

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201656Orig1s000**

**CLINICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201656
Priority or Standard	Standard
Submit Date(s)	February 4, 2016
Received Date(s)	February 4, 2016
PDUFA Goal Date	December 4, 2016
Division / Office	DBRUP/ODE 3
Reviewer Name(s)	Olivia J. Easley, M.D. (efficacy) and Martin Kaufman, D.P.M., M.B.A. (safety)
Review Completion Date	February 17, 2017
Established Name	Desmopressin acetate
(Proposed) Trade Name	Noctiva
Therapeutic Class	Vasopressin 2 receptor agonists
Applicant	Serenity, Pharmaceuticals
Formulation(s)	Nasal spray 0.83 / 1.66 mcg
Dosing Regimen	One spray 30 minutes before going to bed
Indication(s)	Nocturia due to nocturnal polyuria
Intended Population(s)	Adults who awaken at least 2 times per night to void

## Contents

1	Executive Summary .....	5
1.1.	Product Introduction.....	5
1.2	Conclusion on the Substantial evidence of Effectiveness.....	5
1.3	Benefit-Risk Assessment.....	6
2	Therapeutic Context.....	8
2.1.	Analysis of Condition.....	8
2.2.	Analysis of Current Treatment Options .....	9
3	Regulatory Background .....	9
3.1.	U.S. Regulatory Actions and Marketing History .....	9
3.2.	Summary of Pre-submission/Submission Regulatory Activity.....	10
3.3.	Foreign Regulatory Actions and Marketing History.....	11
4	Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety .....	12
4.1.	Office of Scientific Investigations (OSI) .....	12
4.2.	Product Quality .....	12
4.3.	Clinical Microbiology .....	12
4.4.	Nonclinical Pharmacology/Toxicology.....	12
4.5.	Clinical Pharmacology .....	13
4.6.	Division of Medication Error Prevention and Analysis (DMEPA) .....	13
4.7.	Division of Pharmaceutical Analysis (DPA) .....	13
4.8.	Clinical Outcomes Assessment (COA).....	14
4.9.	Center for Devices and Radiologic Health (CDRH).....	14
4.10.	Division of Medical Policy and Prevention (DMPP), Office of Prescription Drug Promotion (OPDP).....	14
5	Sources of Clinical Data and Review Strategy .....	14
5.1.	Table of Clinical Studies .....	14
5.2.	Review Strategy .....	16
6	Review of Relevant Individual Trials Used to Support Efficacy' .....	16
6.1.	Design of Studies DB3 and DB4.....	16
6.2.	Results of Studies DB3 and DB4.....	21
7	Integrated Review of Effectiveness .....	24
7.1	Assessment of Efficacy Across Trials.....	24
7.1.1.	Analysis of Co-Primary Endpoints .....	24
7.1.2	Secondary Endpoints .....	25
	INTU.....	25
	Additional Secondary Endpoints .....	27
7.1.3	Subpopulations.....	28
7.1.3.1	Nocturnal Polyuria Sub-population.....	28
7.1.3.2	Gender .....	30
7.1.3.3	Age Group.....	30
7.1.3.4	Baseline Nocturia Episode Frequency .....	31
7.1.4	Dose and Dose-Response.....	32
7.1.5	Onset, Duration and Durability of Efficacy .....	34

7.1.5.1	Onset.....	34
7.1.5.2	Duration and Durability of Efficacy.....	35
7.1.6	Exploratory responder analysis.....	39
7.2	Efficacy Summary.....	41
7.3	Integrated Assessment of Effectiveness.....	41
8	Review of Safety.....	43
8.1	Methods.....	44
8.1.2	Studies/Clinical Trials Used to Evaluate Safety.....	44
8.1.3	Categorization of Adverse Events.....	44
8.1.4	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 44	
8.2	Adequacy of Safety Assessments.....	44
8.2.2	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	44
8.2.3	Explorations for Dose Response.....	47
8.2.4	Special Animal and/or In Vitro Testing.....	48
8.2.5	Routine Clinical Testing.....	48
8.2.6	Metabolic, Clearance, and Interaction Workup.....	48
8.2.7	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	48
8.3	Major Safety Results.....	49
8.3.2	Deaths.....	49
8.3.3	Nonfatal Serious Adverse Events.....	50
8.3.4	Dropouts and/or Discontinuations.....	53
8.3.5	Submission Specific Primary Safety Concerns.....	54
8.4	Supportive Safety Results.....	60
8.4.2	Common Adverse Events.....	60
8.4.3	Laboratory Findings.....	64
8.4.4	Vital Signs.....	64
8.4.5	Electrocardiograms (ECGs).....	64
8.4.6	Special Safety Studies/Clinical Trials.....	68
8.4.7	Immunogenicity.....	69
8.5	Other Safety Explorations.....	69
8.5.2	Dose Dependency for Adverse Events.....	69
8.5.3	Time Dependency for Adverse Events.....	69
8.5.4	Drug-Demographic Interactions.....	69
8.5.5	Drug-Disease Interactions.....	71
8.5.6	Drug-Drug Interactions.....	71
8.6	Additional Safety Evaluations.....	71
8.6.2	Human Carcinogenicity.....	71
8.6.3	Human Reproduction and Pregnancy Data.....	71
8.6.4	Pediatrics and Assessment of Effects on Growth.....	71
8.6.5	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	71
8.7	Additional Submissions / Safety Issues.....	72
9	Advisory Committee Meeting and Other External Consultations.....	73
10	Labeling Recommendations.....	74
11	Risk Evaluation and Mitigation Strategies (REMS).....	75

12	Post-marketing Requirements and Commitments .....	75
13	Appendices.....	77
13.1	Appendix I.....	77
13.2	Appendix II.....	78
13.3	Appendix III .....	79

**Tables:**

Table 1	New Drug Applications for Desmopressin Products in FDA.....	10
Table 2.	Clinical Trials Conducted in support of NDA Marketing Application .....	15
Table 3.	Summary of Subject Disposition in Trials DB3 and DB4.....	21
Table 4.	Summary of Demographic Characteristics for the ITT Population, Studies DB4 and DB4 .....	22
Table 5.	Nocturia Etiology, Trials DB3 and DB4, Intent-to-Treat Population.....	23
Table 6	Summary of Co-primary Efficacy Endpoints for Trials DB3 and DB4 (Intent-to-Treat Population).....	25
Table 7.	Secondary Efficacy Variable – Change from Screening to Treatment Period in the INTU Overall Impact Score in Trial DB4 (Intent-to-Treat Population).....	26
Table 8.	Summary of Secondary Efficacy Endpoints in Trials DB3 and DB4, Intent-to-Treat population .....	27
Table 9.	Summary of Co primary Efficacy endpoints – Study DB3 and DB4 (ITT nocturnal polyuria patients) .....	28
Table 10.	Summary of Co primary Efficacy endpoints – Study DB3 and DB4 (ITT Non-nocturnal polyuria).....	29
Table 11.	Primary Efficacy Endpoints According to Gender, ITT Population .....	30
Table 12.	Primary Efficacy Endpoints According to Age, ITT Population.....	31
Table 13.	Primary Efficacy Endpoints According to Baseline Nocturia Episode Frequency Category (> or <3 episodes per night), ITT Population.....	32
Table 14.	Primary efficacy variables, ITT population, Phase 3 trials DB1 and DB2.....	34
Table 15.	Nocturia Episode Frequency at screening and at each follow-up visit during Trials DB3 and DB4, ITT population .....	35
Table 16.	Number of Patients with Exposure to SER120 by dose category, study DB3 A2 .....	37
Table 17.	Number of Nocturic Episodes per Night at each time point, ITT population study DB3-A2.....	37
Table 18:	Summary of Treatment Benefit Scale <b>Used in</b> Trial DB4 (Intent-to-Treat population) .....	39
Table 19.	Summary of Responder Rates (defined based on TBS) –Trial DB4, Intent-to-Treat population .....	40
Table 20	Number of Subjects with Exposure of SER120 by Dose Category.....	45
Table 21.	Summary of Demographic Variables (DB1/DB2/DB3/DB4) .....	46
Table 22.	Summary of Demographic Variables (A2 – Intent to Treat Population).....	47
Table 23.	Summary of Deaths Occurring During the Clinical Trials for SER120.....	50
Table 24.	Most Common Adverse Events Leading to Discontinuation-DB3/DB4.....	53
Table 25.	Categorical Analysis of Nadir Serum Sodium Values - DB3/DB4.....	55
Table 26:	Subjects with Nadir Serum Sodium Value $\leq$ 125 mmol/L – .....	56
Table 27.	Subjects with Nadir Serum Sodium Value 126-129 mmol/L – .....	57

Table 28. Number and Percent of Subjects with Serum Sodium $\leq$ 125, 126 – 129, and 130 – 134 mmol/L at Each Study Visit – Extension Study A2 .....	59
Table 29. Common ( $\geq$ 2%) Adverse Events-DB3 and DB4 .....	60
Table 30. Incidence of the Most Common Adverse Events (Those Occurring in $\geq$ 2% of Subjects) – A2.....	63
Table 31. Electrocardiogram - Overall Evaluation - Safety Population A2 .....	67
Table 32 Categorical Analysis of Nadir Serum Sodium Value - DB3/DB4 – Age $<$ 65 and $\geq$ 65 years .....	70
Table 33: Categorical Analysis of Nadir Serum Sodium Value - DB3/DB4 – Male and Female	70

**Figures**

Figure 1. Screening, exit and change from screening to exit in nightly nocturia episode frequency, study (phase2a) .....	33
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 .....	40

# 1 Executive Summary

## 1.1. *Product Introduction*

SER120 (proposed trade name NOCTIVA) 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 higher dose nasal spray formulations of desmopressin are already approved by FDA for the treatment of central diabetes insipidus, primary nocturnal enuresis in children, and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgical procedures. None of the FDA-approved desmopressin products are indicated for the treatment of nocturia. The most significant risk of desmopressin is development of hyponatremia.

The Applicant developed SER120 with the goal of minimizing the incidence of hyponatremia. SER120 is a low-dose version of desmopressin that contains an excipient, cyclopentadecanolide (CPD). The Applicant asserts that CPD enhances the absorption of desmopressin across the nasal mucosa and allows for use of lower doses of desmopressin to achieve clinical effect. The 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. This proposed dose regimen was not studied in any of the SER120 clinical trials.

## 1.2 *Conclusion on the Substantial Evidence of Effectiveness*

From a clinical perspective, the review team believes that substantial evidence of effectiveness has been demonstrated for SER120 1.5 mcg qhs in the treatment of nocturia. 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, an exploratory analysis suggests the benefit of SER120 1.5 mcg is clinically meaningful to approximately 13% more patients than the benefit achieved with placebo. In addition, 18-19% more subjects receiving SER120 1.5 mcg experienced a minimum fifty percent reduction in nocturia episode frequency compared to placebo.

SER120 1.5 mcg also met all secondary efficacy endpoints. 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, however. 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.

The pre-specified efficacy criteria were not 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. 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.

In a retrospective sub-group analysis of patients who had nocturnal polyuria as defined by 24-hour urine volume criterion, results were essentially identical for the primary and key secondary efficacy endpoints compared to the overall population. These findings support the efficacy of SER120 in the treatment of patients with nocturia secondary to nocturnal polyuria.

### **1.3 Benefit-Risk Assessment**

We 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 too great in this setting. In addition, the phase 3 trials had numerous exclusion criteria so the clinical trial population does not support the broad indication of nocturia. The BRUDAC panelists expressed similar concerns.

Consistent with the recommendation from the BRUDAC, the clinical review team believes that SER120 1.5 mcg nightly has a favorable risk/benefit 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 awaken two or more times per night to void. We recommend approval of SER120 1.5 mcg nightly only if the Applicant agrees to modify 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 exclusively 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, we recommend initiating treatment with SER120 0.75 mcg. The dose may be escalated to 1.5 mcg if no response to the lower dose, provided their serum sodium has remained in the normal range on the lower dose.

Our 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 addition, approximately 7-8% more subjects had at least a 50% reduction in nocturia episode frequency compared to placebo. Although these differences did not meet statistical significance, they may be meaningful to some patients.

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.

- 2) There were no cases of severe hyponatremia observed in elderly subjects in the phase 3 trials (DB3 and DB4).
- 3) 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.
- 4) SER120 0.75 mcg is reasonably safe in the elderly, and may provide a clinically meaningful benefit to these patients who have no other treatment options.

Although the phase 3 trials did not enroll patients younger than 50 years of age (at the advice of FDA), we do not believe that the indicated population should be limited to patients >50 years.

(b) (4)



Our approval recommendation is contingent on the Applicant's agreement to modify the indication statement and to other labeling changes that reflect the population studied in the clinical trials (see Section 10 Labeling Recommendations).

## 2 Therapeutic Context

### 2.1. Analysis of Condition

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

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

- 1) *Polyuria* (increase in 24-hour urine volume): Causes include uncontrolled diabetes mellitus, diabetes insipidus, hypokalemia, medication side effects.
- 2) *Nocturnal polyuria* (increase in nighttime urine production with a corresponding decrease in daytime urine production, resulting in a normal 24-hour urine volume): Nocturnal polyuria is defined as a nocturnal urine volume that exceeds 20% of the total 24-hour volume in adults younger than 35 years and 33% of the total 24-hour volume in adults older than 65 years.<sup>2</sup> Causes include excessive evening fluid intake, medications, and edematous states, such as congestive heart failure.
- 3) *Bladder storage problems*: Decreases in bladder compliance or changes in neuronal input can reduce the threshold volume for voiding, for example, in patients with overactive bladder (OAB), benign prostatic hyperplasia (BPH), or hypotonic bladder.<sup>3</sup>

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

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

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

---

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

<sup>2</sup> Van Kerrebroeck P, et. al., op cit.

<sup>3</sup> Cornu JN, Abrams P, Chapple CR, Dmochowski RR, et. al. A Contemporary Assessment of Nocturia: Definition, Epidemiology, Pathophysiology, and Management – a Systematic Review and Meta-analysis. *European Urology* 62 (2012): 877-890.

<sup>4</sup> Bosch JL, Weiss JP. The prevalence and causes of nocturia. *J Urol*. 2013 Jan; 189 (1 Suppl): S86-92.

<sup>5</sup> Pesonen JS, Cartwright R, Mangera A, et. Al. Incidence and Remission of Nocturia: A systematic Review and Meta-analysis. *Eur Urol*. 2016 Aug; 70 (2): 372-81.

<sup>6</sup> Cornu, *op. cit.*

<sup>7</sup> Kari AO, Tikkinen TM, Johnson II, Tuevo L.J., et. al. Nocturia Frequency, Bother, and Quality of Life: How Often is Too Often? A population-based study in Finland. *European Urology*. 57 (3): March 2010, pp 488-498.

## **2.2. *Analysis of Current Treatment Options***

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

## **3 Regulatory Background**

### **3.1. *U.S. Regulatory Actions and Marketing History***

The sponsor's product is a novel formulation of desmopressin. As discussed section 1.1, other formulations of desmopressin are already approved for a variety of indications (see Table 1).

---

<sup>8</sup> Kurtzman JT, Bergman AM, et. al. Nocturia in women. [Curr Opin Urol.](#) 2016 Mar 10. Epub ahead of print.

**Table 1 New Drug Applications for Desmopressin Products in FDA**

Application No. (trade name)	Sponsor	Formulation, dose	Indication(s)	status
NDA 17922 (DDAVP®), NDA 21333 (Minirin)	Ferring	0.01% nasal solution; 0.1-0.4 mL qd	CDI, PNE*	Approved
NDA 18938 (DDAVP®)	Ferring	Injectable solution, 4 mcg/mL	For hemostasis in patients with hemophilia A and type I von Willebrand's disease; central diabetes insipidus (CDI)	Approved
NDA 19955 (DDAVP®), NDA 21795 (desmopressin acetate)	Ferring	0.1 mg and 0.2 mg Tablet, dose range 0.1mg -0.8 mg qd	CDI, PNE, renal concentrating capacity test	Approved
NDA 20355 (Stimate)	CSL Behring LLC	1.5 mg/mL nasal spray	hemophilia A and mild-moderate von Willebrand	Approved
NDA 022517 (Nocdurna)	Ferring	Orally disintegrating tablet	(b) (4)	
NDA 201656	Serenity	Nasal spray, 0.75 ug and 1.5 ug qhs	Nocturia in adults who awaken $\geq 2$ times each night to void	In review

\*In 2007, FDA withdrew the PNE indication due to post-marketing reports of severe hyponatremia in children

### **3.2. Summary of Pre-submission/Submission Regulatory Activity**

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

Initially, the Applicant conducted two identical phase 3 trials (DB1 and DB2). These were randomized, double-blind, placebo-controlled trials that investigated the safety and efficacy of a 0.5 mcg dose (which could be 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 for SPA. Protocol DB4 would test two doses of SER120 (0.75 mcg and 1.5 mcg) and include a novel PRO measure, the INTU questionnaire, to measure the clinical impact of nocturia. The co-primary efficacy endpoints were the same as those used in study DB3, and the INTU was a secondary endpoint.

In April 2014, the application was transferred back to DBRUP where it has remained since. Soon after, a Type C Guidance meeting between DBRUP and the Applicant on September 17, 2015, was held to discuss the efficacy of their product and the possibility of NDA submission.

The NDA for SER120 was opened in DBRUP on February 4, 2016. DBRUP presented efficacy and safety findings at a meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) on October 19, 2016. As discussed in Section 9 of this document, the BRUDAC recommended limiting the indication for SER120 to patients with nocturnal polyuria. In response to an October 28, 2016, request from DBRUP, on November 4, 2016, the Applicant submitted efficacy data focusing on the subgroup of patients in the clinical trials who had nocturnal polyuria at baseline. DBRUP considered the submission to be a major amendment to the application and extended the PDUFA goal date by three months to provide time for a full review.

### ***3.3. Foreign Regulatory Actions and Marketing History***

Outside of the United States, in over 80 countries around the world, oral and sublingual formulations of desmopressin (trade names of Minirin® and Minirin Melt®, respectively) are

approved for the symptomatic treatment of adults with nocturia associated specifically with nocturnal polyuria. The Minirin and Minirin Melt package inserts contain the following key information regarding use in patients with nocturia (location within the package insert depends on the country but the content is generally the same):

- A frequency/volume chart should be used to diagnose nocturnal polyuria for at least 2 days and nights before starting treatment. Nocturnal polyuria is diagnosed when night-time urine production exceeds the functional bladder capacity or exceeds one-third of the 24-hour urine production.
- Serum sodium must be measured before beginning treatment and 3 days after dose initiation or dose increase.
- Use in the elderly is not recommended (*specific age threshold not provided*)
- In patients with urgency or urge urinary incontinence, an underlying cause should be identified and treated.<sup>9,10</sup>

## **4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

### ***4.1. Office of Scientific Investigations (OSI)***

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).”

### ***4.2. Product Quality***

The product quality review is pending at the time of this writing.

### ***4.3. Clinical Microbiology***

The microbiology reviewer concluded that the microbiology control for the product is adequate according to current quality standards.

### ***4.4. Nonclinical Pharmacology/Toxicology***

The DBRUP non-clinical review team concluded that, from a non-clinical perspective, the application is considered reasonably safe for approval. The reviewer recommended close monitoring for hyponatremia based on lack of data regarding changes in Na electrolyte balances in the 28-day nonclinical bridging toxicology study in rats.

---

<sup>9</sup>Minirin prescribing information. (n.d.) Retrieved from <http://www.medsafe.govt.nz/profs/datasheet/m/Minirintab.pdf>

<sup>10</sup>Ibid.

#### **4.5. Clinical Pharmacology**

In a review dated January 18, 2017, the Clinical Pharmacology review team recommends “approval of this NDA from a clinical pharmacology perspective provided that the Applicant agrees to 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.” Specifically, the clinical pharmacology team recommends the following risk mitigation strategies:

Restriction of fluid intake before and after desmopressin administration

Monitor serum sodium within one week of dose initiation or dose increase.

Restrict use of product to adults older than 50 years of age.

#### **Reviewer’s comments:**

- **A recommendation to monitor sodium within 7 days after dose initiation or dose increase has been added to the label.**
- **We, the clinical reviewers, disagree with the other risk mitigation strategies proposed by the clinical pharmacology team. Fluid intake was not restricted in the pivotal phase 3 trials. As such, we have no basis to recommend fluid restriction, or to provide instruction on the quantity or duration of fluid restriction. We believe that the risk benefit profile of SER120 is favorable without fluid restriction.**
- **We also disagree with their recommendation to limit use of SER120 to adults older than 50 for reasons outlined in section 1.3. Of note, the BRUDAC expressed no concern with use of the product in patients under age 50 although trial enrollment was limited to adults >50 years of age (see Section 9).**

#### **4.6. Division of Medication Error Prevention and Analysis (DMEPA)**

DMEPA concluded that the proposed proprietary name, NOCTIVA, for desmopressin nasal spray is acceptable.

