

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201656Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	February 28, 2017
From	Suresh Kaul, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	201656
Applicant	SERENITY Pharmaceuticals, LLC
Date of Submission	February 4 th , 2016
PDUFA Goal Date	March 4 th , 2017 (after Extension)
Proprietary Name / Established (USAN) names	Desmopressin Noctiva
Dosage forms / Regimen	0.75 mcg and 1.5 mcg desmopressin (equivalent to 0.83 mcg and 1.66 mcg of desmopressin acetate) nasal spray
Proposed Indication(s)	Treatment of nocturia due to nocturnal polyuria in adults who wake up 2 or more times per night to void.
Recommended:	Approval

1. Background

Description of Product

NOCTIVA (SER 120) is a nasal spray formulation of desmopressin, which is a synthetic analogue of the endogenous human antidiuretic hormone, vasopressin. SER120 is proposed for the treatment of nocturia in adults who awaken two or more times per night to void. The proposed starting dose is 0.75 mcg in one nostril 30 minutes before bedtime, which may be increased to 1.5 mcg each night depending on individual patient efficacy and tolerability.

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 nasal spray formulations of desmopressin are already approved by FDA for the treatment of central diabetes insipidus, 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.

SER120 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 Applicant proposed 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 (b) (4) each night depending on the treatment response and tolerability. However, this proposed dose regimen was not studied in any of the SER120 clinical trials.

There are no approved products in the U.S. for the treatment of nocturnal polyuria.

Regulatory History

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 up-titrated 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.

The Applicant next decided to investigate higher doses of SER120 for the treatment of nocturia. They proposed a new placebo-controlled trial (DB3) to evaluate 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 protocol for trial DB3 was submitted for Special Protocol Assessment (SPA) in spring 2011. DMEP issued an SPA no agreement letter for protocol DB3. DMEP 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.

In 2013 the Applicant submitted phase 3 protocol DB4. Protocol DB4 would test two doses of SER120 (0.75 mcg and 1.5 mcg) and include a novel PRO measure, the INTU (Impact of Nighttime Urination) 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 key secondary endpoint. In April 2014, the application was transferred back to DBRUP where it has remained since. A Type C Guidance meeting between DBRUP and the Applicant was held on September 17, 2015, to discuss the efficacy of their product and the possibility of NDA submission.

2. Recommendation for Approvability

I recommend approval of Noctiva 1.5 mcg for patients who are 50 years of age and above with nocturnal polyuria who wake up 2 or more times per night to void. I also recommend approval of the 0.75 mcg dose as the starting dose for patients 65 years of age and above and those who are at increased risk for hyponatremia.

From a clinical perspective, the review team including Drs. Olivia Easley and Martin Kaufman believes that substantial evidence of effectiveness has been demonstrated for SER120 1.5 mcg once daily at night for the treatment of nocturnal polyuria. Over 12 weeks of treatment, SER120 1.5 mcg resulted in a mean reduction of 0.3-0.4 nocturia episodes per night compared to placebo. Although the magnitude of that absolute difference is small, data from other endpoints provide evidence of clinical meaningfulness. This includes the second co-primary endpoint showing that 18-19% more subjects receiving SER120 1.5 mcg experienced a minimum fifty percent reduction in nocturia episode frequency compared to placebo, as well as data from secondary endpoints that assessed the percentage of nights with no nocturia or at most one nocturic episode.

SER120 1.5 mcg also met all secondary efficacy endpoints. The percentage of nights with no nocturia was about 5% greater for SER120 1.5 mcg than for placebo and the percentage of nights with one or less nocturia episodes was 10% greater for SER120 1.5 mcg than for placebo. SER120 1.5 mcg reduced the Impact of Nighttime Urination (INTU) Overall Impact score (0-100 point scale) from a baseline of ~30 by 2.6 points more than placebo, a numerically small difference that was statistically significant, although the clinical significance of this treatment effect on the INTU is unclear. Nearly all of the Bone, Reproductive and Urology Drugs Advisory Committee (BRUDAC) members voted affirmatively that SER120 1.5 mcg provides a clinically meaningful benefit to patients in reducing nocturia episode frequency.

Not all the pre-specified efficacy criteria were met for SER120 0.75 mcg. This dose produced a mean reduction of 0.2 nocturia episodes per night compared to placebo in both phase 3 trials; this was statistically significant in one of the trials and not to be tested statistically in the second trial based on the prespecified hierarchical testing procedure. The percentage of subjects with a $\geq 50\%$ reduction in nocturia episode frequency was 7-8% greater for SER120 0.75 mcg compared to placebo in both trials. Although statistical significance was not achieved for either endpoint, the data suggest that SER120 0.75 mcg reduces nocturia episode frequency more than does placebo. This dose also appears to have less hyponatremia than the 1.5 mcg dose. For this reason, it is reasonable to approve the 0.75 mcg dose as a starting dose for those who are at increased risk for hyponatremia (e.g., those over 65 years of age) and approve the 1.5 mcg dose for everyone else.

In a sub-group analysis of patients who had nocturia secondary to nocturnal polyuria (~80% of the randomized patients) as defined by 24-hour urine volume criterion, results were consistent with the overall results from the trial.

3. CMC/Device

Recommendations and Conclusion on Approvability

Mark Seggel, PhD, Chemistry review team lead, made the following notification:

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the **identity, strength, quality, purity, potency and bioavailability** of the drug product.

The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. CDRH-OC has determined that the applicant is in compliance with the applicable Quality System Requirements under 21 CFR 820, although post-approval inspections of two sites are recommended. (see CDRH-OC consult review dated February 6, 2017).

CDRH-ODE has determined that the spray pump component of this drug-device combination product is suitable for the intended use. The device is suitable for preventing microbial contamination of the product in the absence of a preservative (see CDRH-ODE consult review dated December 14, 2016).

I. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	NOCTIVA is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.
Duration of Treatment	Indefinite.
Maximum Daily Dose	1.66 micrograms desmopressin acetate (equivalent to 1.5 micrograms desmopressin), delivered in a single 0.1 mL spray at bedtime.
Alternative Methods of Administration	Not applicable.

Desmopressin is a synthetic 9-amino acid analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone which affects renal water conservation.

Desmopressin differs from 8-arginine vasopressin in the stereochemistry of the arginine amino acid (D-isomer) and the cysteine amino acid (b) (4).

Desmopressin acetate is the active ingredient in several FDA-approved drug products and their generic equivalents. It is available as a nasal spray, an injection, in rhinal tubes for intranasal application, and as an oral tablet. Noctiva is a low-dose desmopressin product supplied in a metered-dose nasal spray. Two strengths are proposed for marketing:

0.83 mcg desmopressin acetate per 0.1 mL spray equivalent to 0.75 mcg desmopressin per 0.1 mL spray and 1.66 mcg desmopressin acetate per 0.1 mL spray equivalent to 1.5mcg desmopressin per 0.1 mL spray. (b) (4)

It is unknown if they are bioequivalent.

Unlike the approved desmopressin acetate nasal sprays which are formulated as true solutions, Noctiva is formulated as a sterile oil-in-water emulsion. In addition, Noctiva contains cyclopentadecanolide (CPD), a permeation enhancer. CPD is present in Testim (testosterone gel). However CPD has not previously been used in an approved nasal spray. The safety of CPD administered by the intranasal route was evaluated by Dr. Deepa Rao (see her review).

The drug delivery system consists of an (b) (4) mechanical multidose pump and a 3.5 mL amber glass bottle. The pump is designed to prevent ingress of microbial contamination. The metered dose pump was reviewed by CDRH.

Note that although Noctiva is manufactured as a sterile product, nasal sprays are not typically required to be sterile and Noctiva is not labeled as sterile.

Accurate and consistent dosing of the drug product is critical. Under-dosing may result in lack of efficacy, while over-dosing could result in dangerously low blood sodium levels (hyponatremia).

B. Quality Assessment Overview

Drug Substance: Desmopressin acetate is the established name for 1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate trihydrate. It is soluble in water and ethyl alcohol, and is hygroscopic.

The chemistry, manufacturing and controls of desmopressin acetate drug substance are documented in (b) (4), Type II DMF (b) (4). The DMF was most recently reviewed by Dr. Ben Stevens and found to be adequate.

The information on the drug substance provided in the NDA and in the DMF is adequate to support approval of the NDA. The application is recommended for approval from the drug substance perspective.

Drug Product: Noctiva (desmopressin acetate) nasal spray is a preservative-free oil-in-water emulsion formulation containing water for injection, cottonseed oil, polysorbate 20, sorbitan monolaurate, citrate (b) (4) and cyclopentadecanolide (CPD). Cyclopentadecanolide, also known as pentadecalactone, is a permeation enhancer included in the formulation to enhance absorption of desmopressin through the nasal mucosa.

The chemistry, manufacturing and controls for the cyclopentadecanolide used in the manufacture of Noctiva are adequately documented in (b) (4) Type IV DMF (b) (4).

Each bottle of Noctiva contains 3.8 mL of 16.6 mcg/mL or 8.3 mcg/mL desmopressin acetate nasal spray. The content is sufficient to provide up to 30 individual 0.1 mL doses in addition to the amount required for priming the device.

The drug product specification includes tests, and appropriate acceptance criteria, for identity, assay, CPD content, emulsion particle size distribution, spray content uniformity, pump delivery, spray droplet size, and spray pattern. The product is also tested for endotoxins and sterility. Note that a test for degradation products is not included in the specification. Potential levels of impurities in the maximum daily dose of 1.5 mcg desmopressin are not expected to present any safety concerns.

The long-term stability of Noctiva when stored upright at 2C - 8C for 24 months before opening has been established. Determination of an appropriate in-use period, i.e., the time after dispensing in which the product may be stored at room temperature by the patient, and the time that the product should be discarded, was more problematic. The in-use stability protocol was poorly designed and the resulting data limited. Nevertheless, we conclude that the patient can store Noctiva nasal spray upright at room temperature 20°C to 25°C (68°F to 77°F) for 60 days after opening.

The drug delivery device requires five priming actuations before patient dosing to ensure that the full 0.1 mL spray is delivered. While the applicant performed a re-priming study and determined that re-priming of the pump was not necessary, the available data do not support this conclusion. If the pump has not been used in more than 3 days, the pump should be re-primed with two actuations. The labeling and instructions for use have been revised accordingly.

Leachables and extractables (L&E) testing of the drug contacting components of the nasal spray was conducted. While from the CMC perspective adequate information regarding the L&E testing, including the analytical methods was eventually provided, assessment of the results was deferred to CDRH.

Overall, this NDA is recommended for approval from the drug product CMC perspective.

