

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA Serial Number:** 201656

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**Indication(s):** Adult Nocturia

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## EXECUTIVE SUMMARY

In this submission, the Applicant is seeking approval of NOCTIVA for the treatment of adult nocturia. To support this approval, the safety and efficacy data from two Phase 3, double-blind, randomized, placebo-controlled clinical studies (DB3 and DB4) were submitted. This review evaluates to determine from a statistical perspective if the submitted information supports such approval.

Study DB3 had three NOCTIVA dose levels (0.75 mcg, 1.0 mcg and 1.5 mcg) while study DB4 had two NOCTIVA dose levels (0.75 mcg and 1.5 mcg) in addition to placebo in both studies. The two studies were conducted in US and Canada. Each study contained a two-week screening period, a two-week double blind placebo lead-in period, and a twelve-week treatment period.

The co-primary efficacy variables were:

1. Mean number of nocturic episodes per night during the efficacy assessment period (change from screening during the treatment period).
2. Percentage of patients with  $\geq 50\%$  reduction of the mean number of voids per night during the treatment period compared to screening period.

The Applicant pre-defined the modified intent-to-treat (mITT) population (excluding placebo responders) as the primary efficacy analysis population in both study protocols. The mITT population (non-responders) was comprised of about 70% of the intent-to-treat (ITT) population. This review noted that placebo responders had fewer nocturic episodes per night compared with non-responders. After the application was transferred to DBRUP, the review team determined that such enrichment analysis strategy that only focused on placebo non-responders rather than the overall ITT population (for which the labelling was intended) is inappropriate. Hence, this statistical review is focused on the results of analyses using the ITT population.

Efficacy data from the two studies demonstrated that NOCTIVA 1.5 mcg dose achieved statistically significant improvement in the two pre-specified co-primary efficacy endpoints compared with placebo. The 0.75 mcg dose achieved statistical significance only on the first co-primary efficacy endpoint in study DB4.

During the review process, the review team and the Advisory Committee determined that the indication of nocturnal polyuria is more appropriate than nocturia from clinical perspective. The treatment effects of each dose on the co-primary efficacy endpoints for the nocturnal polyuria subpopulation maintained at the same magnitude as for the overall study population.

Although NOCTIVA 0.75 mcg dose did not achieve statistical significance on both co-primary efficacy endpoints, it showed numerically greater treatment effect in patients  $\geq 65$  years old than in patients  $< 65$  years. This may support DBRUP's potential recommendation for approving the 0.75 mcg as the starting dose for patients who were  $\geq 65$  years old due to the safety consideration.

# 1 INTRODUCTION

## 1.1 Overview

The Applicant, Serenity Pharmaceutical LLC., seeks approval of NOCTIVA (desmopressin 0.75 mcg and 1.5 mcg) (b) (4) spray every night for the treatment of adult nocturia.

According to the Applicant, NOCTIVA is a low dose reformulation of the FDA approved drug desmopressin which is a synthetic peptide analogue of human anti-diuretic hormone (vasopressin) and a selective V2 agonist. 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.

The Applicant opened an Investigational New Drug Application (IND) for NOCTIVA 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. This NDA was presented to Bone, Reproductive and Urologic Drugs Advisory Committee on 10/19/2016.

The current statistical review is based on two double-blind phase 3 studies, DB3 and DB4, which are briefly summarized in Table 1. During the development of NOCTIVA, the protocols for studies DB3 and DB4 were submitted to FDA for Special Protocol Assessment (SPA) by DMEP in December 2007. No agreement was reached by DMEP.

**Table 1: List of all Studies included in the Statistical Review**

Study	Phase and Design	Treatment Period	# of Patients per Arm	Study Population
DB3	Phase 3, randomized, double blind, parallel group, placebo controlled	14 weeks (including a 2-week double blind placebo lead in period)	Randomized: Placebo: 188 0.75 mcg: 188 1.0 mcg: 188 1.5 mcg: 186	<ul style="list-style-type: none"><li>• <math>\geq 50</math> years of age</li><li>• Documented nocturia (<math>\geq 2</math> nocturic episodes/night or at least 6 months by history).</li></ul>
DB4	Phase 3 randomized, double blind, parallel group, placebo controlled		Randomized: Placebo: 270 0.75 mcg: 270 1.5 mcg: 266	<ul style="list-style-type: none"><li>• Documented nocturia by diary (<math>\geq 2.16</math> nocturic episodes/night for 2 weeks [3 days per week] during screening or <math>\geq 13</math> total nocturic episodes for 2 weeks [3 days per week]).</li></ul>

Source: Statistical reviewer's summary.

## 1.2 Data Sources

The study reports, data and additional information were submitted electronically. These items are located in the Electronic Document Room at [\\Cdsub1\evsprod\NDA201656](#) under submission dates 02/04/2016, 02/19/2016, 04/28/2016, 06/02/2016, 07/05/2016, 8/12/2016, 8/16/2016, 10/03/2016, 10/25/2016, and 11/03/2016.

## **2 STATISTICAL EVALUATION**

### **2.1 Data and Analysis Quality**

The Applicant submitted both tabulation data and analysis data for the two studies. The data sets were complete and study reports were documented. Additional data and statistical programs were submitted to FDA per reviewer's request during the review process. Interim analysis in study DB3 and statistical analyses of efficacy endpoints in each study were carried out following the pre-specified statistical analysis plan.

### **2.2 Evaluation of Efficacy**

#### **2.2.1 Study Design and Endpoints**

Both studies were randomized, double blind, placebo controlled, parallel group, multicenter study to investigate efficacy and safety of NOCTIVA in patients with nocturia. In addition to the placebo in both studies, study DB3 had three NOCTIVA dose levels, 0.75 mcg, 1.0 mcg and 1.5 mcg and study DB4 had two NOCTIVA dose levels, 0.75 mcg and 1.5 mcg. Both studies were conducted in US and Canada.

Each study contained a two-week screening period, a two-week double blind placebo lead-in period, and a twelve-week treatment period. In the screening period, patients were asked to complete a consecutive 3-day voiding diary to confirm a total of at least 7 episodes over the 3-day period prior to any other screening assessments. Once confirmed, patients continued with an additional consecutive 3-day voiding diary completion and underwent additional screening procedures during the second week. All patients were required to have a mean of  $\geq 2.16$  nocturic episodes per night on 3 consecutive nights per week for 2 weeks or a total of at least 13 episodes during the 2 weeks of screening to be eligible for the study. 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.

On Day 1, patients who met all eligibility criteria were enrolled in the study. For the first two weeks, all patients received placebo. On Day 15, all enrolled patients were randomized to one of the treatment groups and entered the 12-week treatment period. Patients were instructed to administer the study medication approximately 30 minutes prior to bedtime and complete 3 consecutive day voiding diaries during study weeks 1, 2, 3, 4, 6, 8, 10, 12 and 14.

Diaries collected during Weeks 1 and 2 were used to assess if a patient was a placebo responder or non-responder. If the reduction in the mean number of nocturic episodes during Weeks 1 and 2 was  $\geq 50\%$  as compared to the screening period (Weeks -2 and -1) or the mean nocturic episode collected during Weeks 1 and 2 was  $< 1.8$ , the patient was considered a placebo responder, otherwise as placebo non-responder.

In study DB4, patients were also instructed to complete 3 corresponding Impact of Night Time Urination (INTU) questionnaires during the screening period, Week 8 and Week 14 diary collection periods and a Treatment Benefit Scale (TBS) questionnaire at the Day 99/Exit Visit. This was a single item questionnaire which evaluated the patient's self-assessment of treatment benefit compared to the patient's baseline.

The primary and most of the secondary efficacy variables) were obtained from the patient’s voiding diaries. The following information was collected on each day of the diary:

1. Date patient went to sleep
2. Time patient went to sleep
3. Time of patient’s first nocturic void
4. Time patient woke-up to start the day
5. Time of patient’s first void after waking up to start the day
6. Number of nocturic voids

The co-primary efficacy variables for both studies were:

- Mean number of nocturic episodes per night during the efficacy assessment period (change from screening versus the treatment period).
- Percentage of patients with  $\geq 50\%$  reduction in the mean number of voids per night between the screening period and the treatment period.

The table below lists all secondary endpoints in each study in the order of hierarchical testing.

**Table 2: Secondary efficacy endpoints and statistical analysis methods**

Secondary Efficacy Endpoints (in order)	DB3	DB4	Analysis method
1. Change in the patient reported INTU questionnaire in the overall impact score between screening and the treatment period		X	ANCOVA
2. Change in time from going to sleep to first nocturic void (or first morning void in the absence of nocturic void) between the screening and the treatment period.	X	X	ANCOVA
3. Change from screening in the percentage of nights with 0 nocturic episodes, on a per patient basis, during the treatment period.	X	X	ANCOVA
4. Change from screening in the percentage of nights with $\leq 1$ nocturic episodes, on a per patient basis, during the treatment period.	X	X	ANCOVA
5. Change in nocturic urine volume between screening and the last week of the treatment period.	X	X	ANCOVA
6. Reduction in mean number of nocturic episodes between screening and <b>each of</b> the treatment period weeks in which diary data are recorded (weeks 3, 4, 6, 8, 10, 12 and 14).	X		Repeated Measures Analysis of Covariance
7. percentage of patients with $\geq 50\%$ reduction between screening and <b>each of</b> the treatment period weeks in which diary data are recorded (weeks 3, 4, 6, 8, 10, 12 and 14) with respect to the mean number of voids per night.	X		Generalized Estimating Equations

Source: Reviewer’s summary based on study SAP.

Per the reviewer’s request, the applicant submitted a clarification letter for the multiplicity control of overall type I error on 4/28/2016. According to this letter, “The modified Intent-to-Treat (mITT) population was the primary population used in the analysis of the co-primary efficacy endpoints in the DB3 and DB4 studies. To protect the overall Type 1 error rate for the primary efficacy analysis in the mITT population, the treatment dose groups were tested in sequential order. The first test compared the highest dose with placebo for both primary endpoints. If this first test was successful (the P-value for both primary endpoints is  $\leq 0.05$ ) then the next highest dose was compared to placebo for both primary endpoints. For DB3, if this second test was successful (the P-value for both primary endpoints is  $\leq 0.05$ ) then the lowest dose was compared to placebo for both primary endpoints. The secondary efficacy

endpoints were tested similar to the co-primary endpoints in the pre-specified order”. The reviewer applied the same multiplicity control approach to the analyses using ITT population as well.

## **2.2.2 Statistical Methodologies**

The first co-primary efficacy variable, the mean number of nocturic episodes per night during the efficacy assessment period (change from screening versus the treatment period based on the 3-day diaries during each period) was analyzed by Analysis of Covariance model. The model included treatment group, study center, age group (<65 vs. ≥65) and gender (male vs. female), placebo responder status, and the number of nocturic episodes as the covariate.

The second co-primary efficacy variable, the percentage of patients with ≥ 50% reduction to the mean number of voids per night based on the 3-day diaries between the screening period and the treatment period. The treatment groups were compared using the Cochran-Mantel-Haenszel test stratifying by the strata of age group (<65 years old vs. ≥65 years old), gender (male vs. female) and placebo responder status.

