FDA Briefing Document

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

October 19, 2016

Agenda: *The committee will discuss the efficacy and safety of new drug application (NDA) 201656 (desmopressin), 0.75 mcg/0.1 mL and 1.5 mcg/0.1 mL nasal spray, submitted by Serenity Pharmaceuticals, LLC, for the proposed treatment of adult onset nocturia.*

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF BONE, REPRODUCTIVE AND UROLOGIC PRODUCTS

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 201656 to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Center for Drug Evaluation and Research

Division of Bone, Reproductive and Urologic Products,
Office of New Drugs

Introductory Memorandum

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20093

INTRODUCTORY MEMORANDUM

Date: September 21, 2016

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Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

To: Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

Subject: New Drug Application 201656 for desmopressin nasal spray
Advisory Committee meeting
October 19, 2016

Introduction:

The FDA has convened this advisory committee meeting to discuss the New Drug Application (NDA) submitted by Serenity Pharmaceuticals, LLC, for SER120 (desmopressin nasal spray), proposed for the treatment of adults with nocturia who awaken two or more times per night to urinate.

This introductory memorandum provides a brief overview of the issues we will discuss at the October 19, 2016, advisory committee meeting. More detailed information is included in the accompanying memoranda prepared by the FDA reviewers.

We look forward to an in-depth discussion of the issues, and will carefully consider the advisory committee's recommendations and advice before reaching a decision on the application. Thank you, in advance, for participating in this meeting and for your contributions to public health.

Background:

The Applicant is seeking approval of desmopressin nasal spray for the treatment of nocturia in adults. The proposed starting dose is 0.75 mcg (one nasal spray) 30 minutes before bedtime, which can be increased, if needed, to 1.5 mcg (two nasal sprays) nightly.

Desmopressin is a synthetic analog of vasopressin (antidiuretic hormone) that stimulates reabsorption of water in the kidney, leading to more concentrated urine and less water excretion.

Several desmopressin formulations, including a nasal spray formulation, are FDA-approved for the treatment of central diabetes insipidus, primary nocturnal enuresis in children, and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgery. There are no FDA-approved drugs indicated for the treatment of nocturia.

Nocturia is a symptom that can be caused by various underlying condition(s), some of which may co-exist in the same patient. Causes include edema-associated states (e.g., peripheral edema, congestive heart failure, nephrotic syndrome), sleep disorders (e.g., obstructive sleep apnea), neurodegenerative conditions (e.g., Parkinson's disease), poorly-controlled diabetes mellitus, diabetes insipidus, drugs (e.g., diuretics), excessive fluid intake, and idiopathic nocturnal polyuria (overproduction of urine at night). Intrinsic bladder conditions can also cause nocturia, such as bladder outlet obstruction (e.g., benign prostatic hyperplasia), bladder detrusor overactivity (overactive bladder), and low bladder capacity.

The desmopressin Phase 3 trials had extensive exclusion criteria, including diabetes insipidus, uncontrolled diabetes mellitus, congestive heart failure (New York Heart Association Class II-IV), polydipsia, uncontrolled hypertension, nephrotic syndrome, peripheral edema (>2+ pretibial edema on physical exam), history of urinary retention, neurogenic detrusor overactivity, obstructive sleep apnea, loop diuretics, glucocorticoids, and severe lower urinary tract symptoms due to benign prostatic hypertrophy, overactive bladder, or severe stress urinary incontinence.

In addition, the Phase 3 trials did not systematically assess whether a reduction in urine output at night could have adverse effects on other aspects of the underlying condition(s). For example, it is unclear whether daytime excretion of the retained nighttime water could exacerbate daytime frequency or urgency in patients with nocturia due to overactive bladder or benign prostatic hyperplasia. It is also uncertain whether a treatment that focuses on the symptom of nocturia, which is common to many conditions, could adversely impact timely diagnosis and management of the underlying condition.

The Applicant is proposing a broad, general indication for nocturia regardless of the underlying etiology. This is one area where we will be seeking advice from the advisory committee panel.

Efficacy Issues:

Study Designs: The Applicant conducted two randomized, double-blind, placebo-controlled, parallel-arm, Phase 3 trials (DB3 and DB4) to support the proposed dosing regimen. These trials were restricted to patients 50 years of age or older. During the phase 3 protocol development phase, the FDA advised the Applicant to limit enrollment to this older age group to better assess the risk of hyponatremia, a known side effect of desmopressin that is greater in older patients. At that time, the FDA did not envision an impact of this age restriction on the indication, but this will require further discussion with the advisory committee panel, as the Applicant is seeking an indication for nocturia in adults regardless of age.

To qualify for the trials, patients must have reported a six-month history of at least two nocturic

episodes per night, on average. In addition, they must have had at least 13 episodes of nocturia documented over six days in voiding diaries collected during the screening period.

After screening, there was a double-blind, two-week, lead-in period during which all patients received placebo. The purpose of this lead-in period was to identify placebo non-responders, defined as those with less than 50% reduction in the mean number of nocturic episodes per night compared to screening.

DB3 randomized patients to 0.75 mcg, 1.0 mcg, or 1.5 mcg of desmopressin nasal spray or placebo nightly. DB4 randomized patients to 0.75 mcg or 1.5 mcg of desmopressin nasal spray or placebo nightly. Both trials had a 12-week treatment period, during which patients periodically completed three-day voiding diaries. There were no restrictions on fluid intake during the trials.

Both trials had the following co-primary efficacy endpoints:

- Change from baseline in the mean number of nocturic episodes per night
- Percentage of patients with ≥50% reduction in mean number of nocturic voids per night

DB4, but not DB3, included a patient-reported outcome instrument known as the Impact of Nighttime Urination (INTU) Questionnaire as a secondary endpoint. The INTU was developed with input from the FDA to measure the impact of nocturia on daily living. The FDA's briefing documents include a memorandum by the Clinical Outcome Assessments Staff that provides a critique of the instrument's strengths and limitations.

The Applicant defined the intent-to-treat population (ITT) as all randomized patients with at least three days of post-randomization efficacy data. The modified intent-to-treat (mITT) population comprised about 70% of the ITT and was limited to those patients who were placebo non-responders during the two-week, placebo lead-in period. The Applicant specified the mITT as the primary statistical population for the key efficacy analyses in DB3. The FDA recommended the mITT also be used as the primary statistical population for DB4 because the treatment effect in DB3 was slightly greater for placebo non-responders compared to placebo responders, suggesting that an enrichment strategy could be useful. However, after both DB3 and DB4 were completed and the results were known, the FDA instead recommended that the Applicant focus on the ITT population, which is the typical primary statistical population for efficacy analyses. Because both trials randomized patients to the treatment arms regardless of placebo-responder status, the FDA views the mITT population as a subgroup analysis of placebo non-responders.

Co-Primary Efficacy Results: Only the 1.5 mcg dose of desmopressin was statistically superior to placebo on both co-primary efficacy endpoints.

With regard to the first co-primary efficacy endpoint, the 1.5 mcg dose in both DB3 and DB4, the 1.0 mcg dose in DB3, and the 0.75 mcg dose in DB4 resulted in statistically significantly greater reductions in the mean number of nocturic episodes per night compared to placebo. However, these mean changes were numerically small. For example, from a baseline of about three nightly nocturia episodes on average, there was a mean reduction of 0.3-0.4 episodes per night with the

1.5 mcg dose compared to placebo. The clinical significance of this finding is unclear.

Only the 1.5 mcg dose met the second co-primary efficacy endpoint of at least 50% reduction in mean number of nocturic voids per night compared to placebo, and it did so in both DB3 and DB4. In DB3, 52% given the 1.5 mcg dose vs. 33% given placebo met this endpoint ($p<0.001$). In DB4, 46% given the 1.5 mcg dose vs. 29% given placebo met the endpoint ($p<0.0001$).

Neither the 1.0 mcg dose in DB3 (the only trial that tested this dose) nor the 0.75 mcg dose in DB4 showed a statistically significant difference compared to placebo on this second co-primary endpoint. The FDA will not be reporting statistical testing of the 0.75 mcg dose in DB3 because the 1.0 mcg dose failed on its second co-primary efficacy endpoint, which stops further statistical testing based on the prespecified hierarchical testing procedure.

INTU Secondary Endpoint: The INTU Overall Impact score used as a secondary efficacy endpoint in DB4 has a range from 0 to 100, with higher scores indicating more severe impacts of nocturia. At baseline, the mean score was approximately 30. There was a 14-point reduction (improvement) in the INTU Overall Impact score for the 1.5 mcg group compared to a 12-point reduction with placebo. While both the 14-point and 12-point reductions appear meaningful to patients, the 1.5 mcg desmopressin dose decreased the INTU Overall Impact score by only 2.6 points more than placebo. This 2.6 point difference is statistically significant but of unclear clinical significance.

In summary, the Applicant is seeking approval of desmopressin for the treatment of nocturia. The Applicant is proposing a dosing regimen starting with desmopressin 0.75 mcg and uptitrating to 1.5 mcg, if needed. In the Phase 3 trials only the 1.5 mcg dose met all the prespecified statistical criteria for efficacy. However, the clinical meaningfulness of the treatment effects of the 1.5 mcg dose is unclear when compared to placebo, particularly for the mean change in nightly nocturic episodes and the impact on daily living. In addition, the appropriateness of a broad indication for nocturia regardless of the underling etiology requires further discussion.

Safety Issues:

Hyponatremia is the most important safety concern with desmopressin. Symptoms of hyponatremia include nausea, headache and lethargy. Seizures, coma and death can also occur, particularly if the hyponatremia is severe and acute. The incidence of hyponatremia was numerically higher with desmopressin than placebo, and numerically higher with the 1.5 mcg dose than with the 0.75 mcg dose. The incidence of hyponatremia with desmopressin was also numerically higher among those ≥65 years of age compared to those 50-65 years of age.

FDA's safety memorandum discusses the safety findings in detail.

If the advisory committee concludes that the Applicant has established substantial evidence of effectiveness for desmopressin, it will then need to assess whether those benefits outweigh the risks.

Draft Points to Consider:

1. The Applicant's trials limited enrollment to adults at least 50 years of age, had extensive exclusion criteria, and had no restrictions on fluid intake. Discuss whether the Applicant studied desmopressin in the appropriate patient population.

2. Discuss the clinical significance of the observed treatment effects of desmopressin on nocturia compared to placebo.

3. Discuss whether the safety of desmopressin has been adequately characterized, and whether additional safety data are needed.

4. 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 proposed broad 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, discuss what data would be needed to support the broad indication.

5. Is there sufficient evidence to conclude that at least one of the desmopressin doses is effective? (Yes/No/Abstain)

   Provide rationale for your answer. If you voted "Yes", specifically comment on which dose(s) are effective and whether the data support the proposed regimen of starting with 0.75 mcg nightly then titrating to 1.5 mcg nightly, if needed, after 2-4 weeks.

6. Do the benefits of desmopressin outweigh the risks and support approval? (Yes/No/Abstain)

   Provide rationale for your answer. If you voted "Yes," specify the indication that is supported by your benefit/risk assessment. If you voted "No," include recommendations for additional data that might support a favorable benefit/risk assessment.

Center for Drug Evaluation and Research

Division of Bone, Reproductive and Urologic Products, Office of New Drugs

Division of Biometrics III, Office of Biostatistics

Overview of Clinical Efficacy

B

1 Background

1.1 Brief Summary of Product Information and Development, and Meeting Objectives

The purpose of this advisory committee (AC) meeting is to review the efficacy and safety findings of SER120 (proposed trade name Noctiva) for the treatment of nocturia in adults who awaken two or more times per night to void.

SER120 is a nasal spray formulation of desmopressin, which is a synthetic analogue of the endogenous human antidiuretic hormone, vasopressin. Desmopressin's pharmacological effect is to stimulate reabsorption of water from the lumen of renal collecting ducts resulting in more concentrated urine and less water excretion. Intravenous, tablet, and higher dose nasal spray formulations of desmopressin are already approved by FDA for the treatment of central diabetes insipidus, primary nocturnal enuresis in children, and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgical procedures. None of the FDA-approved desmopressin products are indicated for the treatment of nocturia. The most significant risk of desmopressin is development of hyponatremia.

The Applicant developed SER120 with the goal of minimizing the incidence of hyponatremia. SER120 is a low-dose version of desmopressin that contains an excipient, cyclopentadecanolide (CPD). The Applicant asserts that CPD enhances the absorption of desmopressin across the nasal mucosa and allows for use of lower doses of desmopressin to achieve clinical effect. The recommended starting dose is one intranasal spray (i.e. 0.75 mcg) in one nostril 30 minutes before bedtime, which may be increased to 1.5 mcg (i.e. 2 sprays) each night depending on the treatment response and tolerability. This proposed dose regimen was not studied in any of the SER120 clinical trials.

1.2 Indication and Available Therapies

Nocturia is defined by the International Continence Society as the complaint that the individual has to awaken at night one or more times to void. To qualify as nocturia, each void must be preceded by and followed by sleep in an otherwise continent patient.[1]

Nocturia is a result of one of three pathophysiologic processes, acting alone or in combination:

1) *Polyuria* (increase in 24-hour urine volume): Causes include uncontrolled diabetes mellitus, diabetes insipidus, hypokalemia, medication side effects.

[1] Van Kerroebroeck, P., et. al., The Standardization of Terminology in Nocturia: Report from the Standardization sub-committee of the International Continence Society. *Neurourol and Urodynamics.* 2002; 00: 179-183.

2) *Nocturnal polyuria* (increase in nighttime urine production with a corresponding decrease in daytime urine production, resulting in a normal 24-hour urine volume): Nocturnal polyuria is defined as a nocturnal urine volume that exceeds 20% of the total 24-hour volume in adults younger than 35 years and 33% of the total 24-hour volume in adults older than 65 years.[2] Causes include excessive evening fluid intake, medications, and edematous states, such as congestive heart failure.

3) *Bladder storage problems*: Decreases in bladder compliance or changes in neuronal input can reduce the threshold volume for voiding, for example, in patients with overactive bladder (OAB), benign prostatic hyperplasia (BPH), or hypotonic bladder. [3]

The prevalence of nocturia increases with age with greater than two-thirds of men and women older than 70 years reporting one or more void per night.[4] A recent systematic review suggests that the annual incidence of nocturia is 12% among adults older than 60 years of age.[5]

Nocturia is a symptom of one or more underlying conditions or disease processes, and is not in-and-of-itself, a disease. Numerous clinical conditions are associated with the development of nocturia, including OAB, obstructive sleep apnea, diabetes mellitus, BPH, and edematous states such as congestive heart failure. Medications such as diuretics can also cause nocturia.[6]

Observational and cross-sectional studies have suggested a possible association between nocturia and sleep disruption, decreased quality of life, falls and fracture.[7,8]

In the United States there are currently no medications approved for the treatment of nocturia. Management focuses on treating the suspected underlying cause – for example, management of volume overload in a patient with congestive heart failure, and behavioral modifications (e.g. fluid restriction before bedtime). Desmopressin has been used off-label in some patients who do not respond to these measures.

Outside of the United States, in over 80 countries around the world, oral and sublingual formulations of desmopressin (trade names of Minirin® and Minirin Melt®, respectively) are approved for the symptomatic treatment of adults with nocturia associated specifically with nocturnal polyuria. The Minirin and Minirin Melt package inserts contain the following key information regarding use in patients with nocturia (location within the package insert depends on the country but the content is generally the same):

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[2] Van Kerrebroeck P, et. al., op cit.
[3] Cornu JN, Abrams P, Chapple CR, Dmochowski RR, et. al. A Contemporary Assessment of Nocturia: Definition, Epidemiology, Pathophysiology, and Management – a Systematic Review and Meta-analysis. European Urology 62 (2012): 877-890.
[4] Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol. 2013 Jan; 189 (1 Suppl): S86-92.
[5] Pesonen JS, Cartwright R, Mangera A, et. Al. Incidence and Remission of Nocturia: A systematic Review and Meta-analysis. Eur Urol. 2016 Aug; 70 (2): 372-81.
[6] Cornu, *op. cit.*
[7] Kari AO, Tikkinen TM, Johnson II, Tuevo L.J., et. al. Nocturia Frequency, Bother, and Quality of Life: How Often is Too Often? A population-based study in Finland. *European Urology*. 57 (3): March 2010, pp 488-498.
[8] Kurtzman JT, Bergman AM, et. al. Nocturia in women. Curr Opin Urol. 2016 Mar 10. Epub ahead of print.

- A frequency/volume chart should be used to diagnose nocturnal polyuria for at least 2 days and nights before starting treatment. Nocturnal polyuria is diagnosed when night-time urine production exceeds the functional bladder capacity or exceeds one-third of the 24-hour urine production.

- Serum sodium must be measured before beginning treatment and 3 days after dose initiation or dose increase.

- Use in the elderly is not recommended (*specific age threshold not provided*)

- In patients with urgency or urge urinary incontinence, an underlying cause should be identified and treated.[9,10]

1.3 Important Safety Issues with Consideration to Related Drugs

The most significant risk with desmopressin is the development of hyponatremia which, if severe enough, can result in seizures and death. The incidence of severe hyponatremia from desmopressin therapy is unknown. On December 7, 2007, the FDA issued an alert to inform healthcare professionals of the risk of severe hyponatremia associated with desmopressin use. This alert was based on postmarketing reports of hyponatremic seizures occurring predominantly in pediatric patients taking intranasal desmopressin for primary nocturnal enuresis. In addition to the alert, the FDA removed this indication from the currently marketed intranasal desmopressin formulations.

1.4 Pre-Submission Regulatory Activity

The Applicant opened an Investigational New Drug Application (IND) for SER120 in June 2008 with the Division of Reproductive and Urologic Products (now known as the Division of Bone, Reproductive and Urologic Products or DBRUP). The IND was transferred to the Division of Metabolism and Endocrinology Products (DMEP) in February 2009, and then transferred back to DBRUP in April 2014, where it has remained to date.

Initially, the Applicant conducted two identical phase 3 trials (DB1 and DB2). These were randomized, double-blind, placebo-controlled trials that investigated the safety and efficacy of a 0.5 mcg dose (which could be uptitrated to 0.75 mcg) administered nightly compared to placebo. The co-primary endpoints were the change from baseline to the last week of treatment (Week 7) in the mean number of nocturic episodes per night and the percentage of patients with a $\geq$ 50% reduction in mean number of voids per night. Both trials failed to demonstrate efficacy of SER120. There was no statistically significant difference between SER120 and placebo with respect to either co-primary endpoint.

[9]Minirin prescribing information. (n.d.) Retrieved from http://www.medsafe.govt.nz/profs/datasheet/m/Minirintab.pdf
[10]Ibid.

The Applicant next decided to investigate higher doses of SER120 for the treatment of nocturia. They conducted a new placebo-controlled trial (DB3) that evaluated three SER120 doses (0.75 mcg, 1.0 mcg and 1.5 mcg) compared to placebo. The co-primary efficacy endpoints were the change from baseline to the 12-week treatment period in the mean number of nocturic episodes per night and the percentage of patients experiencing a $\geq$50% reduction in the mean number of nocturic voids per night. To assess the clinical meaningfulness of the treatment effect, the Applicant added the Nocturia Quality of Life (NQoL) questionnaire as a tertiary efficacy endpoint. The FDA agreed with the co-primary endpoints, but stated that the NQoL instrument had deficiencies and would not support labeling claims and recommended that the Applicant instead develop a new patient reported outcome (PRO) instrument to measure the direct impact of nocturia. The Applicant decided to proceed with NQoL in DB3 and developed a new PRO for another trial, DB4.

Study DB4 tested two doses of SER120 (0.75 mcg and 1.5 mcg) and included a novel PRO instrument, the Impact of Night Time Urination (INTU) questionnaire, to measure the clinical impact of nocturia. The co-primary efficacy endpoints were the same as those used in study DB3, and the INTU was a secondary endpoint.

This memorandum will focus on the efficacy results from Study DB3 and DB4. The two failed earlier trials (DB1 and DB2) will not be discussed further.

2 Study Designs for the DB3 and DB4 Phase 3 Trials

DB3 and DB4 were randomized, double-blind, placebo-controlled, parallel group trials in adults aged 50 years of age and older with nocturia. During the phase 3 protocol development phase, the FDA advised the Applicant to only enroll patients at least 50 years of age in order to better assess the risk of hyponatremia, which is greater in elderly patients. At that time, the FDA did not envision an impact on the indication, but this will need further discussion at the advisory committee meeting as the Applicant is seeking an indication for adult-onset nocturia regardless of age.

The trial designs were nearly identical. Protocol features that differ are addressed in the relevant sections below. The primary objectives of the trials were to evaluate the efficacy and safety of SER120 for the treatment of nocturia.

The trials consisted of a two-week screening period, a two-week, double-blind, placebo lead-in period, and then a 12 week treatment period. During each week of screening, subjects were required to document the following information in a consecutive 3-day voiding diary:

1. Date and time subject went to bed with the intention of going to sleep
2. Time of subject's first nocturic void
3. Time subject woke up to start the day
4. Time of subject's first void after waking up to start the day
5. Total number of times urinated during the night

To qualify for study participation, patients must have reported a 6-month history of at least 2 nocturic episodes per night, on average. In addition they should have documented at least 13 nocturic episodes over six days, assessed using three-day voiding diaries collected during each week of the two-week screening period (for a mean of 2.16 episodes per night). The protocol defined a nocturic episode as a non-incontinent (non-bedwetting) urinary void of any volume that occurred at night during the patient's normal hours of sleep following an initial period of sleep and, thereafter, preceded and followed by sleep or an attempt to sleep.

After the two-week screening period, eligible subjects began the double-blind, two-week placebo lead-in period. All subjects administered placebo 30 minutes before bedtime each night and completed the 3-day voiding diary each week during this two-week period. The purpose of the lead-in phase was to identify placebo non-responders – defined as patients with less than 50% reduction in the mean number of nocturic episodes per night compared to screening.

Following the two-week placebo lead-in period, all subjects (both placebo responders and non-responders) were then randomized (regardless of responder status) to placebo or to SER120. Study DB3 evaluated three SER120 doses (0.75, 1.0 or 1.5 mcg); Study DB4 evaluated two doses (0.75 or 1.5 mcg). There were no restrictions on fluid intake during the trial. Study medication (SER120 or placebo, depending on randomization group) was taken nightly for 12 weeks. Subjects completed consecutive 3-day voiding diaries every week for the first two weeks of treatment (i.e., at weeks 3 and 4 of the trial) and then every two weeks thereafter until the end of the 12-week double-blind treatment phase (i.e., at weeks 6, 8, 10, 12 and 14).