CDTL Comment: I concur with the Chemistry review team's recommendation.

Analytical Methods Verification: Because of the low concentration of desmopressin in the emulsion formulations and the very low amount of desmopressin in each 0.1 mL spray actuation, and reported variability due to analytical method variation, CDER/OPQ/OTR/Division of Pharmaceutical Analysis was consulted to perform laboratory verification of the RP-HPLC desmopressin assay and the RP-HPLC spray content uniformity assay.

DPA concluded that these methods are acceptable for control and regulatory purposes (see Methods Verification Report and Summary dated August 18, 2016 for details in DARRTS).

Environmental Assessment: A categorical exclusion from the environmental assessment requirements has been requested in accordance with 21 CFR 25.31(b). The estimated introduction concentration (EIC) is (b) (4) ppb, which is well below the 1 ppb threshold. No extraordinary circumstances are known to the applicant. **The categorical exclusion is therefore granted.**

CDTL Comment: *Agree with the Chemistry reviewer's conclusion.*

Labeling: From the CMC perspective, the primary deficiencies associated with the package insert and container /carton labels are related to the expression of strength (free base versus salt), the long-term and in-use storage statements, and the instructions for use (priming and re-priming). Recommendations have been incorporated into the label and conveyed to the Applicant. Proposed revisions were submitted by the Applicant on February 8 and 9, 2017.

Product Manufacturing Process: The drug product manufacturing process is currently based on (b) (4)

(b) (4)
Suitable in-process controls have been established. ***Based on the rationale and batch results, Dr. Li-Shan Hsieh, OPF Process reviewer, concluded that it appears that the applicant has developed a reasonable, validated manufacturing process suitable for ensuring product strength and sterility.***

CDTL Comment: *I concur with the Chemistry reviewer's conclusion.*

The applicant submitted (b) (4)
The proposed change is not anticipated to adversely impact product quality, and is therefore acceptable. (b) (4)

Facilities: ***Dr. Juandria Williams, OPF Division of Inspectional Assessment concludes that, "[t]here are no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities' inspectional history, relevant experience, and capabilities. The facilities are determined acceptable to support***

approval of NDA 201656.” However, it is recommended that the next routine inspections of Serenity Pharmaceuticals, LLC, New York, NY as the NDA applicant, and (b) (4) as the drug product manufacturer, cover medical device GMPs.

CDTL Comment: *I agree with the determination.*

Biopharmaceutics: The drug product consists of a liquid formulation for which no in vitro release testing is required. A bio-waiver has not been requested. Therefore, a biopharmaceutics review is not needed for this NDA.

Product Quality Microbiology: Although Noctiva is manufactured as a sterile oil-in-water emulsion, it will not be labeled and marketed as such. The approved desmopressin acetate nasal sprays are not sterile products but do contain a preservative (b) (4)

Microbial contamination could result in degradation of desmopressin, a small synthetic peptide. To ensure that the product remains free of microbial contamination, it is packaged with the (b) (4) pump which is designed to prevent ingress of bacteria.

Although the subject drug product is manufactured under aseptic conditions (b) (4)

Antimicrobial effectiveness testing (AET) is not applicable as the formulation does not have antimicrobial properties especially with respect to *P. aeruginosa*.

Therefore, the product quality microbiology review focused on container closure integrity testing (CCIT) and on sterility assurance testing (per USP<71>) were found adequate. Dr. Yarery Smith, OPF microbiologist recommends approval of the NDA.

CDTL Comment: *I concur with Dr. Smith’s recommendation.*

CDRH-ODE: The (b) (4) mechanical multi-dose pump constitutes the device component of this drug-device combination product.

The review encompassed device design, device functionality, biocompatibility, microbiology (sterility), and device stability materials provided in the NDA and (b) (4) Drug Master File # (b) (4), as well as materials submitted in response to information requests. Overall, the CDRH-ODE review team “determined that the device constituent parts of the combination product have been designed appropriately for the product’s intended use and essential performance requirements.” See the CDRH-ODE consult review dated December 14, 2016 for details.

C. Special Product Quality Labeling Recommendations

Based upon the recommendations from DMEPA, the USP Salt Nomenclature Policy is not being implemented with this drug product. Because there is numeric overlap in the strengths for Noctiva (1.5 microgram/spray) and Stimate (0.15 mg/spray), Serenity was asked to revise the product strengths to 0.83 mcg desmopressin acetate per 0.1 mL spray and 1.66 mcg desmopressin acetate per 0.1 mL spray, equivalent to 1.5 mcg desmopressin and 0.75 mcg desmopressin, respectively. Note that other approved desmopressin acetate nasal sprays (e.g., DDAVP) deliver (b) (4) (10 mcg) per 0.1 mL spray.

CDTL Comment: I agree with Mark Seggel's overall recommendation to approve Noctiva nasal spray (1.5 mcg and 0.75 mcg doses). All Chemistry recommendations for the label and for the carton container were incorporated into the label and successfully negotiated with the Applicant.

4. Nonclinical Pharmacology/Toxicology

Recommendation

The Pharmacology/Toxicology review team, Drs. Deepa Rao and Mukesh Summan made the following recommendation:

From the nonclinical perspective, Noctiva appears to be reasonably safe for approval.

Additional Non-Clinical Recommendation

Based on lack of data regarding changes in sodium balance in the 28-day non-clinical bridging toxicology study in rats, monitoring for hyponatremia is recommended.

CDTL Comment

I concur with the Pharmacology/Toxicology review team's recommendation.

Non-Clinical Findings

Based on the long history of clinical use of desmopressin, and a proposed clinical dose for Noctiva which is 6 to 13 times lower than DDAVP® Nasal Spray, there are no specific concerns regarding the use of the active pharmaceutical ingredient, desmopressin, in Noctiva. The sponsor's reformulation of Noctiva however, contains an excipient not previously used by the nasal route, **cyclopentadecanolide (CPD)**, also known as CPE- 215 or pentadecalactone. CPD has been included in the sponsor's formulation to facilitate absorption of desmopressin through the nasal mucosa to result in higher bioavailability. Although CPD is used in another FDA-approved drug, it is via different route of administration (transdermal product Testim®). Noctiva is the first proposed use of CPD in an *intranasal* formulation.

Systemic exposure to CPD could not be confirmed with bioanalytical methods. Pharmacokinetic analyses showed high variability and low sporadic measurements for CPD. Studies conducted support the sponsor's conclusion that CPD undergoes rapid hydrolysis by endogenous esterases following exposure to CPD and does not accumulate.

The concern of CPD as a novel excipient (not previously used by the nasal route) was allayed given the high dose multiples observed in the chronic nonclinical studies.

CDTL Comment

For a detail review of CPD, refer to Dr. Deepa Rao's review in DARRTS.

A 28-day rat bridging toxicology study comparing Noctiva with the marketed desmopressin product (DDAVP® Nasal Spray) did not reveal any remarkable findings. Based on nasal surface area, the dose of 150 ng/rat translates to a dose multiple that is approximately equivalent to the proposed maximum 1.5 mcg for clinical dose.

Sodium was not evaluated in the 28-day bridging nonclinical toxicology study with Noctiva in the rat. However, hyponatremia is a well-known adverse effect with desmopressin products and serum sodium was adequately monitored in the clinical trials.

Genetic Toxicology

No genetic toxicity studies were performed.

Carcinogenicity

There have been no long-term studies in animals to assess the carcinogenic or mutagenic potential of Noctiva nasal spray.

Carcinogenicity studies with CPD were not conducted based on negative genetic toxicology data, limited systemic exposure, absence of accumulation based on nonclinical and clinical pharmacokinetic data, and negative histopathology data from the two chronic toxicology studies. A carcinogenicity waiver request was submitted by the sponsor.

CDTL Comment

Dr. Rao further states that after the review of the toxicology studies, the review team agrees with the fact that carcinogenicity studies are not required.

Reproductive and Developmental Toxicology

There have been no long-term studies in animals to assess the impairment of fertility in Noctiva nasal spray.

CPD

Male fertility tests in rats were conducted and reviewed under IND (b) (4) by Dr. Herman Rhee (October 17, 2006). No remarkable CPD-related effects were noted in sperm evaluation (cauda weight, sperm motility, progressive motility, and velocity), reproductive organ weights (epididymis, prostate, seminal vesicles and testes), and pregnancy performance.

CDTL Comment

There are no outstanding issues or concerns pointed out by the Pharm/Tox review team. The Pharmacology/Toxicology review team also provided language revisions to Sections 8 and 13 of the label. Those revisions were included in the label and communicated and agreed by the Applicant.

5. Clinical Pharmacology/Biopharmaceutics

Recommendation:

The Clinical Pharmacology Review Team including Jihong Shon PhD, Doanh Tran PhD, Luning (Ada) Zhuang, PhD, Jeffrey Florian, PhD, Dennis Bashaw, Pharm D in the Office of Clinical Pharmacology, Division of Clinical Pharmacology III and Pharmacometrics, have reviewed the information submitted for NDA 201656 for doses 0.75 mcg and 1.5 mcg desmopressin nasal spray. ***The review team recommends approval of this NDA from a clinical pharmacology perspective, provided that the Applicant agrees to the risk mitigation elements proposed to prevent serious hyponatremic events and an agreement on the language in the package insert is reached between the Applicant and the Division.***

Some of the specific comments/recommendations are summarized below:

Post-Marketing Requirement and Commitment

As both doses 0.75 mcg/mL and 1.5 mcg/mL are recommended for approval, the following Post-Marketing Requirement (PMR) study is recommended:

“A comparative bioavailability study between two sprays of the 0.75 mcg/mL strength and one spray of 1.5 mcg/mL strength”.

CDTL Comment

I concur with the PMR recommendation made by the Clinical Pharmacology review team.

Pharmacokinetic Characteristics

Mechanism of Action

Desmopressin is a synthetic analogue of vasopressin, an antidiuretic hormone that is normally secreted by the pituitary gland, and has a highly selective affinity to vasopressin V2 receptors on renal cells in the collecting ducts, which results in an increase in water reabsorption by the kidneys and a reduction in urine production.

QT Prolongation

The QT interval after daily administration of 1.5 or 0.75 mcg desmopressin nasal spray doses for 12 weeks showed no significant change from baseline in patients with nocturia in two phase 3 trials (Study DB3 and DB4). No supra therapeutic doses were used.

Bioanalysis

The plasma concentrations of desmopressin in clinical studies were analyzed using radioimmunoassay (RIA) or Liquid Chromatography–Mass Spectrometry/Mass Spectrometry (LC-MS/MS).

Pharmacokinetic profile

The pharmacokinetic 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. The median 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 AUC values tended to have a slightly greater than dose proportional increase between 0.75 mcg and 1.5 mcg.

