Desmopressin Nasal Spray for the Treatment of Nocturia

Opening Remarks

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Director
Division of Bone, Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Outline

• Overview of desmopressin and nocturia
• Issues with the proposed indication
• Efficacy and safety issues
• Discussion and voting questions
Desmopressin Nasal Spray

• **Drug:** Desmopressin nasal spray (SER120)

• **Proposed indication:** Treatment of nocturia in adults who awaken at least two times per night to urinate

• **Proposed regimen:** Start with 0.75 mcg/night then increase to 1.5 mcg/night, if needed, after 2-4 weeks
Desmopressin, In General

• Synthetic analogue of vasopressin

• Stimulates renal water reabsorption, leading to more concentrated urine and less water excretion

• Other formulations are FDA-approved for
  – Diabetes insipidus
  – Primary nocturnal enuresis
  – Hemostasis in von Willebrand disease and Hemophilia A

• Most important risk is hyponatremia
  – Led to removal of the primary nocturnal enuresis indication for the intranasal formulations
Nocturia

- Nocturia is defined as wakening at night to urinate, with each voiding episode preceded and followed by sleep
- Often considered clinically meaningful when ≥2 episodes/night
- Prevalence increases with advancing age
- Associated with sleep disruption, decreased quality of life, falls and fracture
- No FDA-approved treatments, but some drugs used off-label
- Other desmopressin formulations are approved outside the United States for nocturia associated with nocturnal polyuria
Nocturia

• Nocturia is a symptom caused by underlying condition(s) such as
  – **Bladder dysfunction** (e.g., overactive bladder; bladder outlet obstruction from benign prostatic hyperplasia)
  – **Edema-associated states** (e.g., heart failure, renal disease, peripheral edema)
  – **Neurodegenerative conditions** (e.g., Parkinson’s, Alzheimer’s)
  – **Endocrine/Metabolic abnormalities** (e.g., diabetes insipidus, uncontrolled diabetes mellitus, hypokalemia, hypercalcemia)
  – **Medications** (e.g., diuretics), caffeine, alcohol
  – **Excessive fluid intake**
Issues Related to the Indication

• The Applicant is proposing a broad indication, but...
  – Nocturia is a symptom of underlying condition(s)
  – The trials had numerous exclusion criteria
  – Did not systematically assess whether the drug adversely affects other aspects of the underlying condition(s)

• This is one area where we will be seeking advice from the advisory committee panel
Issues Related to the Designs of the Pivotal Trials (DB3 and DB4)

• Enrollment was limited to adults ≥50 years old

• No restrictions on fluid intake

• Numerous exclusion criteria

• Did not test the proposed titration regimen

• Modified intent-to-treat (placebo non-responders) was the primary statistical population
Key Efficacy Endpoints

- Two co-primary efficacy endpoints
  - Change from baseline in mean number of nocturia episodes per night
  - Percentage of patients with ≥50% reduction from baseline in mean number of nocturia episodes per night

- Secondary efficacy endpoints
  - Impact of Nighttime Urination (INTU) Overall Impact score (DB4 only)
  - Percentage of nights with 0 and ≤1 nocturia episodes
Efficacy Issues

• DB3 studied three desmopressin doses
  – 0.75 mcg, 1.0 mcg and 1.5 mcg vs. placebo

• DB4 studied two desmopressin doses
  – 0.75 mcg and 1.5 mcg vs. placebo

• In both DB3 and DB4, only the 1.5 mcg dose met both co-primary efficacy endpoints
## Efficacy Issues

<table>
<thead>
<tr>
<th>1.5 mcg Dose</th>
<th>Baseline (Mean)</th>
<th>Improvement Compared to Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction from baseline in nocturia episodes</td>
<td>~3 per night</td>
<td>DB3: 0.4 per night (mean) DB4: 0.3 per night (mean)</td>
</tr>
<tr>
<td>Percentage of patients with ≥50% reduction in nocturia</td>
<td>-</td>
<td>DB3: 52% drug vs. 33% placebo DB4: 47% drug vs. 29% placebo</td>
</tr>
<tr>
<td>INTU Overall Impact score (Range 0-100)†</td>
<td>~30</td>
<td>DB4: 2.6 (mean)</td>
</tr>
</tbody>
</table>

*All treatment differences are statistically significant
†Higher scores indicate more severe impacts of nocturia; INTU was only used in DB4
Safety Issues

• Hyponatremia is the most important risk
  – Higher incidence with the 1.5 mcg dose compared to the 0.75 mcg dose
  – Higher incidence among those ≥65 years old compared to those <65 years of age
Discussion and Voting Questions
Question 1

• The Applicant’s trials limited enrollment to adults at least 50 years of age, had numerous exclusion criteria, and had no restrictions on fluid intake. Discuss whether the Applicant studied desmopressin in the appropriate patient population.
Question 2

• Discuss the clinical significance of the observed treatment effects of desmopressin on nocturia compared to placebo.
Question 3

• Discuss whether the safety of desmopressin has been adequately characterized, and whether additional safety data are needed.
Question 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.
Question 5

• Is there sufficient evidence to conclude that at least one of the desmopressin doses is effective?

