CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201656Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA Number	201656
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Submission Dates	02/04/16, 03/21/16, 06/02/16 and 08/24/16
Submission Type	Original/ 505(b)(2)
PDUFA Date	12/04/16
Brand Name	Noctiva
Generic Name	Desmopressin
Dosage Form and Strength	0.75 mcg and 1.5 mcg desmopressin (equivalent to 0.83 mcg and 1.66 mcg of desmopressin acetate) nasal spray emulsion
Route of Administration	Intranasal
Proposed Indication	Treatment of nocturia in adults who wake up 2 or more times per night to void.
Applicant	SERENITY Pharmaceuticals, LLC
Associated IND	IND 076667
OCP Review Team	Jihong Shon, M.D., Ph.D.; Luning (Ada) Zhuang, Ph.D.; Doanh Tran, Ph.D.; Jeffry Florian, Ph.D.
OCP Final Signatory	Capt. E. Dennis Bashaw, Pharm D Division Director Division of Clinical Pharmacology Ⅲ

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1 EXECUTIVE SUMMARY

Desmopressin is a synthetic analogue of vasopressin, an antidiuretic hormone that is normally secreted by the pituitary gland. Desmopressin is currently approved for indications of treatment of central diabetes insipidus, primary nocturnal enuresis, type I von Willebrand's disease, and hemophilia A (initial US approval: 1978) in formulations of nasal solution, injection, and oral tablet.

The Applicant has developed a nasal spray of desmopressin acetate in a lower dose than those in the approved desmopressin products. The Applicant is seeking an indication for the treatment of nocturia in adults who awaken 2 or more times per night to void. The proposed dosage and administration is a single spray in either the left or right nostril each night approximately 30 minutes before going to bed. The proposed starting dose is 0.75 mcg desmopressin (equivalent to 0.83 mcg desmopressin acetate) each night for 2-4 weeks. Based on individual patient efficacy and tolerability, the dose may be increased to 1.5 mcg desmopressin (equivalent to 1.66 mcg of desmopressin acetate) each night. In support of this NDA, the Applicant conducted 10 clinical studies including two phase 1, one phase 2, five phase 3 and two long-term extension studies in either healthy volunteers or target patient population

This clinical pharmacology review focuses on the pharmacokinetics and pharmacodynamics of desmopressin and hyponatremia following administration of desmopressin nasal spray in patients with nocturia.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology III and Pharmacometrics have reviewed the information submitted for NDA 201656 of 0.75 mcg and 1.5 mcg desmopressin nasal sprays. The review team recommends approval of this NDA from a clinical pharmacology perspective, provided that the Applicant agrees to the risk mitigation elements proposed below to prevent serious hyponatremic events and an agreement on the language in the package insert is reached between the Applicant and the Division.

The key review issues with specific comments/recommendations are summarized below:

Review issues	Comments and recommendations
Supportive evidence of effectiveness	The primary evidence of effectiveness comes from two pivotal phase 3 trials in patients 50 years of age or older with nocturia where 1.5 mcg desmopressin nasal spray demonstrated statistically significant difference on two primary endpoints (mean number of nocturic episodes per night and percentage of patients with ≥ 50% reduction in the mean number of voids per night) when compared to placebo treatment. Supportive evidence of effectiveness comes from a dose-response analysis of data from the same phase 3 trials in patients with noturia and a dose-ranging study in healthy male and female subjects in water-loaded state assessing the antidiuretic effect of desmopressin.

Dosing regimen for the general patient population	The Applicant proposed a starting dose of 0.75 mcg each night for 2-4 weeks with an option to increase the dose to 1.5 mcg each night based on individual efficacy and tolerability. However, the clinical pharmacology review team recommends starting at 1.5 mcg desmopressin nasal spray each night approximately 30 minutes before going to bed in all patients with increased risk mitigation strategies such as restriction of fluid intake before and after administration of desmopressin and earlier monitoring of serum sodium (e.g., begin monitoring within one week rather than two weeks after initiation or dose increase). The conducted studies demonstrated that the 1.5 mcg desmopressin nasal spray was superior compared to placebo and produces a consistently higher clinical benefit compared to 0.75 mcg across all primary and secondary endpoints. However, the 1.5 mcg dose has a safety concern regarding the risk of hyponatremia in treated subjects, especially elderly patients (≥ 65 years old). In addition, the currently proposed risk management plans do not appear to be sufficient to prevent clinically significant hyponatremic events.
Dosing or alternative management plan in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic or extrinsic factors. Hyponatremic events are more prevalent in patients 65 years or older. Additional risk mitigation plans, such as that proposed for the general population, should also be applied in elderly patients. The use of desmopressin nasal spray should be restricted in adults younger than 50 years of age as such patients were not included in the phase 3 trials and may be expected to derive the greater benefit on placebo or with lifestyle modifications.
Bioavailability assessment between proposed dosing strengths	In the event that the lower dose is approved, there is a possibility that patients may want to use two sprays of the 7.5 mcg/mL strength instead of one spray of the 15 mcg/mL strength for the 1.5 mcg dose when there is a dose escalation. However, it has not been assessed as to whether the exposure of desmopressin is comparable between two sprays of the 7.5 mcg/mL strength and one spray of the 15 mcg/mL strength for the 1.5 mcg dose. A comparative bioavailability between two strengths for 1.5 mcg dosing should be evaluated.

1.2 Post-Marketing Requirement and Commitment

If both the 7.5 mcg/mL and 15 mcg/mL strengths will be approved, the following Post-Marketing Requirement (PMR) study is recommended:

- A comparative bioavailability study between two sprays of the 7.5 mcg/mL strength and one spray of the 15 mcg/mL strength.

2 SUMMARY OF CLINICAL PHARMACOLPGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Desmopressin is a synthetic analogue of vasopressin, an antidiuretic hormone, and has a highly selective affinity to vasopressin V2 receptors, which results in an increase in water reabsorption by the kidneys and a reduction in urine production. The antidiuretic effect (i.e., changes of urine osmolality and output) following administration of desmopressin nasal sprays has a duration of effect of 4 to 6 hours in healthy subjects in water-loaded state.

The clinical pharmacokinetics of desmopressin following administration of desmopressin nasal sprays is summarized as follows:

Absorption: The absolute bioavailability of desmopressin following administration of the proposed to-be-marketed desmopressin nasal spray products was not assessed.

The median time to reach maximum plasma concentration (T_{max}) was 0.25 hour for 0.75 mcg desmopressin nasal spray and 0.75 hour for 1.5 mcg desmopressin nasal spray. The mean (± S.D.) maximum concentration (C_{max}) and area under the curve to infinity (AUC_{inf}) values were 4.00 (± 3.85) pg/mL and 16.0 (±11.6) pg·h/mL for the 0.75 mcg dose and 9.11 (± 6.90) pg/mL and 41.3 (±19.5) pg·h/mL for the 1.5 mcg dose, respectively.

Distribution and elimination: Desmopressin is mainly excreted in urine. The mean half-life of desmopressin following administration of 0.75 mcg and 1.5 mcg desmopressin nasal sprays was 1.87- and 2.79-hour, respectively.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The Applicant's proposed dosing is to initiate treatment at 0.75 mcg desmopressin nasal spray each night approximately 30 minutes before going to bed for 2-4 weeks. Based on individual patient and efficacy, the dose may be increased to 1.5 mcg each night.

The clinical pharmacology review team recommends starting at 1.5 mcg desmopressin nasal spray each night approximately 30 minutes before going to bed in all patients. In the two phase 3 trials, 0.75 mcg desmopressin failed to demonstrate superiority on both co-primary endpoints compared to placebo. In addition, there was a consistent improvement on all primary and secondary endpoints for 1.5 mcg compared to 0.75 mcg. Finally, there was no specific subgroup where 0.75 mcg showed comparable benefit on 1.5 mcg, suggesting that all patients would derive increased clinical benefit from the higher dose.

While treatment with 1.5 mcg desmopressin nasal spray demonstrated a clinical benefit in patients with nocturia when compared to placebo treatment, there is still a safety concern regarding hyponatremia and water retention. Two pivotal phase 3 trials demonstrated that there is a risk of clinically significant hyponatremia at the proposed doses, particularly in elderly subjects 65 years of age and older on 1.5 mcg desmopressin. Specific warnings and strategies to prevent the risk of hyponatremia should be proposed to warrant that clinical benefit of the 1.5 mcg dose outweighs the risk. Specifically, the proposed risk mitigation strategy should include restriction of fluid intake before and after administration of

desmopressin and earlier monitoring of serum sodium (e.g., begin monitoring after one week of rather than two weeks after initiating therapy or increasing dose) to better mitigate hyponatremic events.

2.2.2 Therapeutic individualization

The Applicant proposed contraindication and warnings and precautions information to prevent a clinically significant hyponatremia. In addition, the Applicant proposed a monitoring scheme for serum sodium concentration and risk evaluation and mitigation strategy (REMS) to reduce the risk of hyponatremia. However, it is not clear whether these plans can prevent clinically significant hyponatremia in the target patient population who receive the currently proposed doses, especially for the 1.5 mcg desmopressin dose in elderly patients. Given that hyponatremic events are more prevalent in patients of 65 years or older, additional risk mitigation strategies such as restriction of fluid intake before and after administration of desmopressin and earlier monitoring of serum sodium (e.g., begin monitoring after one week rather than two weeks after initiating therapy or increasing dose) should be included in labeling.

The use of desmopressin nasal spray should be restricted in adults younger than 50 years of age due to lack of efficacy and safety data from the phase 3 trials. While patients in this age-range may be expected to have the least risk of hyponatremia with desmopressin, such patients would also derive the greater benefit on placebo or with lifestyle modifications. Combined with the lower prevalence in younger patients and as such patients were not included in the phase 3 trials, labeling should restrict the age of use to that of subjects included in the phase 3 trials.

Patients whose intranasal route is compromised (nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and chronic or acute rhinitis) should discontinue treatment with desmopressin nasal spray because there is a lack of information to support safety of this product in those conditions. In addition, the use of desmopressin nasal spray is not recommended when patients require treatment with other drugs via the nasal route.

2.3 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling revisions:

- Instruction regarding lack of interchangeability of two spray of the 0.75 mcg strength with one spray of the 1.5 mcg strength should be described in section of Dosage and Administration.
- Earlier and more frequent monitoring of serum sodium concentration after initiating therapy should be proposed, especially for elderly patients.
- Restriction of fluid intake before and after administration of desmopressin should be recommended to reduce the risk of hyponatremia and fluid retention.
- The use of desmopressin nasal spray should be discontinued in patients with the conditions that their intranasal routes are compromised such as nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and chronic or acute rhinitis
- Information of drug interaction (7 DRUG INTERACTION) should include a description of the clinical implication regarding clinically significant interactions with sufficient supporting evidence. (b) (4) .

The use of desmopressin nasal spray should be discontinued when patients require treatment with other drugs via the nasal route.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1. Development background of Noctiva

Desmopressin is a synthetic analogue of vasopressin, an antidiuretic hormone that is normally secreted by the pituitary gland and acts on the kidneys and blood vessels to retain water in the body. Desmopressin is currently approved for indications of treatment of central diabetes insipidus, primary nocturnal enuresis, type I von Willebrand's disease, and hemophilia A (initial US approval: 1978). The nasal solution, injection and oral tablet formulations are available for the currently approved indications in the United States (U.S.). The Applicant has developed a nasal spray formulation of desmopressin acetate for the treatment of nocturia in adults who wake up 2 or more times per night to void. The proposed dosages of desmopressin, 0.75 mcg and 1.5 mcg per spray (0.83 mcg and 1.66 mcg of desmopressin acetate, respectively), are lower than that (10 mcg of desmopressin acetate per spray) of the desmopressin nasal spray product approved for other indications.

3.1.2. Regulatory background of Noctiva

The Applicant submitted a NDA for Noctiva on February 4, 2016. This product is formulated as nasal spray emulsions in 7.5 mcg/mL or 15 mcg/mL of desmopressin (equivalent to 8.3 mcg/mL or 16.6 mcg/mL of desmopressin acetate, respectively). The proposed regimen is one spray in only one nostril in the evening approximately 30 minutes before going to bed. Each spray delivers 0.75 mcg desmopressin for the 7.5 mcg/mL strength and 1.5 mcg desmopressin for the 15 mcg/mL strength. In support of this NDA, the Applicant conducted 10 clinical studies including two phase 1, one phase 2, five phase 3 and two long-term extension studies in healthy subjects or target patient population. In addition, the Applicant submitted non-clinical studies and literature publications to support this NDA.

The pharmacokinetic profile of desmopressin following administration of 0.75 mcg or 1.5 mcg desmopressin nasal sprays in male or female patients with nocturia was characterized from a subset of patients in one of the phase 3 trials (Study DB3).

3.2 General Pharmacology and Pharmacokinetic Characteristics

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

<table>
<tr><td>QT Prolongation</td><td>The QT interval after daily administration of 1.5 or 0.75 mcg desmopressin nasal spray dose for 12 weeks showed no statistically significant change from baseline in patients with nocturia in two phase 3 trials (Study DB3 and DB4). Literature search did not result in any case report of adverse events related to QT prolongation following use of the approved desmopressin products.</td></tr>
<tr><td colspan="2">General Information</td></tr>
<tr><td>Bioanalysis</td><td>The plasma concentrations of desmopressin in clinical studies were analyzed using radioimmunoassay (RIA) or Liquid Chromatography–Mass Spectrometry / Mass Spectrometry (LC-MS/MS) (refer to appendix 4.1).</td></tr>
<tr><td>The pharmacokinetic profile of desmopressin following administration of Noctiva</td><td>The pharmacokinetic profile of desmopressin following administration of 0.75 mcg or 1.5 mcg desmopressin nasal sprays in male or female patients with nocturia was characterized. The median T_{max} was 0.25 hour for the 0.75 mcg dose and 0.75 hour for the 1.5 mcg dose. The C_{max} and AUC values tended to increase slightly greater than dose proportional increase between 0.75 mcg and 1.5 mcg. The plasma concentrations of desmopressin in most subjects were lower than the lower limit of quantitation (LLoQ: 2 pg/mL) after 6 hours post-dose. There is no accumulation between doses. Large interindividual variability in systemic exposure of desmopressin was observed (CV% of C_{max} and AUC_t: 96% and 146%, respectively, for 0.75 mcg desmopressin and 76% and 82%, respectively, for 1.5 mcg desmopressin).
Table 3.2-1. Summary of pharmacokinetics of desmopressin in patients with nocturia following administration of 0.75 or 1.5 mcg desmopressin nasal spray (Pharmacokinetic sub-study from DB3).
<table>
<tr><th></th><th>0.75 mcg</th><th>1.5 mcg</th></tr>
<tr><td>The number of subjects (male : female)</td><td>18 (9:9)</td><td>18 (9:9)</td></tr>
<tr><td></td><td colspan="2">mean ± S.D (the number of subjects)</td></tr>
<tr><td>C_{max} (pg/mL)</td><td>4.00 ± 3.85 (16)</td><td>9.11 ± 6.90 (15)</td></tr>
<tr><td>T_{max} (hour)</td><td>0.25 (0.25-0.5)* (12)</td><td>0.75 (0.25–3.0)* (15)</td></tr>
<tr><td>AUC_t (pg·h/mL)</td><td>5.13 ± 7.49 (16)</td><td>23.10 ± 18.95 (13)</td></tr>
<tr><td>AUC_{inf} (pg·h/mL)</td><td>15.96 ± 11.58 (9)</td><td>41.33 ± 19.54 (10)</td></tr>
<tr><td>$t_{1/2}$ (hour)</td><td>1.87 ± 1.13 (9)</td><td>2.79 ± 0.87 (10)</td></tr>
</table>
*median (range); AUC_t and AUC_{inf}, AUC to last detection time and to infinity
There is no relative bioavailability data between two sprays of the 0.75 mcg desmopressin strength and one spray of the 1.5 mcg desmopressin strength. In addition, comparative bioavailability between two sprays of the 7.5 mcg/mL strength and one spray of the 15 mcg/mL strength has not been assessed.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Bioavailability</td><td>Bioavailability of desmopressin nasal spray (1 mcg and 2 mcg desmopressin using a formulation strength of 5 mcg/mL) appeared to be approximately 8% compared to subcutaneous desmopressin injection formulation. However, bioavailability of</td></tr>
</table>

	the desmopressin nasal sprays in the proposed final concentrations of 7.5 mcg/mL and 15 mcg/mL was not assessed. Due to differences in the volume applied (0.2 – 0.4 mL vs. 0.1 mL) and formulation strength, no conclusion can be drawn regarding the relative bioavailability of the proposed to-be-marketed formulation.
Elimination	
Excretion	Desmopressin is mainly excreted in urine. Impaired renal function significantly affects the pharmacokinetics of desmopressin.

3.3 Clinical Pharmacology Questions

3.3.1 Does the available clinical pharmacology information provide supportive evidence of effectiveness?

Yes, supportive evidence of effectiveness for desmopressin nasal spray is available from the pivotal phase 3 trials, dose-response analyses from the phase 3 trials, and dose-response analyses of changes in urine osmolality and output in healthy volunteers.

- Efficacy results of 0.75 mcg to 1.5 mcg desmopressin nasal spray from pivotal phase 3 trials in patients with nocturia.

In two pivotal phase 3 trials (Studies DB3 and DB4) of patients 50 years of age or older with nocturia, treatment with 1.5 mcg desmopressin nasal spray for 12 weeks showed statistically significant difference on two primary efficacy endpoints: 1) mean number of nocturic episodes per night; and 2) percentage of patients with ≥ 50% reduction in the mean number of voids per night, compared to the placebo group (Table 3.3.1-1). Treatment with the lower dose, 0.75 mcg desmopressin, did not reach statistical significance for the percentage of patients with ≥ 50% reduction in mean nocturic episodes (ITT population in Study DB4 and both ITT and mITT populations in Study DB3). However, 0.75 mcg desmopressin did achieve statistical significance on change from baseline in mean nocturic episodes compared to placebo in both studies. The placebo group also showed a significant reduction in nocturic frequency from baseline. This result suggests that the placebo effect and (or) lifestyle modification would have clinically meaningful impact on the reduction of nocturic events in patients.

Table 3.3.1-1. Results of the primary efficacy variables in Studies DB3 and DB4 (Table adapted from Applicant's Summary of Clinical Efficacy)**.**

			Study DB 3			**Study DB 4**		
			1.5 mcg (N = 131)	**0.75 mcg** (N = 137)	**Placebo** (N = 133)	**1.5 mcg** (N = 196)	**0.75 mcg** (N = 197)	**Placebo** (N = 193)
mITT Population	**Mean nocturic episodes**	Screening	3.3	3.5	3.4	3.4	3.4	3.3
		Treatment period	1.9	2.1	2.4	2	2.2	2.4
		Change from baseline	-1.5	-1.3	-1.0	-1.4	-1.3	-1.1
		p-value	<0.0001	0.0229		0.0002	0.0179	
	# of patients = 50% reduction in mean nocturic episodes		55 (42.0%)	37 (27.0%)	24 (18.0%)	67 (34.2%)	47 (23.9%)	29 (15.0)
		p-value	<0.0001	0.0854		<0.0001	0.0364	

			(N = 179)	(N = 186)	(N = 186)	(N = 260)	(N = 262)	(N = 260)
ITT Population	**Mean nocturic episodes**	Screening	3.2	3.4	3.4	3.3	3.3	3.2
		Treatment period	1.7	1.9	2.1	1.8	1.9	2.1
		Change from baseline	-1.6	-1.4	-1.2	-1.5	-1.4	-1.2
		p-value	<0.0001	0.0093		0.0002	0.007	
	# of patients = 50% reduction in mean nocturic episodes		93 (52.0%)	77 (41.4%)	61 (32.8%)	120 (46.2%)	92 (35.1%)	74 (28.5%)
		p-value	0.0002	0.0899		<0.0001	0.122	

Mean nocturic episodes are the values of least square mean; p-value from comparison to placebo

Treatment with 1.5 mcg desmopressin demonstrated statistically significant differences on the secondary efficacy endpoints (time from going to sleep to the first nocturic episode, percent of nights with 0 nocturic voids, percent of nights with 0 or 1 nocturic void and the change in nocturnal urine volume from baseline) which reflect clinical elements related with nocturia when compared to the placebo group, except for the change in INTU score. The 0.75 mcg desmopressin showed statistically significant difference of time from going to sleep to the first nocturic episode, but showed inconsistent statistical results for the other secondary endpoints when compared to the placebo group. These results indicate that the 1.5 mcg dose had greater efficacy across all of the primary and secondary efficacy endpoints than the 0.75 mcg dose. The INTU score is a qualitative and quantitative tests of quality of life questionnaire and was evaluated only in Study DB4 (Table 3.3.1-2). Improvements in the INTU score are reflected by a reduction in the score from baseline. This score improved following both active treatments and for placebo. However, the INTU score for the 1.5 mcg dose showed greater improvement compared to either the placebo group or the 0.75 mcg group. There was no statistically significant difference between the two groups in the mITT population, and only the 1.5 mcg dose showed statistically significant improvements compared to the placebo group for the ITT population.

Table 3.3.1-2. Results of INTU score as a secondary variable in Study DB4 (Table adapted from Applicant's Summary of Clinical Efficacy)

			1.5 mcg (N = 181)	**0.75 mcg** (N = 190)	**Placebo** (N = 186)
mITT Population	INTU Impact Score	Screening	33.9	32.3	32.0
		Treatment period	20.6	23.0	23.1
		Change from baseline	-12	-9.7	-9.5
	p-value		0.0653	0.9010	
			(N = 243)	(N = 247)	(N = 249)
ITT Population	INTU Impact Score	Screening	33.0	31.8	31.3
		Treatment period	18.9	20.7	21.5
		Change from baseline	-14.1	-12.4	-11.5
	p-value		0.0225	0.4452	

The results values are least square means; p-value from comparison to placebo

- Dose-response of desmopressin nasal spray for primary endpoints

Dose-response analyses for the primary efficacy endpoints (i.e., change from baseline in mean nocturia episodes and percentage of patients with more than 50% reduction in nocturia episodes) were conducted based on data from DB3 and DB4. This assessment included patients on placebo, 0.75 mcg, 1.0 mcg

(DB3 only), and 1.5 mcg. The analyses showed that higher desmopressin doses were associated with a greater change from baseline in mean nocturia episodes (Figure 3.3.1-1). Similarly, based on the same dataset, the percentage of patients with more than a 50% reduction in nocturia episodes was observed to increase with increasing dose. These analyses support that higher desmopressin doses are associated with progressively increasing effect up to the highest evaluated dose (e.g., 1.5 mcg).