The plasma concentrations of desmopressin in most subjects were lower than the lower limit of quantitation (LLoQ: 2 pg/mL) after 6 hours post-dose. There is no accumulation between doses. Large inter-individual variability in systemic exposure of desmopressin was observed (CV% of C_{max} and AUC: 96% and 146%, respectively, for 0.75 mcg desmopressin and 76% and 82%, respectively, for 1.5 mcg desmopressin).

Table 1. Summary of pharmacokinetics of desmopressin in patients with nocturia following administration of 0.75 or 1.5 mcg desmopressin nasal spray Study DB3

	0.75 mcg	1.5 mcg
The number of subjects (male : female)	18 (9:9)	18 (9:9)
	mean ± S.D (the number of subjects)	
C_{max} (pg/mL)	4.00 ± 3.85 (16)	9.11 ± 6.90 (15)
T_{max} (hour)	0.25 (0.25-0.5)* (12)	0.75 (0.25-3.0)* (15)
AUC_t (pg·h/mL)	5.13 ± 7.49 (16)	23.10 ± 18.95 (13)
AUC_{inf} (pg·h/mL)	15.96 ± 11.58 (9)	41.33 ± 19.54 (10)
t_{1/2} (hour)	1.87 ± 1.13 (9)	2.79 ± 0.87 (10)

*median (range); AUC_t and AUC_{inf}, AUC to last detection time and to infinity

There is no relative bioavailability data between two sprays of the 0.75 mcg desmopressin strength and one spray of the 1.5 mcg desmopressin strength. In addition, comparative bioavailability between two sprays of the 7.5 mcg/mL strength and one spray of the 15 mcg/mL strength has not been assessed.

CDTL Comment

Since, there is no known available bioavailability data between 2 sprays of 0.75 mcg each and 1 spray of 1.75 mcg, the applicant is required to conduct a comparative study as a post-marketing requirement (PMR). This determination was made by both clinical and clinical pharmacology review teams. This will be included in the action letter.

Bioavailability

Bioavailability of desmopressin nasal spray (1 mcg and 2 mcg desmopressin using a formulation strength of 5 mcg/mL) appeared to be approximately 8% compared to subcutaneous desmopressin injection formulation. However, bioavailability of the desmopressin nasal sprays in the proposed final concentrations of 7.5 mcg/mL and 15 mcg/mL was not assessed. Due to differences in the volume applied (0.2 – 0.4 mL vs. 0.1 mL) and formulation strength, no conclusion can be drawn regarding the relative bioavailability of the proposed to-be-marketed formulation.

Excretion

Desmopressin is mainly excreted in urine. Impaired renal function significantly affects the pharmacokinetics of desmopressin.

Following additional notifications were made during the review:

Dose-response of desmopressin nasal spray

Dose-response analyses for the primary efficacy endpoints (i.e., change from baseline in mean nocturia episodes and for greater than 50% reduction in nocturia episodes) were conducted based

on data from DB3 and DB4. The analyses showed that higher desmopressin doses were associated with a greater change from baseline in mean nocturia episodes. Similarly, based on the same dataset, the percentage of patients with more than a 50% reduction in nocturia episodes was observed to increase with increasing dose.

Pharmacodynamics of Desmopressin nasal spray

The pharmacodynamic measurements reached a maximum effect within 1 hour and were effective for 4 to 6 hours following administration of desmopressin nasal spray. These pharmacodynamic changes appeared to be dose dependent. This action and its duration may produce better clinical outcomes in patients with nocturnal polyuria in whom urine output increases at night (defined as >33% of total 24 hour production).

Renal Impairment

DB3 and DB4 studies enrolled patients with a GFR > 50 mL/min/1.73m². Renal PK study showed desmopressin exposures increased 3-4 fold with eGFR<50 compared to eGFR >50.

Hepatic Impairment

Given that there is insufficient information on the use of desmopressin in patients with hepatic impairment, patients with liver disease should use desmopressin nasal spray with caution.

Compromised Nasal Route

Patients with a compromised intranasal route (atrophy of nasal mucosa, and chronic or acute rhinitis), could have increased absorption of desmopressin, which could increase the risk for hyponatremia. They should discontinue treatment with desmopressin nasal spray until those conditions are resolved.

Geriatric Use

65 years or older subjects showed a higher incidence of hyponatremia compared to the group younger than 65 years of age.

Drug-Drug Interactions:

When considering the excretion and metabolic properties, desmopressin nasal spray may have minimal potential for pharmacokinetic interaction with concomitant drugs administered via a non-nasal route which are absorbed into the systemic circulation.

For the purpose of this application review, no drug-drug interaction studies or analyses were performed. However, labeling for the currently marketed desmopressin acetate nasal spray includes a precaution regarding the concomitant administration of drugs that may increase the risk of water intoxication with hyponatremia, (e.g., tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine).

CDTL Comment:

Following recommendations were added to the Label:

Monitor sodium within 7 days after dose initiation or dose increase. Fluid intake in the evening and night-time hours should be moderated to decrease the risk of hyponatremia...

6. Clinical Microbiology

The microbiology reviewer conducted a product quality microbiology review of the submission and concluded that the microbiology control for the product is adequate according to current quality standards.

7. Clinical/Statistical - Efficacy

Overview of Clinical Program

The sponsor conducted a total of four phase 3 efficacy studies, but only the two most recent trials (DB3 and DB4) support efficacy for the current application. DB1 and DB2 which investigated lower doses of SER120 (0.5 mcg once at night with possible up-titration to a maximum of 0.75 mcg once nightly) failed to demonstrate statistical significance for both co-primary endpoints. Therefore the efficacy review will focus on results of studies DB3 and DB4.

Design of Studies DB3 and DB4

Phase 3 trials DB3 and DB4 had essentially identical designs. Both were randomized, double-blind, placebo-controlled, parallel group trials in adults 50 years of age and older with 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, and 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 INTU (Impact of Nighttime Urination) questionnaire each evening along with the 3-day voiding diaries during screening, and at treatment weeks 8 and 14. The INTU consists of 10 questions categorized into day time (6 questions) and night time (4 questions) domains (see Dr. Easley's and Dr. Kovacs's Review for details).

Follow-up clinic visits occurred every two weeks until the end of study at Week 14.

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): α 1-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 Inclusion criteria (DB3 and DB4)

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

CDTL Comment

During the phase 3 protocol development, FDA (DMEP) advised the Applicant to only enroll patients 50 years of age and above in order to better assess the risk of hyponatremia, which is greater in elderly patients.

Exclusion criteria (DB3 and DB4)

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. Neurogenic detrusor overactivity
19. Obstructive sleep apnea
20. Hyperkinetic limb disorders
21. Work or lifestyle activities which interfere with night time sleep
22. Alcohol or substance abuse within 12 months of enrollment

Efficacy Endpoints for both trials

Co-Primary Endpoint

Pre-specified co-primary 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 $\geq 50\%$ 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 Endpoints

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. 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 for the secondary endpoints.

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 DB3, although this essentially means that the missing data were imputed as being equal to the available 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. 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.

CDTL Comment

Both primary and secondary endpoints described above were pre-specified and controlled for type 1 error.

Nocturia Etiology (DB3 and DB4) ITT Population:

	DB3				DB4		
	SER120 1.5 mcg	SER120 1.0 mcg	SER120 0.75 mcg	Placebo	SER120 1.5 mcg	SER120 0.75 mcg	Placebo
N	179	183	186	186	260	262	260
Investigator assessment N (%)							
Nocturnal polyuria +/- other etiology	148 (83)	147 (80)	147 (79)	148 (80)	197 (76)	216 (82)	211 (81)
BPH	68 (38)	77 (42)	79 (43)	81 (44)	94 (36)	90 (34)	106 (41)
OAB	60 (34)	56 (31)	57 (31)	61 (33)	71 (27)	65 (25)	52 (20)
Unknown	30 (17)	41 (22)	39 (21)	38 (20)	62 (24)	72 (28)	68 (26)
% with nocturnal polyuria based on 24 hour urine collection at screening							
present	143 (80)	146 (80)	145 (78)	145 (78)	199 (77)	209 (80)	204 (78)

Source: MO's Review, Page 21

At screening, the investigator provided or confirmed the probable etiology of nocturia based on patient interview and review of each subject's medical records. In the majority of subjects, more

than one etiology of nocturia was cited – e.g., BPH and nocturnal polyuria. All subjects were also 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*.

CDTL Comment

Majority of subjects enrolled in both trials (about 80%) as shown above were diagnosed with nocturnal polyuria. This is consistent with the current scientific thinking and input from the advisory committee, that the indication should be nocturnal polyuria and not a broad condition like nocturia.

Subject Disposition

In the two pivotal trials (DB3 and DB4), a total of 3565 subjects were screened, with 1707 ultimately enrolled. 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.

CDTL Comment

Disposition of Subjects is acceptable.

Proposed Indication

Treatment of nocturnal polyuria in adults 50 years of age and above, who wake up 2 or more times per night to void.

Demographics

Table 2. Summary of Demographic Characteristics for the ITT Population, (Studies DB3 and DB4)

	Study DB3				Study DB4		
	SER120 1.5 mcg	SER120 1.0 mcg	SER120 0.75 mcg	Placebo	SER120 1.5 mcg	SER120 0.75 mcg	placebo
N	179	183	186	186	260	262	260
Median (min, max) age (years)	65 (51, 89)	65 (50, 89)	66 (50, 87)	66 (50, 86)	66 (50, 87)	66 (50, 89)	65 (50, 90)
Age ≥65 years [N (%)]	94 (53)	98 (54)	100 (54)	100 (54)	144 (55)	145 (55)	144 (55)
Median BMI (kg/m ²) (min, max)	28 (19, 48)	28 (18, 57)	28 (17, 47)	28 (18, 56)	30 (17, 63)	29 (18, 49)	29 (17, 52)
Gender [N (%)]							
Male	104 (58)	109 (60)	107 (58)	112 (60)	147 (57)	145 (55)	146 (56)
Female (post-menopausal)	74 (41)	73 (40)	79 (43)	70 (38)	107 (41)	110 (42)	107 (41)
Female (child-bearing potential)	1 (1)	1 (1)	0	4 (2)	6 (2)	7 (3)	7 (3)
Race [N (%)]							
Caucasian	144 (80)	159 (87)	157 (84)	152 (82)	188 (72.3)	204 (77.9)	200 (76.9)
Black	20 (11)	18 (10)	15 (8)	21 (11)	40 (15.4)	26 (9.9)	39 (15)
Asian	5 (3)	2 (1)	4 (2)	6 (3)	6 (2.3)	4 (1.5)	1 (0.4)
Hispanic	8 (5)	4 (2)	8 (4)	3 (2)	24 (9.2)	25 (9.5)	20 (7.7)
Other	2 (1)	0	2 (1)	4 (2)	2 (1)	3 (1)	0

Source: MO's Review of Efficacy, P 20.