DMEPA evaluated the proposed container label, carton labeling, and prescribing information (PI) for NDA 201656 for areas that could lead to medication errors. The DMEPA consultant recommended several areas that needed improvement which are outlined in a memorandum of consultation dated November 16, 2016, and which were conveyed to the Applicant in an advice letter dated November 23, 2016.

In a memorandum of consultation dated November 22, 2016, DMEPA identified several areas of concern with the sponsor’s proposed human factors validation protocol and with the container labeling. Comments from DMEPA regarding these issues were forwarded to the sponsor in advice letters dated November 28, 2016. The Applicant submitted a revised human factors validation protocol on December 2, 2016 (sequence 0048). At the time of this writing, DMEPA’s final review of the human factors protocol is pending.

#### **4.7. Division of Pharmaceutical Analysis (DPA)**

In a memorandum of consultation dated August 18, 2016, the DPA found that the assay, desmopressin area percent, net content, identification and determination of spray actuation for desmopressin nasal spray are acceptable for quality control and regulatory purposes.

#### **4.8. *Clinical Outcomes Assessment (COA)***

In one of the phase 3 trials, the Applicant used the INTU questionnaire to assess the clinical impact of nocturia on daily living, including restfulness, concentration, and level of emotional concern about needing to get out of bed to urinate. DBRUP consulted COA to review the INTU and the evidentiary dossier in support of the questionnaire. The COA consultant concluded in a memorandum of consultation dated November 4, 2016, that the evidence submitted by the Applicant demonstrates that “the INTU instrument’s content validity, domain structure, and measurement properties and performance are acceptable.” The consultant also noted that “while the INTU instrument was deemed acceptable for inclusion as a pre-specified secondary endpoint in Trial DB4, the Agency cautions against its future use, without modification, in future drug development programs as it may have floor effects for some of the items, leading to its insensitivity in detecting treatment effects.”

#### **4.9. *Center for Devices and Radiologic Health (CDRH)***

Because desmopressin nasal spray is a combination (drug/device) product, DBRUP consulted CDRH to evaluate the applicant’s compliance with applicable Quality System Requirements. In a memorandum dated February 7, 2017, CDRH recommends approval of the application.

#### **4.10. *Division of Medical Policy and Prevention (DMPP), Office of Prescription Drug Promotion (OPDP)***

In a memorandum of consultation dated November 22, 2016, DMPP provide comments regarding the medication guide (MG) and the instructions for use to be forwarded to the Applicant, and concluded that the “MG and IFU are acceptable with our recommended changes.”

## **5 Sources of Clinical Data and Review Strategy**

### **5.1. *Table of Clinical Studies***

Clinical trials conducted in support of the marketing application are shown in Table 2.

**Table 2. Clinical Trials Conducted in support of NDA Marketing Application**

Trial ID	Design/duration/primary endpoint (s)	Total N	N receiving study medication					
			0.5 µg	0.75 µg	1.0 µg	1.5 µg	2.0 µg	pla
<b>Controlled efficacy/safety studies</b>								
DB1	P3, R, DB, PC, 50 days Randomized to placebo or SER120 50 mcg with up-titration to 75 mcg if nocturic episodes >1/night at day 8 or day 15.	301	148 <sup>[1]</sup>	98				153
DB2	Fluid restriction: nothing within hour of bedtime, then 8 oz during night Co-primary endpoints: Change from screening vs last week of treatment in <ul style="list-style-type: none"> <li>mean number of nocturic episodes per night</li> <li>Percentage of patients with a &gt;50% reduction in mean number of voids per night</li> </ul>	326	167 <sup>[2]</sup>	105				159
DB3	P2/3, R, DB, PC, parallel group, 99 days No fluid restriction Co-primary endpoints: change from screening vs. 12-week treatment period in: <ul style="list-style-type: none"> <li>mean number of nocturic episodes per night</li> <li>Percentage of patients with a &gt;50% reduction in mean number of voids per night</li> </ul>	745		186	183	179		186
DB4	Secondary endpoint (DB4 only): Change in INTU questionnaire score between screening and treatment period	782		262		260		260
<b>Studies to support safety</b>								
OL1-200903	P3, LT, OL safety extension study of DB1 and DB2, 43 weeks	376	162	214				
DB3-20110, A2	P3, LT, OL extension of study DB3, up to 126 weeks	395			38	355		
<b>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</b>								
DESMO-NS-200802	P2A, OL, dose-titration PK and PD study in nocturia patients. 12 days	43	32		11			
ELD-201001	P3, OL, safety and pk study in elderly patients with nocturia, 56 days	32	15	17				

[1] 140 patients started at the 0.5 ug dose. Fifty remained on 0.5 ug and 98 were up-titrated to 0.75 ug

[2] 167 patients started at the 0.5 ug dose. Sixty-two remained at the 0.5 ug dose and 105 patients were up-titrated to the 0.75 ug dose.

## **5.2. Review Strategy**

This application was reviewed jointly by Dr. Olivia Easley who was responsible for the efficacy portion and Dr. Martin Kaufman conducting the safety review.

The sponsor conducted a total of four phase 3 efficacy studies (see Table 2), but only the two most recent trials (studies DB3 and DB4) support efficacy for the current application. DB1 and DB2 which investigated lower doses of SER120 (0.50 mcg qhs with possible up-titration to maximum of 0.75 mcg qhs) failed to demonstrate statistical significance for both co-primary endpoints. Therefore the efficacy review will focus on results of studies DB3 and DB4, with data from DB1 and DB2 examined for issues related to dose selection.

## **6 Review of Relevant Individual Trials Used to Support Efficacy'**

### **6.1. 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 aged 50 years of age and older with nocturia. Protocol features that differ are addressed in the relevant sections below. The primary objectives of the trials were to evaluate the efficacy and safety of SER120 for the treatment of nocturia.

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

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

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

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

Following the two-week placebo lead-in period, all subjects (both placebo responders and non-responders) were then randomized (regardless of responder status) to placebo or to SER120.

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

In trial DB4, subjects also completed the INTU 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 Appendix I).

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

**Reviewer's comment: The psychometric evaluation of the INTU was reviewed by the Clinical Outcome Assessment (COA) team in a memorandum of consultation dated September 10, 2015. The COA consultant concluded that "the sponsor's qualitative work appears adequate to support the concepts and items included in the measure," and that the preliminary review of the psychometric evaluation study report appears to support the final version of the measure's three scores (two domain scores and one total score):**

- **Daytime Impact Score (average of items 1-4, 6, and 10)**
- **Nighttime Impact Score (average of items 5, 7-9)**
- **INTU Overall Impact Score (average of the Daytime and Nighttime Impact Scores)**

## **Key Entry Criteria for Both Trials**

### **Inclusion criteria**

1. Male or female subject  $\geq 50$  years of age.
2. Documented nocturia by history ( $\geq 2$  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  $\geq 2.16$  nocturic episodes/night or
  - b)  $\geq 13$  total nocturic episodes
4. 24-hour urine output  $\leq 57$  mL/kg or up to 4500 mL/24 hours.
5. Normal serum sodium concentration
6. Serum triglycerides  $< 400$  mg/dL

### **Reviewer's comments:**

- 1) **During the phase 3 protocol development phase, DMEP advised the Applicant to only enroll patients at least 50 years of age in order to better assess the risk of hyponatremia, which is greater in elderly patients.**
- 2) **The basis for the 24-hour urine output criteria are unclear and appear too liberal if the intent was to exclude polyuria.**

### **Exclusion criteria for Both Trials**

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

23. Alcohol or substance abuse within 12 months of enrollment

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

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

**Restricted medications** (allowed only if on a stable dose for at least 2 months prior):  $\alpha$ 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.

### **Efficacy Endpoints for Both Trials**

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

- the mean number of nocturic episodes per night, and
- the percentage of subjects with a  $\geq 50\%$  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 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  $\leq 1$  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.

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

In trial DB4, the first ranked secondary efficacy endpoint was the change between screening and treatment period in the INTU overall impact score. The change from baseline in the INTU score was calculated as the average of the INTU scores over six days during the treatment period (three

days during Week 8 and three days during Week 14) compared to the average of the scores over the six days during screening. The subsequent secondary endpoints were the same as those listed above for trial DB3.

### **Statistical Analysis Plan for Both Trials**

There were four analysis populations:

- ITT population -- all randomized subjects who had at least 3 days of post-randomization efficacy data recorded in their diaries and consisted of both placebo responders and placebo non-responders.
- 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.

**Reviewer’s comment: In an SPA no agreement letter regarding protocol DB3, DMEP stated that use of the mITT population for the analysis of the co-primary efficacy endpoints would not be suitable because, “exclusion of placebo responders is impractical in clinical practice.” However, during the protocol design phase for study DB4, DMEP recommended the mITT as primary because in study DB3 the treatment effect was greater for placebo non-responders compared to placebo responders (-0.5 and -0.3, respectively), suggesting that an enrichment strategy could be useful. Upon reconsideration, DBRUP views the ITT as more scientifically valid for the primary statistical population because it accounts for all subjects who were randomized and who had some post-randomization efficacy data, whereas the mITT is a subgroup analysis limited to placebo non-responders. The mITT and ITT results are similar, but for the reasons stated above, this review will focus on the ITT results.**

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

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

For the first co-primary efficacy endpoint the treatment groups were compared using an Analysis of Covariance (ANCOVA). The model included the treatment group, study center, the

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

## 6.2. Results of Studies DB3 and DB4

### Subject Disposition

In the two pivotal trials, a total of 3565 subjects were screened, with 1707 ultimately enrolled. As shown in [Table 3](#), the majority of subjects completed the trials although the completion rates were slightly lower in the SER120 groups. The primary reason for early discontinuation was the occurrence of an adverse event, the incidence of which was dose proportional.

**Table 3. Summary of Subject Disposition in Trials DB3 and DB4**

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

Source: DB3 study report, Table 2, p. 71.

\*mITT = randomized patients who were placebo non-responders

### Protocol Violations/Deviations

The majority of subjects in each treatment group experienced at least one protocol violation with rates similar across groups. The review team found there was no significant impact on efficacy findings when subjects with major protocol violations (i.e. inclusion criteria violations, subjects who received wrong treatment or incorrect dose) were excluded from the analyses.

Medication compliance was assessed by measuring bottle weight at each follow-up visit. Although non-compliance at any individual visit was more common in placebo and in the SER120 7.5 mcg group, medication compliance throughout the study was the same across groups in the ITT population.

## Demographic Characteristics

The majority of subjects in the ITT population were overweight white males older than 65 years of age (see [Table 4](#)).

**Table 4. Summary of Demographic Characteristics for the ITT Population, Studies DB4 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 <sup>2</sup> ) (min, max)	28 (19, 48)	28 (18, 57)	28 (17, 47)	28 (18, 56)	30 (17, 63)	29 (18, 49)	29 (17, 52)
<b>Gender [N (%)]</b>							
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)
<b>Race [N (%)]</b>							
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: DB3 Clinical Study Report, Table 5, p. 77.

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

At screening, the investigator provided or confirmed the probable etiology of nocturia based on patient interview and review of each subject's medical records. As shown in [Table 5](#), in the majority of subjects, more than one etiology of nocturia was cited – e.g., BPH and nocturnal polyuria. In those in whom a single etiology was considered likely, nocturnal polyuria was most common. 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 (see [Table 5](#)).

**Table 5. Nocturia Etiology, Trials DB3 and DB4, Intent-to-Treat 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:

Efficacy findings from trials DB3 and DB4 are discussed in section 7.

## 7 Integrated Review of Effectiveness

### 7.1 *Assessment of Efficacy Across Trials*

#### 7.1.1. Analysis of Co-Primary Endpoints

##### First Co-Primary Efficacy Endpoint

SER120 1.5 mcg in study DB3 and DB4, 1.0 mcg in study DB3, and 0.75 mcg in study DB4 resulted in a statistically significantly greater reduction in mean nightly number of nocturia episodes compared to placebo; however, these mean changes were numerically small. For example, from a baseline of about 3 nightly nocturia episodes on average, there was a mean reduction of 0.3-0.4 episodes per night with the 1.5 mcg dose compared to placebo (see [Table 6](#)). The clinical significance of these findings is unclear. The FDA's analysis which is shown in [Table 5](#) is consistent with analyses performed by the Applicant.

##### Second Co-Primary Efficacy Endpoint

About one-third of subjects in the placebo arms in DB3 and DB4 had  $\geq 50\%$  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 co-primary endpoint (see [Table 6](#)). Statistical testing of the 0.75 mcg dose is not reported in DB3 in accordance with the pre-specified, hierarchical testing procedure.

**Table 6 Summary of Co-primary Efficacy Endpoints for Trials DB3 and DB4 (Intent-to-Treat Population)**

	DB3				DB4		
	SER 120 1.5 mcg (N=179)	SER120 1.0 mcg (N=183)	SER120 0.75 mcg (N=186)	Placebo (N=186)	SER120 1.5 mcg (N=260)	SER120 0.75 mcg (N=262)	Placebo (N=260)
<b>First Co-Primary Endpoint: Mean Nocturic Episodes Per Night</b>							
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 <sup>1</sup> (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	
<b>Second Co-Primary Endpoint: ≥50% Reduction in Nocturic Voids</b>							
n/N (%)	93/179 (52%)	73/183 (40%)	77/186 (41%)	61/186 (33%)	120/260 (46%)	92/262 (35%)	74/260 (29%)
Absolute difference vs. placebo	19%	7%	8%		17%	6%	
P-value (vs. placebo)†	<0.001	0.16	N/A**		<0.0001	0.12	

Source: FDA Office of Biostatistics (OB), Division of Biometrics III (DBIII) statistical reviewer analysis  
SD = standard deviation; SE = standard error; CI = confidence interval

1-- average of recorded diaries during the treatment period

\* Change from baseline was calculated using an ANCOVA model.

† P-values from pair-wise comparisons vs. placebo using the Cochran-Mantel-Haenszel test.

\*\*In keeping with the pre-specified statistical analysis plan hierarchical testing procedure, p-values are not reported for SER120 0.75 mcg in Study DB3 because the 1.0 mcg dose did not demonstrate statistical significance on both co-primary efficacy endpoints.

## 7.1.2 Secondary Endpoints

Secondary endpoints for the 1.5 mcg dose are presented in order of rank according to the statistical analysis plans for protocols DB3 and DB4. Secondary efficacy analyses are not presented for the 1.0 or 0.75 mcg doses. The 1.0 mcg dose did not meet both of its co-primary efficacy endpoints in DB3. The 0.75 mcg dose was not tested statistically in DB3 because of the failed 1.0 mcg dose, and did not meet both co-primary efficacy endpoints in DB4.

### INTU

The aim of the INTU instrument was to assess the impact of nocturia on daily living, including restfulness, concentration, and level of emotional concern about needing to get out of bed to urinate. The contents, methodology, strengths and limitations of the INTU instrument are described in detail in the 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.

The INTU’s Overall Impact score ranges on a scale from 0 to 100. At baseline, the mean Overall Impact score was about 30. There was an observed 14-point improvement in the INTU Overall Impact score for the 1.5 mcg group versus a 12-point improvement with placebo. SER120 1.5 mcg decreased the INTU Overall Impact score by 2.6 points more than placebo (see [Table 7](#)).

**Table 7. Secondary Efficacy Variable – Change from Screening to Treatment Period in the INTU Overall Impact Score in Trial DB4 (Intent-to-Treat Population)**

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

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

\* Change from baseline was calculated using an ANCOVA model.

**Reviewer’s comment: Although the difference in the change from baseline in the INTU Overall Impact Score was greater for SER120 1.5 mcg than for placebo, the clinical importance of a 2.6-point difference to patients is unclear. The COA team was consulted to assist in interpreting this difference. In a memorandum of consultation dated November 4, 2016, the COA consultant wrote,**

*“Interpreting the efficacy findings from the Trial DB4 is challenging because there was no a priori specified threshold for a meaningful change in INTU Overall Impact scores for use with the phase 3 data. .. the Agency reviewed exploratory post-hoc analysis of the INTU data from the DB4 clinical trial and concludes that the INTU can reasonably detect changes in nocturia impacts over time. In addition, the Agency concludes 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 adequate and meaningful.”*

## 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 (see [Table 8](#)). 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 8. Summary of Secondary Efficacy Endpoints in Trials DB3 and DB4, Intent-to-Treat population**

	DB3		DB4	
	SER120 1.5 mcg (N=179)	Placebo (N=186)	SER120 1.5 mcg (N=260)	Placebo (N=260)
<b>Time from bedtime to first nocturic void (hours)</b>				
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	
<b>Percent of nights with no nocturic episodes†</b>				
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	
<b>Percent of nights with ≤1 nocturic episodes‡</b>				
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	
<b>Nocturnal urine volume (mL/night)</b>				
N	156	173		
Baseline Mean (SD)	724 (319)	699 (297)	732 (384)	772 (370)
Mean Week 14 (SD)	500 (300)	608 (324)	466 (270)	597 (317)
Change from baseline*	-221	-114	-282	-148
Difference vs. placebo	-108		-134	
95% CI	-179, -40		-187, -81	
p-value (vs. placebo)	<0.01		<0.0001	

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

\*Change from baseline was obtained using an ANCOVA model

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

## 7.1.3 Subpopulations

### 7.1.3.1 Nocturnal Polyuria Sub-population

Desmopressin is approved outside the United States for the treatment of nocturnal polyuria. Based on desmopressin's mechanism of action, the product may be more effective in treating nocturia due to nocturnal polyuria than due to other etiologies (particularly mechanical causes like OAB or BPH). Consistent with advice from the BRUDAC that the product should be indicated in patients with nocturia secondary to nocturnal polyuria only, DBRUP requested that the sponsor submit efficacy analyses on the nocturnal polyuria sub-population (defined using the 24-hour urine screening criteria). The submission of these data on November 3, 2016, constituted a major amendment, and resulted in a 3-month review clock extension.

The Office of Biostatistics (OB) statistical reviewer conducted the same efficacy analysis in the nocturnal polyuria sub-population to confirm the Applicant's findings. In patients with nocturnal polyuria in both studies DB3 and DB4, SER120 1.5 mcg produced on average 0.4 fewer nocturia episodes per night compared to placebo. In addition, the placebo-corrected percentage of patients experiencing at least a 50% reduction in nocturia episode frequency increased by 20% over placebo. The effect was consistent with that observed in the overall nocturia population. The effect of the lower SER120 doses on nocturia episode frequency and responder rate was similar in the nocturnal polyuria population as in the overall population (see [Table 9](#)).

**Table 9. 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)
<b>Mean Nocturic Episodes</b>							
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) <sup>†</sup>		0.0049	0.0207	<0.0001		0.0049	<0.0001
<b>≥50% Reduction in Nocturic Voids</b>							
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) <sup>†</sup>		N/A	0.1387	0.0291		0.0754	<0.0001

Source: 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.

1 –nominal p-values (not controlled for type 1 error) because the nocturnal polyuria subgroup analysis was post-hoc

In the population without nocturnal polyuria, no dose of SER120 was successful with respect to either co-primary efficacy endpoint (see [Table 10](#)). However, the sample size was small.

**Table 10. Summary of Co primary Efficacy endpoints – Study DB3 and DB4 (ITT Non- nocturnal polyuria)**

	Study DB3				Study DB4		
	Placebo (N=41)	SER120 0.75 mcg (N=41)	SER120 1.0 mcg (N=37)	SER120 1.5 mcg (N=37)	Placebo (N=35)	SER120 0.75 mcg (N=209)	SER120 1.5 mcg (N=199)
<b>Mean Nocturic Episodes</b>							
Baseline (SD)	3.3 (0.9)	3.3 (0.8)	3.1 (0.8)	3.0 (0.7)	3.1 (0.7)	2.9 (0.7)	3.0 (0.7)
Treatment Period (SD)	1.8 (0.9)	1.8 (1.0)	1.8 (1.1)	1.3 (0.9)	1.9 (1.1)	1.7 (0.9)	1.6 (0.9)
Change from baseline* (SE)	-1.5 (0.2)	-1.5 (0.2)	-1.5 (0.1)	-1.8 (0.2)	-1.3 (0.1)	-1.2 (0.1)	-1.3 (0.1)
Difference vs. placebo (SE)		0.02 (0.2)	0.09 (0.2)	-0.30 (0.2)		0.02 (0.2)	0 (0.2)
95% CI		-0.7, 0.2	-0.4, 0.5	-0.8, 0.2		-0.4, 0.4	-0.4, 0.3
P-value (vs. placebo)		0.9127	0.6833	0.2160		0.8993	0.8227
<b>≥50% Reduction in Nocturic Voids</b>							
n/N (%)	19/41 (46%)	18/41 (44%)	19/37 (51%)	23/35 (66%)		20/53 (38%)	27/61 (44%)
P-value (vs. placebo) †		0.4707	0.9332	0.1392		0.7530	0.3118

Source: 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.