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.
Question 6

• Do the benefits of desmopressin outweigh the risks and support approval?

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.
Efficacy

Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)
October 19, 2016

Olivia J. Easley, M.D.
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
SER120 (desmopressin nasal spray)  
Proposed Indication and Dose

• Treatment of nocturia in adults who awaken two or more times per night to void (without respect to nocturia etiology)

• Proposed dose:
  – 0.75 mcg thirty minutes before bedtime which may be increased to 1.5 mcg nightly depending on response and tolerability.
Efficacy Database

- Two phase 3, randomized, double-blind, placebo-controlled trials, 12-week treatment period (Trials DB3 and DB4)
  - 452 subjects → SER120 1.5 mcg nightly
  - 183 subjects → SER120 1.0 mcg nightly (Trial DB3 only)
  - 458 subjects → SER120 0.75 mcg nightly
  - 446 subjects → placebo
Design of Efficacy Trials

2-week screening period

- Each week:
  - Consecutive 3-day voiding diary
  - Impact of Nighttime Urination (INTU) questionnaire (Study DB4 only)

2-week double-blind placebo run-in phase

- All subjects assigned to placebo
- Each week: 3-day voiding diary and INTU (Study DB4 only)

12-week treatment period

- All subjects randomized to SER120 or placebo taken nightly
- No restrictions on fluid intake
- Complete 3-day voiding diary every two weeks and in Study DB4, INTU at weeks 6 and 12
Analysis Populations

• Intent-to-treat (ITT) population – All randomized patients with at least 3 days of post-randomization efficacy data; consisted of both placebo responders and placebo non-responders

• Modified intent-to-treat (mITT) population – All placebo non-responders with at least 3 days of post-randomization efficacy data
Primary Efficacy Endpoints

• Co-primary: Change from 2-week screening period to 12-week treatment period in
  • Mean number of nocturia episodes per night
  • Percentage of patients with a \( \geq 50\% \) reduction in mean nocturia episodes per night
Selected Pre-specified Secondary Efficacy Endpoints

- Change from 2-week screening period to 12-week treatment period in
  - INTU overall impact score (Trial DB4 only)
  - Percent of nights with 0 nocturia episodes
  - Percent of nights with ≤1 nocturia episode
Key Inclusion Criteria

• Men and women ≥50 years of age
• History of nocturia (≥6 month history of ≥ 2 nocturia episodes/night)
• Documented nocturia by voiding diary (≥13 nocturia episodes over six days)
• 24-hour urine output ≤ 4500 mL/24 hours
• Normal serum sodium concentration
Key Exclusion Criteria

- **Urologic conditions**
  - Nocturnal enuresis
  - Urinary bladder surgery or radiotherapy within 24 months prior
  - Neurogenic detrusor overactivity
  - UTI, hematuria, interstitial cystitis

- **Signs/symptoms of bladder dysfunction:**
  - Urinary retention (post-void residual > 150 mL) by history
  - Severe daytime lower urinary tract symptoms due to BPH, OAB or stress incontinence.
  - Daytime urinary frequency (> 8 episodes per day)

- **Sleep disorders**
  - Obstructive sleep apnea
  - Hyperkinetic limb disorder
  - Work interfering with nighttime sleep

- **Edematous states:**
  - Congestive heart failure (NYHA Class II through IV)
  - Nephrotic syndrome
  - >2+ pretibial edema on exam

- **Disorders of free water intake/excretion:**
  - Diabetes insipidus
  - Polydipsia or thirst disorders
  - Syndrome of inappropriate secretion of anti-diuretic hormone (SIADH)

- **Other:**
  - Unstable diabetes mellitus
  - Uncontrolled hypertension
  - Unstable angina
  - Hepatic or renal impairment
  - Alcohol/substance abuse
  - Malignancy
Concomitant Medications

- **Prohibited:**
  - Loop diuretics
  - Systemic corticosteroids

- **Restricted medications** (only if at stable dose ≥2 months):
  - $\alpha$-1-adrenoceptor antagonists
  - 5-$\alpha$ reductase inhibitors
  - Anti-cholinergics
  - Anti-spasmodics
  - Sedative/hypnotics
  - SSRI/SNRIs
  - NSAIDs
  - Thiazide diuretics
## Subject Disposition in Trials DB3 and DB4, Intent-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>Trial DB3</th>
<th>Trial DB4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SER120 1.5 mcg</td>
<td>SER120 1.5 mcg</td>
</tr>
<tr>
<td></td>
<td>SER120 0.75 mcg</td>
<td>SER120 0.75 mcg</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Randomized N</td>
<td>186</td>
<td>266</td>
</tr>
<tr>
<td>Completed</td>
<td>85%</td>
<td>86%</td>
</tr>
<tr>
<td>Discontinued</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>188</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>88%</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>12%</td>
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</table>
### Subject Demographics, Trials DB3 and DB4 Pooled Intent-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>SER120 1.5 mcg</th>
<th>SER120 0.75 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>66</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>57%</td>
<td>56%</td>
<td>58%</td>
</tr>
<tr>
<td>Female</td>
<td>41%</td>
<td>42%</td>
<td>40%</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White/Caucasian</td>
<td>76%</td>
<td>81%</td>
<td>79%</td>
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<tr>
<td>Black/African American</td>
<td>13%</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Asian</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>
## Nocturia Etiology, Trials DB3 and DB4 Pooled, Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Investigator assessment (% of subjects)</th>
<th>SER120 1.5 mcg</th>
<th>SER120 0.75 mcg</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Nocturnal polyuria +/- additional etiology</td>
<td>76</td>
<td>79</td>
<td>80</td>
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<tr>
<td>Nocturnal polyuria alone</td>
<td>21</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Overactive bladder alone</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>BPH alone</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