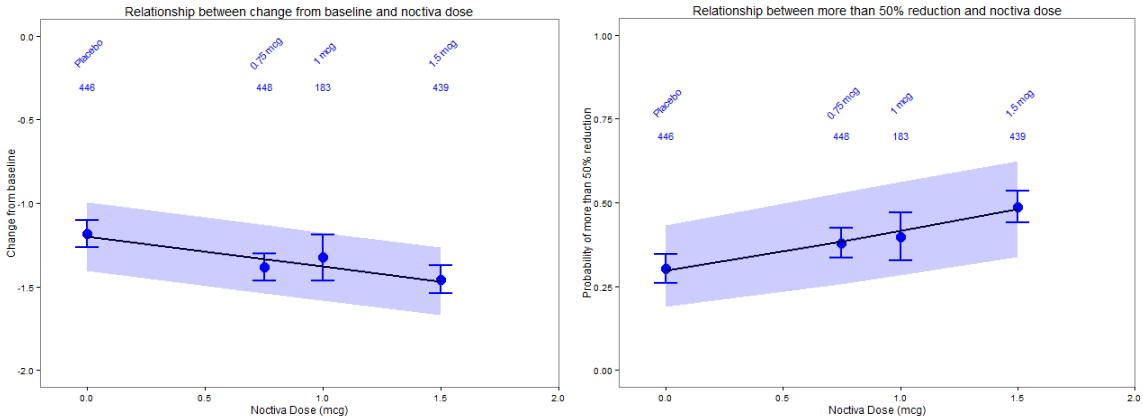
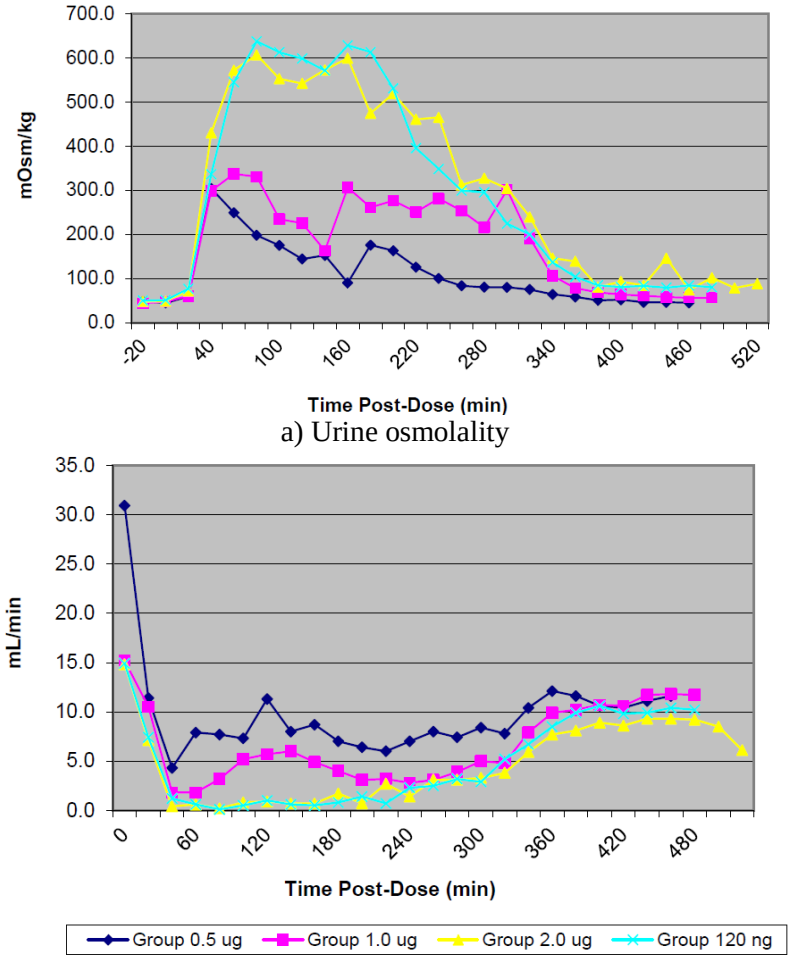


Figure 3.3.1-1 Dose-response relationship between desmopressin nasal spray dose and (left) nocturia episode change from baseline and (right) percentage of patients with more than 50% reduction in nocturia episode. The error bars represent 95% confidential interval of response rates. (*Reviewer's analysis based on data from DB3 and DB4)*

- Pharmacodynamics of desmopressin nasal spray in healthy subjects in water-loaded state

Dose-response study (Study 200801) of antidiuretic effect was conducted in healthy male and female subjects in water-loaded state using three dose strengths (0.5, 1 or 2 mcg desmopressin) of desmopressin nasal spray. Urine osmolality and output were assessed up to 8 hours post-dose (Figure 3.3.1-2). Tendency toward increase in urine osmolality and decrease in urine output from baseline were observed at the first assessment time, 20 minutes, after dosing of desmopressin nasal spray. The changes in both pharmacodynamic measurements reached a maximum effect within 1 hour and were effective for 4 to 6 hours following administration of desmopressin nasal spray. These pharmacodynamic changes appeared to be in a dose dependent manner. This temporal antidiuretic effect may delay urine production in night time following application of desmopressin nasal spray before going to bed and lead to a reduction in the number of voids per night (refer to individual summary of Study 200801). In particular, this pharmacological action and its duration may produce better clinical outcome in patients with nocturnal polyuria whose urine output occurs abnormally at night (defined as >33% urine production overnight).



a) Urine osmolality

b) Urine output

Figure 3.3.1-2. Mean urine osmolality (a) and output (b) over time following single dose of 0.5, 1, or 2 mcg desmopressin nasal spray or injection of 120 ng desmopressin in 12 healthy male or female subjects who were water-loaded prior to dosing (Figure adapted from Applicant's report of Study 200801)

Serum sodium concentrations were also assessed every 2 hours up to 8 hours post dose (Figure 3.3.1-3). The most-pronounced decreases in serum sodium concentrations following administration of desmopressin nasal spray were observed at 2 and 4 hours following administration of 0.5 and 1 mcg desmopressin nasal spray. While water-loaded condition may cause a trend toward lowered serum sodium concentrations, the time-course of change in serum sodium concentrations appears to be consistent with the duration of antidiuretic action based on changes in urine osmolality and output following administration of desmopressin nasal spray. These changes in serum sodium concentrations suggest that hyponatremic events may occur within a few hours after taking desmopressin nasal spray if fluid intake is not restricted before and after administration. For unclear reasons, administration of the 2 mcg dose did not lead to much decrease in serum sodium concentrations although the baseline sodium concentrations prior to this dose were slightly lower than those in the other study periods.

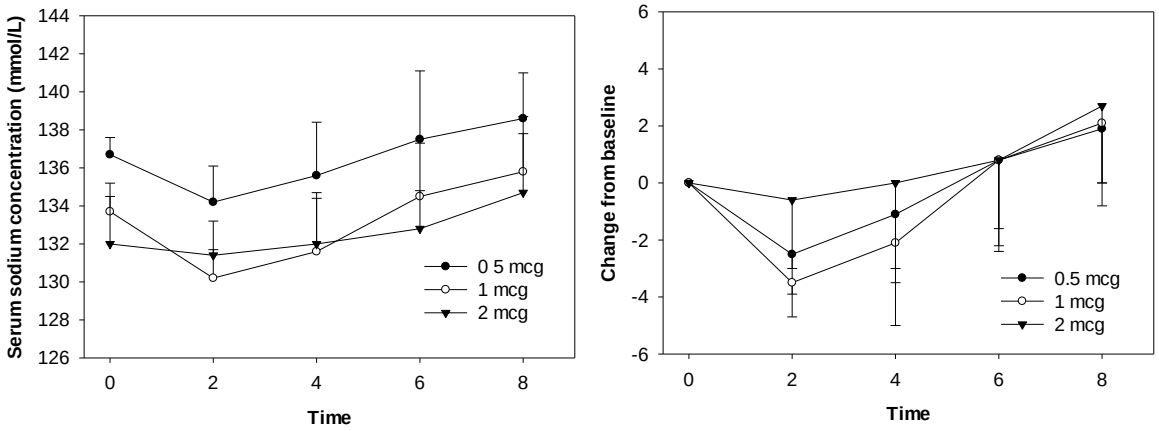


Figure 3.3.1-3. Mean serum sodium concentrations (left) and their changes from baseline (right) over time following single dose of 0.5, 1, or 2 mcg desmopressin nasal spray in 12 healthy male or female subjects who were water-loaded prior to dosing. Error bars indicate standard deviation (these graphs were generated based on the study results).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. The Applicant proposed a starting dose of 0.75 mcg each night for 2-4 weeks with the option to increase the dose to 1.5 mcg each night based on individual efficacy and tolerability. The clinical pharmacology review team's recommendation is to start treatment in all patients with 1.5 mcg, administered each night based on efficacy results discussed above in Section 3.3.1. In addition, the clinical pharmacology review team recommends additional risk mitigation strategies, such as a restriction of fluid intake before and after administration of desmopressin and a more intense monitoring of serum sodium concentration (e.g., begin monitoring after one week of treatment rather than waiting until week 2) to better mitigate the risk of hyponatremia.

- Incidence of hyponatremia following administration of desmopressin nasal spray

Data from the serum sodium concentrations monitored bi-weekly after randomization in two phase 3 studies (Studies DB3 and DB4) demonstrated that the patients that had a serum sodium concentration lower than 135 mmol/L were observed predominantly in active treatment groups. The incidence of hyponatremia appeared to trend up in a dose-dependent manner (Table 3.3.2-1). Five cases ((b) (6) in Study DB3 and (b) (6) in Study DB4) out of 6 patients who had a serum sodium concentration of 125 mmol/L or lower received 1.5 mcg desmopressin and older than 65 years. Out of them, three patients ((b) (6)) discontinued from the study due to hyponatremic event and one subject ((b) (6)) was reported to have a serious adverse event related to hyponatremia. One subject ((b) (6) in Study DB4) in the placebo group was hospitalized with hyponatremia (112 mmol/L) and possibly related symptoms and discontinued from the study.

Table 3.3.2-1. Incidence of subjects with serum sodium < 135 mmol/L after randomization at Day 15 including unscheduled visits in two phase 3 studies, DB3 and DB4 (reviewer's reanalysis using the applicant's dataset)

	Dose	**1.5 mcg**	**0.75 mcg**	**Placebo**
	Number of subjects	447	447	454

Serum sodium	< 135 mmol/L	61 (13.7%)	47 (10.5%)	17 (3.7%)
	< 130 mmol/L	13 (2.9%)	10 (2.2%)	1 (0.2%)
	≤ 125 mmol/L	5 (1.1%)	0 (0%)	1 (0.2%)

It is noted that blood samplings for serum sodium concentrations measured in all phase 3 studies were collected in the morning of next day after taking a dose the prior evening. Given that the decreases in serum sodium concentrations appears to be most pronounced a few hours following administration of desmopressin nasal spray, there may have been a larger number of patients who had a hyponatremic state in the early period (within 4 hours) after administration of desmopressin nasal spray compared to the observed rate based on next morning serum sodium concentration measurement, particularly if fluid intake was not restricted.

When considering the pharmacodynamics of desmopressin nasal spray and a noticeable trend in the incidence of hyponatremia in elderly patients with the 1.5 mcg dose, data of the serum sodium concentrations from phase 3 trials may not provide clear evidence to rule out a clinically significant hyponatremic risk in target patient population following administration of the proposed desmopressin doses. It may warrant an additional strategic plan beyond that proposed by the Applicant to prevent serious hyponatremic events.

- Management plan for mitigating the risk of hyponatremia with nasal spray desmopressin

The Applicant proposed contraindication and warnings and precautions information to prevent a clinically significant hyponatremia. The Applicant also proposed a monitoring scheme for serum sodium concentration and REMS to reduce the risk of hyponatremia. Details on the proposed strategies are listed below:

Contraindications, warnings and precautions to prevent a risk of hyponatremia

The Applicant proposed contraindication for the use of desmopressin nasal spray for patients with renal impairment (estimated glomerular filtration rate, eGFR < 50 mL/min/1.73 m^2), severe cardiac insufficiency (NYHA Class III and IV), known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion, diabetes insipidus, polydipsia, and uncontrolled hypertension. (b) (4)

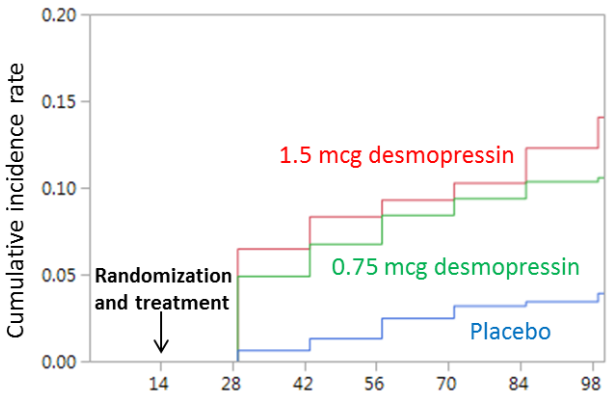
Risk management plan for a risk of hyponatremia

The Applicant proposed that serum sodium concentrations 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. If serum sodium concentrations decrease below the normal range during treatment, considerations should be given to discontinuing treatment until sodium concentrations return to normal. The Applicant also proposed a REMS to reduce the risk of hyponatremia. This plan is summarized as follows:

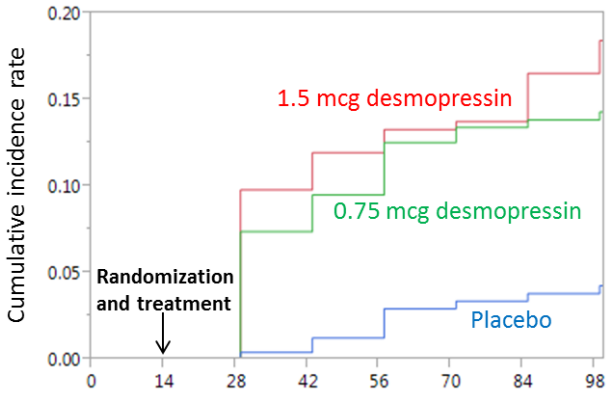
· All candidate patients should start at the lower dose of (0.75 mcg desmopressin).

- Only escalating patients to the higher dose of 1.5 mcg for those who do not have an adequate response to the lower dose and have serum sodium values in the normal range.
- Candidate patients should have serum sodium within the normal range.
- Candidate patients should have renal function with calculated glomerular filtration rates (GFRs) greater or equal to 50 mL/min/1.73m^2.
- All patients who have the first dose (0.75 mcg) or have a dose increase (1.5 mcg) should have serum sodium values monitored within 14 days of treatment and discontinue any patients whose serum sodium is low (<130 mmol/L).
- Patients who discontinued following dose increase may be re-challenged at the lower dose based on clinical judgment.
- Candidate patients should not use any systemic corticosteroid medications including inhaled pulmonary corticosteroids. All patients who are being treated with Noctiva should temporarily discontinue Noctiva while administering systemic or inhaled pulmonary corticosteroids and for at least 3 days after discontinuation of the steroid.
- All patients who are being treated with Noctiva and develop an intercurrent illness, especially gastrointestinal illnesses accompanied with vomiting and/or diarrhea and other conditions which affect normal eating and drinking, should temporarily discontinue using Noctiva until the intercurrent illness is fully resolved.
- Cautioning all patients with medical conditions which lead to sodium losing states such as adrenocortical insufficiency, salt losing nephropathies and other acute illnesses (e.g. systemic infections, fever, etc.) that may cause electrolyte imbalance.
- Ensuring that all patients and health care providers understand the risks associated with Noctiva in terms of hyponatremia and signs and symptoms to watch for through a patient package insert and medical education.

While there is general agreement with the Applicant's proposed risk mitigation plan, it is not clearly assessed as to whether these plans can prevent a clinically significant hyponatremia event in the target patient population who receive the currently proposed doses, especially for 1.5 mcg desmopressin in elderly patients. In addition, a time-course assessment of hyponatremia occurrence following treatment with desmopressin nasal spray was performed based on data from placebo, 0.75 mcg, and 1.5 mcg from DB3 and DB4 (Figure 3.3.2-1). These analyses showed that the first event in approximately 50% of patients who had a serum sodium concentration lower than 135 mmol/L was already observed at the earliest monitoring time, 2 weeks after starting an active treatment. It may suggest that monitoring earlier after initiating treatment of desmopressin nasal spray is necessary to detect a possible hyponatremic event in patients at the earliest time.



(a) All safety population



(b) 65 years or older

Figure 3.3.2-1. Cumulative incidence of first abnormal sodium concentration (<135 mmol/L) after randomization in all safety population (a) and elderly (65 years or older).

The reviewer has several additional recommendations as means to mitigate hyponatremic events. First, the currently proposed contraindications, warnings and precautions should include patients' conditions that can increase the risk of hyponatremia following administration of desmopressin nasal spray. Given that restriction of fluid intake during the night and after administration of desmopressin can prevent potential occurrence of hyponatremia and water intoxication, a caution of fluid restriction should be provided to patients with nocturia after administration of desmopressin nasal spray and during the nighttime. Second, the time-course analysis for hyponatremic events suggest that an earlier safety monitoring than that proposed by the Applicant (i.e. at day 7 rather than day 14) after initiating treatment of desmopressin nasal spray is necessary to detect a possible hyponatremic event in patients at the earliest time.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes. Given that hyponatremic event is significantly more prevalent in patients of 65 years or older when treated with the higher dose, 1.5 mcg desmopressin, an earlier serum sodium monitoring plan should be considered in elderly patients. Also, as patients less than 50 years of age were not included in the phase 3 trials and as such patients may obtain benefit on placebo or with lifestyle modifications, the recommendation is to restrict usage to only those patients ≥ 50 years of age. The Applicant proposed a contraindication for patients with an eGFR below 50 ml/min/1.73 m^2. The conducted phase 3 studies enrolled patients with an eGFR > 50 mL/min/1.73m^2 and there was no clear relationship between systemic exposure of desmopressin and patients' renal function within the range tested in the pharmacokinetic study in phase 3 trial (Study DB3). This supports the Applicant's proposal. The Applicant did not propose any restriction for the use of desmopressin nasal spray in nocturic patients with hepatic impairment. Given that there is insufficient information to support safe use of desmopressin in patients with hepatic impairment and liver disorders can cause water-electrolyte imbalance, patients with hepatic impairment should use desmopressin nasal spray with caution. Patients whose intranasal route is compromised (nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and chronic or acute rhinitis) should discontinue treatment with desmopressin nasal spray because there is a lack of information to support safety use of this product in those conditions. Additional details are discussed below.

- The effect of age on the occurrence of hyponatremia and efficacy outcomes

It has been well addressed that the elderly population is at risk of hyponatremia associated with the use of desmopressin (Lose et al. 2004; Choi et al. 2015). The approved nasal spray of desmopressin acetate has a recommendation that 'dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy'.

Data from two phase 3 trials of desmopressin nasal spray (Studies DB3 and DB4) demonstrated that the elderly group, 65 years or older, showed a much higher incidence of hyponatremia compared to the group younger than 65 years (Table 3.3.3-1). The cases that had a serum sodium concentration lower

than 130 mmol/L were mainly observed in the elderly subjects with active treatments. However, there was no significant difference in the incidence of hyponatremia between two elderly groups, ≥ 65 years and < 75 years versus ≥ 75 years. The pharmacokinetic study in DB3 trial showed that there was no significant difference in the systemic exposure of desmopressin between patients 65 years and older and those younger than 65 years (refer to summary of the pharmacokinetic study of DB3 trial). It may suggest that intrinsic and extrinsic factors in elderly population other than the pharmacokinetic characteristics may contribute to a higher incidence of hyponatremia.

Table 3.3.3-1. Incidence of subjects with serum sodium < 135 mmol/L after randomization at Day 15 including unscheduled visits in the age groups of two phase 3 studies, DB3 and DB4 (Reanalysis using the Applicant's dataset)

	Dose		**1.5 mcg**	**0.75 mcg**	**Placebo**
	Number of subjects	< 65	201	202	205
		65 ≤, < 75	145	145	152
		75 ≤	101	100	97
Serum sodium	< 135 mmol/L	< 65	17 (8.5%)	12 (5.9%)	7 (3.4%)
		65 ≤, < 75	24 (16.6%)	17 (11.7%)	5 (3.3%)
		75 ≤	20 (19.8%)	18 (18.0%)	5 (5.2%)
	< 130 mmol/L	< 65	0 (0%)	2 (1.0%)	0 (0%)
		65 ≤, < 75	8 (5.5%)	4 (2.8%)	1 (0.7%)
		75 ≤	5 (5.0%)	4 (4.0%)	0 (0%)
	≤ 125 mmol/L	< 65	0 (0%)	0 (0%)	0 (0%)
		65 ≤, < 75	3 (2.1%)	0 (0%)	1 (0.7%)
		75 ≤	2 (2.0%)	0 (0%)	0 (0%)

When considering the risk of hyponatremia, restriction of dose escalation to the 1.5 mcg dose can be considered in elderly population. However, based on the submitted efficacy data, the proposed lower dose, 0.75 mcg desmopressin, did not achieve its pre-specified endpoints compared to the placebo treatment. In addition, the middle dose, 1.0 mcg desmopressin, did not showed any difference in effectiveness compared to the 0.75 mcg dose (Study DB3). Thus, there is no alternative dosage option of desmopressin nasal spray for elderly population to achieve a desired effectiveness and prevent the risk of hyponatremia. This circumstance may warrant an intensive safety management plan in elderly patients such as earlier monitoring of serum sodium concentration as described in Section 3.3.2. However, there is no clear evidence as to whether the currently proposed monitoring scheme is sufficient to prevent the risk of hyponatremia in elderly patients or if more frequent monitor while on treatment (i.e., every week) may be needed.

For change from baseline in mean number of nocturia episodes and percentage of patients with more than 50% reduction of nocturia episodes, age was identified as a significant covariate effecting response despite a similar number of baseline episodes for each group. Younger age was associated with both a greater decrease from baseline in mean nocturia episodes as well as a greater percentage of patients achieving a 50% reduction in total episodes. This suggests that utilizing a lower dose in elderly as a means of mitigating safety would also result in a lower overall effect. Conversely, the analyses also show that younger patients are those that derive the greatest benefit, even on placebo. As patients less than 50 years of age were not included in the phase 3 studies, and because such patients would also

derive the largest benefit on placebo or lifestyle recommendations, the recommendation is to limit the treatment population to patients 50 years of age or older, as was studied in the phase 3 trials.

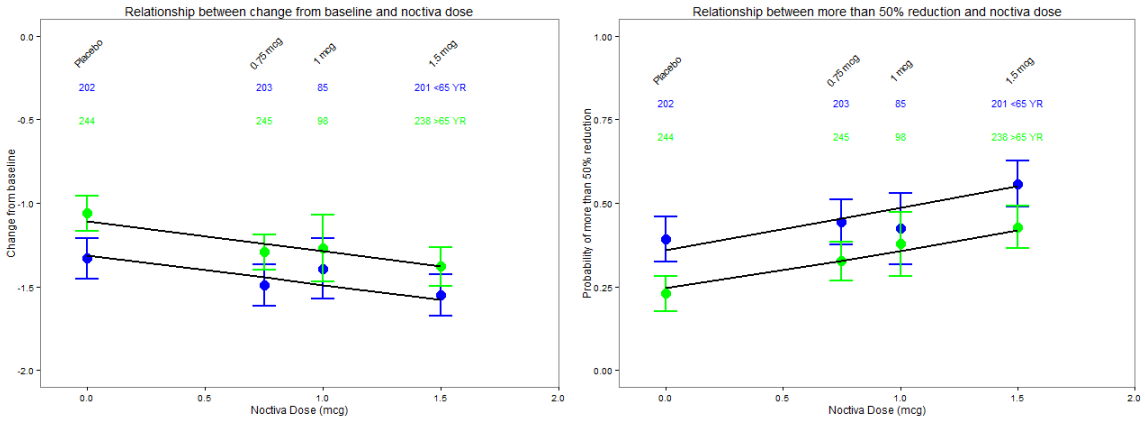


Figure 3.3.3-1 Dose-response relationship, grouped by age category, between desmopressin nasal spray dose and (left) nocturia episode change from baseline and (right) percentage of patients with more than 50% reduction in nocturia episode. The error bars represent 95% confidential interval of response rates. (*Reviewer's analysis based on data from DB3 and DB4)*

- The effect of sex on the occurrence of hyponatremia and efficacy outcome

It was reported that females showed more sensitive antidiuretic effect to desmopressin than males, which leads to gender difference in the incidence of hyponatremia following oral administration of up to 100 mcg desmopressin (Juul et al. 2011). Data from two phase 3 trials (Studies DB3 and DB4) demonstrated that a higher incidence of abnormal sodium concentration in female patients was not observed when compared to that in males (Table 3.3.3-2). In addition, the pharmacokinetic study in the DB3 trial demonstrated that sex did not have a significant impact on the systemic exposure to desmopressin following administration of desmopressin nasal spray (refer to summary of the pharmacokinetic study of DB3 trial).