### 7.1.3.2 Gender

A retrospective 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 11](#)).

**Table 11. 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
<b>Nightly Nocturic Episode Frequency</b>						
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	
<b>&gt;50% reduction in nocturic episodes (treatment vs screening)</b>						
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

### 7.1.3.3 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 ([Table 12](#)) according to a post-hoc analysis of efficacy data. The percentage of men experiencing a  $\geq 50\%$  reduction in nocturia episode frequency was slightly greater than the percentage of women.

**Table 12. 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
<b>Nightly Nocturic Episode Frequency</b>						
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	
<b>≥50% reduction in nocturic episodes (treatment vs screening)</b>						
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: DBRUP clinical reviewer's analysis

#### 7.1.3.4 Baseline Nocturia Episode Frequency

No consistent trend was noted when efficacy data were analyzed according to baseline nocturia episode frequency. Absolute placebo-corrected reduction in nocturia episode frequency was slightly greater in subjects with more severe nocturia at baseline. However, the opposite finding was noted when examining the percentage of subjects achieving ≥50% reduction in nocturia episode frequency (see [Table 13](#)).

**Table 13. Primary Efficacy Endpoints According to Baseline Nocturia Episode Frequency Category (> or <3 episodes per night), ITT Population**

>3 voids per night			
	SER120 15 mcg/mL	SER120 7.5 mcg/mL	placebo
N	219	230	213
Mean (SD) change from baseline in nocturia episode frequency	-1.7 (1.0)	-1.6 (1.0)	-1.3 (1.0)
Placebo-corrected change in nocturia episode frequency	-0.4	-0.3	
N (%) with $\geq 50\%$ reduction	99 (45.2)	73 (31.7)	62 (29.1)
Placebo-corrected % with $\geq 50\%$ reduction	16.1	2.6	
$\leq 3$ voids per night			
N	220	218	233
Mean (SD) Change from baseline in nocturia episode frequency	-1.2 (0.7)	-1.2 (0.7)	-1.0 (0.7)
Placebo-corrected change in nocturia episode frequency	-0.2	-0.2	
N (%) with $\geq 50\%$ reduction	115 (52.2)	97 (44.5)	73 (31.3)
Placebo-corrected % with $\geq 50\%$ reduction	20.9	13.2	

#### 7.1.4 Dose and Dose-Response

The proposed therapeutic dose is 0.75 mcg nightly which may be increased to 1.5 mcg nightly if clinically indicated. Dose selection was based on data obtained from phase 1, 2 and 3 trials which are summarized below.

The Applicant conducted two proof of concept studies in which standard marketed formulations of desmopressin were administered intravenously and subcutaneously. In one study, an intravenous dose of 30-40 ng desmopressin achieved anti-diuretic effects in water-loaded subjects. In the second study, a subcutaneous dose of 64 ng desmopressin was effective. The Applicant concluded that the target systemic desmopressin dose should be between the range of (b) (4).

Assuming a 10% bioavailability of the Applicant's desmopressin nasal spray formulation, one spray (containing (b) (4) ng) would produce a systemic dose of (b) (4) ng. For their initial Phase I trial, the Applicant investigated SER120 doses between (b) (4) ng, which would capture the therapeutic dose for anti-diuresis.

In the opening phase I study (Study 200801) 12 water loaded healthy male and female subjects, received a total of four doses of SER120 0.5 mcg, 1.0 mcg, or 2.0 mcg. Urine osmolality increased in a manner proportion to SER120 dose with peak effect observed between 60 and 80 minutes post dose. Urine output also decreased starting at approximately 20 minutes post-dose with the greatest decrease observed with the 2.0 mcg dose group.

In a follow-up phase 2a multi-center dose titration study, the Applicant investigated the anti-diuretic effects of SER120 0.5 mcg to 2.0 mcg in adult male and female patients with nocturia. Patients were required to have 10 or more nocturic episodes per week for at least 6 months prior

to enrollment by medical history. In addition, patients must have had 2 or more nocturic episodes per night, 5 or more days per week for at least 2 weeks prior to treatment to objectively document the nocturia diagnosis.

All eligible patients initially received 1 spray (0.5 µg) of SER120. Response to therapy in terms of nocturic episodes per night was assessed every 2-3 days over the course of the 14 day treatment period. Non-responders i.e. ≤ 1 nocturic voids per night were eligible to increase the dose of SER120 by 0.5 mcg up to a maximum of 2.0 mcg/night.

Forty-three patients were enrolled in the study. Thirty-two patients (Group 1) responded to a single spray (0.5 µg) of SER120 and were maintained at that dose for the duration of the trial. Eleven patients (Group 2) required up-titration to 2 sprays (1.0 µg) and were maintained at that dose.

Both dose groups showed statistically significant reductions in nocturic episode frequency from baseline to endpoint (see [Figure 1](#)). Both doses were well tolerated with no events of hyponatremia. The results of this study suggested that SER120 doses in the range of 0.5 to 1.0 µg would be appropriate to evaluate further for the treatment of nocturia.

**Figure 1. Screening, exit and change from screening to exit in nightly nocturia episode frequency, study (phase2a)**

		Observed			Change From Baseline		
		Group 1 1 Spray (0.5 µg) (N = 32)	Group 2 2 Sprays (1.0 µg) (N = 11)	Overall (N = 43)	Group 1 1 Spray (0.5 µg) (N = 32)	Group 2 2 Sprays (1.0 µg) (N = 11)	Overall (N = 43)
Screening (episodes/ night)	Mean	2.3	3.3	2.6			
	Std. Dev.	0.5	1.0	0.7			
Exit (episodes/ night)	Mean	0.4	0.7	0.5	-1.9	-2.6	-2.1
	Std. Dev.	0.4	0.9	0.6	0.5	1.4	0.8
P-Value					<0.0001	0.0001	<0.0001

Source: NDA 201656 seq 000 submitted Feb 4, 2016, module 5.3.4.2, 200802 clinical study report, Table 7, p. 58.

In the first two phase 3 trials (DB1 and DB2) for the adult nocturia indication, male and female patients >50 years of age with documented nocturia (>2 nocturic episodes per night, with >14 episodes per week for at least 6 months by history) were randomized in a 1:1 ratio to placebo or SER120 0.5 mcg qhs and entered a 3-week dose titration phase for dose optimization. At days 8 or 15 of treatment, patients whose nocturic episode frequency had not decreased to <1 episode per night during the previous week were dose-escalated to 0.75 mcg qhs. On treatment day 22, subjects started the 4-week maintenance phase during which they remained on the final titrated dose (i.e. SER120 0.5 or 7.5 mcg qhs or placebo).

Study drug was administered in the evening ½ hour prior to bedtime. Patients were not to ingest fluid for 1 hour prior to bedtime but were allowed to consume one glass (approximately 8 oz) of

fluid after falling asleep and before their usual wake-up time. Patients were also instructed to avoid caffeine and alcohol after the evening meal.

In neither study DB1 nor DB2 did SER120 demonstrate statistically significant efficacy compared to placebo for either primary efficacy endpoint (see [Table 14](#)). Therefore, in the subsequent Phase 3 studies DB3 and DB4, the Applicant studied a higher range of doses – 0.75 mcg – 1.5 mcg.

**Table 14. Primary efficacy variables, ITT population, Phase 3 trials DB1 and DB2**

		DB1		DB2	
		SER120 (0.5 mcg and 0.75 mcg doses pooled)	Placebo	SER120 (0.5 mcg and 0.75 mcg doses pooled)	Placebo
Primary Efficacy Variable #1: Nightly Nocturia Episode Frequency					
screening	N	145	149	162	156
	Least squares mean (LSM)	3.0	3.0	2.9	2.8
Day 50 (exit)	LSM	1.7	1.8	1.6	1.7
	Change from screening (LSM)	-1.3	-1.2	-1.3	-1.2
	p-value	0.59		0.15	
Primary Efficacy Variable #2: N (%) of subjects experiencing a $\geq$ 50% reduction in NEF from screening to exit					
Day 50 (exit)	Yes N (%)	58 (40.0)	58 (38.9)	83 (51.2%)	64 (41.0%)
	p-value	0.83		0.06	

Source: NDA 201656 seq 000 submitted Feb 4, 2016, module5.3.5.1.200901 clinical study report, Table 6 and module 5.3.5.1.200902, Table 6.

**Reviewer’s comment: The selection of the 0.75 mcg and 1.5 mcg doses for further study in phase 3 was reasonable based on earlier trial results.**

## 7.1.5 Onset, Duration and Durability of Efficacy

### 7.1.5.1 Onset

Following nasal spray administration, time to maximum serum concentration (t<sub>max</sub>) of SER120 is achieved between 0.25 and 0.75 hours for the 0.75 mcg and 1.5 mcg doses, respectively. The Applicant assessed efficacy at each follow-up visit during the double-blind, placebo-controlled phase 3 trials. Nocturia episode frequency decreased compared to baseline for all dose groups at the first assessment at week 3. The greatest decrease in nocturia episode frequency was observed for all dose groups at the week 14 visit (see [Table 15](#)).

**Table 15. Nocturia Episode Frequency at screening and at each follow-up visit during Trials DB3 and DB4, ITT population**

Time point	Statistic	SER120		Placebo
		15 mcg/mL	7.5 mcg/mL	
screening	N	439	448	446
	LS mean	3.3	3.3	3.3
Weeks 3 &4	N	439	447	445
	LS mean	1.9	2.0	2.4
	LS mean change	-1.4	-1.3	-1.1
	N (%) with 50% reduction	189 (43.2)	154 (34.5)	126 (28.3)
Week 6	N	419	428	435
	LS mean	1.7	1.9	2.1
	LS mean change	-1.6	-1.4	-1.2
	N (%) with 50% reduction	217 (51.8)	191 (44.6)	138 (31.7)
Week 8	N	410	417	427
	LS mean	1.7	1.8	2.0
	LS mean change	-1.6	-1.5	-1.2
	N (%) with 50% reduction	218 (53.2)	182 (43.6)	159 (37.2)
Week 14	N	384	403	409
	LS mean	1.6	1.8	2.0
	LS mean change	-1.7	-1.5	-1.3
	N (%) with 50% reduction	221 (57.6)	198 (49.1)	164 (40.1)

Source: NDA 201656 seq 0016 submitted June 28, 2016, module 1.11.3, Tables 3 and 4.

**Reviewer’s comment: Based on the drug’s pharmacokinetics, efficacy should be immediate (i.e. after the first dose). At the first follow-up visit at which nocturia frequency was assessed, a greater reduction in nocturia episodes was observed for both SER120 dose groups than for placebo. Maximum efficacy was observed after 12 weeks of treatment. However, this finding likely reflects selection bias in that subjects who did not respond to medication may have prematurely discontinued from the trials.**

### 7.1.5.2 Duration and Durability of Efficacy

The applicant assessed durability of response to SER120 in study DB3 A2 which was an open-label, long-term safety extension of study DB3. Subjects who successfully completed the double-blind portion of study DB3 as well as patients who had not participated in the double-blind study were eligible to enroll.

Patients were categorized into 3 groups:

- **Group 1 patients** were limited to those who had completed the DB3 double-blind study within 3 weeks of enrollment in the open-label extension study. These patients were allowed to roll over on the same day they completed the Day 99 (final) visit of the DB3 double-blind study.
- **Group 2 patients** were those who had completed the DB3 double-blind study more than 3 weeks before enrolling in the open-label trial. Group 2 patients were required to undergo re-screening to determine eligibility prior to entry in the open-label study. The re-screening process was identical to the screening process in the double-blind study except that the 24 hour fractionated urine collection was not required.
- **Group 3 patients** were new patients who had not participated in the DB3 study and required full screening to determine eligibility prior to enrollment. Inclusion criteria were identical to those used in double-blind study DB3.

Eligible patients were enrolled and initiated treatment with SER120 nasal spray 1.0 mcg qhs. The initial study design called for 30 weeks of open-label treatment. Following regulatory input, the Applicant extended the trial duration first to 78 weeks and then further to 126 weeks, or up to study closure on December 1, 2014.

Patients followed up at the study clinic on Days 10, 15, 23, 29, Weeks 8, 14, 22, and 30, and every 8 weeks thereafter until study conclusion. Between visits subjects recorded the following information in a 3-day voiding diary (the same used in the double-blind study):

- Date patient went to sleep.
- Time patient went to sleep.
- Time of patient's first nocturic void.
- Time patient woke-up to start the day.
- Time of patient's first void after waking up to start the day.
- Number of nocturic voids

Consistent with the double-blind studies, a nocturic void was defined as a non-incontinent urinary void of any volume 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.

A total of 393 patients were enrolled and comprised the ITT population. All subjects initiated treatment with the 1.0 mcg dose regardless of the dose received in the double-blind study (if applicable) except for one subject who began at 1.5 mcg. Duration of exposure according to dose is shown in [Table 16](#). The majority of subjects escalated to the 1.5 mcg dose by the end of treatment month 1.

**Table 16. Number of Patients with Exposure to SER120 by dose category, study DB3 A2**

Exposure duration	SER120	
	1.0 mcg/day	1.5 mcg/day
At least one dose	N=391	N=358
>1 month	47	343
>3 months	25	319
>6 months	19	302
>12 months	5	217
>18 months	0	129
>24 months	0	42

Source: Adapted from NDA 201656 seq 000, module 5.3.5.4.200301, Table 5, page 70.

The mean number of nocturic episodes per night at each regularly scheduled study visit for the ITT population for Group 1 and Groups 2/3 is shown in [Table 17](#). The baseline value is the original double-blind DB3 study baseline for Group 1 patients and the re-screening or new screening value for Groups 2 and 3.

**Table 17. Number of Nocturic Episodes per Night at each time point, ITT population study DB3-A2.**

Time point	Statistic	Group 1	Group 2/3
Baseline	N	212	180
	Mean (SD)	3.3 (0.8)	3.3 (0.8)
Day 15	N	211	177
	Mean (SD)	1.7 (1.1)	2.2 (1.0)
	Mean (SD) change from baseline	-1.5 (0.9)	-1.1 (0.9)
Week 8	N	193	165
	Mean (SD)	1.6 (1.0)	1.6 (1.0)
	Mean (SD) change from baseline	-1.7 (1.0)	-1.7 (0.9)
Week 22	N	178	152
	Mean (SD)	1.5 (1.0)	1.4 (0.9)
	Mean (SD) change from baseline	-1.8 (1.1)	-1.9 (1.0)
Week 38	N	131	184
	Mean (SD)	1.4 (0.9)	1.4 (1.0)
	Mean (SD) change from baseline	-1.9 (0.9)	-1.8 (1.1)
Week 54	N	99	124
	Mean (SD)	1.3 (0.9)	1.4 (1.0)
	Mean (SD) change from baseline	-1.9 (1.0)	-1.9 (1.1)
Week 102	N	42	6
	Mean (SD)	1.1 (0.7)	1.8 (1.2)
	Mean (SD) change from baseline	-2.1 (0.7)	-1.1 (1.5)

Source: NDA 201656 seq 000, module 5.3.5.4.200301, Table 5, page 118.

Results show that efficacy is maintained up to week 102. Efficacy is similar in Group 1 as in Group 2/3.

**Reviewer's comment: Among patients who respond to SER120 and remain on treatment, efficacy is maintained with chronic use up to 102 weeks.**

### 7.1.6 Exploratory responder analysis

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

The TBS questionnaire was administered only in study DB4. [Table 18](#) 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 18: Summary of Treatment Benefit Scale Used in Trial DB4 (Intent-to-Treat population)**

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

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

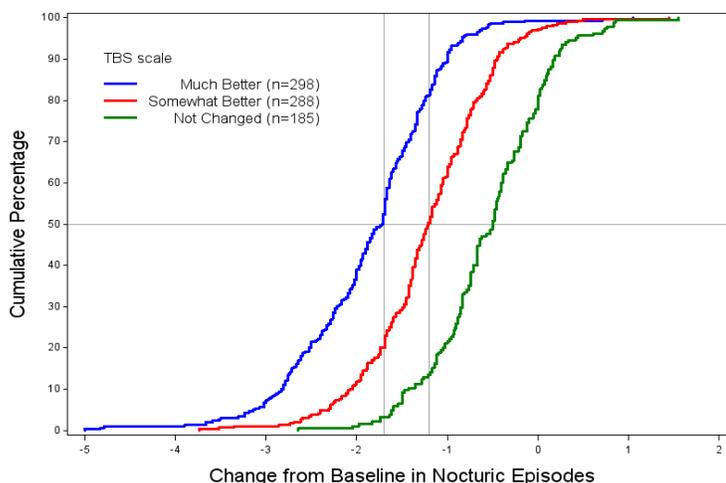
Data from all subjects in the ITT population in DB4 irrespective of treatment assignment were used to calculate cumulative distribution function (CDF) curves (see Figure 1). This plot has the change from baseline in nocturic episodes on the x-axis and cumulative percentage of patients on the y-axis.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

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

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

reduction in nocturnal episodes per night was at least 1.7) or non-responder (if the mean reduction in nocturnal episodes per night was less than 1.7 or if there was no change or a mean increase in nocturnal 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 2](#)).

**Figure 2 CDF plot of change from baseline in nocturnal episodes by TBS scale in Trial DB4 – all patients in the Intent-to-Treat population irrespective of treatment assignment**



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

We next calculated the percentage of responders in DB4 separately for the SER120 1.5 mg group and placebo group. Specifically, we calculated the percentage of subjects in the SER120 group who had a mean reduction in nocturnal 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 nocturnal episodes compared to placebo. These exploratory analyses are shown only for DB4 because the TBS questionnaire was not administered in DB3 (see Table 19).

**Table 19. Summary of Responder Rates (defined based on TBS) –Trial DB4, Intent-to-Treat population**

Change in Nocturnal 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

## 7.2 *Efficacy Summary*

- The proposed starting dose is 0.75 mcg per night which may be increased to 1.5 mcg per night based on individual patient efficacy and tolerability. This proposed dosing regimen was not studied in any of the SER120 clinical trials. In addition, the SER120 0.75 mcg dose did not meet the pre-specified statistical criteria for efficacy. SER 0.75 mcg should not be tested statistically in Study DB3 because the pre-specified hierarchical testing stopped after the 1.0 mcg dose failed on one of its co-primary efficacy endpoints. In Study DB4, the 0.75 mcg dose was not statistically superior to placebo for one of its co-primary efficacy endpoints.
- On the advice of the FDA, the clinical trial population consisted of adults  $\geq 50$  years of age.
- In pivotal trials DB3 and DB4, SER120 1.5 mcg resulted in statistically significant improvements in both co-primary efficacy endpoints (change in nocturia episode frequency and percentage of patients with a  $>50\%$  reduction in nocturia episode frequency) compared to placebo. Compared to placebo, SER120 1.5 mcg resulted in a mean reduction of 0.3-0.4 nocturic episodes per night over the 12 week treatment period, and approximately 19% more subjects experiencing a  $\geq 50\%$  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  $\leq 1$  nocturic episode was 46%-50%, on average, in the SER120 1.5 mcg dose group versus 34-35%, on average, with placebo.
- Based on post hoc analyses, SER120 appears to have a slightly greater treatment effect on the INTU night time domain than on the daytime domain. The daytime domain assesses daytime symptoms that could be related to nocturia, but which could also be related to other comorbidities or psychosocial stressors.
- Post hoc analyses that explore the clinical meaningfulness of the treatment effect in trial DB4 suggest that SER 120 1.5 mcg may benefit 13% more subjects than placebo in reducing nocturic episode frequency.
- In a post-hoc analysis, SER120 1.5 mcg met both primary efficacy endpoints in patients with nocturnal polyuria (defined by 24-hour urine volume criteria) in the two phase 3 trials, but not in patients without nocturnal polyuria. SER0.75 mcg did not meet both primary endpoints in either population.

## 7.3 *Integrated Assessment of Effectiveness*

- SER120 is proposed as a treatment for nocturia in adults who awaken 2 or more times per night to void without respect to nocturia etiology. The appropriateness

of studying a treatment for nocturia (which is a symptom, not a disease) without regard to underlying etiology is unclear. Although subjects with medical conditions associated with significant fluid overload, diuresis, or overt bladder dysfunction were excluded, subjects with other intrinsic factors that can contribute to nocturia (e.g., BPH or OAB) were allowed. Also, it is not clear how the cause(s) of nocturia were accurately determined in the enrolled patients. Enrollment of a heterogeneous population that is not well-defined may lead to the inclusion of conditions that may not respond to desmopressin, which may have diluted the overall treatment effect.

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

## 8 Review of Safety

### Safety Summary

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 is primarily based on the pooled DB3/DB4 data and the long-term safety data from A2. Data from studies of lower doses of SER120 are used to assess the dose relationship of serious adverse events and to evaluate potential safety signals.

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 placebo 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.

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  $\leq 125$  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  $\leq 125$

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 will be incorporated into labeling.

With the exception of decreases in serum sodium, 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.