% with nocturnal polyuria based on 24 hour urine collection at screening

| Present | 78 | 79 | 78 |
Efficacy Findings
Co-primary Efficacy Endpoint #1: Change in Nightly Nocturia Episode Frequency, Trials DB3 and DB4, Intent-to-Treat population

<table>
<thead>
<tr>
<th></th>
<th>SER120 1.5 mcg</th>
<th>SER120 0.75 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB3 N</td>
<td>179</td>
<td>186</td>
<td>186</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>3.2</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-1.6</td>
<td>-1.4</td>
<td>-1.2</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-0.4</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-0.6, -0.2</td>
<td>-0.4, -0.1</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SER120 1.5 mcg</th>
<th>SER120 0.75 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB4 N</td>
<td>260</td>
<td>262</td>
<td>260</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>3.3</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-1.5</td>
<td>-1.4</td>
<td>-1.2</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-0.3</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-0.4, -0.1</td>
<td>-0.4, -0.1</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
Co-primary Efficacy Endpoint #2: Percentage of Subjects with ≥50% Reduction in Nightly Nocturia Episodes During Treatment Period, Trials DB3 and DB4, Intent-to-Treat population

**Trial DB3**
- SER120 1.5 mcg (N=179): 52%*
- SER120 0.75 mcg (N=186): 41%**
- Placebo (N=186): 33%

**Trial DB4**
- SER120 1.5 mcg (N=260): 47%+
- SER120 0.75 mcg (N=262): 36%++
- Placebo (N=260): 29%

* p-value vs. placebo <0.001
** p-value vs. placebo = N/A
++ p-value vs. placebo = 0.09
Secondary Efficacy Endpoint #1 – Change in INTU Overall Impact score, Trial DB4, Intent-to-Treat population

<table>
<thead>
<tr>
<th></th>
<th>SER120 1.5 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>260</td>
<td>260</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>34.4</td>
<td>32.3</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-14.1</td>
<td>-11.5</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-2.6</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-4.8, -0.4</td>
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</tr>
<tr>
<td>p-value</td>
<td>0.02</td>
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</tbody>
</table>
## Select Secondary Efficacy Endpoints, Trials DB3 and DB4, ITT population: Percent of Nights with 0 Nocturia Episodes

<table>
<thead>
<tr>
<th></th>
<th>DB3</th>
<th>DB4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SER120 1.5 mcg</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>179</td>
<td>186</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Mean change from baseline*</td>
<td>11.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>2.2, 9.6</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.002</td>
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</tbody>
</table>

*Change from baseline was obtained from an ANCOVA model
Select Secondary Efficacy Endpoints, Trials DB3 and DB4, ITT population: Percent of Nights with ≤1 Nocturia Episode

<table>
<thead>
<tr>
<th></th>
<th>DB3</th>
<th>DB4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>179</td>
<td>186</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Mean change from baseline*</td>
<td>41.9</td>
<td>32.9</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>8.1, 22.9</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
An Exploratory Analysis of Clinical Meaningfulness

October 19, 2016

Jia Guo, Ph.D. – Statistical Reviewer
Division of Biometrics III
Office of Biostatistics/CDER
Efficacy

• SER 120 1.5 mcg dose efficacy (mean change from baseline in nocturia episodes vs. placebo)
  – Study DB3: -1.6 vs. -1.2 (p-value: <0.0001)
  – Study DB4: -1.5 vs. -1.2 (p-value: 0.0005)

• FDA conducted an exploratory analysis to evaluate if the reductions in nocturia episodes of this magnitude is potentially “meaningful” to patients
Anchor-based Approach

TREATMENT BENEFIT SCALE (DAY 99 (STUDY EXIT))

Please complete the following question by considering your current nighttime urination compared to before you received any study treatment in this trial.