In trial DB4, subjects also completed the Impact of Night Time Urination Questionnaire (INTU) each evening along with the 3-day voiding diaries during screening, and at treatment weeks 8 and 14. The INTU questionnaire consists of 10 questions categorized into day time (6 questions) and night time (4 questions) domains (see Appendix 1). Please refer to the memorandum by the Clinical Outcome Assessment staff, which discusses the INTU questionnaire in detail.

Follow-up clinic visits occurred every two weeks until the end of study at Week 14. A complete schedule of events for the trials is shown in **Appendix II**.

Key Entry Criteria for Both Trials
Inclusion criteria

1. Male or female subject ≥ 50 years of age.
2. Documented nocturia by history (≥ 2 nocturic episodes/night for at least 6 months)
3. Documented nocturia by diary administered for 3 days during each week of the 2-week screening period:
    a) Mean of ≥ 2.16 nocturic episodes/night or
    b) ≥ 13 total nocturic episodes
4. 24-hour urine output ≤ 57 mL/kg or up to 4500 mL/24 hours.
5. Normal serum sodium concentration
6. Serum triglycerides < 400 mg/dL

Reviewer's comment: The basis for the 24-hour urine output criteria are unclear and appear too liberal if the intent was to exclude polyuria.

Exclusion criteria for Both Trials

1. Nocturnal enuresis
2. Diabetes insipidus
3. Unstable diabetes mellitus
4. Congestive heart failure (New York Heart Association Class II-IV)
5. Polydipsia or thirst disorders
6. Uncontrolled hypertension
7. Unstable angina
8. Urinary retention (post-void residual > 150 mL) by medical history
9. Hepatic impairment
10. Renal impairment
11. History of syndrome of inappropriate secretion of anti-diuretic hormone (SIADH)
12. Nephrotic syndrome
13. >2+ pretibial edema on physical exam
14. Urinary bladder surgery or radiotherapy within the last 24 months prior to enrollment
15. Severe daytime lower urinary tract symptoms (LUTS) secondary to BPH, OAB or severe stress urinary incontinence. Daytime urinary frequency > 8 episodes per day by medical history or by 24 hour urine frequency/volume chart during screening
16. Females with unexplained pelvic masses or greater than stage II pelvic prolapse
17. Current or past malignancy (except cured basal cell carcinoma or squamous cell carcinoma of the skin), unless in remission for at least 5 years and with approval of the medical monitor
18. Urinary bladder dysfunction of neurologic etiology that in the judgment of the investigator would interfere with study assessments
19. Neurogenic detrusor overactivity
20. Obstructive sleep apnea
21. Hyperkinetic limb disorders
22. Work or lifestyle activities which interfere with night time sleep
23. Alcohol or substance abuse within 12 months of enrollment

Reviewer's comment: The protocols did not explicitly define "severe" daytime LUTS. The Applicant states that severe daytime LUTS is captured in exclusion criteria 1, 8, 15 and 16.

***Prohibited medications*:** Loop diuretics within the previous 6 months, systemic glucocorticoids, or any investigational drug within 30 days

Restricted medications (allowed only if on a stable dose for at least 2 months prior): α1-adrenoceptor antagonists, 5-alpha reductase inhibitors, anti-cholinergics and anti-spasmodics, sedative/hypnotic medications, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, nonsteroidal anti-inflammatory medications, and thiazide diuretics.

Key Efficacy Endpoints for Both Trials

The **co-primary efficacy endpoints** were the change from baseline to the treatment period in

- the mean number of nocturic episodes per night, and
- the percentage of subjects with a ≥50% reduction in mean number of voids per night.

Primary efficacy data were obtained from the consecutive 3-day voiding diaries that subjects completed during the trials.

Secondary efficacy endpoints in trial DB3 were the change between screening and the treatment period in

1) time from when the subject went to bed with the intention of falling asleep to first nocturic void (or first morning void in the absence of a nocturic void)
2) percentage of nights with 0 nocturic episodes
3) percentage of nights with ≤1 nocturic episodes
4) nocturnal urine volume

For diary derived efficacy endpoints (e.g., nocturic episode frequency), the baseline assessment was calculated using the three days of diary data collected during each of the two weeks of screening. A total of six diary days were required to determine the baseline value. The treatment period assessment was based on all diary data collected at weeks 3, 4, 6, 8, 10, 12 and 14.

In trial DB3, a minimum of three nights of diary data collection was required to determine the post-baseline assessment. There was no imputation for missing diary data. In trial DB4, three nights of diary data was required for at least one collection week during the treatment period, to determine the post-baseline assessment, with imputation for missing data using the multiple imputation approach. A sensitivity analysis was also conducted for the co-primary efficacy endpoints in DB4 without imputing for missing data.

In trial DB4, the first ranked secondary efficacy endpoint was the change between screening and treatment period in the INTU overall impact score. The change from baseline in the INTU score was calculated as the average of the INTU scores over six days during the treatment period (three days during Week 8 and three days during Week 14) compared to the average of the scores over the six days during screening. The subsequent secondary endpoints were the same as those listed above for trial DB3.

Statistical Analysis Plan for Both Trials

There were four analysis populations:

- ITT population -- all randomized subjects who had at least 3 days of post-randomization efficacy data recorded in their diaries and consisted of both placebo responders and placebo non-responders.
- Modified intent-to-treat (mITT) population -- all subjects in the ITT population who were placebo non-responders during the two-week placebo run-in period, and who had at least 3 days of post-randomization efficacy data recorded in their diaries for at least one visit.

- Evaluable population -- all subjects in the ITT population who completed the study without important protocol violations.
- Safety population – all subjects enrolled in the study who received treatment and had some post-randomization safety data.

The Applicant specified the mITT as the primary statistical population for the key efficacy analyses in studies DB3 and DB4. The mITT population was comprised of about 70% of the ITT population. The FDA agreed to the use of the mITT population as primary for protocol DB3. During the protocol design phase for study DB4, the FDA recommended the mITT as primary because in study DB3 the treatment effect was greater for placebo non-responders compared to placebo responders (-0.5 and -0.3, respectively), suggesting that an enrichment strategy could be useful. However, after the application was transferred to DBRUP, and after the trials were completed and results were known, the FDA recommended that the focus for both DB3 and DB4 instead be on the ITT population. The trials had randomized all subjects to SER120 or placebo, including subjects who were placebo responders. Randomization did not take into account the placebo-responder status. Therefore, upon reconsideration, the FDA views the ITT as more scientifically valid for the primary statistical population because it accounts for all subjects who were randomized and who had some post-randomization efficacy data, whereas the mITT is a subgroup analysis limited to placebo non-responders. The mITT and ITT results are similar, but for the reasons stated above, this memorandum will focus on the ITT results.

To protect the overall Type I error rate, the treatment dose groups were tested in sequential order with the highest dose compared to placebo first and only if this was successful (two-sided p-value was ≤ 0.05), would testing proceed to the next highest dose. Regardless of the outcome for the mITT population, the same hierarchical approach was used for the co-primary efficacy endpoints in the ITT population.

If both co-primary efficacy endpoints showed statistically significant results, the secondary efficacy variables were then analyzed. A hierarchical approach was used – if the first ranked secondary efficacy variable was tested and if it was successful, the second secondary efficacy variable was tested and so forth until a secondary variable did not achieve statistical significance.

For the first co-primary efficacy endpoint the treatment groups were compared using an Analysis of Covariance (ANCOVA). The model included the treatment group, study center, the stratification variables age (< 65 vs. ≥ 65 years) and gender (male vs. female), and a covariate, which was the baseline number of nocturic episodes. For the second co-primary efficacy endpoint, the treatment groups were compared using the Cochran-Mantel-Haenszel test stratifying by age group and gender.

3 Efficacy Results

As noted previously, Study DB3 also included a SER120 1.0 mcg treatment arm. Because the sponsor is not seeking approval of the 1.0 mcg dose, we focus only on the SER120 0.75 mcg and 1.5 mcg doses.

3.1 Subject Disposition

In the two pivotal trials, a total of 3565 subjects were screened, with 1707 ultimately enrolled. As shown in Table 1, the majority of subjects completed the trials although the completion rates were slightly lower in the SER120 groups. The primary reason for early discontinuation was the occurrence of an adverse event, the incidence of which was dose proportional.

Table 1. Summary of Subject Disposition in Trials DB3 and DB4

	DB3			DB4		
Status	**SER120 1.5 mcg**	**SER120 0.75 mcg**	**Placebo**	**SER120 1.5 mcg**	**SER120 0.75 mcg**	**placebo**
Randomized	186	188	188	266	270	270
Completed, n (%)	158 (85)	166 (88)	171 (91)	229 (86)	235 (87)	237 (89)
Discontinued, n (%)	28 (15)	22 (12)	17 (9)	37 (14)	35 (13)	33 (12)
Reason for discontinuation, n (%):						
Adverse event	15 (8)	11 (6)	9 (5)	18 (7)	17 (6)	15 (6)
Withdrawal of consent	10 (5)	7 (4)	5 (3)	11 (4)	13 (5)	12 (4)
Lost to follow-up	3 (2)	3 (2)	1 (1)	3 (1)	2 (1)	2 (1)
Other	0	1 (1)	2 (1)	5 (2)	3 (1)	4 (2)
Intent-to-treat population (ITT), n (%)	179 (96)	186 (99)	186 (99)	260 (98)	262 (97)	260 (96)
Modified ITT population, n (%)	131 (70)	137 (73)	133 (71)	196 (74)	197 (73)	193 (72)

3.2 Demographics

The majority of subjects in the ITT population were overweight white males older than 65 years of age (see Table 2).

Table 2. Summary of Demographics, Pooled from Trials DB3 and DB4 (Intent-to-Treat Population)

Demographic characteristic	SER120 1.5 mcg N=439	SER120 0.75 mcg N=448	Placebo N=446
Mean age (years)	66	66	66
<65 years, n (%)	201 (46)	203 (45)	202 (45)
≥65 years, n (%)	238 (54)	245 (55)	244 (55)
Mean Body Mass Index (kg/m^2), n (%)	30.0	29.2	29.5
Gender, n (%):			
Male	251 (57)	252 (56)	258 (58)
Female (post-menopausal)	181 (41)	189 (42)	177 (40)
Female (child-bearing potential)	7 (2)	7 (2)	11 (3)
Race, n (%):			
Caucasian	332 (76)	361 (81)	352 (79)
African American	60 (14)	41 (9)	60 (14)
Asian	11 (3)	8 (2)	7 (2)
Hispanic	32 (7)	33 (7)	23 (5)
Other	4 (1)	5 (1)	4 (1)

In terms of baseline nocturia severity, approximately 40% of subjects in the pooled DB3 and DB4 study populations had between two and three nocturic episodes per night, approximately 40% reported between three and four nocturic episodes per night, 14% reported between four and five nightly episodes and approximately 5.5% had more than five nocturic episodes per night.

At screening, the investigator provided or confirmed the probable etiology of nocturia based on medical history from the patient interview or a review of each subject's medical records. As shown in Table 4, in the majority of subjects, more than one etiology of nocturia was cited – e.g., BPH and nocturnal polyuria. In those in whom a single etiology was considered likely, nocturnal polyuria was most common.

Objective data were also obtained at screening to further clarify the etiology of the nocturia. A 24-hour urine collection was obtained from each subject during the screening period. Subjects with a calculated screening nighttime urine volume >33% of the total 24 hour urine volume were considered to have nocturnal polyuria. The majority of subjects had nocturnal polyuria by this criterion (see Table 3).

Table 3. Etiology of Nocturia, Pooled from Trials DB3 and DB4, Intent-to-Treat Population

	SER120 1.5 mcg N=439 n (%)	SER120 0.75 mcg N=448 n (%)	Placebo N=446 n (%)
Nocturia etiology (investigator assigned etiology)			
>1 etiology	263 (60)	297 (66)	299 (67)
Nocturnal polyuria alone	92 (21)	78 (17)	71 (16)
OAB alone	28 (6)	21 (5)	18 (4)
BPH alone	28 (6)	22 (5)	25 (6)
Unknown alone	26 (6)	27 (6)	33 (7)
Polyuria alone	2 (1)	3 (1)	0
Nocturnal polyuria (based on 24-hour urine collection during screening)			
Present	342 (78)	354 (79)	349 (78)
Absent	96 (22)	93 (21)	97 (22)

Source: FDA clinical reviewer analysis

3.3 Analysis of the Co-Primary Endpoints

First Co-Primary Efficacy Endpoint

SER120 1.5 mcg in DB3 and DB4, 1.0 mcg in DB3, and 0.75 mcg in DB4 resulted in a statistically significantly greater reduction in mean nightly number of nocturia episodes compared to placebo; however, these mean changes were numerically small. For example, from a baseline of about 3 nightly nocturia episodes on average, there was a mean reduction of 0.3-0.4 episodes per night with the 1.5 mcg dose compared to placebo (see Table 4). The clinical significance of these findings is unclear. The FDA's analysis which is shown in Table 5 is consistent with analyses performed by the Applicant.

Second Co-Primary Efficacy Endpoint

About one-third of subjects in the placebo arms in DB3 and DB4 had ≥50% reduction in nightly nocturia episodes. The percentage of subjects experiencing a ≥50% reduction in nightly nocturia episodes was statistically significantly greater for SER120 1.5 mcg than for placebo in both DB3 and DB4. The treatment difference between SER120 1.5 mcg and placebo in these responder rates was 17-19%. Neither the 1.0 mcg dose in DB3 nor the 0.75 mcg dose in DB4 showed a statistically significant difference compared to placebo with respect to this co-primary endpoint (see Table 4). Statistical testing of the 0.75 mcg dose is not reported in DB3 in accordance with the pre-specified, hierarchical testing procedure.

Table 4 Summary of Co-primary Efficacy Endpoints for Trials DB3 and DB4 (Intent-to-Treat Population)

		DB3			DB4		
	SER 120 1.5 mcg (N=179)	SER120 1.0 mcg (N=183)	SER120 0.75 mcg (N=186)	Placebo (N=186)	SER120 1.5 mcg (N=260)	SER120 0.75 mcg (N=262)	Placebo (N=260)
	First Co-Primary Endpoint: Mean Nocturic Episodes Per Night						
Baseline (SD)	3.2 (0.8)	3.3 (1.0)	3.4 (0.8)	3.3 (1.0)	3.3 (0.8)	3.3 (0.9)	3.3 (0.8)
Treatment period[1] (SD)	1.7 (0.9)	2.0 (1.1)	1.9 (1.1)	2.1 (1.1)	1.9 (1.1)	1.9 (1.0)	2.1 (1.0)
Change from baseline* (SE)	-1.6 (0.1)	-1.4 (0.1)	-1.4 (0.1)	-1.2 (0.1)	-1.5 (0.1)	-1.4 (0.1)	-1.2 (0.1)
Difference vs. placebo	-0.4	-0.2	-0.2		-0.3	-0.2	
95% CI	-0.6, -0.2	-0.4, 0	-0.4, -0.1		-0.4, -0.1	-0.4, -0.1	
p-value (vs. placebo)	<0.0001	0.04	N/A**		<0.001	<0.01	
	Second Co-Primary Endpoint: ≥50% Reduction in Nocturic Voids						
n/N (%)	93/179 (52%)	73/183 (40%)	77/186 (41%)	61/186 (33%)	120/260 (46%)	92/262 (35%)	74/260 (29%)
Absolute difference vs. placebo	19%	7%	8%		17%	6%	
P-value (vs. placebo)†	<0.001	0.16	N/A**		<0.0001	0.12	

Source: FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis
SD = standard deviation; SE = standard error; CI = confidence interval
1-- average of recorded diaries during the treatment period
* Change from baseline was calculated using an ANCOVA model.
† P-values from pair-wise comparisons vs. placebo using the Cochran-Mantel-Haenszel test.
**In keeping with the pre-specified statistical analysis plan hierarchical testing procedure, p-values are not reported for SER120 0.75 mcg in Study DB3 because the 1.0 mcg dose did not demonstrate statistical significance on both co-primary efficacy endpoints.

Sensitivity analyses that assessed the impact of missing data yielded results consistent with the primary efficacy analyses.

3.4 Analysis of Secondary Endpoints

Secondary endpoints for the 1.5 mcg dose are presented in order of rank according to the statistical analysis plans for protocols DB3 and DB4. Secondary efficacy analyses are not

presented for the 1.0 or 0.75 mcg doses. The 1.0 mcg dose did not meet both of its co-primary efficacy endpoints in DB3. The 0.75 mcg dose was not tested statistically in DB3 because of the failed 1.0 mcg dose, and did not meet both of its co-primary efficacy endpoints in DB4.

3.4.1 INTU

The aim of the INTU instrument was to assess the impact of nocturia on daily living, including restfulness, concentration, and level of emotional concern about needing to get out of bed to urinate. The contents, methodology, strengths and limitations of the INTU instrument are described in detail in the accompanying memorandum by the Clinical Outcome Assessments Staff. The INTU was only used in DB4; its overall impact score was the first ranked secondary efficacy endpoint in that trial.

The INTU's Overall Impact score ranges on a scale from 0 to 100. At baseline, the mean Overall Impact score was about 30. There was an observed 14-point improvement in the INTU Overall Impact score for the 1.5 mcg group versus a 12-point improvement with placebo. As discussed in the memorandum by the Clinical Outcome Assessments staff, both a 14- and 12-point change in INTU overall impact score may be meaningful to patients. However, SER120 1.5 mcg decreased the INTU Overall Impact score by only 2.6 points more than placebo. While this 2.6 point difference is statistically significant (see Table 5), it is unclear whether it represents an adequate separation that is clinically meaningful to patients.

Table 5. Secondary Efficacy Variable – Change from Screening to Treatment Period in the INTU Overall Impact Score in Trial DB4 (Intent-to-Treat Population)

	SER120 1.5 mcg (N=260)	Placebo (N=260)
Baseline Mean (SD)	34 (18)	32 (17)
Treatment Period Mean (SD)	20 (14)	21 (14)
Change from baseline*	-14	-12
Difference vs. placebo	-2.6	
p-value	0.02	

Source: FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis
* Change from baseline was calculated using an ANCOVA model.

3.4.2 Additional Secondary Efficacy Endpoints

Differences between SER120 1.5 mcg and placebo were statistically significant for all other secondary efficacy endpoints in both DB3 and DB4 (see Table 6). Compared to placebo, SER120 1.5 mcg increased the mean time from bedtime to first nocturic void by 0.6-0.7 hours (36-42 minutes), increased the percentage of nights with no nocturnal voiding episodes by approximately 5%, on average, increased the percent of nights with one or less nocturnal

episodes by 11-16%, on average, and decreased mean nocturnal urine voided volume by 108-134 mL.

Table 6. Summary of Secondary Efficacy Endpoints in Trials DB3 and DB4, Intent-to-Treat population

	DB3		DB4	
	SER120 1.5 mcg (N=179)	Placebo (N=186)	SER120 1.5 mcg (N=260)	Placebo (N=260)
Time from bedtime to first nocturic void (hours)				
Baseline Mean (SD)	2.4 (0.8)	2.3 (0.7)	2.4 (0.8)	2.5 (0.8)
Treatment Period Mean (SD)	4.3 (1.5)	3.5 (1.4)	4.1 (1.6)	3.6 (1.4)
Change from baseline*	1.9	1.1	1.8	1.2
Difference vs. placebo	0.7		0.6	
95% CI	0.5, 1.0		0.3, 0.8	
p-value (vs. placebo)	<0.0001		<0.0001	
Percent of nights with no nocturic episodes†				
Baseline Mean (SD)	0.1 (1.2)	0	0	0
Treatment Period Mean (SD)	11 (21)	6 (16)	10 (20)	5 (15)
Change from baseline*	12 (1)	6 (2)	10 (1)	5 (1)
Difference vs. placebo	6		5	
95% CI	2.2, 9.6		2.1, 8.6	
p-value (vs. placebo)	<0.01		<0.01	
Percent of nights with ≤1 nocturic episodes†				
Baseline Mean (SD)	2 (6)	1 (5)	1 (5)	1 (4)
Treatment Period Mean (SD)	49 (37)	35 (34)	44 (38)	34 (35)
Change from baseline*	48 (3)	33 (3)	45 (3)	34 (3)
Difference vs. placebo	16		11	
95% CI	8, 23		4, 17	
p-value (vs. placebo)	<0.0001		0.001	
Nocturnal urine volume (mL/night)				
N	156	173		
Baseline Mean (SD)	724 (319)	699 (297)	732 (384)	772 (370)
Mean Week 14 (SD)	500 (300)	608 (324)	466 (270)	597 (317)
Change from baseline*	-221	-114	-282	-148
Difference vs. placebo	-108		-134	
95% CI	-179, -40		-187, -81	
p-value (vs. placebo)	<0.01		<0.0001	

Source: FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis
*Change from baseline was obtained using an ANCOVA model

†For each subject, the percentage of nights with no nocturic episodes was calculated based on available diary data. These percentages obtained from all subjects in the same treatment group were applied to a regression model to obtain LS means for that treatment group. A similar analysis was used for subjects with ≤1 nocturic episodes.

3.4.3 Exploratory Efficacy Endpoints

The INTU questionnaire includes 10 items and two domains. Items 1, 2, 3, 4, 6, and 10 comprise the Daytime Impact domain while the remaining items form the Nighttime Impact domain (refer to Appendix I for individual item content and to the memorandum by the Clinical Outcome Assessments Staff). The Overall Impact Score is computed by taking the mean of the Daytime and Nighttime Impact scores.

The INTU Overall Impact score was a pre-specified secondary efficacy endpoint in study DB4; the individual INTU domain scores were exploratory endpoints. As shown in Table 7, the effect of SER120 appears greater on the nighttime domain than on the daytime domain, although when compared to placebo, the treatment differences for both domains are numerically small. These are exploratory analyses so no p-values are shown.