Table 3.3.3-2. Incidence of subjects with serum sodium < 135 mmol/L after randomization at Day 15 including unscheduled visits in the age groups of two phase 3 studies, DB3 and DB4 (Reanalysis using the dataset)

	Dose		**1.5 mcg**	**0.75 mcg**	**Placebo**
	Number of subjects	Male	256	250	262
		Female	191	197	192
Serum sodium	< 135 mmol/L	Male	38 (14.8%)	24 (9.6%)	9 (3.4%)
		Female	23 (12.0%)	23 (11.7%)	8 (4.2%)
	< 130 mmol/L	Male	10 (4.0%)	5 (2.0%)	1 (0.4%)
		Female	3 (1.6%)	5 (2.5%)	0 (0%)
	≤ 125 mmol/L	Male	4 (1.6%)	0 (0%)	1 (0.4%)
		Female	1 (0.5%)	0 (0%)	0 (0%)

For change from baseline in mean number of nocturia episodes and percentage of patients with more than 50% reduction of nocturia episodes, sex was identified as a significant covariate effecting response despite a similar number of baseline episodes for each group. Female gender was associated with both a

greater decrease from baseline in mean nocturia episodes as well as a greater percentage of patients achieving a 50% reduction in total episodes. This result suggests that women could derive the same benefit as men if given a lower dose. However, women also had a greater response on placebo compared to men. Altogether, the information suggests that no dose adjustment is warranted based on sex as there is similar safety between genders and higher doses were associated with even greater responses in females compared to males.

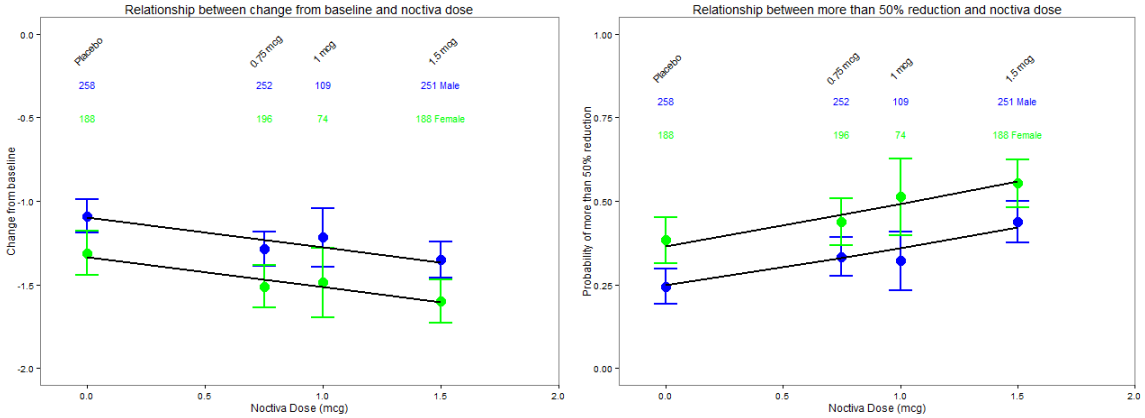


Figure 3.3.3-2 Dose-response relationship, grouped by sex, between desmopressin nasal spray dose and (left) nocturia episode change from baseline and (right) percentage of patients with more than 50% reduction in nocturia episode. The error bars represent 95% confidential interval of response rates. (*Reviewer's analysis based on data from DB3 and DB4)*

- The use of desmopressin nasal spray in patients with renal impairment

Desmopressin is excreted mainly by kidney and renal function has a significant impact on the systemic exposure of desmopressin. The currently approved desmopressin products are contraindicated in patients with moderate to severe renal impairment, which is defined as a creatinine clearance below 50 mL/min.

The Applicant conducted a pharmacokinetic study (Study 201002) in patients with renal impairment. This study demonstrated that the systemic exposure of desmopressin following administration of desmopressin nasal spray in patients with severe or moderate renal impairment significantly increased compared to matched patients with normal or mild renal impairment (refer to section 4.2.1). Pivotal phase 3 studies excluded subjects with an eGFR of less than 50 mL/min/1.73m^2. In the pharmacokinetic study of a subgroup of subjects in the phase 3 trial (Study DB3), while there was a trend toward an increase in dose-normalized desmopressin C_{max} and AUC_t with decreasing renal function based on eGFR, the relationship was not statistically significant between pharmacokinetic parameters and renal function. The Applicant proposed a contraindication for patients with an eGFR below 50 ml/min/1.73 m^2. Given that the conducted phase 3 studies enrolled patients with an eGFR > 50 mL/min/1.73m^2 and there was no clear relationship between systemic exposure of desmopressin and patients' renal function in the pharmacokinetic study in phase 3 trial (Study DB3), the Applicant's proposal is acceptable.

- The use of desmopressin nasal spray in patients with hepatic impairment

The currently approved desmopressin products do not have any restriction for use in patients with hepatic impairment. While the Applicant has not evaluated the effect of hepatic impairment on the

pharmacokinetic of desmopressin and the conducted phase 3 studies excluded patients with evidence of hepatic impairment or inflammation, they have not proposed any contraindication or dose modification for the use of desmopressin nasal spray in nocturic patients with hepatic impairment. Given that there is insufficient information to support safe use of desmopressin in patients with hepatic impairment and liver disorders can cause water-electrolyte imbalance, desmopressin nasal spray should be used with caution in patients with hepatic impairment. This patient population may need a close monitoring of safety following administration of desmopressin nasal spray.

- The use of desmopressin nasal spray in patients whose nasal routes are compromised

When the intranasal route is compromised (nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and chronic or acute rhinitis), it may affect the absorption of desmopressin after administration of desmopressin nasal spray. However, the absorption profile in patients with those conditions (e.g. rhinitis) has not been assessed. The Applicant submitted the adverse event profile in the subgroups of the patients who had a medical history of rhinitis at baseline in two phase 3 trials. There was no noticeable difference in the adverse events in this subgroup compared to the general population. There were a total of 13 patients who reported an adverse event of rhinitis during the study (5 on placebo, 5 on 0.75 mcg desmopressin and 3 on 1.5 mcg desmopressin). Safety information in active period of rhinitis among the treatment groups was not submitted.

This reviewer concluded that the current information that the Applicant submitted is not sufficient to support safe use in patients whose intranasal routes are compromised. Therefore, patients whose intransal route is compromised should discontinue treatment with desmopressin nasal spray during active period of those conditions.

3.3.4 Are there any clinically relevant drug-drug interactions and what is the appropriate management strategy?

Yes. Desmopressin nasal spray should be used with caution and have a close monitoring of serum sodium concentration when treated concomitantly with drugs that may cause water retention and lower serum sodium concentrations. A clinically significant pharmacokinetic interaction of desmopressin nasal spray with concomitant drugs of which administration is via a non-nasal route is unlikely to happen. However, concomitant use of other drugs via the nasal route such as intranasal decongestants may affect the absorption profile of desmopressin. (b) (4) However, given that the use of desmopressin nasal spray is not recommended in patients with active rhinitis and drug-drug interaction potential between desmopressin nasal spray and nasally administered drugs has not been assessed, the use of desmopressin nasal spray is not recommended when patients require treatment with other drugs via the nasal route. Additional details are provided below.

- Concomitant medication of drugs that increase the risk of water intoxication with hyponatremia

Concomitant administration of drugs which have a potential of inappropriate water reabsorption and electrolyte imbalance leads to increase the risk of water intoxication and hyponatremia. Pivotal phase 3

studies excluded subjects who were on the medication of loop diuretics and systemic steroids. It is found that 4 patients ((b) (6) in Study DB3 and (b) (6) in Study DB4) who had serum sodium ≤ 125 mmol/L in the 1.5 mcg desmopressin group had received systemic or inhaled steroid while taking a corticosteroid was contrary to the protocol. This finding suggests that concomitant medication of systemic steroids is a major contributing factor to the occurrence of hyponatremia in patients who are on treatment of desmopressin nasal spray. The Applicant proposed warnings and precautions information regarding concomitant use of diuretics and corticosteroids. In addition, the proposed label includes the caution regarding the concomitant administration of drugs that may cause water retention and increase the risk for hyponatremia such as tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine.

- Concomitant medication of other drugs via a non-nasal route which are absorbed into the systemic circulation

The Applicant did not perform any study to evaluate a potential pharmacokinetic interaction with other drugs. Desmopressin is a small peptide molecule (1.2 kDa) and filtrated rapidly through the kidneys. Desmopressin can be degraded by non-specific proteolytic enzymes such as peptidases although it is not known as to how much this metabolic pathway contributes to total elimination of desmopressin in human (Janaky et al. 1984; Andersson et al. 1988). When considering these excretion and metabolic properties, desmopressin nasal spray may have minimal potential of pharmacokinetic interaction with concomitant drugs administered via a non-nasal route which are absorbed into the systemic circulation.

- Concomitant medication of other drugs via the nasal route

Concomitant use of other drugs via the nasal route such as intranasal decongestants may affect absorption profile of desmopressin. The Applicant submitted the distribution of patients who took concomitant nasal spray for allergic rhinitis in two phase 3 trials (Studies DB3 and DB4). The proportion of those patients in each treatment group was 4.1% for 1.5 mcg desmopressin, 2.6% for 0.75 mcg desmopressin and 2.5% for placebo. The concomitant intranasal drugs included corticosteroids, antihistamines and decongestants. The Applicant described that there was no difference in treatment effect in patients using concomitant nasal spray, but did not provide any safety information in those patients.

Intranasal decongestants relieve inflamed blood vessels via local vasoconstriction. It is not clear as to whether this physiologic change in nasal mucosa affects absorption of desmopressin applied via the nasal route. The effect of nasal decongestant on administration of testosterone and nicotine via the nasal route has been reported. Nasal decongestant containing xylometazoline had a minimal effect on the exposure of both drugs in patients with rhinitis (Nicotrol®NS prescribing information; Natesto nasal gel prescribing information). However, the absorption profile of desmopressin when desmopressin nasal spray is concomitantly used with other drugs via the nasal route was not evaluated.

Given that the use of desmopressin nasal spray is not recommended in patients with active rhinitis and interaction potential between desmopressin nasal spray and nasally administered drugs has not been assessed, desmopressin nasal spray is not recommended when patients take other drugs via the nasal route.

3.3.5 Is one spray of 1.5 mcg desmopressin switchable to two sprays of 0.75 mcg desmopressin?

No. Comparative bioavailability between one spray of 1.5 mcg desmopressin and two sprays of 0.75 mcg desmopressin has not been assessed and switching between such dosing methods should not be permitted.

The Applicant proposed two desmopressin strengths, the 7.5 mcg/mL for the 0.75 mcg dose and the 15 mcg/mL for the 1.5 mcg dose, respectively. While the clinical pharmacology review team is recommending against approval of the low dose strength, such an option may be included in labeling. In the event that such a dosing option is included, there is also a possibility that patients may want to use two sprays of the 7.5 mcg/mL strength instead of one spray of the 15 mcg/mL strength for the 1.5 mcg dose when there is a dose escalation. However, comparative bioavailability between two desmopressin strengths was not assessed. Thus, two sprays of the 7.5 mcg/mL strength should not be used for 1.5 mcg dosing because an equivalency between two sprays of the 7.5 mcg/mL strength and one spray of the 15 mcg/mL strength has not been established.

The pharmacokinetic study (Study 200802) using the concentration of the 5 mcg/mL strength showed that the dose of 1 mcg desmopressin applied into two nostrils in split (one spray in each nostril) had higher exposure (more than 2-fold based on AUC_t) of desmopressin than when the same dose was applied into one nostril (two sprays in one nostril) (refer to individual study summary of Study 200802). This result suggests that the exposure of desmopressin following desmopressin nasal spray may increase when the applied dose is divided and given in both nostrils than given in one nostril. In addition, the proposed two strengths of desmopressin nasal spray contain same amount of cyclopentadecanolide (2 mg/spray) as an enhancer. If patients use two sprays of the 7.5 mcg/mL strength for the 1.5 mcg dose, a two-fold higher amount of enhancer would be applied when compared to one spray of the 1.5 mcg/mL. It may lead to enhance bioavailability of desmopressin following two sprays of the 7.5 mcg/mL strength compared to one spray of the 15 mcg/mL strength. These circumstances may warrant that a safety concern following the use (two sprays) of the 7.5 mcg/mL strength for the 1.5 mcg dose should be raised.

Given that there is a safety concern regarding hyponatremia and water retention for the 1.5 mcg desmopressin dose and it has not been assessed as to whether the exposure of desmopressin is comparable between two sprays of the 7.5 mcg/mL strength and one spray of the 15 mcg/mL strength, a comparative bioavailability study between both strengths for 1.5 mcg dosing should be conducted as a PMR study.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The plasma concentrations of desmopressin in clinical studies were analyzed using validated RIA or LC-MS/MS. The results of bioanalytical methods are summarized in table 4.1-1.

Table 4.1-1. Bioanalytical methods and their performance characteristics for the measurement of desmopressin in clinical study samples

Methods	Affected studies	Quality control samples	Performance characteristics				Long term stability
			Intra-run accuracy	Intra-run precision	Inter-run accuracy	Inter-run precision	
RIA	RIA200801, 200802, 200901(DB1) 201001201002	2.5pg/mL (LLoQ) 5 -40 pg/mL 50pg/mL (ULoQ)	-18.3% -15.2 - -7.6% -8.2%	13.8% 3.9- 11.8% 23.7%	-2.9% -5.1 - +2.5% -8.9%	15.2% 10.8- 17.1 % 8.7%	Up to 367 days at -20°C
LC-MS/MS	201101(DB3)	2pg/mL (LLoQ) 6-200 pg/mL	+4.0 - +15.9% -5.5 - +3.9%	7.4 – 13.5% 1.2- 9.8%	+9.7% -3.9 - -0.6%	11.6% 2.5- 7.2 %	Up to 79 days at -20°C

ULoQ: Upper limit of quantification

It is noted that the performance of the quality control determinations for the applied RIA method did not meet the Agency's acceptance criteria (≤ 20% for precision [CV%] and within ±20% for accuracy at the LLoQ and ≤15% or within ±15% at all other concentrations). However, the Applicant determined this performance to be acceptable based on the acceptance criteria proposed in their bioanalytical plan (< 25% for precision [CV%] and within ±25% for accuracy at the LLoQ and ULoQ and <20% or within ±20% at all other concentrations). It is noted that clinical pharmacokinetic information for the proposed to-be-marketed products is provided from the pharmacokinetic assessment within Study DB3, which used the LC-MS/MS method.

A number of concentrations of desmopressin in the blood samples from the clinical studies using RIA method were lower than its LLoQ (2.5 pg/mL). LC-MS/MS method used for the pharmacokinetic study in Study DB3 had a better detection limit (2 pg/mL). Cross-comparison of pharmacokinetic parameters following administration of 0.75 mcg desmopressin between Study DB1 using RIA and Study DB3 using LC-MS/MS showed that C_{max} and AUC values were greater by around 2-fold in Study DB3 than Study DB1 (refer to summaries of Study DB1 and Study DB3). Pooled pharmacokinetics analysis also identified the bioanalytical method as a critical factor in the desmopressin plasma concentration.

4.2 Clinical Pharmacology Assessment

4.2.1 The pharmacokinetic assessment of desmopressin following administration of desmopressin nasal spray

- Clinical pharmacokinetics of the to-be-marketed desmopressin nasal spray products

The pharmacokinetic profile of desmopressin following administration of 0.75 mcg, 1 mcg and 1.5 mcg desmopressin nasal sprays in a subset of the patients who participated in the DB3 study was characterized (Table 3.2-1: refer to summary of the pharmacokinetic study of the DB3 trial). The effect of intrinsic factors including age, sex, body weight and renal function on the pharmacokinetics of desmopressin was also assessed using this dataset. There was no significant difference in the dose-normalized C_{max} and AUC_t of desmopressin between the elderly group (65 years of age and older) and the group younger than 65 years of age. There was no significant difference in the dose-normalized C_{max} and AUC_t of desmopressin between gender groups. The dose-normalized C_{max} and AUC of desmopressin tended to be decreased in a body weight-dependent manner, but showed no significant relationship with the patients' body weight (refer to summary of the pharmacokinetic study of the DB3 trial).

- Pooled pharmacokinetic analysis

The Applicant performed pooled pharmacokinetic analysis using data from the 5 clinical studies. This analysis did not identify any significant covariate out of intrinsic factors on the pharmacokinetic parameters of desmopressin (refer to individual study summary of pooled pharmacokinetic analysis). These results were consistent with the finding from sub-analysis from the DB3 trial.

- Effect of renal impairment on the pharmacokinetics of desmopressin nasal spray

It has been well addressed that renal excretion is a major elimination route of desmopressin following its systemic administration (Fjellestad-Paulsen et al. 1993; Agersø, et al. 2004). The Applicant conducted a pharmacokinetic study of nasal spray formulation in subjects with impaired renal function. The terminal half-life was significantly prolonged in patients with severe or moderate renal impairment (3.4 ± 1.8 hour, n=4) compared to matched patients (1.1 ± 0.2 hour, n=3) with normal or mild renal impairment. The AUC_t increased by approximately three-fold (4.7 ± 4.3 pg·h/mL, n=8 vs. 1.6 ± 1.7 pg·h/mL, n=9) in patients with severe or moderate renal impairment compared to matched patients with normal or mild renal impairment (refer to individual study summary of Study 201002). This result suggests that impaired renal function results in a significant increase in the systemic exposure of desmopressin, which is consistent with the finding from the study of desmopressin injection product (Agersø, et al. 2004). However, in this study, a number of concentrations of desmopressin were below the LLoQ (RIA method, 2.5 pg/mL). In the pharmacokinetic study of a subgroup of subjects in the DB3 phase 3 trial, there was a trend toward an increase in dose-normalized C_{max} and AUC_t of desmopressin with decreasing renal function. However, the relationship between PK parameters and patients' eGFR was not statistically significant. It is noted that this study did not include subjects with an eGFR of less than 50 mL/min/1.73m^2. This exclusion criterion may lead to the observation of no significant association between systemic exposure of desmopressin and eGFR.

- Metabolism of desmopressin

Desmopressin is a peptide molecule which can be degraded by proteolysis (Di. 2015). A study in male rats demonstrated that desmopressin is metabolized by proteolystic degradation in the liver and kidney (Janaky et al. 1984). It may suggest that this peptide catabolism is involved in the elimination of desmopressin in human. However, it is not known as to how much this catabolic pathway contribute to total elimination of desmopressin in human and which organ, liver, kidneys and others, is mainly involved in this non-specific metabolism, particularly when desmopressin is administered via the nasal route.

- Relative bioavailability of desmopressin following administration of desmopressin nasal spray

The systemic exposure of desmopressin following 0.5, 1 and 2 mcg doses using a desmopressin nasal spray formulation with a desmopressin concentration of 5 mcg/mL was compared to that following subcutaneous injection of 120 ng desmopressin (Study 200801). Relative bioavailability of desmopressin nasal spray appeared to be approximately 8% (7.8% for 1 mcg desmopressin and 9.1% for 2 mcg desmopressin, and data not evaluable for the 0.5 mcg dose) compared to that of subcutaneous desmopressin injection (refer to individual study summary of 200801). However, this comparative pharmacokinetic study used a higher dosing volume (0.2 mL and 0.4 mL for the 1 mcg and 2 mcg doses, respectively compared to 0.1 mL proposed for labeling) and did not use the final concentrations (7.5 mcg/mL and 15 mcg/mL) of desmopressin nasal spray that the Applicant proposed. Thus, absolute bioavailability of desmopressin following administration of the proposed desmopressin nasal spray products is not known.

4.2.2 Exposure-response assessment following administration of desmopressin nasal spray

The Applicant analyzed the exposure-response relationship using the pharmacokinetic sub-population in the DB3 phase 3 trial. The AUC_t of desmopressin appeared to be higher in the responder group than the non-responder group following administration of 0.75 and 1.5 mcg desmopressin nasal sprays, but this trend was not observed in 1 mcg treatment (refer to summary of the pharmacokinetic study of the DB3 trial). In general, the distribution of individual AUCt appeared overlapped between the responders and non-responder in each treatment group. This data-set may have limitations for exposure-response analysis for the following reasons: 1) A limited number of subjects per the responder or non-responder groups, 2) Large interindividual variability of parameters among the patients and 3) A number of blood samples in the study population were below the LLoQ. Reviewer analyses instead focused on dose-response analyses.

4.2.3 Dose-response safety analysis for hyponatremia events

The same dataset of dose-response analysis for efficacy was used for safety. The primary endpoint was defined as percentage of patients with serum sodium concentration less than a certain value including 125, 130, 135 mmol/L. As there is no definitive criteria to define hyponatremia regarding serum sodium concentration cut-off, all three cut-off values (125, 130 and 135 mmol/L) were in the Reviewer's analysis. The dose-response analysis for hyponatremia was plotted in Figure 4.2.3-1. For cut-off of 125 mmol/L, the trend is not significant, which may be due to the low event of patients with serum sodium concentration less than 125 mmol/L. For higher cut-off values (130 and 135 mmol/L), there were obvious

trends showing that the higher dose and the higher percentage of patients with hyponatremia. The covariate analysis illustrated that only age was statistically significant for cut-off values of 130 and 135 mmol/L, but not 125 mmol/L (Figure 4.2.3-2). Gender was not identified as a significant covariate for all cut-off values.

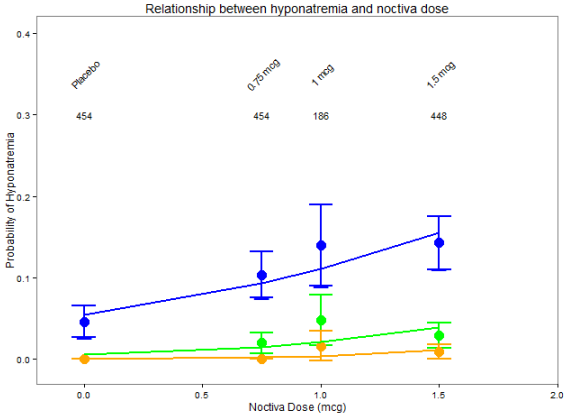


Figure 4.2.3-1 Dose-response relationship between desmopressin nasal spray dose and percentage of patients with hyponatremia defined as less than 125 mmol/L (orange), 130 mmol/L (green), and 135 mmol/L (blue). The error bars represent the 95% confidential interval of response rates. (*Reviewer's independent analysis based on data from DB3 and DB4*)

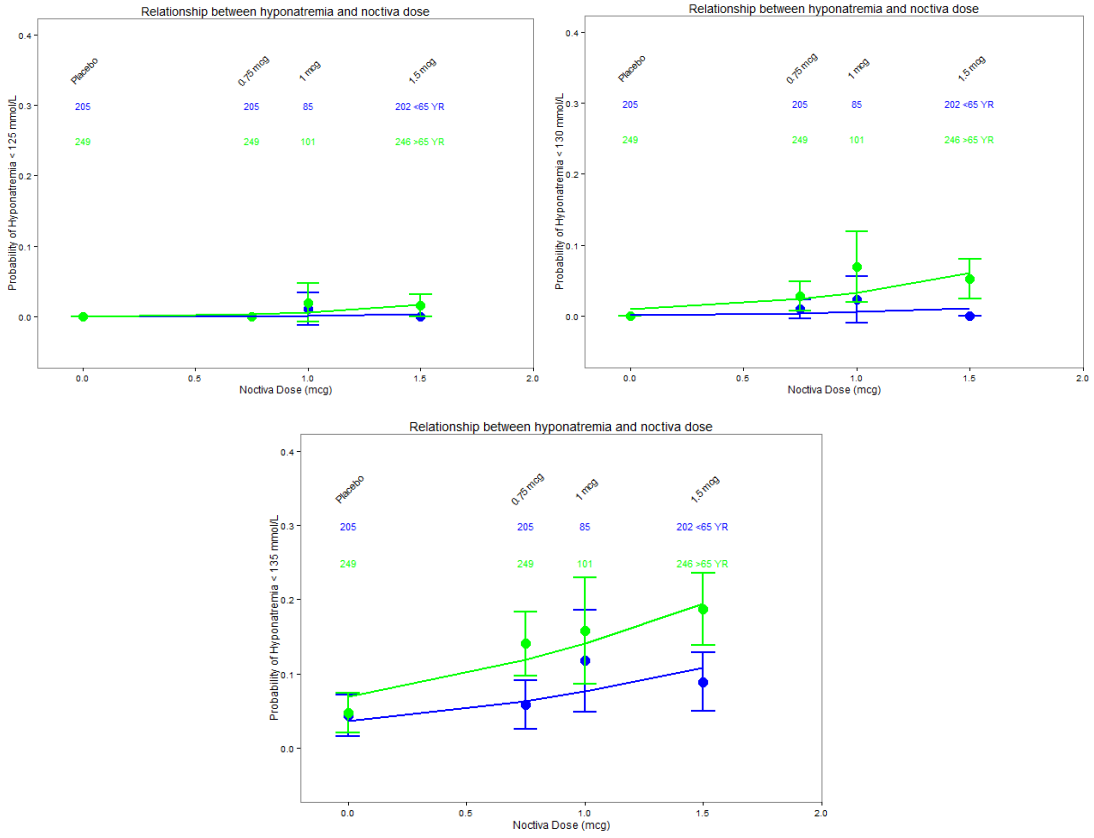


Figure 4.2.3-2 Dose-response relationship between desmopressin nasal spray dose and percentage of patients with hyponatremia defined as less than 125 mmol/L (upper left), 130 mmol/L (upper right), and 135 mmol/L (bottom) separated by age. The error bars represent 95% confidential interval of response rates. (*Reviewer's independent analysis based on data from DB3 and DB4*)

Although the dose-response analysis for safety showed that a higher dose would result in a higher percentage of patients with hyponatremia, it is worth noting that the low dose (0.75 mcg) and middle dose (1 mcg) had similar response rates and that the middle dose had even more safety events than the low dose in some scenarios (note: the 1 mcg dose was only evaluated in DB3). These observations were consistent with the results of time-to-event analyses presented in Section 3.3.2, in which the time to hyponatremia event, separated by dose, was plotted. No significant difference regarding response rate was observed for the low dose and middle dose with all cut-off values (Figure 4.2.3-3). Possible explanations include that the middle dose group had relative small sample size of patients, or that the low safety event rates observed in the trials hinder identification in the differences in the safety profile between these doses.