My condition (waking up at night to urinate) is now:

- much better
- somewhat better
- not changed
- somewhat worse
- much worse

Change in Nocturia Episodes  mapping  Treatment Benefit Scale (TBS)
### Exploratory Data Summary (DB4)

**Response Rate**

- **Much Better**: 43% (SER 120 1.5 mcg) vs. 35% (Placebo)
- **Somewhat Better**: 37% (SER 120 1.5 mcg) vs. 38% (Placebo)
- **Not Changed**: 20% (SER 120 1.5 mcg) vs. 27% (Placebo)
- **Somewhat Worse/Much Worse**: 0% vs. 0%

**Change in Nocturia Episodes per night**

<table>
<thead>
<tr>
<th></th>
<th>Much Better (n=298)</th>
<th>Somewhat Better (n=288)</th>
<th>Not Changed (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>-1.9 (0.8)</td>
<td>-1.2 (0.7)</td>
<td>-0.5 (0.6)</td>
</tr>
<tr>
<td>(min, max)</td>
<td>(-5, 1.0)</td>
<td>(-3.7, 1.5)</td>
<td>(-2.6, 1.6)</td>
</tr>
</tbody>
</table>
Cumulative Distribution Function (CDF) (DB4, pooled across treatment arms)

Change from Baseline in Nocturia Episodes

Cumulative Percentage (Responder Rate)

- Much Better (n=298)
- Somewhat Better (n=288)
- Not Changed (n=185)
Cumulative Distribution Function (CDF) (DB4, pooled across treatment arms)

Change from Baseline in Nocturia Episodes

Cumulative Percentage (Responder Rate)

- Much Better (n=298)
- Somewhat Better (n=288)
- Not Changed (n=185)

Key:
- 81% at -1.7
- 50% at -1.2
- 20% at -2
- 3% at -6
CDF Plot by Treatment Arms (DB4)

SER 120 1.5 mcg (n=260)

Placebo (n=260)

Responder Rate vs. Change from Baseline in Nocturia Episodes

Improvement
Comments

• A mean reduction of at least 1.2 to 1.7 nocturia episodes per night may be potentially meaningful to patients.

• The CDF plot of mean reduction in nocturia episodes per night showed a separation between SER 1.5 mcg vs. placebo.

• SER 1.5 mcg may potentially benefit approximately 13% more subjects than placebo in reducing nocturia episodes.
Impact of Nighttime Urination (INTU) Instrument
First-ranked Secondary Endpoint in Study DB4

Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)
October 19, 2016

Sarrit M. Kovacs, Ph.D. - Reviewer
Clinical Outcome Assessments (COA) Staff
Office of New Drugs
- **Drug**: SER120 (desmopressin) 0.75 mcg and 1.5 mcg nasal spray
- **Proposed indication**: *SER120 is indicated for the treatment of nocturia in adults who awaken two or more times per night to void*
- **Study DB4 Endpoints**:

<table>
<thead>
<tr>
<th>Efficacy Concept</th>
<th>Hierarchy of Endpoints</th>
<th>Assessment Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-primary</td>
<td>Mean number of nocturic episodes per night during the efficacy assessment period (change from screening versus the treatment period).</td>
<td>PRO</td>
</tr>
<tr>
<td>Reduction in nocturic episodes</td>
<td>Percentage of patients with ≥50% reduction between screening and the treatment period with respect to the mean number of nocturic episodes per night.</td>
<td>PRO</td>
</tr>
<tr>
<td>Reduction in nocturic episodes per night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in impact of nocturia</td>
<td>Change in the patient-reported INTU score between screening and the treatment period (Weeks 8 and 14).</td>
<td>PRO</td>
</tr>
<tr>
<td>Change in time from sleep to first nocturic void</td>
<td>Change in time from when patient went to sleep to first nocturic void, or first morning void in the absence of nocturic void, between the screening and the treatment period.</td>
<td>PRO</td>
</tr>
<tr>
<td>Percentage of nights with 0 (absence) nocturic episodes</td>
<td>Change in the percentage of nights with 0 nocturic episodes between the screening and the treatment period.</td>
<td>PRO</td>
</tr>
<tr>
<td>Percentage of nights with ≤1 nocturic episodes</td>
<td>Change in the percentage of nights with ≤1 nocturic episode between the screening and the treatment period.</td>
<td>PRO</td>
</tr>
<tr>
<td>Reduction in nocturic urine volume</td>
<td>Change in nocturic urine volume between screening and the last week of treatment period.</td>
<td>Clinician-Reported Outcome</td>
</tr>
</tbody>
</table>
Impact of Nighttime Urination (INTU) Instrument

- 10-item instrument
- Pen/paper format
- Concept of interest: Impact of nighttime urination
- Context of use: Adults with nocturia
- Two domains:
  - Daytime Impact (Items 1-4, 6, 10)
  - Nighttime Impact (Items 5, 7, 8, 9)
- Scoring (0-100 point scale):
  - Daytime Impact score
  - Nighttime Impact score
  - Overall Impact score (avg. of Daytime & Nighttime scores)
Figure 1. Most frequently patient-reported impacts of nocturia

- Difficulty falling back asleep after an episode: 36%
- Interruption/disturbed sleep: 39%
- Inadequate amount of sleep: 46%
- Sleep: 21%

KEY TAKE-AWAY:
- In general, the measured concepts in the INTU appear to be relevant to, and understood by, patients.
- Tiredness appears to be the most commonly reported impact of nocturia.
INTU Instrument: Psychometric Evaluation

• Two-week interventional (behavioral modification), observational study to psychometrically evaluate the INTU instrument in 193 patients with clinically-confirmed nocturia