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.

Efficacy Findings

Analysis of Primary Efficacy Endpoint

First Co-Primary Efficacy Endpoint

SER120 1.5 mcg in study DB3 and DB4 and 0.75 mcg in study DB4 resulted in a statistically significantly greater reduction in mean nightly number of nocturia episodes compared to placebo. From a baseline of about 3 nightly nocturia episodes on an average, there was a mean reduction of 0.3-0.4 episodes per night with the 1.5 mcg dose compared to placebo. The FDA's analysis which is shown in Table 3 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 $\geq 50\%$ reduction in nightly nocturia episodes. The percentage of subjects experiencing a $\geq 50\%$ 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 (second) co-primary endpoint. Statistical testing of the 0.75 mcg dose is not reported in DB3 in accordance with the pre-specified, hierarchical testing procedure.

Table 3. Summary of Co-primary Efficacy Endpoints for Trials DB3 and DB4 (ITT-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: $\geq 50\%$ 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: MO Review, FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical review

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.

CDTL Comment:

The Applicant pre-defined the mITT population as the primary efficacy analysis population in both study protocols. However, the mITT population included about 70% of the ITT population. During the protocol design phase for study DB4, the FDA (DMEP) had

recommended the mITT as the primary analysis population 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. In both studies, all patients (including placebo responders) were randomized after placebo lead-in period and the screening assessment was used as baseline. It is noted that in both studies, placebo responders had fewer nocturic episodes per night compared with non-responders. After the application was transferred to DBRUP, the Biometrics review team determined that this approach is essentially a subgroup analysis and that the ITT population, which accounts for a greater percentage of randomized patients, is preferred. Therefore, for the purpose of this review ITT population was taken into consideration and all efficacy results were calculated for ITT population with an agreement from the Applicant.

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 for the 1.0 or 0.75 mcg doses are descriptive. 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.

INTU

The goal of the Impact of Nighttime Urination (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 Clinical Outcome Assessments Staff memorandum dated November 4, 2016. The INTU was only used in DB4; its overall impact score was the first ranked secondary efficacy endpoint in that trial.

Sarrit Kovacs and Selena Daniels, (COA review team) concluded that the evidence submitted by the Applicant demonstrates that INTU instrument's content validity, measurement properties and performance are acceptable for inclusion as a pre-specified secondary endpoint in DB4 trial. Dr. Kovacs further in her review states that interpreting the efficacy findings from Trial DB4 were 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 need to be demonstrated.

In order to help determine what constitutes a clinically meaningful change in INTU Overall Impact scores, the Agency reviewed exploratory post-hoc analyses of the INTU data from Trial DB4 and concluded that the INTU can reasonably detect changes in nocturia impacts over time. In addition, the Agency concluded that the mean, within-group INTU Overall Impact score improvement (reduction) of 14 points (on a 0-100 point scale) for the SER120 1.5 mcg arm in Trial DB4 appears clinically meaningful. However, the 12-point mean, within-group improvement (reduction) in INTU scores for the placebo arm in Trial DB4 appears clinically meaningful as well. While the 2.6 mean treatment difference in INTU scores between the SER120 1.5 mcg and placebo arms in Trial DB4 is statistically significant ($p=0.02$), the

exploratory analyses were unable to inform whether this small difference is clinically meaningful.

Dr. Kovacs further stated in her review that the results from the exploratory analysis are consistent with the Nighttime Impact items which appear to be more sensitive to change than the Daytime Impact items. As with any composite score, the Agency strongly recommends 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.

CDTL Comment

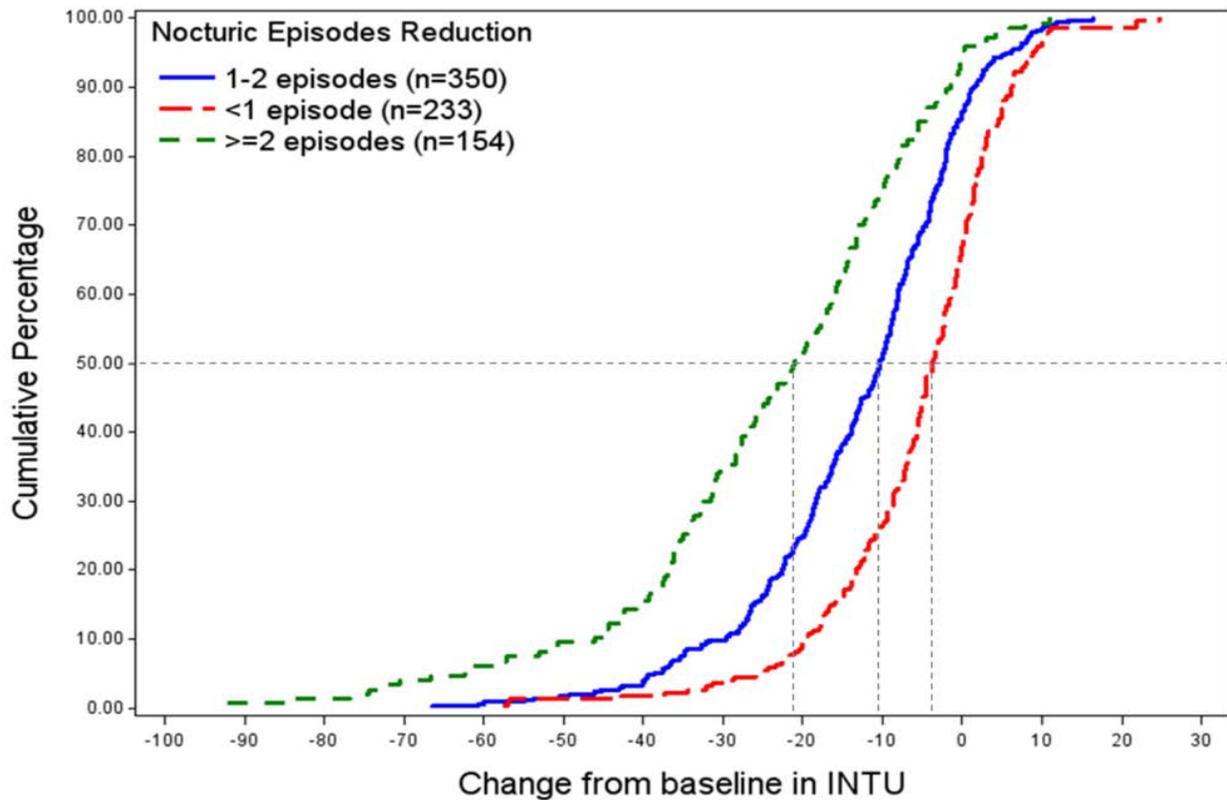
The INTU’s Overall Impact score ranges on a scale from 0 to 100. At baseline, the mean Overall Impact score was about 30. There was an observed 14-point mean improvement in the INTU Overall Impact score for the 1.5 mcg group versus a 12-point mean improvement with placebo. Noctiva 1.5 mcg decreased the INTU Overall Impact score by 2.6 points more than placebo. The clinical relevance of this treatment effect is unclear. However, it still made an impact in the right direction as seen on CDF plots. For descriptive view of CDF plots see Dr. Kovacs review in DARRTS.

Table 4. Secondary Efficacy Variable – Change from Screening to Treatment Period in the INTU Overall Impact Score in Trial DB4 (ITT- 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: MO Review, FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical Review, * Change from baseline was calculated using an ANCOVA model

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



Additional Secondary Endpoints

Differences between SER120 1.5 mcg and placebo were statistically significant for all other secondary efficacy endpoints in both DB3 and DB4 (**Table 5**). 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 5. Summary of Secondary Efficacy Endpoints in Trials DB3 and DB4, (ITT-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: MO Review, FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical review

*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.

CDTL Comment

All secondary endpoints for the 1.5 mcg dose were statistically significant. These secondary end points especially the percent of nights with no nocturic episodes and percent of nights with ≤ 1 nocturic episodes are considered particularly relevant for a patient who suffers from nocturia due to nocturnal polyuria and has to get up at least two times a night to void.

Subpopulations

Nocturnal Polyuria

CDTL Comment

Consistent with advice from the advisory panel (BRUDAC) that the product should be indicated in patients with nocturia secondary to nocturnal polyuria, DBRUP requested that the sponsor submit efficacy analyses on the nocturnal polyuria sub-population (defined using the 24-hour urine screening criteria). The data were submitted on November 3, 2016 by the Applicant, and triggered a major amendment.

The statistical reviewer conducted the same efficacy analysis in the nocturnal polyuria sub-population to confirm the Applicant’s findings. Results were consistent with the findings in the overall nocturia population, which is not surprising because about 80% of randomized patients had nocturnal polyuria. P-values are nominal because these analyses were not prespecified (see Table 6).

Table 6. Summary of Co primary Efficacy endpoints – Study DB3 and DB4 (ITT nocturnal polyuria patients)

	Study DB3				Study DB4		
	Placebo (N=145)	SER120 0.75 mcg (N=145)	SER120 1.0 mcg (N=146)	SER120 1.5 mcg (N=143)	Placebo (N=204)	SER120 0.75 mcg (N=209)	SER120 1.5 mcg (N=199)
Mean Nocturic Episodes							
Baseline (SD)	3.3 (1.0)	3.4 (0.9)	3.3 (1.0)	3.2 (0.8)	3.3 (0.9)	3.4 (0.9)	3.4 (0.9)
Treatment Period (SD)	2.2 (1.1)	2.0 (1.1)	2.0 (1.1)	1.8 (0.9)	2.2 (1.0)	2.0 (1.1)	2.0 (1.1)
Change from baseline* (SE)	-1.1 (0.1)	-1.4 (0.1)	-1.4 (0.1)	-1.5 (0.1)	-1.2 (0.1)	-1.5 (0.1)	-1.5 (0.1)
Difference vs. placebo (SE)		-0.3 (0.1)	-0.2 (0.1)	-0.4 (0.1)		-0.2 (0.1)	-0.4 (0.1)
95% CI		-0.5, -0.1	-0.4, 0	-0.6, -0.2		-0.40, -0.1	-0.5, -0.1
P-value (vs. placebo)		0.0049	0.0207	<0.0001		0.0049	<0.0001
$\geq 50\%$ Reduction in Nocturic Voids							
n/N (%)	42/145 (29%)	59/145 (41%)	54/146 (37%)	70/143 (49%)	54/204 (27%)	73/209 (35%)	94/199 (47%)
P-value (vs. placebo) †		N/A	0.1387	0.0004		0.0754	<0.0001

Source: MO Review, FDA OB Reviewer’s analysis

*Change from baseline was obtained from an ANCOVA model.