Table 7. Change from baseline to treatment period in INTU domain scores, Trial DB4 Intent-to-Treat

	SER120 1.5 mcg (N=260)	Placebo (N=260)
INTU Nighttime domain		
Baseline Mean (SD)	38 (21)	35 (20)
Treatment Period Mean (SD)	20 (17)	22 (17)
Change from baseline*	-18	-15
Difference vs. placebo	-3.4	
95% CI	-6.1, -0.8	
INTU Daytime domain		
Baseline Mean (SD)	31 (17)	29 (17)
Treatment Period Mean (SD)	20 (14)	21 (13)
Change from baseline*	-10	-9
Difference vs. placebo	-1.8	
95% CI	-3.9, 0.4	

FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis
*Change from baseline was obtained using an ANCOVA model

3.5 Additional Efficacy Analyses

3.5.1 Nocturnal Polyuria Sub-population

All subjects entering studies DB3 and DB4 were required to submit a 24-hour fractionated urine collection sample during screening to determine the number of daytime and nighttime voids and urine volume. When the calculated screening nighttime volume was greater than 33% of the total 24-hour urine volume, the subject was considered to have nocturnal polyuria.

Desmopressin is approved outside the United States for the treatment of nocturnal polyuria. Based on desmopressin's mechanism of action, the product theoretically may be more effective in treating nocturia due to nocturnal polyuria than due to other etiologies (particularly mechanical causes like OAB or BPH).

The FDA pooled the data from DB3 and DB4 and conducted post-hoc analyses of the two co-primary efficacy endpoints according to the presence or absence of nocturnal polyuria at screening (as defined by results from the screening 24-hour urine volume). Compared to placebo, the reduction in mean number of nocturic episodes was similar in those subjects with nocturnal polyuria (-0.2 to -0.3) and in those without nocturnal polyuria (-0.1 to -0.2). When examining the second co-primary endpoint, the response to SER120 was similar in the two populations, but the placebo response was larger in subjects without nocturnal polyuria (see Table 8). These are exploratory analyses so no p-values are shown.

Table 8. Post-hoc subgroup analyses of the co-primary endpoint in patients with and without nocturnal polyuria (defined by results from the 24-hour urine collection during screening), Trials DB3 and DB4, Intent-to-Treat population

	Nocturnal polyuria present				Nocturnal polyuria absent		
	SER120 1.5 mcg (N=342)	SER120 0.75 mcg (N=354)	Placebo (N=349)		SER120 1.5 mcg (N=96)	SER120 0.75 mcg (N=94)	Placebo (N=97)
Mean number of nocturic episodes							
Baseline (SD)	3.3 (0.9)	3.4 (0.9)	3.3 (0.9)		3.0 (0.7)	3.1 (0.8)	3.2 (0.8)
Treatment period (SD)	1.9 (1.1)	2.0 (1.1)	2.2 (1.1)		1.5 (0.9)	1.7 (0.9)	1.9 (1.0)
Change from baseline	-1.5	-1.4	-1.2		-1.5	-1.4	-1.3
Difference vs. placebo	-0.3	-0.2			-0.2	-0.1	
≥50% reduction in nocturic episodes (treatment vs. screening)							
n/N (%)	164/342 (48)	132/354 (37)	96/349 (28)		50/96 (52)	38/94 (40)	39/97 (40)
Difference vs. placebo	21	10			12	-0.4	

FDA clinical reviewer analysis

3.5.2 Exploratory responder analysis

To try and assess the clinical meaningfulness of the observed treatment effects with the SER 120 1.5 mcg dose, the FDA performed a post hoc responder analysis by mapping the observed nocturia episodes to the subject's end of study self-assessment of benefit compared to baseline. The end of study self-assessment was evaluated by the treatment benefit scale (TBS), which consisted of the following single-item question: "My condition (waking up at night to urinate) is now:" with five possible responses: "Much Better", "Somewhat Better", "Not Changed", "Somewhat Worse" and "Much Worse". As the TBS was only asked at the conclusion of treatment, there is potential for recall bias.

The TBS questionnaire was administered only in study DB4. Table 9 shows the percentage of each TBS outcome by treatment group. No subject in the study reported feeling "Somewhat Worse" or "Much Worse". Compared to placebo, 8% more subjects in the SER 120 1.5 mcg dose group reported feeling "Much Better."

Table 9: Summary of Treatment Benefit Scale Used in Trial DB4 (Intent-to-Treat population)

Outcome (n %)	Placebo (N=260)	SER120 0.75 mcg (N=262)	SER120 1.5 mcg (N=260)
Much Better	91 (35%)	96 (37%)	111 (43%)
Somewhat Better	97 (38%)	95 (37%)	96 (37%)
Not Changed	69 (27%)	66 (26%)	50 (20%)
Somewhat worse/ Much worse	0	0	0

FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis

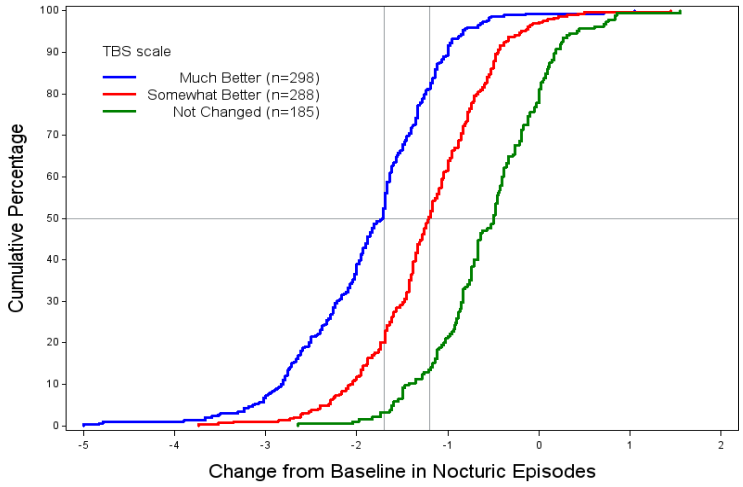
Data from all subjects in the ITT population in DB4 irrespective of treatment assignment were used to calculate cumulative distribution function (CDF) curves (see Figure 1). This plot has the change from baseline in nocturic episodes on the x-axis and cumulative percentage of patients on the y-axis. Three separate curves were generated based on the TBS response – one for subjects who reported being "Much Better", another for subjects who reported "Somewhat Better", and one for subjects who reported "Not Changed." The curves show the percentage of subjects in each of these categories who reached a particular threshold for change from baseline in nocturic episodes. For example, 50% of patients in the "Much Better" group had a 1.7 or greater mean reduction in nocturia episodes per night. In the "Somewhat Better" group, 50% of patients had a 1.2 or greater mean reduction in nocturia episodes per night. Therefore, a change from baseline in nocturic episodes in the range of -1.7 to -1.2 may be clinically meaningful.

The majority (10th percentile to 90th percentile) of subjects who felt "Much Better" had 1.0 to 2.8 fewer nocturic episodes per night during the treatment period compared to 0.4 to 2.1 fewer episodes per night in subjects who felt "Somewhat Better" and 1.4 fewer to 0.2 more episodes per night among subjects who reported "No Change".

As mentioned above, in the "Much Better" group, 50% of patients had a 1.7 or greater mean reduction in nocturia episodes per night. We categorized each subject in the ITT population – regardless of whether the subject had received SER120 or placebo – as a responder (if the mean reduction in nocturic episodes per night was at least 1.7) or non-responder (if the mean

reduction in nocturic episodes per night was less than 1.7 or if there was no change or a mean increase in nocturic episodes per night). Using this methodology, the responder rates were 50%, 20% and 3% in the "Much Better", "Somewhat Better" and "No Change" categories. Using 1.2 as the threshold, the responder rates were 81%, 50% and 14%, respectively (see Figure 1).

Figure 1.: CDF plot of change from baseline in nocturic episodes by TBS scale in Trial DB4 – all patients in the Intent-to-Treat population irrespective of treatment assignment



FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis

We next calculated the percentage of responders in DB4 separately for the SER120 1.5 mg group and placebo group. Specifically, we calculated the percentage of subjects in the SER120 group who had a mean reduction in nocturic episodes per night of at least 1.7, and calculated the corresponding percentage for the placebo group. We conducted similar analyses using the -1.2 threshold. These responder rates by treatment group in DB4 are shown in Table 10. This approach suggests that SER 120 1.5 mcg can benefit about 13% more subjects in reducing nocturic episodes compared to placebo. These exploratory analyses are shown only for DB4 because the TBS questionnaire was not administered in DB3.

Table 10. Summary of Responder Rates (defined based on TBS) –Trial DB4, Intent-to-Treat population

Change in Nocturic Episodes	Study DB4	
	Placebo	15 µg/mL
≤-1.7		
n/N (%)	60/260 (23%)	94/260 (36%)
≤-1.2		
n/N (%)	116/260 (45%)	150/260 (58%)

FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis

3.6 Efficacy Summary

- **SER120 is proposed as a treatment for nocturia in adults who awaken 2 or more times per night to void without respect to nocturia etiology. The appropriateness of studying a treatment for nocturia (which is a symptom, not a disease) without regard to underlying etiology is unclear. Although subjects with medical conditions associated with significant fluid overload, diuresis, or overt bladder dysfunction were excluded, subjects with other intrinsic factors that can contribute to nocturia (e.g., BPH or OAB) were allowed. Also, it is not clear how the cause(s) of nocturia were accurately determined in the enrolled patients. Enrollment of a heterogeneous population that is not well-defined may lead to the inclusion of conditions that may not respond to desmopressin, which may have diluted the overall treatment effect.**
- **The proposed starting dose is 0.75 mcg per night which may be increased to 1.5 mcg per night based on individual patient efficacy and tolerability. This proposed dosing regimen was not studied in any of the SER120 clinical trials. In addition, the SER120 0.75 mcg dose did not meet the prespecified statistical criteria for efficacy. SER 0.75 mcg should not be tested statistically in Study DB3 because the prespecified hierarchical testing stopped after the 1.0 mcg dose failed on one of its co-primary efficacy endpoints. In Study DB4, the 0.75 mcg dose was not statistically superior to placebo for one of its co-primary efficacy endpoints.**
- **On the advice of the FDA, the clinical trial population consisted of adults ≥50 years of age.**
- **In pivotal trials DB3 and DB4, SER120 1.5 mcg resulted in statistically significant improvements in both co-primary efficacy endpoints (change in nocturia episode frequency and percentage of patients with a >50% reduction in nocturia episode frequency) compared to placebo. Compared to placebo, SER120 1.5 mcg resulted in a mean reduction of 0.3-0.4 nocturic episodes per night over the 12 week treatment period, and approximately 19% more subjects experiencing a ≥50% reduction in nocturia episode frequency.**
- **In trial DB4, SER120 1.5 mcg reduced the INTU overall score from a baseline of about 30 by 2.6 points more than placebo – a statistically significant difference of unclear clinical significance given the score range of 0-100. The INTU was not assessed in trial DB3.**
- **During treatment, the percentage of nights with no nocturic episodes was 10-12%, on average, for subjects receiving SER120 1.5 mcg compared to 5-6%, on average, for placebo. The percentage of nights with ≤1 nocturic episode was 46%-50%, on average, in the SER120 1.5 mcg dose group versus 34-35%, on average, with placebo.**
- **Based on post hoc analyses, SER120 appears to have a slightly greater treatment effect on the INTU night time domain than on the daytime domain. The daytime domain assesses daytime symptoms that could be related to nocturia, but which could also be related to other comorbidities or psychosocial stressors.**

- **Post hoc analyses that explore the clinical meaningfulness of the treatment effect in trial DB4 suggest that SER 120 1.5 mcg may benefit 13% more subjects than placebo in reducing nocturic episode frequency.**
- **Post hoc analyses suggest that patients with nocturnal polyuria might have a slightly greater response to SER120 than those without nocturnal polyuria.**

3.7 Efficacy Conclusions

- **SER120 1.5 mcg demonstrated statistically significant reductions in nocturia with respect to both co-primary endpoints in both phase 3 trials, and for the key secondary – the INTU overall impact score – in the single phase 3 trial in which it was assessed. The clinical relevance of numerically small placebo-corrected changes is not clear.**
- **SER 0.75 mcg has not met the prespecified statistical criteria for efficacy in the treatment of nocturia.**
- **The Applicant did not study the proposed dose-titration scheme of initiating treatment at 0.75 mcg and titrating, as needed to 1.5 mcg. Instead the Applicant tested 0.75 mcg and 1.5 mcg in separate treatment arms.**
- **The Applicant is seeking approval for adults regardless of age; however, efficacy in subjects younger than 50 years of age has not been assessed.**

Appendix I

Questionnaire on the Impact of Nighttime Urination (INTU)®

Instructions: For each question, put a ✓ in the box that best describes how you have felt during the day. Complete this questionnaire in the evening before you go to bed.

Date Completed: ☐☐:☐☐☐:☐☐☐☐

DAY MONTH YEAR

Thinking over the day since you woke up:	Not at all	A little of the day	About half of the day	Most of the day	All day
Have you had difficulty concentrating?					
Have you felt tired?					
Have you had difficulty getting things done?					
Have you been irritable?					

Thinking about this evening:	Not at all	Somewhat	Quite a Bit	Very Much
Have you been concerned about having to get up tonight to urinate?				

Thinking about how you felt when you woke up this morning:	Not at all	Somewhat	Quite a Bit	Very Much
How rested did you feel this morning?				
Did getting up out of bed to go to the bathroom this morning cause you to start your day earlier than you would have liked?				
How difficult was it to get enough sleep last night?				
How bothered were you by having to get out of bed to go to the bathroom last night?				
How drowsy did you feel this morning?				

Appendix II

Schedule of Assessments for the Phase 3, Randomized, Double-blind, Placebo-controlled Trials DB3[1] and DB4

Assessments	Screening (2 Weeks from Enrollment)		Day 1 Visit	Day 15 Visit	Day 29 Visit	Day 43 Visit	Day 57 Visit	Day 71 Visit	Day 85 Visit	Day 99 (Study Exit) Visit
	(-) ≤ 2 Weeks	(-) ≤ 1 Week	Placebo lead in		Treatment period					
Informed Consent	X									
Inclusion/Exclusion	X	X	X							
Medical History [a]	X									
Night time fluid intake history	X									
Instruction on Completing and/or Review of Consecutive 3-Day Voiding diary[b]	X	X	X	X	X	X	X	X	X	X
Physical Exam		X								X
Nasal Exam		X								X
Rectal Exam (only on male patients)		X								
Height		X								
Vitals		X	X	X	X	X	X	X	X	X
Weight		X								X
12-Lead ECG		X								X
Pregnancy Test (for females of child bearing potential)		X	X[c]							X[c]
CBC, Serum Chemistry, Urinalysis		X								X
24-Hour Fractionated Urine Collection/Frequency Chart [d]		X								X
Serum Sodium	X									
Serum Sodium & Serum Osmolality			X	X	X	X	X	X	X	X[f]
Enrollment			X							
Study Medication Dispense, Collection and Compliance Assessment [e]			X	X	X	X	X	X	X	X

Assessments	Screening (2 Weeks from Enrollment)		Day 1 Visit	Day 15 Visit	Day 29 Visit	Day 43 Visit	Day 57 Visit	Day 71 Visit	Day 85 Visit	Day 99 (Study Exit) Visit
	(-) ≤ 2 Weeks	(-) ≤ 1 Week								
Review of PRO - Questionnaire on the Impact of Night-time Urination (INTU) [g]		X	X				X			X
Treatment Benefit Scale (TBS)										X
Adverse Events/Intercurrent Illness	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X

1 – schedule shown is for Trial DB4 but is essentially identical for study DB3 with the exception of review of the INTU PRO.
[a] PI to provide or confirm probable etiology of nocturia
[b] Patients were instructed to maintain a consecutive 3-day voiding diary each week for 2 weeks during the screening period. Prior to enrollment, site study personnel reviewed patients' diaries to ensure that they met eligibility criteria. Following enrollment, patients were instructed to complete a consecutive 3-day voiding diary during Weeks 1, 2, 3, 4, 6, 8, 10, 12 and 14. Study personnel reviewed the diaries
at each of the study visits.
[c] Urine pregnancy test results must be negative on Day 1 for patients to be eligible for the study.
[d] One 24-hour fractionated urine collection with time of collection and urine volume recorded for each void at screening and on one day during Week 14 prior to Day 99 visit.
[e] A new bottle of study medication was dispensed on Days 1, 15, 29, 43, 57, 71 and 85. The used study medication bottle dispensed at the previous visit was collected and weighed on Days 15, 29, 43, 57, 71, 85 and 99 to assess for study drug compliance.
[g] the INTU questionnaire was completed during screening week -2 and -1, week 8 and week 14.

Center for Drug Evaluation and Research

Clinical Outcome Assessments Staff, Office of New Drugs

The Impact of Nighttime Urination (INTU) Instrument

C

1 Introduction and Background

Desmopressin acetate nasal spray (SER120 nasal spray formulation; hereinafter referred to as SER120) has been developed as a treatment for nocturia. During clinical development, the Applicant proposed an existing patient-reported outcome (PRO) instrument (Nocturia Quality of Life Questionnaire) for inclusion in their phase 3 trial; however, the FDA concluded that this instrument was not fit-for-purpose to assess the impacts of nocturia on daily living. Therefore, the Applicant, with advice from the FDA, developed the Impact of Nighttime Urination (INTU) instrument for use as the first key secondary endpoint in one of their phase 3 clinical trials (SPC-SER120-DB4-201301; hereinafter referred to as DB4 clinical trial) to support the efficacy assessment of SER120.

This memorandum, prepared by FDA's Clinical Outcome Assessments (COA) Staff, provides a description of the INTU instrument, a summary of available evidence on its content validity, psychometric properties and performance, and a high-level overview of the INTU-related efficacy results for the DB4 clinical trial. See the Clinical Efficacy memorandum by the Division of Bone, Reproductive, and Urologic Products for further details.

2 Summary of INTU Review

The findings from the Applicant's qualitative research support the assertion that nocturia affects multiple aspects of patients' lives and identify the key impacts associated with nocturia (e.g., feeling tired, inadequate sleep).

The Applicant used the INTU's Overall Impact score (computed by taking the mean of the Daytime and Nighttime Impact domain scores) as their first key secondary endpoint in their DB4 clinical trial. The Nighttime Impact items in the INTU measure the intensity or severity of sleep-related impacts of nocturia on patients' lives, which are likely more sensitive to change with treatment than the Daytime Impact items, which measure more distal impacts on patients' lives (e.g., irritability, difficulty concentrating, difficulty getting things done). These distal concepts included in the Daytime Impact domain could be impacted by factors other than nocturia (e.g., other comorbidities or psychosocial stressors) that increase variability ("noise") in the INTU Overall Impact score and lead to insensitivity of the endpoint in detecting a treatment benefit.

When the Applicant examined the INTU items' descriptive statistics in a two-week observational study, they found that a number of items showed floor effects (a floor effect is when a high percentage of patients select the least severe response option, i.e., "Not at all") indicating that some of the items were not relevant to, or experienced by, many of the patients. With the exception of the item assessing whether patients "felt tired," the items showing floor effects did not appear to be among the most frequently-reported impacts of nocturia from the qualitative research with patients. The floor effects indicate that a significant proportion of the patients are not experiencing those particular nocturia impacts and, therefore, would not be able to show improvement on those impacts. These items should have been dropped from the INTU instrument; however, the Applicant did not make any modification to the INTU items based on these floor effects.

The Applicant believes that the floor effects seen for some of the INTU items in the two-week observational study were due to inclusion of less severe patients in that study. However, based on FDA's analysis, it appears that floor effects are also present in the DB4 clinical trial data for the same items.

In order to examine the sensitivity of the INTU items to detect treatment effects, the FDA conducted an exploratory analysis evaluating the change in raw (non-transformed) INTU item responses from screening to treatment. The results from this exploratory analysis are consistent with our assessment that the Nighttime Impact items appear to be more sensitive to change than the Daytime Impact items. If the product can be approved, our findings may have implications for potential labeling claims using the pre-specified INTU Overall Impact score, which includes some Daytime Impact items that have floor effects and appear to be insensitive to change. As with any composite score, we strongly recommend evaluation of the drug effect on each domain contributing to the overall score. It would be misleading to report study results on only the overall score, if it were driven by only one of the two domains.

The results of the INTU instrument's psychometric properties and performance analyses (i.e., internal consistency, test-retest reliability, convergent validity, and known-groups validity) from both the two-week observational study and DB4 clinical trial data appear acceptable and consistent across studies. In addition, based on FDA-requested post-hoc analyses, the Applicant found that the INTU appears to be able to detect a change in scores over time for groups differing in severity of nocturia. However, it remains unclear why some items with high floor effects were retained in the INTU instrument. It is likely that the INTU's ability to detect change could have been improved if the items with floor effects were omitted.

Interpreting the efficacy findings from the DB4 clinical trial is challenging because there was no *a priori* specified threshold for a meaningful change in INTU Overall Impact scores for use with the phase 3 data. Small changes in PRO endpoint scores can be statistically significant but not necessarily clinically meaningful. Both clinical and statistical significance should be demonstrated. Also, given that the INTU instrument was included only in a single pivotal trial, 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.

In order to help determine what constitutes a clinically meaningful change in INTU Overall Impact scores, the FDA requested that the Applicant generate post-hoc cumulative distribution function (CDF) plots using a number of scales as anchors (e.g., the patient global impression of change (PGI-C) item and reduction in nocturic episodes) from their two-week observational study and from their DB4 clinical trial. The results of these anchor-based analyses and CDF plots provide support that improvement in the INTU Overall Impact change scores is consistent with the changes seen in the anchor scale categories.

While the INTU instrument was deemed acceptable for inclusion as a key secondary endpoint in the DB4 clinical trial, the FDA cautions against its continued use, without modification to the items, in future drug development programs as it may have floor effects for some of the items leading to its insensitivity in detecting treatment effects. Also, there is concern with using paper data for a daily diary with no time and date stamp; back-filling of data by patients may introduce

recall error and potentially lead to inaccurate data, unlike with the use of electronic modes of administration. In addition, a threshold for meaningful improvement in impacts of nocturia relies on the assumption that the current INTU instrument is fit-for-purpose. Given the large floor effects of several of the items in the INTU, the current instrument would benefit from modification (e.g., through removal of items of lesser relevance and re-evaluation of the domain structure), if it will be used in future drug development programs.