Measurement Properties:
Reliability and Validity
• Acceptable internal consistency reliability
• Acceptable test-retest reliability
• Acceptable convergent and discriminant validity
• Acceptable known-groups validity

Measurement Property:
Item Response Distribution and Floor/Ceiling Effects
• Some INTU items had high floor effects indicating they may not be relevant to, or experienced by, patients:
  • Items 1 (difficulty concentrating); 2 (difficulty getting things done); 3 (been irritable); and 7 (starting the day earlier)

KEY TAKE-AWAY:
• INTU appears to have acceptable reliability and validity results. HOWEVER, there are some items that do not seem relevant to, or experienced by, these patients.
• Interpretation of the DB4 trial’s efficacy findings is challenging without a pre-specified threshold for clinically meaningful change.
## DB4 Trial Results: INTU Overall Impact Score

<table>
<thead>
<tr>
<th>ITT Population</th>
<th>First Ranked Secondary Efficacy Variable</th>
<th>Statistics</th>
<th>SER120 1.5µg (N=260)</th>
<th>Placebo (N=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTU Overall Impact Score</td>
<td>Screening (SD)</td>
<td>34.4 (17.5)</td>
<td>32.3 (17.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment Period (SD)</td>
<td>20.1 (14.2)</td>
<td>21.3 (13.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean Change from Baseline (SE)</td>
<td>-14.1 (0.9)</td>
<td>-11.5 (0.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference vs. placebo (SE)</td>
<td>-2.6 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% Confidence Interval</td>
<td>-4.8, -0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (vs. placebo)</td>
<td>0.0225</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA's calculations; SD=standard deviation; SE=standard error

Is an improvement/reduction of 14 points (SER120 arm) on a 0-100 point scale meaningful to how patients feel and function in their daily lives?

Is an improvement/reduction of 12 points (placebo arm) just as meaningful?
INTU Instrument—Ability to Detect Meaningful Change Over Time (Intent-to-Treat DB4 pooled across study arms)

FDA Requested Post-Hoc Analyses:

- Anchor-based analyses
  - TBS
  - Nocturic Episodes

- Cumulative Distribution Function (CDF) Plots
  - TBS

Please complete the following question by considering your current nighttime urination compared to before you received any study treatment in this trial.

**My condition (waking up at night to urinate) is now:**

- much better
- somewhat better
- not changed
- somewhat worse
- much worse
### INTU Instrument (Mean Score Change) - Ability to Detect Meaningful Change Over Time

(Intent-to-Treat DB4 pooled across study arms)

**TBS Categories:**

<table>
<thead>
<tr>
<th>Change in INTU Overall Impact Score</th>
<th>“Much Better” (n=298)</th>
<th>“Somewhat Better” (n=288)</th>
<th>“Not Changed” (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) (min, max)</td>
<td>-19 (18) (-92, 16)</td>
<td>-10 (14) (-61, 25)</td>
<td>-5 (11) (-58, 22)</td>
</tr>
</tbody>
</table>

Applicant’s calculations; range in INTU score is 0-100 points

### Mean Reduction in Nocturic Episodes:

<table>
<thead>
<tr>
<th>Change in INTU Overall Impact Score</th>
<th>Reduction of ≥1 (n=504)</th>
<th>Reduction of &lt;1 (n=278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>-16 (16)</td>
<td>-5 (12)</td>
</tr>
</tbody>
</table>

**KEY TAKE-AWAY:**

- BOTH a 14-point improvement (1.5 mcg arm) and a 12-point improvement (placebo arm) fall between “somewhat better” and “much better,” but do not correspond with a reduction of nocturic episodes (i.e., ≥1 episodes or 50% reduction in episodes).
KEY TAKE-AWAY: • BOTH a 14-point improvement (1.5 mcg arm) and a 12-point improvement (placebo arm) fall between “somewhat better” and “much better” and appear to be clinically meaningful to patients.
Change in INTU Overall Impact Score from Screening to Post-Treatment by Treatment Group (Intent-to-Treat DB4 clinical trial)

- Placebo (N=248)
- 0.75 mcg SER120 (N=247)
- 1.5 mcg SER120 (N=243)

CDF=Cumulative Distribution Function.
INTU = Impact of Nighttime Urination Questionnaire.
Screening is defined as the average of all available assessments at both Week 1 and Week 2 of the Screening period.
Post-treatment = average of Week 8 and Week 14.
Summary

• Some Daytime Impact items measure more distal (less direct) impacts of nocturia (e.g., concentration, efficiency, irritability) and yielded high floor effects in both the observational study and the DB4 clinical trial.

• The Nighttime Impact items appear to measure more direct impacts of nocturia and appear to be more sensitive to treatment effects in the DB4 clinical trial data.
Summary

• Interpreting the efficacy findings from the DB4 clinical trial is challenging.
  – No pre-specified threshold for meaningful change in INTU Overall Impact Score for use in phase 3
  – *Both* a 14-point (SER120 arm) and 12-point (placebo arm) mean improvement/reduction in INTU Overall Impact score appear meaningful to how patients feel and function in their daily lives.
  – Is the magnitude of a 2.6-point mean difference between treatment and placebo arms’ scores adequate?

