drug, and some of the reservations in fact that we just heard. But I also understand that any addition to the arsenal for people like me is a benefit.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: I voted yes based on what Dr. Joffe said when he restated the question, which

is how do you vote based on what indication you believe, because if this were the indication of nocturia, I would have voted no. But if the indication is idiopathic nocturnal polyuria, then I think the benefits outweigh the risks, and I would favor it. But if it's pure nocturia, I think that the risks would far outweigh the benefits, and I'd be very concerned.

DR. LEWIS: Thank you. Dr. Pavlovich?

DR. PAVLOVICH: Well, I voted yes, and I would say that I voted yes for nocturia. So that may be different than everyone else in the room, but to me, that's the population that was studied. It was statistically and clinically efficacious, extremely minimal risk. Patients get labs checked all the time, and they would be checked more often if this drug was approved. But compared to many drugs out there, this is not something that needs to be a controlled substance, far from it.

So I think that it would be nice to change the wording somewhat. That's probably not easy to do for all the reasons we've heard: idiopathic

nocturnal polyuria, urologic nocturia, I don't know. I mean, I think you're stuck with what you've got. And nocturia is what was studied, and nocturia was the symptom, and nocturia is what was improved. So I'll give it a thumbs up on that count. But if FDA can refine it in some way without having to do a large phase 3 study, then that's their prerogative.

DR. LEWIS: Thank you. Dr. Johnson?

DR. JOHNSON: Yes. This is Ted Johnson. I voted no. I believe that the risks outweigh the benefits in the oldest old and those with multiple comorbidities. I think the combination of a poorly adherent patient plus an inadequately educated provider is potentially dangerous. I have had people who have taken once-daily drugs, and on their own doubled them. A combination of a nighttime SER 120 with a morning SER 120 would be devastating.

I asked earlier about a number of people in the trial that were over the age of 85. I'm not sure how many there were. And I believe that if

you treat older patients with nocturia long enough over time, that they are highly at risk for developing exclusionary criteria during maintenance therapy. And I didn't really hear anything about a plan to reassess eligibility for the drug with long longitudinal follow-up.

DR. LEWIS: Thank you. Dr. Smith?

DR. A. SMITH: Ashley Smith. Interesting to follow the two perspectives just shared. I voted yes. I think that the benefits outweigh the risks and support approval for the 1.5 microgram dose. But specifically in the patient population studied, obviously there -- I think what we're hearing, and I agree with, is that there's a concern about messaging, and there's concern about communication, and that there's a concern about challenges related to how these drugs are going to be used by educational providers and also misused by patients potentially, which leaves the FDA in a very challenging situation around how to appropriately message and ensure that this would be used appropriately.

I think that the REMS strategy is going to be really important, but again also complex. I think a lot of people are identifying the idea of having nocturnal polyuria, or primary maybe nocturnal polyuria as one way of handling that. That's obviously an approach, but that's not how the study was designed. However, because of subgroups, one can actually look at that. And I don't know where the FDA can fall on that topic. But I think, really, the issue is messaging and wanting to make sure that this is not misused, and that, therefore, the few but very substantial adverse event possibilities would be mitigated.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: Walid Gellad. I voted yes. The risks can be mitigated, and the benefits are really important. I think the main issue is to make sure prescribers prescribe it only within the confines of the trial. So how do you do that? You can essentially do that with the indication, with a REMS, and to some extent, payers are going to do that.

But I was going to say, if I had to pick an indication, it would be for nocturnal polyuria for patients over the age of 50 who have not responded to lifestyle interventions or treatment of underlying conditions. If it's difficult from a regulatory standpoint because that's not what was studied, there are other options. One is to run another trial in that specific population. The other is to just go with nocturia as the indication, but I think with a very specific REMS, again, with the issue that you want to make sure prescribers are doing it within the confines of the trial. And you all are familiar with the kinds strictness around REMS, but it may be a very strict REMS, and in the case of an indication of nocturia, would be worthwhile.

I would consider a black box for hyponatremia only because -- not because it was that common, but because people have died from desmopressin or have had adverse events from desmopressin from higher doses, and physicians need to be aware of this. And I would also encourage

limitations on direct-to-consumer advertising from the sponsor.

DR. LEWIS: Thank you. Dr. Alexander?

DR. ALEXANDER: So one comment on overdosing -- and I'm glad that someone mentioned it because I wanted to earlier, but I didn't. I think that's a great point. If I think about how I use my nasal steroid, it's like 1, maybe 2, maybe 3 or 4 if it's a bad day. But I think one can design drug-device combinations that help to decrease the likelihood of this. And what I'm thinking about is whether it's possible to devise a metered-dose inhaler -- a metered-dose dispenser that has a lock-out essentially; so not just metered-dose but metered-dose -- but essentially, it would preclude you from taking a second meter dose within some period of time.

I thought that the argument to approve the 0.75 microgram titration label, even though some of you said that you didn't think it was efficacious, was just odd. I mean, why not approve a placebo then and have patients start on placebo, and then

go to 1.5 micrograms? So I didn't fully -- I guess I'm still not sold on that.

So with respect to this question, it feels me a little bit that there's a disproportion of focus on indications rather than age. I'm comfortable with a restriction to nocturnal polyuria, and I think it would improve the risk-benefit balance because it would bring the population in which the product is used in greater concordance with the population in which it was studied. But I don't know if that's going to fly or not for the sponsor, and that's for the sponsor and the FDA to figure out.

But from a public health perspective, I actually think age is going to be more operative than indication. And this is just a hunch. I don't have a lot of data to support it, other than that 91 percent of adverse events occurred among people who are over 65. But I just wonder whether age isn't going to be the more important mediator of the overall risk-benefit balance.

Age is also much easier for prescribers and

patients to get, and for the label to communicate than as indication; that is, it's much clearer for a product to be labeled among the non-elderly, and therefore, for it to be largely restricted to the non-elderly than it is for a product to be labeled for a population based on a specific indication. In other words, there's much more off-label use as a function of indication rather than age.

So I wonder about a label for non-elderly with moderate to severe nocturia. I don't disagree with the idea of 3 or more episodes, although that, again, is for the FDA and the sponsor to work out, or for the non-elderly with moderate to severe nocturnal polyuria.

DR. LEWIS: Thank you. Thank you, everyone.

At this point, we'll now proceed with closing remarks fro the FDA.

DR. JOFFE: I want to thank everybody for coming today and for giving some wise advice on a difficult NDA or marketing application. I will say I'm looking for an easy application, and they don't seem to coming knocking on our doors. And the ones

we think are easy often turn out to be complicated as well.

I would like to thank the entire advisory committee panel for your time and effort coming out here and for the wise advice. I'd like to also thank Dr. Lewis for being our chairperson, Kalyani Bhatt, our AC staff who helped with a lot of odds and ends behind the scenes; the same with Suresh Kaul, who's the team leader for this project and also has been involved behind the scenes.

Am I missing anyone? I think that's all. So the presenters, I thought both FDA and the sponsor had very good presentations, and it was a professional meeting, so good job. Thanks, everyone.

Adjournment

DR. LEWIS: Thank you all, We will now adjourn the meeting. Panel members, please remember to take all your personal belongings with you. The room is cleaned at the end of the day. Any material left on the table will be disposed of. And thank you all again.

(Whereupon, at 4:26 p.m., the meeting was adjourned.)