† P-values were from pair-wise comparisons vs. placebo within CMH test.

Gender

An analysis of the two primary efficacy endpoints according to gender finds a slightly greater placebo-corrected responder rate in men than women. The absolute reduction in nocturia episode frequency was similar in men and women (see [Table 7](#)).

Table 7. Primary Efficacy Endpoints According to Gender, ITT Population

	Males			Females		
	SER120 1.5 mcg	SER120 0.75 mcg	placebo	SER120 1.5 mcg	SER120 0.75 mcg	placebo
Nightly Nocturic Episode Frequency						
N	251	252	258	188	196	188
Screening Mean (SD)	3.3 (0.8)	3.4 (1.0)	3.4 (0.9)	3.3 (0.8)	3.3 (0.9)	3.2 (0.8)
Treatment Mean (SD)						
Mean (SD) Change from screening	-1.4 (0.9)	-1.3 (0.8)	-1.1 (0.8)	-1.6 (0.9)	-1.5 (0.9)	-1.3 (0.9)
Placebo-corrected mean change from screening	-0.4	-0.2		-0.3	-0.2	
>50% reduction in nocturic episodes (treatment vs screening)						
Yes [n(%)]	110 (43.8)	84 (33.3)	63 (24.4)	104 (55.3)	86 (43.9)	72 (38.3)
Placebo-subtracted % Yes	19.4	8.9		11.4	5.6	

Source: DBRUP clinical reviewer's analysis

Age Group

Efficacy was not notably different in subjects older than 65 years of age compared to those younger with respect to the absolute reduction in nocturia episode frequency according to a post-hoc analysis of efficacy data.

Table 8. Primary Efficacy Endpoints According to Age, (ITT Population)

	≥65 years			<65 years		
	SER120 1.5 mcg	SER120 0.75 mcg	placebo	SER120 1.5 mcg	SER120 0.75 mcg	placebo
Nightly Nocturic Episode Frequency						
N	238	245	244	201	203	202
Screening Mean (SD)	3.4 (0.9)	3.4 (0.9)	3.4 (0.9)	3.2 (0.8)	3.3 (0.9)	3.2 (0.8)
Treatment Mean (SD)	-1.4 (0.9)	-1.3 (0.8)	-1.1 (0.8)	-1.6 (0.9)	-1.5 (0.9)	1.3 (0.9)
Placebo-corrected mean change from screening	-0.3	-0.2		-0.3	-0.2	
>50% reduction in Nocturic Episodes (treatment vs screening)						
Yes [n(%)]	102 (42.9)	80 (32.7)	56 (22.9)	112 (55.7)	90 (44.3)	79 (39.1)
Placebo-subtracted % Yes	20	9.8		16.6	5.2	

Source: MO review analysis

Exploratory responder analysis

In order to explore in another way 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 (ITT)

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

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

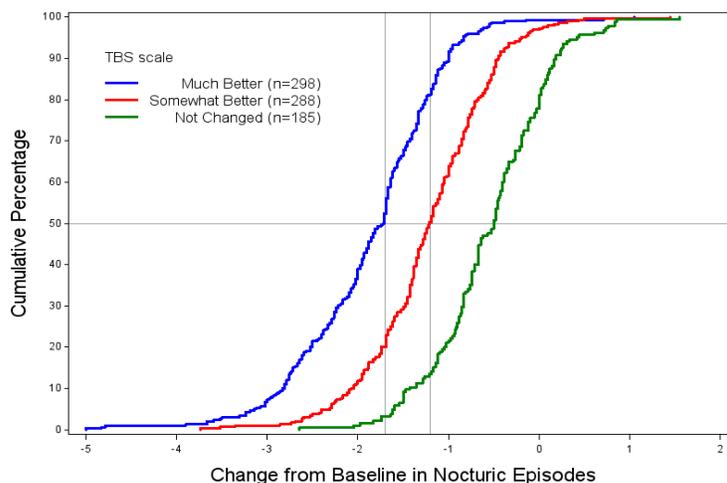
Data from all subjects in the ITT population in DB4 irrespective of treatment assignment were used to calculate cumulative distribution function (CDF) curves. This plot has the change from baseline in nocturic episodes on the x-axis and cumulative percentage of patients on the y-axis. Three separate 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 2: 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

The percentage of responders in DB4 was separately calculated 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 (by TBS scale) – Trial DB4, ITT- Pop

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

CDTL Comment

The anchor-based exploratory responder analyses indicated that, 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 consistent separation between SER 1.5 mcg vs. placebo.

Therefore, these analyses suggest that Noctiva 1.5 mcg may potentially benefit approximately 13% more patients than placebo in reducing nocturia episodes.

Efficacy Summary

On the advice of the FDA, the clinical trial population studied consisted of adults ≥ 50 years of age.

- **The Applicant proposed a starting dose of 0.75 mcg per night which may be increased to 1.5 mcg per night based on individual patient efficacy and tolerability. However, 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.**
- **SER120 0.75 mcg dose did not meet all of the pre-specified statistical criteria for efficacy. SER 0.75 mcg was not tested statistically in Study DB3 because the pre-specified hierarchical testing stopped after 1.0 mcg dose failed on one of its co-primary efficacy endpoints. Additionally, in Study DB4, the 0.75 mcg dose was not statistically significant for one of its co-primary efficacy endpoints.**

Although the 0.75 mcg dose did not achieve statistical significance on both the co-primary efficacy endpoints, it had greater treatment effect in patients ≥ 65 years of age than in patients < 65 years of age. This supports DBRUP's recommendation for approving the 0.75 mcg as the starting dose for patients who are ≥ 65 years of age and are at higher risk for hyponatremia.

- 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 $\geq 50\%$ 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.
- A post hoc analysis that explores 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.
- In a post-hoc analysis, the efficacy findings with SER120 in patients with nocturnal polyuria (defined by 24-hour urine volume criteria) in the two phase 3 trials were consistent with the overall results.

Statistical Review and Evaluation

The Division of Biometrics III review team, Drs. Jia Guo and Mahboob Shobhan, reviewed this application and made the following recommendation:

Conclusions and Recommendations:

The two studies provided evidence demonstrating efficacy of NOCTIVA 1.5 mcg over placebo for overall study population. The treatment effect in the subgroup of nocturnal polyuria patients remained at the same magnitude as the ITT population. Based on the recommendation of the Advisory Committee, nocturnal polyuria is an appropriate indication. From statistical perspective, the 1.5 mcg was effective in treating nocturnal polyuria.

CDTL Comment

I concur with the conclusion and recommendation from the statistical review team. While I agree with approval of the 1.5 mcg dose for patients at average risk of hyponatremia, I also recommend approval of the 0.75 mcg dose as a starting dose for patients who are at increased

risk for hyponatremia because the 0.75 mcg dose did show some separation from placebo and because it may have a lower risk of hyponatremia than the 1.5 mcg dose.

Statistical Issues

The Applicant submitted two double-blind phase 3 studies (DB3 and DB4) to demonstrate efficacy of NOCTIVA (0.75 mcg and 1.5 mcg) compared to placebo.

- The 1.5 mcg dose achieved statistical significance with respect to both co-primary and secondary efficacy endpoints in both studies.
- Exploratory analysis of clinical meaningfulness also demonstrated that NOCTIVA 1.5 mcg may potentially benefit approximately 13% more patients than placebo in reducing nocturia episodes.
- The 1.0 mcg dose was only studied in DB3 and not proposed for marketing. This dose failed to demonstrate efficacy on the second co-primary efficacy endpoint in DB3. Therefore, the statistical testing on the lower dose 0.75 was not performed according to the pre-specified multiplicity control plan in study DB3.
- The 0.75 mcg dose achieved statistical significance only on the reduction of nocturic episodes per night compared to placebo in study DB4. The treatment effect of 0.75 mcg on reducing nocturia episodes compared to placebo in DB3 was very similar to that in study DB4.

The analysis results on co-primary and secondary efficacy endpoints for the nocturnal polyuria subgroup were very similar to those for the whole ITT population.

Statistical Analysis Plan for Both Trials (DB3 and DB4)

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.
- 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.

CDTL Comment

During the protocol design phase for study DB4, DMEP recommended the mITT as the primary efficacy analysis 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, upon reconsideration, DBRUP in

consultation with our Biometrics Division 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.

Additionally, the mITT and ITT results are similar, but for the reasons stated above, this review focused on the ITT results.

Statistical Methodologies

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), testing proceeded 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.

Statistical Review Summary

The Applicant submitted two double-blind phase 3 studies (DB3 and DB4) to demonstrate efficacy of NOCTIVA (0.75 mcg and 1.5 mcg) compared to placebo.

- The 1.5 mcg dose achieved statistical significance with respect to both co-primary and secondary efficacy endpoints in both studies.
- Exploratory analysis of clinical meaningfulness also demonstrated that NOCTIVA 1.5 mcg may potentially benefit approximately 13% more patients than placebo in reducing nocturia episodes.
- The 1.0 mcg dose was only studied in DB3 and not proposed for marketing. This dose failed to demonstrate efficacy on the second co-primary efficacy endpoint in DB3. Therefore, the statistical testing on the lower dose 0.75 was not performed according to the pre-specified multiplicity control plan in study DB3.
- The 0.75 mcg dose achieved statistical significance only on the reduction of nocturic episodes per night compared to placebo in study DB4. The treatment effect of 0.75 mcg on reducing nocturia episodes compared to placebo in DB3 was very similar to that in study DB4.

CDTL Comment

The analysis results on co-primary and secondary efficacy endpoints for the nocturnal polyuria subgroup were very similar to those for the whole ITT population. (See Dr. Olivia Easley's Clinical Review).

8. Safety

Methods

The safety review is primarily based on the data from the following Phase 3 trials: placebo controlled trials DB3 and DB4; and the open label extension of DB3 (trial A2). These trials used the 0.75 and 1.5 mcg dose of SER120 to treat patients with nocturia.

Overall Exposure

A total of 1867 patients with nocturia received SER120 for periods of time ranging from less than one month to more than 24 months. Across all the doses tested, 607 patients received SER120 for six or more months and 347 patients received the drug for 12 or more months. The highest dose level tested in patients with nocturia was 1.5 µg. A total of 748 patients received this dose: 304 for six or more months and 218 patients for 12 or more months.

CDTL Comment

The duration and extent of exposure to SER120 in nocturnal polyuria patients was adequate.