## **8.1 Methods**

### **8.1.2 Studies/Clinical Trials Used to Evaluate Safety**

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. The earlier studies of the drug, DB1, DB2, and OL1, which evaluated only the 0.5 and 0.75 doses of the drug, were used to assess the dose relationship of serious adverse events and to evaluate potential safety signals.

### **8.1.3 Categorization of Adverse Events**

Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term.

### **8.1.4 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

Data from pivotal trials DB3 and DB4 were pooled to evaluate safety. In addition, data from all of the placebo controlled trials (DB1, DB2, DB3, and DB4) were pooled for the analysis of serious adverse events.

## **8.2 Adequacy of Safety Assessments**

### **8.2.2 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

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. Exposure duration to SER120 by dose is summarized in [Table 20](#).

**Table 20 Number of Subjects with Exposure of SER120 by Dose Category**

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

Source: NDA 201656 (SDN 001), Module 5.3.5.3, Table 1 p. 557.

**Reviewer comment: The duration and extent of exposure to SER120 in nocturia patients was adequate.**

Table 21 summarizes the baseline demographic variables for the placebo controlled trials (DB1, DB2, DB3, and DB4).

**Table 21. Summary of Demographic Variables (DB1/DB2/DB3/DB4)**

<b>Demographic Characteristic</b>	<b>Statistic</b>	<b>1.5 µg (N=448)</b>	<b>1.0 µg (N=186)</b>	<b>0.75 µg (N=657)</b>	<b>0.5 µg (N=112)</b>	<b>Placebo (N=766)</b>
<b>Age (yrs)</b>	N	448	186	657	112	766
	Mean	66.2	66.2	65.9	62.8	65.2
	Median	66.0	65.0	65.0	62.0	65.0
	Minimum	50	50	50	50	49
	Maximum	89	89	89	87	90
<b>Age Group</b>	N	448	186	657	112	766
	< 65	202 (45.1%)	85 (45.7%)	308 (46.9%)	67 (59.8%)	377 (49.2%)
	≥ 65	246 (54.9%)	101 (54.3%)	349 (53.1%)	45 (40.2%)	389 (50.8%)
<b>Gender</b>	N	448	186	657	112	766
	Male	256 (57.1%)	111 (59.7%)	390 (59.4%)	55 (49.1%)	450 (58.7%)
	Female-Postmenopausal	185 (41.3%)	74 (39.8%)	253 (38.5%)	52 (46.4%)	298 (38.9%)
	Female-Child Bearing Potential	7 (1.6%)	1 (0.5%)	14 (2.1%)	5 (4.5%)	18 (2.3%)
<b>Race</b>	N	448	186	657	112	766
	Caucasian	338 (75.4%)	162 (87.1%)	524 (79.8%)	88 (78.6%)	593 (77.4%)
	African American	62 (13.8%)	18 (9.7%)	55 (8.4%)	13 (11.6%)	93 (12.1%)
	Asian	11 (2.5%)	2 (1.1%)	11 (1.7%)	1 (0.9%)	15 (2.0%)
	Hispanic	33 (7.4%)	4 (2.2%)	60 (9.1%)	8 (7.1%)	56 (7.3%)
	Other	4 (0.9%)	0	7 (1.1%)	2 (1.8%)	9 (1.2%)
<b>Height (cm)</b>	N	447	186	657	112	766
	Mean	170.3	171.4	170.8	169.2	170.9
	Median	170.2	170.5	171.5	168.0	170.3
	Minimum	140	146	132	147	147
	Maximum	197	196	196	196	196
<b>Weight (kg)</b>	N	448	186	657	112	766
	Mean	87.1	86.1	84.9	82.1	86.0
	Median	85.0	85.5	82.6	81.8	83.8
	Minimum	46	42	43	39	42
	Maximum	170	181	157	161	164
<b>BMI (kg/m<sup>2</sup>)</b>	N	447	186	657	112	766
	Mean	30.0	29.2	29.1	28.6	29.4
	Median	28.7	28.4	28.2	28.0	28.5
	Minimum	17	18	17	17	17
	Maximum	63	57	61	61	56

Source: NDA 201656 (SDN 001), Module 5.3.5.3, Table 3.1 p. 127.

The patients randomized to each of the 4 active groups and one combined placebo group 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.

**Table 22** summarizes the baseline demographic variables for A2, the long term open label extension of DB3.

Table 22. Summary of Demographic Variables (A2 – Intent to Treat Population)

<b>Characteristic</b>	<b>Statistic</b>	<b>(N = 393)</b>	
<b>Age (years)</b>	N	393	
	Mean	65.7	
	Median	65.0	
	Minimum	50	
	Maximum	89	
<b>Gender</b>			
	<b>Male</b>	N (pct)	235 (59.8)
	<b>Female-Postmenopausal</b>	N (pct)	154 (39.2)
	<b>Female-Child Bearing Potential</b>	N (pct)	4 (1.0)
<b>Race</b>			
	<b>Caucasian</b>	N (pct)	324 (82.4)
	<b>Black</b>	N (pct)	44 (11.2)
	<b>Asian</b>	N (pct)	4 (1.0)
	<b>Hispanic</b>	N (pct)	17 (4.3)
	<b>Other</b>	N (pct)	4 (1.0)
<b>Height (cm)</b>	N	384	
	Mean	170.7	
	Median	171.5	
	Minimum	132	
	Maximum	196	
<b>Weight (kg)</b>	N	393	
	Mean	86.0	
	Median	83.9	
	Minimum	50	
	Maximum	160	
<b>BMI (kg/m<sup>2</sup>)</b>	N	384	
	Mean	29.5	
	Median	28.5	
	Minimum	19	
	Maximum	56	

Source: NDA 201656 (SDN 001), Module 5.3.5.1, Table 3.1 p. 1-3.

### 8.2.3 Explorations for Dose Response

The applicant conducted two studies, SPC Desmo-NS 200801 and SPC Desmo-NS 200802 to assess the safety, tolerability, and PK of escalating doses of SER120.

#### **8.2.4 Special Animal and/or In Vitro Testing**

##### **Study 8279849: A 28-Day Intranasal Toxicity and Toxicokinetic Study in Rats Evaluating SER120 Nasal Spray Compared to Commercial Desmopressin Nasal Spray Formulation with a 4-Week Recovery Phase.**

No remarkable findings were noted in this study based on a dose multiple equivalent to the proposed clinical dose.

##### **Study 8297078: A 39-Week Intranasal Chronic Toxicity Study in Dogs Evaluating Cyclopentadecalactone in Bland Emulsions For Nasal, Oral, and Pulmonary Effects with an 8-Week Recovery Phase.**

Based on nasal surface area, the dose levels of CPD evaluated in the study ( $(b) (4)$  mg/animal) translate to dose multiples of 970, 2889, and 5789 times the proposed maximum clinical dose of 1.5  $\mu$ g.

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

##### **Study 8297079: A 26-Week Intranasal Chronic Toxicity Study in Rats Evaluating Cyclopentadecalactone in Bland Emulsions For Nasal, Oral, and Pulmonary Effects with a 4-Week Recovery Phase.**

Based on nasal surface area, the dose levels of CPD evaluated in the study ( $(b) (4)$  mg/animal) translate to dose multiples of 458, 1525, 4574, 9136 times the maximum proposed clinical dose of 1.5  $\mu$ g.

There were no remarkable findings in CPD or emulsion treated animals.

For detailed review of CPD in a nonclinical setting, see Pharmacology/Toxicology reviewer, Dr. Deepa Rao's, review.

#### **8.2.5 Routine Clinical Testing**

Routine clinical testing was adequate.

#### **8.2.6 Metabolic, Clearance, and Interaction Workup**

The applicant conducted study SPC-SER120-CRI-2010-02 to evaluate the pharmacokinetics of SER120 in subjects with impaired renal function.

#### **8.2.7 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Desmopressin belongs to the class of vasopressin 2 receptor agonists. No other vasopressin 2 agonists are currently approved. Hyponatremia is a known risk of treatment with desmopressin and was specifically evaluated in the phase 3 trials (see section 7.3.5 Submission Specific Primary Safety Concerns).

## 8.3 Major Safety Results

### 8.3.2 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 (b) (6)/DB1: 57 year old male with no known risk factors for coronary artery disease was randomized to the 0.5 µg dose and then up-titrated to the 0.75 µg dose at his Day (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)/DB3: 77 year old male randomized to the 1.0 µg dose after the two week placebo lead-in period. His serum sodium values were within normal limits at each study visit, including his last visit on Day (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)/DB4: 80 year male with a history of diabetes mellitus, hyperlipidemia, hypertension, myocardial infarction, chronic obstructive pulmonary disease, and asthma. The subject was randomized to the 0.75 µg dose after the two week placebo lead-in period. Four days after starting the drug, he was found dead in his home. Twelve weeks before starting the treatment phase of the study, the subject was examined by his cardiologist and found to be medically stable. Two weeks before starting the treatment phase, his family physician performed a routine physical examination and found no acute problems; an electrocardiogram at that time was normal. An autopsy was performed, however, neither the autopsy report nor death certificate was made available to the study site. The Applicant estimates that the subject administered two or three doses of active study drug prior to the event.

Deaths occurring in the open-label, uncontrolled trials:

- Subject (b) (6)/OL1: 79 year old male with a history of hypertension, hyperlipidemia, and previous myocardial infarction and transient ischemic attack. The subject completed

DB2 (randomized to placebo), started OL1 at the 0.5 µg dose, and was up-titrated to the 0.75 µg dose at his Day (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)/A2: 76 year old male who completed DB3 (randomized to placebo), started A2 at the 1.0 µg dose, and was up-titrated to the 1.5 µg dose at his Day (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 23 summarizes information regarding the five deaths reported during the clinical trials.

**Table 23. Summary of Deaths Occurring During the Clinical Trials for SER120**

Subject	Age (yrs)	Dose (µg)	Cause of Death	Source	Role of Drug
<b>Controlled Trials</b>					
(b) (6) DB1	57	0.75	Atherosclerosis/sarcoidosis	Autopsy	Unlikely
DB3	77	1.0	Cardiac arrest/abdominal aneurysm/hypotension	Hospital records	Unlikely
DB4	80	0.75	Unknown	Investigator	Cannot be ruled out
<b>Uncontrolled Trials</b>					
(b) (6) OL1	79	0.75	Probable myocardial infarction	Death certificate	Cannot be ruled out
/A2	76	1.5	Cecal perforation	Hospital records	Unlikely

**Reviewer comment: A role of SER120 in the deaths due to coronary atherosclerosis ((b) (6)/DB1), bleeding aortic aneurysm ((b) (6)/DB3), and cecal perforation ((b) (6)/A2) is unlikely. A role of the drug in the other two deaths ((b) (6)/DB4 and ((b) (6)/OL1) cannot be definitively ruled out.**

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.

### 8.3.3 Nonfatal Serious Adverse Events

#### Placebo Controlled Trials

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.

**Reviewer 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. Hyponatremia is discussed in detail later in this review. 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.

**Reviewer comment: It is unlikely that SER120 caused this subject's cardiac abnormalities, but it is not possible to rule out an adverse effect of SER120 on his underlying cardiac status due to fluid retention related to the pharmacologic effects of the drug.**

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.

**Reviewer 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.**

The narratives submitted by the applicant for the other SAEs were reviewed. It is unlikely that SER120 was the cause of any of the events.

**Reviewer summary comment: The incidence of SAEs for SER120-treated subjects was low and similar to placebo across all dose groups. The only SAE reported by more than one SER120-treated subject was basal cell carcinoma. Prior history and short duration of study drug exposure before diagnosis make treatment relatedness unlikely for these lesions.**

### Open-Label Safety Extension Study - A2

Study A2 is the uncontrolled, open-label extension of DB3. Initially, A2 enrolled subjects who completed DB3, but the protocol was subsequently amended to allow enrollment of additional subjects who had not participated in that study. All subjects started A2 at the 1.0 µg dose of SER120, but could be up-titrated to the 1.5 µg dose during both the titration and the maintenance phases of the study. Subjects on the 1.0 µg dose could participate in the study for a maximum of 78 weeks, while subjects on the 1.5 µg dose could participate for a maximum of 126 weeks.

During 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.

#### **Reviewer comment:**

- **All of the five subjects who reported basal cell carcinoma were white males whose ages ranged from 52 to 79 years. The events occurred at study days 71, 100, 157, 354, and 504. All of the subjects reporting this SAE continued in the study after the event. A study by Wu et al.<sup>11</sup> reported the incidence of basal cell carcinoma in males as 1,488 cases per 100,000 person-years. Based on total exposure to SER120 of 414 person-years in A2, the incidence of basal cell carcinoma in this trial is similar to the background incidence reported in the Wu paper. It is unlikely that these events were related to the study drug.**
- **Each of the three subjects who reported knee arthroplasty had a previous history of arthritis of the knee and underwent elective joint replacement surgery. 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 on (b) (6). A CT scan revealed pulmonary emboli in both lungs and an ultrasound showed DVT in the right lower extremity involving the soleal vein. The subject had undergone surgery on her right foot on (b) (6), 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 conditions (recent lower extremity surgery and ongoing Cushing's disease).**

---

<sup>11</sup> Wu S, et al, Basal-Cell Carcinoma Incidence and Associated Risk Factors in US Women and Men, Am J Epidemiol 2013;178(6):890-897.

- 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 next 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 borderline 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. A role for SER120 in these cases is assessed as unlikely.

#### Open-Label Safety Extension Study – OL1

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

#### **Reviewer comment:**

- Two subjects reported basal cell carcinoma as a SAE. One was a 78 year old Hispanic male who reported the event after about 16 weeks of treatment at the 0.5 µg dose level. The other was a 76 year old white male who reported the event after (b) (6) days of treatment at the 0.75 µg dose level. It is unlikely that these events were related to the study drug.
- Narratives for the other SAEs were reviewed. Role of SER120 in these cases is assessed as unlikely.

### **8.3.4 Dropouts and/or Discontinuations**

#### Studies DB3 and DB4

During DB3 and DB4, the incidence of adverse events (AEs) that resulted in discontinuation of the subject from the study was 4.9%, 4.2%, and 4.0% in the 1.5 µg, 0.75 µg, and placebo treatment groups, respectively. Table 24 shows the most common AEs leading to study discontinuation.

**Table 24. Most Common Adverse Events Leading to Discontinuation-DB3/DB4**

<b>Preferred Term</b>	<b>1.5 µg SER120 (N=448)</b>	<b>0.75 µg SER120 (N=454)</b>	<b>Placebo (N=454)</b>
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: NDA 201656 (SDN 001), Module 5.3.5.3, Table 7.4.2 p. 543.

The most common AEs resulting in discontinuation from the study were nasal discomfort and hyponatremia. However, the incidence of subjects discontinuing due to nasal discomfort was numerically greater for placebo-treated subjects than for subjects treated with SER120. Hyponatremia is discussed in detail in Section 8.3.5 of this review.

#### Open-Label Safety Extension Study - A2

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

#### Open-Label Safety Extension Study - OL-1

There were 48 treatment emergent adverse events which resulted in subjects discontinuing study drug and terminating early from the study. The most commonly reported adverse events leading to discontinuation were nasal discomfort and sinusitis, reported by 12 subjects (3%) and 3 subjects (1%), respectively.

### **8.3.5 Submission Specific Primary Safety Concerns**

#### **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 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.

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

#### Studies DB3 and DB4

All subjects enrolled in DB3 and DB4 were required to have a serum sodium concentration within normal limits as an inclusion criterion. Fasted serum sodium concentration was assessed on Days 1 (baseline), 15 (end of placebo run-in period), 29, 43, 57, 71, 85, and 99 of the studies. At any time during the study, a patient who had a hyponatremic event, defined as serum sodium of 126 to 129 mmol/L with clinical symptoms related to hyponatremia or serum sodium of 125 mmol/L or less with or without clinical symptoms, was required to be withdrawn from the study. One (0.2%) SER120-treated subject, receiving the 1.5 µg dose of the drug, met the 126-129 mmol/L criterion for withdrawal and was prematurely discontinued. Five (1.1%) SER120-treated subjects, all receiving the 1.5 µg dose of the drug, met the ≤125 mmol/L criterion for withdrawal and discontinued treatment. These discontinuations are discussed below.

During DB3 and DB4, in the 1.5 µg, 0.75 µg, and placebo treatment groups, 1.1%, 0%, and 0.2% of the subjects had nadir serum sodium values of ≤125 mmol/L; 2.0%, 2.0%, and 0% had nadir serum sodium values of 126-129 mmol/L; and 11.2%, 8.4%, and 4.4% had nadir serum sodium values of 130-134 mmol/L. The results of this analysis are summarized in Table 25.

**Table 25. Categorical Analysis of Nadir Serum Sodium Values - DB3/DB4**

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

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

Source: 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 26. As noted above, all of these subjects were prematurely discontinued from the trial per protocol.

**Table 26: Subjects with Nadir Serum Sodium Value  $\leq$  125 mmol/L –  
DB3 and DB4 (SER120-Treated Subjects)**

Subject/ Study	M/F	Age (yrs)	Dose ( $\mu$ g)	Baseline Sodium	Lowest Sodium	Study Day	Symptoms	Comments/ concomitant medications
(b) (6) DB3	M	75	1.5	135	125	(b) (6)	None	1/ A, C
DB3	M	70	1.5	136	124		None	2/ A, B
DB3	M	67	1.5	140	125		None	3/ A, B
DB4	M	75	1.5	138	124		None	4/
					122*		None	5/ A, B
DB4	F	72	1.5	137	117*		Weakness, nausea, vomiting	

M=male; F=female  
 \*Sodium assessments performed at laboratories other than the central laboratory (e.g., emergency room, physician's office) and were not included in the laboratory database.  
**Comments:**  
 1. Subject's serum sodium was 128 mmol/L on Day (b) (6).  
 2. In addition to an inhaled corticosteroid, the patient 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 5 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  $\leq$  125 mmol/L, all were being treated with the 1.5  $\mu$ g 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 21 (six days after starting active treatment with SER120) and the latest at Day 99 (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 a nadir serum sodium in the range of 126 – 129 mmol/L are shown in **Table 27**.

**Table 27. Subjects with Nadir Serum Sodium Value 126-129 mmol/L – DB3 and DB4 (SER120-Treated Subjects)**

Subject/ Study	M/F	Age	Dose (µg)	Baseline Sodium (mmol/L)	Lowest Sodium (mmol/L)	Study Day	Symptoms	Completed/ Discontinued
(b) (6) DB3	F	73	0.75	137	129	(b) (6)	None	Completed
(b) (6) DB3	F	64	0.75	137	127 <sup>1</sup>	(b) (6)	None	Completed
(b) (6) DB3	F	67	0.75	141	129	(b) (6)	None	Completed
(b) (6) DB3	F	65	0.75	140	129	(b) (6)	None	Completed
(b) (6) DB3	M	67	0.75	139	128	(b) (6)	None	Completed
(b) (6) DB3	M	78	0.75	136	128	(b) (6)	None	Completed
(b) (6) DB3	M	76	0.75	142	128	(b) (6)	None	D/C day (b) (6)
(b) (6) DB3	M	81	0.75	136	127	(b) (6)	None	Completed
(b) (6) DB4	F	64	0.75	137	126	(b) (6)	None	D/C day (b) (6)
(b) (6) DB3	M	73	1.5	139	127	(b) (6)	None	D/C day (b) (6)
(b) (6) DB3	F	76	1.5	144	127	(b) (6)	None	Completed
(b) (6) DB4	M	79	1.5	135	127	(b) (6)	None	Completed
(b) (6) DB4	M	73	1.5	135	128	(b) (6)	None	Completed
(b) (6) DB4	M	72	1.5	134	129	(b) (6)	Weakness/ tiredness	D/C day (b) (6)
(b) (6) DB4	M	73	1.5	141	127	(b) (6)	None	Completed
(b) (6) DB4	M	82	1.5	142	128	(b) (6)	None	Completed
(b) (6) DB4	M	73	1.5	137	128	(b) (6)	None	Completed
(b) (6) DB4	F	67	1.5	133	127	(b) (6)	None	Completed

M=male; F=female; EV=exit visit; D/C=discontinue

<sup>1</sup>Subject's serum sodium was 129 mmol/L on Day (b) (6)

<sup>2</sup>D/C due to an adverse event of low sodium level.

<sup>3</sup>D/C due to an adverse event of hyponatremia.

<sup>4</sup>Subject (b) (6) withdrew consent on Day (b) (6) after taking one dose of SER120. Serum sodium was 133 mmol/L on Day (b) (6) (prior to starting SER120) and 127 at the exit visit, which occurred (b) (6) days after the subject's last (only) dose of SER120.

<sup>5</sup>D/C due to an adverse event of blood sodium decreased.

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

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: all nine of the subjects treated with the 1.5 µg dose and seven of the nine subjects treated with the 0.75 µg dose. Eleven of the eighteen (61%) subjects were male and seven (39%) were female.