3 Development of the Impact of Nighttime Urination (INTU) Instrument

The INTU instrument includes 10 items and is administered as a pen-and-paper instrument (Table 1). The aim of the INTU instrument is to assess the impact of nocturia on daily living, including impact on restfulness, concentration, and level of emotional concern about needing to get out of bed to urinate. The first four items ask patients to think back over the day since awakening and evaluate the frequency with which they experienced difficulty concentrating, feeling tired, difficulty getting things done, and irritability. These items are assessed using a five-point response scale ranging from "Not at all" to "All day." Item 5 asks patients to think about the evening and report their level of concern with having to get up "tonight" to urinate. The final five items, items 6-10, ask patients to think about how they felt when they awoke and assess their level of concern regarding feeling rested, having to get up at night to urinate, starting the day earlier because of having to get up to go to the bathroom, difficulty getting enough sleep, feeling bothered by getting out of bed to go to the bathroom, and feeling drowsy. These items are assessed using a four-point response scale that ranges from "Not at all" to "Very Much."

FDA's comments: The Applicant used a paper-and-pen mode of administration for the INTU instrument. When appropriate and feasible, the FDA recommends electronic data capture for daily diaries, using a device with a reminder or alarm function to minimize the extent of missing data and potential back-filling of data by patients. The concern with paper data is that there is no time and date stamp, as with an electronic mode of administration; back-filling of data by patients would introduce recall error and potentially lead to inaccurate and/or "noisy" data.

Each item in the INTU was transformed to a scale ranging from 0 to 100 points. The transformation was done by changing the range of scores to have zero as the lowest response category, dividing by the value of the highest response category, and multiplying by 100.

These transformed scores were then used to generate domain scores (i.e., subscores that in the case of the INTU instrument are combined to calculate an overall score) and a total score (i.e., Overall Impact score). The domain scores were calculated by averaging the transformed item scores for each domain after any necessary reverse-scoring (i.e., item 6 ["How rested did you feel this morning?"]), so that higher scores for the INTU indicate more severe impacts of nocturia.

The Overall Impact Score was computed by taking the mean of the Daytime and Nighttime Impact scores:

- INTU Daytime Impact score: Items 1, 2, 3, 4, 6, and 10
- INTU Nighttime Impact score: Items 5, 7, 8, and 9
- INTU Overall Impact score: Mean of Daytime Impact and Nighttime Impact Scores

$$Transformed \quad Scale \quad Score = \left[\frac{Actual\ Raw\ Score - Lowest\ Possible\ Raw\ Score}{Possible\ Raw\ Score\ Range} \right] \times 100$$

<u>FDA's comments</u>: The Applicant did not provide an *a priori* conceptual framework for the INTU instrument's domain structure (daytime versus nighttime domains) based on qualitative research with patients or clinicians. If this instrument is used in future trials, it seems appropriate to also consider a single overall score (without the use of domain scores) that includes only the most relevant and important items based on qualitative and quantitative research.

If the INTU instrument is unidimensional, it may be inappropriate to average the domains before calculating the Overall Impact score. Therefore, the FDA requested that the Applicant recalculate the Overall Impact score by taking the mean of all 10 transformed items (without taking into account separate domains) to compare with the original transformed scores. These scoring algorithms did not differ much; the alternate calculation supports the pre-specified efficacy analysis results.

Table 1. INTU Instrument

Questionnaire on the Impact of Nighttime Urination (INTU)©

Instructions: For each question, put a ✓ in the box that best describes how you have felt during the day. Complete this questionnaire in the evening before you go to bed.

Date Completed: ☐☐:☐☐☐:☐☐☐☐

DAY MONTH YEAR

	Thinking over the day since you woke up:	Not at all	A little of the day	About half of the day	Most of the day	All day
Item 1.	Have you had difficulty concentrating?					
Item 2.	Have you felt tired?					
Item 3.	Have you had difficulty getting things done?					
Item 4.	Have you been irritable?					

	Thinking about this evening:	Not at all	Somewhat	Quite a Bit	Very Much
Item 5.	Have you been concerned about having to get up tonight to urinate?				

	Thinking about how you felt when you woke up this morning:	Not at all	Somewhat	Quite a Bit	Very Much
Item 6.	How rested did you feel this morning?				
Item 7.	Did getting up out of bed to go to the bathroom this morning cause you to start your day earlier than you would have liked?				
Item 8.	How difficult was it to get enough sleep last night?				
Item 9.	How bothered were you by having to get out of bed to go to the bathroom last night?				
Item 10.	How drowsy did you feel this morning?				

Note: FDA added in item numbers.

In the DB4 clinical trial, the Overall Impact score was pre-specified as the first key secondary endpoint to document the impact of nocturia on patients' daily lives.

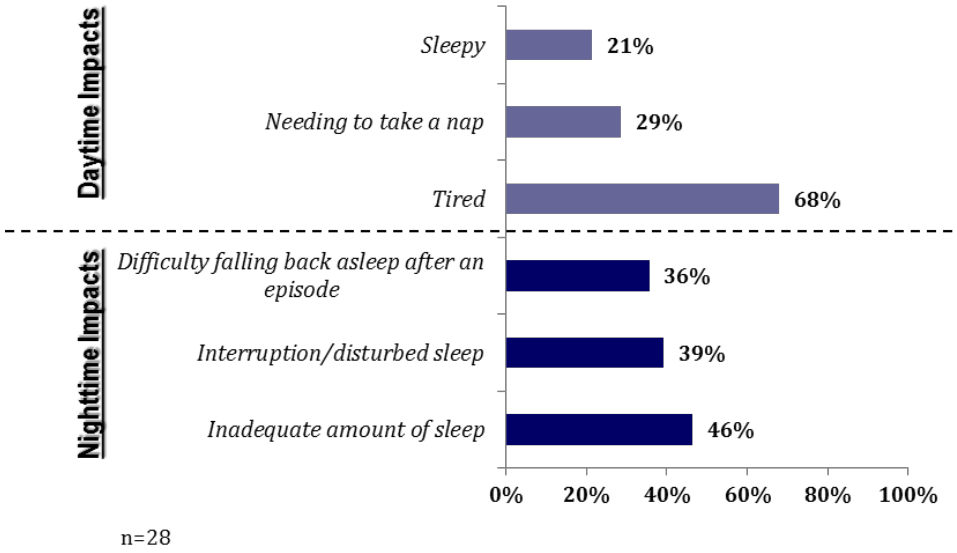
4 Documentation of Content Validity of the INTU Instrument

In line with recommendations from the FDA's PRO Guidance for Industry,[1] the INTU instrument was developed using a qualitative approach. The Applicant's qualitative research consisted of a systematic review of published literature and input from patients with nocturia (one-on-one qualitative interviews). The qualitative sample of 28 English-speaking patients from four United States (U.S.) sites appears to be representative of the DB4 clinical trial patient population. Within the qualitative sample, 50% were men with a mean age of 64 years (SD 8, range 52-79 years) and a mean of 3 nocturia episodes per night (SD 1, range 2-5). The majority of patients were Caucasian (*n*= 21/28, 75%), and the remaining ethnic groups were African American/Black (*n*= 3/28, 11%), Hispanic (*n*= 2/28. 7%), and Asian (*n*= 2/28. 7%).

The patient interviews were conducted in-person and combined both concept elicitation and cognitive debriefing elements; patients were asked both open-ended questions, targeted at eliciting the relevant and important impacts of nocturia, as well as targeted questions about the PRO items and response options to ensure that the questions were understandable and that the response options made sense and were meaningful to the patients.

Based on spontaneous input from the concept elicitation interview segment, the three most frequently reported nighttime and daytime impacts associated with nocturia are summarized in Figure 1.

Figure 1. Most frequently reported impacts of nocturia



The Applicant created item tracking matrices from each of the four rounds of the interviews (seven patients in each of the four rounds) from four different U.S. sites. The item tracking

[1] US Food and Drug Administration. Guidance for Industry—Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Silver Spring, MD: Food and Drug Administration, 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

matrices documented any deletion, addition, or modification made to the items or response options included in the instrument, along with documentation of the rationale for the changes to the instrument based on the patient interview data.

FDA's comments: The findings from the Applicant's systematic literature review and concept elicitation/cognitive interviews support the assertion that nocturia affects multiple aspects of patients' lives and identify the key impacts associated with nocturia (e.g., feeling tired, inadequate sleep). In general, patients appear to understand and interpret the final INTU instructions, item stems, response options, and recall period appropriately.

We have the following general comments about the INTU items:

- **In general, the Nighttime Impact items measure the intensity or severity of sleep-related impacts of nocturia on patients' lives and appear likely to be sensitive to treatment effects. However, item 5 ("have you been concerned about having to get up tonight to urinate?") appears to relate to patients' feelings of concern (or worry) about the future, which might be based on the feelings encompassed by items 7, 8, and 9 relating to how the patient felt when they awoke in the morning (i.e., whether they had to start their day earlier than they would have liked due to getting up to urinate, having a difficult time getting enough sleep the prior night, and how bothered they felt by having to get out of bed to urinate the prior night). Items which assess patients' feelings of concern and worry about the future are most likely related to their previous experience and may not be indicative of, or sensitive to, treatment effects. Furthermore, five of the seven (71%) patients in Round 1 and six of the seven (86%) patients in Round 2 of the qualitative interviews stated that an item asking about their worry about having to get up to urinate is not relevant to their experience. Based on the first round, we would have dropped the item from the questionnaire; however, the Applicant changed the wording from "worried" to "concerned" based on patients' suggestions in Round 2 and tested it in Rounds 3 and 4 where four of the seven (57%) patients in each respective round stated that this item was relevant to their experience with nocturia.**

- **Some of the Daytime Impact items appear to be less common (see below) and less direct impacts on patients' lives (i.e., ability to concentrate, get things done, and level of irritability), which are less likely sensitive to treatment effects and could be impacted by factors other than nocturia (e.g., other comorbidities, psychosocial stressors). While the emotional and physical concepts covered by Daytime Impact items 2, 6, and 10 (i.e., feeling tired, feeling rested, and feeling drowsy) appear to overlap conceptually, a large number of patients in qualitative research (68%) endorsed the concept of tiredness during the day, which supports the inclusion of one, or perhaps more than one item, assessing this concept.**

  Based on the qualitative patient interviews, item 1 (difficulty concentrating) was not highly endorsed by patients; four of the seven (57%) patients in Round 1, three of the seven (43%) patients in Round 2, and six of the seven (86%) patients in Round 3 reported this item was not relevant to their nocturia, but this item was retained by the Applicant for testing in Round 4 and found to be relevant to those patients. In addition, item 3 (difficulty getting things done) was not highly endorsed; four of the seven (57%) patients in Round 1, four of the seven (57%) patients in Round 2, and five

of the seven (71%) patients in Round 3 felt that this item was not relevant to their experiences with nocturia. However, the Applicant retained the item for testing in Round 4 and found that six of the seven (86%) patients stated that this item was relevant to their experiences. Only Round 4 patients endorsed "irritability" as a daytime impact of nocturia. In summary, there was greater endorsement of the more distal or indirect impacts of nocturia by the Round 4 patients compared to the previous three rounds of patients. The reason(s) for this are unclear.

Inclusion of some of these Daytime Impact items may increase variability ("noise") in the INTU Overall Impact score and impair the interpretability of any treatment effect. Sections 5.1 and 5.2 below include information about the floor effects observed for some of the INTU items.

After review of the patients' transcripts from the interviews, we found the following patient input worthy of mention:

- **Patients' interpretation of meaningful change in number of nocturnal voids: Interviewers asked 21* patients whether decreasing the number of nocturic episodes by one episode per night would have a meaningful impact on how they feel and function.**
  - **10/21* patients (48%) stated that decreasing the number of nocturic episodes by one episode per night would be a "good night" or make a significant difference to them.**

- **Patients' interpretation of the INTU response options:**
  - **7/21* (33%) patients could not differentiate between the response options "quite a bit" and "very much," and 5/21* (24%) patients could not differentiate between the response options "most of the day" and "all day." Most of these patients suggested eliminating the "very much" and "all day" response options given that they were synonymous with "quite a bit" and "most of the day," or irrelevant as they would never select them. Therefore, a 1-category change moving from "very much" to "quite a bit" or moving from "all day" to "most of the day" may be less meaningful than a 1-category change from "quite a bit" to "somewhat" or from "most of the day" to "about half of the day."**

***Note: The final response options were only tested in 21 patients (rounds 2-4).**

5 Psychometric Properties and Performance of the INTU Instrument

5.1 Observational Study: Psychometric Evaluation of INTU

The Applicant conducted a two-week multicenter, U.S.-based, prospective, interventional (behavioral modification), observational study to psychometrically evaluate the INTU instrument in 193 patients with clinically-confirmed nocturia. During week 1, patients were given a three-day voiding diary (to be completed during the mornings of days 4, 5, and 6) and three INTU instrument forms (to be completed during the evenings of days 4, 5, and 6). On Day 8 (first day

of week 2), patients completed a patient global impression of change (PGI-C) scale, which asked the patients to rate the change in their nocturia symptoms over the past 7 days of the study.[2] On Day 8, patients also received three more voiding diaries and INTU instrument forms to complete during week 2 (voiding diaries were to be completed in the mornings of days 11, 12, and 13 and INTU instruments were to be completed during the evenings of days 11, 12, and 13). For the behavioral modification intervention, patients qualifying for the week 2 assessment period[3] were instructed to maintain normal fluid intake until 8:00 PM and stop fluid intake from 8:00 PM until the start of the next day. During the final visit (day 15), patients were asked to complete another PGI-C scale and other questionnaires.

All patients who met the inclusion and exclusion criteria and who completed the INTU instrument at least one of the days (4, 5, or 6) in week 1 **and** at least one of the days (11, 12, and 13) in week 2 were included in the cross-sectional analysis population.

- Demographics
  Most of the patients (>80%) reported either mild (two to three episodes/night, n=90) or moderate (three to four episodes/night, n=83) nocturia, while about one-tenth of the patients reported severe nocturia (>4 episodes/night, n= 20). Similarly, clinicians classified the majority of patients (>80%) as mild (n=89) and moderate (n=81).

- Item-level Analyses
  Item-level scores for the INTU instrument were evaluated on day 5. On day 5, patients generally used the entire range of the scale when responding to each item with the exception of item 1 (difficulty concentrating) where the response option "all day" was not endorsed at all. Most of the INTU items were skewed towards lower impact response options (i.e., "Not at all"/"A little of the day"/"Somewhat"), except for item 9 (bothered by getting out of bed to go to the bathroom last night) where 10% (n=20) of patients reported being bothered "Very much".

  The Applicant reported no notable ceiling effects for the INTU items (a ceiling effect is when a high percentage of patients select the most severe response option). However, they found some INTU items had floor effects (a floor effect is when a high percentage of patients select the least severe response option, i.e., "Not at all"). The Applicant specified thresholds greater than 25% for items 1–4 and 20% for items 5–10 to determine the presence of floor or ceiling effects. The following items had floor effects based on these criteria:

  - Item 1 "Have you had difficulty concentrating?" (49% responded "Not at all");
  - Item 2 "Have you felt tired?" (22%);

[2] The PGI-C scale consisted of the following item: "Over the past 7 days of your participation in this study, how have your nocturia symptoms changed?" The response options for the PGI-C were on a seven-point scale (i.e., Very much improved, Much improved, Minimally improved, No change, Minimally worse, Much worse, and Very much worse).

[3] Patients with a minimum of two nocturic episodes each night, for a total minimum of six nocturic episodes over a three-day period in week 1, qualified for the week 2 assessment period.

- Item 3 “Have you had difficulty getting things done?” (43% responded “Not at all”);
- Item 4 “Have you been irritable?” (57% responded “Not at all”);
- Item 5 “Have you been concerned about having to get up tonight to urinate?” (35% responded “Not at all”);
- Item 7 “Did getting up out of the bed to go to the bathroom this morning cause you to start your day earlier than you would have liked?” (50% responded “Not at all”); and
- Item 10 “How drowsy did you feel this morning?” (29% responded “Not at all”).

The Applicant believes that the floor effects were due to inclusion of patients with mostly mild or moderately severe nocturia in the observational study, without inclusion of many severely-affected patients.

FDA’s comments: The observed floor effects indicate that some of the items were not relevant to, or experienced by, the patients.

With the exception of item 2 (felt tired), the items showing floor effects did not appear to be among the most frequently-reported impacts of nocturia from the qualitative research (Figure 1). It is unclear why items 1, 3, 4, and 7 with the highest floor effects appear in the final INTU instrument. The floor effects indicate that a significant proportion of the patients are not experiencing those particular nocturia impacts and, therefore, would not be able to show improvement on those impacts. These items should have been dropped from the INTU instrument; however, the Applicant did not make any modification to the INTU items based on these floor effects.

The Applicant examined the INTU instrument’s domain structure, measurement properties and performance (i.e., internal consistency reliability, test-retest reliability, convergent validity, known-groups validity, and ability to detect change over time) in the observational study. The Applicant’s results appear acceptable. See Appendix A for detailed information on these results and the FDA’s comments.

The FDA requested that the Applicant explore what would be considered a meaningful change in INTU Overall Impact scores from week 1 to week 2 in the observational study. See Appendix B for detailed information on these results and the FDA’s comments.

5.2 DB4 Clinical Trial: FDA-requested Post-hoc Psychometric Evaluation of INTU

The FDA requested that the Applicant conduct exploratory analyses using their DB4 clinical trial data, to provide support for the INTU’s psychometric properties and performance. The results from these INTU psychometric evaluation analyses (i.e., reliability, validity, ability to detect change) using the DB4 clinical trial data were compared with the INTU psychometric evaluation results obtained in the two-week observational study, and were found to be similar and acceptable. See Appendix C for detailed information on these results and the FDA’s comments.

6 DB4 Clinical Trial Efficacy Results for INTU Overall Impact Score

See the Clinical Efficacy memorandum for an overview of the DB4 study design and complete efficacy findings. The Applicant included the INTU instrument as the first key secondary in their DB4 clinical trial. There was a statistically significant difference between the 14-point improvement (reduction) in the INTU Overall Impact score for the desmopressin 1.5 mcg group versus the 12-point improvement (reduction) for the placebo group (p=0.02); however, the treatment difference was numerically small (-2.6).

FDA's comments: Small changes in PRO endpoint scores can be statistically significant but not necessarily clinically meaningful. Both clinical and statistical significance should be demonstrated.

Given that the INTU instrument was included only in a single pivotal trial, determination of the INTU Overall Impact score being fit-for-purpose and yielding meaningful results should be evaluated in the overall context of evidence. A major limitation when interpreting the efficacy findings from the DB4 clinical trial is that there was no pre-specified threshold for meaningful change in INTU Overall Impact scores for use with the phase 3 data. Therefore, the FDA requested additional exploratory analyses from the Applicant to try to interpret the meaningfulness of the INTU Overall Impact change scores obtained in the DB4 clinical trial.

Based on these exploratory analyses using the INTU data from the DB4 clinical trial, the FDA concludes that the INTU can reasonably detect changes in nocturia impacts over time. The detailed methodology and results supporting FDA's conclusion are included in Appendix D.

Based on exploratory analyses using the INTU data from the DB4 clinical trial, the FDA concludes that the mean, within-group INTU Overall Impact score improvement (reduction) of 14 points for the desmopressin 1.5 mcg group in Trial DB4 appears clinically meaningful. However, the 12-point mean, within-group improvement (reduction) in INTU scores with placebo in Trial DB4 appears clinically meaningful, as well. While the 2.6 mean treatment difference in INTU scores between desmopressin 1.5 mcg and placebo in Trial DB4 is statistically significant (p=0.02), the exploratory analyses are unable to inform whether this small difference is clinically meaningful. The detailed methodology and results supporting FDA's conclusion are included in Appendix E.

Appendix A: INTU's Psychometric Properties and Performance (Observational Study Data)

- Domain Factor and Structure

  The Applicant conducted an exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) to determine the number of domains or factors that were present within the INTU instrument. EFA was performed on week 1 (day 4) data to identify the underlying factor structure for the INTU instrument with no pre-specified numbers of factors. The total sample size for the EFA was 182 patients. The INTU instrument had two factors with eigenvalues greater than one; the first was 4.22 and the second was 1.21. The Applicant interpreted this to mean that the INTU may have two underlying factors.

  FDA's comments: Before conducting the INTU psychometric evaluation study, the Applicant did not provide a conceptual framework proposing separate Nighttime Impact and Daytime Impact domains. Items should not be placed into domain scores based only on statistical considerations, such as factor analysis. It is important to also include conceptual considerations based on clinical knowledge of the disease or condition and patient input. Additionally, the item content should have been modified to only include the most relevant items in the target population prior to conducting further psychometric analyses (i.e., items with high floor effects should have been removed prior to proceeding further). Therefore, many of the Applicant's statistical analyses, such as factor analysis and Rasch modeling, may be difficult to interpret and are not further discussed in this memorandum.

- Reliability

  Internal consistency reliability

  Internal consistency reliability was evaluated using day 5 INTU data. A Cronbach's alpha coefficient of 0.88 was obtained for the assessment of internal consistency of the INTU Overall Impact score, which exceeded the Applicant's specified threshold of ≥0.70. The magnitude of the Cronbach's alpha coefficient did not show any appreciable change with potentially removing any of the items from the INTU Overall Impact score. Cronbach's alpha coefficients for the two INTU domain scores were 0.83 (Daytime Impact) and 0.78 (Nighttime Impact).

  Test-retest reliability

  Test-retest reliability was evaluated using day 4 and day 6 INTU data, with patient stability assumed based on no treatment/intervention during these 48 hours. An intra-class coefficient (ICC) of 0.89 was derived for the assessment of test-retest reliability of the INTU Overall Impact score, which exceeded the Applicant's specified threshold of ≥0.70. Test-retest reliability (using ICC) for the INTU domain scores were 0.81 (Daytime Impact) and 0.88 (Nighttime Impact).

  FDA's comments: The INTU instrument's internal consistency and test-retest reliability results appear acceptable. However, it remains unclear why some items with high floor effects were retained in the INTU instrument.

- Construct Validity

  Convergent validity

  Convergent validity was measured using the day 8 correlations (correlation coefficients) of the INTU scores with two other PRO instruments, the Pittsburgh Sleep Quality Index (PSQI) and the Nocturia Quality of Life (N-QOL) questionnaire. A moderate positive correlation was observed between the INTU Overall Impact and domain scores with the PSQI scores. Higher INTU Overall Impact scores (implying worsening nocturia impact) also had moderate negative correlations with the N-QOL total score and with the N-QOL domains (Sleep/Energy, Bother/Concern) (greater scores on N-QOL indicate an improvement in health-related quality of life).