CDTL Comment

The patients randomized to each of the 4 active groups, one combined placebo group and study A2, the long term open label extension of DB3 were, in general, similar in terms of mean age, age group (percentage < 65 and percentage ≥ 65 years), percentage of males and females, race, mean height, mean weight, and mean BMI.

For a summary of demographic variables, see the MO's safety review.

Safety Results

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. The five deaths are summarized below.

Deaths occurring in the placebo controlled trials:

- **Subject 1** (b) (6): 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 (b) (6) visit. His serum sodium values were within normal limits at each visit up to and including his last visit on Day (b) (6). Ten days after his Day (b) (6) 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** (b) (6): 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 (b) (6). Three days before his scheduled Day (b) (6) 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** (b) (6): 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. (b) (6) 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.

Deaths occurring in the open-label, uncontrolled trials:

- **Subject** (b) (6): 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 (b) (6) visit. His serum sodium values were within normal limits at each visit up to and including his last visit on Day (b) (6). Four days after his Day (b) (6) 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** (b) (6): 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 (b) (6) 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.

Table 11. Summary of Deaths Occurring During the Clinical Trials for SER120

Subject	Age (yrs)	Dose (µg)	Cause of Death	Source	Role of Drug
Controlled Trials					
(b) (6)	57	0.75	Atherosclerosis/sarcoidosis	Autopsy	Unlikely
(b) (6)	77	1.0	Cardiac arrest/abdominal aneurysm/hypotension	Hospital records	Unlikely
(b) (6)	80	0.75	Unknown	Investigator	Cannot be ruled out
Uncontrolled Trials					
(b) (6)	79	0.75	Probable myocardial infarction	Death certificate	Cannot be ruled out
(b) (6)	76	1.5	Cecal perforation	Hospital records	Unlikely

CDTL Comment

In my clinical opinion the role of SER120 in the deaths due to coronary atherosclerosis ((b) (6)), bleeding aortic aneurysm ((b) (6)), and cecal perforation ((b) (6)) is unlikely. However, role of the drug in the other two deaths ((b) (6) and (b) (6)) cannot be definitively ruled out.

Dr. Martin Kaufman states in his review that during the 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.

Nonfatal Serious Adverse Events (SAE)

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.

CDTL Comment

The prior history and short duration of SER120 exposure before diagnosis make treatment relatedness unlikely for these lesions.

Two subjects, one in the 1.5 µg treatment group and one in the placebo group, reported hyponatremia as a SAE. There were no reports of seizure or coma.

One subject in the 0.75 µg dose group reported congestive heart failure as a SAE. This 56 year old male had a prior history of hyperlipidemia and hypertension. About three months after starting treatment with SER120, he was found to have a dilated cardiomyopathy with ejection fraction of 40%, valvular abnormalities, left atrial enlargement, and pulmonary hypertension after presenting with chest tightness and shortness of breath.

CDTL Comment

It is unlikely that SER120 caused this subject's cardiac abnormalities.

One subject in the 1.5 µg dose group reported hypertension as a SAE. This 84 year old male had a prior history of hypertension, myocardial infarction, angina, and coronary artery disease. Concomitant medications for these conditions included nitroglycerin, clopidogrel, metoprolol, and lisinopril. His blood pressure was 122/72 mmHg at baseline and 160/85 mmHg at Day (b) (6) (end of placebo lead-in period). (b) (6) days after actual randomization, the patient complained of chest tightness and dizziness and was seen in the emergency room where his blood pressure was 183/101 mmHg. He was hospitalized, had a negative work-up for acute cardiac problems, and was discharged with a diagnosis of atypical chest pain and vertigo. The patient returned to the study site off study drug for a few days with a blood pressure of 133/75 mmHg and was restarted on study drug. The next day his blood pressure was 188/89 mmHg and the investigator discontinued him from the study. At the early termination visit two days later, his blood pressure was 121/74 mmHg.

CDTL Comment

The study drug appears to have exacerbated this subject's pre-existing hypertension. However, it should be noted that the increase in systolic blood pressure was first noted at Day (b) (6), after treatment with placebo.

Open-Label Safety Extension Study - A2 (uncontrolled)

In study A2, 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.

CDTL Comment

- ***All of the five subjects who reported basal cell carcinoma were males whose ages ranged from 52 to 79 years. The events occurred at study days (b) (6). All subjects who reported this SAE continued in the study after the event. Per Dr. Kaufman, clinical safety reviewer, it is unlikely that these events were related to the study drug. I concur with the clinical safety reviewer.***
- ***Each of the three subjects who reported knee arthroplasty had a previous history of arthritis of the knee and underwent elective joint replacement surgery. Therefore, it is unlikely these cases were related to the drug.***

- *Two subjects reported a SAE of pulmonary embolism. One subject was a 70 year old female who was hospitalized with shortness of breath and chest pain. CT scan revealed pulmonary emboli in both lungs and an ultrasound showed DVT in the right lower extremity. The subject had undergone surgery on her right foot which may have increased her risk of VTE.*

The other subject was a 53 year old female who was admitted to the hospital with dyspnea on exertion and palpitations. Diagnostic workup included a lung scan which revealed multiple pulmonary emboli bilaterally. Ultrasound revealed left DVT. This subject had a history of Cushing’s disease, which was reported as ongoing when she was screened for the trial and may have increased her risk of VTE.

A role for SER120 in both of these cases cannot be definitively ruled out, though both cases are confounded by pre-existing co-morbid conditions (recent lower extremity surgery and ongoing Cushing’s disease).

- *A 60 year old male, reported the SAE of thrombocytopenia after taking one dose of SER120. The patient reported mild epistaxis with administration of this single dose of study drug and the (b) (6) day, noted mucosal hemorrhages and a petechial rash on the trunk and all extremities, which the patient said may have started prior to his first dose of the drug. The patient had a low platelet count of 150,000 at screening. He also reported not feeling well for a period of one to two weeks prior to starting the study drug with symptoms of lightheadedness and decreased endurance.*

A role for SER120 in this case cannot be definitively ruled out, though the event is confounded by the subject experiencing signs and symptoms of thrombocytopenia prior to exposure to the drug.

- *Narratives for the other SAEs were reviewed by Dr. Kaufman, the safety reviewer, who determined that the role of SER120 in these cases is unlikely.*
- *I concur with Dr. Kaufman’s judgement.*

Dropouts and/or Discontinuations

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 12. Most Common Adverse Events Leading to Discontinuation-DB3/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

Source: MO Review, NDA 201656 (SDN 001), Module 5.3.5.3, Table 7.4.2 p. 543.

CDTL Comment

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

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 (b) (6) was randomized to the 1.5 µg dose during DB4. (b) (6) 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 (b) (6) and (b) (6) and had serum sodium values of 131 mmol/L, 131 mmol/L, and 133 mmol/L, during those visits. Three days after her Day (b) (6) 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 (b) (6) was randomized to placebo during DB4. On Day (b) (6) 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.

Studies DB3 and DB4

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.

Table 13. 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)

* Source: MO Review, NDA 201656 (SDN 001), Module 5.3.5.3, Table 6.1.2 p. 286.

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 14**. All of these subjects were prematurely discontinued from the trial per protocol.

Table 14: 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
(b) (6)	M	75	1.5	135	125	(b) (6)	None	1/ A, C
	M	70	1.5	136	124		None	2/ A, B
	M	67	1.5	140	125		None	3/ A, B
	M	75	1.5	138	124		None	4/
	F	72	1.5	137	122* 117*		None Weakness, nausea, vomiting	5/ A, B

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 (b) (6).
2. In addition to an inhaled corticosteroid, the patient (b) (6) also had one injection of triamcinolone, 40 mg, 8 days prior to the Day (b) (6) visit.
3. Subject was treated with oral prednisone 10 mg three times daily x 4 days, starting (b) (6) days before the Day (b) (6) visit.
4. Subject’s serum sodium was 128 mmol/L on Days (b) (6).
5. Investigator believes subject may have had an acute gastrointestinal illness that started prior to the Day (b) (6) assessment. The Day (b) (6) 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

Source: NDA 201656 (SDN 001), Module 5.3.5.3, Reviewer analysis of information in patient narratives, pp. 63-114.

Of the five SER120-treated subjects with nadir serum sodium values ≤ 125 mmol/L, all were being treated with the 1.5 µg dose at the time of the event. All were 65 years of age or older. Four were male, one was female. Four of the five were being treated with corticosteroids: three with an inhaled corticosteroid and one with oral prednisone. One of the subjects being treated with an inhaled corticosteroid had also received an injection of 40 mg of triamcinolone eight days prior to the event. 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 (b) (6) ((b) (6) days after starting active treatment with SER120) and the latest at Day (b) (6) (the final visit of the trial).

Only one subject ((b) (6)) with documented hyponatremia was symptomatic (serum sodium 117 mmol/L on Day (b) (6) 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 nadir serum sodium in the range of 126 – 129 mmol/L:

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 the eighteen (89%) were 65 years of age or older: nine treated with the 1.5 µg dose and seven 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 (b) (6) days after starting active treatment) and the latest at Day (b) (6) (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 (b) (6) day after starting active treatment).

Hyponatremia during Open Label Safety Extension Study - A2

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 these subjects were asymptomatic and continued in the study except for one subject who discontinued at Day (b) (6) with a serum sodium value of 131 mmol/L from Day (b) (6) 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 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 (b) (6), 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

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 (b) (6) had been randomized to placebo during DB3 and was first on active drug during A2. The Day (b) (6) 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 (b) (6) 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. (b) (6) days prior to his Week 30 visit, he was diagnosed with diverticulitis and was treated with hydromorphone, ciprofloxacin and metronidazole for (b) (6) 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 (b) (6) 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.

Age Specific Hyponatremia

Of the 1356 subjects in the 1.5 μg , 0.75 μg , and placebo dose groups in DB3 and DB4, 744 (55%) were age 65 years or older. **Table 16** summarizes a subgroup analysis of nadir serum sodium values comparing subjects younger than 65 years to subjects 65 years or older.

Table 16: 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.

Source: MO Review, NDA 201656 (SDN 001), Module 5.3.5.3, Table 6.4.2 p. 328 and Table 6.5.2 p. 342.

CDTL Comment

For the 1.5 µg dose group, no subjects in the younger (<65 years) age group had a nadir serum sodium value that was less than 130 mmol/L, compared to 14 (5.7%) subjects in the older age group. For the 0.75 µg dose group, two (1.0%) subjects in younger (<65 years) age group had a nadir serum sodium value that was less than 130 mmol/L, compared to 7 (2.8%) subjects in the older age group.