• Determination of the INTU Overall Impact score being fit-for-purpose and yielding meaningful results needs to be evaluated in overall context of evidence.
Efficacy Summary

• SER120 1.5 mcg met both co-primary efficacy endpoints. Over 12 weeks of treatment:
  – Mean reduction of 0.3-0.4 nocturia episodes per night vs. placebo
  – 18-19% more subjects experiencing ≥50% reduction in nocturia episode frequency vs. placebo
• SER120 1.5 mcg reduced the INTU Overall Impact score (0-100 point scale) from a baseline of ~30 by 2.6 points more than placebo
• Pre-specified criteria for efficacy was not met for SER120 0.75 mcg dose
• Exploratory analysis suggests SER120 1.5 mcg may benefit ~13% more subjects than placebo in reducing nocturia episodes
Efficacy Concerns

- Suitability of a treatment for nocturia without regard to underlying etiology
- Clinical relevance of numerically small changes relative to placebo in nocturia episode frequency and INTU Overall Impact score for SER120 1.5 mcg
- Proposed dose-titration scheme was not studied in the clinical trials, and the 0.75 mcg dose did not meet the pre-specified statistical criteria for efficacy
- Efficacy in subjects younger than 50 years of age has not been assessed
Clinical Review of Safety
NDA 201656
SER120 (desmopressin) nasal spray
Serenity Pharmaceuticals, LLC

Bone, Reproductive and Urologic Drugs
Advisory Committee Meeting
FDA White Oak Conference Center
October 19, 2016
Martin Kaufman, D.P.M., M.B.A.
Safety Database

- 1867 subjects with nocturia received SER120 for periods of time ranging from less than 1 month to more than 24 months

<table>
<thead>
<tr>
<th>Exposure Duration</th>
<th>0.5 µg N=567</th>
<th>0.75 µg N=806</th>
<th>1.0 µg N=518</th>
<th>1.5 µg N=748</th>
<th>Overall N=1867</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 Months</td>
<td>118</td>
<td>145</td>
<td>20</td>
<td>304</td>
<td>607</td>
</tr>
<tr>
<td>&gt; 12 Months</td>
<td>32</td>
<td>7</td>
<td>6</td>
<td>218</td>
<td>347</td>
</tr>
</tbody>
</table>
## Sources of Safety Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Dose (μg)</th>
<th>Fluid Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo-Controlled Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DB1</td>
<td>50 days</td>
<td>0.5 to 0.75 (titration)</td>
<td>Yes</td>
</tr>
<tr>
<td>DB2</td>
<td>50 days</td>
<td>0.5 to 0.75 (titration)</td>
<td>Yes</td>
</tr>
<tr>
<td>DB3</td>
<td>99 days</td>
<td>0.75, 1.0, 1.5</td>
<td>No</td>
</tr>
<tr>
<td>DB4</td>
<td>99 days</td>
<td>0.75, 1.5</td>
<td>No</td>
</tr>
<tr>
<td><strong>Open-Label Extension Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OL1</td>
<td>43 weeks</td>
<td>0.5 to 0.75 (titration)</td>
<td>Yes</td>
</tr>
<tr>
<td>A2</td>
<td>Up to 126 weeks</td>
<td>1.0 to 1.5 (titration)</td>
<td>No</td>
</tr>
</tbody>
</table>
Deaths

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Dose (μg)</th>
<th>Cause of Death</th>
<th>Source</th>
<th>Role of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlled Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15S021/DB1</td>
<td>57</td>
<td>0.75</td>
<td>Atherosclerosis/ sarcoidosis</td>
<td>Autopsy</td>
<td>Unlikely</td>
</tr>
<tr>
<td>77S003/DB3</td>
<td>77</td>
<td>1.0</td>
<td>Cardiac arrest/abdominal aneurysm/hypotension</td>
<td>Hospital records</td>
<td>Unlikely</td>
</tr>
<tr>
<td>65S004/DB4</td>
<td>80</td>
<td>0.75</td>
<td>Unknown</td>
<td>Investigator</td>
<td>Cannot be ruled out</td>
</tr>
<tr>
<td><strong>Uncontrolled Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>82S007/OL1</td>
<td>79</td>
<td>0.75</td>
<td>Probable myocardial infarction</td>
<td>Death certificate</td>
<td>Cannot be ruled out</td>
</tr>
<tr>
<td>59S024/A2</td>
<td>76</td>
<td>1.5</td>
<td>Cecal perforation</td>
<td>Hospital records</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

- The randomization ratio during the controlled trials was ~2:1 (SER120=1413; placebo=770). The number of deaths in the SER120 group compared to the placebo group could be consistent with the randomization scheme.
### Selected Serious Adverse Events (DB1/DB2/DB3/DB4)