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

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

### Open Label Safety Extension Study - A2

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

During the entire treatment period there were 64 (16%) subjects who had a serum sodium value in the range of 130 to 134 mmol/L. All of these subjects were asymptomatic and continued in the study except for one subject who discontinued at Day (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 range varied from 0.3% at extension baseline (one subject who should not have been enrolled, based on the inclusion/exclusion criteria) to 1.1% (2/184 subjects) at Week 38. After Week 38, there were no subjects who had a serum sodium value in the 126 to 129 mmol/L range. A total of nine (2%) subjects in A2 had a serum sodium value between 126 and 129 mmol/L at any time during the study. All nine were being treated with the 1.0 µg dose of the study drug at the time of the serum sodium assessment, and all were asymptomatic and continued in the study. Seven were 65 years of age or older (the other two subjects were 64 and 62 years of age). Six were male and three were female.

Three (0.8%) subjects had a serum sodium value less than or equal to 125 mmol/L during the entire study. This occurred in one subject out of 386 (0.3%) at Day (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. Table 28 shows the number and percent of subjects in each serum sodium category at each study visit.

**Table 28. Number and Percent of Subjects with Serum Sodium  $\leq$  125, 126 – 129, and 130 – 134 mmol/L at Each Study Visit – Extension Study A2**

Visit Day	# of Patients	$\leq$ 125 mmol/L n (%)	126–129 mmol/L n (%)	130–134 mmol/L n (%)
Baseline	(b) (6)	0	1 (0.3)	6 (1.6)
Day 10		1 (0.3)	2 (0.5)	16 (4.1)
Day 15		0	0	11 (2.9)
Day 23		0	1 (0.3)	15 (4.1)
Day 29		0	2 (0.5)	17 (4.6)
Week 8		0	2 (0.6)	14 (4.0)
Week 14		0	1 (0.3)	15 (4.5)
Week 22		1 (0.3)	0	11 (3.4)
Week 30		1 (0.3)	2 (0.6)	9 (2.6)
Week 38		0	2 (1.1)	2 (1.1)
Week 46		0	0	9 (4.0)
Week 54		0	0	10 (5.1)
Week 62		0	0	6 (3.5)
Week 70		0	0	5 (3.9)
Week 78		0	0	9 (3.6)
Week 86		0	0	2 (3.5)
Week 94		0	0	1 (2.1)
Week 102		0	0	2 (5.3)
Week 110		0	0	1 (5.0)
Week 118		0	0	1 (10.0)
Week 126		0	0	4 (6.6)

One patient can appear multiple times in different categories and study visits.

Source: NDA 201656 (SDN 001), Module 5.3.5.1, CSR 201101A2, Table 13 p. 95.

The three subjects with serum sodium concentrations  $\leq$  125 mmol/L were all being treated with the 1.0  $\mu$ g 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  $\mu$ g 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 seven days. Because of his abdominal symptoms, which were ongoing at the Week 30 visit, the subject was not eating much and was drinking extra fluids. Except for the Day (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.

## 8.4 Supportive Safety Results

### 8.4.2 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 29 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 29. 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 <sup>1</sup>	18 (4.0%)	7 (1.5%)	7 (1.5%)
Hypertension/Blood Pressure Increased	14 (3.1%)	7 (1.5%)	8 (1.8%)

<sup>1</sup>Blood Pressure Increased data shown below are not included in the incidence rates reported in this row because those data are derived from the Investigations SOC

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

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

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

The next most commonly reported SOC was Musculoskeletal/Connective Tissue Disorders. Most of the AEs reported in this SOC were assessed by the investigators as mild or moderate in

severity. The most commonly reported preferred term in the SOC was back pain. The incidence of back pain was greater for both SER120 doses than placebo and appeared dose-related.

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

There were 29 reports of hypertension or blood pressure increased – 14 (3.1%) in the 1.5 µg dose group, seven (1.5%) in the 0.75 µg dose group, and eight (1.8%) in the placebo group. For the 1.5 µg dose group, 16 events were reported by 14 subjects: the severity of the events was assessed as severe in one (discussed in 7.3.2-Nonfatal Serious Adverse Events), moderate in seven, and mild in eight. For the 0.75 µg dose group, 7 events were reported by 7 subjects: the severity was assessed as moderate in two and mild in five (see Section 7.4.3 - Vital Signs for addition information on mean systolic and diastolic blood pressures).

The incidence of decreased serum sodium coded as an AE was 2.5%, 1.1%, and 0% for the 1.5 µg, 0.75 µg, and placebo treatment groups, respectively. The incidence of hyponatremia coded as an AE was 0.9%, 0.2%, and 0.2% for the 1.5 µg, 0.75 µg, and placebo treatment groups, respectively (see Section 7.3.5-Submission Specific Primary Safety Concerns for a detailed discussion of hyponatremia, including analyses based on the serum sodium laboratory data). The incidences of the following AEs, which are potential symptoms of low serum sodium, were similar in the SER120 and placebo treatment groups: headache, nausea, vomiting, muscle spasms (cramps), and fatigue. The incidence of peripheral edema in SER120-treated subjects was also similar to the incidence in placebo-treated subjects.

**Reviewer comment: In general, the most common adverse events reported involved the nasal cavity and nasopharynx, which is consistent with the route of administration of the drug. Though the incidence of atrial fibrillation in both SER120 dose groups was greater than the incidence in placebo, it was less than the reported US prevalence of 2% in people younger than 65 years and 9% in people aged 65 years or older (all six subjects reporting this event were 65 years or older).<sup>12</sup> In addition, none of the six subjects had any serum sodium assessments that were less than 130 mmol/L (in four of the six subjects, all assessments were in the normal range).**

#### Open-Label Safety Extension Study - A2

The safety population of A2 included 393 subjects. Of the 393 subjects, one subject started treatment at the 1.5 µg dose, 357 were up-titrated to the 1.5 µg dose level during the course of the study, and 35 subjects remained on the 1.0 µg dose. Three hundred two (302) subjects were exposed to the 1.5 µg dose for six or more months, 217 for 12 or more months, 129 for 18 or

---

<sup>12</sup> *Atrial Fibrillation Fact Sheet*, Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, [http://www.cdc.gov/dhdsp/data\\_statistics/fact\\_sheets/fs\\_atrial\\_fibrillation.htm](http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm) August 2015. Accessed 29 August 2016.

more months, and 42 for more than 24 months. Of these 393 subjects, 325 (83%) experienced at least one AE. [Table 30](#) summarizes the incidence of commonly occurring ( $\geq 2\%$ ) AEs in A2. Note that the uncontrolled design of this study limits conclusions particularly for AEs that have a common background incidence in this patient population.

Nasal symptoms (e.g., nasal discomfort and sneezing) were the most commonly reported AEs during this study, which is consistent with the findings in DB3 and DB4 and plausibly related to the nasal route of administration of SER120.

Twenty-six (6.6%) subjects in either the 1.0 or 1.5 mcg dose groups reported 27 events of increased blood pressure or hypertension. None of the events met the criteria for a serious adverse event. In the 1.0 mcg dose group, 2 subjects reported 2 events of increased blood pressure or hypertension. Both of the events were assessed as mild and both subjects continued in the study after the event; one was started on a medication for hypertension, one continued without additions or changes to their medications. In the 1.5 mcg dose group, 24 subjects reported 25 events of increased blood pressure or hypertension. Of the 25 events, none was assessed as severe, 9 were assessed as moderate, and 16 were assessed as mild. Two subjects were discontinued from the trial due to the adverse event; 22 continued in the trial. Seventeen subjects were started on a medication for hypertension or had the dose of their current hypertension medication increased, six had no additions or changes to their medications, one had non-drug therapy.

**Table 30. Incidence of the Most Common Adverse Events (Those Occurring in ≥ 2% of Subjects) – A2**

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

Source: NDA 201656 (SDN 001), Module 5.3.5.1, CSR 201101A2, Table 11 p. 78.

### 8.4.3 Laboratory Findings

With the exception of decreases in serum sodium (see Section 7.3.5-Submission Specific Primary Safety Concerns for a detailed discussion of hyponatremia), during DB3, DB4, and A2, there were no chemistry, hematology, or urinalysis findings that were clinically significant.

### 8.4.4 Vital Signs

During DB3 and DB4, vital signs including blood pressure, heart rate, oral temperature and respiration were assessed at Screening, on Day 1 and on Days 15, 29, 43, 57, 71, 85 and 99 (exit).

During A2, vital signs were assessed at Week -1 (in those patients who required screening) and on Days 1, 15 and 29 and at each subsequent visit.

Blood pressure (systolic and diastolic) and heart (pulse) rate were measured after 3 minutes of sitting during each visit. A blood pressure value higher than 100 mmHg diastolic or 165 mmHg systolic during the Screening Visit excluded the patient from the study if the values were confirmed. During the study, if the blood pressure values rose above these limits the readings were to be repeated for verification.

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.

**Reviewer comment: In general, there were no clinically meaningful changes in vital signs in SER120 treated subjects during the course of the study.**

### 8.4.5 Electrocardiograms (ECGs)

#### Studies DB3 and DB4

During DB3 and DB4, each patient had a 12-lead ECG at screening and the Day 99/Exit Visit. The ECG was conducted with the patient at rest in a supine position for 5 minutes before the recording. There were 15 subjects with abnormal-clinically significant ECGs at the Day 99/Exit Visit: five in the 1.5 µg dose group, four in the 0.75 µg dose group, and six in the placebo group. The Day 99/Exit Visit clinically significant ECG findings in the placebo group consisted of four arrhythmias and two conduction abnormalities. The findings for the 1.5 and 0.75 µg SER120 dose groups are presented below.

#### 1.5 µg dose group:

- (b) (6)/DB3: 53 year old female whose medical history included bradycardia since 1986, which was ongoing at screening. ECGs at screening and the Day 99/Exit Visit were

abnormal-clinically significant; both showed sinus bradycardia that was consistent with previous ECGs. Serum sodium levels were in the normal range at all assessments.

- (b) (6)/DB3: 76 year old female whose medical history included ablation for atrial flutter in 2007. Screening ECG was normal; Day 99/Exit Visit ECG was abnormal-clinically significant (atrial fibrillation). Serum sodium levels: three were between 130 and 135, all others were in the normal range.
- (b) (6)/DB3: 89 year old male whose medical history included heart arrhythmia, which was ongoing at screening. Screening ECG was abnormal-clinically significant (sinus arrhythmia, occasional PAC, LAD, poor R wave progression); Day 99/Exit Visit ECG was abnormal-clinically significant (uncontrolled atrial fibrillation). Serum sodium levels: two were between 130 and 135, all others were in the normal range.
- (b) (6)/DB4: 85 year old male whose medical history included atrial fibrillation and atrial fibrillation cardioversion. Screening ECG was abnormal-not clinically significant (sinus bradycardia); Day 99/Exit Visit ECG was abnormal-clinically significant (atrial fibrillation). Serum sodium levels were in the normal range at all assessments.
- (b) (6)/DB4: 63 year old male whose medical history included hypertension, coronary artery disease, premature ventricular complexes, which were all ongoing at screening. Screening ECG was normal; Day 99/Exit Visit ECG was abnormal-clinically significant (ventricular premature complexes). Serum sodium levels were in the normal range at all assessments.

**Reviewer comment:**

- **All five of the Day 99/Exit Visit clinically significant ECG findings were arrhythmias. Three subjects had atrial fibrillation: all three had a history of arrhythmia and one also had a screening ECG that was clinically significant for sinus arrhythmia. None of the three had any serum sodium assessments that were less than 130 mmol/L (most assessments were in the normal range).**
- **One subject had premature ventricular complexes. This subject had a history of premature ventricular complexes; his serum sodium assessments were all in the normal range.**
- **One subject had bradycardia that was also present and clinically significant at screening.**
- **It is unlikely that these arrhythmias were caused by the study drug.**

**0.75 µg dose group:**

- (b) (6)/DB3: 70 year old male whose medical history included hypertension, which was ongoing at screening. Screening ECG was abnormal-not clinically significant (sinus bradycardia); Day 99/Exit Visit ECG was abnormal-clinically significant (atrial fibrillation). Serum sodium levels were in the normal range at all assessments. Assessed as probably related to drug.
- (b) (6)/DB3: 78 year old female whose medical history included pacemaker for sinus bradycardia, which was ongoing at screening. Screening ECG was abnormal-not clinically significant (pacemaker stable); Day 99/Exit Visit ECG was abnormal-clinically significant (patient has a pacemaker-no change from baseline). Serum sodium levels: two were between 130 and 135, all others were in the normal range.

- (b) (6)/DB3: 72 year old male whose medical history included atrial fibrillation, which was ongoing at screening. Screening ECG was abnormal-not clinically significant (controlled atrial fibrillation); Day 99/Exit Visit ECG was abnormal-clinically significant (uncontrolled atrial fibrillation). Serum sodium levels were in the normal range at all assessments.
- (b) (6)/DB4: 56 year old male whose medical history included hyperlipidemia and hypertension, which was ongoing at screening. Screening ECG was abnormal-not clinically significant (lateral T Wave changes are nonspecific); Day 99/Exit Visit ECG was abnormal-clinically significant (inferior/ lateral ST-T changes may be due to myocardial ischemia). Serum sodium levels were in the normal range at all assessments. This subject also reported a SAE of congestive heart failure (see Section 7.3.2 Nonfatal Serious Adverse Events).

**Reviewer comment:**

- **Of the four subjects with Day 99/Exit Visit clinically significant ECG findings, two had atrial fibrillation. Of the two, one subject had a history of atrial fibrillation and the other had no previous history of arrhythmia. Both had serum sodium assessments that were all in the normal range. A role for the drug in the subject without a history of arrhythmia cannot be ruled out; A role for the drug in the other subject with a history of arrhythmia is unlikely.**
- **One subject had ST-T changes that may have been due to myocardial ischemia (this subject had a SAE of congestive heart failure). It is unlikely that SER120 caused this subject's cardiac abnormalities, but it is not possible to rule out an adverse effect of the drug on his underlying cardiac status due to fluid retention related to the pharmacologic effects of the drug.**
- **For the subject with the Day 99/Exit Visit clinically significant ECG finding of "patient has a pacemaker-no change from baseline," it does not appear that the drug is related to this finding.**

Open-Label Safety Extension Study - A2

Subjects who enrolled into study A2 within 3 weeks after completing the double-blind phase of DB3 had the baseline 12-lead ECG at Day 99 (exit from DB3 study). Subjects who required screening had a 12-lead ECG at Week -1. All subjects had repeat ECGs on Weeks 30, 54, 78, 102 and 126 or Study Exit. The ECG was conducted with the patient at rest in a supine position for 5 minutes before the recording. Table 31 summarizes the ECG evaluations during A2.

**Table 31. Electrocardiogram - Overall Evaluation - Safety Population A2**

Visit Day	Outcome	(N=393) n (%)
Baseline <sup>1</sup>	Normal Abnormal – NCS Abnormal - CS	180 (45.9) 210 (53.6) 2 (0.5)
Week 30	Normal Abnormal – NCS Abnormal – CS	152 (43.6) 192 (55.0) 5 (1.4)
Week 54	Normal Abnormal – NCS Abnormal – CS	74 (37.8) 119 (60.7) 3 (1.5)
Week 78	Normal Abnormal – NCS Abnormal – CS	102 (41.6) 143 (58.4) 0
Week 102	Normal Abnormal – NCS Abnormal – CS	14 (35.9) 23 (59.0) 2 (5.1)
Week 126/Exit	Normal Abnormal – NCS Abnormal - CS	30 (48.4) 31 (50.0) 1 (1.6)

<sup>1</sup>Results from the Day 99/End of Study assessment at the end of DB3, re-screening period, or screening period.

Source: NDA 201656 (SDN 001), Module 5.3.5.1, CSR 201101A2, Table 16.6 p. 320-321.

Subjects (n = 5) with abnormal-clinically significant ECGs at Week 30.

- (b) (6): 73 year old female. Baseline ECG showed abnormal findings of low QRS voltages in precordial leads but was considered to be NCS. The Week 30 ECG showed abnormal findings consisting of non-specific ST junctional depression, mild ischemia and ST-changes. The finding was considered clinically significant when the ECG was conducted, but additional tests revealed that the patient had atypical angina and was deemed to be not related to the study drug. Abnormalities were noted in subsequent ECGs conducted at Week 54 and Week 78. These abnormalities were considered to be not clinically significant and no significant changes were noted among these ECGs.
- (b) (6): 61 year old male. Baseline ECG showed bradycardia and the abnormal finding was considered to be NCS. At Week 30 and Week 54, the ECGs showed right bundle branch block in addition to bradycardia, which were considered to be abnormal and clinically significant but unlikely to be related to the study drug. The patient had one more ECG at Week 78 which showed only the right bundle branch block without the bradycardia. At this time, this abnormal finding was considered to be abnormal but not clinically significant.
- (b) (6): 61 year old female who had a normal baseline ECG. At Week 30, the ECG showed low amplitude T waves but not inverted, significant changes in QT intervals and prolonged QT. This ECG was considered to be abnormal and clinically significant. The patient remained in the study and at the Week 54 visit, the ECG was found to be within normal limit.
- (b) (6): 67 year old male whose baseline showed 1st degree AV block. This condition was considered to be abnormal but not clinically significant. At the Week 30 visit, the ECG showed 1st degree AV block and incomplete right bundle branch block. These

findings were considered to be clinically significant and the patient was referred for further cardiac workup. Neither one of these findings were considered to be related to the study medication.

- (b) (6): 72 year old male with a normal ECG at baseline. At Week 30, ECG showed atrial fibrillation with a competing junctional pacemaker. This abnormal finding is considered to be clinically significant but unrelated to the study drug. The ECGs performed at the Week 54 and at Week 70 (Exit visit) were normal.

Subjects (n = 3) with abnormal-clinically significant ECGs at Week 54.

- (b) (6): 65 year old female whose baseline ECG showed irregular sinus bradycardia. This finding was considered to be abnormal but not clinically significant. The same finding was also seen at the Week 30 ECG. At Week 54, the ECG showed low QRS voltage in standard lead limbs. This abnormal finding was considered clinically significant but unrelated to the study drug. The Week 78 ECG also showed low QRS voltage in precordial leads but was considered to be abnormal NCS. Subsequent ECGs at Week 102 and Week 126 were found to be normal.
- (b) (6): 61 year old male, whose ECGs at Week 30 and Week 54 showed right bundle branch block and bradycardia as described above. These findings were not related to the study medication.
- (b) (6): 64 year old male who was enrolled into the study (b) (6). The Week 54 ECG showed slight high-lateral repolarization disturbance, consider ischemia, LV overload or aspecific changes, negative AVL with small negative T in I. These abnormal findings were considered to be unrelated to the study drug. The patient was diagnosed with coronary artery disease with further cardiac work-ups. He underwent a cardiac bypass surgery and withdrew from the study.

Subjects with abnormal-clinically significant ECGs at Week 102 (Subjects (b) (6)) and at Week 126 (Subject (b) (6)).

- (b) (6): 69 year old male whose ECGs conducted prior to the Week 102 visit showed bradycardia with a ventricular rate in the mid 50's with the exception of the Week 78 ECG, which showed a ventricular rate of 45. ECGs at Week 102 and 126 showed atrial fibrillation and were considered to be clinically significant. These ECG findings were not considered to be related to the study drug.
- (b) (6): 77 year old white male with a history of myocardial infarction in 1993, and heart murmur and mild congestive heart failure in 2009. In the same year, the patient had pacemaker implant and stent placement times 3 due to coronary artery disease. The ECG at Week 102 showed uncertain irregular rhythm, marked right axis deviation, right bundle branch block and moderate T-wave abnormality. The abnormal findings were clinically significant but unrelated to study drug. Week 126 ECG showed atrial and ventricular pacing.

#### 8.4.6 Special Safety Studies/Clinical Trials

The applicant conducted a phase 3, randomized open-label study, SPC-SER120-ELD-2010-01, to evaluate the safety, pharmacokinetics, and tolerability of SER120 in elderly ( $\geq 75$  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 below 130 mmol/L. The most frequently occurred AEs were nasal discomfort followed by sneezing, rhinorrhea and increased lacrimation.

#### **8.4.7 Immunogenicity**

No immunogenicity studies were submitted to support this application. Desmopressin has a long history of human use with no immunogenicity issues.

### **8.5 Other Safety Explorations**

#### **8.5.2 Dose Dependency for Adverse Events**

For the pooled DB3/DB4 data, the percentage of subjects reporting at least one TEAE was higher for the 0.75 µg dose group (48.9%) than for the 1.5 µg dose group (46.7%) or placebo (44.9%).

For most SOCs, no obvious dose dependency of AEs was noted. The percentage of adverse events appeared to increase slightly with increasing dose for: cardiac disorders, eye disorders, investigations, musculoskeletal and connective tissue disorders, and renal and urinary disorders.