Table 2 highlights the analysis method for the secondary efficacy endpoints that were controlled for overall type I error. The ANCOVA model for each secondary efficacy endpoint included treatment group, study center, age group, gender, and the baseline value for the endpoint being analyzed as the covariate. The repeated measures analysis of covariance model included treatment group, study center, age group, gender, visit, treatment group by visit interaction, and the baseline value for the variable as covariate. The Generalized Estimating Equations (GEE) model included treatment group, study center, age group, gender, visit, treatment group by visit interaction, and the covariate, which was the baseline value for the variable being analyzed.

No data imputation was used except for data collected in the patient diary. For diary derived parameters the baseline assessment was based on the 3 days of diary data collected during each of the two weeks of screening. A total of 6 days were required to determine the baseline. The post-baseline assessment were based on the 3 days of diary data collected at weeks 3, 4, 6, 8, 10, 12, and 14. A minimum of 3 days were required to determine the post-baseline assessment. For each of the diary derived variables, all data collected during the baseline period were combined into a single outcome for each patient. Similarly, for each of the diary derived variables all data collected during the post-baseline period were combined into a single outcome for each patient.

For study DB3, it was emphasized that if the patient did not complete the study but had at least three post-baseline assessments were based on the data that were available. In effect, the “missing” data were imputed as being equal to the data that were available. For DB4, if a patient had at least three post-baseline assessments for at least one time point but was missing sufficient diary data for one or more post-baseline time points the “missing data” were imputed using the multiple imputation method for the primary analysis of the primary efficacy variables. No missing data imputations were done for the secondary diary –derived efficacy endpoints.

## **2.2.3 Patient Disposition, Demographic and Baseline Characteristics**

The disposition of study patients are summarized by treatment groups in Table 3 and Table 4. In study DB3, a total of 750 patients were randomized to four treatment groups and the study discontinuation rate was 12.3%, ranging from 9.0% to 15.1% across the treatment groups. In study DB4, a total of 806

patients were randomized to three treatments and the study discontinuation rate was 13.0%, ranging from 12.2% to 13.9% across the treatment groups. For both studies, the most common reasons for discontinuation from the study were adverse events and withdrawal of consent.

**Table 3: Summary of Patient Disposition – Study DB3**

	NOCTIVA			Placebo N (%)	Overall N (%)
	1.5 mcg N (%)	1.0 mcg N (%)	0.75 mcg N (%)		
Overall Randomized	186 (100.0)	188 (100.0)	188 (100.0)	188 (100.0)	750 (100.0)
Completed Study	158 (84.9)	163 (86.7)	166 (88.3)	171 (91.0)	658 (87.7)
Discontinued Study	28 (15.1)	25 (13.3)	22 (11.7)	17 (9.0)	92 (12.3)
Reason for Discontinuation					
Adverse Event	15 (8.1)	11 (5.9)	11 (5.9)	9 (4.8)	46 (6.1)
Withdrawal of Consent	10 (5.4)	7 (3.7)	7 (3.7)	5 (2.7)	29 (3.9)
Lost to Follow-up	3 (1.6)	5 (2.7)	3 (1.6)	1 (0.5)	12 (1.6)
Other	0 (0.0)	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.7)

Source: Table 2 in Study DB3 study report.

**Table 4: Summary of Patient Disposition – Study DB4**

	NOCTIVA		Placebo N (%)	Overall N (%)
	1.5 mcg N (%)	0.75 mcg N (%)		
Overall Randomized	266 (100.0)	270 (100.0)	270 (100.0)	806 (100.0)
Completed Study	229 (86.1)	235 (87.0)	237 (87.8)	701 (87.0)
Discontinued Study	37 (13.9)	35 (13.0)	33 (12.2)	105 (13.0)
Reason for Discontinuation				
Adverse Event	18 (6.8)	17 (6.3)	15 (5.6)	50 (4.5)
Withdrawal of Consent	11 (4.1)	13 (4.8)	12 (4.4)	36 (4.5)
Lost to Follow-up	3 (1.1)	2 (0.7)	2 (0.7)	7 (0.9)
Other	5 (1.9)	3 (1.1)	4 (1.5)	12 (1.5)

Source: Table 2 in Study DB4 study report.

For primary efficacy evaluation, the Applicant pre-defined the following analyses population in each study:

- Intent-to-Treat population (ITT) – All patients who completed the two-week post-screening placebo lead-in phase, who were then randomized and received study drug, and who had at least three days of post-randomization efficacy data recorded in their diary.
- Modified Intent-to-Treat population (mITT) – All patients in the Intent-to-Treat population who were classified as placebo non-responders during the two-week placebo lead-in period prior to randomization.
- Evaluable population – All patients in the intent-to-treat population who completed the study and who had no important protocol violations.

The numbers of patients in the defined efficacy analysis sets are presented in Table 5 and Table 6.

**Table 5: Summary of Efficacy analysis sets– Study DB3**

Analysis population	NOCTIVA			Placebo N (%)	Overall N (%)
	1.5 mcg N (%)	1.0 mcg N (%)	0.75 mcg N (%)		
Overall Randomized	186 (100.0)	188 (100.0)	188 (100.0)	188(100.0)	750(100.0)
ITT Population	179 (96.2)	183 (97.3)	186 (98.9)	186 (98.9)	734 (97.9)
MITT Population	131 (70.4)	134 (71.3)	137 (72.9)	133 (70.7)	535 (71.3)
Evaluable Population	153 (82.3)	161 (85.6)	160 (85.1)	167 (88.8)	641 (85.5)

Source: Table 2 in the study report for DB3.

**Table 6: Summary of Efficacy analysis sets– Study DB4**

	NOCTIVA		Placebo N (%)	Overall N (%)
	1.5 mcg N (%)	0.75 mcg N (%)		
Overall Randomized	266 (100.0)	270 (100.0)	270 (100.0)	806 (100.0)
Intent-to-Treat Population (ITT)	260 (97.7)	262 (97.0)	260 (96.3)	782 (97.0)
Modified Intent-to-Treat	196 (73.7)	197 (73.0)	193 (71.5)	586 (72.7)
Evaluable Population	217 (81.6)	221 (81.9)	226 (83.7)	664 (82.4)

Source: Table 2 in study report for DB4.

### **Reviewer’s comments on the primary efficacy analysis population**

The Applicant pre-defined the mITT population as the primary efficacy analysis population in both study protocols. The mITT population was comprised of about 70% of the ITT population. During the protocol design phase for study DB4, the FDA had recommended the mITT as primary analysis population because in study DB3 the treatment effect was greater for placebo non-responders compared to placebo responders (-0.5 and -0.3, respectively), suggesting that an enrichment strategy could be useful. In both studies, all patients (including placebo responders) were randomized after placebo lead-in period and the screening assessment was used as baseline. This review noted that in both studies, placebo responders had fewer nocturic episodes per night compared with non-responders (see Table 7). After the application was transferred to DBRUP, the review team determined that such enrichment analysis strategy that only focused on a subgroup instead of the ITT population was not appropriate because the intended labelling is for the general nocturia population. Hence, the reviewer’s analysis is based on ITT population from this point forward.

**Table 7: Summary of baseline nocturic episodes by responder status (ITT population)**

Baseline mean nocturic episodes	Study DB3	Study DB4
Responders		
N	199	196
Mean (SD)	3.0 (0.8)	2.9 (0.7)
Median (25%, 75%)	2.7 (2.5, 3.3)	2.7 (2.5, 3.2)
Non-responders		
N	535	586
Mean (SD)	3.4 (0.9)	3.4 (0.9)
Median (25%, 75%)	3.2 (2.8, 3.8)	3.2 (2.8, 3.8)
P value (2-sample t test)	<0.0001	<0.0001

Source: Reviewer’s analysis.

The demographics and baseline characteristics of the treatment groups are summarized in the Appendix for each of the two studies (Table 29 and Table 30). The mean age of patients was 66.1 years in both studies. The percentages of male patients were 58.9% for study DB3 and 56% for DB4. In both studies, the majority of patients were Caucasian (83.4% for DB3; 75.7% for DB4), and the percentages of each

race group were comparable across treatment groups in each study. Overall, the demographics across treatment groups were similar in each study.

## 2.2.4 Results and Conclusions

This review replicated the Applicant's results for the co-primary and secondary efficacy endpoints.

### 2.2.4.1 Analysis results for Study DB3

In study DB3, the 1.5 mcg group demonstrated statistically significant improvements in the co-primary efficacy endpoints compared to the placebo group. During the treatment period, the 1.5 mcg group had 0.38 more nocturic episodes reduction per night compared with placebo group. 52% of patients in 1.5 mcg group had  $\geq 50\%$  reduction in nocturic episodes vs. 32.8% in placebo group. The 1.0 mcg dose, which was not proposed for marketing, failed to show statistical significance over placebo on the second co-primary endpoint. Therefore no further testing was conducted on for the lowest dose 0.75 mcg (see Tables 9, 10, 11 and 12) and the P-values were only for exploratory purposes.

**Table 8: Summary of Co primary Efficacy endpoints – Study DB3 (ITT)**

	<b>Placebo (N=186)</b>	<b>NOCTIVA 0.75 mcg (N=186)</b>	<b>NOCTIVA 1.0 mcg (N=183)</b>	<b>NOCTIVA 1.5 mcg (N=179)</b>
<b>Mean Nocturic Episodes</b>				
Baseline (SD)	3.3 (1.0)	3.4 (0.8)	3.3 (1.0)	3.2 (0.8)
Treatment Period (SD)	2.1 (1.1)	1.9 (1.1)	2.0 (1.1)	1.7 (0.9)
Change from baseline* (SE)	-1.2 (0.07)	-1.4 (0.07)	-1.4 (0.07)	-1.6 (0.07)
Difference vs. placebo (SE)		-0.23 (0.09)	-0.18 (0.09)	-0.38 (0.09)
95% CI		-0.40, -0.06	-0.35, -0.01	-0.56, -0.21
P-value (vs. placebo)		0.0093	0.0377	<0.0001
<b><math>\geq 50\%</math> Reduction in Nocturic Voids</b>				
n/N (%)	61/186 (32.8%)	77/186 (41.4%)	73/183 (39.9%)	93/179 (52.0%)
Difference vs. placebo†		9.6%	7.9%	19.5%
95% CI		(-0.2%, 19.2%)	(-1.9%, 17.5%)	(9.4%, 29.1%)
P-value (vs. placebo)		0.0899	0.1608	0.0002

Source: Reviewer's analysis; Table 8 and 8.2.1 in DB3 study report.

\*Change from baseline was obtained from an ANCOVA model.

†Difference and 95% CI were obtained from stratified CMH analysis. P-values were from pair-wise comparisons vs. placebo within CMH test.

The 1.5 mcg group achieved statistical significance on all secondary efficacy endpoints under the pre-specified multiplicity controlling procedure. Compared to placebo group, patients in the 1.5 mcg group delayed the time from going to sleep to first nocturia void by 0.7 hours, the percentage of nights with 0 episode increased by 5.9%, percentage of nights with  $\leq 1$  episode increased by 15.5%, and nocturic urine volume was decreased by 107.8 ml.