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>1.5 μg (N=448)</th>
<th>1.0 μg (N=186)</th>
<th>0.75 μg (N=657)</th>
<th>0.5 μg (N=112)</th>
<th>Placebo (N=766)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one adverse event</td>
<td>8 (1.8%)</td>
<td>3 (1.6%)</td>
<td>11 (1.7%)</td>
<td>2 (1.8%)</td>
<td>13 (1.7%)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>0</td>
<td>1 (0.5%)</td>
<td>2 (0.3%)</td>
<td>1 (0.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Arteriosclerosis coronary artery</td>
<td>0</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism/nutrition Disorders</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>
Most Common Adverse Events Leading to Discontinuation (DB3/DB4)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>1.5 μg SER120 (N=448)</th>
<th>0.75 μg SER120 (N=454)</th>
<th>Placebo (N=454)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one adverse event</td>
<td>22 (4.9%)</td>
<td>19 (4.2%)</td>
<td>18 (4.0%)</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>3 (0.7%)</td>
<td>1 (0.2%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3 (0.7%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

Adverse events leading to discontinuation occurring in at least 0.5% of subjects in the 1.5 μg treatment group.
# Most Common Adverse Events (DB3/DB4)

<table>
<thead>
<tr>
<th>System Organ Class/ Preferred Term</th>
<th>1.5 μg (N=448)</th>
<th>0.75 μg (N=454)</th>
<th>Placebo (N=454)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>209 (46.7%)</td>
<td>222 (48.9%)</td>
<td>204 (44.9%)</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>79 (17.6%)</td>
<td>65 (14.3%)</td>
<td>74 (16.3%)</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>25 (5.6%)</td>
<td>16 (3.5%)</td>
<td>25 (5.5%)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>10 (2.2%)</td>
<td>10 (2.2%)</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>12 (2.7%)</td>
<td>7 (1.5%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>69 (15.4%)</td>
<td>71 (15.6%)</td>
<td>62 (13.7%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17 (3.8%)</td>
<td>14 (3.1%)</td>
<td>12 (2.6%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (1.6%)</td>
<td>16 (3.5%)</td>
<td>6 (1.3%)</td>
</tr>
</tbody>
</table>
### Adverse Events Coded as Decreased Serum Sodium or Hyponatremia (DB3/DB4)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>1.5 μg (N=448)</th>
<th>0.75 μg (N=454)</th>
<th>Placebo (N=454)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sodium decreased</td>
<td>11 (2.5%)</td>
<td>5 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>4 (0.9%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>
Hyponatremia: DB3/DB4

Nadir Serum Sodium Values

<table>
<thead>
<tr>
<th>Serum Sodium Range (mmol/L)</th>
<th>SER 1.5 μg (N=448) n (%)</th>
<th>SER 0.75 μg (N=454) n (%)</th>
<th>Placebo (N=454) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 – 134</td>
<td>50 (11.2%)</td>
<td>38 (8.4%)</td>
<td>20 (4.4%)</td>
</tr>
<tr>
<td>126 – 129</td>
<td>9 (2.0%)</td>
<td>9 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 125</td>
<td>5 (1.1%)</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

Serum sodium normal range: 135-146 mmol/L
# Hyponatremia: DB3/DB4

SER120-Treated Subjects with Nadir Serum Sodium ≤ 125 mmol/L

<table>
<thead>
<tr>
<th>Subject/Study</th>
<th>Age (yrs)</th>
<th>Dose (μg)</th>
<th>Baseline Sodium</th>
<th>Lowest Sodium</th>
<th>Study Day</th>
<th>Symptoms</th>
<th>Concomitant medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>08S007/DB3</td>
<td>75</td>
<td>1.5</td>
<td>135</td>
<td>125</td>
<td>99</td>
<td>None</td>
<td>Corticosteroid Thiazide diuretic</td>
</tr>
<tr>
<td>17S004/DB3</td>
<td>70</td>
<td>1.5</td>
<td>136</td>
<td>124</td>
<td>29</td>
<td>None</td>
<td>Corticosteroid NSAID</td>
</tr>
<tr>
<td>20S039/DB3</td>
<td>67</td>
<td>1.5</td>
<td>140</td>
<td>125</td>
<td>71</td>
<td>None</td>
<td>Corticosteroid NSAID</td>
</tr>
<tr>
<td>11S005/DB4</td>
<td>75</td>
<td>1.5</td>
<td>138</td>
<td>124</td>
<td>99</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>42S033/DB4</td>
<td>72</td>
<td>1.5</td>
<td>137</td>
<td>122</td>
<td>21</td>
<td>None</td>
<td>Corticosteroid NSAID</td>
</tr>
</tbody>
</table>

| 117           | 60        | Weakness, nausea, vomiting | Corticosteroid NSAID |
## Hyponatremia: DB3/DB4

Characteristics: Nadir Sodium \(<125 \text{ and } 126-129 \text{ mmol/L}\)

<table>
<thead>
<tr>
<th>Serum Sodium Range (mmol/L)</th>
<th>(&lt;125) (N=5)</th>
<th>(&lt;125) (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;125) (N=5)</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>(126-129) (N=18)</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