The following common ( $\geq 2\%$ ) adverse event preferred terms demonstrated dose dependency: nasopharyngitis, decreased blood sodium, back pain, dizziness, and nasal congestion.

#### **8.5.3 Time Dependency for Adverse Events**

During DB3 and DB4, the events of hyponatremia occurred throughout the trials. For the five subjects with severe hyponatremia (serum sodium  $\leq 125$  mmol/L), the earliest event occurred on Study Day 21 (day 6 - 7 of active treatment with SER120) and the latest event occurred on Study Day 99 (the final study visit). For the 18 subjects with nadir serum sodium of 126 - 129 mmol/L, the earliest event occurred on Study Day 29 (the first on treatment assessment of serum sodium during the trial) and latest event occurred on Study Day 99.

During A2, the open label safety extension trial, the latest occurrence of serum sodium  $\leq 125$  mmol/L occurred at Week 30 and the latest occurrence of serum sodium 126 - 129 mmol/L occurred at Week 38.

#### **8.5.4 Drug-Demographic Interactions**

##### Age

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 32](#) summarizes a subgroup analysis of nadir serum sodium values comparing subjects younger than 65 years to subjects 65 years or older.

**Table 32 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: NDA 201656 (SDN 001), Module 5.3.5.3, Table 6.4.2 p. 328 and Table 6.5.2 p. 342.

**Reviewer 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 low regardless of age.**

Gender

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 33 summarizes a subgroup analysis of nadir serum sodium values comparing female and male subjects.

**Table 33: Categorical Analysis of Nadir Serum Sodium Value - 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.

**Reviewer 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.

### **8.5.5 Drug-Disease Interactions**

The applicant conducted study SPC-SER120-CRI-2010-02 to investigate the pharmacokinetics of SER120 in subjects with impaired renal function and in normal healthy volunteers. During the study, SER120 nasal spray, administered intranasally as a single 750 ng dose to subjects with chronic renal impairment and matched normal healthy subjects, showed similar PK profiles in terms of C<sub>max</sub> and T<sub>max</sub> but divergent profiles in terms of systemic exposure (AUC<sub>t</sub>) and terminal half-life.

The phase 3 studies excluded subjects with evidence of renal insufficiency (GFR < 50 mL/min/1.73m<sup>2</sup>).

### **8.5.6 Drug-Drug Interactions**

No drug-drug interaction studies or analyses were performed. 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).

## **8.6 Additional Safety Evaluations**

### **8.6.2 Human Carcinogenicity**

No studies to assess the carcinogenic or mutagenic potential of SER120 were submitted. Labeling for the currently marketed desmopressin acetate nasal spray states that studies have not been performed to evaluate carcinogenic or mutagenic potential.

### **8.6.3 Human Reproduction and Pregnancy Data**

No human reproduction or pregnancy data were submitted with this application. During the phase 3 clinical studies, female subjects of child bearing potential were required to use medically acceptable contraceptive measures to prevent pregnancy during the study period; therefore no pregnancy data were obtained during these studies.

### **8.6.4 Pediatrics and Assessment of Effects on Growth**

SER120 is indicated for adults with nocturnal polyuria and has not been evaluated in patients less than (b) (4) of age. SER120 is contraindicated for use in the treatment of primary nocturnal enuresis because of reports of hyponatremic-related seizures in pediatric patients with use of other intranasal formulations of desmopressin acetate.

### **8.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

There were no reports of SER120 overdose during the development program for the drug. Treatment of overdosage would include discontinuation of the drug, fluid restriction, electrolyte monitoring, and appropriate symptomatic and supportive care.

No formal abuse potential studies or studies to evaluate withdrawal or rebound were conducted as part of the clinical research program for SER120.

### ***8.7 Additional Submissions / Safety Issues***

The applicant submitted a 120-day safety update report on November 3, 2016. The submission confirmed that all clinical trials of SER120 were completed prior to NDA submission and all safety data from these clinical trials were incorporated into the NDA. The applicant has not initiated any trials since the NDA was submitted.

## 9 Advisory Committee Meeting and Other External Consultations

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 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 that age group.

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

Discussion: Most felt that the 1.5 mcg dose, but not the 0.75 mcg dose, produced a meaningful, albeit modest, difference to patients

*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 numerical excess of deaths in the SER120 group and 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 insufficient 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 trials study 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, Not Voting - 1

**Committee Discussion:** *One committee member was not present to vote as noted for the record. Seventeen of the eighteen voting committee members agreed that there is sufficient evidence that the SER120 1.5 mcg dose is effective. Most agreed that there was insufficient evidence to show that the SER120 0.75 mcg dose is effective, and did not endorse the proposed regimen of titrating the dose upward from 0.75 mcg. Some members liked the option of having the 0.75 mcg dose available because it appears to have a lower risk of hyponatremia, although they acknowledged the efficacy data did not clearly support this approach. The one committee member who voted “no” to this question explained that she did not believe the evidence supported a clinically meaningful effect of either SER120 dose in treating the broad indication of nocturia.*

**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, Not Voting – 1

**Committee Discussion:** *One committee member was not present to vote as noted for the record. Fourteen of the eighteen voting committee members agreed that the benefits of desmopressin outweigh the risks and supported approval. Thirteen of the 14 members who voted “yes” opposed a general indication of nocturia and recommended instead an indication for nocturnal polyuria. Other comments included that the label should reflect the trials’ exclusion criteria, that the product should not be recommended in institutionalized patients and that use should be carefully monitored in patients older than 65 years of age.*

*Those who voted “No” were concerned that the benefits were modest compared to the risks and that the product may be used inappropriately in clinical settings (e.g., in the very elderly patients, without adequate monitoring for hyponatremia, or by practitioners who do not understand the seriousness of hyponatremia or the underlying conditions that predispose to nocturia). Another concern was that the trials did not limit enrollment only to patients with nocturnal polyuria.*

*Some members recommended additional strategies to mitigate the risk of hyponatremia, such as a Boxed Warning and Risk Evaluation and Mitigation Strategies.*

## 10 Labeling Recommendations

The following changes should be made to the label:

- The **INDICATION** should be 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 qhs. Patients >65 years of age should start at SER120 0.75 mcg which can be increased to 1.5 mcg qhs after 2-4 weeks 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. If the serum sodium level decreases below 125 mmol/L, treatment with SER120 should be permanently discontinued.
- **CONTRAINDICATIONS** should 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, corticosteroids).
- Consistent with recommendations from the BRUDAC, the risk of hyponatremia should 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 retrospective analysis of efficacy in the nocturnal polyuria sub-population.

## 11 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, a 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 is adequate to manage the risks of this product.

## 12 Post-marketing Requirements and Commitments

The Applicant is proposing marketing the two SER120 dose strengths (0.75 mcg or 1.5 mcg) separately. 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. A post-marketing pharmacokinetic study should be required that compares the systemic exposure of the two dose formulations.

# 13 Appendices

## 13.1 Appendix I

### Schedule of Assessments for the Phase 3, Randomized, Double-blind, Placebo-controlled Trials DB3<sup>1</sup> and

#### DB4

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

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

1 – schedule shown is for Trial DB4 but is essentially identical for study DB3 with the exception of review of the INTU PRO.

[a] PI to provide or confirm probable etiology of nocturia

[b] Patients were instructed to maintain a consecutive 3-day voiding diary each week for 2 weeks during the screening period. Prior to enrollment, site study personnel reviewed patients' diaries to ensure that they met eligibility criteria. Following enrollment, patients were instructed to complete a consecutive 3-day voiding diary during Weeks 1, 2, 3, 4, 6, 8, 10, 12 and 14. Study personnel reviewed the diaries at each of the study visits.

[c] Urine pregnancy test results must be negative on Day 1 for patients to be eligible for the study.

[d] One 24-hour fractionated urine collection with time of collection and urine volume recorded for each void at screening and on one day during Week 14 prior to Day 99 visit.

[e] A new bottle of study medication was dispensed on Days 1, 15, 29, 43, 57, 71 and 85. The used study medication bottle dispensed at the previous visit was collected and weighed on Days 15, 29, 43, 57, 71, 85 and 99 to assess for study drug compliance.

[g] the INTU questionnaire was completed during screening week -2 and -1, week 8 and week 14.

**13.2 Appendix II**

**Questionnaire on the Impact of Nighttime Urination (INTU)<sup>®</sup>**

(b) (4)



13.3 Appendix III

Clinical Investigator Financial Disclosure Review Template

Application Number: 201656

Submission Date(s): February 4, 2016

Applicant: Serenity Pharmaceuticals, LLC

Product: Desmopressin acetate (nasal spray) 0.83 / 1.66 mcg

Reviewer: Olivia Easley, M.D., Martin Kaufman, D.P.M., M.B.A.

Date of Review: March 2, 2017

Covered Clinical Study (Name and/or Number): SPC-SER-120-DB3-201101, SPC-SER-120-DB4-201301

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No (Request list from applicant)
Total number of investigators identified: <u>177</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator:</p> <p>Significant equity interest held by investigator in sponsor of covered study:</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes	No (Request explanation)

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

/s/  
-----

OLIVIA J EASLEY  
03/03/2017

MARTIN E KAUFMAN  
03/03/2017

SURESH KAUL  
03/03/2017

### 13.3 Appendix III

#### Clinical Investigator Financial Disclosure Review Template

Application Number: 201656

Submission Date(s): February 4, 2016

Applicant: Serenity Pharmaceuticals, LLC

Product: Desmopressin acetate (nasal spray) 0.83 / 1.66 mcg

Reviewer: Olivia Easley, M.D., Martin Kaufman, D.P.M., M.B.A.

Date of Review: March 2, 2017

Covered Clinical Study (Name and/or Number): SPC-SER-120-DB3-201101, SPC-SER-120-DB4-201301

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>177</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation)

		from applicant)
--	--	-----------------

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>13</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Form FDA 3454 (4/13), dated December 8, 2015, and signed by Seymour Fein, MD, Chief Medical Officer for Serenity Pharmaceuticals, was submitted. The sponsor certified that he had not entered into any financial arrangement for any clinical investigator in the phase 3 pivotal trials, and that none of the investigators, all of whom were listed, disclosed a proprietary interest in the product or a significant equity in the sponsor.

---

<sup>13</sup> See [web address].

---

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

---

/s/

---

MARTIN E KAUFMAN  
03/02/2017

OLIVIA J EASLEY  
03/02/2017

SURESH KAUL  
03/02/2017

**NDA 201656**

**45-Day Filing Memorandum (Clinical Safety)**

**Application Letter Date:** February 4, 2016

**45-Day Filing Review Date:** March 19, 2016

**Prescription Drug User Fee Act (PDUFA) Goal Date:** December 4, 2016

**Related Submissions:** IND 76667

**Product:** Noctiva (desmopressin) nasal spray

**Route of Administration/Dosage Form/Strengths:** Intranasal/nasal spray/75 µg/mL and 15 µg/mL

**Proposed Indication:** Treatment of nocturia in adults who awaken 2 or more times per night to void.

**1. Objective:**

This review assesses whether New Drug Application (NDA) 201656 meets the regulatory requirements for filing. The review also documents potential clinical review issues identified during the initial review of the application that will be communicated to the applicant in the 74-day letter.

This review focuses only on whether the application may be filed from a clinical safety perspective. Clinical efficacy data will not be addressed in this memorandum.

**2. Background**

SER120 (desmopressin nasal spray) is a low dose nasal spray formulation of desmopressin which is a synthetic analogue of the endogenous human antidiuretic hormone vasopressin. In the United States, desmopressin products have been approved for treatment of central diabetes insipidus, primary nocturnal enuresis and mild von Willebrand disease and mild hemophilia. SER120 is being developed for treatment of adult nocturia, which will be a new indication for the drug.

Serenity Pharmaceuticals, LLC, opened IND 076667 on May 29, 2008 to study SER120 for the indication of nocturia in adults. The IND initially resided in the Division of Reproductive and Urologic Products (DRUP), but was transferred to the Division of Metabolism and Endocrinology Products (DMEP) on February 25, 2009. Subsequently, the IND was again transferred to the Division of Bone, Reproductive and Urologic Products (DBRUP) on April 21, 2014.

The SER120 clinical development program consisted of 10 studies including two Phase 1, one Phase 2, one Phase 3 open-label study in elderly patients, four Phase 3 double blind placebo controlled and two open-label, long term safety extension trials.

### **3. Regulatory History**

**December 10, 2007:** Type B pre-IND meeting

Key meeting discussion:

- Proposed nonclinical program
- Proposed clinical program
- Required safety data if a NDA is submitted
- Appropriateness of the 505(b)(2) regulatory pathway for a NDA

**May 30, 2008:** IND 076667 opened in DBRUP

**February 19, 2009:** Type B EOP 2 meeting

Key meeting discussion:

- Data from the phase 1 and phase 2 trials
- Proposed phase 3 trial

**March 13, 2013:** Type A guidance meeting.

Key meeting discussion:

- Data from the phase 3 trial DB3
- Proposed phase 3 trial DB4
- Development of sponsor's Patient Reported Outcome (PRO) instrument

**August 18, 2015:** Type C guidance meeting

Key meeting discussion:

- Data from the phase 3 trials DB3 and DB4
- Data from sponsor's Patient Reported Outcome (PRO) instrument (Impact of Night Time Urination (INTU) questionnaire)
- Adequacy of the nonclinical package for NDA filing
- Adequacy of the CMC package for NDA filing
- Adequacy of the clinical data for NDA filing

### **4. NDA Filing Review**

This review is based on three criteria proposed in the FDA guidance for conducting a filing review, based on the Agency's interpretation of 21 CFR 314.101 (d) (3) and 21 CFR 314.50.

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner.
- Omission of critical data, information or analyses needed to evaluate safety or failure to provide adequate directions for use.

#### 4.1. Does this NDA contain complete information for the clinical review of safety?

Response: Yes.

##### 4.1.1. Safety Exposure

The clinical program to evaluate the safety of SER120 for treatment of nocturia in adults consists of 8 studies: DB1, DB2, DB3 and DB4, which are randomized, double-blind, placebo controlled Phase 3 studies; SPC-DESMONS-200802, an open-label Phase 2 dose titration study; ELD, a Phase 2/3 open-label study in elderly patients; and OL1 and DB3-A2, which are open-label, safety extension trials.

A total of 1867 patients with nocturia received SER120 for periods of time ranging from less than one month to more than 24 months. There were 607 patients who received SER120 across all the doses tested for  $\geq 6$  months and 347 patients who received SER120 across all the doses tested for  $\geq 12$  months. The highest dose level tested in patients with nocturia was 1.5  $\mu\text{g}$  and 748 patients were administered this dose of SER120. Of these, 530 patients at the 1.5  $\mu\text{g}$  dose received SER120 for  $< 12$  months, 304 for  $\geq 6$  months and 218 patients received this dose of SER120 for  $\geq 12$  months. Table 1 summarizes the number of patients with exposure to SER120 by dose level and overall across all doses.

Table 1: Number of Patients with Exposure Duration to SER120 by Dose in DB1, DB2, DB3, DB4, OL1, ELD, DB3-A2 and 200802 Clinical Studies

Exposure Duration <sup>[1]</sup>	SER120				Overall <sup>[2]</sup> (N = 1867)
	1.5 $\mu\text{g}$ (N = 748)	1.0 $\mu\text{g}$ (N = 518)	0.75 $\mu\text{g}$ (N = 806)	0.5 $\mu\text{g}$ (N = 567)	
< 1 Month	43	305	59	306	177
1 Month to < 3 Months	142	51	260	121	443
3 Months to < 6 Months	259	142	342	22	640
6 Months to < 9 Months	62	10	21	4	63
9 Months to < 10 Months	11	0	3	4	12
10 Months to < 12 Months	13	4	114	78	185
12 Months to < 14 Months	25	2	7	31	138
14 Months to < 16 Months	22	3	0	0	23
16 Months to < 18 Months	40	0	0	1	41
18 Months to < 20 Months	54	0	0	0	30
20 Months to < 22 Months	10	1	0	0	7
22 Months to < 24 Months	19	0	0	0	50
$\geq 24$ Months	48	0	0	0	58

[1] 1 Month = 28 Days

[2] Patients can be in more than one dose group and the overall may not be the sum of all dose. Overall numbers reflect the combined duration of exposure of patients who received different dose levels.

Source: NDA 201656 ser 000, Summary of Clinical Safety, Module 2.7.4, Table 11 (page 27).

*Reviewer comment: The safety database of SER120 in subjects with nocturia appears adequate.*

#### 4.1.2. Demographics and baseline characteristics

In general, patients randomized to each of the 4 active treatment groups and one combined placebo group were similar in terms of mean age, mean height, mean weight, mean BMI, percentage of males and females, race, percentage < 65 and percentage ≥ 65 years.

**Table 2: Summary of Demographic Variables - DB1/DB2/DB3/DB4 Double Blind Placebo Controlled Studies**

Characteristic	Statistic	SER120				
		1.5 µg	1.0 µg	0.75 µg	0.5 µg	Placebo
<b>Age (yrs)</b>	N	448	186	657	112	766
	Mean	66.2	66.2	65.9	62.8	65.2
	SD	9.3	8.9	9.0	8.9	9.3
	Median	66.0	65.0	65.0	62.0	65.0
	Min	50	50	50	50	49
	Max	89	89	89	87	90
<b>Age Group</b>	N	448	186	657	112	766
	< 65	202 ( 45.1)	85 ( 45.7)	308 ( 46.9)	67 ( 59.8)	377 ( 49.2)
	≥ 65	246 ( 54.9)	101 ( 54.3)	349 ( 53.1)	45 ( 40.2)	389 ( 50.8)
<b>Height (cm)</b>	N	447	186	657	112	766
	Mean	170.3	171.4	170.8	169.2	170.9
	SD	11.0	9.1	10.8	11.5	10.3
<b>Weight (kg)</b>	N	448	186	657	112	766
	Mean	87.1	86.1	84.9	82.1	86.0
	SD	20.4	19.7	18.5	19.2	18.2
<b>BMI (kg/m<sup>2</sup>)</b>	N	447	186	657	112	766
	Mean	30.0	29.2	29.1	28.6	29.4
	SD	6.4	6.0	5.8	6.1	5.8
<b>Gender</b>	N	448	186	657	112	766
	Male	256 ( 57.1)	111 ( 59.7)	390 ( 59.4)	55 ( 49.1)	450 ( 58.7)
	Female	192 ( 42.9)	75 ( 40.3)	267 ( 40.6)	57 ( 50.9)	316 ( 41.3)
<b>Race</b>	N	448	186	657	112	766
	Caucasian	338 ( 75.4)	162 ( 87.1)	524 ( 79.8)	88 ( 78.6)	593 ( 77.4)
	African American	62 ( 13.8)	18 ( 9.7)	55 ( 8.4)	13 ( 11.6)	93 ( 12.1)
	Asian	11 ( 2.5)	2 ( 1.1)	11 ( 1.7)	1 ( 0.9)	15 ( 2.0)
	Hispanic	33 ( 7.4)	4 ( 2.2)	60 ( 9.1)	8 ( 7.1)	56 ( 7.3)
	Other	4 ( 0.9)	0 ( 0.0)	7 ( 1.1)	2 ( 1.8)	9 ( 1.2)

Note: The sample from 7.5 µg/mL and the placebo group is based on the number of patients from DB1, DB2, DB3 and DB4. Treatment period for DB1 and DB2 was 7 weeks; treatment period for DB3 and DB4 was 12 weeks.

Source: NDA 201656 ser 000, Integrated Summary of Safety, Module 5.3.5.3, Table 3.1 (pages 127-130).

#### 4.1.3. Integrated Summary of Safety

The Integrated Summary of Safety for SER120 consists of pooled data for the four randomized, double-blind, placebo controlled Phase 3 studies (DB1, DB2, DB3 and DB4); pooled data for studies DB3 and DB4; pooled data for the 2 open-label, long term safety extension studies (OL-1 and DB3-A2) and one 8 week,

randomized, non-placebo controlled study in elderly patients age 75 and older (32 patients).

*Reviewer comment: The safety review will focus primarily on the pooled data from studies DB3 and DB4.*

#### **4.1.4. Common Treatment-Emergent Adverse Events**

The overall incidence of patients with at least one TEAE in the DB1, DB2, DB3 and DB4 studies was 46.7% for the 1.5 µg group, 54.5% for the 0.75 µg group, 72.3% for the 0.5 µg group, and 54.0% for the combined placebo group. The SOC which had the most adverse events across all the treatment groups was respiratory disorders. The most frequently reported TEAEs in the class were nasal discomfort, sneezing, rhinorrhea and nasal congestion. Nasal discomfort was reported by 5.6% of patients in the 1.5 µg group, 4.8% in the 1.0 µg group, 11.9% in the 0.75 µg group, 31.3% in the 0.5 µg group and 17.1% in the placebo group. Infections and infestations was the second most reported SOC followed by gastrointestinal disorders.