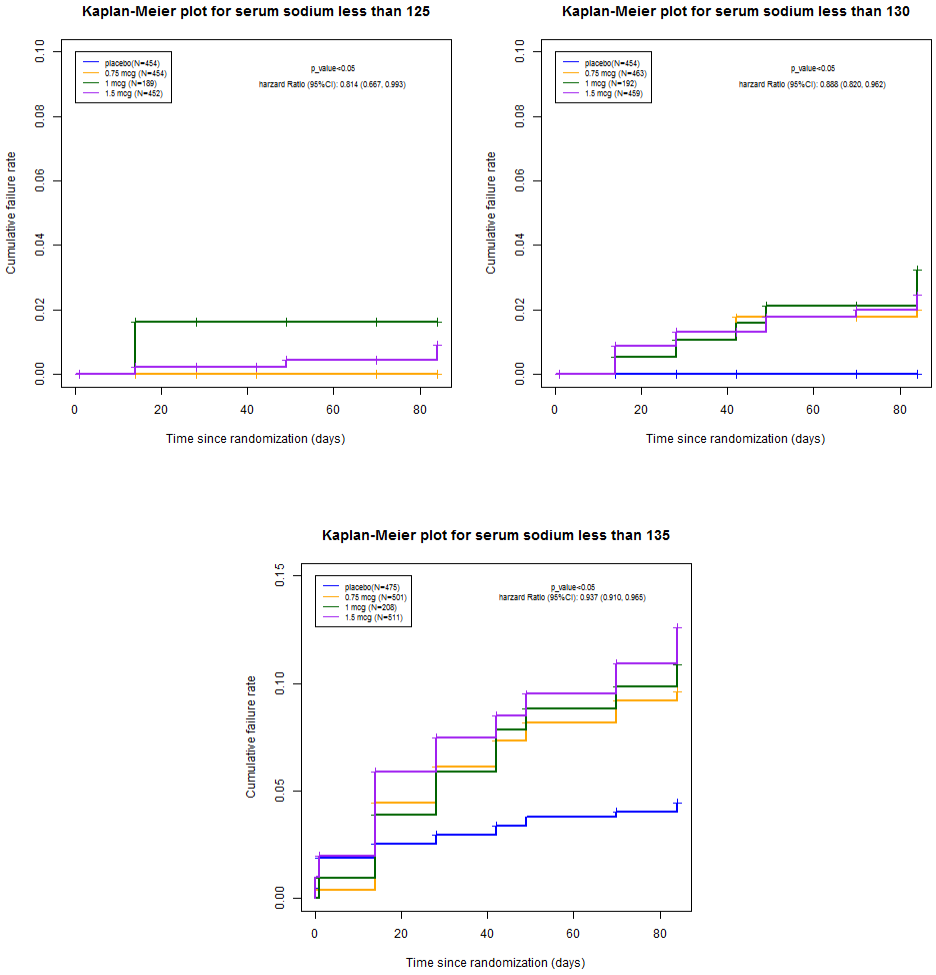


Figure 4.2.3-3 Kaplan-Meier plot of hyponatremia defined as serum sodium concentration less than 125 mmol/L (upper left), 130 mmol/L (upper right), and 135 mmol/L (bottom). In each arm (blue is placebo arm, orange is treatment arm with dose of 0.75 mcg, green is treatment arm with dose of 1 mcg, and purple is treatment arm with dose of 1.5 mcg) (*Reviewer's independent analysis based on data from DB3 and DB4*)

Overall, there was a trend showing that higher dose, e.g. 1.5 mcg, would result in higher percentage of patients with hyponatremia. It is highly recommended to have earlier monitoring of serum sodium concentration during the treatment (i.e. at day 7 instead of day 14) as there may be no obvious symptoms for hyponatremia.

4.2.4 Dose-response efficacy analysis in patients with nocturnal polyuria

Following the October 19th Advisory Committee, one of the internal review team discussions was with regards to treatment effect in patients with nocturnal polyuria. An exploratory dose-response analysis was conducted by the review team, evaluating the relationship with regards to those subjects with the condition at screening/baseline and those without. In all, approximately 80% of the phase 3 population was listed as having nocturnal polyuria at baseline. Overall, the dose-response relationship on both co-primary endpoints were comparable between those subjects defined as having nocturnal polyuria and the overall population (Figures 4.2.4-1 and 4.2.4-2).

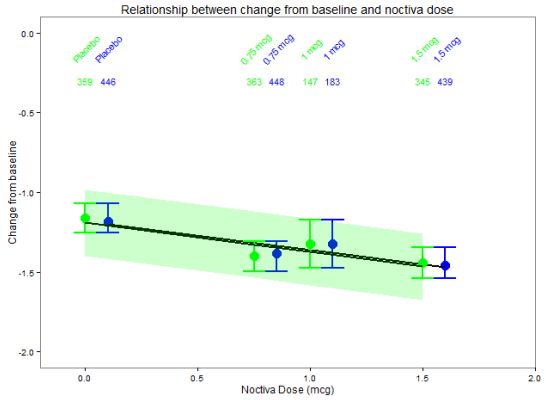


Figure 4.2.4-1 Dose-response relationship between desmopressin nasal spray dose and nocturia episode change from baseline for (blue) all the subjects and (green) subjects with nocturnal polyuria. The error bars represent 95% confidential interval of response rates. The doses for all the subjects (blue) are modified to help visualize the difference between two populations. (*Reviewer's independent analysis based on data from DB3 and DB4)*

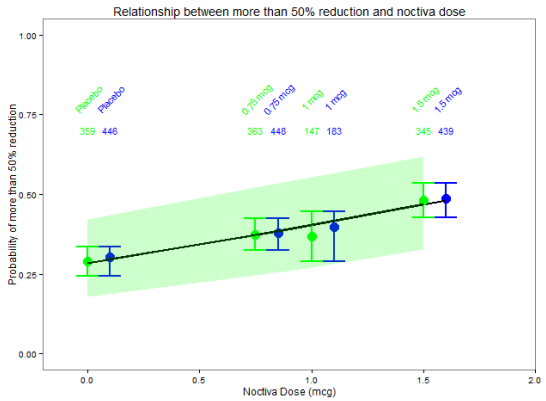


Figure 4.2.4-2 Dose-response relationship between desmopressin nasal spray dose and percentage of patients with more than 50% reduction of nocturia episode for (blue) all the subject and (green) subjects with nocturnal polyuria. The error bars represent 95% confidential interval of response rates. The doses for all the subjects (blue) are modified to help visualize the difference between two populations. (*Reviewer's independent analysis based on data from DB3 and DB4)*

4.3 Individual Study Reports

Tables and figures under this section are numbered independently.

SPC-DESMO-NS 200801

Title: A dose titration study to investigate the anti-diuretic effect and pharmacokinetics of a low dose nasal spray formulation of desmopressin in water loaded healthy non-smoking male and female volunteer subjects

Objectives:

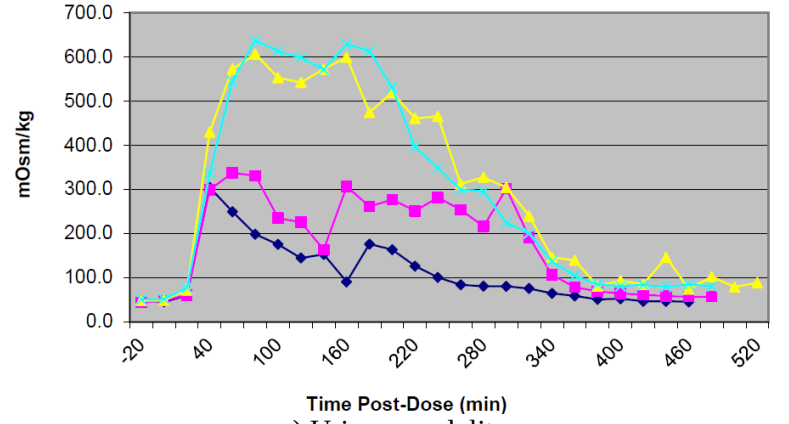
· The primary objective:
  - To evaluate the antidiuretic effect of up to 3 doses of low dose desmopressin nasal spray formulation in water-loaded healthy, non-smoking male and female volunteer subjects.
· The secondary objective:
  - To evaluate the pharmacokinetics (PK) of up to 3 low doses of the desmopressin nasal spray formulation.
  - To evaluate the safety profile of up to 3 low doses of desmopressin nasal spray formulation.
  - To evaluate the dose-response relationship of up to 3 low doses of desmopressin nasal spray formulation in comparison to single bolus intradermal (ID) or subcutaneous (SC) injections of low dose desmopressin.

Study Design:

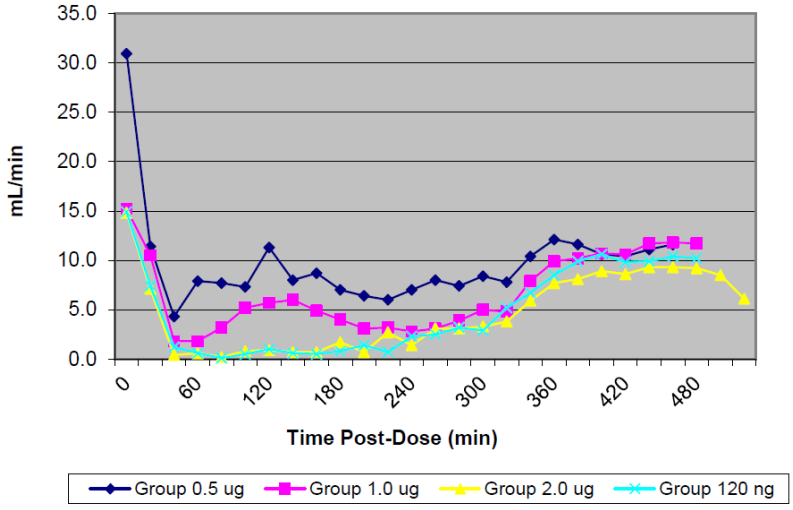
· Open-label, escalating dose study
· Six healthy male and female subjects who were water-loaded prior to dosing
· Treatments:
  - Day 1, 3 and 5: single dose of 0.5, 1 and 2 mcg desmopressin nasal spray (0.1, 0.2, and 0.4 mL of 5 mcg/mL) in water-loaded state.
  - Day 7: single ID injection for 3 males and females or SC injection for 3 males and females injection of 120 ng desmopressin (150 µL of 0.8 µg/mL solution) as reference
· Pharmacodynamic (PD) study
  - Water loading: the subjects were required to drink a volume of water corresponding to 1.5 to 3% of their body weight to achieve a minimum urine output of 10 mL/minute.
  - Subjects were asked to void every 20 minutes and urine output was replaced with an equal volume of ingested water to maintain a constant water-loaded state.
  - Each subject was dosed with desmopressin in the water-loaded state. Urine volume and osmolality were assessed every 20 minutes up to 8 hours post dose and hourly thereafter until the urine output returned to baseline or exceeded 10 mL/minute in one hourly collection or the urine osmolality was < 200 mOsm/kg on one occasion.
  - Urine specific gravity was measured at -20 minutes, 0 and at hourly intervals up to 8 hours post dosing. Serum sodium and osmolality was measured prior to dosing and at 2, 4, 6 and 8 hours post dose.
· PK study
  - Pre-dose (0), and at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, and 360 minutes post dose
  - Assay: radioimmunoassay, the lower limit of quantitation (LLoQ) – 2.5 pg/mL
· Safety evaluation
  - Serum sodium and osmolality, vital signs, adverse events, physical examination, clinical laboratories and ECG

Results:

· PD results



a) Urine osmolality



b) Urine output

Figure 1. Mean urine osmolality (a) and output (b) over time following single dose of 0.5, 1, or 2 mcg desmopressin nasal spray or injection of 120 ng desmopressin in 12 healthy male or female subjects who were water-loaded prior to dosing.

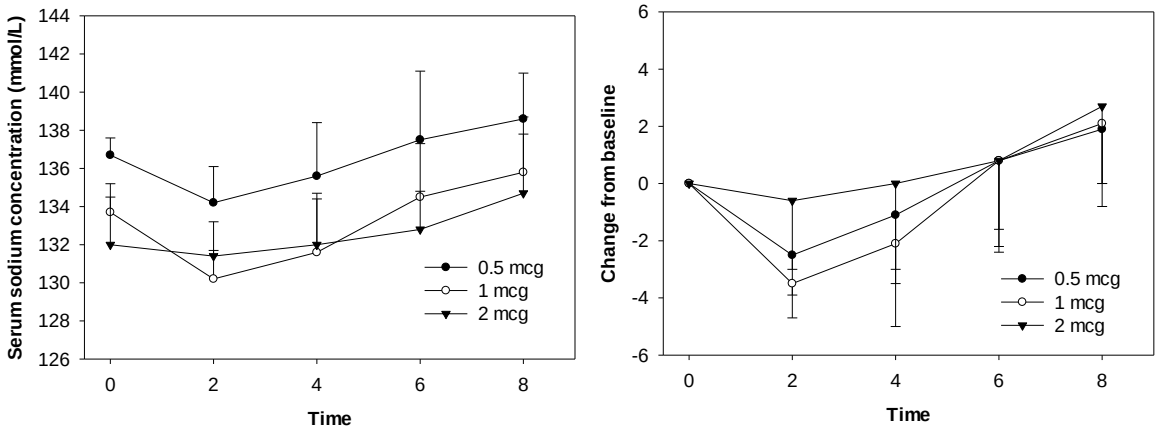


Figure 2. Mean serum sodium concentrations and their changes from baseline over time following single dose of 0.5, 1, or 2 mcg desmopressin nasal spray in 12 healthy male or female subjects who were water-loaded

prior to dosing. Error bars indicate standard deviation. (These graphs were generated by the reviewer based on the study results).

· PK results
  - Blood concentrations in the period of 0.5 mcg desmopressin were all below the LLoQ. A summary of PK parameters for the 1 and 2 mcg doses are shown below.

Table 1. Mean desmopressin PK parameters after single dose of 0.5, 1, or 2 mcg desmopressin nasal spray and IM and SC injection of 120 ng desmopressin in 12 healthy male or female subjects.

	T_{lag} (h)	C_{max} (pg/m L)	T_{max} (h)	AUC_t (pg·h/ mL)	AUC_∞ (pg·h/ mL)	Relative BA* to SC injection
1.0 mcg Intranasal	0.286	2.79	1.08	2.42	5.36	7.8 %
2.0 mcg Intranasal	0.118	6.24	0.354	9.16	11.6	9.1 %
120 ng SC	0.500	2.77	0.883	3.40	7.85	
120 ng ID	0.495	1.93	0.800	1.87	6.42	

*Relative bioavailability (BA) is calculated based on the comparison of dose-normalized AUC values.

  - The systemic BA of the nasal spray dosage form was approximately 8% compared to the SC injection.

Sponsor's conclusions:

· SER120 nasal spray at single administered doses of 0.5, 1 and 2 mcg desmopressin produced rapid and substantial anti-diuretic effects in healthy water-loaded subjects. The magnitude and duration of the anti-diuretic effect increased with dose and produced durations of anti-diuresis in the range of 3 to 6 hours.

· The PK results showed dose proportionality for C_{max} and AUC with a relatively high BA of 8% and a low coefficient of variation (CV). The SER120 nasal spray formulation produced a rapid mean T_{max} of approximately 20 minutes to about 1 hour which was faster than the mean T_{max} for the subcutaneous and intradermal bolus injection given to these subjects.

Reviewer's comments:

· Changes of the mean urine osmolality and output appeared to be in a dose-dependent manner of desmopressin in healthy subjects in water-loaded state. Tendency toward increase in urine osmolality and decrease in urine output from baseline were observed at the first assessment, 20 minutes, after dosing and these changes reached a maximum effect within 1 hour following administration of desmopressin nasal spray. The pharmacological action, anti-diuresis, was effective for 4 to 6 hours following administration of desmopressin nasal spray. This temporal antidiuretic effect can delay urine production in night time following administration of desmopressin nasal spray and may lead to a reduction in the number of voids per night. In particular, this pharmacological action and its duration may produce better clinical outcome in patients with nocturnal polyuria whose urine output occurs abnormally at night.

· The lowest dose that could have antidiuretic dynamic effect was not determined because this study did not include an arm with placebo and the target range of antidiuretic effect was not pre-defined.

· The most-pronounced decreases in serum sodium concentrations following administration of 0.5 and 1 mcg desmopressin nasal spray were observed at 2 and 4 hours following administration of desmopressin nasal spray. While water-loaded condition may cause a trend toward lowered serum sodium concentrations, the time-course change of serum sodium concentration appears to be consistent

with the duration of antidiuretic action following administration of desmopressin nasal spray. These changes of serum sodium concentrations may suggest that a hyponatremic event can be more likely observed in the early period, within a few hours, after administration of desmopressin nasal spray. For unclear reasons, administration of 2 mcg desmopressin nasal spray did not have a decrease pattern in serum sodium concentrations, although the baseline sodium concentrations in this period were relatively lower than those in other study periods.

- Nasal administration of desmopressin using spray showed a shorter lag time of systemic exposure to desmopressin compared to ID and SC injection of desmopressin. Relative BA of desmopressin nasal spray appeared to be approximately 8 % for two doses, 1 mcg and 2 mcg, to that of SC desmopressin injection which is known to have an equivalent BA to intravenous desmopressin injection.
- The desmopressin concentrations used for this study were different from those for the pivotal phase 3 studies (7.5 mcg/mL and 15 mcg/mL).

SPC-SER120-CRI-201002

Title: A phase 1 study to investigate the pharmacokinetics of SER120 nasal spray formulation in subjects with impaired renal function and in normal healthy volunteers

Objectives:

· The primary objective:
  - To evaluate the pharmacokinetics (PK) of 7.5 mcg/mL SER120 nasal spray formulation administered via intranasal administration in subjects with impaired renal function and in normal healthy volunteers.
  - To investigate the safety and tolerability of 7.5 mcg/mL SER120 nasal spray formulation administered via intranasal administration in subjects with impaired renal function and in normal healthy volunteers.

Study Design:

· Renal impairment (RI): 8 subjects with estimated glomerular filtration rate (eGFR) between 30 and 49 mL/min/1.73m^2
· Normal healthy volunteer group: eGFR > 50 mL/min/1.73m^2 and matched in terms of gender, age (±10 years) and BMI (±10%)
· Treatments: single nasal spray of 0.75 mcg desmopressin
· PK study
  - Blood samples were collected at 0, 15, 30, 45, 60, 120, 180, 240, 300, 360, 420 and 480 minutes post-dose.
  - Assay: radioimmunoassay, the lower limit of quantitation (LLoQ) – 2.5 pg/mL
· Safety evaluation
  - Serum sodium and osmolality, vital signs, adverse events, physical examination, clinical laboratories and ECG

Results:

· Seven males and 1 female were enrolled in the RI group and the subject's eGFR ranged from 22 to 43 mL/min/1.73m^2. The eGFR of the control subjects in the matched healthy group ranged from 69 to 103 mL/min/1.73m^2
· PK results: Plasma concentrations of desmopressin were low. An extended LLoQ of 1.25 pg/mL was applied for the PK analysis. The concentrations were detectable in 67 of 240 (27.9%) samples in 6 of 8 CRI subjects and 5 of 8 normal subjects with this LLoQ.

Table 1. PK parameters of desmopressin following administration of 0.5 or 0.75 mcg desmopressin nasal spray in the RI group and the matched healthy group.

	T_{max} (h)	C_{max} (pg/mL)	AUC_t (pg•h/ mL)	AUC_{inf} (pg•h/ mL)	$t_{1/2}$ (h)
RI group	0.5 (0.25, 2) (N=7)	2.09 (±1.3) (N=8)	4.72 (± 4.28) (N=8)	14.32 (± 7.51) (N=4)	3.40 ± 1.80 (N=4)
Matched healthy group	0.5 (0.25, 1.5) (N=6)	1.80 (±1.35) (N=8)	1.55 ± 1.67 (N=9)	5.60 (± 1.21) (N=3)	1.05 ±0.24 (N=3)

N = Number of patients included in the calculation, T_{max}: median value; PK analysis using the extended LLOQ of 1.25 pg/mL

Sponsor's conclusions:

· Similar PK profiles in terms of C_{max} and T_{max} but divergent profiles in terms of systemic exposure (AUC_t) and terminal half-life. The renal route of excretion is an important one for desmopressin and

significant renal impairment prolongs terminal half-life approximately three-fold and increases systemic exposure approximately five-fold.

Reviewer's comments:

- The terminal half-life was significantly prolonged in patients with severe or moderate renal impairment compared to the matched patients with normal or mild renal impairment. The AUC_t increased by approximately three-fold (4.7 ± 4.3 pg·h/mL, n=8 vs. 1.6± 1.7 pg·h/mL, n=9). The RI group showed a significantly prolonged half-life and higher AUC of desmopressin when compared to those in the control healthy group. . However, the results for half-life should be interpreted with caution due to limited sample size (n= 3 to 4) and the use of the extended LLoQ.
- In this study, a number of desmopressin concentrations were below the assay's LLoQ. In addition, the PK parameters in the study were derived using the concentrations using an extended LLoQ (1.25 pg/mL).
- The currently approved desmopressin products for treatment of central diabetes insipidus are contraindicated in patients with moderate to severe renal impairment (creatinine clearance is lower than 50 mL/min). The Sponsor proposed a contraindication of the proposed desmopressin nasal spray for patients with an eGFR less than 50 ml/min/1.73 m^2.

SPC-SER120-ELD-201001

Title: A phase 3 randomized, open-label, multicenter study to investigate the safety and pharmacokinetics of SER120 nasal spray formulations in elderly patients (≥ 75 years old) with nocturia

Objectives:

· The primary objective:
  - To evaluate the safety and tolerability of desmopressin nasal spray formulations in elderly (≥ 75 years old) patients with nocturia
  - To evaluate the pharmacokinetics (PK) of desmopressin nasal spray formulations in elderly (≥ 75 years old) patients with nocturia.

· The secondary objective:
  - To evaluate the reduction in mean number of nocturic episodes between the lead-in period and the last week of the maintenance period.
  - To evaluate the percentage of patients with ≥ 50% reduction between the lead-in period and the last week of the maintenance period with respect to the mean number of voids per night.
  - To evaluate the percentage of nights, on a per patient basis, during the last week of the maintenance period with 0 or 1 nocturic episodes.
  - To evaluate the percentage of nights, on a per patient basis, during the last week of the maintenance period with 0 nocturic episodes.
  - To evaluate the percentage of patients with a mean of ≤ 1 nocturic episode per night during the last week of the maintenance period.
  - To evaluate the duration from bedtime to first nocturic void (or first morning void in the absence of nocturic void) during the last week of the maintenance period.