  FDA's comment: The INTU instrument's convergent validity results appear acceptable. However, it remains unclear why some items with high floor effects were retained in the INTU instrument.

  Known-groups validity

  Known-groups validity was performed for weeks 1 and 2 using the INTU weekly average scores to categorize the severity of nocturia as mild (1 to <2 episodes/night), moderate (2-3 episodes/night) or severe (>3 episodes per night). The INTU Overall Impact score and domain scores differed (nominal $p<0.05$) across these nocturia severity groups. The INTU Overall Impact score and INTU domain scores moved monotonically, with greater nocturia severity resulting in greater nocturia impacts.

  FDA's comments: The INTU instrument's known-groups validity results appear acceptable. However, it remains unclear why some items with high floor effects were retained in the INTU instrument.

- Ability to Detect Change Over Time

  The Applicant used three anchor scales to create responder groups, or improvement categories, of patients in order to evaluate the ability of the INTU Overall Impact scores to detect change over time (Table 4). This analysis evaluated how the INTU scores relate to actual change in patients' nocturia severity status, and was performed by categorizing patients as responders based on three anchor scales. The following three scales were used to anchor the responder groups for the evaluation:

  - The PGI-C (day 15)
  - A 50% reduction in nocturic events between days 4 (week 1) and 8 (week 2)
  - A mean decrease in one nocturic event between week 1 and week 2.

Table 4. Change in INTU scores between days 4 and 8 by responder groups

INTU Score[1]	Improved [2]							
	2-Grade Change in PGI-C (*n*=193)		1-Grade Change in PGI-C (*n*=193)		50% Reduction in Nocturic Events (*n*=193)		Mean Decrease of One Nocturic Event (*n*=193)	
	n	Mean Change score (SD)	n	Mean Change score (SD)	n	Mean Change score (SD)	n	Mean Change score (SD)
INTU Overall Impact score	17	-9 (13)	63	-3 (11)	14	-10 (14)	38	-6 (12)

[1] INTU scores are calculated as the average score over week 1 (days 4-8) and week 2 (days 11-13). INTU scores range from 0 to 100, with higher scores associated with greater negative impact of nighttime urination on health-related quality of life.
[2] Evaluation of "Improved" categorization used week 1 to week 2 change scores.
Source: Adapted from Table 26 in Applicant's Psychometric Study Report

FDA's comments: The "improved group" appeared to have fairly small mean changes in the INTU Overall Impact score from week 1 (day 4) to week 2 (day 8), ranging from -3 to -10 depending on the anchor used (a negative score reflects a decrease in impact of nocturia). While there appears to be ability to detect change, it remains unclear why some items with high floor effects were retained in the INTU instrument. It is likely that the INTU's ability to detect change could have been improved if the items with floor effects had been omitted; patients cannot show improvements on such items if they are not experiencing those nocturia impacts at baseline.

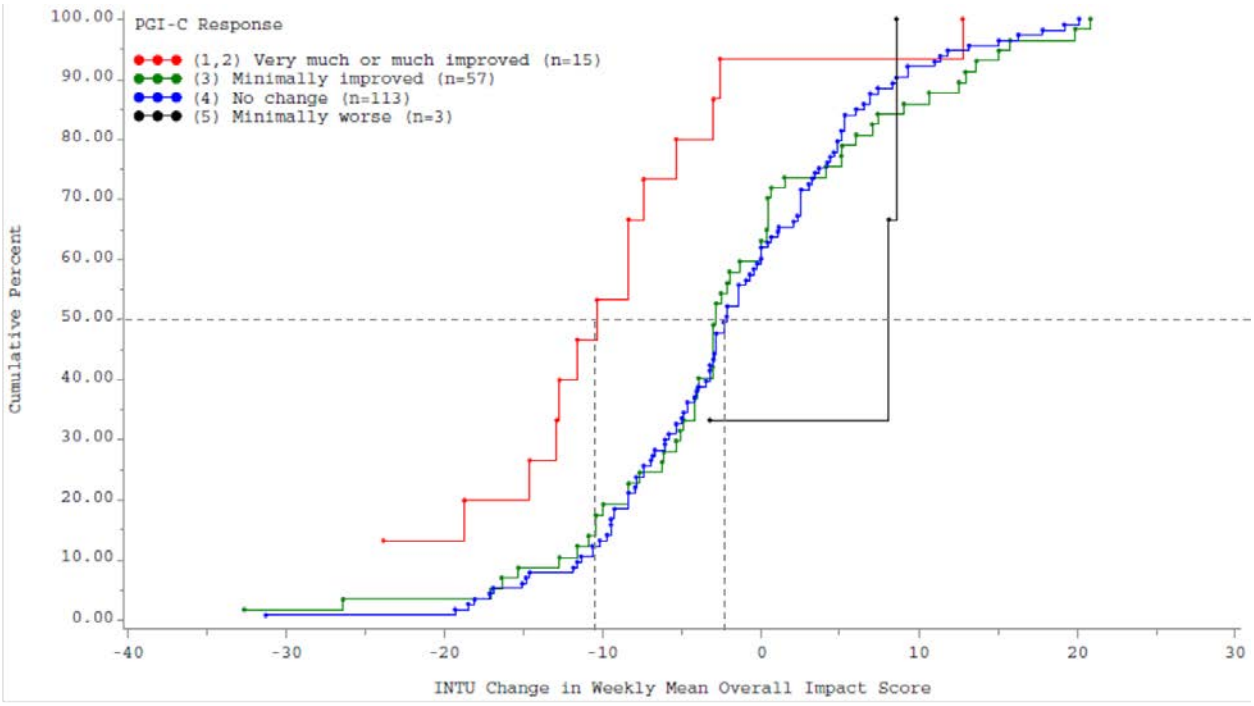
Appendix B: FDA-requested Post-Hoc CDF Analysis (Observational Study)

In order to explore what would be considered a meaningful change in INTU Overall Impact scores from week 1 to week 2 in the observational study, the FDA requested that the Applicant treat both the PGI-C and reduction in number of nocturic episodes as improvement anchor scales in cumulative distribution function (CDF) plot analyses.

In the two CDF plots below (Figures 2 and 3), the change in the INTU Overall Impact scores from week 1 to week 2 are plotted on the x-axis. The y-axis represents the cumulative percentage of the patients having up to a particular change in the INTU Overall Impact score (from the x-axis). When exploring a meaningful change score, we typically look at the intersection between the median line on the y-axis (representing one-half of the patients) and each curve, then trace those intersection points down to the x-axis to see the corresponding change in the INTU Overall Impact score.

The curves shown in Figure 2 represent each PGI-C category response option ("Very much or much improved," "Minimally improved," "No change," or "Minimally worse"). (Note: The category responses "Very much improved" and "Much improved" were collapsed together.) Looking at the median line in Figure 2 (the superimposed dashed horizontal line), 50% of patients who reported that their nocturia symptoms were "very much or much improved" on the PGI-C achieved an 11-point or greater improvement (reduction) in the INTU Overall Impact score (x-axis values to the left of the superimposed dashed vertical line corresponding with the red curve). In contrast, 50% of patients who reported that their nocturia symptoms had "no change" on the PGI-C achieved a 2.5-point or greater improvement (reduction) in the INTU Overall Impact score (x-axis values to the left of the superimposed dashed vertical line corresponding with the blue curve).

Figure 2. Change in INTU Overall Impact score from Week 1 to Week 2 by PGI-C

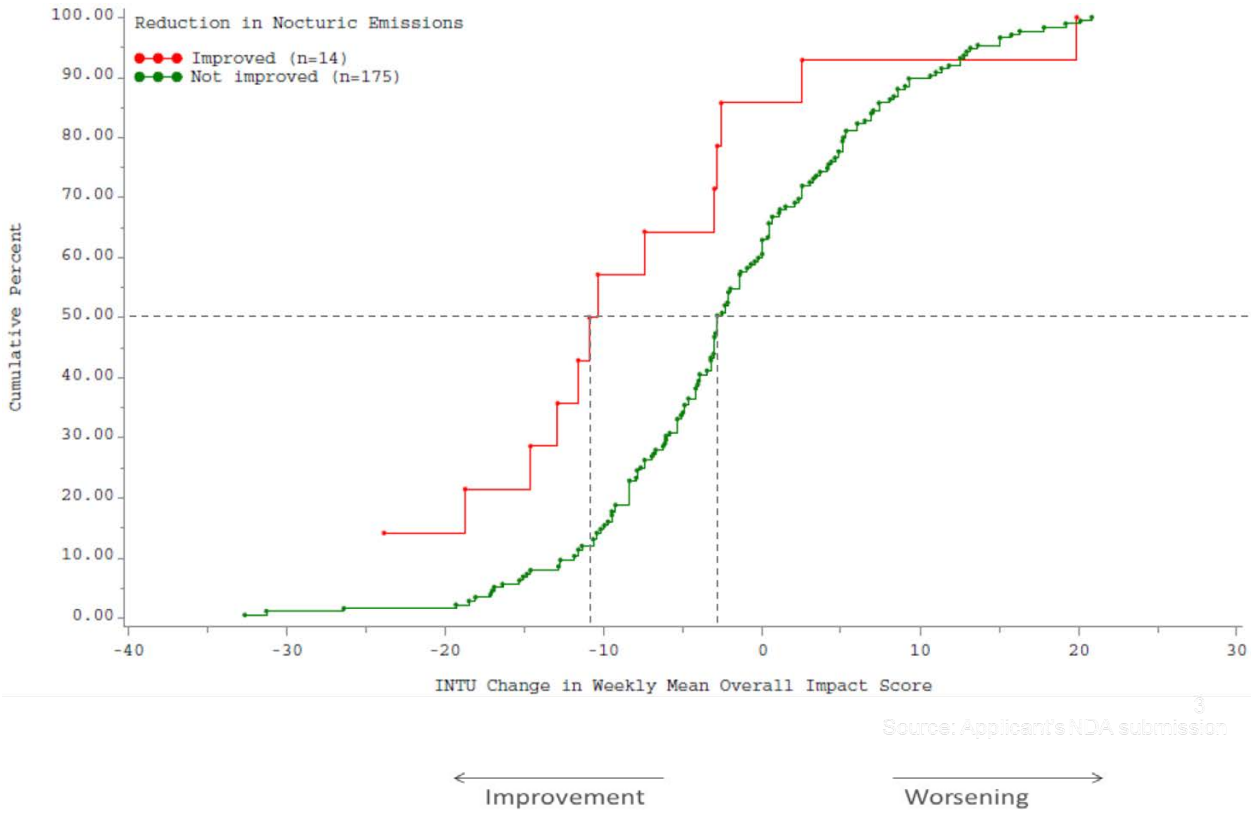


<u>FDA's comment</u>: The results of the CDF plot in Figure 2 are consistent with changes seen in the anchor scale categories, as expected.

The curves shown in Figure 3 represent the responders ("Improved") and non-responders ("Not improved") based on reduction of nocturic episodes. "Improved" was defined as ≥50% decrease in nocturic episodes between week 1 and week 2 and "Not improved" was defined by a <50% decrease or an increase in nocturic episodes).

Looking at the median line in Figure 3 (superimposed dashed horizontal line), similar to the results from Figure 2, 50% of patients who had "improved" (a ≥50% decrease in nocturic episodes) achieved at least an 11-point improvement (reduction) in the INTU Overall Impact score (leftmost superimposed dashed vertical line corresponding with the red curve), whereas 50% of patients who did not improve" (<50% decrease or an increase in nocturic episodes) achieved at least a 3-point improvement (reduction) in the INTU Overall Impact score (rightmost superimposed dashed vertical line corresponding with the green curve).

Figure 3. Change in INTU Overall Impact score from Week 1 to Week 2 by Nocturic Emissions



Source: Applicant's NDA submission

FDA's comment: The results of the plot in Figure 3 are very similar to those obtained in Figure 2 and are consistent with changes seen in the anchor scale categories, as expected.

Appendix C: FDA-requested Post-hoc Psychometric Evaluation of INTU (DB4 Clinical Trial Data)

- Reliability

  Internal consistency reliability

  The Cronbach's alpha coefficients for the INTU Overall Impact, Daytime Impact, and Nighttime Impact scores obtained from about 770 patients in the DB4 clinical trial data (0.91, 0.89, and 0.83, respectively) informing the internal consistency of the INTU appear to be similar to those obtained in the observational study (0.88, 0.83, and 0.78, respectively). The Cronbach's alpha coefficient for the INTU Overall Impact score would increase from 0.91 to 0.92 and for the Daytime Impact score would increase from 0.89 to 0.90 if item 6 ("How rested did you feel this morning?"; the only reverse-scored item) were deleted. The Nighttime Impact score's Cronbach's alpha coefficient would increase from 0.83 to 0.84 if item 7 ("Did getting up out of bed to go to the bathroom this morning cause you to start your day earlier than you would have liked?") were deleted. These changes appear small. The Applicant did not delete any items from the INTU instrument.

  Test-retest reliability

  ICCs were calculated on INTU scores from 782 patients obtained during both weeks 1 and 2 of the DB4 clinical trial screening phase, comparing the average of the three consecutive daily INTU instruments from each week. The ICCs for the INTU Overall Impact, Daytime Impact, and Nighttime Impact scores were 0.94, 0.92, and 0.92, respectively.

  FDA's comment: The INTU instrument's internal consistency and test-retest reliability results appear acceptable. The ICCs obtained from the DB4 clinical trial appear to be similar to those obtained in the two-week observational study for the INTU Overall Impact, Daytime Impact, and Nighttime Impact scores (0.89, 0.81, and 0.88, respectively).

- Validity

  Known-groups validity

  Patients were classified into severity groups based on whether they experienced ≤3 or >3 daily average nocturic episodes per day. The average of the daily INTU scores and daily total nocturic episodes during the treatment phase was used for the known-groups validity analysis. The results obtained from the DB4 clinical trial showed that the greatest magnitude in score difference between known groups was obtained for the Nighttime Impact score, followed by the Overall Impact score, and then the Daytime Impact score, with 9-point, 7-point, and 4-point score differences, respectively.

  FDA's comments: The known-groups validity results obtained from the DB4 clinical trial appear to be consistent with the results from the two-week observational study in that the greatest magnitude in score difference between known groups was obtained for the Nighttime Impact score, followed by the Overall Impact score, and then the Daytime Impact score, with 9-point, 7-point,

and 4-point score differences, respectively, for the DB4 clinical trial, and 13-point, 10-point, and 8-point score differences, respectively, for the observational study. It appears that the Nighttime Impact domain may be more sensitive to treatment than the other two scores.

The Applicant believes that the floor effects seen for many of the INTU items in the two-week observational study were due to inclusion of mostly less severe patients in that study. The FDA could not find descriptive statistics, including floor effect analysis, for the DB4 clinical trial population within the Applicant's submission. However, an FDA analysis using the histograms of the response option distribution for each INTU item in the DB4 clinical trial data appears to show that high floor effects for some INTU items are present in the DB4 clinical trial data for the same items that had the highest floor effects in the two-week observational study – items 1 (difficulty concentrating), 3 (difficulty getting things done), 4 (been irritable), and 7 (getting out of bed to go to the bathroom this morning caused you to start your day earlier than you would have liked).

In order to examine the sensitivity of the INTU items in detecting treatment benefit, the FDA conducted an exploratory analysis assessing the change in raw (non-transformed) INTU item responses from screening to treatment. The results from this exploratory analysis are consistent with our assumption that the Nighttime Impact items appear to be more sensitive to treatment benefit. If the product can be approved, this finding may have implications for potential labeling claims using the pre-specified INTU Overall Impact score, which includes many items that have floor effects and appear to be insensitive to treatment.

In general, the Applicant's cross-sectional psychometric evaluation results from the DB4 clinical trial data appear consistent with the results obtained in the observational study and appear acceptable.

Appendix D: FDA-requested Post-Hoc INTU Analyses (DB4 Clinical Trial)

Ability of the INTU to Detect Change Over Time (Using DB4 Data):
The FDA requested that the Applicant conduct exploratory, anchor-based analyses to evaluate the INTU's ability to detect change over time using the DB4 clinical trial data with the following anchor scales:

- Treatment Benefit Scale (TBS)

- Mean reduction of ≥1 vs. <1 nocturic episodes per night between screening and treatment (in the qualitative patient transcript review, patients reported that a decrease in one nocturic episode per night would constitute a meaningful change or benefit in how they feel and function in their daily lives.)

- 50% reduction in nocturic episodes per night between screening and treatment

The TBS was completed by patients only at the week 14 (day 99) exit visit. The TBS consisted of the following item: "My condition (waking up at night to urinate) is now:" The response options for the TBS were on a five-point scale (i.e., Much better, Somewhat better, Not changed, Somewhat worse, Much worse).

The 3-day voiding diary was used for the other two anchor scales (mean reduction of ≥1 versus <1 nocturic episodes per night and a 50% reduction in nocturic episodes per night from screening to the treatment phase).

The mean change in INTU scores from screening to the treatment phase was calculated for each of the three anchors (Tables 5-7). For example, among the patients in the DB4 clinical trial who reported feeling "Much Better" on the TBS, the mean improvement (reduction) in the INTU Overall Impact Score was a reduction of 19 points, whereas those who reported "Not Changed" had a mean improvement (reduction) of 5 points (Table 5). Similarly, those who had a mean reduction of at least one nocturic episode per night had a mean improvement (reduction) in the INTU Overall Impact Score of 16 points compared to a 5-point improvement (reduction) among those who had a decrease of less than one nocturic episode per night (Table 6).

Table 5. Change in INTU Overall Impact score between screening and treatment phases by TBS anchor responder categories

	TBS Categories		
INTU Score	"Much Better" (*n*=298)	"Somewhat Better" (*n*=288)	"Not Changed" (*n*=185)
Change in INTU Overall Impact Score Mean (SD) min, max	-19 (18) min, max (-92 , 16)	-10 (14) min, max (-61 , 25)	-5 (11) min, max (-58 , 22)
TBS=Treatment Benefit Scale			

Table 6. Change in INTU Overall Impact score between screening and treatment phases by mean reduction of ≥1 versus <1 nocturic episodes responder categories

	Mean reduction of ≥1 versus <1 nocturic episodes	
INTU Score	Reduction of ≥1 (*n*=504)	Reduction of <1 (*n*=278)
Change in the INTU Overall Impact Score Mean (SD)	-16 (16)	-5 (12)

Table 7. Change in INTU Overall Impact score between screening and treatment phases by reduction of ≥50% versus <50% in nocturic episodes

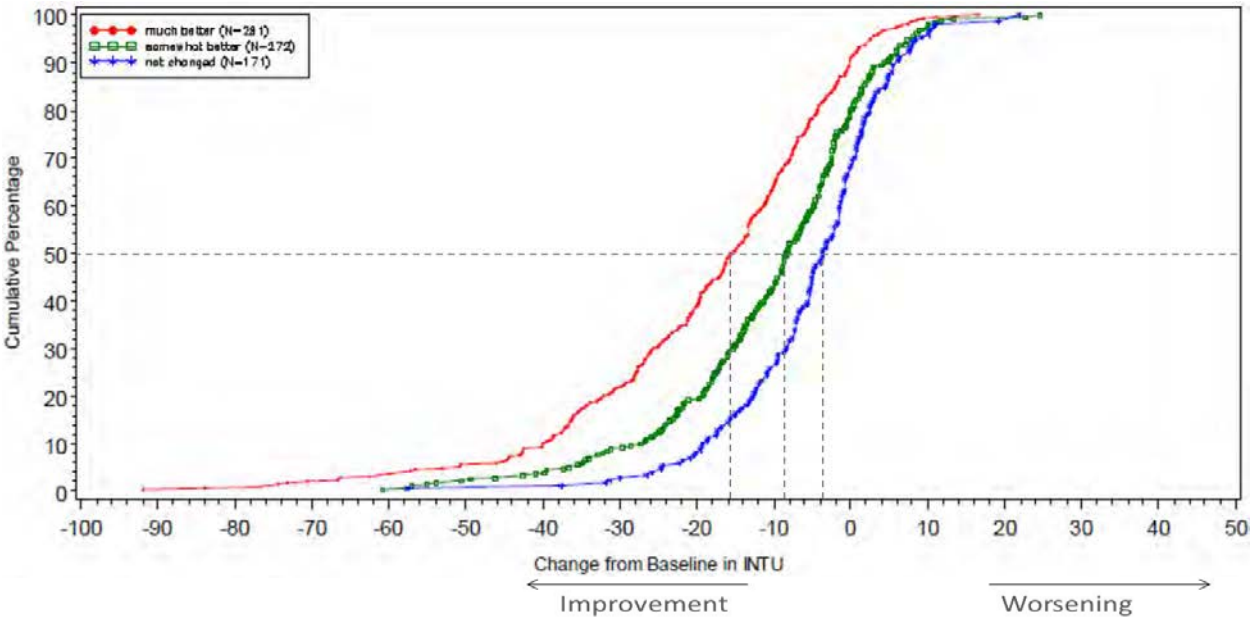
	50% reduction of nocturic episodes	
INTU Score	≥50% Reduction (*n*=273)	<50% Reduction (*n*=278)
Change in the INTU Overall Impact Score Mean (SD)	-20 (18)	-8 (12)

FDA's comments: Improvements in the TBS categories and nocturic episode anchors corresponded with improvements in INTU change scores (Tables 5, 6, and 7). The INTU's ability to detect change over time appears acceptable. Based on these anchor-based analyses, a reduction in the INTU Overall Impact score within the range of 10 and 20 points appears to correspond with an improvement between "somewhat better" and "much better" using the TBS anchor categories, and a reduction in nocturic episodes (reduction or ≥1 nocturic episode and a ≥50% reduction of nocturic episodes).

Appendix E: Clinically Meaningful Change (Using DB4 Clinical Trial Data)

In order to explore what would be considered a meaningful change in INTU Overall Impact scores on a 0 to 100 point scale, the FDA requested that the Applicant submit CDF plots from the DB4 clinical trial data by treatment group (1.5 mcg, 0.75 mcg, and placebo) for the change in INTU Overall Impact scores, as well as CDF plots (pooled treatment and placebo groups) using both the TBS as an improvement anchor scale and any other potential anchor scales. (See Appendix B for details on how to interpret a CDF plot.)