For the 1.5 µg dose group, the risk of hyponatremia, and importantly severe hyponatremia (serum sodium ≤ 125 mmol/L), appears to be low for younger (<65 years) subjects, compared to the 0.75 µg dose group, where the risk appears to be lower regardless of age.

Gender Specific Hyponatremia

Of the 1356 subjects in the 1.5 µg, 0.75 µg, and placebo dose groups in DB3 and DB4, 582 (43%) were female and 774 (57%) were male.

Table 17: Categorical Analysis of Nadir Serum Sodium - DB3/DB4 – Male and Female

Serum Sodium Range (mmol/L)	1.5 µg		0.75 µg		Placebo	
	Males (N=256) n/N (%)	Females (N=192) n/N (%)	Males (N=256) n/N (%)	Females (N=198) n/N (%)	Males (N=262) n/N (%)	Females (N=192) n/N (%)
130–134	28/256 (10.9)	22/192 (11.5)	20/256 (7.8)	18/198 (9.1)	10/262 (3.8)	10/192 (5.2)
126–129	7/256 (2.7)	2/192 (1.0)	4/256 (1.6)	5/198 (2.5)	0/262 (0)	0/192 (0)
≤ 125	4/256 (1.6)	1*/192 (0.5)	0/256 (0)	0/198 (0)	1*/262 (0.4)	0/192 (0)

*Includes 1 patient whose serum sodium value was obtained outside the study central laboratory and was, therefore, not included in the laboratory database.

Source: NDA 201656 (SDN 001), Module 5.3.5.3, Table 6.2.2 p. 300 and Table 6.3.2 p. 314.

CDTL Comment

The effect of gender on hyponatremia from these data is not clear. For the 1.5 µg dose group, the incidence of nadir serum sodium values less than 130 mmol/L is greater in males (4.3%) than females (1.5%). However, for the 0.75 µg dose group the incidence is greater in females (2.5%) than males (1.6%). This finding may reflect the effect of the age distribution in each group: in the female group 47% of the subjects were 65 years or older versus 61% in the male group.

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 18** 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 18. 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%)

¹Blood 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

Source: MO's Review, NDA 201656 (SDN 001), Module 2.7.4, Table 19 p. 36.

CDTL Comment

The most common adverse events reported involved the nasal cavity and nasopharynx, which is consistent with the route of administration of the drug.

Common adverse events in open label A2 study were similar to those in DB3 and DB4. For details, see Dr. Kaufman's clinical safety review.

Laboratory Findings

With the exception of decrease in serum sodium during DB3, DB4, and A2, there were no chemistry, hematology, or urinalysis findings that were clinically significant.

Vital Signs

During DB3 and DB4, vital signs including blood pressure, heart rate, oral temperature and respiration were assessed.

CDTL Comment

There were no clinically meaningful changes in vital signs in SER120 treated subjects during the course of the study however, for the pooled DB3/DB4 data, the change from baseline in mean systolic and diastolic blood pressure was less than 1 mm Hg at each assessment time point for both the 1.5 and 0.75 µg dose groups.

During the open-label extension study (A2), the change in mean systolic blood pressure was not statistically significantly different from baseline at most time points. The changes that were statistically significantly different ranged from 2.1 mm Hg at Week 14 to 3.8 mm Hg at Weeks 62 and 78. The change in mean diastolic blood pressure was not statistically significantly different from baseline at all time points.

Electrocardiograms

Studies DB3 and DB4

During DB3 and DB4, each patient had a 12-lead ECG at screening and the Day (b) (6)/Exit Visit. There were 15 subjects with abnormal-clinically significant ECGs at the Day (b) (6)/Exit Visit: five in the 1.5 µg dose group, four in the 0.75 µg dose group, and six in the placebo group. For a detailed review of these cases see Dr. Kaufman's review.

CDTL Comment

In my clinical opinion after reviewing these cases with the safety clinical reviewer, it is unlikely that these arrhythmias were caused by the study drug as all these subjects had past medical history of cardiac disease that could have very well contributed to these arrhythmias.

Overall Safety assessment

The applicant conducted four randomized, double-blind, placebo-controlled phase 3 trials (DB1, DB2, DB3 and DB4) and two open-label, long-term, uncontrolled, safety extension trials (OL1-the extension of DB1 and DB2, and A2-the extension of DB3) to confirm the safety of SER120. Because the applicant is requesting approval to market the 0.75 and 1.5 µg doses of SER120 and the 1.5 µg dose was used only in DB3, DB4, and A2, the review of safety primarily focused on the pooled DB3/DB4 data and the long-term safety data from A2.

The duration and extent of exposure to SER120 in nocturia patients was adequate. A total of 1867 subjects with nocturia received SER120 for periods of time ranging from less than one month to more than 24 months. The highest dose level tested in patients with nocturia was 1.5 µg. A total of 748 patients received this dose: 304 for six or more months and 218 patients for 12 or more months.

Five deaths were reported during the clinical trials for SER120, all occurred while the subject was being treated with SER120. Three deaths occurred during the controlled trials: a role of the drug is unlikely in two of the deaths, a role of the drug cannot be definitively ruled out for the

other. 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. Two deaths occurred during the uncontrolled trials: a role of the drug is unlikely in one and cannot be definitively ruled out for the other.

During the four controlled phase 3 trials, the incidence of treatment emergent serious adverse events (SAEs) for SER120-treated subjects was low and similar to the placebo group across all dose groups. Two subjects, one in the 1.5 µg treatment group and one in the placebo group, reported hyponatremia as a SAE. There were no reports of seizure or coma.

During DB3 and DB4, the overall incidence of subjects with at least one adverse event (AE) was slightly greater in the SER120 treatment groups (47%-49%) than in the placebo group (45%). AEs were most commonly reported in the Respiratory Disorders system organ class (SOC). The most commonly reported preferred terms in this SOC were nasal discomfort, sneezing, and nasal congestion. The incidence of AEs that resulted in discontinuation of the subject from the study was also slightly greater in the SER120 treatment groups (4.2%-4.9%) than in the placebo group (4.0%). The most common AE resulting in discontinuation from the study, and that occurred at a greater incidence in SER120 treated subjects than in placebo, was hyponatremia.

CDTL Comment

Hyponatremia is a known risk of desmopressin drugs and is the most important risk of SER120 in patients being treated for nocturia. 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 and 2.0%, 2.0%, and 0% had nadir serum sodium values of 126-129 mmol/L. For the SER120-treated subjects with nadir serum sodium values ≤ 125 mmol/L (severe hyponatremia) all were being treated with the 1.5 µg dose at the time of the event, all were 65 years of age or older, and all but one was also being treated with an inhaled or systemic corticosteroid. These findings regarding the development of severe hyponatremia have been incorporated into labeling.

The applicant also conducted a phase 3, randomized open-label study, SPC-SER120-ELD-2010-01, to evaluate the safety, pharmacokinetics, and tolerability of SER120 in elderly (≥ 75 years old) patients with nocturia. A total of 32 subjects were randomized. All 32 were included in the safety population with 15 subjects in the 0.5 µg dose group and 17 subjects in the 0.75 µg dose group. No serious adverse events were reported during this study. There were no subjects in this study in either treatment group with serum sodium values lower than 130 mmol/L. The most frequently occurring AEs were nasal discomfort followed by sneezing, rhinorrhea and increased lacrimation.

With the exception of decreases in serum sodium in this drug development program, there were no chemistry, hematology, or urinalysis findings that were clinically significant during DB3, DB4, and A2. Changes in vital signs were also not clinically meaningful during the course of these trials.

Review of the adverse event, clinical laboratory, and vital sign data generated during the phase 3 studies indicate SER120 can be safely used to treat nocturnal polyuria in properly selected patients age 50 years or older.

9. Advisory Committee Meeting

FDA held a meeting with the Bone, Reproductive and Urologic Drugs Advisory Committee on October 19, 2016, to discuss the efficacy and safety of SER120 in treating adult nocturia. Questions posed to the committee along with discussion that followed are presented below:

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.

Discussion: Most members expressed no issues with age restriction and absence of restriction on fluid intake, but there were concerns that the numerous exclusion criteria limit the generalizability of the data. The panel noted that the vast majority of patients who have nocturia are over 50 years of age, and the risk of hyponatremia would be less in the younger age group.

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

Discussion: Most members felt that the 1.5 mcg dose, but not the 0.75 mcg dose, produced a meaningful, albeit modest, difference to patients, but some members recommended having the 0.75 mcg dose available as well.

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

Discussion: The panelists had concerns about the potential for widespread use, including in nursing homes. They also noted that most of the clinically significant hyponatremia occurred in patients older than 65 years of age, and monitoring in "real life" will be less than in the clinical trials. Other comments were that the lack of good understanding of hyponatremia in the general medical community is high and that there are limited safety data beyond one year of use.

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.

Discussion: The majority agreed that nocturia is a symptom and that the clinical trial population does not support an indication as broad as nocturia. Most panelists believed that an indication of nocturnal polyuria was reasonable, but acknowledged that that was as a sub-population.

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.

Yes – 17, No – 1

- 17 “Yes”:
 - The majority said “Yes” for 1.5 mcg dose only and stated there was insufficient evidence to approve the 0.75 mcg dose
 - One panelist referred to the 0.75 mcg dose as “expensive placebo” and its approval would “set bad precedent.” but some members liked the option of starting with a lower dose but stated that the evidence did not clearly support this approach
- 1 “No”:
 - The sole dissenter did not favor a product indicated for nocturia regardless of underlying cause.

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.

Yes – 14, No – 4

- 14 “Yes” votes:
 - 13/14 opposed a general indication of *nocturia* and recommended the indication be treatment of adults with **nocturnal polyuria** (as defined by the protocol, i.e. >33% of 24 hour urine produced at night)
 - Label should reflect the trials’ exclusion criteria
 - Other recommendations not to use in institutionalized patients, and to carefully monitor patients over 65 years old
- 4 “No” votes :
 - Threshold of ≥ 2 voids per night too liberal
 - Concern for indiscriminate use of the product
 - Concern for serious side effects
 - If approved, recommend risk minimization strategies (e.g., boxed warning) for hyponatremia

10. Post-marketing Requirements and Commitments

The Applicant is proposing to market the two SER120 dose strengths (0.75 mcg or 1.5 mcg). The two dose formulations are not interchangeable – i.e., the Applicant has not compared the systemic exposure of two nasal sprays of SER120 0.75 mcg to one nasal spray of SER120 1.5 mcg. In clinical practice, patients who are dose-escalated from SER120 0.75 mcg to SER120 1.5 mcg may substitute two nasal sprays of SER120 0.75 mcg to achieve the 1.5 mcg dose, rather than purchase a new prescription for the SER120 1.5 mcg dose. This issue could pose a risk to patients if systemic exposure following two nasal sprays of SER120 0.75 mcg exceeds that following one spray of SER120 1.5 mcg. Therefore, a post-marketing pharmacokinetic study is being required to compare the systemic exposure of the two dose formulations.