**Table 9: Summary of Secondary Efficacy endpoints – Study DB3 (ITT)**

	<b>Placebo (N=186)</b>	<b>NOCTIVA 0.75 mcg (N=186)</b>	<b>NOCTIVA 1.0 mcg (N=183)</b>	<b>NOCTIVA 1.5 mcg (N=179)</b>
<b>Time from going to sleep to first Nocturic Void (or first morning void in the absence of nocturic void)</b>				
Baseline (SD)	2.3 (0.7)	2.3 (0.8)	2.4 (0.8)	2.4 (0.8)
Treatment Period (SD)	3.5 (1.4)	3.9 (1.5)	4.0 (1.5)	4.3 (1.5)
Change from baseline* (SE)	1.1 (0.11)	1.5 (0.11)	1.7 (0.11)	1.9 (0.11)
Difference vs. placebo (SE)		0.4 (0.15)	0.5 (0.15)	0.7 (0.15)
95% CI		0.12, 0.69	0.22, 0.80	0.46, 1.03
P-value (vs. placebo)		0.0059	0.0005	<0.0001
<b>Percentage of nights with 0 nocturic episodes</b>				
Baseline (SD)	0 (0)	0.1 (1.2)	0.1 (1.2)	0.1 (1.2)
Treatment Period (SD)	6.0 (15.5)	8.5 (18.9)	7.4 (17.2)	11.1 (21.3)
Change from baseline* (SE)	5.6 (1.50)	8.7 (1.41)	8.6 (1.42)	11.5 (1.44)
Difference vs. placebo (SE)		3.0 (1.86)	2.9 (1.88)	5.9 (1.87)
95% CI		-0.65, 6.66	-0.78, 6.61	2.19, 9.55
P-value (vs. placebo)		0.1066	0.1216	0.0018
<b>Percentage of nights with &lt;=1 nocturic episodes</b>				
Baseline (SD)	1.1 (4.5)	1.5 (5.7)	1.5 (5.4)	1.6 (5.8)
Treatment Period (SD)	35.3 (34.0)	42.4 (37.3)	43.4 (37.1)	49.1 (37.0)
Change from baseline* (SE)	32.9 (2.94)	39.2 (2.84)	48.3 (2.91)	41.9 (2.85)
Difference vs. placebo (SE)		6.3 (3.74)	9.0 (3.78)	15.5 (3.8)
95% CI		-1.0, 13.7	1.6, 16.4	8.1, 22.9
P-value (vs. placebo)		0.0906	0.0178	<0.0001
<b>Nocturic urine volume</b>				
<b>N</b>	173	166	161	156
Baseline (SD)	698.5 (296.6)	704.2 (304.1)	722.3 (393.0)	724.1 (318.6)
Final Week (SD)	607.6 (323.5)	521.8 (316.5)	535.2 (401.0)	500.2 (299.2)
Change from baseline* (SE)	-113.5 (27.6)	-185.0 (27.2)	-183.9 (27.5)	-221.3 (28.3)
Difference vs. placebo (SE)		-71.5 (35.7)	-70.5 (36.1)	-107.8 (36.1)
95% CI		-141.6, -1.4	-141.4, 0.5	-178.7, -40.0
P-value (vs. placebo)		0.0455	0.0515	0.0029

Source: Reviewer's analysis; Table 9.2, 10.2, 11.2, 12.2 in DB3 study report.

\*Change from baseline was obtained from an ANCOVA model.

**Table 10: Summary of Mean Nocturic Episodes by Week – Study DB3 (ITT)**

Mean Nocturic Episodes By Week	Placebo (N=186)	NOCTIVA 0.75 mcg (N=186)	NOCTIVA 1.0 mcg (N=183)	NOCTIVA 1.5 mcg (N=179)
<b>Week 4</b>				
Change from baseline* (SE)	-1.1 (0.07)	-1.3 (0.07)	-1.2 (0.07)	-1.5 (0.07)
Difference vs. placebo (SE)		-0.23 (0.09)	-0.13 (0.09)	-0.40 (0.09)
95% CI		-0.41, -0.05	-0.31, 0.05	-0.58, -0.21
P-value (vs. placebo)		0.0113	0.1543	<.0001
<b>Week 6</b>				
Change from baseline* (SE)	-1.1 (0.07)	-1.5 (0.07)	-1.4 (0.07)	-1.6 (0.07)
Difference vs. placebo (SE)		-0.33 (0.09)	-0.23 (0.09)	-0.44 (0.09)
95% CI		-0.52, -0.15	-0.41, -0.04	-0.62, -0.25
P-value (vs. placebo)		0.0004	0.0151	<.0001
<b>Week 8</b>				
Change from baseline* (SE)	-1.3 (0.07)	-1.5 (0.07)	-1.5 (0.07)	-1.6 (0.07)
Difference vs. placebo (SE)		-0.29 (0.10)	-0.28 (0.10)	-0.38 (0.10)
95% CI		-0.48, -0.11	-0.47, -0.09	-0.57, -0.20
P-value (vs. placebo)		0.0022	0.0031	<.0001
<b>Week 10</b>				
Change from baseline* (SE)	-1.3 (0.07)	-1.5 (0.07)	-1.5 (0.07)	-1.7 (0.07)
Difference vs. placebo (SE)		-0.20 (0.10)	-0.22 (0.10)	-0.33 (0.10)
95% CI		-0.39, -0.01	-0.41, -0.03	-0.52, -0.14
P-value (vs. placebo)		0.0386	0.0243	0.0006
<b>Week 12</b>				
Change from baseline* (SE)	-1.4 (0.07)	-1.6 (0.07)	-1.5 (0.07)	-1.7 (0.07)
Difference vs. placebo (SE)		-0.20 (0.10)	-0.18 (0.10)	-0.31 (0.10)
95% CI		-0.38, -0.01	-0.37, 0.01	-0.50, -0.12
P-value (vs. placebo)		0.0435	0.0693	0.0012
<b>Week 14</b>				
Change from baseline* (SE)	-1.3 (0.07)	-1.6 (0.07)	-1.5 (0.07)	-1.7 (0.07)
Difference vs. placebo (SE)		-0.27 (0.10)	-0.18 (0.10)	-0.39 (0.10)
95% CI		-0.46, -0.08	-0.37, 0.01	-0.58, -0.20
P-value (vs. placebo)		0.0061	0.0618	<.0001

Source: Reviewer’s analysis; Table 13.2 in DB3 study report. \*Change from baseline was obtained from an ANCOVA model.

**Table 11: Summary of Percentage of patients who had ≥50% Reduction in Nocturic Voids by Week – Study DB3 (ITT)**

≥50% Reduction in Nocturic Voids	Placebo (N=186)	NOCTIVA 0.75 mcg (N=186)	NOCTIVA 1.0 mcg (N=183)	NOCTIVA 1.5 mcg (N=179)
<b>Week 4</b>				
n/N (%)	58/185 (31.4%)	72/186 (38.7%)	62/183 (33.9%)	86/179 (48.0%)
P-value (vs. placebo)		0.1401	0.6362	0.0018
<b>Week 6</b>				
n/N (%)	62/183 (33.9%)	92/175 (52.6%)	77/174 (44.3%)	90/170 (52.9%)
P-value (vs. placebo)		0.0004	0.0497	0.0006
<b>Week 8</b>				
n/N (%)	59/178 (33.2%)	85/172 (49.4%)	88/173 (50.9%)	85/165 (51.5%)
P-value (vs. placebo)		0.0025	0.0011	0.0012
<b>Week 10</b>				
n/N (%)	82/175 (46.9%)	79/170 (46.5%)	85/165 (51.5%)	100/162 (61.7%)
P-value (vs. placebo)		0.8946	0.4311	0.0105
<b>Week 12</b>				
n/N (%)	82/174 (47.1%)	88/169 (52.1%)	88/165 (53.3%)	99/161 (61.5%)
P-value (vs. placebo)		0.3833	0.2768	0.0156
<b>Week 14</b>				
n/N (%)	66/172 (38.4%)	90/166 (54.2%)	79/163 (48.5%)	96/156 (61.5%)
P-value (vs. placebo)		0.0039	0.0764	<.0001

Source: Reviewer’s analysis; Table 14.2 in DB3 study report.

## 2.2.4.2 Analysis results for Study DB4

The analysis results of the co-primary efficacy endpoints in study DB4 were very similar with or without imputation for missing data. To be consistent across the two studies, the reviewer presented the analysis results for all diary-derived efficacy endpoints without data imputation for missing data.

In study DB4, the 1.5 mcg group demonstrated statistically significant improvements compared to the placebo group for the co-primary efficacy endpoints. During the treatment period, compared with placebo group, the 1.5 mcg group had 0.27 more nocturic episodes reduction per night. 46.5% of patients in the 1.5 mcg group had  $\geq 50\%$  reduction in nocturic episodes compared to 28.5% in the placebo group. The 0.75 mcg group failed to show statistical significance over placebo on the second co-primary endpoint. Therefore no further testing was conducted on the secondary efficacy endpoints (see Table 13).

**Table 12: Summary of Co primary Efficacy endpoints – Study DB4 (ITT)**

	<b>Placebo (N=260)</b>	<b>NOCTIVA 0.75 mcg (N=262)</b>	<b>NOCTIVA 1.5 mcg (N=260)</b>
<b>Mean Nocturic Episodes</b>			
N	260	262	260
Baseline (SD)	3.3 (0.8)	3.3 (0.9)	3.3 (0.8)
Treatment Period (SD)	2.1 (1.0)	1.9 (1.1)	1.9 (1.1)
Change from baseline* (SE)	-1.2 (0.06)	-1.4 (0.06)	-1.5 (0.06)
Difference vs. placebo (SE)		-0.21 (0.08)	-0.27 (0.08)
95% CI		-0.36, -0.06	-0.42, -0.12
P-value (vs. placebo)		0.0055	0.0005
<b><math>\geq 50\%</math> Reduction in Nocturic Voids</b>			
n/N (%)	74/260 (28.5%)	93/262 (35.5%)	121/260 (46.5%)
Difference vs. placebo <sup>†</sup>		7.0%	18.1%
95% CI		(-1.0%, 14.9%)	(9.8%, 26.0%)
P-value (vs. placebo)		0.0854	<0.0001

Source: Reviewer's analysis and Tables 7.5 and 8.5 in study report.

\*Change from baseline and P-value were obtained from an ANCOVA model.

<sup>†</sup> Difference and 95% CI were obtained from stratified CMH analysis. P-values were from pair-wise comparisons vs. placebo within CMH test.

The 1.5 mcg group achieved statistical significance on all secondary efficacy endpoints under the pre-specified multiplicity controlling procedure. The INTU's Overall Impact score ranges on a scale from 0 to 100. At baseline, the mean Overall Impact score was about 32 to 34 in all three treatment groups. The 1.5 mcg group reduced about 14 points from baseline on average and the difference vs. placebo was 2.6, which was statistically significant (refer to Clinical Outcome Assessments staff's memo for detailed discussion of INTU). Compared to placebo group, patients in the 1.5 mcg group delayed the time from going to sleep to first nocturia void by 0.6 hours, the percentage of nights had 0 episode increase by 5.3%, the percentage of nights with  $\leq 1$  episode increased by 10.8%, and nocturic urine volume was decreased by 134.1ml. The 0.75 dose achieved statistical significance on the reduction of nocturia episodes per night compared to placebo but failed on the second co-primary efficacy endpoint.