Figure 4. Change in INTU Overall Impact score from screening to post-treatment by TBS (pooled treatment and placebo groups)



Looking at the median line in Figure 4 (superimposed dashed horizontal line), 50% of patients who reported that their nocturia symptoms were "much better" achieved about a 16-point or greater improvement (reduction) in the INTU Overall Impact score (leftmost superimposed, dashed, vertical line corresponding with the red curve), 50% of patients who reported that their nocturia symptoms were "somewhat better" achieved about an 8-point or greater improvement (reduction) in the INTU Overall Impact score (middle superimposed, dashed, vertical line corresponding with the green curve), and 50% of patients who reported "no change" in their nocturia symptoms achieved about a 4-point or greater improvement (reduction) in the INTU Overall Impact score (rightmost superimposed, dashed, vertical line corresponding with the blue curve).

To examine whether the within-group improvement (reduction) in the INTU Overall Impact score of 14 points observed in the DB4 clinical trial for the desmopressin 1.5 mcg group is meaningful to patients, one can superimpose a vertical line corresponding with a 14-point

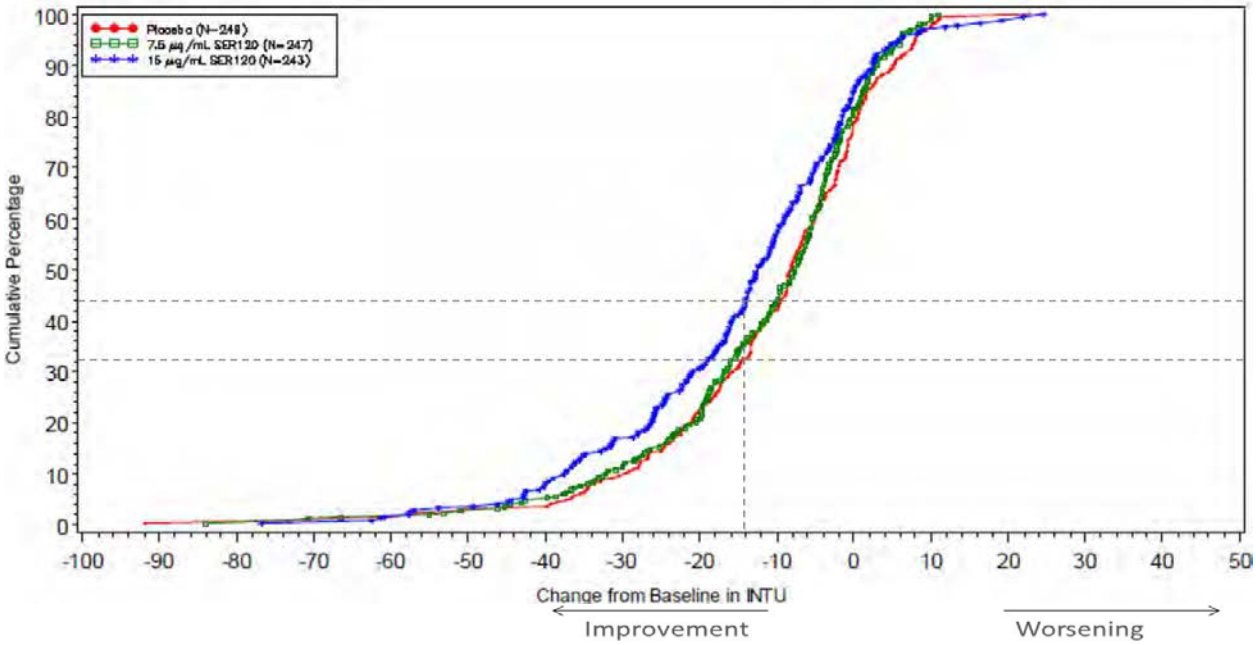
improvement (reduction) onto Figure 4. Doing so, it appears that approximately 52% of patients would characterize their nocturia symptoms as "much better," approximately 33% would characterize their symptoms as "somewhat better," and about 17% would characterize their symptoms as "not changed." Note, however, that this exploratory analysis cannot take into account how the desmopressin 1.5 mcg group compared with placebo in the DB4 trial with regard to change in INTU score.

FDA's comments: The findings observed in Figure 4 are in line with the anchor-based analyses conducted to evaluate the INTU's ability to detect change over time. It appears that a 10- to 16-point improvement (reduction) in the INTU Overall Impact score appears to correspond with an improvement between the "somewhat better" and "much better" TBS anchor categories.

It is also important to mention that the above threshold for meaningful change relies on the assumption that the current INTU instrument is fit-for-purpose. However, given the large floor effects and that the INTU Overall Impact score is comprised of a 2-domain composite score, which has one seemingly insensitive domain (i.e., Daytime Impact), we suggest that the current INTU instrument should be modified before use in future drug development programs to minimize the risk of failure to detect clinical benefit.

Because the treatment difference in INTU scores between the desmopressin 1.5 mcg and placebo groups cannot be assessed in Figure 4 (that figure pools data from all treatment groups), the FDA requested CDF curves for the treatment and placebo groups separately (Figure 5).

Figure 5. Change in INTU Overall Impact score from screening to post-treatment by treatment group

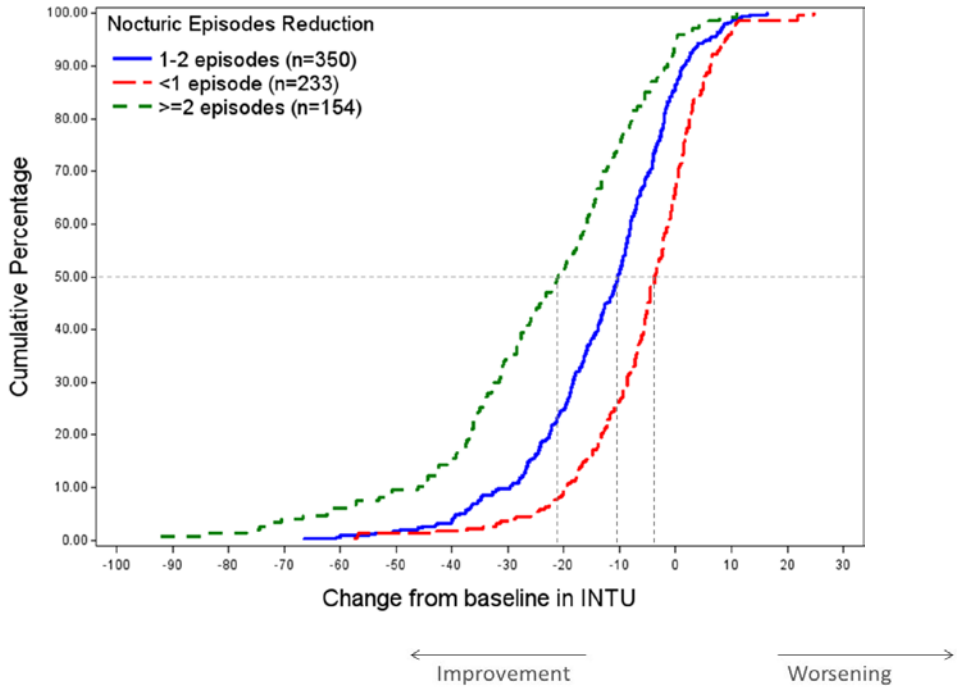


When looking at Figure 5 and considering the 14-point within-group, mean improvement (reduction) in the INTU Overall Impact score for the desmopressin 1.5 mcg group, obtained in the DB4 clinical trial (superimposed dashed, vertical line), approximately 44% of patients in the 1.5 mcg group (top superimposed dashed horizontal line) achieved a 14-point or greater

improvement (reduction) in the INTU Overall Impact score compared to approximately 32% of patients in the placebo group (bottom superimposed dashed horizontal line). This corresponds to about a 12% absolute difference between desmopressin 1.5 mcg and placebo groups. However, it is important to note that the 12-point within-group, mean improvement (reduction) achieved by the placebo group also falls between the "somewhat better" and "much better" improvement TBS anchor categories.

The FDA conducted one additional exploratory analysis to try and interpret the clinical meaningfulness of the INTU results in DB4. Because patients in the qualitative study stated that a reduction of at least one nocturic episode would be meaningful to how they functioned in their daily lives, the FDA created a CDF plot of the INTU Overall Impact change scores from screening to post-treatment according to the reduction in nocturic episodes (reduction of <1 episode, 1-2 episodes, and ≥2 episodes).

Figure 6. Change in INTU Overall Impact score from screening to post-treatment by nocturic episodes



Looking at the median line in Figure 6 (superimposed dashed, horizontal line), 50% of patients who reported a decrease of ≥2 nocturic episodes achieved about a 21-point or greater improvement (reduction) in the INTU Overall Impact score (leftmost superimposed, dashed, vertical line corresponding with the green curve), 50% of patients who reported a decrease of 1-2 nocturic episodes achieved about an 11-point or greater improvement (reduction) in the INTU Overall Impact score (middle superimposed, dashed, vertical line corresponding with the blue curve), and 50% of patients who reported a decrease of <1 nocturic episodes achieved about a 4-point or greater improvement (reduction) in the INTU Overall Impact score (rightmost superimposed, dashed, vertical line corresponding with the red curve).

When superimposing the within-group, mean change (reduction) in INTU score of 14 points observed in the DB4 clinical trial for the 1.5 mcg group onto this graph, this 14-point improvement (reduction) appears to be meaningful to patients reporting a reduction of at least one nocturic episode. However, it is important to note that the 12-point improvement (reduction) achieved by the placebo group falls into the 1-2 nocturic episode reduction anchor category, which also appears to be a clinically meaningful change to patients.

FDA's comments: In comparison to the 14-point improvement (reduction) in the mean score achieved by the 1.5 mcg group, the placebo group achieved a 12-point mean improvement (reduction), which also appears to be meaningful to patients reporting a reduction of at least one nocturic episode.

Center for Drug Evaluation and Research

Division of Bone, Reproductive and Urologic Products, Office of New Drugs

Overview of Clinical Safety

D

Safety of SER120

Clinical Studies Used to Evaluate Safety

The clinical program evaluating the safety of SER120 for treatment of nocturia in adults consists of eight studies: four randomized, double-blind, placebo-controlled phase 3 trials (DB1, DB2, DB3 and DB4); one open-label phase 2 dose titration study (SPC-DESMONS- 200802); one phase 2/3 open-label, uncontrolled study in elderly patients (ELD); and two open-label, long-term, uncontrolled, safety extension trials (OL1-the extension of DB1 and DB2, and A2-the extension of DB3).

The DB1 and DB2 studies, which tested the 0.5 and 0.75 μg doses of SER120, had treatment periods of seven weeks, including a three week titration phase and a four week maintenance phase. The DB3 study, which tested the 0.75, 1.0, and 1.5 μg doses, and the DB4 study, which tested the 0.75 and 1.5 μg doses, had treatment periods of 12 weeks at a set dose of SER120 in addition to a two week double-blind, placebo lead-in period. Each of these studies had a randomized, placebo-controlled study design. The uncontrolled, open-label safety extension studies had treatment periods up to 43 weeks (OL1 at the 0.5 and 0.75 μg doses) and 126 weeks (A2 at the 1.0 and 1.5 μg doses). The elderly study treated 32 subjects, aged 75 years or older for eight weeks and randomized subjects to either the 0.5 or 0.75 μg doses.

During these studies, 1867 subjects with nocturia received SER120 for periods of time ranging from less than one month to more than 24 months. Across all the doses tested (0.5, 0.75, 1.0, and 1.5 μg), 607 subjects received SER120 for 6 or more months and 347 subjects received SER120 for 12 or more months. The highest dose tested in subjects with nocturia was 1.5 μg. This dose was used in placebo-controlled studies DB3 and DB4 and in the uncontrolled, open-label extension study A2. During these studies, 748 subjects received the 1.5 μg dose of SER120, 304 for 6 or more months and 218 for 12 or more months. Exposure duration to SER120 by dose is summarized in Table 1.These exposures to the study drug appear adequate.

Table 1: Number of Subjects with Exposure of SER120 by Dose Category

Exposure Duration	**0.5 μg N = 567**	**0.75 μg N = 806**	**1.0 μg N = 518**	**1.5 μg N = 748**	**Overall N = 1867**
< 1 month	306	59	305	43	177
1 month to < 3 months	121	260	51	142	443
3 months to < 6 months	22	342	142	259	640
6 months to < 9 months	4	21	10	62	63
9 months to < 10 months	4	3	0	11	12
10 months to < 12 months	78	114	4	13	185
12 months to < 14 months	31	7	2	25	138
14 months to < 16 months	0	0	3	22	23
16 months to < 18 months	1	0	0	40	41
18 months to < 20 months	0	0	0	54	30
20 months to < 22 months	0	0	1	10	7
22 months to < 24 months	0	0	0	19	50
≥ 24 months	0	0	0	48	58

The focus of this review is on the safety of the 0.75 and 1.5 μg doses of SER120, which are the doses proposed for clinical use in patients with nocturia. Because the 1.5 μg dose was used only in DB3, DB4, and A2, this review is primarily based on the pooled DB3/DB4 data and the long-term safety data from A2. Data from the studies of lower doses of SER120 were used to assess the dose relationship of serious adverse events and to evaluate potential safety signals.

In DB3 and DB4, the safety population was defined as all patients who completed the two-week, post-screening placebo lead-in phase, who were then randomized and received study drug, and who had some post-randomization safety data. The safety population in A2 included all patients who enrolled in the extension study, received any study drug, and had any post-treatment safety data.

In these studies, 16 subjects were excluded from the safety population. The reasons for exclusion were either the subject did not receive any study drug or there was no post-randomization safety data.

Deaths

There were five deaths reported in the clinical trials conducted during development of SER120. One death occurred in each of the placebo controlled trials DB1, DB3, and DB4; and one occurred in each of the open-label, uncontrolled extension studies (OL1 and A2). All five deaths occurred while the subject was being treated with SER120. No deaths occurred while a subject was being treated with placebo, either during the treatment phase or during the placebo lead-in phase of a trial.

These five deaths are summarized below:

- Subject 15S021/DB1: 57 year old male with no known risk factors for coronary artery disease was randomized to the 0.5 μg dose and then up-titrated to the 0.75 μg dose at his Day 15 visit. His serum sodium values were within normal limits at each visit up to and including his last visit on Day 29. Ten days after his Day 29 visit, the subject was found dead in his apartment. An autopsy was performed and the death was attributed to coronary atherosclerosis with sarcoidosis being a contributing factor. The autopsy noted hemorrhage in the left ventricle and ischemic changes.
- Subject 82S007/OL1: 79 year old male with a history of hypertension, hyperlipidemia, and previous myocardial infarction and transient ischemic attack. The subject completed DB2 (randomized to placebo), started OL1 at the 0.5 μg dose, and was up-titrated to the 0.75 μg dose at his Day 15 visit. His serum sodium values were within normal limits at each visit up to and including his last visit on Day 15. Four days after his Day 15 visit, the subject was found dead in his home. An autopsy was not performed. His death certificate listed the cause of death as probable myocardial infarction.
- Subject 77S003/DB3: 77 year old male randomized to the 1.0 μg dose after the two week placebo lead-in period. His serum sodium values were within normal limits at each study visit, including his last visit on Day 85. Three days before his scheduled Day 99 visit, the subject fell at home and became unresponsive. He was taken to the emergency room in cardiac arrest and was resuscitated and intubated. The patient was noted to have an increasing abdominal girth while in the emergency room and an ultrasound revealed aortic

enlargement with a possible aortic dissecting aneurysm. The patient began bleeding from his nasogastric tube. Serial hemoglobin concentrations decreased rapidly from 12.2 to 8.1 g/dL (the hematocrit decreased from 37% to 24%), consistent with a dissecting aortic aneurysm and intra-abdominal bleeding. The patient died in the emergency room. An autopsy was not performed. His death was attributed to cardiac arrest, abdominal aneurysm, and hypotension.

- Subject 59S024/A2: 76 year old male who completed DB3 (randomized to placebo), started A2 at the 1.0 μg dose, and was up-titrated to the 1.5 μg dose at his Day 15 visit. Serum sodium values were within normal limits at each study visit, including his last visit during Week 8. Six weeks after his Week 8 visit, he was admitted to the hospital with a diagnosis of cecal perforation with peritonitis, pneumonia, and multi-organ failure including renal failure secondary to septic shock. The subject underwent surgery, but died two weeks later.
- Subject 65S004/DB4: 80 year male with a history of diabetes mellitus, hyperlipidemia, hypertension, myocardial infarction, chronic obstructive pulmonary disease, and asthma. The subject was randomized to the 0.75 μg dose after the two week placebo lead-in period. Four days after starting the drug, he was found dead in his home. Twelve weeks before starting the treatment phase of the study, the subject was examined by his cardiologist and found to be medically stable. Two weeks before starting the treatment phase, his family physician performed a routine physical examination and found no acute problems; an electrocardiogram at that time was normal. An autopsy was performed, however, neither the autopsy report nor death certificate was made available to the study site. The Applicant estimates that the subject administered two or three doses of active study drug prior to the event.

In summary, all of the deaths occurred while subjects were being treated with SER120. During the four placebo controlled trials (DB1, DB2, DB3, DB4), 1413 subjects were randomized to treatment with SER120 and 770 subjects were randomized to treatment with placebo. This equates to a randomization ratio of slightly less than 2:1. In these controlled trials, the number of deaths in SER120-treated subjects (n=3) compared to the number of deaths in placebo-treated subjects (n=0) could be consistent with the randomization scheme. A role of SER120 in the deaths due to cecal perforation, coronary atherosclerosis, and bleeding aortic aneurysm is unlikely; a role cannot be definitively ruled out for the other two deaths. Four of the five deaths (82S007/OL1, 77S003/DB3, 59S024/A2, and 65S004/DB4) occurred in subjects who were older than 75 years of age.

Serious Adverse Events

Studies DB1, DB2, DB3 and DB4

During the four placebo-controlled phase 3 trials, the incidence of treatment-emergent serious adverse events (SAEs) for SER120-treated subjects was 1.8%, 1.7%, 1.6%, and 1.8% for the 0.5 μg, 0.75 μg, 1.0 μg, and 1.5 μg treatment groups, respectively; which was similar to the incidence for the placebo group (1.7%). The only treatment-emergent SAE reported by more than one SER120-treated subject was basal cell carcinoma. This SAE was reported by three SER120-treated subjects – two (0.4%) in the 1.5 μg group and one (0.2%) in the 0.75 μg group – and no placebo-treated subjects. Each of the three subjects who reported the SAE of basal cell carcinoma had a prior history of basal cell carcinoma. The lesions diagnosed during the study

were reported approximately one to three months after starting SER120. The prior history and short duration of SER120 exposure before diagnosis make treatment relatedness unlikely.

Two subjects, one in the 1.5 μg treatment group and one in the placebo group, reported hyponatremia as a SAE. Hyponatremia is discussed in detail later in this memorandum. There were no reports of seizure or coma.

Four subjects, all in a SER120 treatment group, reported SAEs in the cardiac disorders System-Organ-Class: one case each of coronary artery arteriosclerosis (0.75 μg treatment group, discussed in the Deaths section above), cardiac arrest (1.0 μg treatment group, discussed in the Deaths section above), congestive cardiac failure (0.75 μg treatment group), and coronary artery disease (0.5 μg treatment group).

The subject with congestive heart failure (87S030) was a 56 year old male with a history of hyperlipidemia and hypertension who was found to have a dilated cardiomyopathy with ejection fraction of 40%, valvular abnormalities, left atrial enlargement, and pulmonary hypertension about three months after starting treatment with 0.75 μg of SER120, after presenting with chest tightness and shortness of breath. It is unlikely that SER120 caused these abnormalities but it is not possible to rule out an adverse effect of SER120 on his underlying cardiac status due to fluid retention related to the pharmacologic effects of the drug.

The subject who reported coronary artery disease (81S011) saw his cardiologist for left arm pain eight days before his Day 43 study visit. At that time, it was determined he had extensive blockage of a coronary artery and he underwent coronary angioplasty with stent placement. Extensive blockage of a coronary artery diagnosed only 43 days after initiation of SER120 makes treatment relatedness unlikely.

Open-Label Safety Extension Study - A2

During A2, the uncontrolled, open-label extension of DB3, a total of 46 SAEs were reported by 40 (10%) of the 393 subjects in the safety population. Generally, the number of subjects reporting any given adverse event was one. SAEs reported by more than one subject included: basal cell carcinoma, reported by five subjects; knee arthroplasty, reported by three subjects; and pneumonia, femoral neck fracture, osteoarthritis, cerebrovascular accident, and pulmonary embolism, reported by two subjects each.

Open-Label Safety Extension Study – OL1

During OL1, the uncontrolled, open-label extension of DB1 and DB2, a total of 34 SAEs were reported by 30 (8%) of the 376 subjects in the safety population. Except for osteoarthritis, reported by three subjects, and basal cell carcinoma reported by two subjects, the number of subjects reporting any given adverse event was one.

Adverse Events Leading to Discontinuation

Studies DB3 and DB4

During DB3 and DB4, the incidence of adverse events (AEs) that resulted in discontinuation of the subject from the study was 4.9%, 4.2%, and 4.0% in the 1.5 μg, 0.75 μg, and placebo

treatment groups, respectively. Table 2 shows the most common AEs leading to study discontinuation.

Table 2: Most Common Adverse Events Leading to Discontinuation-DB3 and DB4

Preferred Term	1.5 µg SER120 (N=448)	0.75 µg SER120 (N=454)	Placebo (N=454)
Patients with at least one adverse event	22 (4.9%)	19 (4.2%)	18 (4.0%)
Nasal discomfort	3 (0.7%)	1 (0.2%)	5 (1.1%)
Hyponatremia	3 (0.7%)	1 (0.2%)	1 (0.2%)
Dizziness	1 (0.2%)	2 (0.4%)	1 (0.2%)
Blood sodium decreased	1 (0.2%)	2 (0.4%)	0
Dysuria	1 (0.2%)	2 (0.4%)	0
Nasal congestion	2 (0.4%)	1 (0.2%)	0

The most common AEs resulting in discontinuation from the study were nasal discomfort and hyponatremia. However, the incidence of subjects discontinuing due to nasal discomfort was numerically greater for placebo-treated subjects than for subjects treated with SER120. Hyponatremia is discussed in detail later in this memorandum.