Study Design:

· Open-label, multicenter, dose titration study

· Nocturia patients who are 75 years and older and had ≥ 2 nocturic episodes each night for 5 or more nights per week totaling ≥14 nocturic episodes per week for at least 6 months.

· Treatments:
  - Randomized to either the 0.5 mcg (100 µL of 5 µg/mL) or 0.75 mcg (0.1 mL of 7.5 µg/mL) desmopressin spray
  - Down- or up-titration if the serum sodium was ≤ 130 mmol/L or the mean number of nocturic episodes was not decreased to ≥ 50% of baseline for a 3-week dose titration phase
  - The final titrated dose for 5 weeks

· Efficacy
  - Reduction from the baseline to the last week in the mean number of nocturic episodes.
  - Percentage of patients with ≥ 50% reduction between the baseline and the last week of the maintenance period with respect to the mean number of voids per night.
  - On a per patient basis the percentage of nights with 0 or 1 nocturic episodes during the last week.
  - On a per patient basis the percentage of nights with 0 nocturic episodes during the last week.
  - Percentage of patients with ≤ 1 nocturic episode per night during the last week.
  - Time from bedtime to the first nocturic void or the first morning void in the absence of a nocturic void during the last week.

· PK study
  - Patients skipped the evening dose at Day 14 and were dosed for the PK study on the morning of Day 15.
  - Blood samples were collected at 0, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post-dose.
  - Assay: radioimmunoassay, the lower limit of quantitation (LLoQ) – 2.5 pg/mL

· Safety evaluation

- Serum sodium and osmolality, vital signs, adverse events, physical examination, clinical laboratories and ECG

Results:

· Efficacy results

Table 1. Efficacy parameters after treatment with 0.5 or 0.75 mcg desmopressin nasal spray in elderly nocturic patients for 8 weeks.

	Number of subject	Change in the mean number of nocturic episodes per night (baseline → Day 57)	The percentage of patients with ≥ 50% reduction
0.5 mcg	15	2.6 → 1.1 (-1.5)*	11/15 (73.3%)
0.75 mcg	16	2.5 → 1.1 (-1.4)*	11/16 (68.8%)

* $p < 0.0001$ compared to the baseline; ** mean number of nocturic episodes ≤ 1

· PK results

Table 2. Disposition of the subjects enrolled in the PK study

Dose	Number of subject	Age range	Mean eGFR
0.5 mcg	10 (7 males/3 females)	75 – 84	80.0 mL/min/1.73 m2
0.75 mcg	12 (8 males/4 females)	75 - 84	71.4 mL/min/1.73 m2

eGFR: estimated glomerular filtration rate

- Most desmopressin concentrations were lower that the LLoQ (9 subjects in the 0.5 mcg group and 8 subjects in the 0.75 mcg group).

Table 3. PK parameters of desmopressin following administration of 0.5 or 0.75 mcg desmopressin nasal spray in elderly subjects.

	T_{max} (h)	C_{max} (pg/mL)	AUC_t (pg•h/ mL)	$t_{1/2}$ (h)
0.5 mcg	0.5 (0.25, 1) (N=8)	1.60 (±0.82) (N=9)	0.721 ± 0.675 (N=9)	N.A
0.75 mcg	0.75 (0.5, 1) (N=7)	2.04 (±2.26) (N=12)	2.72 ± 4.11 (N=12)	2.97 ±2.66 (N=4)

T_{max}: median value; PK analysis using an extended LLOQ of 1.25 pg/mL

· Safety
- The most frequently occurred adverse events were nasal discomfort followed by sneezing, rhinorrhea and increased lacrimation.
- There was no patient who showed serum sodium concentration lower than 130 mmol/L.

Sponsor's conclusions:

· The study drug was safe at both dose levels. Most treatment emergent adverse events (TEAEs) were mild and none were rated as severe. There were no serious adverse events observed in this study. No patients developed hyponatremia and the lowest serum sodium value observed in the study was 133 mmol/L.

· Patients in both treatment groups showed a good pharmacological response to SER120 in terms of a reduction in the mean number of nocturic episodes. The majority of patients in this study had a 50% or greater decrease in the mean number of nocturic voids.

· The PK analysis of these 2 doses of SER120 showed that in those patients with measurable concentrations of desmopressin, peak concentrations were in the desired and expected range and were generally in the low to mid-single digits (pg/mL). These peak plasma levels of desmopressin correlate

with the desired PD duration of 4 to 6 hours which enables the anti-diuretic effect to be largely if not entirely eliminated by the time the patient awakens in the morning and is able to begin ingesting fluids.

- This study demonstrated that doses of 0.5 mcg and 0.75 mcg of SER120 were safe, well tolerated and clinically effective for treatment of nocturia in elderly patients, age 75 years and older.

Reviewer's comments:

- Both treatment groups showed a significant reduction in the mean number of nocturic episodes per night. However, this study did not include a control arm treated with placebo.
- There was no serious hyponatremic case such as a serum sodium concentration lower than 125 mmol/L.
- The concentrations of desmopressin in the blood samples of most patients were lower than LLoQ. The PK analysis in this study was conducted using an extended LLOQ of 1.25 pg/mL. Therefore, the PK parameters reported in the study is limited to be used for PK characterization in elderly population. This study also had no control group of younger patients.

SPC DESMO-NS 200802

Title: A multi-center dose titration study to investigate the pharmacodynamics, pharmacokinetics and safety of daily doses of desmopressin nasal spray in patients with nocturia

Objectives:

· The primary objective:
  - To evaluate the anti-diuretic (pharmacodynamic) effect of daily doses of desmopressin nasal spray in patients with nocturia.

· The secondary objective:
  - To evaluate the pharmacokinetics (PK) of up to four doses of desmopressin nasal spray.
  - To investigate the safety and tolerability of several doses of desmopressin nasal spray.
  - To investigate the efficacy and dose-response relationship of desmopressin nasal spray.

Study Design:

· Open-label, multicenter, dose titration study

· 40 subjects who have 10 or more nocturic episodes per week for at least 6 months and 2 or more nocturic episodes per night, 5 or more days per week for at least 2 weeks.

· Treatments: on day 1 and 2, all subjects received 0.5 mcg desmopressin and then the doses were titrated based on the response (reduction of nocturia frequency ≤ 1) as follows:

Screening (< 28 days)	Treatment (Day)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Group 1	T1	T1	M1	M1	M1	M1	M1	M1	M1	M1	PK			
Group 1B	T1	T1	M1	M1	M1	M2	M2	M2	M2	M2	PK			
Group 2	T1	T1	T2	M2	M2	M2	M2	M2	M2	M2	M2	M2	PK	
Group 2B	T1	T1	T2	M2	M2	M2	M3	M3	M3	M3	M3	M3	PK	
Group 3	T1	T1	T2	T3	M3	M3	M3	M3	M3	M3	M3	M3	M3	PK
Group 4*	T1	T1	T2	T3	M3	M3	M3	M4	M4	M4	M4	M4	M4	PK

T1 = Titration Dose Level 1; M1 = Maintenance Dose Level 1; Dose Level 1 = 1 spray equivalent to 500 ng

T2 = Titration Dose Level 2; M2 = Maintenance Dose Level 2; Dose Level 2 = 2 sprays equivalent to 1000 ng

T3 = Titration Dose Level 3; M3 = Maintenance Dose Level 3; Dose Level 3 = 3 sprays equivalent to 1500 ng

*Patients in Group 3 who did not show response and had normal serum sodium level were to have dose increased on Day 8 to M4 = 4 sprays per night (equivalent to 2000 ng per night) are designated as Group 4 patients.

· Efficacy evaluation: number of nocturic episodes, time from going to sleep to first nocturic void, total sleep time, and urine osmolality and output.

· PK study
  - Selected patients were enrolled in the PK study on the day of the exit visit.
  - Blood samples were collected at 0, 15, 30, 45, 60, 120 and 180 minutes post-dose.
  - Assay: radioimmunoassay, the lower limit of quantitation (LLoQ) – 2.5 pg/mL

· Safety evaluation: serum sodium and osmolality, vital signs, adverse events, physical examination, clinical laboratories and ECG

Results:

· Efficacy results
  - Out of enrolled 43 patients, 32 responded to 0.5 mcg desmopressin dose and were maintained at that dose. Eleven patients were up-titrated to 1 mcg and maintained at that dose.

Table 1. Summary of efficacy responses following administration of 0.5 or 1 mcg desmopressin nasal spray in nocturic patients.

	Number of subject	Change in the mean number of nocturic episodes per night (10 nights)	Incidence of responder**
Group 1	32	2.3 → 1.9 (-0.4)*	31/32 (96.9%)

Group 2	11	3.3 → 2.6 (-0.7)*	8/11 (72.7%)

· * p < 0.0001 compared to the baseline; ** mean number of nocturic episodes ≤ 1

· PK results
  - Plasma concentrations in some patients were lower than the LLoQ.

Table 2. Mean desmopressin PK parameters after single dose of 0.5, 1, or 1.5 mcg desmopressin nasal spray in the patients with nocturia.

	C_{max} (pg/m L)	T_{max} (h)	AUC_t (pg·h/ mL)	AUC_∞ (pg·h/ mL)
0.5 mcg	1.53±1.68 (N=5)	0.5 (0.25, 3.0) (N=3)	0.980 ± 1.187 (N=5)	4.39 ± NE (N=1)
1 mcg (2 sprays in one nostril)	1.83±1.16 (N=5)	0.5 (0.50, 0.75) (N=4)	1.47 ± 1.38 (N=5)	7.03 ± NE (N=1)
1 mcg (1 spray in each nostril)	2.60±2.67 (N=5)	0.5 (0.50, 0.50) (N=4)	3.24 ± 5.11 (N=5)	16.8 ± NE (N=1)
1.5 mcg (2 sprays in one and 1 spray in other nostril)	3.18±4.37 (N=5)	0.25 (0.25, 0.25) (N=2)	3.96 ± 5.44 (N=5)	13.3 ± 0.5 (N=2)

N = Number of patients included in the calculation; the subjects with 1 or more concentrations greater than the extended LLOQ of 1.25 pg/mL were included.

· Safety
  - The most common treatment emergent adverse events (TEAEs) were nasal discomfort (6), headache (6) and dysgeusia (3). Twelve patients (10 in Group 1 and 2 in Group 2) had 20 TEAEs which were classified as possibly or probably related to study drug. Of these, 6 were nasal discomfort, 3 dysgeusia and 2 each coughing and sneezing. There were no serious TEAEs and no adverse events which interrupted dosing of study drug or required medical treatment. There were no clinically significant or meaningful changes or abnormalities in clinical laboratories including serum sodium and serum osmolality, physical examination, vital signs and ECG findings.

Sponsor's conclusions:

· The low dose desmopressin nasal spray formulation demonstrated a clinically meaningful, therapeutic effect in terms of decreasing the mean number of nocturic episodes in patients with nocturia at doses of 0.5 and 1 mcg.
· The study drug demonstrated a good safety profile and was well tolerated by the patient population in this study.
· The PK results confirm the low dose/low plasma concentration hypothesis and show that desmopressin was pharmacologically active and therapeutically effective at blood concentrations in the single picomolar range.
· This new dosage form of desmopressin showed promising results as a treatment for nocturia which is an unmet medical need.

Reviewer's comments:

· Treatments with 0.5 mcg or 1 mcg desmopressin nasal sprays significantly reduced the nocturic episodes in the patients. However, this study did not include a placebo-control arm.
· There was no reported hyponatremic case.
· There was a trend toward increased desmopressin absorption when the dose was split and administered to two nostrils.

SPC-SER120-**DB1**-200901

Title: A phase 3 randomized, double blind, placebo control, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia

Objectives:

· The primary objective:
  - To evaluate the efficacy of SER120 nasal spray formulation in terms of reduction in the mean number of nocturic episodes between the lead-in period and the last week in patients given SER120 versus patients given placebo control.
  - To evaluate the efficacy of SER120 nasal spray formulation in terms of the percentage of patients with ≥ 50% reduction in the mean number of voids per night between the lead-in period and the last week compared to placebo.
· The secondary objective:
  - To compare the percentage of nights on a per patient basis during the last week of the maintenance period with 0 or 1 nocturic episodes between treatment groups.
  - To compare the percentage of nights on a per patient basis during the last week of the maintenance period with 0 nocturic episodes between treatment groups.
  - To compare the percentage of patients with a mean of ≤ 1 nocturic episode per night during the last week of the maintenance period between treatment groups.
  - To compare the duration from bedtime to first nocturic void during the last week of the maintenance period between the treatment groups.
· Safety
· Pharmacokinetics (PK)

Study Design:

· Randomized, double blind, placebo controlled, parallel group, multicenter study
· Patients: ≥ 2 nocturic episodes each night for 5 or more nights per week totaling ≥ 14 nocturic episodes per week for at least 6 months
· The planned subject number: enrollment - 300 to 330 nocturic patients, at least 132 patients per each group
· Treatments: Placebo, 0.5 mcg or 0.75 mcg (0.1 mL of 5 or 7.5 mcg/mL) desmopressin nasal spray
  - Randomized to either the 0.5 mcg or placebo
  - A 3-week dose titration phase: patients were up-titrated or mock up-titrated (for placebo group) if their serum sodium was acceptable and their mean number of nocturic episodes during the previous 7 days was > 1 per night.
  - The maintenance phase with the final titrated dose for 4 weeks
· Visits for evaluation: on Day 1, 8, 15, 22, 29 and 43
· Efficacy evaluation
  - Primary efficacy parameters
    1) Mean number of nocturic episodes per night during the efficacy assessment period (change from screening/lead-in period versus the last week of the maintenance phase).
    2) Percentage of patients with ≥ 50% reduction between the lead-in period and the last week of the maintenance period with respect to the mean number of voids per night.
· Safety evaluation: serum sodium, serum osmolality, vital signs, adverse events, concomitant medications, 24 hours urine volume and diary assessments
· The PK sub-study
  - Administration of one additional dose on the morning of Day 50 in the patients who had consented to participate
  - PK sampling at pre-dose and at 15,30, 45, 60, 90, 120, 180, and 270 minutes post-dose

- Assay: radioimmunoassay, the lower limit of quantitation (LLoQ) – 2.5 pg/mL

Results:

Table 1. Number of subjects in each study population

	Total	Desmopressin	Placebo
Safety population	301	148	153
ITT population	294	145	149
Completion of study	263	129	134

ITT: intention to treat

· Efficacy variables

Table 2. Results of the primary efficacy variables in the ITT populations

			Desmopressin	Placebo	Comparison*
ITT Population	Mean nocturic episodes	Screening	3.0	3.0	
		Day 50/Exit	1.7	1.8	
		Change from baseline	- 1.3	-1.2	P = 0.5872
		p-value	<0.0001	<0.0001	
	# of patients with ≥ 50% reduction in mean nocturic episodes		58 (40.0%)	58 (38.9%)	P = 0.8292

Mean nocturic episodes are the value of least square mean; p-value from comparison to placebo; * p-value of comparison between desmopressin and placebo groups

· Safety results
  - There were no meaningful differences in the incidence, type or severity of adverse events between the treatment groups. The most frequently reported treatment emergent adverse events (TEAEs) in the SER120 patients included nasal discomfort (29.7%), sneezing (12.2%) rhinorrhea (8.8%), nasopharyngitis (4.7%), post nasal drip (4.7%) headache (4.1%) and throat irritation (4.1%). The most frequently reported TEAEs in the placebo patients included nasal discomfort (37.9%), sneezing (14.4%), rhinorrhea (14.4%), headache (10.5%), epistaxis (5.2%), nasal congestion (4.6%), diarrhea (4.6%) and dizziness (4.6%).
  - There was no patient who had serum sodium value < 130 mmol/L in the desmopressin group.
· PK results: many of the 48 patients that received the desmopressin PK dose did not have any desmopressin concentrations that exceeded the assay LLoQ. Only 13/48 patients had at least one desmopressin concentration greater than the validated LLoQ of 2.50 pg/mL.

Sponsor's conclusions:

· The study did not achieve statistically significant results for the overall ITT population for either of the co-primary efficacy endpoints. The study drug was shown to be safe and well tolerated. Patients on the active drug, SER120 did not have a single serum sodium value below 130 mmol/L at any time during the study.
· Patients in both treatment arms had a statistically significant and clinically meaningful reduction in the mean number of nocturic episodes from baseline to the last 7 available days of treatment of approximately 1.2 to 1.3 episodes from a baseline value of approximately 3.0.
· The pharmacokinetic evaluation showed detectable but low peak plasma concentrations of desmopressin which were in the low single digit pg/mL range and which showed approximate dose proportionality.
· While this study produced negative statistical results, it did generate signals suggesting the potential for low dose desmopressin nasal spray to achieve statistically significant outcomes and be therapeutically

effective for patients with nocturia. Additional studies are warranted which explore higher doses and new trial designs and methods which correct the factors in this study which are believed to have contributed to a high placebo response rate.

Reviewer's comments:

- Both, desmopressin and placebo, groups showed a statistically significant reduction in the mean number of nocturic episodes from baseline. However, there was no statistical difference in the change from baseline and the number of patients with ≥ 50% reduction of mean nocturic episodes between desmopressin and placebo groups.
- There was no significant difference in the incidence, type or severity of adverse events between two groups. There was no case which had a single serum sodium value below 130 mmol/L.
- The concentrations of desmopressin in the blood samples of many patients were lower than the LLoQ. This PK data from this study is limited and not useful for characterization of desmopressin PK following administration of desmopressin nasal spray.

SPC-SER120-**DB2**-200902

Title: A phase 3 randomized, double blind, placebo control, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia (Non-PK Study)

Objectives:

· The primary objective:
  - To evaluate the efficacy of SER120 nasal spray formulation in terms of reduction in the mean number of nocturic episodes between the lead-in period and the last week.
  - To evaluate the efficacy of SER120 nasal spray formulation in terms of the percentage of patients with ≥ 50% reduction in the mean number of voids per night.
· The secondary objective:
  - To compare the percentage of nights on a per patient basis during the last week of the maintenance period with 0 or 1 nocturic episodes between treatment groups.
  - To compare the percentage of nights on a per patient basis during the last week of the maintenance period with 0 nocturic episodes between treatment groups.
  - To compare the percentage of patients with a mean of ≤ 1 nocturic episode per night during the last week of the maintenance period between treatment groups.
  - To compare the duration from bedtime to first nocturic void during the last week of the maintenance period between the treatment groups.
· Safety

Study Design:

· Randomized, double blind, placebo controlled, parallel group, multicenter study
· Patients: ≥ 2 nocturic episodes each night for 5 or more nights per week totaling ≥ 14 nocturic episodes per week for at least 6 months
· The planned subject number: enrollment - 300 to 330 nocturic patients and at least 132 patients per each group completing the study
· Treatments: 0.5 mcg or 0.75 mcg (0.1 mL of 5 or 7.5 mcg/mL) desmopressin nasal spray
  - Randomized to either the 0.5 mcg or placebo
  - A 3-week dose titration phase: patients were up-titrated or mock up-titrated (for placebo group) if their serum sodium was acceptable and their mean number of nocturic episodes during the previous 7 days was > 1 per night.
  - The maintenance phase with the final titrated dose for 4 weeks
· Visits for evaluation: Day 1, 8, 15, 29 and 43
· Efficacy evaluation
  - Primary efficacy parameters
    1) Mean number of nocturic episodes per night during the efficacy assessment period (change from screening/lead-in period versus the last week of the maintenance phase).
    2) Percentage of patients with ≥ 50% reduction between the lead-in period and the last week of the maintenance period with respect to the mean number of voids per night.
· Safety evaluation
  - Serum sodium, serum osmolality, vital signs, adverse events, concomitant medications, 24 hours urine volume and diary assessments

Results:

· Study population:

Table 1. Number of subjects in each study population

	Total	Desmopressin	Placebo

Safety population	326	167	159
ITT population	318	162	156
Completion of study	290	149	141

· Efficacy variables

Table 2. Results of the primary efficacy variables in the ITT populations

			Desmopressin	Placebo	Comparison*
ITT Population	Mean nocturic episodes	Screening	2.9	2.8	
		Day 50/Exit	1.6	1.7	
		Change from baseline	- 1.3	-1.2	P = 0.1524
		p-value	<0.0001	<0.0001	
	# of patients with ≥ 50% reduction in mean nocturic episodes		83 (51.2%)	64 (41.0%)	P = 0.0558

Mean nocturic episodes are the value of least square mean; p-value from comparison to placebo; * p-value of comparison between desmopressin and placebo groups

- The male patients (N=206, 63% of the total patients) showed a statistically significant difference in the proportion of patients with ≥ 50% reduction in mean nocturic episodes (45.8% vs. 32.3%, p = 0.0445.)

· Safety results
- The frequency, type and severity of adverse events were similar in both treatment groups. The most frequently reported treatment emergent adverse events (TEAEs) in the SER120 patients included nasal discomfort (31.7%), sneezing (14.4%) rhinorrhea (12%), headache (7.8%), lacrimation increased (6.6%), nasal congestion (6%), nasopharyngitis (3.6%) and post nasal drip (3.6%). The most frequently reported TEAEs in the placebo patients included nasal discomfort (30.2%), sneezing (17%), rhinorrhea (10.1%), lacrimation increased (6.3%), nasal congestion (5%), oropharyngeal pain (4.4%) and headache (3.8%).
- There were three patients who had serum sodium value < 130 mmol/L and all received desmopressin nasal spray.
- There were only 4 patients with a serious adverse event in this study. Three patients were in the SER120 group and 1 was in the placebo group. All were judged to be unrelated to the study drug.

Sponsor's conclusions:

· Patients in both treatment arms had a statistically significant and clinically meaningful reduction in the mean number of nocturic episodes from baseline to the last 7 available days of treatment. There was a numerical trend in favor of SER120 for this primary endpoint with a p-value = 0.1524. The second co-primary efficacy endpoint of the percentage of narrowly missed statistical significance.
· Males showed a good response to SER120 in this study and both genders showed responses in terms of primary and secondary efficacy endpoints which favored SER120.
· Additional studies are warranted which evaluate modestly higher doses of SER120 and employ different study designs and methodologies to mitigate factors contributing to a high placebo response rate and enhance the anti-diuretic pharmacology of desmopressin to achieve clinically meaningful and statistically significant treatment effects for patients with nocturia.

Reviewer's comments:

· Both groups, desmopressin and placebo, showed a statistically significant reduction in the mean number of nocturic episodes from baseline. However, there was no statistical difference in the change from

baseline of mean nocturic episodes between desmopressin and placebo groups. The percentage in the number of patients with ≥ 50% reduction tended to be higher in the desmopressin than placebo group, but it did not reach statistically significant difference.

- The proportion of patients with ≥ 50% reduction in mean nocturic episodes in the male population of the desmopressin group appeared to be significantly higher than that in the placebo group. It may indicate a gender specific efficacy response.
- There was no significant difference in the incidence, type or severity of adverse events between two groups. However, three cases which had a single serum sodium value below 130 mmol/L were reported in the desmopressin group.