**Table 13: Summary of Secondary Efficacy endpoints – Study DB4 (ITT)**

	<b>Placebo (N=260)</b>	<b>NOCTIVA 0.75 mcg (N=262)</b>	<b>NOCTIVA 1.5 mcg (N=260)</b>
<b>Impact of Night Time Voiding Score</b>			
Baseline (SD)	32.3 (17.0)	32.2 (18.3)	34.4 (17.5)
Treatment Period (SD)	21.3 (13.7)	20.7 (13.7)	20.1 (14.2)
Change from baseline* (SE)	-11.5 (0.9)	-12.4 (0.9)	-14.1 (0.9)
Difference vs. placebo (SE)		-0.8 (1.1)	-2.6 (1.1)
95% CI		-3.0, 1.3	-4.8, -0.4
P-value (vs. placebo)		0.4452	0.0225
<b>Time from going to sleep to first Nocturic Void (or first morning void in the absence of nocturic void)</b>			
Baseline (SD)	2.5 (0.8)	2.4 (0.8)	2.4 (0.8)
Treatment Period (SD)	3.6 (1.4)	4.0 (1.6)	4.1 (1.6)
Change from baseline* (SE)	1.2 (0.11)	1.6 (0.11)	1.8 (0.11)
Difference vs. placebo (SE)		0.4 (0.13)	0.6 (0.14)
95% CI		0.16, 0.68	0.30, 0.83
P-value (vs. placebo)		0.0017	<0.0001
<b>Percentage of nights with 0 nocturic episodes</b>			
Baseline (SD)	0	0	0
Treatment Period (SD)	5.1 (14.5)	7.9 (18.8)	10.0 (19.5)
Change from baseline* (SE)	5.0 (1.40)	7.7 (1.33)	10.3 (1.37)
Difference vs. placebo (SE)		2.7 (1.62)	5.3 (1.64)
95% CI		-0.44, 5.91	2.09, 8.55
P-value (vs. placebo)		0.0914	0.0013
<b>Percentage of nights with &lt;=1 nocturic episodes</b>			
Baseline (SD)	1.0 (4.3)	0.8 (3.9)	1.2 (5.0)
Treatment Period (SD)	34.3 (35.2)	39.5 (36.3)	44.1 (38.4)
Change from baseline* (SE)	34.2 (2.69)	40.1 (2.64)	45.0 (2.72)
Difference vs. placebo (SE)		5.9 (3.22)	10.8 (3.27)
95% CI		-0.5, 12.2	4.4, 17.2
P-value (vs. placebo)		0.0692	0.0010
<b>Nocturic urine volume</b>			
Baseline (SD)	772.1 (369.9)	775.6 (376.4)	732.1 (383.6)
Final Week (SD)	596.9 (317.3)	544.2 (309.6)	466.3 (270.0)
Change from baseline* (SE)	-147.8 (21.6)	-204.3 (21.3)	-281.8 (22.2)
Difference vs. placebo (SE)		-56.5 (26.0)	-134.1 (26.8)
95% CI		-107.7, -5.4	-186.7, -81.4
P-value (vs. placebo)		0.0302	<0.0001

Source: Reviewer’s analysis, Tables 9.2, 10.2, 11.2, 12.2, 13.2 in the study report.

\*Change from baseline was obtained from an ANCOVA model.

### 2.2.4.3 Exploratory analysis

#### *Primary endpoint – Change from baseline in nocturic episodes*

The primary efficacy analysis results showed that the 1.5 mcg dose achieved statistical significance on both co-primary efficacy endpoints and the mean reductions in nocturia episodes were about 1.5 to 1.6 episodes per night compared to 1.2 episodes in the placebo group. To evaluate if the reductions of this magnitude are potentially “meaningful” to patients and to better understand such treatment effect, this

review conducted additional analysis using an anchor-based approach by mapping the observed nocturia episodes to the patient’s end of study self-assessment of benefit compared to baseline.

In study DB4, 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”. This questionnaire had a three month recall period and may have potential recall bias.

Table 14 shows the rates of each response to TBS by treatment groups. At the end of the study, the response rate of “much better” was 43% in the 1.5 mcg group, which was 8% higher than that in the placebo group. For “somewhat better”, the response rates were very similar, 37 vs. 38%. And for “not changed”, the response rate was 20% in 1.5 mcg group, which was 7% lower than that in placebo group. No patient in the study reported feeling “somewhat worse” or “much worse”. Overall, more than 70% of the patients reported some benefit.

**Table 14: Summary of Treatment Benefit Scale – Study DB4 (ITT population)**

Outcome (n %)	Placebo (N=260)	NOCTIVA 0.75 mcg (N=262)	NOCTIVA 1.5 mcg (N=260)
Much Better	91 (35.4%)	96 (37.4%)	111 (43.2%)
Somewhat better	97 (37.7%)	95 (37.0%)	96 (37.4%)
Not Changed	69 (26.8%)	66 (25.5%)	50 (19.5%)
Somewhat worse/ Much worse	0	0	0

Source: Table 21.1 in study DB4 report.

In addition, the cumulative distribution function (CDF) for change from baseline in nocturia episodes per night by TBS response categories was also explored by pooling all patients across treatment groups in the ITT population. The CDF (Figure 1) shows a continuous plot of the proportion of patients at each point along the scale score continuum who experience reduction in nocturic episodes at that level or greater.

Figure 1 shows that half the patients had at least 1.7 episodes reduction in the “much better” category, 1.2 episodes reduction in “somewhat better” category and 0.5 episodes reduction in “not changed” category. The top 10% of patients of each response category had at least 2.8, 2.1 and 1.4 episodes reductions, respectively. For the bottom 10% of the patients in each response category, they had at least 1 and 0.4 episodes reduction in the “much better” and “somewhat better” categories, and 0.2 episodes increase in the “not changed” category. Of note, this CDF plot shows that for a fixed cumulative percentage, there is consistent separation between the three response categories with respect to nocturia episodes reduction.

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

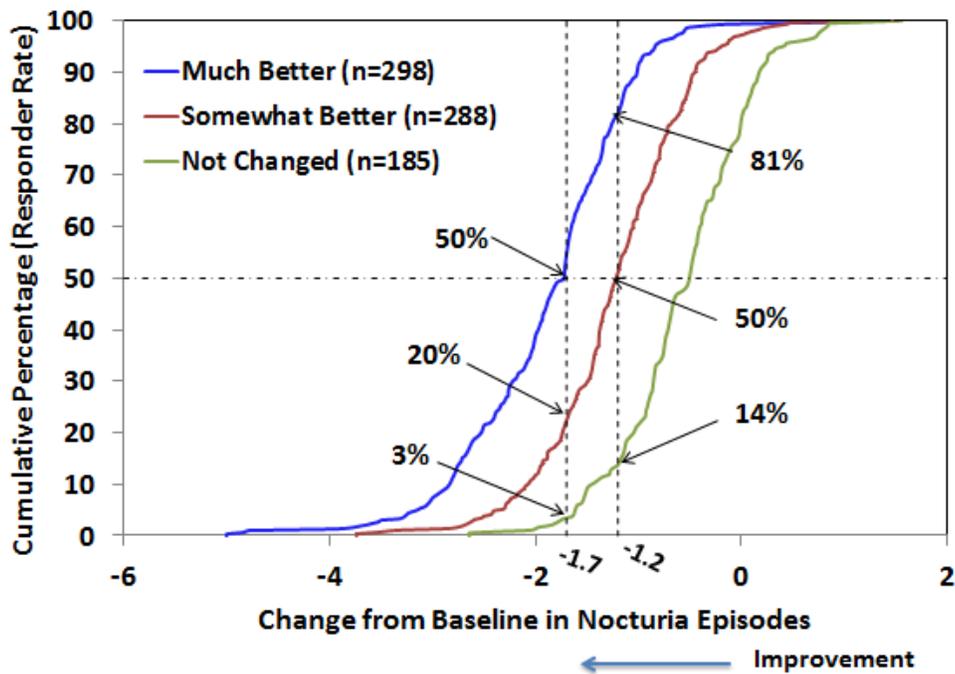
Taking the median -1.7 as the threshold, all patients in the ITT population, irrespective of treatment assignment, were categorized as responders (if the change in nocturic episodes is  $\leq -1.7$ ) or non-responders (change in nocturic episodes is  $> -1.7$ ). The responder rates are 50%, 20% and 3.2% in the “much better”, “somewhat better” and “no change” categories. And using -1.2 as the cutoff value, the responder rates are 81%, 50% and 13.5% respectively (see Figure 1). In this CDF plot, for a fixed

threshold value there is consistent separation between the three response categories with respect to the responder rate.

This CDF plot provides visual comparison between the three CDF curves along the x-axis and y-axis. It supported that the reduction in the nocturia episodes was consistent with the difference seen between the anchor scale responses. Based on this CDF plot, it appears that a mean reduction of approximately 1.5 episodes seen in the 1.5 mcg group and 1.2 episodes in the placebo group fall between “somewhat better” and “much better” and appear to be meaningful to patients.

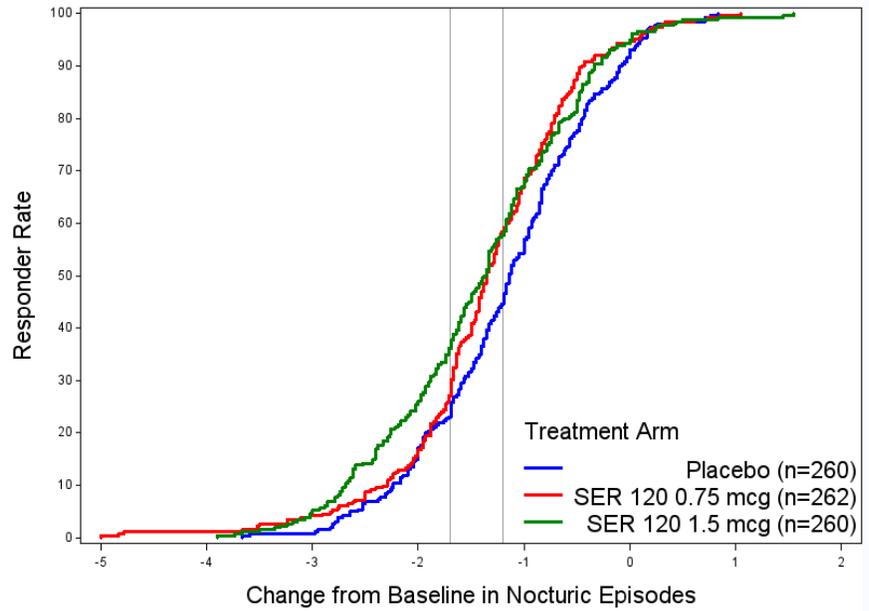
The CDF curves of nocturia episode reduction by treatment groups are shown in Figure 2. For Study DB4, using 1.7 episodes reduction as the threshold value to define responders, the responder rates were 36% and 23% between the 1.5 mcg group and placebo group. Using 1.2 episodes reduction as the threshold value, the responder rates were 58% vs. 45% in the 1.5 mcg group and placebo group. Within the range between 1.2 to 1.7 episodes reduction, the 1.5 mcg group had consistently higher responder rate than placebo group using different threshold values to define responder. And the differences in rates are approximately 13%.

Figure 1: CDF plots of change from baseline in nocturic episodes by TBS scale –DB4 (ITT)



Source: Reviewer’s analysis.

**Figure 2: CDF plots of change from baseline in nocturic episodes by treatment group**



Source: Reviewer's analysis.

In summary, the anchor-based exploratory responders analyses indicated that,

- A mean reduction of at least 1.2 to 1.7 nocturia episodes per night may be potentially meaningful to patients.
- The CDF plot of mean reduction in nocturia episodes per night showed a consistent separation between SER 1.5 mcg vs. placebo.
- NOCTIVA 1.5 mcg may potentially benefit approximately 13% more patients than placebo in reducing nocturia episodes.