- **Age > 65 years**: 5, 16
- **Dose**: 1.5 μg: 5, 9; 0.75 μg: 0, 9
- **Gender**: Male: 4, 11; Female: 1, 7
- **Concomitant medications**: Corticosteroid/NSAID: 3, 0
- **Occurrence**: Days 21-99, Days 29-99
- **Subjects with Symptoms**: 1, 1
# Hyponatremia: Age

Nadir Serum Sodium Values - DB3/DB4
Age <65 and ≥ 65 years

<table>
<thead>
<tr>
<th>Serum Sodium Range (mmol/L)</th>
<th>1.5 μg</th>
<th>0.75 μg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;65 yrs (N=202) n (%)</td>
<td>&gt;65 yrs (N=246) n (%)</td>
<td>&lt;65 yrs (N=205) n (%)</td>
</tr>
<tr>
<td>130–134</td>
<td>18 (8.9%)</td>
<td>32 (13.0%)</td>
<td>10 (4.9%)</td>
</tr>
<tr>
<td>126–129</td>
<td>0</td>
<td>9 (3.7%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>&lt; 125</td>
<td>0</td>
<td>5 (2.0%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Applicant’s Proposed Risk Mitigation-Labeling

• Contraindications
  – Hyponatremia or a history of hyponatremia
  – Renal impairment (GFR <50 mL/min/1.73 m²)
  – Severe heart failure (NYHA Class III and IV)
  – SIADH, diabetes insipidus, polydipsia, uncontrolled HTN

• Warnings and Precautions
  – Sodium losing conditions, heart failure (NYHA Class II), uncontrolled diabetes mellitus
  – Concomitant meds: loop diuretics, systemic or inhaled corticosteroids, and drugs that potentiate inappropriate ADH secretion and/or increase the risk of hyponatremia
Applicant’s Proposed Risk Mitigation-Labeling

• Serum sodium monitoring
  – Prior to initiating therapy or increasing dose
  – 14 days after initiating therapy or increasing dose
  – Periodically, as clinically appropriate
  – If sodium decreases below normal range, consider discontinuing treatment until sodium returns to normal

• Initiating treatment
  – Serum sodium should be normal
  – Starting dose: 0.75 μg each night for 2 - 4 weeks
  – Dose may be increased to 1.5 μg each night, based on efficacy and tolerability
Applicant’s Proposed Risk Mitigation-Risk Evaluation and Mitigation Strategy (REMS)

• Sponsor voluntarily proposed a REMS to mitigate the risk of hyponatremia
  – Medication Guide
    – Informs patients about the risk of hyponatremia, describes its symptoms and warns about its serious side effects (e.g., seizure, coma)
  – Communication plan
    • One time mass mailed Dear Healthcare Provider Letter with labeling recommendations
  – Timetable for submission of assessment of the REMS
Summary Overall Safety

• Deaths
  – Controlled trials (n=3, all with SER120): A role of drug is unlikely in two; cannot be definitively ruled out for one
  – Uncontrolled trials (n=2): A role of drug is unlikely in one and cannot be definitively ruled out for the other

• Serious Adverse Events (DB1, DB2, DB3, DB4)
  – Similar incidence across all doses and placebo
  – 1 report of congestive heart failure (0.75 μg)
  – 2 reports of hyponatremia (1 in 1.5 μg; 1 in placebo)
Summary Overall Safety (DB3/DB4)

• Adverse Events Leading to Discontinuation
  – Slightly greater incidence for SER120 than placebo
  – Most common: nasal discomfort, hyponatremia; incidence of nasal discomfort was greater for placebo than for either SER120 dose

• Common Adverse Events
  – Slightly greater incidence for SER120 than placebo
  – Most commonly reported in the Respiratory Disorders and Infections and Infestations System-Organ-Classes
Summary – Hyponatremia (DB3/DB4)

- **0.75 μg dose**: No subject had a nadir serum sodium ≤ 125 mmol/L, 2.0% had a value between 126–129 mmol/L, and 8.4% had a value between 130–134 mmol/L

- **1.5 μg dose**: 1.1% had a nadir serum sodium ≤ 125 mmol/L, 2.0% had a value between 126–129 mmol/L, and 11.2% had a value between 130–134 mmol/L
Backup Slide Shown
## Desmopressin

### Reason for Use by Age Group

<table>
<thead>
<tr>
<th>Reason for Use</th>
<th>0 - &lt; 17 years†</th>
<th>17 - &lt; 50 years†</th>
<th>≥ 50 years</th>
<th>N=644</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia, enuresis, or related urinary indication</td>
<td>225</td>
<td>76</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>76</td>
<td>149</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Bleeding disorder or coagulopathy</td>
<td>57</td>
<td>93</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
<td>43</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>756</td>
<td>331</td>
<td>250</td>
<td></td>
</tr>
</tbody>
</table>

† Reports may be coded with more than one reason for use for desmopressin

^ Reports have not been deduplicated

† Age group of 0 - < 17 is 0 – 16.99 years and 17 - < 50 is 17 – 49.99 years in FAERS database

FAERS Cases 1/1/1969 - 9/30/2016