#### **4.1.5. Deaths and Other Serious Adverse Events**

There were five deaths reported in the clinical trials conducted during development of SER120. One death occurred in each of the following trials: DB1, DB3, DB4, OL1 and A2. All five deaths occurred while the subject was being treated with SER120: three at the 0.75 µg dose, one at the 1.0 µg dose, and one at the 1.5 µg dose.

The incidence of serious adverse events (SAEs) in DB1, DB2, DB3 and DB4 were 1.8% (8/448) in the 1.5 µg group, 1.6% (3/186) in the 1.0 µg group, 1.7% (11/657) in the 0.75 µg group, and 1.8% (2/112) in the 0.5 µg group. The incidence of SAEs in the placebo group was 1.7% (13/766). There was one SAE in the respiratory SOC which occurred in the 0.75 µg group and consisted of aspiration pneumonia which was considered unrelated to the study drug. Infections and infestations were the most commonly represented SOC with incidences ranging from 0.2% in the 1.5 µg group to 0.9% in the 0.5 µg group. Placebo showed an incidence of 0.4%.

The incidences of patients with at least one treatment emergent SAE observed in the long-term, open-label safety extension studies (OL-1 and DB3-A2) and ELD study were 10.3% (37/358) in the 1.5 µg group, 8.6% (3/35) in the 1.0 µg group, 8.8% (21/238) in the 0.75 µg group and 5.3% (9/170) in the 0.5 µg group.

*Reviewer comment: Narratives for subjects with serious adverse events were included in the ISS.*

#### **4.1.6. Adverse Events Leading to Discontinuation**

The most common adverse events 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.

#### **4.1.7. Assessment of hyponatremia**

Because hyponatremia is a known risk of desmopressin, the applicant assessed serum sodium concentration throughout the trials. Analyses of these data were included in the ISS. Narratives for subjects with serum sodium  $\leq 125$  mmol/L and with serum sodium between 126 and 129 mmol/L were also submitted in the ISS.

#### **4.1.8. Labeling**

The submitted proposed draft label complies with the basic requirements of the Physician Labeling Rule (PLR) and includes the following clinically relevant sections:

- Indications and Usage
- Dosage and Administration
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Clinical Studies

### **5. Conclusion**

From a clinical perspective, NDA 201656 meets the regulatory requirements for filing and may be filed.

### **6. Clinical Comments for the 74-day letter**

The following clinical comments should be communicated to the applicant in the 74-day letter:

Hyponatremia appears to be an important risk with your product. The incidence and severity of hyponatremia will be a review issue.





	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	mapping investigator verbatim terms to preferred terms?				
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?				
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?				
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?				
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?				
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

---

Reviewing Medical Officer Date

---

Clinical Team Leader Date

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

/s/  
-----

MARTIN E KAUFMAN  
02/17/2017

SURESH KAUL  
02/17/2017

## NDA 201656 Filing Review

### Medical Officer's 45-Day Filing Memorandum

**Application Letter Date:** February 4, 2016

**45-Day Filing Review Date:** March 19, 2016

**Prescription Drug User Fee Act (PDUFA) Goal Date:** December 4, 2016

**Product, route, dose:** SER120 (desmopressin nasal spray), intranasal, 0.75 mcg and 1.5 mcg

**Related Submissions:** IND 76667  
NDA 022517[sublingual formulation of desmopressin (Nocturna) sponsored by Ferring)

**Indication:** treatment of adult patients with nocturia defined as two or more nighttime voids each night interrupting sleep

#### 1 Scientific Background

SER120 is a nasal spray formulation of desmopressin which is a synthetic analogue of the endogenous human antidiuretic hormone vasopressin that the Applicant proposes as a treatment for adult nocturia. The formulation contains cyclopentadecanolide (CPD), an excipient that the sponsor believes enhances absorption of desmopressin across the nasal mucosa and allows for use of lower doses of desmopressin to achieve clinical effect.

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

The prevalence of nocturia increases with age and affects men and women equally. It is a result of one of three pathophysiologic processes, acting alone or in combination:

- 1) Polyuria (increase in 24-hour urine volume)
- 2) nocturnal polyuria (increase in nighttime urine production with a corresponding decrease in daytime urine production, resulting in a normal 24-hour urine volume)
- 3) bladder storage problems.

Numerous clinical conditions are associated with nocturia, including overactive bladder, insomnia, sleep apnea, diabetes mellitus, benign prostatic hyperplasia and congestive heart failure. Medications such as diuretics can also cause nocturia.<sup>2</sup> Treatment of nocturia includes addressing any contributing underlying conditions, behavioral modification (e.g. fluid restriction), and pharmacotherapy.

---

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

<sup>2</sup> Ibid.

Desmopressin is a synthetic analogue of the naturally occurring pituitary hormone vasopressin which has anti-diuretic effects via its actions on the renal collecting duct. Desmopressin is approved for the treatment of central diabetes insipidus (CDI), primary nocturnal enuresis (PNE) in children, and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgical procedures. It is currently available in three formulations – intravenous, tablet form and a nasal spray – and is marketed under the trade names DDAVP®, Stimate and Minirin (refer to Table 1 for desmopressin NDAs that are open in FDA).

The most significant risk of desmopressin treatment is the development of hyponatremia which, if severe enough, can result in seizures and death. The exact incidence of severe hyponatremia from desmopressin therapy is not known. On December 7, 2007, the FDA issued an alert to inform healthcare professionals of the risk of severe hyponatremia associated with desmopressin use. This alert was based on post-marketing reports of hyponatremic seizures occurring predominantly in pediatric patients taking intranasal desmopressin for PNE. In addition to the alert, the FDA removed the PNE indication from the currently marketed intranasal desmopressin formulations.

There are currently no FDA approved drugs for the indication of adult nocturia. In 2014, Ferring resubmitted NDA 22517 for an oral disintegrating tablet formulation of desmopressin (proposed trade name Nocdurna) for the treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void. The application had not been approved (b) (4)

[Redacted]

Reviewer's comment: [Redacted] (b) (4)

The application for Nocdurna was discussed at a January 12, 2015, EMDAC meeting. The majority of the EMDAC voted against approval (b) (4)

---

<sup>3</sup> Van Kerrebroeck et. al. Neurourol Urodyn. 2002; 21 (2): 179-83.

Table 1. New Drug Applications for Desmopressin Products in FDA

Application No. (trade name)	Sponsor	Formulation, dose	Indication(s)	status
NDA 17922 (DDAVP®), NDA 21333 (Minirin)	Ferring	0.01% nasal solution; 0.1-0.4 mL qd	CDI, PNE*	Approved
NDA 18938 (DDAVP®)	Ferring	Injectable solution, 4 mcg/mL	For hemostasis in patients with hemophilia A and type I von Willebrand's disease; central diabetes insipidus (CDI)	Approved
NDA 19955 (DDAVP®), NDA 21795 (desmopressin acetate)	Ferring	0.1 mg and 0.2 mg Tablet, dose range 0.1mg -0.8 mg qd	CDI, PNE, renal concentrating capacity test	Approved
NDA 20355 (Stimate)	CSL Behring LLC	1.5 mg/mL nasal spray	hemophilia A and mild-moderate von Willebrand	Approved
NDA 022517 (Nocdurna)	Ferring	Orally disintegrating tablet	(b) (4)	
NDA 201656	Serenity	Nasal spray, 0.75 ug and 1.5 ug qhs	Nocturia in adults who awaken $\geq 2$ times each night to void	In review

\*In 2007, FDA withdrew the PNE indication due to post-marketing reports of severe hyponatremia in children

**Brief Regulatory History:**

A pre-IND meeting between DBRUP and the Applicant occurred on December 10, 2007, and the IND opened in DBRUP in June, 2008. An End-of Phase 2 meeting was held on February 19, 2009. The application was transferred to DMEP on February 25, 2009, and transferred back to DBRUP on April 21, 2014.

Between 2009 and 2014, the following key communications occurred between FDA and Serenity:

- May 22, 2009: **Special Protocol Agreement** for study DB1, “A phase III randomized, double-blind, placebo-controlled multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia.” This study investigated SER120 doses of 0.5 ug and 0.75 ug administered nightly compared to placebo. The two co-primary endpoints were the mean number of nocturic episodes per night during the efficacy assessment period (last week of maintenance treatment) relative to the screening period (baseline) and the percentage of patients with  $\geq 50\%$  reduction between the screening period (baseline) and the last week of the maintenance period with respect to

the mean number of voids per night. A second protocol DB2, submitted simultaneously, was identical to design of DB1.

- July 30, 2010: pre-NDA meeting with DMEP

Studies DB1 and DB2 were completed and neither identified a statistically significant difference between SER120 and placebo with respect to either co-primary endpoint.

- January 18, 2011: Type A Guidance meeting with DMEP to discuss design of new phase 3 trial(s) of SER120 (protocol DB3).
- May 5, 2011 and June 27, 2011 – **DMEP issued SPA no agreement letters for protocol DB3.** DMEP considered the proposed study, which included three SER120 dose groups (0.75 ug, 1.0 ug and 1.5 ug) to be a Phase 2/3 dose-finding study that did not meet regulatory criteria for a special protocol assessment.
  - DMEP agreed to the proposed co-primary endpoints (reduction in mean number of nocturic episodes from screening, and the percentage of patients with a 50% or greater reduction in the mean number of nocturic episodes).
  - DMEP disagreed with the use of the modified intent-to-treat (mITT) population as the primary analysis population for the co-primary efficacy endpoints.
- June 14, 2013: **SPA no agreement for protocol DB4.** DMEP stated that the design and planned analysis did not adequately address the objectives necessary to support a regulatory submission, and provided the following additional comment:
  - The co-primary endpoints (reduction in mean number of nocturic episodes from screening, and the percentage of patients with a 50% or greater reduction in the mean number of nocturic episodes) are acceptable. Both endpoints must be statistically significant at  $p < 0.05$  for a given dose to be considered efficacious
  - Use of the modified intent-to-treat (mITT) population for the primary efficacy analysis is acceptable.
  - The Impact of Night Time Voiding Questionnaire should be the first ranked secondary endpoint
  - The mean of the 3 consecutive days of diary data at each visit will be used to assess efficacy. A multiple imputation method is proposed to manage data. Clarify how to calculate a visit value when only 1 or 2 days out of 3 consecutive days of nocturnal voids were recorded.
- April 2014 -- IND transferred back to DBRUP.
- September 17, 2015: Type C Guidance meeting occurred with DBRUP. DBRUP advised sponsor that NDA submission premature because it appears product has similar risk/benefit profile as Nocdurna which the AC concluded was unfavorable.

## **2. NDA Filing Review**

### **REVIEW RESULTS**

#### ***1. Does this supplement contain complete information for the clinical review?***

**Response: Yes.**

This sBLA contains the critical sections in sufficient detail (see Appendix A).

2. **Does the sBLA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:**
  - a. **Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints**
  - b. **Presentation or what appears to be only a single adequate and well controlled trial without adequate explanation**
  - c. **Use of a study design clearly inappropriate**

**Response: No.**

### 2.1 Efficacy Findings

The sponsor conducted a total of four phase 3 efficacy studies (see Figure 1), but only the most recent two (studies DB3 and DB4), which used higher doses of SER120, support efficacy for the current application.

*Reviewer’s comment: The protocols for the four trials were subject to special protocol assessments in DMEP, but only DB1 was agreed to. DB1 used lower doses of SER120 that was used in trials DB3 and DB4, and failed to demonstrate statistical significance for both co-primary endpoints.*

**Figure 1. Completed pivotal phase 3 efficacy trials of SER120 for the adult nocturia indication**

Clinical Phase	Study #	Study Duration	Total # of Subj Pt	# of Patients/Subjects Received Study Medication					
				0.5 µg	0.75µg	1.0 µg	1.5 µg	2.0 µg	Placebo
III	Protocol SPC-SER120-DB1-200901: Randomized, double-blind, placebo control study to assess the efficacy, safety and PK of SER120 in nocturia patients	50 days	301	148 <sup>[1]</sup>	98				153
III	Protocol SPC-SER120-DB2-200902: Randomized, double-blind, placebo control study to assess the efficacy and safety of SER120 in nocturia patients	50 days	326	167 <sup>[2]</sup>	105				159
II/III	Protocol SPC-SER120-DB3-201101: Randomized, double-blind, placebo control, parallel group study to assess the efficacy, safety and PK of SER120 in nocturia patients	99 days	745		188	186	184		187
III	Protocol SPC-SER120-DB4-201301: Randomized, double-blind, placebo control, parallel group study to assess the efficacy and safety of SER120 in nocturia patients	99 days	797		266		264		267

[1] 140 patients started at the 0.5 ug dose. Fifty remained on 0.5 ug and 98 were up-titrated to 0.75 ug

[2] 167 patients started at the 0.5 ug dose. Sixty-two remained at the 0.5 ug dose and 105 patients were up-titrated to the 0.75 ug dose.

### 2.1 Study design of pivotal phase 3 studies DB3 and DB4

DB3 and DB4 were randomized, double-blind, placebo-controlled, parallel group trials designed to assess the efficacy and safety of SER120 in adult patients 50 years of age or older with nocturia. The design of the trials was identical except that DB4 included only two dose levels compared to three dose levels used in DB3, and also incorporated a patient-reported outcome measure [the Impact of Night Time Urination (INTU) questionnaire] as a secondary efficacy endpoint.

*Reviewer's comment: The INTU questionnaire is designed to measure the impact of nocturia to the patient. The psychometric evaluation of the questionnaire was reviewed by the Clinical Outcome Assessment (COA) team in a memorandum of consultation dated September 10, 2015. The COA consultant concluded that "the sponsor's qualitative work appears adequate to support the concepts and items included in the measure," and that the preliminary review of the psychometric evaluation study report appears to support the final version of the measure's three scores (two domain scores and one total score):*

- Daytime Impact Score (average of items 1-4, 6, and 10)*
- Nighttime Impact Score (average of items 5, 7-9)*
- INTU Overall Impact Score (average of the Daytime and Nighttime Impact Scores)*

*The COA consultant noted that a thorough examination of the INTU questionnaire's qualitative and quantitative work will need to be conducted during the NDA phase.*

*DBRUP has consulted COA again to review the complete INTU development dossier.*

To qualify for study participation, patients must have reported a 6-month history of  $\geq 2$  nocturic episodes per night on average. In addition, they should have documented a mean of  $\geq 2.16$  nocturic episodes per night in the 3-day voiding diary that was collected each week during the two-week screening period. A nocturic episode was defined as a non-incontinent (non-bedwetting) urinary void of any volume 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 screening phase, eligible subjects began a double-blind (blinding of both subjects and the investigators), placebo lead-in period of two weeks in which all subjects received placebo which was administered 30 minutes before bedtime. This was done in order to identify placebo non-responders (i.e. patients with a  $< 50\%$  reduction in the mean number of nocturic episodes per night documented in the 3-day voiding diary that was collected each week during this two-week lead-in period).

Following the two-week placebo run-in, all patients (both placebo responders and non-responders) were then randomized in equal numbers to placebo or to one of two (or three in the case of study DB3) doses of SER120. Inclusion of both placebo responders and non-responders enabled two patient populations to be designated – the intent-to-treat (ITT) population which included all randomized patients with at least 3 days of post-randomization efficacy data recorded in their diaries, and the modified ITT (mITT) population which excluded the placebo responders. These 2 populations could then be separately analyzed to determine if placebo responders and non-responders had significantly different responses to SER120.

Study medication was taken nightly for 12 weeks. Patients completed 3-day voiding diaries during study weeks 1, 2, 3, 4, 6, 8, 10, 12 and 14. Follow-up clinic visits occurred every two weeks until the end of study at week 14. The co-primary efficacy endpoints were change in the mean number of nocturic episodes between screening and the 12-week treatment period, and the

percentage of patients with a >50% reduction between screening and the treatment period with respect to mean number of voids per night.

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

- Patient reported INTU questionnaire score (study DB4 only)
- time from when patient went to sleep to first nocturic void (or first morning void in the absence of a nocturic void)
- percentage of nights with 0 nocturic episodes
- percentage of nights with <1 nocturic episodes
- nocturnal urine volume

The primary efficacy population was the modified intent-to-treat (mITT) population which included all patients 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 one visit. Efficacy analyses were also conducted on the ITT population which included all randomized patients who had at least 3 days of post-randomization efficacy data recorded in their diaries.

For the first primary efficacy variable the treatment groups were compared using an analysis of covariance. The model included the treatment group, study center, the stratification variables (age group < 65 vs. ≥ 65) and gender (male vs. female), and the covariate, which was the baseline number of nocturic episodes. For the second primary efficacy endpoint, the treatment groups were compared using the Cochran-Mantel-Haenszel test stratifying by age group and gender. To protect the overall Type I error rate for the testing of the primary efficacy measures, the treatment dose groups were tested in sequential order. The first test compared the highest dose group that was used for the entire study with placebo. If this test was successful then the next highest dose group was compared to placebo.

For diary derived efficacy variables, the baseline assessment was based on 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 post-baseline assessment was based on the three days of diary data collected at weeks 3, 4, 6, 8, 10, 12 and 14. A minimum of three days during at least one week was required to determine the post-baseline assessment. For three-day diaries with only one or two complete days, the arithmetic average was used as the daily value for the visit. A 3-day diary with less than one complete day was considered missing. In protocol DB3, no imputation method was used to manage missing data. In protocol DB4, the Multiple Imputation (MI) statistical methodology was employed to estimate missing voiding diary data.

*Reviewer's comment: In an SPA non-agreement letter dated June 14, 2013, DMEP agreed with multiple imputation method proposed for primary analysis in study DB4. Analyses were done using multiple imputation and all available data in the DB4 study and using all available data in the DB3 study.*

**Inclusion criteria**

1. Male or female patient  $\geq 50$  years of age.
2. Documented nocturia ( $\geq 2$  nocturic episodes/night for at least 6 months by history).
3. Documented nocturia by diary ( $\geq 2.16$  nocturic episodes/night for 2 weeks [3 days per week] during screening or  $\geq 13$  total nocturic episodes for 2 weeks [3 days per week]).
4. 24-hour urine output  $\leq 57$  mL/kg or up to 4500 mL/24 hours.
5. Serum sodium concentration within normal limits.
6. Serum triglycerides  $< 400$  mg/dL.

**Exclusion criteria:**

1. Nocturnal enuresis (occasional stress or urge incontinence during daytime or at night on the way to void was not necessarily exclusionary but required discussion with the medical monitor).
2. Diabetes insipidus (central or nephrogenic).
3. Unstable diabetes mellitus (type I or II).
  - a. Fasting blood glucose  $> 140$  mg/dL.
  - b. Admitted to the hospital for treatment of diabetes mellitus or related illnesses in the past 12 weeks.
  - c. Not under the care of a physician for diabetes mellitus.
  - d. Had not been on stable doses of oral hypoglycemic drugs and/or long acting insulin for the 4 weeks prior to enrollment. For thiazolidinediones (glitazones) this period was required to be not less than 8 weeks.
4. Congestive heart failure (NYHA Class II through IV).
5. Polydipsia or thirst disorders.
6. Uncontrolled hypertension (systolic  $> 165$  mmHg and diastolic  $> 100$  mmHg), unstable angina or other unstable clinical findings or conditions that, in the opinion of the investigator, would be negatively affected by the study medication or that potentially would affect the study drug.
7. Urinary retention (post-void residual  $> 150$  mL) by medical history.
8. Evidence of hepatic insufficiency or inflammation, i.e.  $\geq 1.5$  X upper limit of normal for total bilirubin or  $\geq 2.5$  X upper limit of normal for hepatic enzymes.
9. Evidence of renal insufficiency (GFR  $< 50$  mL/min/1.73m<sup>2</sup>) by the MDRD calculation method.
10. History of SIADH.
11. Nephrotic syndrome.
12. Evidence of significant peripheral edema on physical exam, e.g.  $> 2+$  pre-tibial edema, noticeably pitting edema  $> 6$  mm with the dependent extremity full, swollen or distorted, etc.).
13. History of urinary bladder surgery or radiotherapy within the last 24 months prior to enrollment. Patients with BPH who had surgery for urinary outlet obstruction more than 6 months prior to screening and were not incontinent were allowed into the study. Urinary bladder tacking was also allowed.
14. Severe daytime LUTS secondary to BPH, overactive bladder or severe stress urinary incontinence.

15. 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 pelvic prolapse (greater than stage II).
17. Current or past malignancy (except cured basal cell carcinoma or squamous cell carcinoma or the skin), unless in remission for at least 5 years and with approval of the medical monitor.

**Prohibited medications:** loop diuretics within the last 6 months, systemic steroids, any investigational drug within 30 days

**Restricted medications** (allowed only if on a stable dose for at least 2 months prior): alpha-blockers, 5-alpha reductase inhibitors; anti-cholinergics and anti-spasmodics, sedative/hypnotic medications, SSRI/SNRIs, NSAIDs, thiazide diuretics.