SPC-SER120-DB3-201101

Title: A randomized, double blind, placebo-controlled, parallel group, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulations in patients with nocturia

Objectives:

· The primary objective:
  - To evaluate the efficacy of 3 dose levels of SER120 nasal spray formulation in terms of reduction in the mean number of nocturic episodes.
  - To evaluate the efficacy in terms of the percentage of patients with ≥ 50% reduction.
· The secondary objective:
  - To evaluate the efficacy in terms of the change in the time from going to sleep to first nocturic void.
  - To evaluate the efficacy in terms of the percentage of nights on a per patient basis during the treatment period with 0 nocturic episodes.
  - To evaluate the efficacy in terms of the percentage of nights on a per patient basis during the treatment period with ≤ 1 nocturic episode.
  - To evaluate the efficacy in terms of the change in nocturnal urine volume.
· Safety
· Pharmacokinetics (PK)

Study Design:

· Randomized, double blind, placebo controlled, parallel group, multicenter study
· The planned subject number: 720 nocturia patients (180 per treatment group)
· Treatments: daily application approximately 30 minutes prior to bedtime for 14 weeks
  - Placebo, 0.75 mcg, 1 mcg and 1.5 mcg desmopressin acetate nasal spray
· Main criteria for eligibility
  - ≥ 50 years
  - ≥ 2 nocturic episodes per night for at least 6 months
  - ≥ 2.16 nocturic episodes/night for 2 weeks (3 days per week) at screening totaling ≥ 13 total episodes for 2 weeks (3 days per week) at screening
  - 24 hour urine output ≤ 57 mL/kg or up to 4500 mL
  - Serum sodium concentration within normal limits
  - Glomerular filtration rate (GFR) ≥ 50 ml/min/1.73m^2
· Study scheme
  - A 2-week screening: medical history, night time fluid intake, a Quality of Life questionnaire, two 3-day voiding diary, physical and nasal cavity exam, vital sign, clinical laboratories, 24-hour fractionated urine collection with urine frequency/volume and ECG
  - 2 weeks lead-in period with placebo to identify placebo non-responder and responder (≥ 50% reduction in the mean number of nocturic episodes per night from the screening or less than 1.8 nocturic episodes per night)
  - Randomization on Day 15 to placebo or three active treatment arms
  - Visit for evaluation on Day 15, 29, 43, 57, 85 and 99
· Efficacy evaluation
  - 3 consecutive day voiding diaries during study weeks 1, 2, 3, 4, 6, 8, 10, 12 and 14
  - Diary assessment and Quality of Life questionnaire on Day 15 and 57
  - 24-hour fractionated urine collection with urine frequency/volume
  - The placebo non-responders were part of the modified Intent-to-Treat (mITT) population which excluded the placebo responders.
  - Primary efficacy parameters: 1) Mean number of nocturic episodes per night and 2) Percentage of patients with ≥ 50% reduction in the mean number of voids per night

· Safety evaluation : serum sodium, serum osmolality, vital signs, adverse events, concomitant medications, 24 hours urine volume and diary assessments
· The PK sub-study: administration of one additional dose on the morning of Day 99 in the patients who had consented to participate (18 per each treatment group)

Results:
· Study population: randomization – 750, safety population – 745, ITT – 734 (completion of the study – 641), mITT – 535
· Efficacy variables

Table 1. Results of the primary efficacy variables in the mITT and ITT populations

			1.5 mcg (N = 131)	1.0 mcg (N = 134)	0.75 mcg (N = 137)	Placebo (N = 133)
mITT Population	Mean nocturic episodes	Screening	3.3	3.3	3.5	3.4
		Treatment period	1.9	2.2	2.1	2.4
		Change from baseline	-1.5	-1.2	-1.3	-1.0
		p-value	<0.0001	0.0652	0.0229	
	# of patients = 50% reduction in mean nocturic episodes		55 (42.0%)	33 (24.6%)	37 (27.0%)	24 (18.0%)
	p-value		<0.0001	0.1985	0.0854	
			(N = 179)	(N = 183)	(N = 186)	(N = 186)
ITT Population	Mean nocturic episodes	Screening	3.2	3.3	3.4	3.4
		Treatment period	1.7	1.9	1.9	2.1
		Change from baseline	-1.6	-1.4	-1.4	-1.5
		p-value	<0.0001	0.0377	0.0093	
	# of patients = 50% reduction in mean nocturic episodes		93 (52.0%)	73 (39.9%)	77 (41.4%)	61 (32.8%)
	p-value		0.0002	0.1608	0.0899	

Mean nocturic episodes are the value of least square mean; p-value from comparison to placebo

· Safety results
- Eighteen treatment emergent adverse events (TEAEs) that occurred in ≥ 2% of the patients in one or more treatment groups were reported. The incidence of adverse events is summarized in the table 2.

Table 2. Incidence of TEAEs occurring in > 2% in any active treatment group

Adverse event	1.5 mcg (N = 184)	1.0 mcg (N = 186)	0.75 mcg (N = 188)	Placebo (N = 187)
Nasal Discomfort	11 (6.0%)	9 (4.8%)	6 (3.2%)	7 (3.7%)
Headache	2 (1.1%)	5 (2.7%)	8 (4.3%)	8 (4.3%)
Rhinorrhea	7 (3.8%)	4 (2.2%)	5 (2.7%)	5 (2.7%)
Nasopharyngitis	7 (3.8%)	2 (1.1%)	4 (2.1%)	5 (2.7%)
Blood Pressure Increased/Hypertension	8 (4.3%)	1 (0.5%)	4 (2.1%)	4 (2.1%)
Back Pain	4 (2.2%)	4 (2.2%)	3 (1.6%)	2 (1.1%)
Nasal Mucosa Disorder	2 (1.1%)	4 (2.2%)	3 (1.6%)	4 (2.1%)
Sinusitis	4 (2.2%)	5 (2.7%)	2 (1.1%)	2 (1.1%)
Sneezing	3 (1.6%)	2 (1.1%)	4 (2.1%)	3 (1.6%)
Blood Sodium Decreased*	3 (1.6%)	3 (1.6%)	5 (2.7%)	0 (0.0%)
Cough	3 (1.6%)	4 (2.2%)	2 (1.1%)	2 (1.1%)

Dizziness	4 (2.2%)	0 (0.0%)	3 (1.6%)	4 (2.1%)
Epistaxis	3 (1.6%)	3 (1.6%)	4 (2.1%)	0 (0.0%)
Upper Respiratory Tract Infection	5 (2.7%)	0 (0.0%)	2 (1.1%)	3 (1.6%)
Urinary Tract Infection	2 (1.1%)	3 (1.6%)	4 (2.1%)	1 (0.5%)
Contusion	2 (1.1%)	1 (0.5%)	0 (0.0%)	5 (2.7%)
Muscle Strain	4 (2.2%)	1 (0.5%)	2 (1.1%)	1 (0.5%)
Influenza	4 (2.2%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Throat Irritation	0 (0.0%)	4 (2.2%)	1 (0.5%)	2 (1.1%)
Fatigue	0 (0.0%)	4 (2.2%)	0 (0.0%)	1 (0.5%)
* serum sodium values ≤ 125 mmol/L				
Serious adverse event (SAE)	5	3	3	6

- Fourteen of 16 SAEs in 14 patients which were reported after randomization were determined to be unrelated with the treatments.
- Chest pain and aggravated hypertension reported in one patient ((b) (6), 84 years male, 1.5 mcg treatment group) were determined to be not related and probably related to study drug, respectively. The study was discontinued after hypertension event.
- There was a death event with a dissecting aortic aneurysm in 73-year old male ((b) (6), 1 mcg treatment group). This SAE was classified as unlikely related to the study.
- Hyponatremia

Table 3. Incidence of subjects with serum sodium < 135 mmol/L after randomization at Day 15 including unscheduled visits (Analysis by the reviewer using the Applicant's dataset)

Serum sodium	1.5 mcg (n = 184)	1.0 mcg (n = 183)	0.75 mcg (n = 187)	Placebo (n = 185)
< 135 mmol/L	31 (16.85%)	26 (14.21%)	21 (11.23%)	4 (2.16%)
< 130 mmol/L	4 (2.17%)	9 (4.92%)	9 (4.81%)	0 (0%)
≤ 125 mmol/L	3 (1.63%)	4 (2.19%)	0 (0%)	0 (0%)

Table 4. Incidence of subjects with serum sodium < 135 mmol/L after randomization at Day 15 including unscheduled visits in the age groups (Analysis by the reviewer using the Applicant's dataset)

Serum sodium	Dose	1.5 mcg	1.0 mcg	0.75 mcg	Placebo
	n	(<65=85; ≥ 65=99)	(<65=84; ≥ 65=99)	(<65=86; ≥65=101)	(<65=85; ≥65=100)
< 135 mmol/L	< 65	9 (10.59%)	9 (10.71%)	3 (3.49%)	1 (1.18%)
	≥ 65	22 (22.22%)	17 (17.17%)	18 (17.82%)	3 (3%)
< 130 mmol/L	< 65	0 (0%)	2 (2.38%)	1 (1.16%)	0 (0%)
	≥ 65	4 (4.04%)	7 (7.07%)	8 (7.92%)	0 (0%)
≤ 125 mmol/L	< 65	0 (0%)	2 (2.38%)	0 (0%)	0 (0%)
	≥ 65	3 (3.03%)	2 (2.02%)	0 (0%)	0 (0%)

· PK results: refer to a separate summary.

Sponsor's conclusions:

· This study demonstrated statistically significant efficacy results for the 1.5 mcg of SER120 for both co-primary endpoints and all of the secondary endpoints for both the ITT and mITT patient populations. The two lower doses of SER120 showed several statistically significant results and many strong numerical trends relative to placebo for the efficacy endpoints.

- Although only the 1.5 mcg group demonstrated uniformly statistically significant results, the results for the two lower dose groups indicate that many patients can be effectively treated and, in particular, that the 0.75 mcg dose might be a safe and effective starting dose for many patients including older patients with more concomitant medical conditions.
- The PK results demonstrate that each of these doses of SER120 produced rapid systemic absorption of desmopressin with peak plasma concentrations in the single digit pg/mL range. The short terminal half-life (1.5 to 2.5 hour) which, in combination with the low peak plasma levels produce antidiuretic effects limited to 6 hours or less in most patients during the night.
- PK parameters were not shown to be dependent on sex or age in this study and were independent of renal function in terms of GFR within the limited range allowed in this trial.
- SER120 was shown to be safe and well tolerated in this study. The incidences of TEAEs were similar across the treatment groups including placebo. The only exception to this was the occurrence of hyponatremia (serum sodium values of ≤ 125 mmol/L) in 3 patients in each of the 1.5 and 1.0 mcg SER120 dose groups. This constituted a 1.6% incidence. There were no patients in the 0.75 mcg dose group or placebo group with serum sodium values in this range. This was not statistically significant but was a clinically meaningful signal. There was an observation, however, that 5 of these 6 cases were associated with high dose systemic administration of corticosteroids and 1 with intercurrent illness with increased fluid ingestion. These findings suggest the use of systemic corticosteroids is a risk factor for hyponatremia when used in combination with even low doses of desmopressin. SER120 should be discontinued during any period of time when patients are taking systemic corticosteroids to mitigate this risk factor.
- Although nasal discomfort and other signs and symptoms of a local effect on the nasal mucosa such as rhinorrhea and sneezing were the most commonly reported TEAEs, these were usually mild to moderate and transient. Many patients found these side effects disappeared with continued administration. There were few patients who discontinued study drug because of nasal irritation and the physical examination of the nasal mucosa at the end of treatment did not reveal signs of nasal inflammation. These findings were found across the treatment groups including placebo in similar incidences and are commonly reported with any nasal spray. The overall tolerability of SER120 at all three dose levels was good in this study.
- SER120 at doses of 1.5, 1.0 and 0.75 mcg was safe, well tolerated and effective for the treatment of nocturia in this older, adult patient population.

Reviewer's comments:

- While 1.5 mcg treatment group showed statistically significant difference of two primary efficacy endpoints compared to the placebo group in both the ITT and mITT patient populations, the two lower dose groups, 1.0 and 0.75 mcg, did not reach statistically significant difference for the proportion of subjects with 50% reduction in mean nocturic episodes.
- The results of efficacy parameters in the 1.0 mcg group were not significantly different from those in the 0.75 mcg group.
- A significant reduction in nocturic frequency was also observed in the placebo group. It implies that placebo effect and (or) lifestyle modification would have clinically meaningful impact on the reduction of nocturic events.
- The cases which showed the serum sodium concentration lower than 135 mmol/L were observed dominantly in the active treatment groups. The incidence appeared to be a dose-dependent treatment effect.
- The elderly group, 65 years of age or older, showed a much higher incidence of hyponatremia compared to the group younger than 65 years of age. The cases having a serum sodium concentration lower than 130 mmol/L were mainly observed in the elderly group.

SPC-SER120-**DB4**-201301

Title: A randomized, double blind, placebo controlled, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia

Objectives:

· The primary objective:
  - To evaluate the efficacy of 2 dose levels in terms of reduction in the mean number of nocturic episodes compared to placebo control.
  - To evaluate the efficacy of 2 dose levels in terms of the percentage of patients with ≥ 50% reduction with respect to the mean number of voids per night compared to placebo control.
· The secondary objective:
  - To evaluate the patient reported Impact of Night Time Urination (INTU) Questionnaire score of 2 dose levels compared to placebo.
  - To evaluate the efficacy of 2 dose levels compared to placebo in terms of the change in the time from going to sleep to first nocturic void.
  - To evaluate the efficacy of 2 dose levels compared to placebo in terms of the percentage of nights on a per patient basis during the treatment period with 0 nocturic episodes.
  - To evaluate the efficacy of 2 dose levels compared to placebo in terms of the percentage of nights on a per patient basis during the treatment period with ≤ 1 nocturic episode.
  - To compare the efficacy of 2 dose levels compared to placebo in terms of the nocturic urine volume between the screening period and the last week of the treatment period.

Study Design:

· Randomized, double blind, placebo controlled, parallel group, multicenter study
· The planned subject number: 750 nocturia patients (250 per treatment group)
· Treatments: daily application approximately 30 minutes prior to bedtime for 14 weeks
  - Placebo, 0.75 mcg and 1.5 mcg desmopressin acetate nasal spray
· Main criteria for eligibility
  - ≥ 50 years of age
  - ≥ 2 nocturic episodes per night for at least 6 months
  - ≥ 2.16 nocturic episodes/night for 2 weeks (3 days per week) at screening totaling ≥ 13 total episodes for 2 weeks (3 days per week) at screening
  - 24 hour urine output ≤ 57 mL/kg or up to 4500 mL
  - Serum sodium concentration within normal limits
  - Glomerular filtration rate (GFR) ≥ 50 ml/min/1.73m^2
· Study scheme
  - A 2-week screening: medical history, night time fluid intake, a Quality of Life (Impact of Night Time Urination, INTU) questionnaire, two 3-day voiding diary and, serum sodium, physical, rectal (for male) and nasal cavity exam, vital sign, clinical laboratories, 24-hour fractionated urine collection with urine frequency/volume and ECG
  - 2 weeks lead-in period with placebo to identify placebo non-responder and responder (≥ 50% reduction in the mean number of nocturic episodes per night from the screening or less than 1.8 nocturic episodes per night)
  - Randomization on Day 15 to placebo or two active treatment arms
  - Visit for evaluation on Day 15, 29, 43, 57, 85 and 99
· Efficacy evaluation
  - 3 consecutive day voiding diaries during study week 1, 2, 3, 4, 6, 8, 10, 12 and 14
  - INTU questionnaires during the week 8 and 14
  - 24-hour fractionated urine collection with urine frequency/volume chart at week 14

- The placebo non-responders were part of the modified Intent-to-Treat (mITT) population which excluded the placebo responders.
- Primary efficacy parameters: 1) Mean number of nocturic episodes per night and 2) Percentage of patients with ≥ 50% reduction in the mean number of voids per night

· Safety evaluation
- Serum sodium, serum osmolality, vital signs, adverse events and diary assessments on Days 15, 29, 43, 57, 71 and 85
- 24 hours urine volume and diary assessments during week 14 and prior to day 99
- Physical exam, nasal cavity exam, vital signs, laboratories, pregnancy test (for female), ECG, adverse events and voiding diaries on day 99

Results:

· Study population: randomization – 806, safety population – 797, ITT – 782 (completion of the study – 701), mITT – 586

· Efficacy variables

Table 1. Results of the primary efficacy variables in the mITT and ITT populations

			1.5 mcg (N = 196)	0.75 mcg (N = 197)	Placebo (N = 193)
mITT Population	Mean nocturic episodes	Screening	3.4	3.4	3.3
		Treatment period	2	2.2	2.4
		Change from baseline	-1.4	-1.3	-1.1
		p-value	0.0002	0.0179	
	# of patients = 50% reduction in mean nocturic episodes		67 (34.2%)	47 (23.9%)	29 (15.0)
	p-value		<0.0001	0.0364	
			(N = 260)	(N = 262)	(N = 260)
ITT Population	Mean nocturic episodes	Screening	3.3	3.3	3.2
		Treatment period	1.8	1.9	2.1
		Change from baseline	-1.5	-1.4	-1.2
		p-value	0.0002	0.007	
	# of patients = 50% reduction in mean nocturic episodes		120 (46.2%)	92 (35.1%)	74 (28.5%)
	p-value		<0.0001	0.122	

Mean nocturic episodes are the value of least square mean; p-value from comparison to placebo

Table 2. Results of INTU score as a secondary variable in the mITT and ITT populations

			1.5 mcg (N = 181)	0.75 mcg (N = 190)	Placebo (N = 186)
mITT Population	INTU Impact score	Screening	33.9	32.3	32.0
		Treatment period	20.6	23.0	23.1
		Change from baseline	-12	-9.7	-9.5
	p-value		0.0653	0.9010	
			(N = 243)	(N = 247)	(N = 249)
ITT Population	INTU Impact score	Screening	33.0	31.8	31.3
		Treatment period	18.9	20.7	21.5
		Change from baseline	-14.1	-12.4	-11.5

	p-value	0.0225	0.4452

The results values are least square means; p-value from comparison to placebo

· Safety results

- Eighteen treatment emergent adverse events (TEAEs) that occurred in ≥ 2% of the patients in one or more treatment groups were reported. The incidence of adverse events is summarized in the table 2.

Table 3. Incidence of TEAEs occurring in > 2% in any active treatment group

Adverse event	1.5 mcg (N = 264)	0.75 mcg (N = 266)	Placebo (N = 267)
Nasal Discomfort	14 (5.3%)	10 (3.8%)	18 (6.7%)
Urinary Tract Infection	5 (1.9%)	12 (4.5%)	5 (1.9%)
Headache	11 (4.2%)	8 (3.0%)	7 (2.6%)
Nasopharyngitis	10 (3.8%)	10 (3.8%)	7 (2.6%)
Rhinorrhea	4 (1.5%)	3 (1.1%)	9 (3.4%)
Nasal Congestion	9 (3.4%)	4 (1.5%)	3 (1.1%)
Upper Respiratory Tract Infection	5 (1.9%)	8 (3.0%)	9 (3.4%)
Blood Sodium Decreased	8 (3.0%)	0 (0.0%)	0 (0.0%)
Sneezing	7 (2.7%)	6 (2.3%)	3 (1.1%)
Back Pain	6 (2.3%)	5 (1.9%)	2 (0.7%)
Diarrhea	0 (0.0%)	6 (2.3%)	6 (2.2%)
Blood Pressure Increased/Hypertension	6 (2.2%)	3 (1.1%)	4 (1.5%)
Nasal Discomfort	14 (5.3%)	10 (3.8%)	18 (6.7%)
Serious adverse event (SAE)	4	7	5

- The SAEs in the 1.5 mcg group included one patient with pneumonia, one with hyponatremia, one with musculoskeletal chest pain and one with salivary gland cancer. One SAE in the 1.5 mcg group which was related to study drug was the hyponatremia case.
- None of the SAEs (congestive heart failure, Crohn's disease, gastrointestinal hemorrhage, limb abscess, upper respiratory infection and fracture of the radius bone and aspiration pneumonia) in the 0.75 mcg group were considered related to the study drug. The patient with a fracture of the radius bone and aspiration pneumonia led to a death event ((b) (6), 80 years male).
- In the placebo group one patient had chest pain, one developed empyema of the gallbladder, one had squamous cell cancer, one had squamous cell skin cancer and one had prolonged and repeated episodes of hyponatremia.
- Nine SAEs were reported in the placebo lead-in (6) and screening phases (3).
- Hyponatremia

Table 4. Incidence of subjects with serum sodium < 135 mmol/L after randomization at Day 15 including unscheduled visits (Analysis by the reviewer using the Applicant's dataset)

Serum sodium	1.5 mcg (n = 263)	0.75 mcg (n = 260)	Placebo (n = 269)
< 135 mmol/L	30 (11.41%)	26 (10%)	13 (4.83%)
< 130 mmol/L	9 (3.42%)	1 (0.38%)	1 (0.37%)
≤ 125 mmol/L	2 (0.76%)	0 (0%)	1 (0.37%)

Table 5. Incidence of subjects with serum sodium < 135 mmol/L after randomization at Day 15 including unscheduled visits in the age groups (Analysis by the reviewer using the Applicant's dataset)

Serum sodium	Age	1.5 mcg	0.75 mcg	Placebo
	n	<65 = 116; ≥ 65 = 147	<65 = 116; ≥65 = 144	<65 = 120; ≥65 = 149
< 135 mmol/L	< 65	8 (6.90%)	9 (7.76%)	6 (5%)
	≥ 65	22 (14.97%)	17 (11.81%)	7 (4.70%)
< 130 mmol/L	< 65	0 (0%)	1 (0.86%)	0 (0%)
	≥ 65	9 (6.12%)	0 (0%)	1 (0.67%)
≤ 125 mmol/L	< 65	0 (0%)	0 (0%)	0 (0%)
	≥ 65	2 (1.36%)	0 (0%)	1 (0.67%)

Sponsor's conclusions:

- This study demonstrated statistically significant efficacy results for both the 1.5 and 0.75 mcg doses for both co-primary efficacy endpoints. The lower dose was significant for the percent of patients with ≥ 50% decrease in the mean number of nocturic episodes for the mITT population and just missed significance for the ITT population. The 1.5 mcg dose was statistically significant for all secondary efficacy endpoints for both populations, except for the change in INTU score for the mITT population (0.0653). The 0.75 mcg dose was significant for the time from bedtime to first nocturic episode in both the mITT and ITT populations, for the percent of nights with ≤ 1 nocturic episodes for the mITT population and for the change in nocturnal urine volume for the ITT population.
- These results indicate that both the 1.5 and 0.75 mcg doses are effective in treating adult patients with nocturia with any etiology or combination of etiologies including patients on drug treatment for benign prostatic hypertrophy and overactive bladder. The 1.5 mcg dose showed greater efficacy across all of the primary and secondary efficacy endpoints but the 0.75 mcg dose demonstrated statistical efficacy for most of the parameters which were measured and may be an appropriate starting dose for patients.
- SER120 demonstrated a good safety profile in this study. The incidences of TEAEs, SAEs, TEAEs that led to discontinuation, physical examination findings, clinical laboratory abnormalities and ECG findings were similar across the treatment groups including placebo.
- The most important safety parameter was serum sodium and that showed a low incidence of hyponatremia (serum sodium values ≤ 125 mmol/L). There were only 2 patients in the 1.5 mcg dose group, one in the placebo group and none in the 0.75 µg dose group that had serum sodium ≤ 125 mmol/L. The incidence of patients with serum sodium values in the 126 to 129 mmol/L range showed a modestly higher incidence in the high dose group than in placebo but all these patients were asymptomatic. Although nasal discomfort and other signs and symptoms of a local effect on the nasal mucosa such as rhinorrhea and sneezing were the most commonly reported TEAEs, these were usually mild to moderate in intensity and transient. Many patients found these side effects resolved or decreased with continued administration of study drug. There were 15 patients (1.9%) who discontinued study drug because of nasal irritation. These findings were found across the treatment groups including placebo in similar incidences and are commonly reported with any nasal spray. SER-120 was well tolerated at both doses evaluated in this study. SER120 at doses of 1.5 and 0.75 mcg was safe, well tolerated and effective for the treatment of nocturia in adult patients.

Reviewer's comments:

- Both, the 1.5 and 0.75 mcg, doses showed statistically significant difference for the two primary efficacy endpoints compared to the placebo group in the mITT patient populations.