## 2.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

## 3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 3.1 Gender, Race, Age, and Geographic Region

The efficacy of NOCTIVA on the co-primary endpoints were also evaluated by subgroups defined by gender, age and race (post-hoc). The categories for each subgroup variable are defined in the following table.

**Table 15: Subgroup categories defined in each study**

Grouping variable	Subgroups
Gender	Female Male
Age group	< 65 years ≥ 65 years
Race	Caucasian, Black, Other

In both studies, for the change from baseline in nocturic episodes per night, the treatment by subgroup interaction was tested using the same ANCOVA model described previously in section 3.2.2 with additional terms for subgroup and the treatment by subgroup interaction as appropriate. For the second co-primary efficacy endpoint, , the treatment by subgroup interaction was tested using a logistic regression model with age, gender, subgroup variable and the treatment by subgroup interaction as factors.

The table below (Table 16) shows the test results for the treatment by subgroup interaction term in each study. No treatment by subgroup interaction is statistically significant at the 0.1 level.

**Table 16: Treatment by subgroup interaction test results**

	Study DB3	Study DB4
Change from baseline in nocturic episodes		
Treatment by Age subgroup	0.6729	0.4413
Treatment by Gender	0.6215	0.9233
Treatment by Race	0.1939	0.1182
Percentage of ≥50%		
Treatment by Age subgroup	0.4361	0.7320
Treatment by Gender	0.5926	0.8034
Treatment by Race	0.4766	0.5096

Source: Reviewer's analysis.

For each subgroup, the co-primary efficacy endpoints were analyzed using the same approach as described in section 3.2.2. Results are presented in the Appendix (see Table 31- 42).

## **Gender**

In both studies, overall female patients had more nocturic episodes reduction and higher percentage of having  $\geq 50\%$  reduction compared to male patients. However, the treatment effects (vs. placebo) on each co-primary efficacy endpoint for the 1.5 mcg were similar between male and female patients (see Table 31-34).

## **Age group**

In both studies, the treatment effect of 1.5 mcg dose on each co-primary efficacy endpoint was numerically larger in patients who were  $\geq 65$  years old than patients who were  $< 65$  years old (see Table 35-38).

## **Race**

Majority of patients in the two studies were White. Other race subgroups had small sample size and no consistent results were observed across the two studies (see Table 39-42).

### **3.2 Other Special/Subgroup Populations**

The sponsor's proposed indication for NOCTIVA (desmopressin acetate nasal spray) is for the treatment of adult nocturia. Nocturia is a symptom that can be caused by many conditions, some of which may co-exist in the same patient. The risk of not identifying and properly treating underlying serious conditions contributing to nocturia is too great with broad indication. In addition, the two phase 3 trials had numerous exclusion criteria so the clinical trial population does not support the broad indication of nocturia. The Division raised this concern regarding a broad indication at the Advisory Committee (AC) meeting (10/19/2016). The general consensus of the AC panel was that the broad indication of nocturia is not supported by the clinical trial population in which the drug was tested. The majority of the panel members recommended "nocturnal polyuria" as the indication. Nocturnal polyuria is a distinct pathologic condition that causes nocturia. It was defined as having more than 33% the total urine volume produced during a 24-hour period occurring at night.

The co-primary and secondary efficacy variables were reanalyzed for the subgroup of patients who had nocturia due to nocturnal polyuria at screening using the same analysis approach for the ITT population.

In both studies, the analysis results on the co-primary efficacy endpoints in the nocturnal polyuria patients are very similar to the overall ITT population results. P-values are descriptive.

**Table 17: Summary of Co primary Efficacy endpoints – Study DB3 (ITT nocturnal polyuria)**

	Placebo (N=145)	NOCTIVA 0.75 mcg (N=145)	NOCTIVA 1.0 mcg (N=146)	NOCTIVA 1.5 mcg (N=143)
<b>Mean Nocturic Episodes</b>				
Baseline (SD)	3.3 (1.0)	3.4 (0.9)	3.3 (1.0)	3.2 (0.8)
Treatment Period (SD)	2.2 (1.1)	2.0 (1.1)	2.0 (1.1)	1.8 (0.9)
Change from baseline* (SE)	-1.1 (0.08)	-1.4 (0.07)	-1.4 (0.07)	-1.5 (0.08)
Difference vs. placebo (SE)		-0.28 (0.10)	-0.23 (0.10)	-0.41 (0.10)
95% CI		-0.48, -0.09	-0.43, -0.04	-0.61, -0.22
P-value (vs. placebo)		0.0049	0.0207	<0.0001
<b>≥50% Reduction in Nocturic Voids</b>				
n/N (%)	42/145 (29.0%)	59/145 (40.7%)	54/146 (37.0%)	70/143 (49.0%)
Difference vs. placebo†		12.0%	8.1%	21.3%
95% CI		1.0%, 22.6%	-2.7%, 18.7%	10.1%, 31.9%
P-value (vs. placebo)		0.0291	0.1387	0.0004

Source: Reviewer's analysis;

\*Change from baseline was obtained from an ANCOVA model.

† Difference and 95% CI were obtained from stratified CMH analysis; P-values were from pair-wise comparisons vs. placebo within CMH test.

**Table 18: Summary of Co primary Efficacy endpoints – Study DB4 (ITT nocturnal polyuria)**

	Placebo (N=204)	NOCTIVA 0.75 mcg (N=209)	NOCTIVA 1.5 mcg (N=199)
<b>Mean Nocturic Episodes</b>			
Baseline (SD)	3.3 (0.9)	3.4 (0.9)	3.4 (0.9)
Treatment Period (SD)	2.2 (1.0)	2.0 (1.1)	2.0 (1.1)
Change from baseline* (SE)	-1.2 (0.07)	-1.5 (0.07)	-1.5 (0.08)
Difference vs. placebo (SE)		-0.22 (0.09)	-0.27 (0.09)
95% CI		-0.40, -0.05	-0.45, -0.09
P-value (vs. placebo)		0.0122	0.0032
<b>≥50% Reduction in Nocturic Voids</b>			
n/N (%)	54/204(26.5%)	73/209 (34.9%)	94/199 (47.2%)
Difference vs. placebo †		8.5%	20.8%
95% CI		-0.4%, 17.2%	11.4%, 29.7%
P-value (vs. placebo)		0.0754	<0.0001

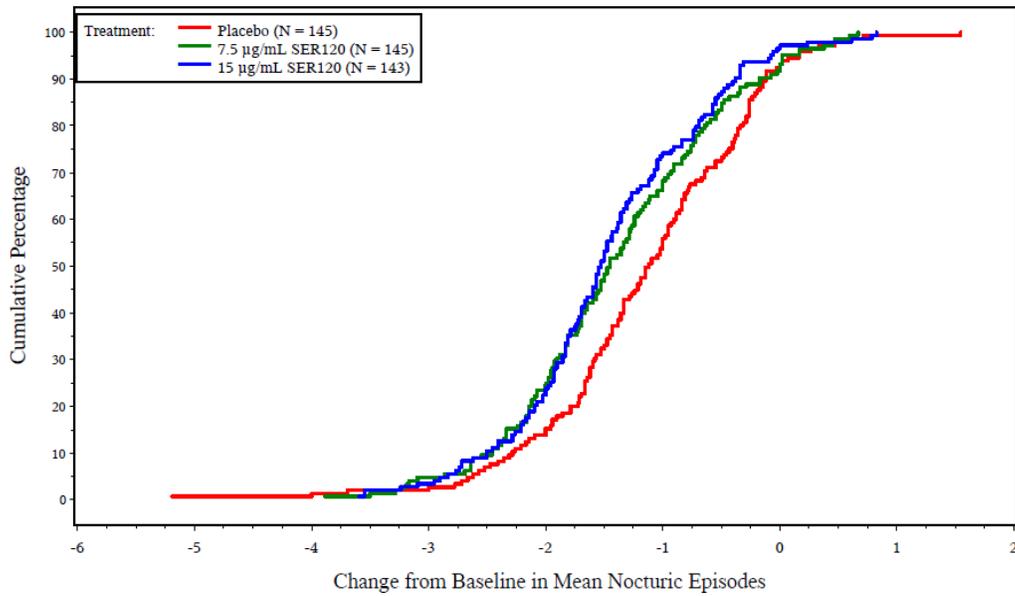
Source: Reviewer's analysis;

\*Change from baseline was obtained from an ANCOVA model.

† Difference and 95% CI were obtained from stratified CMH analysis; P-values were from pair-wise comparisons vs. placebo within CMH test.

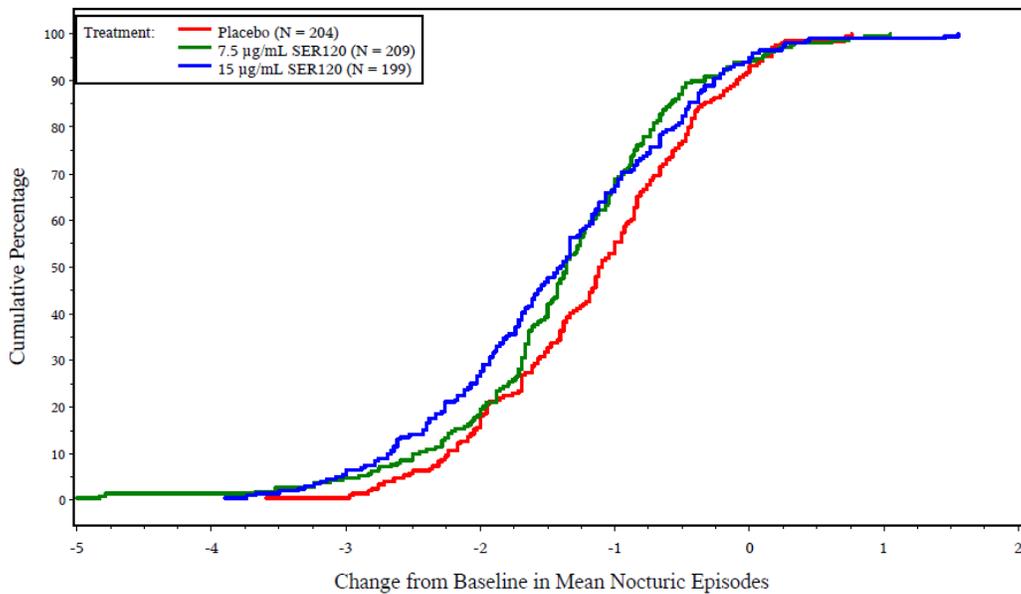
Figure 3 and Figure 4 presents the cumulative distribution function of nocturic episodes reduction from baseline. The CDF curves demonstrate that 1.5 mcg dose had a greater response rate than placebo to reach a specific number of nocturic episodes reduction. Similar trend was observed in study DB3 for the 0.75 mcg with smaller separation from placebo.