## 2.2 Demographics, baseline disease characteristics and disposition of patients of pooled pivotal phase 3 studies

The baseline demographic characteristics were generally similar across treatment groups, with the majority of patients being Caucasian males  $\geq 65$  years of age (see [Table 2](#)).

**Table 2 Demographic Characteristics, Placebo-controlled mITT Population**

Characteristic	Attribute	15 ug/mL (N=327)	7.5 ug/mL (N=334)	Placebo (N=326)
Age (years)	Mean	67	67	66
	<65	201 (46)	203 (45)	202 (45)
	$\geq 65$	238 (54)	245 (55)	244 (55)
Sex	Male	197 (60)	196 (59)	202 (62)
	Female – post-menopausal	126 (39)	132 (40)	117 (36)
	Female – pre-menopausal	4 (1)	6 (2)	7 (2)
Race	Caucasian	246 (75)	272 (81)	255 (78)
	Black	44 (14)	28 (8)	47 (14)
	Asian	10 (3)	7 (2)	3 (1)
	Hispanic	26 (8)	24 (7)	19 (6)
	Other	1 (0)	3 (1)	2 (1)
BMI (kg/m <sup>2</sup> )	Median	29	29	28

Source: NDA 201656 seq 000, module 5.3.5.3, ISE, Table 3.1

Disease characteristics were also similar between groups (see [Table 3](#)). Nocturnal polyuria was the most common presumed etiology for nocturia followed by BPH (in men only). There were no restrictions on fluid intake during the trial. Most patients reported consuming between one and two cups of fluid during the night.

**Table 3. Nocturia History (Placebo-controlled mITT Population)**

Characteristic	15 ug/mL (N=327)	7.5 ug/mL (N=334)	Placebo (N=326)
Presumed etiology for nocturia N(%)			
OAB	97 (30)	90 (27)	83 (26)
BPH	127 (39)	135 (40)	147 (45)
Polyuria	8 (2)	15 (5)	12 (4)
Nocturnal polyuria	22 (80)	272 (81)	266 (82)
Unknown	69 (21)	79 (24)	76 (23)
Total nighttime fluid consumption (evening meal to before waking for the day (ounces))			
<4	21 (6)	15 (5)	15 (5)
4-8	114 (35)	114 (34)	116 (36)
9-16	120 (37)	130 (39)	118 (36)
17-24	36 (11)	51 (15)	50 (15)
>24	35 (11)	24 (7)	27 (8)

Source: NDA 201656 seq 000, module 5.3.5.3, ISE, Table 3.1

**Table 4. Patient Disposition (placebo-controlled mITT population)**

Disposition	15 ug/mL (N=327)	7.5 ug/mL (N=334)	Placebo (N=326)
Enrolled	327	334	326
Completed	285 (87)	301 (90)	300 (92)
Discontinued:	42(13)	33 (10)	26 (8)
Adverse event	19 (6)	16 (5)	10 (3)
Withdrawal of consent	15 (5)	14 (4)	12 (4)
Lost to follow-up	4 (1)	2 (1)	2 (1)
Other	4 (1)	1 (0)	2 (1)

Source: NDA 201656 seq 000, module 5.3.5.3, ISE, Table 1.4

## 2.3 Efficacy Findings of pooled pivotal phase 3 studies

### 2.3.1 Primary endpoints

The co-primary efficacy endpoints were change from the 14-day screening period to the 12-week treatment period based on all of the 3-day voiding diaries completed during those two study periods in:

- mean number of nocturic episodes per night (co-primary #1)
- percentage of subjects reporting a  $\geq 50\%$  reduction in nightly frequency of nocturic voids (co-primary #2).

### 2.3.1.1 Co-primary efficacy endpoint 1

In studies DB3 and DB4, both low and high dose SER120 were statistically significantly more efficacious than placebo for both the mITT and ITT populations (see **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.**). The conclusion was the same regardless of imputation method used in study DB4 (see **Error! Reference source not found.** and **Error! Reference source not found.**).

**Table 5 Co-primary Efficacy Endpoint 1:  
Change from Baseline to Treatment period in mean number of nocturic voids per night, study DB3**

Study population	Statistic	SER120 15 ug/mL	SER120 7.5 ug/mL	Placebo
<b>mITT</b>	N	131	137	133
	Screening (LSM) (SE)	3.3 (0.09)	3.5 (0.09)	3.4 (0.09)
	Treatment period (LSM) (SE)*	1.9 (0.08)	2.1 (0.07)	2.4 (0.08)
	Change from baseline (LSM) (SE)	-1.5 (0.08)	-1.3 (0.07)	-1.0 (0.08)
	p-value (vs placebo)**	<0.0001	0.0229	
<b>ITT</b>	N	179	186	186
	Screening (LSM) (SE)	3.2 (0.07)	3.4 (0.07)	3.4 (0.08)
	Treatment period (LSM) (SE)*	1.7 (0.07)	1.9 (0.07)	2.1 (0.07)
	Change from baseline (LSM) (SE)	-1.6 (0.07)	-1.4 (0.07)	-1.2 (0.07)
	p-value (vs placebo)**	<0.0001	0.0093	

Source: Module 5.3.5.1.201101 -- DB3 study report, Table 7.1.1, p. 161 and 7.2.1, p 167

\*average of recorded diaries as specified by the protocol during the treatment period.

\*\*p-value for change from screening based on ANCOVA. Model is change = screening voids/night + treatment group + study center + age group + gender

**Table 6. Co-primary Efficacy Endpoint 1:  
Change from Baseline to Treatment period in mean nocturic episodes per night,  
mITT population, study DB4 (multiple imputation used to estimate missing data)**

Study population	Statistic	SER120 15 ug/mL	SER120 7.5 mg/mL	Placebo
<b>mITT</b>	N	196	197	193
	Screening (LSM) SE)	3.4 (0.08)	3.4 (0.07)	3.3 (0.08)
	Treatment period (LSM) (SE)*	2.0 (0.07)	2.2 (0.07)	2.4 (0.7)
	Change from baseline (LSM) (SE)	-1.4 (0.07)	-1.3 (0.07)	-1.1 (0.07)
	p-value (vs placebo)**	0.0002	0.0179	
<b>ITT</b>	N	260	262	260
	Screening (LSM) SE)	3.3 (0.07)	3.3 (0.06)	3.2 (0.06)
	Treatment period (LSM) (SE)*	1.8 (0.06)	1.9	2.1
	Change from baseline (LSM) (SE)	-1.5	-1.4	-1.2
	p-value (vs placebo)**	0.0002	0.0070	

Source: Module 5.3.5.1.201301 -- DB4 study report, Table 7.1, p 166.

\* average of recorded diaries as specified by the protocol during the treatment period

\*\*p-value for change from screening based on ANCOVA. Model is change = screening voids/night + treatment group + study center + age group + gender

**Table 7. Co-primary Efficacy Endpoint 1:  
Change from Baseline to Treatment period in mean nocturic episodes per night,  
study DB4 (post-screening based on mean of available diaries)**

	15 ug/mL	7.5 mg/mL	Placebo
mITT population			
N	196	197	193
Screening (LSM) SE)	3.4 (0.08)	3.4 (0.07)	3.3 (0.08)
Treatment period (LSM) (SE)*	2.1 (0.07)	2.2 (0.07)	2.4 (0.07)
Change from baseline (LSM) (SE)	-1.4 (0.07)	-1.3 (0.07)	-1.0 (0.07)
p-value (vs placebo)**	0.0004	0.0162	
ITT population			
N	260	262	260
Screening (LSM) SE)	3.3 (0.07)	3.3 (0.06)	3.2 (0.06)
Treatment period (LSM) (SE)*	1.8 (0.06)	1.9 (0.06)	2.1 (0.06)
Change from baseline (LSM) (SE)	-1.5 (0.06)	-1.4 (0.06)	-1.2 (0.06)
p-value (vs placebo)**	0.0005	0.0055	

Source: module 5.3.5.1

### 2.3.1.2 Co-primary Efficacy Endpoint 2

For the responder endpoint, efficacy was shown for high dose SER120 in studies DB3 and DB4 for both analysis populations and regardless of imputation method utilized (see [Table 8](#), [Table 9](#), and [Table 10](#)). Low dose SER120 was effective only in study DB4 and only for the mITT population (see [Table 8](#), [Table 9](#), and [Table 10](#)).

**Table 8. Co-Primary Efficacy Endpoint 2 – Summary of Percent of Subjects with a >50% Reduction in Nocturic Voids (Treatment period versus Screening), DB3**

	SER120 15 ug/mL	SER120 7.5 mg/mL	Placebo
mITT population			
N	131	137	133
Yes [n (%)]	55 (42)	37 (27)	24 (18)
No [n (%)]	76 (58)	100 (73)	109 (82)
p-value	<0.0001	0.0854	
ITT population			
N	179	186	186
Yes [n (%)]	93 (52)	77 (41)	61 (33)
No [n (%)]	86 (48)	109 (59)	125 (67)
p-value	0.0002	0.0899	

Source: DB3 study report, Table 8.1.1, p. 179 and table 8.2.1 p. 184.

**Table 9. Co-Primary Efficacy Endpoint 2 – Summary of Percent of Subjects with a >50% Reduction in Nocturic Voids (Treatment period versus Screening), DB4 (multiple imputation used to estimate missing data)**

	SER120 15 ug/mL	SER120 7.5 mg/mL	Placebo
mITT			
N	196	197	193
Yes (percent)	67 (34)	47 (24)	29 (15)
No (percent)	129 (66)	150 (76)	164 (85)
p-value	<0.0001	0.0364	
ITT			
N	260	262	260
Yes [n (%)]	120 (46)	92 (35)	74 (29)
No [n (%)]	140 (54)	170 (65)	186 (72)
p-value	<0.0001	0.1220	

DB4 study report, Tables 10 and 11, pp 82-3.

**Table 10. Co-Primary Efficacy Endpoint 2 – Summary of Percent of Subjects with a >50% Reduction in Nocturic Voids (Treatment period versus Screening), DB4 (post-screening based on mean of available diaries)**

	SER120 15 ug/mL	SER120 7.5 mg/mL	Placebo
mITT			
N	196	197	193
Yes (percent)	67 (34)	47 (24)	29 (15)
No (percent)	129 (66)	150 (76)	164 (85)
p-value	<0.0001	0.0329	
ITT			
N	260	262	260
Yes [n (%)]	121 (47)	93 (36)	74 (29)
No [n (%)]	139 (54)	169 (65)	186 (72)
p-value	<0.0001	0.0854	

Source: DB4 study report, Table 8.4 and 8.5 pp 88-89

## 2.3.2 Secondary endpoints

### 2.3.2.1 INTU Overall Impact Score

The INTU questionnaire was administered only in study DB4. The change in the INTU overall impact score was statistically significant different than placebo for SER120 1.5 ug but only in the ITT population (see [Table 11](#)).

**Table 11. Secondary Efficacy Variable 1 (study DB4): Summary of INTU Overall Impact Score, post screening based on all available assessments**

	Secondary Efficacy Variable # 1	Statistics	SER120		Placebo (N = 186)
			15 µg/mL (1.5 µg) (N = 181)	7.5 µg/mL (0.75 µg) (N = 190)	
<b>mITT Population</b>	INTU Impact Score	Screening (LSM*)	33.9	32.3	32.0
		Treatment Period (LSM)	20.6	23.0	23.1
		Change from Baseline (LSM)	-12.0	-9.7	-9.5
		p-value (Treatment Group Comparison to Placebo)	0.0653	0.9010	
	Secondary Efficacy Variable # 1	Statistics	SER120		Placebo (N = 249)
			15 µg/mL (1.5 µg) (N = 243)	7.5 µg/mL (0.75 µg) (N = 247)	
<b>ITT Population</b>	INTU Impact Score	Screening (LSM*)	33.0	31.8	31.3
		Treatment Period (LSM)	18.9	20.7	21.5
		Change from Baseline (LSM)	-14.1	-12.4	-11.5
		p-value (Treatment Group Comparison to Placebo)	0.0225	0.4452	

\*LSM = Least Square Mean

Source: NDA 201656 seq 000, module 5.3.5.1.201301, DB4 study report, Table 9.1, p. 196

### 2.3.2.2 Time from Bedtime to First Nocturic Void

Another key secondary efficacy variable was the change in time from bedtime to first nocturic void. SER120 resulted in a dose-dependent increase in time to first nocturic void (Table 10).

**Table 12. Secondary Efficacy Variable: Summary of Time from Bedtime to First Nocturic Void (hours), post-screening based on mean of available assessments, mITT population**

	Statistic	SER120 15 ug/mL	SER120 7.5 ug/mL	Placebo
<b>DB3</b>	N	131	137	133
	Screening (LSM)	2.3	2.2	2.3
	Treatment period (LSM)	3.9	3.5	3.2
	Change from screening (LSM)	1.6	1.2	0.9
	p-value (treatment group vs. placebo)*	<0.0001	0.0511	
<b>DB4</b>	N	196	197	193
	Screening (LSM)	2.4	2.3	2.4
	Treatment period** (LSM)	3.9	3.6	3.2
	Change from screening (LSM)	1.5	1.2	0.8
	p-value (treatment group vs. placebo)*	<0.0001	0.0016	

\*p-value for change from screening based on ANCOVA. Model is change=screening response + treatment group + study center + age group + gender

\*\* Average of all nights in the recorded diaries as specified by the protocol during the treatment period.

Source: NDA 201656 seq 000, module 5.3.5.1.201101 DB3 study report, Table 9.1, p. 192 and NDA 201656 seq 000, module 5.3.5.1.201301 DB4 study report, Table 10.1, p. 202

### 2.3.3 Other efficacy evaluations

The INTU Nighttime Domain Score was an exploratory efficacy variable. Only the higher dose of SER120 resulted in a statistically significant improvement in this domain score compared to placebo (see Table 11).

**Table 13. Exploratory Efficacy Variable (DB4): Summary of change from baseline to treatment in INTU Nighttime Domain Score, post-screening based on mean of available assessments, mITT population**

Statistic	SER120 15 ug/mL	SER120 7.5 ug/mL	Placebo
N	181	190	186
Screening (LSM)	37	35	35
Treatment period (LSM)	21	23	24
Change from baseline (LSM) screening	-16	-13	-12
p-value (treatment group vs. placebo)	0.0427	0.5251	

Source: NDA 201656 seq 000, module 5.3.5.1.201301 DB4 study report, Table 22.1, p. 256

## 2.4 Preliminary efficacy conclusions

1. With respect to the first co-primary endpoint -- change from screening to treatment in the mean number of nocturic episodes per night:
  - *Primary analysis population (mITT)*: In both pivotal phase 3 trials, low and high dose SER120 resulted in statistically significantly larger reductions than placebo. The placebo-corrected change from baseline was -0.5 and -0.3 episodes per night for high

- and low dose SER120, respectively, in study DB3, and -0.4 and -0.2 episodes per night in study DB4.
- *Secondary analysis population (ITT)*: Efficacy was demonstrated for both doses of SER120 and the findings are essentially identical to the mITT population.
  - Analysis according to imputation method used in DB4 did not affect efficacy findings for this endpoint.
2. For the second co-primary efficacy endpoint – percent of subjects with a  $\geq 50\%$  reduction in nocturic voids:
    - *Primary analysis population (mITT)*: High dose SER120 was statistically significantly greater than placebo in both trials DB3 and DB4. Low dose SER120 demonstrated efficacy only in study DB4.
    - *Secondary analysis population (ITT)*: High dose SER120 was statistically significantly greater in both trials DB3 and DB4. Low dose SER120 was not effective in either trial DB3 or DB4 compared to placebo.
    - Analysis according to imputation method used in DB4 did not affect efficacy findings for this endpoint.
  3. For the key secondary efficacy endpoint of INTU Impact Score, only high dose SER120 was efficacious and only in the ITT population. No statistically significant difference was observed for either dose of SER120 compared to placebo in the mITT population.
  4. The sponsor proposes a starting dose of 7.5 mcg nightly with an increase to 1.5 mcg nightly based on “individual patient efficacy and tolerability.” The efficacy data do not support the proposed starting dose or the proposed titration scheme.
  5. The clinical trial population (adults >50 years of age) does not support the proposed indicated population of adults (b) (4) of age. Efficacy may differ in younger patients because of disparate etiologies of nocturia.
  6. The clinical trial population also does not support the proposed indication of “nocturia” without consideration of underlying cause.

### 3. Other Considerations of Filing Review

#### 3.1 Review of Financial Disclosure Documents

Form FDA 3454 (4/13), dated December 8, 2015, and signed by Seymour Fein, MD, Chief Medical Officer for Serenity Pharmaceuticals, was submitted. The sponsor certified that he had not entered into any financial arrangement for any clinical investigator in the phase 3 pivotal trials, and that none of the investigators, all of whom were listed, disclosed a proprietary interest in the product or a significant equity in the sponsor.

#### 3.2 Labeling

The proposed label complies with the basic requirements of the Physician Labeling Rule (PLR). The proposed draft label included the following key clinically relevant sections:

- Indications and Usage: NOCTIVA is indicated for the “treatment of nocturia in adults who wake up 2 or more times per night to void.”
- Dosage and Administration: Recommended starting dose is 1 intranasal spray only (i.e. 7.5 ug) in one nostril 30 minutes before bedtime. Based on individual patient efficacy and tolerability, the dose may be increased to 1.5 mcg (b) (4) each night. Serum sodium levels should be checked prior to initiating therapy or increasing dose, within 14

days after initiation or dose increase, and periodically during therapy, as clinically appropriate

- **Clinical Studies:** This section contains the co-primary efficacy endpoint results for study DB3 and DB4 for the ITT population only. The sponsor has also included results of secondary endpoints of INTU total score, time to first nocturic episode, nights with 0 nocturic episodes, nights with  $\leq 1$  nocturic episode, change in nocturnal urine volume and the exploratory endpoint of the between group difference at week 12 in the Treatment Benefit Scale.

### **3.3 Consults:**

- Office of Scientific Investigation – Site selection has been completed and consult request has been forwarded to OSI.
- Clinical Outcomes Assessment – Consult has been sent for review of INTU development dossier.
- Division of Risk Management (DRISK) – The sponsor proposes a Risk Evaluation and Mitigation Strategy (REMS) that consists of a Medication Guide, a Communication Plan and a timetable for submission of assessments. DRISK has been consulted for review of the proposed REMS.
- Pediatric Review Committee (PeRC) – DBRUP agreed with the sponsor’s initial pediatric study plan (iPSP) in a regulatory letter dated August 10, 2015, which called for a full pediatric waiver for SER120.

**Recommended Regulatory Action:** The following **clinical efficacy** comments should be conveyed to the sponsor in the 74-Day letter:

- 1) The clinical benefit of treatment of nocturia with SER120 is unclear. While both doses were statistically significantly better than placebo in reducing nocturia frequency in studies DB3 and DB4, the absolute difference between study drug and placebo was small. With respect to the responder co-primary efficacy endpoint, the SER120 7.5  $\mu\text{g}$  dose was effective only in the modified intent-to-treat (mITT) population of study DB4. Importantly, compared to placebo, neither dose of SER120 resulted in a statistically significant improvement in the INTU impact score in the mITT population.
- 2) The mITT population was the primary efficacy analysis population for both trials. The discrepant efficacy results for the mITT and intent-to-treat (ITT) populations will be a review issue.
- 3) We have concerns with the proposed indication of “nocturia.” Without consideration of underlying cause, it may be challenging for prescribers to identify the patients most likely to benefit from SER120.
- 4) The effect of gender and underlying etiology of nocturia on product efficacy will be review issues.

- 5) The efficacy data submitted do not support the proposed SER120 7.5 µg starting dose or titration scheme. Similarly, there is no specific guidance on when dose escalation is warranted.
- 6) Your clinical trial population does not support use of the product in adults under 50 years of age. Different nocturia etiologies in younger patients may affect product efficacy.

## Appendix A: GRMP Clinical Reviewer Filing Checklist

**NDA/BLA Number:** 201656      **Applicant:** Serenity.      **Stamp Date:** 02/04/16

**Drug Name:** SER120      **NDA/BLA Type:** Standard

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2), DDAVP (NDA 17922)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?  Study Number: DB3 and DB4 Study Title: A randomized, double-blind, placebo-controlled, parallel group, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulations	X			

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	in patients with nocturia Sample Size: 531 (DB3), Arms: 4 (DB3) and 3 (DB4)				
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1: DB3 Pivotal Study #2: DB4	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?				
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>4</sup> ) been exposed at the dose (or dose range) believed to be efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary <sup>5</sup> used for mapping investigator verbatim terms to preferred terms?				
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?				

<sup>4</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>5</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?				
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self-selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Requesting full waiver
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted.

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_x**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74 Day letter.

---

Reviewing Medical Officer

Date

---

Clinical Team Leader

Date

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

/s/  
-----

OLIVIA J EASLEY  
03/24/2016

SURESH KAUL  
03/31/2016