Open-Label Safety Extension Study - A2

A total of 49 subjects (12%) discontinued from the A2 extension study because of an adverse event (39 were being treated with the 1.5 µg dose and 10 were being treated with the 1.0 µg dose at the time of the adverse event that led to discontinuation). Twelve subjects (3%) discontinued with an adverse event of nasal discomfort, nasal congestion or epistaxis. Four subjects, all receiving the 1.0 µg dose, discontinued due to an adverse event of decreased serum sodium or hyponatremia.

Common Adverse Events

Studies DB3 and DB4

During DB3 and DB4, the overall incidence of subjects with at least one AE was 47%, 49%, and 45% for the 1.5 µg, 0.75 µg, and placebo treatment groups. Table 3 shows the common (≥ 2%) AEs reported for the 1.5 µg, 0.75 µg, and placebo treatment groups during DB3 and DB4. AEs reported at a higher incidence with placebo are excluded.

Table 3: Common (≥ 2%) Adverse Events-
DB3 and DB4 (Excludes Events Reported at a Higher Incidence with Placebo)

System Organ Class/ Preferred Term	1.5 µg (N=448)	0.75 µg (N=454)	Placebo (N=454)
AT LEAST ONE ADVERSE EVENT	209 (46.7%)	222 (48.9%)	204 (44.9%)
INFECTIONS AND INFESTATIONS	69 (15.4%)	71 (15.6%)	62 (13.7%)
Nasopharyngitis	17 (3.8%)	14 (3.1%)	12 (2.6%)
Urinary Tract Infection	7 (1.6%)	16 (3.5%)	6 (1.3%)
INVESTIGATIONS	24 (5.4%)	20 (4.4%)	12 (2.6%)
Blood Sodium Decreased	11 (2.5%)	5 (1.1%)	0 (0.0%)
MUSCULOSKELETAL DISORDERS	30 (6.7%)	28 (6.2%)	26 (5.7%)
Back Pain	10 (2.2%)	8 (1.8%)	4 (0.9%)
NERVOUS SYSTEM DISORDERS	27 (6.0%)	30 (6.6%)	26 (5.7%)
Headache	13 (2.9%)	16 (3.5%)	15 (3.3%)
Dizziness	9 (2.0%)	8 (1.8%)	5 (1.1%)
RESPIRATORY DISORDERS	79 (17.6%)	65 (14.3%)	74 (16.3%)
Nasal Discomfort	25 (5.6%)	16 (3.5%)	25 (5.5%)
Sneezing	10 (2.2%)	10 (2.2%)	6 (1.3%)
Nasal Congestion	12 (2.7%)	7 (1.5%)	5 (1.1%)
VASCULAR DISORDERS[1]	18 (4.0%)	7 (1.5%)	7 (1.5%)
Hypertension/Blood Pressure Increased	14 (3.1%)	7 (1.5%)	8 (1.8%)

[1]Blood Pressure Increased data shown below are not included in the incidence rates reported in this row because those data are derived from the Investigations SOC

Adverse events were most commonly reported in the Respiratory/Thoracic/Mediastinal Disorders SOC. Most of the AEs reported in this SOC were assessed by the investigators as mild or moderate in severity. The most commonly reported preferred terms in the SOC were nasal discomfort, sneezing, and nasal congestion. The incidences of sneezing and nasal congestion were greater for both SER120 doses than placebo. Only the incidence of nasal congestion appeared dose-related.

The second most commonly reported SOC was Infections/Infestations. Most of the AEs reported in this SOC were assessed by the investigators as mild or moderate in severity. The most frequently reported preferred terms in the SOC were nasopharyngitis and urinary tract infection. The incidence of nasopharyngitis was greater for both SER120 doses than placebo and appeared dose-related.

The next most commonly reported SOC was Musculoskeletal/Connective Tissue Disorders. Most of the AEs reported in this SOC were assessed by the investigators as mild or moderate in severity. The most commonly reported preferred term in the SOC was back pain. The incidence of back pain was greater for both SER120 doses than placebo and appeared dose-related.

The incidence of AEs reported in the cardiac disorders SOC was 1.6%, 1.5%, and 1.3% for the 1.5 µg, 0.75 µg, and placebo treatment groups, respectively. Only three preferred terms had more than one reported event: atrial fibrillation, palpitations, and tachycardia. There were six reports of atrial fibrillation – four (0.9%) in the 1.5 µg dose group, two (0.3%) in the 0.75 µg dose group, and none in the placebo group; three reports of palpitations – two (0.4%) in the 1.5 µg dose group and one (0.2%) in the placebo group; and two reports of tachycardia – both (0.4%) in the 0.75 µg dose group.

The incidence of decreased serum sodium coded as an AE was 2.5%, 1.1%, and 0% for the 1.5 μg, 0.75 μg, and placebo treatment groups, respectively. The incidence of hyponatremia coded as an AE was 0.9%, 0.2%, and 0.2% for the 1.5 μg, 0.75 μg, and placebo treatment groups, respectively. See below for a detailed discussion of hyponatremia, including analyses based on the serum sodium laboratory data. The incidences of the following AEs, which are potential symptoms of low serum sodium, were similar in the SER120 and placebo treatment groups: headache, nausea, vomiting, muscle spasms (cramps), and fatigue. The incidence of peripheral edema in SER120-treated subjects was also similar to the incidence in placebo-treated subjects.

Open-Label Safety Extension Study - A2

The safety population of A2 included 393 subjects. Of the 393 subjects, one subject started treatment at the 1.5 μg dose, 357 were up-titrated to the 1.5 μg dose level during the course of the study, and 35 subjects remained on the 1.0 μg dose. Three hundred two (302) subjects were exposed to the 1.5 μg dose for six or more months, 217 for 12 or more months, 129 for 18 or more months, and 42 for more than 24 months. Of these 393 subjects, 325 (83%) experienced at least one AE. Table 4 summarizes the incidence of commonly occurring (≥ 2%) AEs in A2. Note that the uncontrolled design of this study limits conclusions particularly for AEs that have a common background incidence in this patient population. Nasal symptoms (e.g., nasal discomfort and sneezing) were the most commonly reported AEs during this study, which is consistent with the findings in DB3 and DB4 and plausibly related to the nasal route of administration of SER120.

Table 4: Incidence of the Most Common Adverse Events (Those Occurring in ≥ 2% of Subjects) – A2

System Organ Class/ Preferred Term	Number of Patients (N = 393)	Percentage
PATIENTS WITH AT LEAST ONE ADVERSE EVENT	325	82.7
EYE DISORDER		
Lacrimation Increased	9	2.3
GASTROINTESTINAL DISORDERS		
Diarrhea	11	2.8
Nausea	10	2.5
Constipation	9	2.3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema Peripheral	16	4.1
INFECTIONS AND INFESTATIONS		
Upper Respiratory Tract Infection	33	8.4
Nasopharyngitis	31	7.9
Urinary Tract Infection	31	7.9
Bronchitis	14	3.6
Sinusitis	14	3.6
Influenza	12	3.1
Rhinitis	10	2.5
INVESTIGATION		
Blood Sodium Decreased	9	2.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia	21	5.3
Back Pain	15	3.8
Musculoskeletal Pain	11	2.8
Pain in Extremity	10	2.5
Osteoarthritis	9	2.3
NERVOUS SYSTEM DISORDER		
Headache	16	4.1
Dizziness	8	2.0
Dysgeusia	8	2.0
PYSCHIATRIC DISORDERS		
Anxiety	8	2.0
RENAL AND URINARY DISORDERS		
Hematuria	10	2.5
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Nasal Discomfort	98	24.9
Sneezing	40	10.2
Rhinorrhea	39	9.9
Nasal Congestion	20	5.1
Cough	17	4.3
Epistaxis	9	2.3
Oropharyngeal Pain	8	2.0
VASCULAR DISORDERS		
Hypertension	26	6.6

A subject with more than one event represented by a given Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class).

Clinical Laboratory and Vital Signs Assessments
With the exception of decreases in serum sodium (discussed in the Hyponatremia section below), during DB3, DB4, and A2, there were no chemistry, hematology, or urinalysis findings that were clinically significant. There were no clinically significant changes in vital signs, either.

Hyponatremia

Hyponatremia is a known risk of desmopressin drugs. In the four placebo-controlled studies (DB1, DB2, DB3, and DB4), 31 (2.2%) subjects in the SER120 treatment group reported an AE of either decreased serum sodium or hyponatremia compared to one (0.1%) subject in the placebo group. Two of the events (one in the SER120 treatment group and one in the placebo group) met the criteria for a serious adverse event and 11 (10 in the SER120 treatment group and one in the placebo group) led to discontinuation from the study.

The one SER120-treated subject who reported a serious adverse event of hyponatremia (42S033) was randomized to the 1.5 μg dose during DB4. Six days after starting SER120, the subject went to the emergency room for back pain and intermittent shortness of breath. It is believed that she had symptoms of nausea, vomiting and diarrhea prior to this event. Serum sodium taken at that time was 122 mmol/L. She was treated for back pain, however, the low serum sodium was not addressed and she was discharged and continued in the study. The patient returned for visits on Days 29, 43, and 57 and had serum sodium values of 131 mmol/L, 131 mmol/L, and 133 mmol/L, during those visits. Three days after her Day 57 visit, the subject complained of weakness, nausea and vomiting and was seen by her personal physician. At that time, her serum sodium was 117 mmol/L and she was sent to the emergency room where she was treated with normal saline intravenously, but was not admitted to the hospital. The cause of her low serum sodium was attributed to gastroenteritis.

The other subject who reported a serious adverse event of hyponatremia (11S014) was randomized to placebo during DB4. On Day 66 of the trial, the subject reported nausea and being unable to urinate since early morning despite drinking fluids. He went to the emergency room and was found to have a serum sodium of 112 mmol/L. He was hospitalized overnight, treated with 0.9% saline and discharged the next morning with a serum sodium of 121 mmol/L.

Normal serum sodium generally ranges from 135 – 145 mmol/L, with severe hyponatremia being serum sodium of 125 mmol/L or less.

<u>Studies DB3 and DB4</u>
All subjects enrolled in DB3 and DB4 were required to have a serum sodium concentration within normal limits as an inclusion criterion. Fasted serum sodium concentration was assessed on Days 1 (baseline), 15, 29, 43, 57, 71, 85, and 99 of the studies. At any time during the study, a patient who had a hyponatremic event, defined as serum sodium of 126 to 129 mmol/L with clinical symptoms related to hyponatremia or serum sodium of 125 mmol/L or less with or without clinical symptoms, was required to be withdrawn from the study. One (0.2%) subject, receiving the 1.5 μg dose met the 126-129 mmol/L criterion for withdrawal and was prematurely discontinued. Five (1.1%) subjects, all receiving the 1.5 μg dose met the ≤125 mmol/L criterion for withdrawal and were prematurely discontinued. These discontinuations are discussed below.

During DB3 and DB4, in the 1.5 µg, 0.75 µg, and placebo treatment groups, 1.1%, 0%, and 0.2% of the subjects had nadir serum sodium values of ≤125 mmol/L; 2.0%, 2.0%, and 0% had nadir serum sodium values of 126-129 mmol/L; and 11.2%, 8.4%, and 4.4% had nadir serum sodium values of 130-134 mmol/L. The results of this analysis are summarized in Table 5.

Table 5: Categorical Analysis of Nadir Serum Sodium Values - DB3/DB4

Serum Sodium Range (mmol/L)	1.5 µg (N=448) n/N (%)	0.75 µg (N=454) n/N (%)	Placebo (N=454) n/N (%)
130 – 134	50/448 (11.2)	38/454 (8.4)	20/454 (4.4)
126 – 129	9/448 (2.0)	9/454 (2.0)	0/454 (0.0)
≤ 125	5*/448 (1.1)	0/454 (0.0)	1*/454 (0.2)

*Sodium assessments performed at laboratories other than the central laboratory (e.g., emergency room, physician's office) and were not included in the laboratory database.

Characteristics of the five SER120-treated subjects in the serum sodium category of less than or equal to 125 mmol/L are shown in Table 6. As noted above, all of these subjects were prematurely discontinued from the trial per protocol.

Table 6: Subjects with Nadir Serum Sodium Value ≤ 125 mmol/L - DB3 and DB4 (SER120-Treated Subjects)

Subject/ Study	M/F	Age (yrs)	Dose (µg)	Baseline Sodium	Lowest Sodium	Study Day	Symptoms	Comments/ concomitant medications
08S007/DB3	M	75	1.5	135	125	99	None	1/ A, C
17S004/DB3	M	70	1.5	136	124	29	None	2/ A, B
20S039/DB3	M	67	1.5	140	125	71	None	3/ A, B
11S005/DB4	M	75	1.5	138	124	99	None	4/
42S033/DB4	F	72	1.5	137	122*	21	None	5/ A, B
					117*	60	Weakness, nausea, vomiting	

M=male; F=female
*Sodium assessments performed at laboratories other than the central laboratory (e.g., emergency room, physician's office) and were not included in the laboratory database.
Comments:
1. Subject's serum sodium was 128 mmol/L on Day 71
2. In addition to an inhaled corticosteroid, the patient also had one injection of triamcinolone, 40 mg, 8 days prior to the Day 29 visit.
3. Subject was treated with oral prednisone 10 mg three times daily x 4 days, starting 5 days before the Day 71 visit.
4. Subject's serum sodium was 128 mmol/L on Days 43 and 71.
5. Investigator believes subject may have had an acute gastrointestinal illness that started prior to the Day 21 assessment. The Day 60 assessment was done the day after the subject discontinued study drug.
Concomitant Medications:
A. Corticosteroids including inhalant corticosteroids.
B. Non-steroidal anti-inflammatory drugs (NSAIDs)
C. Thiazide diuretics

Of the five SER-treated subjects with nadir serum sodium values ≤ 125 mmol/L, all were being treated with the 1.5 µg dose. All were 65 years of age or older. Four were male, one was female. Three of the five were being treated with corticosteroids and a non-steroidal anti-inflammatory drug. One was being treated with corticosteroids and a thiazide diuretic.

The nadir serum sodium values in these five subjects occurred throughout the trial, the earliest occurred at Day 21 (six days after starting active treatment) and the latest at Day 99 (the final visit of the trial).

Only one subject (42S033) with documented hyponatremia was symptomatic (serum sodium 117 mmol/L on Day 60 of the trial associated with weakness, nausea and vomiting). This is the same subject described above whose hyponatremia was reported as a serious adverse event.

Characteristics of the 18 SER120-treated subjects in DB3 and DB4 who had a nadir serum sodium in the range of 126 – 129 mmol/L are shown in Table 7.

Table 7: Subjects with Nadir Serum Sodium Value 126-129 mmol/L DB3 and DB4 (SER120-Treated Subjects)

Subject/ Study	M/F	Age	Dose (µg)	Baseline Sodium (mmol/L)	Lowest Sodium (mmol/L)	Study Day	Symptoms	Completed/ Discontinued
14S001/DB3	F	73	0.75	137	129	43	None	Completed
31S003/DB3	F	64	0.75	137	127[1]	71	None	Completed
34S029/DB3	F	67	0.75	141	129	99	None	Completed
38S032/DB3	F	65	0.75	140	129	57	None	Completed
54S009/DB3	M	67	0.75	139	128	57	None	Completed
71S017/DB3	M	78	0.75	136	128	29	None	Completed
77S008/DB3	M	76	0.75	142	128	29	None	D/C day 48[2]
77S017/DB3	M	81	0.75	136	127	29	None	Completed
89S035//DB4	F	64	0.75	137	126	43	None	D/C day 44[3]
12S010/DB3	M	73	1.5	139	127	EV	None	D/C day 16[4]
55S037/DB3	F	76	1.5	144	127	99	None	Completed
36S013/DB4	M	79	1.5	135	127	99	None	Completed
45S003/DB4	M	73	1.5	135	128	29	None	Completed
45S007/DB4	M	72	1.5	134	129	29	Weakness/tiredness	D/C day 37[5]
58S005/DB4	M	73	1.5	141	127	43	None	Completed
76S003/DB4	M	82	1.5	142	128	85	None	Completed
97S008/DB4	M	73	1.5	137	128 128	71 85	None	Completed
97S011/DB4	F	67	1.5	133	127	29	None	Completed

M=male; F=female; EV=exit visit; D/C=discontinued
[1]Subject's serum sodium was 129 mmol/L on Day 29.
[2]D/C due to an adverse event of low sodium level.
[3]D/C due to an adverse event of hyponatremia.
[4]Subject 12S010 withdrew consent on Day 16 after taking one dose of SER120. Serum sodium was 133 mmol/L on Day 15 (prior to starting SER120) and 127 at the exit visit, which occurred 14 days after the subject's last (only) dose of SER120.
[5]D/C due to an adverse event of blood sodium decreased.

Of the eighteen subjects with nadir serum sodium values between 126 and 129 mmol/L, nine were in the 1.5 µg dose group and nine were in the 0.75 µg dose group. No subjects in the placebo group had values in this category. Sixteen of these eighteen subjects (89%) were 65 years of age or older: all nine of the subjects treated with the 1.5 µg dose and seven of the nine subjects treated with the 0.75 µg dose. Eleven of the eighteen (61%) subjects were male and seven (39%) were female.

The nadir serum sodium values between 126 and 129 mmol/L in these 18 subjects occurred throughout the trial, the earliest occurred at Day 29 (14 days after starting active treatment) and the latest at Day 99 (the final visit of the trial). Only one of these eighteen subjects had symptomatic hyponatremia.

Fourteen of the eighteen subjects completed the study. Of the four subjects that discontinued, three discontinued due to the adverse event of decreased serum sodium or hyponatremia and one withdrew consent (one day after starting active treatment).

Open Label Safety Extension Study - A2

Baseline serum sodium concentration was assessed on Day 1 of the A2 extension study. To be included in the study, subjects were to have had a serum sodium concentration that was within normal limits. Fasted serum sodium was assessed throughout the extension study at the following time points: Days 10, 15, 23, 29; and then at Weeks 8, 14, 22, 30, 38, 46, 54, 62, 70, 86, 94, 102, 110, 118, and 126. At any time during the extension study, a patient who had a hyponatremic event, defined as serum sodium of 126 to 129 mmol/L with clinical symptoms related to hyponatremia or serum sodium of 125 mmol/L or less with or without clinical symptoms, was required to be withdrawn.

During the entire treatment period there were 64 (16%) subjects who had a serum sodium value in the range of 130 to 134 mmol/L. All of these subjects were asymptomatic and continued in the study except for one subject who discontinued at Day 15 with a serum sodium value of 131 mmol/L from Day 10 because she could not be up-titrated to the 1.5 μg dose and the 1.0 μg formulation was no longer available.

The percentage of subjects with serum sodium values in the 126 to 129 mmol/L range varied from 0.3% at extension baseline (one subject who should not have been enrolled, based on the inclusion/exclusion criteria) to 1.1% (2/184 subjects) at Week 38. After Week 38, there were no subjects who had a serum sodium value in the 126 to 129 mmol/L range. A total of nine (2%) subjects in A2 had a serum sodium value between 126 and 129 mmol/L at any time during the study. All nine were being treated with the 1.0 μg dose of the study drug at the time of the serum sodium assessment, and all were asymptomatic and continued in the study. Seven were 65 years of age or older (the other two subjects were 64 and 62 years of age). Six were male and three were female.

Three (0.8%) subjects had a serum sodium value less than or equal to 125 mmol/L during the entire study. This occurred in one subject out of 386 (0.3%) at Day 10, one subject out of 324 (0.3%) at Week 22, and one subject out of 348 (0.3%) at Week 30. Each of these subjects had a serum sodium value of 125 mmol/L at those time points. After Week 30, no subject had a serum sodium value of 125 mmol/L or less during the remainder of the study. These three subjects were asymptomatic but were discontinued from the study per protocol. Table 8 shows the number and percent of subjects in each serum sodium category at each study visit.

Table 8: Number and Percent of Subjects with Serum Sodium ≤ 125 mmol/L, 126 – 129 mmol/L, and 130 – 134 mmol/L at Each Study Visit – Extension Study A2

Visit Day	# of Patients	≤ 125 mmol/L n (%)	126–129 mmol/L n (%)	130–134 mmol/L n (%)
Baseline	383	0	1 (0.3)	6 (1.6)
Day 10	386	1 (0.3)	2 (0.5)	16 (4.1)
Day 15	377	0	0	11 (2.9)
Day 23	365	0	1 (0.3)	15 (4.1)
Day 29	366	0	2 (0.5)	17 (4.6)
Week 8	353	0	2 (0.6)	14 (4.0)
Week 14	337	0	1 (0.3)	15 (4.5)
Week 22	324	1 (0.3)	0	11 (3.4)
Week 30	348	1 (0.3)	2 (0.6)	9 (2.6)
Week 38	184	0	2 (1.1)	2 (1.1)
Week 46	223	0	0	9 (4.0)
Week 54	195	0	0	10 (5.1)
Week 62	171	0	0	6 (3.5)
Week 70	129	0	0	5 (3.9)
Week 78	248	0	0	9 (3.6)
Week 86	57	0	0	2 (3.5)
Week 94	48	0	0	1 (2.1)
Week 102	38	0	0	2 (5.3)
Week 110	20	0	0	1 (5.0)
Week 118	10	0	0	1 (10.0)
Week 126	61	0	0	4 (6.6)

The three subjects with serum sodium concentrations ≤ 125 mmol/L were all being treated with the 1.0 μg dose of the study drug and all were 75 years of age or older. Two subjects were female, one was male.

- The subject with serum sodium of 125 mmol/L on Day 10 had been randomized to placebo during DB3 and was first on active drug during A2. The Day 10 assessment was her only "on treatment" serum sodium assessment.

- The subject with serum sodium of 125 mmol/L at the Week 22 visit had been randomized to the 1.0 μg dose during DB3 and completed the study on Day 99 with serum sodium of 138 mmol/L. Her serum sodium values prior to the Week 22 assessment were all greater than 130 mmol/L.

- The subject with serum sodium of 125 mmol/L at the Week 30 visit had also been randomized to placebo during DB3 and was first on active drug during A2. Eleven days prior to his Week 30 visit, he was diagnosed with diverticulitis and was treated with hydromorphone, ciprofloxacin and metronidazole for seven days. Because of his abdominal symptoms, which were ongoing at the Week 30 visit, the subject was not eating much and was drinking extra fluids. Except for the Day 29 visit, when his serum sodium was 128 mmol/L, the subject's serum sodium was greater than 130 mmol/L at all assessments done prior to Week 30.