**Figure 3: CDF of Change from Screening to Treatment Period of Study in Mean Nocturnal Episodes for Study DB3 (ITT nocturnal polyuria patients)**



Source: Sponsor's response to IR, submitted on 11/03/2016

**Figure 4: CDF of Change from Screening to Treatment Period of Study in Mean Nocturnal Episodes for Study DB4 (ITT nocturnal polyuria patients)**



Source: Sponsor's response to IR, submitted on 11/03/2016

**Table 19: Summary of Secondary Efficacy endpoints – Study DB3 (ITT nocturnal polyuria patients)**

	<b>Placebo (N=145)</b>	<b>NOCTIVA 0.75 mcg (N=145)</b>	<b>NOCTIVA 1.0 mcg (N=146)</b>	<b>NOCTIVA 1.5 mcg (N=143)</b>
<b>Time from going to sleep to first Nocturic Void (or first morning void in the absence of nocturic void)</b>				
Baseline (SD)	2.3 (0.7)	2.4 (0.8)	2.4 (0.8)	2.4 (0.8)
Treatment Period (SD)	3.4 (1.3)	4.0 (1.5)	3.9 (1.5)	4.2 (1.5)
Change from baseline* (SE)	1.0 (0.12)	1.5 (0.12)	1.6 (0.12)	1.8 (0.12)
Difference vs. placebo (SE)		0.5 (0.16)	0.6 (0.16)	0.8 (0.16)
95% CI		0.22, 0.86	0.26, 0.90	0.47, 1.10
P-value (vs. placebo)		0.0009	0.0004	<0.0001
<b>Percentage of nights with 0 nocturic episodes</b>				
Baseline (SD)	0 (0)	0.0 (0)	0.0 (0)	0.1 (1.4)
Treatment Period (SD)	4.7 (13.0)	8.1 (17.9)	6.6 (16.2)	8.9 (18.7)
Change from baseline* (SE)	4.0 (1.51)	8.3 (1.48)	6.8 (1.48)	9.3 (1.51)
Difference vs. placebo (SE)		4.3 (1.99)	2.8 (1.99)	5.3 (1.98)
95% CI		0.42, 8.24	-1.07, 6.75	1.43, 9.22
P-value (vs. placebo)		0.0302	0.1550	0.0075
<b>Percentage of nights with ≤1 nocturic episodes</b>				
Baseline (SD)	1.0 (4.5)	1.5(5.9)	1.3 (4.8)	1.3 (4.9)
Treatment Period (SD)	32.7 (33.7)	42.8 (37.4)	41.8 (36.0)	45.7 (36.4)
Change from baseline* (SE)	30.2 (3.23)	39.5 (3.17)	39.7 (3.17)	44.7 (3.23)
Difference vs. placebo (SE)		9.3 (4.26)	9.0 (3.78)	15.5 (3.8)
95% CI		0.9, 17.7	1.2, 17.9	6.2, 22.8
P-value (vs. placebo)		0.0294	0.0257	0.0007
<b>Nocturic urine volume</b>				
Baseline (SD)	742.1 (298.5)	775.6 (283.0)	799.4 (391.2)	782.9 (319.3)
Final Week (SD)	607.8 (318.0)	538.1 (320.4)	566.9 (430.9)	515.0 (312.2)
Change from baseline* (SE)	-166.2 (31.9)	-243.1 (31.9)	-213.4 (32.2)	-251.4 (33.3)
Difference vs. placebo (SE)		-76.9 (42.8)	-47.2 (43.1)	-85.2 (42.9)
95% CI		-161.1, 7.3	-131.9, 37.4	-169.6, -0.8
P-value (vs. placebo)		0.0733	0.2737	0.0479

Source: Reviewer's analysis;

\*Change from baseline was obtained from an ANCOVA model.

**Table 20: Summary of Mean Nocturic Episodes by Week – Study DB3 (ITT nocturnal polyuria)**

Mean Nocturic Episodes By Week	Placebo (N=145)	NOCTIVA 0.75 mcg (N=145)	NOCTIVA 1.0 mcg (N=146)	NOCTIVA 1.5 mcg (N=143)
<b>Week 4</b>				
Change from baseline* (SE)	-1.0 (0.07)	-1.3 (0.07)	-1.2 (0.07)	-1.4 (0.07)
Difference vs. placebo (SE)		-0.32 (0.10)	-0.19 (0.10)	-0.44 (0.10)
95% CI		-0.53, -0.12	-0.39, 0.01	-0.65, -0.24
P-value (vs. placebo)		0.0018	0.0631	<.0001
<b>Week 6</b>				
Change from baseline* (SE)	-1.0 (0.07)	-1.4 (0.08)	-1.4 (0.08)	-1.5 (0.08)
Difference vs. placebo (SE)		-0.40 (0.10)	-0.35 (0.10)	-0.51 (0.11)
95% CI		-0.61, -0.20	-0.55, -0.14	-0.72, -0.30
P-value (vs. placebo)		0.0001	0.0009	<.0001
<b>Week 8</b>				
Change from baseline* (SE)	-1.2 (0.08)	-1.5 (0.08)	-1.5 (0.08)	-1.6 (0.08)
Difference vs. placebo (SE)		-0.34 (0.11)	-0.33 (0.11)	-0.42 (0.11)
95% CI		-0.55, -0.13	-0.53, -0.12	-0.63, -0.21
P-value (vs. placebo)		0.0014	0.0031	0.0001
<b>Week 10</b>				
Change from baseline* (SE)	-1.3 (0.08)	-1.5 (0.08)	-1.5 (0.08)	-1.6 (0.08)
Difference vs. placebo (SE)		-0.22 (0.11)	-0.19 (0.11)	-0.29 (0.11)
95% CI		-0.43, -0.01	-0.40, 0.02	-0.51, -0.08
P-value (vs. placebo)		0.0419	0.0734	0.0065
<b>Week 12</b>				
Change from baseline* (SE)	-1.3 (0.08)	-1.5 (0.08)	-1.5 (0.08)	-1.6 (0.08)
Difference vs. placebo (SE)		-0.22 (0.11)	-0.20 (0.11)	-0.31 (0.11)
95% CI		-0.43, -0.01	-0.42, 0.01	-0.52, -0.09
P-value (vs. placebo)		0.0411	0.0570	0.0048
<b>Week 14</b>				
Change from baseline* (SE)	-1.2 (0.08)	-1.5 (0.08)	-1.4 (0.08)	-1.6 (0.08)
Difference vs. placebo (SE)		-0.31 (0.11)	-0.20 (0.11)	-0.40 (0.11)
95% CI		-0.52, -0.09	-0.42, 0.01	-0.62, -0.19
P-value (vs. placebo)		0.0042	0.0613	0.0002

Source: Reviewer's analysis;

\*Change from baseline was obtained from an ANCOVA model.

**Table 21: Summary of Percentage of patients who had  $\geq 50\%$  Reduction in Nocturnal Voids by Week – Study DB3 (ITT nocturnal polyuria patients)**

$\geq 50\%$ Reduction in Nocturnal Voids	Placebo (N=145)	NOCTIVA 0.75 mcg (N=145)	NOCTIVA 1.0 mcg (N=146)	NOCTIVA 1.5 mcg (N=143)
<b>Week 4</b>				
n/N (%)	40/144 (27.8%)	60/145 (41.4%)	47/146 (32.2%)	67/143 (46.9%)
P-value (vs. placebo) †		0.0136	0.4108	0.0011
<b>Week 6</b>				
n/N (%)	48/144 (33.3%)	71/138 (51.5%)	60/138 (43.5%)	70/135 (51.9%)
P-value (vs. placebo) †		0.0018	0.0778	0.0025
<b>Week 8</b>				
n/N (%)	43/139 (30.9%)	64/135 (47.4%)	68/138 (49.3%)	65/130 (50.0%)
P-value (vs. placebo) †		0.0052	0.0022	0.0023
<b>Week 10</b>				
n/N (%)	62/137 (45.3%)	59/134 (44.0%)	63/132 (47.7%)	74/127 (58.3%)
P-value (vs. placebo) †		0.8558	0.6934	0.0439
<b>Week 12</b>				
n/N (%)	58/136 (42.7%)	67/133 (50.4%)	66/132 (50.0%)	74/126 (58.7%)
P-value (vs. placebo) †		0.1889	0.2313	0.0137
<b>Week 14</b>				
n/N (%)	45/134 (33.6%)	71/130 (54.6%)	58/131 (44.3%)	72/123 (58.5%)
P-value (vs. placebo) †		0.0005	0.0819	0.0001

Source: Reviewer's analysis;

† P-values were obtained from GENMOD model.

**Table 22: Summary of Secondary Efficacy endpoints – Study DB4 (ITT nocturnal polyuria patients)**

	<b>Placebo (N=204)</b>	<b>NOCTIVA 0.75 mcg (N=209)</b>	<b>NOCTIVA 1.5 mcg (N=199)</b>
<b>Impact of Night Time Voiding Score</b>			
Baseline (SD)	32.3 (17.0)	30.6 (17.1)	34.3 (17.9)
Treatment Period (SD)	21.4 (13.0)	19.4 (12.7)	19.1 (14.2)
Change from baseline* (SE)	-11.3 (1.0)	-13.1(1.0)	-14.9 (1.1)
Difference vs. placebo (SE)		-1.8 (1.3)	-3.5 (1.3)
95% CI		-4.2, 0.7	-6.1, -1.0
P-value (vs. placebo)		0.1598	0.0068
<b>Time from going to sleep to first Nocturic Void (or first morning void in the absence of nocturic void)</b>			
Baseline (SD)	2.5 (0.8)	2.4 (0.8)	2.4 (0.9)
Treatment Period (SD)	3.6 (1.4)	4.0 (1.5)	4.2 (1.7)
Change from baseline* (SE)	1.3 (0.31)	1.7 (0.13)	1.9 (0.13)
Difference vs. placebo (SE)		0.4 (0.16)	0.6 (0.16)
95% CI		0.11, 0.70	0.31, 0.92
P-value (vs. placebo)		0.0079	0.0001
<b>Percentage of nights with 0 nocturic episodes</b>			
Baseline (SD)	0	0	0
Treatment Period (SD)	4.5 (12.8)	6.9 (17.7)	10.0 (20.1)
Change from baseline* (SE)	4.6 (1.48)	6.9 (1.48)	10.6 (1.53)
Difference vs. placebo (SE)		2.3 (1.78)	6.0 (1.84)
95% CI		-1.17, 5.82	2.38, 9.60
P-value (vs. placebo)		0.1913	0.0012
<b>Percentage of nights with &lt;=1 nocturic episodes</b>			
Baseline (SD)	1.0 (4.3)	0.6 (3.6)	0.9 (4.5)
Treatment Period (SD)	32.5 (34.4)	37.9 (35.6)	42.7 (39.5)
Change from baseline* (SE)	34.2 (3.00)	39.9 (3.01)	43.7 (3.12)
Difference vs. placebo (SE)		5.7 (3.62)	9.4 (3.74)
95% CI		-1.4, 12.8	2.1, 16.8
P-value (vs. placebo)		0.1184	0.0117
<b>Nocturic urine volume</b>			
Baseline (SD)	833.5 (368.4)	847.0 (371.9)	813.9 (388.6)
Final Week (SD)	606.2 (318.6)	563.1 (324.2)	484.6 (273.7)
Change from baseline* (SE)	-204.1 (24.6)	-246.5 (24.8)	-335.2 (26.1)
Difference vs. placebo (SE)		-42.4 (30.1)	-131.1 (31.6)
95% CI		-101.6, 16.8	-193.2, -68.9
P-value (vs. placebo)		0.1601	<0.0001

Source: Reviewer's analysis.

\*Change from baseline was obtained from an ANCOVA model.

For the nocturnal polyuria patients, a subgroup analysis of the co-primary efficacy endpoints was conducted by age  $\geq 65$  and  $<65$  year old (see Table 25 to Table 28). Compared to placebo, both SER 0.75 mcg and 1.5 mcg doses had numerical greater treatment effects in the patients who were  $\geq 65$  year old than patients  $<65$  years old.