- The 0.75 mcg dose group did not reach statistical significance for the proportion of subjects with 50% reduction in mean nocturic episodes in the ITT patient populations.
- The 1.5 mcg dose group demonstrated statistically significances for all secondary efficacy endpoints for both populations, except for the change in INTU score. The INTU scores as qualitative and quantitative tests of quality of life questionnaire was significantly improved following 1.5 mcg dosing, but there was no statistically significant difference from the placebo group in the mITT population. The 0.75 mcg desmopressin showed statistically significant difference of time from going to sleep to the first nocturic episode, but controversial statistical results of the other secondary endpoints when compared to the placebo group. It may suggest that the 0.75 mcg dose showed lower efficacy results over the secondary endpoints. The change in INTU score in the 0.75 mcg dose also appeared to be similar with that in the placebo group.
- The significant reduction in nocturic frequency was also observed in the placebo group. It implies that placebo effect and (or) lifestyle modification would have clinically meaningful impact on the reduction of nocturic events.
- The cases which showed the serum sodium concentration lower than 135 mmol/L were observed dominantly in the active treatment groups. The incidence results appeared to be a dose-dependent treatment effect. In general, all hyponatremic incidences appear to be lower than those observed in another phase 3 study (Study DB3).
- The elderly group, 65 years of age or older, showed a higher incidence of hyponatremia compared to the group younger than 65 years of age. The cases having a serum sodium concentration lower than 130 mmol/L were mainly observed in the elderly group.

SPC-SER120-**DB3**-201101: The pharmacokinetic evaluation in a subset of subject

Title: A randomized, double blind, placebo-controlled, parallel group, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulations in patients with nocturia

Study Design:

- Administration of one additional dose on the morning of Day 99 in a subset of the patients who participated in the DB3 study (18 patients, 9 males and 9 females, per each treatment group)
- Treatments: 0.75, 1 and 1.5 mcg desmopressin nasal spray
- Blood sampling: pre-dose and at 15,30, 45, 60, 90, 120, 180, 240 and 360 minutes post-dose
- Measurement of plasma concentrations of desmopressin: LC-MS/MS (LLoQ = 2 pg/mL)

Results:

- Desmopressin concentrations in the majority (85%) of patients were below the LLoQ within 6 hours post dose. Seven patients had all concentrations less than the LLoQ.

Table 1. Demography of subjects who received active treatments in the PK study [Source: p 27 in the PK study report of DB3 trial]

	0.75 mcg (n = 18)	**1 mcg (n = 18)**	**1.5 mcg (n = 18)**
Gender (M:F)	9 : 9	9 : 9	9 : 9
Age (years)	65.7 (52 - 81)	64.3 (52 - 84)	62.4 (51 - 80)
Weight (kg)	80.9 (42.7 -133.5)	83.4 (52.3 - 125.0)	91.7 (46.8 - 131.4)
eGFR (mL/min/1.73m^2)	81.42 (52.97 - 114.79)	81.89 (59.17 - 109.75)	80.03 (44.87 - 124.10)

Mean (range): eGFR: estimated glomerular filtration rate

Table 2. Summary of PK of desmopressin in nocturia patients following administration of 0.75, 1 or 1.5 mcg desmopressin nasal sprays [Source: p 29–31 in the PK study report of DB3 trial].

	0.75 mcg	**1 mcg**	**1.5 mcg**
	mean ± SD (the number of subjects)		
C_{max} (pg/mL)	4.00 ± 3.85 (16)	4.43 ± 3.06 (17)	9.11 ± 6.90 (15)
T_{max} (hour)	0.25 (0.25-0.5)* (12)	0.25 (0.25-0.75)* (14)	0.75 (0.25–3.0)* (15)
AUC_t (pg·h/mL)	5.13 ± 7.49 (16)	6.43 ± 6.74 (17)	23.10 ± 18.95 (13)
AUC_{inf} (pg·h/mL)	15.96 ± 11.58 (9)	16.37 ± 10.39 (12)	41.33 ± 19.54 (10)
$t_{1/2}$ (hour)	1.87 ± 1.13 (9)	2.11 ± 1.36 (11)	2.79 ± 0.87 (10)

*median (range)

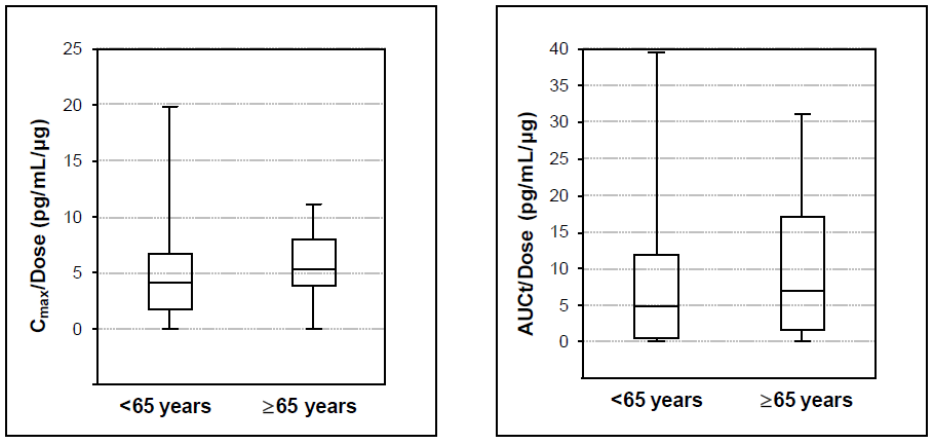


Figure 1. Dose-normalized C_{max} and AUC_t of desmopressin between the elderly group (65 years and older) and the group younger than 65 years [Source: p 37 in the PK study report of DB3 trial].

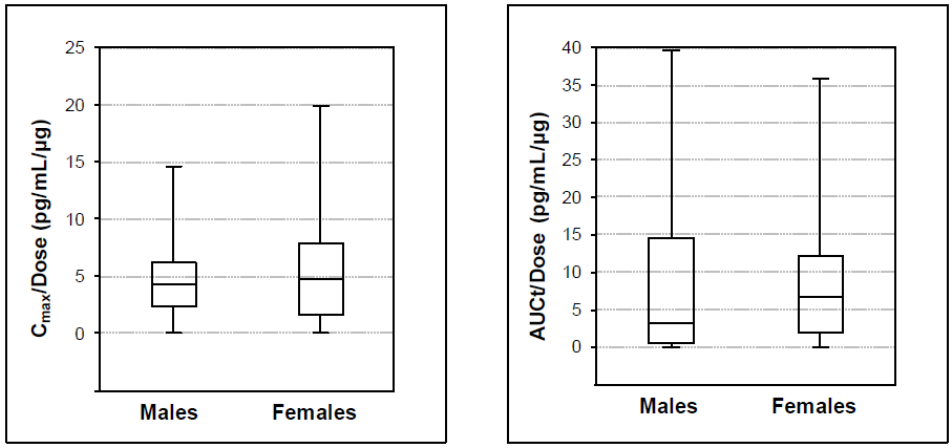


Figure 2. Dose-normalized C_{max} and AUC_t of desmopressin between the male and female groups [Source: p 36 in the PK study report of DB3 trial].

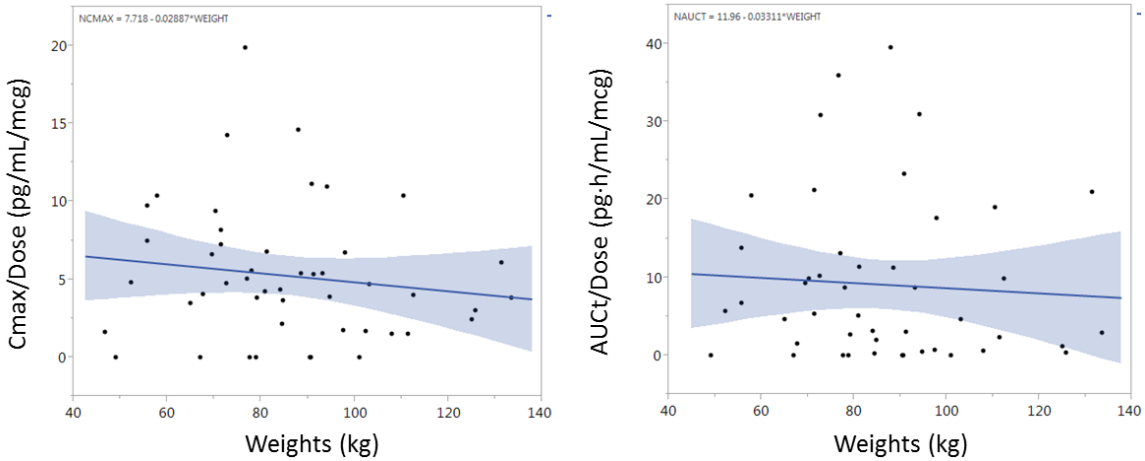
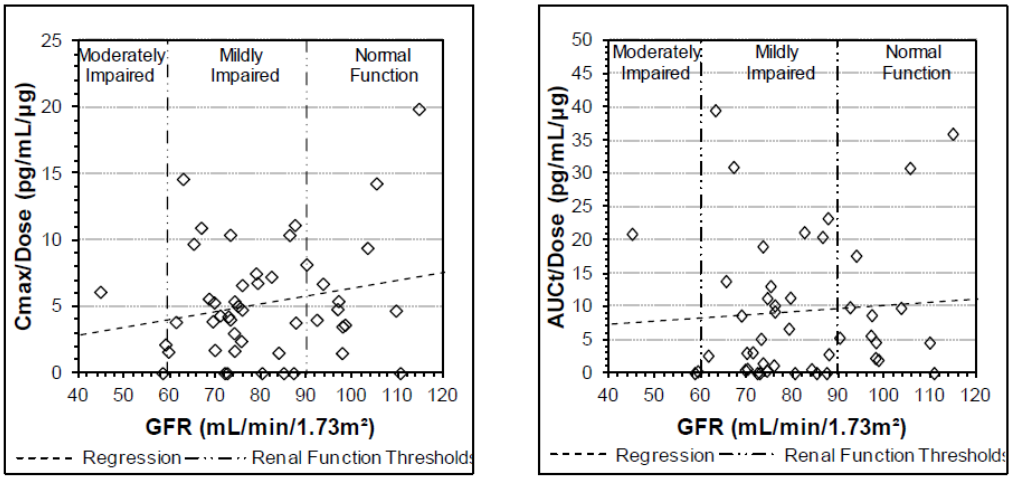


Figure 3. Relationships between dose-normalized C_{max} and AUC_t of desmopressin and patients' weight [Analysis using the dataset of the PK study report of DB3 trial].



Regression for C_{max}/Dose: 0.0591 x GFR + 0.0486; R^2= 0.0444
Regression for AUCt/Dose: 0.0472 x GFR + 5.28; R^2= 0.0048

Figure 4. Relationships between dose-normalized C_{max} and AUC_t of desmopressin and patients' eGFR [Source: p 38 in the PK study report of DB3 trial].

Table 3. Summary of C_{max} and AUC_t of desmopressin for the responder* and non-responder in the PK subpopulation [Source: p 32 in the PK study report of DB3 trial].

		0.75 mcg	1 mcg	1.5 mcg
Mean (range) [the number of subjects]				
C_{max} (pg/mL)	Responder	5.26 (1–14.90) [8]	4.23 (3.28-5.31) [4]	9.03 (2.26-21.90) [10]
	Non-responder	4.30 (1–12.70) [9]	4.62 (1–10.40) [14]	9.28 (2.30-16.70) [5]
AUC_t (pg·h/mL)	Responder	10.72 (0.28-26.99) [6]	4.44 (3.04-5.63) [3]	25.50 (3.39-59.30) [8]
	Non-responder	2.95 (0.37–5.01) [6]	8.73 (0.27–21.19) [11]	7.02 (0.86-46.51) [5]

*responder: 50% decrease in the mean number of nocturic episodes during treatment period; Seven patients that had all concentrations less than the LLOQ were assigned to a C_{max} value of 50% of the LLoQ (1 pg/mL) for this analysis.

Sponsor's conclusions:

- Inter-patient variability in systemic exposure was similar to what had been observed previously in healthy normal volunteer populations administered the same formulation. Systemic exposure increased with increasing dose in a manner consistent with dose proportionality.
- Systemic exposure to desmopressin was not dependent on either patient sex or age. Systemic exposure to desmopressin in elderly patients (≥ 65 years of age) was comparable to that in younger patients (< 65 years of age). In patients with GFR ≥ 50 mL/min/1.73 m², neither sex nor age was helpful in predicting the effective desmopressin dose for the patient. Systemic exposure to desmopressin did not show a dependence on renal function over the limited range of GFR variation encountered in the study population (limited per protocol to patients with GFR ≥ 50 mL/min/1.73 m²). Desmopressin exposure was not increased in patients with mild renal impairment compared to patients with normal renal function.
- SER120 showed a positive exposure-response relationship when using either C_{max} or AUC_t as the "exposure" measure, and the proportion of the population responding positively to the treatment as the "response" measure. Both the mITT and rITT sub-populations showed increasing response rates in the patient population with increasing values of either Cmax or AUC_t.
- A substantial minority of nocturia patients that were placebo responders during the placebo lead-in period reverted to having non-responder status during SER120 treatment if their SER120 exposures were in the low or intermediate range, indicating that a portion of the placebo responder sub-population probably also achieved benefit from receiving the treatment.

Reviewer's comments:

- The PK was reanalyzed using the concentration data by the reviewer. The reanalyzed individual PK results were comparable to those that the Sponsor provided. It is noted that the Applicant considered desmopressin concentrations below the LLoQ as zero. Patients who had concentrations below the LLoQ over the entire PK observation period were considered as having a C_{max} of 0 pg/mL and an AUC of 0 pg·h/mL for descriptive statistics.
- Large interindividual variability in systemic exposure of desmopressin was observed in nocturic patients following administration of desmopressin nasal sprays.
- The C_{max} values were observed at within 1 hour after administration. The C_{max} and AUC values tended to increase slightly greater than dose proportional between 0.75 mcg and 1.5 mcg, but lesser than dose proportional between 0.75 mcg and 1 mcg.
- There was no significant difference in the dose-normalized C_{max} and AUC_t of desmopressin between the elderly group (65 years of age and older) and the group younger than 65 years of age.
- There was no significant difference in the dose-normalized C_{max} and AUC_t of desmopressin between gender groups.

- The dose-normalized C_{max} and AUC of desmopressin tended to be decreased in a body weight-dependent manner, but showed no significant relationship with the patients' body weight.
- There was a trend toward an increase in dose-normalized C_{max} and AUC_t of desmopressin with decreasing renal function. However, the relationship between PK parameters and patients' eGFR was not statistically significant. This study did not include subjects with an eGFR of less than 50 mL/min/1.73m^2. This exclusion criterion may lead to no significant association between systemic exposure of desmopressin and eGFR observed in this study.
- The AUC_t of desmopressin appeared to be higher in the responder group than the non-responder group following administration of 0.75 or 1.5 mcg desmopressin nasal sprays, but this trend was not observed in 1 mcg treatment. In general, the distribution of individual AUC_t appeared overlapped between the responders and non-responder in each treatment group. These data may have limitations for exposure-response analysis as the following reasons: 1) The limited number of subjects per the responder and non-responder groups, 2) Large interindividual variability of parameters among the patients and 3) A number of blood samples had concentration lower than LLoQ.

Pooled pharmacokinetic analysis

Title: An evaluation of the pharmacokinetics of SER120 nasal spray formulation in patients with nocturia using pooled pharmacokinetic results from 5 clinical studies

Study method:

· Pharmacokinetic results from 5 studies were incorporated for the pooled analysis.

Study	Study title	Treatments and sample size
200802	Dose ranging study in patients with nocturia	n=5; 0.5 mcg as a single spray; n=5; 1 mcg as 2 sprays in 1 nostril n=5; 1 mcg as 1 spray in each nostril n=5; 1.5 mcg as 3 sprays
201001	Phase 3 study in elderly patients (≥ 75 years) with nocturia	n=10; 0.5 mcg; elderly (≥75 years) n=12; 0.75 mcg; elderly (≥75 years)
201002	Phase 1 study in patient with impaired renal function	n=8; 0.75 mcg (eGFR <50 mL/min/1.73 m^2) n=8; 0.75 mcg (age, sex, BMI matched with eGFR >50 mL/min/1.73 m^2)
DB1 (200901)	Phase 3 study	n=19; 0.5 mcg dose n=29; 0.75mcg dose
DB3 (201101)	Phase 3 study	n=18; 0.75 mcg dose n=18; 1.0 µg dose n=18; 1.5 µg dose

· Pharmacokinetic parameters: C_{max}, AUC_t and terminal half-life

· The impact of intrinsic factors including sex, age, body weight, BMI and renal function on the pharmacokinetic parameters were evaluated.

· The impact of the used assay methods to determine the plasma desmopressin concentrations was also analyzed.

Applicant's results and conclusion:

· Observed concentrations were generally quite low, often with no plasma concentrations exceeding the lower limit of quantitation (LLOQ), especially following administration at the lower doses.

· Desmopressin exposures, C_{max} nor AUC_t, showed statistically significant associations with patient age, sex, body weight, BMI or renal function. The desmopressin elimination half-life did become prolonged in patients with substantially reduced renal function (creatinine clearance or estimated glomerular filtration rate less than 50 mL/min/1.73 m2), although the trend for a prolongation in half-life with decreasing renal function was not statistically different in patients with mild renal impairment (60-89 mL/min/1.73 m2) compared to patients with normal renal function (≥90 mL/min/1.73 m2).

· The type of assay (RIA or LC-MS/MS) used for the bioanalytical support was a critical factor in the desmopressin plasma concentration obtained, but did not affect the basic conclusions drawn.

Reviewer's comments:

· The data for this pooled pharmacokinetic analysis were collected from the 5 clinical studies performed in diverse study populations in terms of age, sex and renal function. The used desmopressin dosage and concentration and administration methods were different among the studies.

- There was no identified significant covariate out of intrinsic factors on the pharmacokinetic parameters, C_{max} and AUC_t, of desmopressin. These seem to be consistent with the results analyzed using the pharmacokinetic data from Study DB3.
- Given that desmopressin is excreted mainly by the kidneys, renal function significantly affects the systemic exposure of desmopressin. However, this pooled pharmacokinetic analysis did not identify renal function as a significant covariate. It is noted that the data from a limited number of patients with severe or moderate renal impairment were included for this pooled analysis.
- This analysis identified the type of assay method as a critical factor in the desmopressin plasma concentration. It may suggest that the impact of the assay type may impair comparability of the pharmacokinetic parameters among the studies using different bioanalytical methods. However, it is noted that clinical pharmacokinetic information for the to-be-marketed desmopressin nasal spray products was provided from the pharmacokinetic study of Study DB3.

4.4 References

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6) Juul KV, Klein BM, Sandström R, Erichsen L, Nørgaard JP. Am J Physiol Renal Physiol. Gender difference in antidiuretic response to desmopressin. 2011;300:1116-22.

7) Lose G, Mattiasson A, Walter S, Lalos O, van Kerrebroeck P, Abrams P, Freeman R Clinical experiences with desmopressin for long-term treatment of nocturia. J Urol 2004;172:1021–1025

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9) Natesto nasal gel prescribing information
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205488s001lbl.pdf

10) National Kidney Foundation - KDOQI Clinical Practice Guidelines for Chronic Kidney Disease
http://www2.kidney.org/professionals/KDOQI/guidelines_ckd/p4_class_g1.htm

11) Nicotrol®NS prescribing information
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020385s010lbl.pdf

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/s/

JIHONG SHON
01/18/2017

LUNING ZHUANG
01/18/2017

JEFFRY FLORIAN
01/18/2017

DOANH C TRAN
01/18/2017

EDWARD D BASHAW
01/18/2017
concur with need for PMR for comparative BA study at equal doses should both doses be approved.

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	201656	**SDN**	1
Applicant	Serenity Pharma. LLC.	**Submission Date**	02/04/ 2016
Generic Name	Desmopressin acetate	**Proposed Brand Name**	Noctiva
Drug Class	Synthetic analogue of vasopressin		
Indication	Treatment of nocturia in adults (wake up 2 or more times per night to void)		
Dosage Regimen	· The recommended starting dose is 0.75 mcg each night for 2-4 weeks. Based on individual patient efficacy and tolerability, the dose may be increased to 1.5 mcg each night. · A single spray in either the left or right nostril each night approximately 30 minutes before going to bed		
Dosage Form	Spray	**Route of Administration**	Intranasal use
OCP Division	DCP3	**OND Division**	DBRUP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Jihong Shon	Myong Jin Kim
Pharmacometrics	Luning (Ada) Zhuang	Jeffry Florian
Genomics	N/A	N/A

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	4/4/2016	**74-Day Letter Date**	4/18/2016
Review Due Date	10/31/2016	**PDUFA Goal Date**	12/4/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

Major review issues:

- Dosing regimen in elderly population based on benefit-risk (e.g. hyponatremia) assessment
- The proposed regimen in patients with renal impairment including contraindication for the patient with a calculated glomerular filtration rate (GFR) below 50 mL/min/1.73m^2 will be a review issue.
- While the Sponsor proposes that initial dose of 0.75 mcg can be titrated to 1.5 mcg based on individual patient efficacy and tolerability, two pivotal phase 3 studies (Study DB3 and DB4) of 0.75 mcg and 1.5 mcg were conducted in fixed dose of each dose without titration scheme. The proposed titration scheme will be a review issue.
- The Sponsor proposes that the target patient population is adults (b) (4). However, phase 3 studies enrolled patients 50 years of age or older. The age of target population will be a review issue.

Information request:

- Provide the dose-response relationship analysis for efficacy and safety supporting the proposed regimen of desmopressin nasal spray. Include the dataset(s) and analysis scripts used for the dose-response analyses.
- Submit the safety analysis based on other age cut-off points such as 75 years or older.
- Provide supporting information for safe use of desmopressin nasal spray in rhinitis patients.
- The Canadian product monographs of desmopressin products and one published article on in vitro metabolism of vasopressin are submitted to support that desmopressin do not have any effect on 9 cytochrome P450 enzymes. However, these do not contain any direct evidence to support the lack of interaction potential. Submit the relevant information.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☑ Metabolism Characterization		1	A publication of in vitro metabolism study
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		1	Study 200801 (comparative bioavailability study of nasal spray administration, intradermal injection and subcutaneous injection)
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	Study 200801
	☑ Multiple Dose	1	Study 200801
Patients	☐ Single Dose		
	☑ Multiple Dose	5	Study 200802, 201001, 201002, DB1 and DB3
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☑ Sex			Study DB3
☑ Geriatrics			Study 201001 and pooled PK analysis report

☐ Pediatrics		
☐ Hepatic Impairment		
☑ Renal Impairment		Study 201002 and pooled PK analysis report
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients	1	Study 200801
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	1	Pooled PK analysis report
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**	1	**In Vivo**	10
Total Number of Studies to be Reviewed		1		8

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	The to-be-marketed formulation is same as the clinical formulation.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	Desmopressin is a peptide analogue and metabolized by proteolytic degradation.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☑No ☐N/A	No exposure-response analysis
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☑No ☐N/A	No exposure-response analysis
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

❖ **Introduction**

On February 4, 2016, the Sponsor submitted a New Drug Application (NDA) for desmopressin nasal spray for the treatment of nocturia in adults who wake up 2 or more times per night to void. Desmopressin is a synthetic analogue of vasopressin, antidiuretic hormone that is normally secreted by the pituitary gland and acts on the kidneys and blood vessels to retain water in the body. The proposed dosage and administration is a single spray in either the left or right nostril each night approximately 30 minutes before going to bed. The recommended starting dose is 0.75 mcg each night for 2-4 weeks. Based on individual patient efficacy and tolerability, the dose may be increased to 1.5 mcg each night.

Desmopressin is currently approved for indications of central diabetes insipidus, primary nocturnal enuresis, type I von Willebrand's disease, and hemophilia A (initial US approval: 1978). The nasal solution, injection,

and oral tablets are available for the currently approved indications in the US.

In support of this NDA, the Sponsor conducted 10 clinical studies including two phase 1, one phase 2, five phase 3 and two long-term extension studies in healthy volunteers or target patient population. The list of clinical trials is summarized in Table 1. In addition, the Sponsor submitted non-clinical studies and the publication to support this NDA.