11. Pediatrics

SER120 is indicated for adults with nocturnal polyuria and has not been evaluated in patients less than 18 years of age. SER120 was not studied for primary nocturnal enuresis but we will nonetheless add a contraindication for this use because of reports of hyponatremia-related seizures in pediatric patients with use of other intranasal formulations of desmopressin acetate.

Overdose, Drug Abuse Potential and Withdrawal

There were no reports of SER120 overdose during the development program. Treatment of overdosage would include discontinuation of the drug, fluid restriction (if hyponatremia occurs), electrolyte monitoring, and appropriate symptomatic and supportive care. No formal abuse potential studies or studies to evaluate withdrawal were needed or conducted as part of the clinical research program for SER120.

12. Other Relevant Regulatory Issues

DMEPA

Division of Medication Error Prevention and Analysis did the proprietary name review.

Both Irene Chan and Todd Bridges Deputy Director and Director of DMEPA made the following determination:

Conclusion and Recommendation

We conclude that the proposed proprietary name, Noctiva, nasal spray (NDA 201656) is acceptable.

Comments to the Applicant

We have completed our review of the proposed proprietary name, Noctiva, and have concluded that this name is acceptable. If any of the proposed product characteristics as stated in your March 14, 2016 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

CDTL Comment

Conclusion by Irene Chan and Todd Bridges supersedes the earlier determination by Capt. Walter Fava, Safety Evaluator, DMEPA, who earlier had concluded that the name Noctiva could result in medication errors due to confusion with another product under review. For a detailed explanation and review see the DMEPA review in DARRTS.

OPDP

Office of Prescription Drug Promotion reviewed the Package Insert (PI) and proposed carton and container labeling for Noctiva nasal spray. OPDP also, provided comments for the labeling.

DMPP

The Division of Medical Policy Programs and OPDP also provided comments for the Medication Guide and Instruction for Use (IFU).

CDTL Comment

DMEPA reviewer Denise Baugh and Acting Team Leader Lolita White during their review of the IFU in November, 2016, noted that the document needed re-wording of Priming and Re-Priming instructions for clarity which otherwise would result in under-dosing and compromised efficacy. They further stated that these new changes to the IFU need to be re-validated in a Human Factor Study. The Applicant was asked to conduct a new Human Factor study and revalidate these suggested changes to the IFU and submit for review thereafter. The applicant made the necessary changes to the instructions and revalidated their findings as requested. The revised submission with revalidation was reviewed by DMEPA and found to be acceptable. Denise Baugh, DMEPA reviewer made further suggestions for clarity of instructions in the IFU, which have been communicated to the Applicant.

OSI (Office of Scientific Investigations)

The OSI inspected two clinical sites which enrolled subjects into studies DB3 and DB4. The OSI inspector concluded that “the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.” The final classification of one site (Dr. Edelman) was Voluntary Action Indicated and the other site was deemed “No Action Indicated (NAI).”

CDRH

Kathleen Fitzgerald, Consultant and Alan Stevens, Branch Chief made the following determination:

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the device constituent parts of the subject combination product. After examination of the original new drug application (NDA), cross-referenced drug master files (DMF), and responses to information requests, the consulting reviewer has determined that the device constituent parts of the combination product have been designed appropriate for the product’s intended use and essential performance requirements.

Patient Labeling

Patient Labeling Review team, Karen Dowdy and Jina Kwak made the following conclusion and recommendation:

Conclusion

The MG and IFU are acceptable with our recommended changes.

Recommendation

Our collaborative review of the MG and IFU is acceptable.

13. Labeling

The following changes are recommended for the label:

- The **INDICATION** is being changed to the treatment of *nocturnal polyuria* in adults who awaken two or more times per night to void. A 24-hour urine frequency/volume chart should be used to diagnose nocturnal polyuria before starting treatment. A night-time urine production exceeding one-third of the 24-hour urine production is regarded as nocturnal polyuria. In addition, underlying conditions contributing to nocturnal polyuria (e.g. lower urinary tract symptoms associated with overactive bladder or benign prostatic hyperplasia) should be optimized before initiating treatment with NOCTIVA.
- A **LIMITATION OF USE** should be added that SER120 has not been studied in patients less than 50 years of age.
- **RECOMMENDED DOSAGE:** The starting dose in patients under 65 years of age should be SER120 1.5 mcg 30 minutes before bedtime. Patients >65 years of age or those at increased risk for hyponatremia should start at SER120 0.75 mcg which can be increased to 1.5 mcg after at least 1 week if needed based on individual patient efficacy and if the serum sodium is within the normal range. In all patients regardless of age, serum sodium should be checked within 7 days of initiating therapy and periodically thereafter.
- **CONTRAINDICATIONS** will incorporate the phase 3 trial exclusion criteria (e.g., Congestive heart failure, NYHA classes II-IV) and medications prohibited during the trials (i.e., loop diuretics, glucocorticoids).
- Consistent with recommendations from the BRUDAC, the risk of hyponatremia will be included as a **BLACK BOX WARNING**. Conditions and concomitant medications that increase the risk of hyponatremia should be highlighted within the warning.
- **PEDIATRIC USE** should include a contraindication for use in the treatment of primary nocturnal enuresis because of post-marketing reports of hyponatremic related seizures in pediatric patients with the use of other intranasal desmopressin formulations.
- The **CLINICAL STUDIES** section should include results of the analysis of efficacy in the nocturnal polyuria sub-population.

14. Risk Evaluation and Mitigation Strategies (REMS)

The Applicant voluntarily submitted a Risk Evaluation and Mitigation Strategy (REMS) that includes the following elements: a Medication Guide, a communication plan, and a timetable for submission of assessments. The goal of the REMS is to minimize the risk of patients developing hyponatremia. The Applicant's proposed communication plan consists of a Dear Health Care Professional Letter that will be distributed in a one-time mailing to health care professionals. The proposed letter explains the risk of hyponatremia and reiterates the recommendations provided in the product label for reducing this risk.

At this time, REMS is not recommended for this NDA. Products containing desmopressin have been marketed for decades and the risk of hyponatremia with this drug is well known. Professional and patient labeling as well as routine pharmacovigilance are adequate to manage the risks of this product.

15. Recommendations/Risk Benefit Assessment

Recommendation

Approval of 1.5 mcg dose for patients younger than 65 years of age and a 0.75 mcg starting dose for patients 65 years of age and above or those at increased risk of hyponatremia.

Risk Benefit Assessment

I do not believe that the risk/benefit balance is favorable for using SER120 to treat nocturia irrespective of etiology. The risk of not identifying and properly treating underlying serious conditions contributing to nocturia is high in this setting. In addition, the phase 3 trials had numerous exclusion criteria so the clinical trial population studied does not support the broad indication of nocturia. The BRUDAC panelists in October, 2016, expressed similar concerns.

Consistent with the recommendation from the BRUDAC, I believe that SER120 1.5 mcg nightly has a favorable benefit/risk profile for the treatment of adults with nocturia due to nocturnal polyuria (defined as greater than one-third of 24-hour urine volume produced at night) who wake up two or more times per night to void. I recommend approval of SER120 1.5 mcg nightly with modification to the label to reflect this revised indication.

The most significant risk of SER120 is hyponatremia which is dose-proportional and is greater in subjects older than 65 years. In the phase 3 trials (DB3 and DB4), severe hyponatremia (i.e., serum sodium \leq 125 mmol/L) in SER120- treated subjects occurred in subjects older than 65 years of age who were in the 1.5 mcg dose group. Therefore, in patients older than 65 years of age or who are at increased risk of hyponatremia from pre-existing conditions or concomitant medications, I recommend initiating treatment with SER120 0.75 mcg. The dose may be escalated to 1.5 mcg if there is no response to the lower dose, provided their serum sodium has remained in the normal range on the lower dose and will be monitored periodically.

Rationale for recommending approval of 0.75 mcg for use in the elderly and in patients at risk of hyponatremia despite it not meeting the pre-specified efficacy endpoints are as follows:

- 1) In the entire study population, subjects taking SER120 0.75 mcg experienced a mean placebo-corrected reduction of 0.2 fewer nocturia episodes per night in both phase 3 trials. In one of these trials, this comparison was tested statistically and shown to be statistically significant. In addition, approximately 7-8% more subjects had at least a 50% reduction in nocturia episode frequency compared to placebo. *Although the responder differences did not meet statistical significance, they may be meaningful to some patients.*
- 2) In patients with nocturia due to nocturnal polyuria, the mean placebo-corrected reduction in nocturia episodes per night for the SER120 0.75 mcg dose group was 0.3 in both phase 3 trials. Eight to twelve percent more subjects had at least a 50% reduction in nocturia episode frequency compared to those receiving placebo. Statistical testing compared to placebo was not performed because this was a post-hoc sub-group analysis. Nonetheless the absolute difference suggests that a percentage of patients may benefit from treatment with SER120 0.75 mcg.

- 3) The risk of hyponatremia with SER120 0.75 mcg appears lower than that with the 1.5 mcg dose with no cases of severe hyponatremia observed in elderly subjects in the phase 3 trials (DB3 and DB4).
- 4) The incidence of nocturia increases with age so elderly subjects are more likely to seek treatment for this condition for which there are currently no FDA approved therapies.
- 5) SER120 0.75 mcg is reasonably safe in the elderly, and may provide a clinically meaningful benefit for some patients who have no other treatment options.

16. Regulatory Action

Approval of Noctiva 1.5 mcg for patients with nocturia due to nocturnal polyuria, with 0.75 mcg recommended as the starting dose for patients who are at increased risk for hyponatremia.

Consistent with advice from the advisory panel (BRUDAC) in October, 2016, that the product should be indicated in patients with nocturia secondary to **nocturnal polyuria I**, as the Cross Discipline Team Leader (CDTL) for this application, recommend **approval of Noctiva for the treatment of nocturia due to nocturnal polyuria. I recommend approval of the 1.5 mcg dose for patients at average risk for hyponatremia and the 0.75 mcg dose as the starting dose for patients 65 years of age and above and others who are at increased risk for hyponatremia.** The dose may be escalated to 1.5 mcg if there is no response to the lower dose in this group, provided their serum sodium remains in the normal range on the lower dose and will be monitored periodically thereafter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURESH KAUL
02/28/2017

HYLTON V JOFFE
02/28/2017
See the Division Director Memorandum.