**Table 23: Change from Baseline in nocturic episodes per 24 hours by Age – DB3 (ITT nocturnal polyuria)**

Age	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
<65	Placebo	65	3.3 (0.9)	2.0 (1.0)		
	0.75 mcg	62	3.3 (0.8)	1.8 (1.0)	-0.15 (0.17)	-0.48, 0.18
	1.0 mcg	65	3.2 (0.9)	1.8 (1.0)	-0.13 (0.16)	-0.45, 0.19
	1.5 mcg	63	3.1 (0.6)	1.6 (0.8)	-0.24 (0.16)	-0.55, 0.08
≥65	Placebo	80	3.4 (1.1)	2.4 (1.1)		
	0.75 mcg	83	3.5 (0.9)	2.1 (1.2)	-0.35 (0.14)	-0.62, -0.08
	1.0 mcg	81	3.4 (1.1)	2.2 (1.2)	-0.23 (0.14)	-0.50, 0.05
	1.5 mcg	80	3.4 (0.9)	1.9 (1.0)	-0.50 (0.14)	-0.76, -0.23

Source: Reviewer's analysis.

**Table 24: Change from Baseline in nocturic episodes per 24 hours by Age– DB4 (ITT nocturnal polyuria)**

Age	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
<65	Placebo	79	3.2 (0.8)	1.9 (0.9)		
	0.75 mcg	86	3.4 (1.0)	1.8 (1.0)	-0.18 (0.15)	-0.48, 0.11
	1.5 mcg	83	3.3 (0.9)	1.8 (1.1)	-0.19 (0.15)	-0.49, 0.12
≥65	Placebo	125	3.3 (0.9)	2.3 (1.1)		
	0.75 mcg	123	3.4 (0.9)	2.1 (1.1)	-0.21 (0.12)	-0.45, 0.03
	1.5 mcg	116	3.5 (0.9)	2.1 (1.1)	-0.36 (0.13)	-0.60, -0.11

Source: Reviewer's analysis.

**Table 25: Percentage of Patients with ≥50% Reduction in Nocturic Voids by Age – DB3 (ITT nocturnal polyuria)**

≥50% Reduction in Nocturic Voids	Placebo (N=145)	NOCTIVA 0.75 mcg (N=145)	NOCTIVA 1.0 mcg (N=146)	NOCTIVA 1.5 mcg (N=143)
<b>&lt;65</b>				
n/N (%)	26/65 (40.0%)	28/62 (45.2%)	28/65 (43.1%)	35/63 (55.6%)
Diff. vs. placebo		5.2%	3.1%	15.6%
<b>≥65</b>				
n/N (%)	16/90 (20.0%)	31/83 (37.4%)	26/81 (32.1%)	35/80 (43.8%)
Diff. vs. placebo		17.4%	12.1%	23.8%

Source: Reviewer's analysis.

**Table 26: Percentage of Patients with ≥50% Reduction in Nocturic Voids by Age – DB4 (ITT nocturnal polyuria)**

≥50% Reduction in Nocturic Voids	Placebo (N=204)	NOCTIVA 0.75 mcg (N=209)	NOCTIVA 1.5 mcg (N=199)
<b>&lt;65</b>			
n/N (%)	28/79 (35.4%)	36/86 (41.9%)	44/83 (53.0%)
Diff. vs. placebo		6.5%	17.6%
<b>≥65</b>			
n/N (%)	26/125 (20.8%)	37/123 (30.1%)	50/116 (43.1%)
Diff. vs. placebo		9.3%	22.3%

Source: Reviewer's analysis.

## **4 SUMMARY AND CONCLUSIONS**

### **4.1 Statistical Issues and Collective Evidence**

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

In this review, the analysis results show that

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

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

### **4.2 Conclusions and Recommendations**

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

### **4.3 Labeling Recommendations**

Although NOCTIVA 0.75 mcg dose did not achieve statistical significance on both the co-primary efficacy endpoints, it had greater treatment effect in patients  $\geq 65$  years old than in patients  $<65$  years. This supports DBRUP's recommendation for approving the 0.75 mcg as the starting dose for patients who were  $\geq 65$  years old due the safety consideration.

## APPENDICES

### Demographics and Baseline Characteristics

**Table 27 Summary of Patient Demographics and Baseline Characteristics – DB3 (ITT)**

	NOCTIVA			Placebo (N = 186)	Overall (N = 734)
	1.5 mcg (N = 179)	1.0 mcg (N = 183)	0.75 mcg (N = 186)		
Age (SD) in years	66.0	66.1	66.3	66.0	66.1
Height (SD) in cm	170.9	171.4	171.1	171.4	171.2
Weight (SD) in kg	85.5	86.0	84.0	85.3	85.2
BMI (SD) in kg/m <sup>2</sup>	29.2	29.2	28.6	29.0	29.0
Gender (%)	Male	104 (58.1)	109 (59.6)	107 (57.5)	432 (58.9)
	Female (Postmenopausal)	74 (41.3)	73 (39.9)	79 (42.5)	296 (40.3)
	Female (Child Bearing Potential)	1 (0.6)	1 (0.5)	0 (0.0)	4 (2.2)
Race	Caucasian (%)	144 (80.4)	159 (86.9)	157 (84.4)	612 (83.4)
	Black (%)	20 (11.2)	18 (9.8)	15 (8.1)	74 (10.1)
	Asian (%)	5 (2.8)	2 (1.1)	4 (2.2)	17 (2.3)
	Hispanic (%)	8 (4.5)	4 (2.2)	8 (4.3)	23 (3.1)
	Other (%)	2 (1.1)	0 (0.0)	2 (1.1)	4 (2.2)

Source: Table 6 in the Applicant's study DB3 report.

**Table 28 Summary of Patient Demographics and Baseline Characteristics – DB4 (ITT)**

	NOCTIVA		Placebo (N = 260)	Overall (N = 782)	
	1.5 mcg (N = 260)	0.75 mcg (N = 262)			
Age (SD) in years	66.1 (9.2)	66.5 (8.8)	65.8 (9.0)	66.1 (9.0)	
Height (SD) in cm	169.9 (11.2)	169.7 (11.2)	170.1 (10.0)	169.9 (10.8)	
Weight (SD) in kg	88.4 (20.9)	85.5 (18.5)	86.3 (18.9)	86.7 (19.5)	
BMI (SD) in kg/m <sup>2</sup>	30.6 (6.8)	29.7 (5.8)	29.9 (6.5)	30.1 (6.4)	
Gender (%)	Male	147 (56.5)	145 (55.3)	438 (56.0)	
	Female (Postmenopausal)	107 (41.2)	110 (42.0)	324 (41.4)	
	Female (Child Bearing Potential)	6 (2.3)	7 (2.7)	7 (2.7)	20 (2.6)
Race	Caucasian (%)	188 (72.3)	204 (77.9)	592 (75.7)	
	Black (%)	40 (15.4)	26 (9.9)	39 (15.0)	105 (13.4)
	Asian (%)	6 (2.3)	4 (1.5)	1 (0.4)	11 (1.4)
	Hispanic (%)	24 (9.2)	25 (9.5)	20 (7.7)	69 (8.8)
	Other (%)	2 (0.8)	3 (1.1)	0 (0.0)	5 (0.6)

Source: Table 6 in the Applicant's study DB4.

## Subgroup Analysis Results

**Table 29: Change from Baseline in nocturic episodes per 24 hours by Gender – DB3 (ITT)**

Gender	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
Male	Placebo	112	3.4 (1.0)	2.2 (1.1)		
	0.75 mcg	107	3.4 (0.9)	2.1 (1.1)	-0.22 (0.11)	-0.44, 0.00
	1.0 mcg	109	3.4 (1.1)	2.2 (1.1)	-0.16 (0.11)	-0.38, 0.07
	1.5 mcg	104	3.2 (0.8)	1.8 (0.9)	-0.42 (0.11)	-0.64, -0.20
Female	Placebo	74	3.3 (0.9)	1.9 (1.0)		
	0.75 mcg	79	3.3 (0.7)	1.8 (1.0)	-0.22 (0.15)	-0.52, 0.07
	1.0 mcg	74	3.1 (0.9)	1.6 (1.0)	-0.18 (0.16)	-0.48, 0.13
	1.5 mcg	75	3.2 (0.8)	1.6 (1.0)	-0.30 (0.15)	-0.60, 0.00

Source: Reviewer's analysis and Tables 7.2.2 and 7.2.3 in DB3 study report.

**Table 30: Change from Baseline in nocturic episodes per 24 hours by Gender – DB4 (ITT)**

Gender	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
Male	Placebo	146	3.4 (0.9)	2.3 (1.1)		
	0.75 mcg	145	3.3 (0.9)	2.1 (1.1)	-0.15 (0.11)	-0.36, 0.06
	1.5 mcg	147	3.3 (0.9)	2.0 (1.1)	-0.20 (0.11)	-0.41, 0.01
Female	Placebo	114	3.1 (0.7)	1.8 (0.9)		
	0.75 mcg	117	3.3 (0.9)	1.8 (1.0)	-0.17 (0.12)	-0.41, 0.06
	1.5 mcg	113	3.3 (0.8)	1.7 (1.1)	-0.20 (0.13)	-0.46, 0.05

Source: Reviewer's analysis and Tables 7.2.2 and 7.2.3 in DB3 study report.

**Table 31: Percentage of Patients with ≥50% Reduction in Nocturic Voids by Gender – DB3 (ITT)**

≥50% Reduction in Nocturic Voids	Placebo (N=186)	NOCTIVA 7.5 ug/mL (N=186)	NOCTIVA 10 ug/mL (N=183)	NOCTIVA 15 ug/mL (N=179)
<b>Male</b>				
n/N (%)	32/112 (28.6%)	41/107 (38.3%)	35/109 (32.1%)	51/104 (49.0%)
Diff. vs. placebo		9.7%	3.5%	20.4%
<b>Female</b>				
n/N (%)	29/74 (39.2%)	36/79 (45.6%)	38/74 (51.4%)	42/75 (56.5%)
Diff. vs. placebo		6.4%	12.2%	17.3%

Source: Reviewer's analysis and Tables 8.2.2 and 8.2.3 in DB3 study report.

**Table 32: Percentage of Patients with ≥50% Reduction in Nocturic Voids by Gender – DB4 (ITT)**

≥50% Reduction in Nocturic Voids	Placebo (N=260)	NOCTIVA 7.5 ug/mL (N=262)	NOCTIVA 15 ug/mL (N=260)
<b>Male</b>			
n/N (%)	31/146 (21.2%)	43/145 (29.7%)	59/147 (40.1%)
Diff. vs. placebo		8.5%	18.9%
<b>Female</b>			
n/N (%)	43/114 (37.7%)	50/117 (42.7%)	62/113 (54.9%)
Diff. vs. placebo		5%	17.2%

Source: Reviewer's analysis and Tables 8.2.2 and 8.2.3 in DB4 study report.