Table 1. List of clinical trials submitted for NDA of desmopressin nasal spray

Protocol No.	Title	Study description/ objective	Study Design
SPC-DESMO-NS-**200801**	A dose titration study to investigate the anti-diuretic effect and pharmacokinetics of a low dose nasal spray formulation of desmopressin in water loaded healthy non-smoking male and female volunteer subjects	Phase 1 Dose escalating study / comparative bioavailability study Evaluation of 1) anti-diuretic effect, 2) PK, 3) safety and 4) dose-response relationship	· An open-label, escalating dose titration study · 6 healthy male and female subjects who were water-loaded prior to dosing with test drug · 0.5, 1 and 2 mcg single dose (100, 200 and 400 μL of 5 mcg/mL, respectively), · 120 ng intradermal or subcutaneous injection
SPC-SER120-CRI-**201002**	A phase 1 study to investigate the pharmacokinetics of SER120 nasal spray formulation in subjects with impaired renal function and in normal healthy volunteers	Phase 1 Renal impairment study Evaluation of the PK in subjects with impaired renal function	· An open-label, PK study · 8 subjects (eGFR < 50 mL/min/1.73m^2) and matched (sex, age, and body mass index (BMI)) 8 normal healthy subjects (eGFR > 60 mL/min/1.73m^2) · 0.75 mcg (100 μL of 7.5 mcg/mL) single dose
SPC-DESMO-NS **200802**	A multi-center dose titration study to investigate the pharmacodynamics, pharmacokinetics and safety of daily doses of desmopressin nasal spray in patients with nocturia	Phase 2a Dose titration study PK study in a subset Evaluation of 1) antidiuretic effect of daily doses in patient in nocturia 2) PK, 3) safety and 4) dose-response relationship	· An open-label, multicenter, dose titration study · 0.5, 1 or 1.5 mcg (100, 200 or 300 μL of 5.0 mcg/mL, respectively) once daily for 10 to 12 days · 40 nocturia patients from 3 study sites (43 patients: 32 = 0.5 mcg and 11 = 1 mcg) · No. of PK subjects: 0.5 mcg = 5, 1 mcg = 10, and 1.5 mcg = 5
SPC-SER120-ELD-**201001**	A phase 3 randomized, open-label, multicenter study to investigate the safety and pharmacokinetics of SER120 nasal spray formulations in elderly patients (≥ 75 years old) with nocturia	Phase 3 Safety and PK study in elderly patients Evaluation of 1) safety, 2) PK, and 3) efficacy	· A randomized, open, dose optimization study · 0.5 or 0.75 mcg (100 μL of 5.0 or 7.5 mcg/mL, respectively) once daily for 14 days (up- or down-titration during the study) · 32 nocturia patients ≥ 75 years old from 4 study sites · No. of PK subjects: 0.5 mcg = 10 and 0.75 mcg = 12

SPC-SER120-**DB1**-**200901**	A phase 3 randomized, double blind, placebo control, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia	Phase 3 Efficacy and safety study PK study in a subset	· A randomized, double blind, placebo-controlled, parallel group study · Up-titrated only once in a 3-week titration phase · Placebo vs active - 0.5 or 0.75 mcg (100 µL of 5.0 or 7.5 mcg/mL) once daily for 49 days · 150 subjects per each group (placebo = 153 vs active = 148) · PK subjects: 0.5 mcg = 19 and 0.75 mcg = 29
SPC-SER120-**DB2**-200902	A phase 3 randomized, double blind, placebo control, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia	Phase 3 Efficacy and safety study Non-PK study	· A randomized, double blind, placebo-controlled, parallel group study · Up-titrated only once in a 3-week titration phase · Placebo vs active - 0.5 or 0.75 mcg (100 µL of 5.0 or 7.5 mcg/mL) once daily for 49 days · 150 nocturia patients per each group (placebo = 159 vs active = 167)
SPC-SER120-**DB3**-201002	A randomized, double blind, placebo control, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia	Phase 3 Efficacy and safety study PK study in a subset	· A randomized, double blind, placebo-controlled, parallel group study · 2-week screening period to ensure entry criteria · No titration · Placebo, 0.75, 1 or 1.5 mcg (100 µL of placebo, 7.5, 10 or 15 mcg/mL) once daily for 98 days · 180 nocturia patients per each of four groups (placebo = 187, 0.75 mcg = 188, 1 mcg = 186 and 1.5 mcg = 184) · PK subjects: 0.75 mcg = 17, 1 mcg = 18 and 1.5 mcg = 18
SPC-SER120-**DB4**-201301	A randomized, double blind, placebo control, multicenter study to investigate the efficacy and safety of SER120 nasal spray formulation in patients with nocturia	Phase 3 Efficacy and safety study Non-PK study	· A randomized, double blind, placebo-controlled, parallel group study · 2-week screening period to ensure entry criteria · No titration · Placebo, 0.75 or 1.5 mcg (100 µL of 7.5 or 15 mcg/mL) once daily for 98 days · 250 subjects per each of three groups (placebo = 267, 0.75 mcg = 266, and 1.5 mcg = 264)
SPC-SER120-OL1-200903	A phase 3 open-label study to investigate the safety of SER120 nasal spray formulation in patients with nocturia completing study SPC-SER120-DB1-200901 or Study SPC-SER120-DB2-200902	Long-term safety study	
SPC-SER120-DB3-201101 A.2	An open-label, long term safety extension amendment to the SPC-SER120-DB3-2011 to evaluate the safety and tolerability of 1.0 µg and 1.5 µg Doses of SER120 in patients with nocturia	Long-term safety study	

❖ **Regulatory history under IND 076667**

Date	Type of submission or meeting	Major communicated clinical pharmacology issues
11/12/07	Pre-IND meeting	1) The systemic bioavailability of desmopressin from the proposed formulation should be characterized. 2) The Sponsor is advised to improve the analytical capabilities to detect the anticipated concentration of desmopressin. 3) The absence of drug-drug interaction studies in the NDA should be justified.
02/19/09	End of phase 2 meeting	1) The PK of strength formulation used in phase 3 studies should be characterized. 2) The blood sampling time for population PK should be decided based on the detection limit. 3) A more sensitive analytical method needs to be developed. 4) The number of elderly subject needs to be sufficient for analysis.
05/15/09	Submission of phase 3 trial protocol	1) The PK study approach is acceptable, but the Sponsor was advised to collect the sufficient time-points. 2) The PK study plans to address the effect of renal impairment and sex are reasonable. 3) Appropriate information needs to be communicated in the labeling if the Sponsor does not plan to conduct a PK study in rhinitis patients.
07/28/10	PreNDA meeting submission (Written response only)	The sponsor should adequately characterize the PK of desmopressin from the to-be marketed (TBM) formulation at the intended clinical doses and dosing regimen.
03/13/13	Type A meeting to discuss the clinical development program	The approaches to address PK in elderly and renal impairment patients seem reasonable. The acceptability of the data is a review issue.
08/18/15	PreNDA meeting	1) The PK profile of the TBM formulation should be summarized from the most relevant PK studies. 2) The effect of age, sex, specific populations (e.g. renal impairment), and body mass on the PK of desmopressin should be addressed based on the data from the PK studies, 3) What type of data supports the PK and pharmacodynamics (PD) information for labeling in the NDA submission, and 4) The data supporting PK characteristics of the TBM product should be derived from the PK studies using the validated assay method.

· This IND was initially assigned to Division of Bone, Reproductive, and Urologic Products (DBRUP). However, it was transferred to Division of Metabolism and Endocrinology Product (DMEP) after the end of phase 2 meeting took a place on February 19, 2009. It was then transferred back to DBRUP on April 21, 2014.

❖ **Clinical pharmacology findings from the NDA submission package of desmopressin nasal spray**

1) Mechanism of action and pharmacodynamics

· Desmopressin is a synthetic analogue of vasopressin. Desmopressin binds selectively to vasopressin 2 receptors on renal cells in the collecting ducts and increase water re-absorption in the kidney and thereby reduce urine production.

· While desmopressin has strong antidiuretic effect, it does not produce significant vasoconstrictive or uterotonic activity because it exerts minimal vasopressin 1 receptor-mediated effect.

2) Efficacy

· This NDA package includes the reports of five phase 3 studies. Two studies (Study DB3 and DB4) evaluated the efficacy of the proposed doses of 0.75 and 1.5 mcg desmopressin nasal spray. The efficacy results are summarized in table 2.

Table 2. Results of the major efficacy variables in the Study DB3 and DB4

	DB4 study			DB3 study		
	1.5 mcg	0.75 mcg	Placebo	1.5 mcg	0.75 mcg	Placebo
ITT Population*	n=260	n=262	n=260	n=179	n=186	n=186
Baseline and mean change from baseline to the 12-week treatment period in nocturic episodes per night						
Baseline	3.3	3.3	3.2	3.2	3.4	3.4
Change from baseline	-1.5	-1.4	-1.2	-1.6	-1.4	-1.2
Comparison vs. Placebo (p-value)	0.0002	0.0070	-	<0.0001	0.0093	-
Percent of patients achieving ≥50% reduction in nocturic episodes per night from baseline						
12-week treatment period	46.2%	35.1%	28.5%	52.0%	41.4%	32.8%
Comparison vs. Placebo (p-value)	<0.0001	0.1220	-	0.0002	0.0899	-

* the intent-to-treat population included all randomized patients.

- Mean nocturic episode per night in the 12-week treatment period was reduced by more than one episode from baseline in the treatment and the placebo groups. Although significant placebo effect on efficacy was observed, two active treatment groups showed statistically different reduction in nocturic episodes compared to the placebo group.
- Percentage of patients who achieved ≥ 50% reduction in nocturia episodes demonstrated a tendency of dose-dependent improvement. The treatment group of 1.5 mcg showed statistically significant improvement over the placebo group, but the treatment group of 0.75 mcg did not reach to a statistical significance.
- While the Sponsor proposes that initial dose of 0.75 mcg can be titrated to 1.5 mcg based on individual patient efficacy and tolerability, two pivotal phase 3 studies were conducted in fixed dose of two (0.75 and 1.5 mcg) or three (0.75, 1 and 1.5 mcg) doses without titration scheme.
- All phase 3 studies enrolled the patients who were 50 years and older. However, the proposed target patient population is adults (b) (4).

3) Safety

- Safety data were collected from 10 clinical studies including two long-term extension trials performed with desmopressin nasal spray in nocturia patients. Over 1250 patients received active drug at doses from 0.5 to 1.5 mcg from 12 days to over 24 months.
- Adverse reactions reported in two pivotal phase 3 studies of 0.75 mcg and 1.5 mcg (Study DB3 and DB4) are summarized in the table 3.

Table 3. Adverse reactions reported in double-blind, placebo-controlled clinical trials (DB3 and DB4 studies) in Patients with nocturia

Adverse Reactions	NOCTIVA 1.5 mcg (N=448)	NOCTIVA 0.75 mcg (N=454)	Placebo (N=454)
SYSTEMIC			
Hypertension/Blood Pressure Increased	14 (3.1%)	7 (1.5%)	8 (1.8%)

Blood sodium decreased	11 (2.5%)	5 (1.1%)	0 (0.0%)
Hyponatremia	5 (1.1%)	1 (0.2%)	1 (0.2%)
LOCAL			
Nasal Discomfort	25 (5.6%)	16 (3.5%)	25 (5.5%)
Nasopharyngitis	17 (3.8%)	14 (3.1%)	12 (2.6%)
Nasal Congestion	12 (2.7%)	7 (1.5%)	5 (1.1%)
Rhinorrhea	11 (2.5%)	8 (1.8%)	14 (3.1%)
Sneezing	10 (2.2%)	10 (2.2%)	6 (1.3%)
Epistaxis	8 (1.3%)	5 (1.1%)	6 (1.3%)

Hyponatremia: serum sodium concentration ≤ 125 mmol/L

- All cases of hyponatremia and blood sodium decreased were observed in the active treatment groups except for one hyponatremic case in the placebo group. The incidence results showed a dose-dependent treatment effect tendency.
- The analysis of serum sodium concentrations based on age showed that patients 65 years and older had a higher incidence tendency of serum sodium values below the normal range (<135 mmol/L) compared to patients younger than 65 years (Table 4).

Table 4. Serum sodium concentrations below normal range in the 4 phase 3 studies (DB1, DB2, DB3, DB4) in nocturia patients based on age.

Serum sodium Concentrations (mmol/L)	1.5 µg <65 years (N=202)	1.5 µg ≥65 years (N=246)	0.75 µg <65 years (N=308)	0.75 µg ≥65 years (N=349)	Placebo <65 years (N=377)	Placebo ≥65 years (N=389)
130-134	18 (8.9%)	32 (13.0%)	12 (3.9%)	32 (9.2%)	13 (3.4%)	17 (4.4%)
126-129	0 (0%)	9 (3.7%)	2 (0.6%)	7 (2.0%)	1 (0.3%)	0 (0%)
≤125	0 (0%)	5 (2.0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)

- The cases of hypertension or blood pressure increase appeared to be around two-fold higher in the 1.5 mcg group than 0.75 mcg and placebo groups. The incidence of local adverse reactions was comparable among the treatment groups except for sneezing and nasal congestion symptoms (Table 3).

4) Systemic exposure to desmopressin

- The PK of desmopressin in nocturia patients following nasal administration of 0.75, 1.0 or 1.5 mcg desmopressin was evaluated in a subpopulation of the patients that participated in the phase 3 study (Study DB3). The PK parameters of desmopressin are summarized in table 3.

Table 5. Summary of PK of desmopressin in nocturia patients after 98 days treatment of 0.75 or 1.5 mcg desmopressin nasal spray.

PK parameter	0.75 mcg	1 mcg	1.5 mcg
	mean ± SD (range, the number of subjects)		
C_{max} (pg/mL)	4.00 ± 3.85 (0-14.9, 16)	4.43 ± 3.06 (0-10.4, 17)	9.11 ± 6.90 (2.26–21.90, 15)
T_{max} (hour)	0.25* (0.25-0.5, 12)	0.25* (0.25-0.75, 14)	0.75* (0.25–3.0, 15)
AUC_t (pg·h/mL)	5.13 ± 7.49 (0-26.99, 16)	6.43 ± 6.74 (0-21.19, 17)	23.10 ± 18.95 (0.86–59.30, 13)
$t_{1/2}$ (hour)	1.87 ± 1.13 (0.73-4.29, 9)	2.11 ± 1.36 (0.77-5.53, 11)	2.79 ± 0.87 (1.44–3.81, 10)

*median value

- A large inter-subject variability was observed in the values of C_{max} and AUC_t. C_{max} showed dose proportionality over the range of tested doses, but AUC_t tended to increase higher than dose proportionality.

5) Specific populations

· The effect of age

- The PK of desmopressin following nasal spray of 0.5 and 0.75 mcg desmopressin was evaluated in elderly patients (≥ 75 years old) with nocturia. However, the most of desmopressin concentrations were below the lower limit of quantitation (LLoQ) and thus the PK in the elderly population was not characterized from this study.
- The effect of age on the systemic exposure to desmopressin was analyzed using the PK data from the phase 3 study (Study DB3). While the older patient group tended to have higher exposure to desmopressin than the younger patient group, the non-parametric comparison between two age groups, < 65 years and ≥ 65 years, showed no significant difference. High variability in PK parameters was observed in both groups.

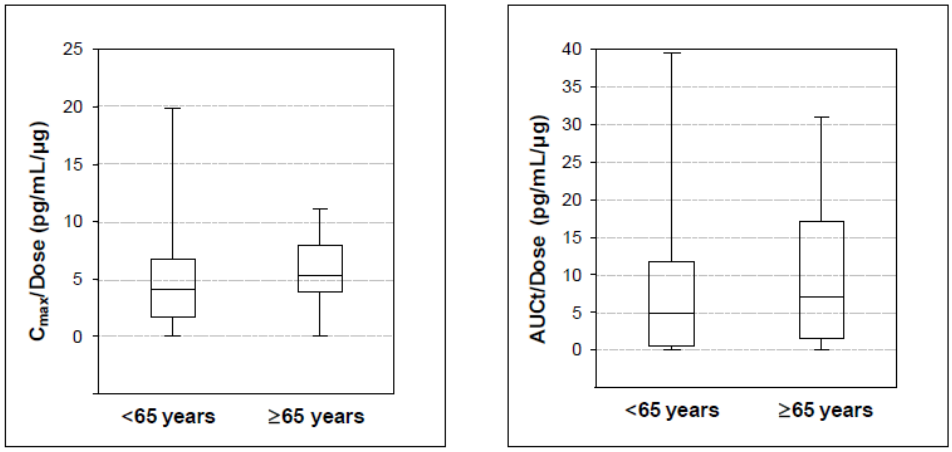

Figure 1. Comparison (box plots) of dose-normalized C_{max} and AUC_t between two age groups, < 65 years (n = 30 for C_{max} and 18 for AUC_t) and ≥ 65 years (n = 18 for both parameters).

· The effect of sex

- The effect of sex on the systemic exposure to desmopressin was analyzed using the PK data from the phase 3 study (Study DB3). While the female group tended to have higher exposure to desmopressin than the male group, the non-parametric comparison between sex groups showed no significant difference.

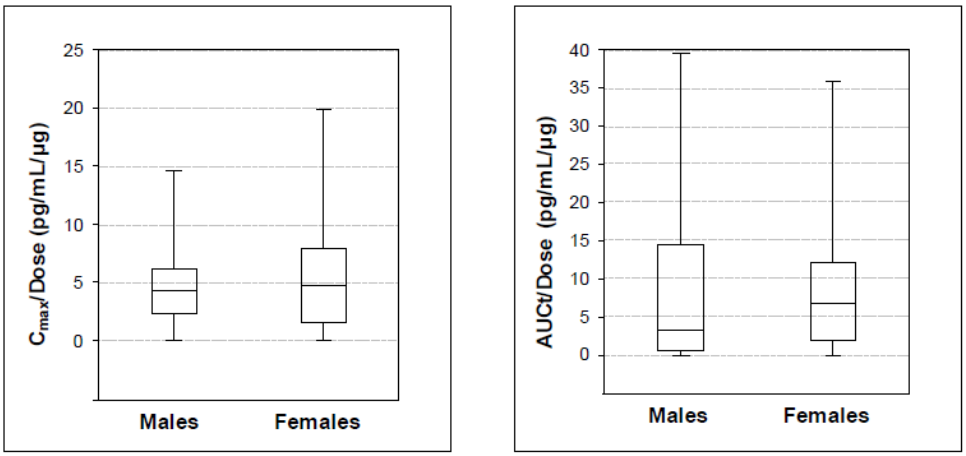

Figure 2. Comparison (box plots) of dose-normalized C_{max} and AUC_t between male and female groups (males - n = 24 for C_{max} and n= 23 for AUC_t and female – n= 23 for both parameters).

- The percentages of female patients in the two pivotal phase 3 studies of 0.75 and 1.5 mcg desmopressin were 38.3% and 40% of the total study populations, respectively.

· Renal impairment:

The effect of renal impairment on the PK of desmopressin following nasal spray of 0.75 mcg desmopressin single dose was evaluated in patients with renal impairment and the matched (age, sex, and BMI) subjects with mild renal impairment or normal renal function (Study 201002). Terminal half-life and AUC_t were prolonged and increased by approximately 3-fold in the group with renal impairment, respectively (Table 6).

Table 6. Summary of PK of desmopressin in subjects with impaired renal function and matched subjects with mild renal impairment and normal renal function after single dose treatment of 0.75 mcg desmopressin nasal spray.

	Renal impairment group	Matched group (Mild renal impairment and normal renal function)
Range of eGFR	22-43 mL/min/1.73^2	69-103 mL/min/1.73^2
PK parameter: mean ± SD (range, the number of subjects)		
C_{max} (pg/mL)	2.09 ± 1.30 (0 – 4.65, 8)	1.80 ± 1.35 (0 – 3.39, 8)
T_{max} (hour)	0.5* (0.25 – 2, 7)	0.5* (0.25 – 1.5, 6)
AUC_t (pg·h/mL)	4.72 ± 4.28 (0 – 11.32, 8)	1.55 ± 1.67 (0 – 4.31, 9)
$t_{1/2}$ (hour)	3.40 ± 1.80 (1.95 – 5.87, 4)	1.05 ± 0.24 (0.85 – 1.31, 3)

*median value

- The effect of renal function on the systemic exposure to desmopressin was analyzed using the PK data from one phase 3 study (Study DB3). There was no significant change in exposure of desmopressin with renal function over the relatively limited range of renal function. The patients with an eGFR of less than 50 mL/min/1.73m^2 were excluded in this study.

6) Potential of drug-drug interaction

· The Sponsor did not submit any data from in vivo PK studies to evaluate potential drug-drug interactions with other medications.

· Desmopressin is a peptide and subject to common peptide catabolism. Therefore, it is unlikely that the route of administration would affect the metabolic pathways of desmopressin.

· The risk of water intoxication and hyponatremia should be considered when concomitantly administered with the drugs that may cause water retention and lower the blood concentration of sodium such as tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine.

· The proposed labeling (section 12.3 pharmacokinetics – Metabolism) describes that desmopressin did not show any effect on any of the nine CYP 450 subtypes. The Sponsor submitted the Canadian product monographs of desmopressin products and one publication of in vitro metabolism of vasopressin as references supporting this labelling information responding to the reviewer's request (March 21, 2016). However, the reviewer concludes that these references are not direct evidence supporting this information.

7) Bioanalysis

- The Sponsor submitted the validation reports for measurements of desmopressin. Two analytical methods, radioimmunoassay (RIA) and Liquid chromatography-tandem mass spectrometry **(**LC-MS/MS**),** were used through the PK studies in the development program.
- In the cross-comparison of the PK results of 0.75 mcg desmopressin from two studies using RIA and LC-MS/MS, respectively, the systemic exposure to desmopressin in the study using LC-MS/MS appeared to be higher significantly than that in the study using RIA.

Table 4. Cross-comparison of PK results of desmopressin between two studies using different assay methods respectively

Study	Study DB1	Study DB3
Design	0.750 mcg (49 days) N=29 (M15/F14)	0.75 mcg (98 days) N=17 (M8/F9)
Assay method	RIA (LLoQ=2.5pg/mL) (the extended LLOQ = 1.25pg/mL)	LC-MS/MS (LLoQ=2pg/mL)
PK results	C_{max} = 1.94±1.82 (0~7.57) pg/mL T_{max} = 0.50 (0.25~3.0) hr AUC = 2.04±3.79 (0~18.4) pg·h/mL	C_{max} = 4±3.85 (0~14.9) pg/mL Tmax = 0.25 (0.25~0.5) hr AUC = 5.13±7.49 (0~26.99) pg·h/mL

8) Evaluation of pooled PK results

- The PK results of desmopressin in nocturia patients of 0.5, 0.75, 1 or 1.5 mcg from 5 studies were collected for the pooled analysis to evaluate the intrinsic and extrinsic factors on the PK of desmopressin.
- This analysis showed that C_{max} and AUC of desmopressin were not affected by patient's age, sex, body weight and BMI.
- The desmopressin elimination half-life was prolonged in patients with eGFR < 50 mL/min/1.73 m^2. However, a prolongation in half-life with decreasing renal function was not statistically different in patients with mild renal impairment (60-89 mL/min/1.73 m^2) compared to patients with normal renal function (≥ 90 mL/min/1.73 m^2).
- The type of assay RIA or LC-MS/MS used for the bioanalytical support appeared to be a critical factor in the desmopressin plasma concentration obtained, but did not affect the basic conclusions drawn.

9) Formulation development

- Clinical and commercial formulations for desmopressin nasal spray are identical since the optimum pH for the formulation was once identified during initial stages of formulation studies. However, the different strengths and administration volumes were used in the early phase trials (Study 200801 and 200802).

10) Major findings of clinical pharmacology in the proposed labeling

- While the Sponsor proposes that desmopressin nasal spray is contraindicated for patients with a calculated GFR below 50 mL/min/1.73 m^2, any dose restriction or adjustment was not proposed for the patients with moderate renal impairment in the borderline range of calculated GFR range from 50 to 60 mL/min/1.73 m^2.
- There is no supporting information for the use of desmopressin nasal spray in patients with rhinitis.
- It is described in section 12.3 Pharmacokinetics that desmopressin did not show any effect on any of the 9

CYP 450 subtypes. The Sponsor did not submit any relevant study report supporting this labeling information.

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/s/

JIHONG SHON
03/25/2016

MYONG JIN KIM
03/25/2016