Subgroup Analysis-Age

Based on the results of the serum sodium assessments during DB3, DB4, and A2 and reports in the literature[1,2,3] suggesting an increased risk of hyponatremia with increased age, a subgroup analysis of the DB3/DB4 data was done comparing subjects younger than 65 years of age to subjects 65 years of age or older. Table 9 summarizes the results of this analysis.

Table 9: Categorical Analysis of Nadir Serum Sodium Value - DB3/DB4 – Age < 65 and ≥ 65 years

Serum Sodium Range (mmol/L)	1.5 µg		0.75 µg		Placebo	
	<65 yrs (N=202) n/N (%)	≥65 yrs (N=246) n/N (%)	<65 yrs (N=205) n/N (%)	≥65 yrs (N=249) n/N (%)	<65 yrs (N=205) n/N (%)	≥65 yrs (N=249) n/N (%)
130–134	18/202 (8.9)	32/246 (13.0)	10/205 (4.9)	28/249 (11.2)	9/205 (4.4)	11/249 (4.4)
126–129	0/202 (0)	9/246 (3.7)	2/205 (1.0)	7/249 (2.8)	0/205 (0)	0/249 (0)
≤ 125	0/202 (0)	5*/246 (2.0)	0/205 (0)	0/249 (0)	0/205 (0)	1*/249 (0.4)

*Includes 1 patient whose serum sodium value was obtained outside the study central laboratory and was, therefore, not included in the laboratory database.
Treatment period for DB3 and DB4 was 12 weeks.

The incidence of subjects with nadir serum sodium values of 125 mmol/L or less was 2.0%, 0%, and 0.4% in the 1.5 µg, 0.75 µg, and placebo treatment groups for subjects who were 65 years or older compared to 0% in all three treatment groups for subjects who were less than 65 year of age.

The incidence of subjects with nadir values between 126-129 mmol/L was 3.7%, 2.8%, and 0% in the 1.5 µg, 0.75 µg, and placebo treatment groups for subjects who were 65 years or older compared to 0%, 1.0%, and 0% for subjects less than 65 years of age.

The incidence of subjects with nadir values between 130-134 mmol/L was 13.0%, 11.2%, and 4.4% in the 1.5 µg, 0.75 µg, and placebo treatment groups for subjects who were 65 years or older compared to 8.9%, 4.9%, and 4.4% for subjects less than 65 year of age.

Risk Mitigation

Labeling

The labeling submitted by the Applicant includes information and recommendations that are intended to reduce the risk of hyponatremia. The proposed prescribing information contains Contraindications for patients with hyponatremia or a history of hyponatremia, renal impairment (glomerular filtration rate below 50 mL/min/1.73 m^2), severe heart failure (New York Heart

[1] Giordano M, et al, Diseases associated with electrolyte imbalance in the ED: age-related differences, Am J Emerg Med (2016), http://dx.doi.org/10.1016/j.ajem.2016.05.056.
[2] Lindner G, Pfortmüller C, A, Leichtle A, B, Fiedler G, M, Exadaktylos A, K, Age-Related Variety in Electrolyte Levels and Prevalence of Dysnatremias and Dyskalemias in Patients Presenting to the Emergency Department. Gerontology 2014;60:420-423.
[3] Upadhyay A, Bertrand JL, et al, Epidemiology of Hyponatremia, Semin Nephrol 2009;29:227-238.

Association Class III and IV), known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion, diabetes insipidus, polydipsia, and uncontrolled hypertension.

The proposed prescribing information also includes Warnings and Precautions explaining the risk of hyponatremia during treatment with SER120 and precautions regarding use of the drug in patients with sodium losing conditions, heart failure (New York Heart Association Class II), uncontrolled diabetes mellitus, and a risk of intracranial pressure increase. Also included are Warnings and Precautions regarding the concomitant use of loop diuretics, systemic or inhaled pulmonary corticosteroids, and drugs known to potentiate inappropriate antidiuretic hormone secretion and/or increase the risk of hyponatremia.

In addition, the proposed prescribing information provides the following instructions for monitoring serum sodium and recommendations for initiating therapy.

> *Serum sodium monitoring*
> Serum sodium levels should be checked prior to initiating therapy or increasing dose. Serum sodium levels should be checked again within 14 days after initiating therapy or increasing dose. Periodically, serum sodium levels should be checked during therapy, as clinically appropriate. If serum sodium level decreases below the normal range during treatment, consideration should be given to discontinuing treatment until sodium levels return to normal based on physician judgment.
>
> *Initiating treatment*
> Serum sodium should be in the normal range before starting treatment. The recommended starting dose is 0.75 μg each night for 2-4 weeks. Based on individual patient efficacy and tolerability, the dose may be increased to 1.5 μg each night.

The Applicant also proposes a Medication Guide, which is labeling directed to patients and caregivers, and dispensed each time a prescription is filled. In general, serious risks could warrant a Medication Guide as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent a serious adverse event.
- The product has serious risk(s) that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial for product effectiveness.

The Applicant's proposed Medication Guide informs the patient about the risk of hyponatremia and describes the symptoms that patients should be alerted to that may indicate that they are experiencing hyponatremia. The proposed Medication Guide also warns that severely low sodium concentrations may result in more serious side effects such as seizure, coma, or breathing difficulties.

Risk Evaluation and Mitigation Strategies (REMS)

The Food and Drug Administration Amendments Act of 2007 authorizes the FDA to require a company to develop and comply with a risk evaluation and mitigation strategy (REMS) for its drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond professional labeling to address certain serious risk(s).

A REMS program can include one or more of the following elements: a Medication Guide or patient package insert, a communication plan to healthcare providers, elements to assure safe use, and an implementation system. All NDA (New Drug Application) and BLA (Biologics License Application) REMS are required to have a timetable for submission of assessments of the REMS.

It is important to note that REMS are risk mitigation tools and do not address efficacy deficiencies. Before considering whether a REMS is needed, a drug must first be shown to have substantial evidence of effectiveness, and then a determination must be made that labeling alone is not sufficient to ensure that the benefits of the drug outweigh the risks.

An applicant may voluntarily submit a proposed REMS. A voluntarily submitted REMS would not be approved unless and until FDA determines that the drug has been shown to be effective and that, because of certain serious risk(s), risk mitigation beyond labeling is necessary to ensure that the benefits outweigh the risks.

The Applicant for SER120 has voluntarily proposed a REMS to mitigate the risk of hyponatremia that includes a Medication Guide, communication plan, and a timetable for submission of assessments. A Medication Guide is part of the FDA-approved labeling and can also be a REMS element, if a REMS is determined necessary to ensure the benefits outweigh the risks. The Applicant's proposed communication plan consists of a Dear Health Care Professional Letter to be distributed in a one-time mass mailing targeted to potential prescribers of SER120 to inform them of the risk of hyponatremia, how SER120 was designed to minimize this risk, and conditions that can increase this risk. The letter also describes dosing, monitoring and precautionary instructions derived from the drug label.

The FDA will be seeking input from the advisory committee panel as to whether the Applicant has provided substantial evidence of effectiveness for the proposed use, including input on whether the treatment effects are clinically meaningful. We will then ask the Advisory Committee members to vote on whether the benefits of SER120 outweigh its risks for the intended use, as proposed by the Applicant. We look forward to the Advisory Committee's input on the discussion and voting questions before we decide whether a REMS will be necessary for the approval of SER120.

Safety Summary

Deaths

Five deaths occurred during the clinical trials for SER120. All deaths occurred during treatment with SER120. Four of the deaths occurred in subjects who were older than 75 years of age. A role of SER120 in the deaths due to cecal perforation, coronary atherosclerosis, and bleeding aortic aneurysm is unlikely; a role cannot be definitively ruled out for the other two deaths.

Serious Adverse Events

During the four placebo controlled trials (DB1, DB2, DB3 and DB4), the incidence of SAEs was similar across all SER120 treatment groups (0.5, 0.75, 1.0, and 1.5 μg) and was similar to the incidence in the placebo group. Four subjects in the SER120 treatment group reported SAEs in the cardiac disorders SOC compared to none in the placebo group. One of these subjects, reported the SAE of congestive heart failure during treatment with the 0.75 μg dose of SER120 during DB4. Two subjects, one in the 1.5 μg treatment group and one in the placebo group, reported hyponatremia as a SAE.

Adverse Events Leading to Discontinuation

During DB3 and DB4 the incidence of subjects discontinuing due to an AE was slightly greater in SER120-treated subjects than in subjects treated with placebo. The most common AEs leading to discontinuation in SER120-treated subjects were nasal discomfort and hyponatremia.

Common Adverse Events

During DB3 and DB4, the incidence of subjects with at least one AE was slightly greater in SER120-treated subjects than in subjects treated with placebo. The common adverse events occurring at a greater incidence in SER120-treated subjects than in subjects treated with placebo were nasopharyngitis, urinary tract infection, hypertension/blood pressure increased, sneezing, nasal congestion, back pain, dizziness, and blood sodium decreased.

Hyponatremia

During DB3 and DB4, in the 1.5 μg, 0.75 μg, and placebo treatment groups, 1.1%, 0%, and 0.2% of the subjects had nadir serum sodium values of ≤125 mmol/L; 2.0%, 2.0%, and 0% had nadir serum sodium values of 126-129 mmol/L; and 11.2%, 8.4%, and 4.4% had nadir serum sodium values of 130-134 mmol/L.

IN DB3 and DB4, the incidence of hyponatremia with SER120 appears lower among subjects younger than 65 years of age compared to those over 65 years of age.

Center for Drug Evaluation and Research

Division of Clinical Pharmacology-3, Office of Clinical Pharmacology,
Office of Translational Sciences

Overview of Clinical Pharmacology

E

Overview of Clinical Pharmacology

This memorandum provides an overview of the key clinical pharmacology findings from the SER120 (demopressin nasal spray) development program. These findings are based on FDA's review of the data submitted to the New Drug Application.

Pharmacokinetics (PK)

1) General PK properties

The PK profile of desmopressin following administration of 0.75 mcg or 1.5 mcg desmopressin nasal spray in male or female patients with nocturia was characterized from a subset of 36 subjects in the DB3 phase 3 trial. The median time to reach maximum plasma concentration (T_{max}) was 0.25 hour for the 0.75 mcg dose and 0.75 hour for the 1.5 mcg dose. The C_{max} and area under the concentration-time (AUC) values of desmopressin increased slightly more than dose-proportional between 0.75 mcg and 1.5 mcg. The mean terminal elimination half-life was 1.9 hours for the 0.75 mcg dose and 2.8 hours for the 1.5 mcg dose (Table 1). A few subjects had concentrations below the lower limit of quantification of the assay (2 pg/mL).

Table 1. Summary of PK parameters of desmopressin in nocturic patients given 0.75 or 1.5 mcg doses of desmopressin nasal spray (Study 201101 - DB3)

		0.75 mcg (n = 18)	**1.5 mcg (n = 18)**
Demographics	Gender (M:F)	9 : 9	9 : 9
	Age (years)	66 (52 - 81)*	62 (51 - 80)*
	Weight (kg)	81 (43 -134)*	92 (47 - 131)*
PK parameter	T_{max} (hour)	0.25 (0.25-0.5)** (n = 12)	0.75 (0.25-3)** (n = 15)
	C_{max} (pg/mL)	4.0 ± 3.9 (n = 16)	9.1 ± 6.9 (n = 15)
	AUC_t (pg·h/mL)	5.1 ± 7.5 (n = 16)	23.1 ± 19.0 (n = 13)
	AUC_{inf} (pg·h/mL)	16.0 ± 11.6 (n = 9)	41.3 ± 19.5 (n = 10)
	$t_{1/2}$ (hour)	1.9 ± 1.1 (n = 9)	2.8 ± 0.9 (n = 10)

* Mean (range) and ** Median (range)

The bioavailability of the nasal spray dosage form is approximately 8% compared to the subcutaneous injection formulation.

2) Intrinsic factors affecting the PK of desmopressin

The PK study in the DB3 phase 3 trial demonstrated that there is no significant difference in the dose-normalized C_{max} and AUC_t of desmopressin between patients 65 years of age and older and those younger than 65 years of age. Analysis of the pooled PK results obtained from 5 studies also did not identify age as a significant covariate.

The PK study in the DB3 phase 3 trial demonstrated that gender and body weight also did not have a significant impact on the systemic exposure to desmopressin.

The terminal half-life was significantly prolonged in patients with severe or moderate renal impairment (3.4 ± 1.8 hour, n=4) compared to matched patients (1.1 ±0.2 hour, n=3) with normal or mild renal impairment. The AUC_t increased by approximately three-fold (4.7 ± 4.3 pg·h/mL, n=8 vs. 1.6 ± 1.7 pg·h/mL, n=9) in patients with severe or moderate renal impairment compared to matched patients with normal or mild renal impairment. However, in this study, a number of concentrations of desmopressin were below the assay's lower limit of quantification. In the PK study of the DB3 phase 3 trial (n = 54), the relationship between systemic exposure to desmopressin and renal function was analyzed. While there was a trend towards an increase in dose-normalized desmopressin C_{max} and AUC_t with decreasing renal function, based on estimated glomerular filtration rate (eGFR), the relationship was not statistically significant. However, this study did not include patients with an eGFR below 50 mL/min/1.73 m^2. The Applicant has proposed a contraindication for patients with an eGFR below 50 ml/min/1.73 m^2.

The Applicant has not evaluated the effect of hepatic impairment on the PK of desmopressin. The phase 3 studies excluded patients with evidence of hepatic impairment and those with abnormal liver tests exceeding certain thresholds (e.g., serum transaminases ≥2.5x upper limit of normal). The Applicant has not proposed any contraindication or dose modification for this patient population.

The intranasal absorption profile of desmopressin may change in situations of abnormal nasal conditions such as chronic or allergic rhinitis, nasal congestion or blockage, nasal discharge, or atrophy of the nasal mucosa. The Applicant did not conduct any PK studies in patients with these conditions. The Applicant submitted safety data for patients with a medical history of rhinitis and patients who reported an event of rhinitis in the DB3 and DB4 phase 3 studies, and concluded that there was no clinically significant safety signal observed.

Drug-drug interaction potential

1) PK interaction potential

The Applicant did not submit any data from *in vitro* or *in vivo* PK studies to evaluate a drug-drug interaction potential of desmopressin with other medications. Desmopressin is a peptide; therefore, concomitant medication is unlikely to affect its metabolic pathways.

2) Pharmacodynamic (PD) interaction potential

The Applicant did not conduct any studies to evaluate a potential PD interaction with other drugs. However, the risk of water intoxication and hyponatremia should be considered when desmopressin is concomitantly administered with drugs that may cause water retention and lower serum sodium concentrations such as tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, nonsteroidal anti-inflammatory drugs, lamotrigine and carbamazepine.

3) Concomitant medication administered via nasal route

It is theoretically possible that a concomitant use of drugs administered via the nasal route, such as nasal decongestants, may affect the absorption profile of desmopressin. While the Applicant did not conduct any studies to evaluate a PK interaction with other drugs administered via the nasal route, they have

proposed that patients may continue to use concomitant nasal sprays, including those containing corticosteroids, antihistamines or decongestants while taking desmopressin nasal spray as long as the last dose of the concomitant nasal spray is taken at least 6 to 8 hours prior to the dose of desmopressin nasal spray. The review of this issue is ongoing.

Pharmacodynamics

The anti-diuretic effect, urine osmolality, and urine output, after administration of 0.5, 1 and 2 mcg of desmopressin nasal spray were evaluated in water-loaded healthy male and female volunteers in a fixed sequence cross-over design. Single administration of desmopressin nasal spray produced rapid and substantial anti-diuretic effects in these subjects. The magnitude and duration of the anti-diuretic effect increased with dose, with the duration of anti-diuresis ranging from 3 to 6 hours. The most-pronounced decreases in serum sodium concentrations following administration of desmopressin nasal spray were observed at 2 and 4 hours following administration of 0.5 and 1 mcg desmopressin nasal spray. The time-course of change in serum sodium concentration appears to be consistent with the duration of antidiuretic action following administration of desmopressin nasal spray (Figure 1). For unclear reasons, administration of the 2 mcg dose did not lead to much decrease in serum sodium concentrations, although the baseline sodium concentrations prior to this dose were slightly lower than those in the other study periods.

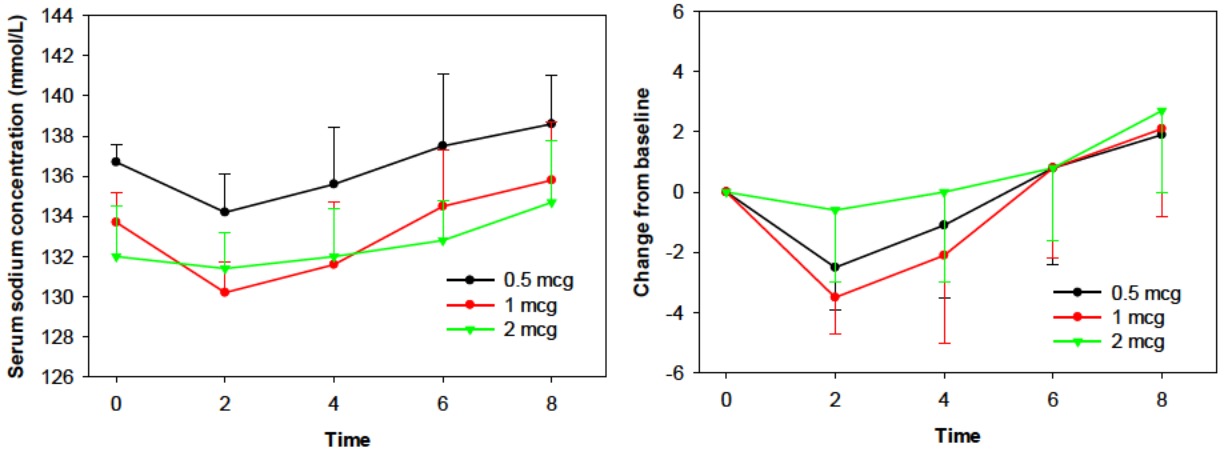


Figure 1. Mean serum sodium concentrations over time following a single dose of 0.5, 1, or 2 mcg desmopressin nasal spray in 12 healthy male or female subjects. Error bars indicate standard deviation.

Center for Drug Evaluation and Research

Division of Bone, Reproductive and Urologic Products,
Office of New Drugs

Overview of Nonclinical Pharmacology/Toxicology

F

Background

The nonclinical evaluation of SER120 includes studies suitable to characterize the toxicology of the drug in comparison to DDAVP® nasal spray, another FDA-approved desmopressin nasal spray. The FDA recommended a 1-month rat bridging study to compare the local and systemic effects of SER120 and DDAVP®, with particular focus on the olfactory neuroanatomical areas because of SER120's intranasal route of administration.

The Applicant's formulation of SER120 contains three excipients cyclopentadecanolide (CPD) ((b) (4)%), cottonseed oil ((b) (4)%) and sorbitan monolaurate ((b) (4)%) not previously used via the intranasal route. The sponsor conducted long-term studies in the dog (39-weeks) and the rat (26-weeks) to assess the toxicity of these excipients via the intranasal route. The animal species used in these studies are relevant to assessing toxicity of SER120. The following discussion summarizes the animal findings considered relevant to the safety assessment of SER120.

Rat 28-day Intranasal Bridging Study

Given the intranasal route of administration, the study design included evaluation of nasal turbinates and neuroanatomical areas specific to olfactory pathways in the brain. No remarkable findings were noted in this study based on a dose about 1.1 times higher than the proposed clinical dose. This dose multiple was calculated based on interspecies comparisons of nasal cavity surface area. The low safety margin relative to the maximum proposed clinical dose of 1.5 µg limits conclusions.

Desmopressin causes hyponatremia in humans. The 28-day rat nonclinical toxicology study with SER120 did not include measurement of electrolytes in the chemistry panel. Hence, potential changes in serum sodium could not be evaluated in this animal study.

Excipient Evaluation: A 39-week Intranasal Dog Study

The potential nasal, oral, and pulmonary effects of CPD in comparison with those of a saline and a cottonseed oil and sorbitan-containing emulsion were assessed via daily intranasal spray to dogs for 39 weeks.

CPD-related findings were limited to histopathology in the nose. These included minimal to slight hyperplasia of the nasal epithelium and mixed cell inflammation consistent with an irritant response and were not considered dose-limiting. No adverse effects were noted in animals treated with the emulsion control.

Based on nasal surface area, evaluation of CPD in the dog occurred at 970-5789 times the proposed maximum clinical dose of 1.5 µg and provided a suitable safety evaluation.

Excipient Evaluation: A 26-week Intranasal Rat Study

The potential nasal, oral, and pulmonary effects of CPD in comparison with those of a saline and a cottonseed oil and sorbitan-containing emulsion were assessed via daily intranasal spray to rats for 26 weeks.

There were no remarkable findings in CPD or emulsion treated animals. Based on nasal surface area, evaluation of CPD in the rat occurred at 458-9136 times the proposed maximum clinical dose of 1.5 µg and provided a suitable safety evaluation.

Neoplasms/Malignancies and Genetic Toxicology Risk for CPD

CPD has been evaluated in the mouse lymphoma forward mutation assay, an *in vivo* mouse micronucleus assay, and in the Ames Assay. All tests were negative for genetic toxicity. On the basis of negative genetic toxicology data, limited systemic exposure, absence of accumulation in nonclinical and clinical pharmacokinetic data, and negative histopathology data from the two chronic nonclinical toxicology studies, carcinogenicity studies were not conducted for CPD. The Applicant submitted a carcinogenicity waiver request and the FDA concurred that carcinogenicity studies are not required at this time.

Conclusion

The safety profile of desmopressin is well established. The Applicant conducted toxicity studies to characterize the local toxicity of desmopressin and to establish safety profiles for different excipients used in SER120 compared to the FDA-approved DDAVP® nasal spray.

The toxicology profile of SER120 did not yield adverse findings in the 28-day rat bridging study when administered via the intranasal route. The chronic dog (39-week) and rat (26-week) evaluation of SER120 excipients also did not reveal dose-limiting toxicities.

Based on nasal surface area, the safety margin for SER120 approximated the maximal clinical dose in the 28-day rat bridging study and the evaluation of CPD in the dog and rat occurred at a maximum of 5789- and 9136- times, respectively, the proposed maximum clinical dose of 1.5 µg. No dose-limiting toxicity was observed in rats or in dogs.