**Table 33: Change from Baseline in nocturic episodes per 24 hours by Age – DB3 (ITT)**

Age	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
<65	Placebo	86	3.2 (0.8)	1.8 (1.0)		
	0.75 mcg	86	3.3 (0.8)	1.7 (1.0)	-0.16 (0.14)	-0.43, 0.11
	1.0 mcg	85	3.2 (0.9)	1.8 (1.1)	0.03 (0.14)	-0.24, 0.29
	1.5 mcg	85	3.1 (0.7)	1.5 (0.8)	-0.32 (0.13)	-0.59, -0.06
≥65	Placebo	100	3.4 (1.1)	2.3 (1.1)		
	0.75 mcg	100	3.4 (0.9)	2.1 (1.1)	-0.23 (0.12)	-0.48, 0.01
	1.0 mcg	98	3.3 (1.1)	2.1 (1.2)	-0.24 (0.12)	-0.48, 0.01
	1.5 mcg	94	3.3 (0.9)	1.9 (1.0)	-0.43 (0.12)	-0.67, -0.18

Source: Reviewer's analysis.

**Table 34: Change from Baseline in nocturic episodes per 24 hours by Age – DB4 (ITT)**

Age	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
<65	Placebo	116	3.2 (0.7)	1.9 (1.0)		
	0.75 mcg	117	3.3 (0.9)	1.8 (1.0)	-0.17 (0.12)	-0.40, 0.06
	1.5 mcg	116	3.2 (0.8)	1.7 (1.1)	-0.21 (0.12)	-0.44, 0.03
≥65	Placebo	144	3.3(0.9)	2.3 (1.1)		
	0.75 mcg	145	3.3 (0.9)	2.1 (1.1)	-0.20 (0.11)	-0.40, 0.01
	1.5 mcg	144	3.4 (0.9)	2.0 (1.0)	-0.30 (0.11)	-0.51, -0.08

Source: Reviewer's analysis.

**Table 35: Percentage of Patients with ≥50% Reduction in Nocturic Voids by Age – DB3 (ITT)**

≥50% Reduction in Nocturic Voids	Placebo (N=186)	NOCTIVA 7.5 ug/mL (N=186)	NOCTIVA 10 ug/mL (N=183)	NOCTIVA 15 ug/mL (N=179)
<b>&lt;65</b>				
n/N (%)	37/86 (43.0%)	41/86 (47.7%)	36/85 (42.4%)	52/85 (61.2%)
Diff. vs. placebo		4.7%	-0.6%	18.2%
<b>≥65</b>				
n/N (%)	24/100 (24.0%)	36/100 (36.0%)	37/98 (37.8%)	41/94 (43.6%)
Diff. vs. placebo		12%	13.8%	19.6%

Source: Reviewer's analysis.

**Table 36: Percentage of Patients with ≥50% Reduction in Nocturic Voids by Age – DB4 (ITT)**

≥50% Reduction in Nocturic Voids	Placebo (N=260)	NOCTIVA 7.5 ug/mL (N=262)	NOCTIVA 15 ug/mL (N=260)
<b>&lt;65</b>			
n/N (%)	42/116 (36.2%)	49/117 (41.9%)	60/116 (51.7%)
Diff. vs. placebo		5.7%	15.5%
<b>≥65</b>			
n/N (%)	32/144 (22.2%)	44/145 (30.3%)	61/144 (42.4%)
Diff. vs. placebo		8.1%	20.2%

Source: Reviewer's analysis.

**Table 37: Change from Baseline in nocturic episodes per 24 hours by Gender – DB3 (ITT)**

Race	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
White	Placebo	152	3.3 (0.9)	2.1 (1.0)		
	0.75 mcg	157	3.4 (0.9)	2.1 (1.0)	-0.23 (0.09)	-0.41, -0.04
	1.0 mcg	159	3.3 (1.0)	2.0 (1.1)	-0.18 (0.09)	-0.37, 0.00
	1.5 mcg	144	3.2 (0.8)	1.7 (1.0)	-0.42 (0.10)	-0.61, -0.24
Black or African American	Placebo	21	3.7 (1.2)	2.6 (1.0)		
	0.75 mcg	15	3.4 (0.7)	1.8 (1.0)	-0.38 (0.35)	-1.08, 0.33
	1.0 mcg	18	3.7 (0.8)	2.0 (1.2)	-0.45(0.41)	-1.30, 0.39
	1.5 mcg	20	3.3 (0.7)	1.9 (0.7)	-0.61 (0.29)	-1.20, -0.01
Other	Placebo	13	3.3 (1.0)	1.5 (1.2)		
	0.75 mcg	14	3.3 (0.8)	1.6 (1.0)	-0.08 (0.63)	-1.42, 1.26
	1.0 mcg	6	2.9 (0.8)	1.7 (1.2)	-0.65 (0.90)	-2.58, 1.27
	1.5 mcg	15	3.0 (0.8)	1.5 (0.9)	0.13 (0.65)	-1.27, 1.53

Source: Reviewer's analysis.

**Table 38: Change from Baseline in nocturic episodes per 24 hours by Gender – DB4 (ITT)**

Race	Treatment	# of patients	Baseline Mean	Treatment period mean	LS Mean change trt vs. placebo	95% CI
White	Placebo	200	3.2 (0.8)	2.1 (1.1)		
	0.75 mcg	204	3.3 (0.9)	1.9 (1.0)	-0.24 (0.09)	-0.41, -0.07
	1.5 mcg	188	3.3 (0.9)	1.9 (1.1)	-0.33 (0.09)	-0.50, -0.15
Black or African American	Placebo	39	3.5 (0.8)	1.9 (0.8)		
	0.75 mcg	26	3.6 (1.2)	2.2 (1.3)	0.44 (0.27)	-0.13, 0.94
	1.5 mcg	40	3.4 (0.9)	1.9 (1.1)	0.22 (0.22)	-0.23, 0.67
Other	Placebo	21	3.3 (0.8)	2.4 (1.2)		
	0.75 mcg	32	3.4 (0.9)	1.9 (0.9)	-0.53 (0.33)	-1.19, 0.12
	1.5 mcg	32	3.2 (0.7)	1.7 (0.9)	-0.44 (0.36)	-1.17, 0.28

Source: Reviewer's analysis.

**Table 39: Percentage of Patients with ≥50% Reduction in Nocturic Voids by Race – DB3 (ITT)**

≥50% Reduction in Nocturic Voids	Placebo (N=186)	NOCTIVA 0.75 mcg (N=186)	NOCTIVA 1.0 mcg (N=183)	NOCTIVA 1.5 mcg (N=179)
<b>White</b>				
n/N (%)	48/152 (31.6%)	62/157 (39.5%)	60/159 (37.7%)	74/144 (51.4%)
Diff. vs. placebo		7.9%	6.1%	19.8%
<b>Black or African American</b>				
n/N (%)	4/21 (19.1%)	7/15 (46.7%)	10/18 (55.6%)	9/20 (45.0%)
Diff. vs. placebo		27.6%	36.5%	25.9%
<b>Other</b>				
n/N (%)	9/13 (69.2%)	8/14 (57.1%)	3/6 (50.0%)	10/15 (66.7%)
Diff. vs. placebo		-17.9%	-19.2%	-2.5%

Source: Reviewer's analysis.

**Table 40: Percentage of Patients with  $\geq 50\%$  Reduction in Nocturic Voids by Race – DB3 (ITT)**

$\geq 50\%$ Reduction in Nocturic Voids	Placebo (N=260)	NOCTIVA 0.75 mcg (N=262)	NOCTIVA 1.5 mcg (N=260)
<b>White</b>			
n/N (%)	53/200 (26.5%)	73/204 (35.8%)	83/188 (44.2%)
Diff. vs. placebo		9.3%	15.7%
<b>Black or African American</b>			
n/N (%)	17/39 (43.6%)	8/26 (30.8%)	21/40 (52.5%)
Diff. vs. placebo		-12.8%	8.9%
<b>Other</b>			
n/N (%)	4/21 (19.1%)	12/32 (37.5%)	17/32 (53.1%)
Diff. vs. placebo		18.4%	34.0%

Source: Reviewer's analysis.

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/s/  
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JIA GUO  
01/11/2017

MAHBOOB SOBHAN  
01/11/2017

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 20-1656**      **Applicant: SERENITY PHARMACEUTICALS Stamp Date: 02/04/2016**  
CORP

**Drug Name: Desmopressin**      **NDA/BLA Type: New**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	√			By racial groups analysis was not conducted.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

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

If the NDA/BLA is not fileable from the statistical 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.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		√		Missing data handling approach is not clear to reviewer

File name: Statistics Filing Checklist for a New NDA\_201656

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

## **Requests to the Applicant on 74-day letter:**

1. In study protocol and statistical analysis plan for DB3, you pre-specified “missing data will be imputed as being equal to the data that are available”. Please clarify what this exactly means.
2. Provide analysis results for efficacy endpoints by racial subgroups for DB3 and DB4 respectively.
3. Submit the statistical programs for conducting efficacy analyses.
4. As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on [www.fda.gov/drugtrialsnapshot](http://www.fda.gov/drugtrialsnapshot).  
The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:
  - Information written in consumer-friendly language
  - “MORE INFORMATION” sections that provide more technical, data-heavy information
  - Information that focuses on subgroup data and analyses
  - Links to the PI for the product and to the FDA reviews at Drugs@FDA

We are requesting your assistance in populating the following tables.

**Table 1. Baseline Demographics, Pooled DB3 and BD4**

Demographic Parameters	Treatment Group(s)				Total (N=XX) n (%)
	7.5 µg/mL (N=XX) n (%)*	10 µg/mL (N=XX) n (%)*	15 µg/mL (N=XX) n (%)*	Placebo (N=XX) n (%)*	
<b>Sex</b>					
Male					
Female					
<b>Age</b>					
Mean years (SD)					
Median (years)					
Min, Max (years)					

File name: Statistics Filing Checklist for a New NDA\_201656

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

<b>Age Group</b>					
<65 years					
>=65 years					
<b>Race</b>					
White					
Black or African American					
Asian					
Hispanic					
Other					

Source:

\*Percentages are calculated based on the total number of subjects in the respective arm.

**Table 2 Subgroup Analysis of Each Co-primary Endpoint, Pooled DB3 and BD4**

Subgroup	7.5 µg/mL	10 µg/mL	15 µg/mL
	(N=xx)	(N=xx)	(N=xx)
<b>Endpoint</b>			
<b>Sex</b>			
Male	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Female	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
<b>Age Group</b>			
<65 years	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
>=65 years	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
<b>Race</b>			
White	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Black or African American	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Asian	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Hispanic	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Other	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

Source:

File name: Statistics Filing Checklist for a New NDA\_201656

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

xx (xx, xx) is the treatment effect vs. placebo and the 95% CI.

**Table 3 Subgroup Analysis of AEs, Pooled DB3 and BD4**

Subgroup	7.5 µg/mL (N=xxx)		10 µg/mL (N=xxx)		15 µg/mL (N=xxx)		placebo (N=xxx)	
	x (%)**	Total, n	x (%)**	Total, n	x (%)**	Total, n	x (%)**	Total, n
<b>Any TEAEs</b>								
<b>Sex</b>								
Male								
Female								
<b>Age Group</b>								
<65 years								
>=65 years								
<b>Race</b>								
White								
Black or African American								
Asian								
Hispanic								
Other								

Source:

\*\* Percentages are calculated based on the number of subjects in the subgroup per arm.

Provide a table in the same format for hyponatremia separately.

Jia Guo, Ph.D.	03/24/2016
Reviewing Statistician	Date
Mahboob Sobhan, Ph.D.	03/25/2016
Supervisor/Team Leader	Date

File name: Statistics Filing Checklist for a New NDA\_201656

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/s/  
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JIA GUO  
03/25/2016

MAHBOOB SOBHAN  
03/25/2016