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RESEARCH**

APPLICATION NUMBER:

022517Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Class 2 Resubmission
Application Number(s)	022517
Priority or Standard	Standard
Submit Date(s)	December 21, 2017
Received Date(s)	December 21, 2017
PDUFA Goal Date	June 21, 2018
Division/Office	Division of Bone, Reproductive and Urologic Products (DBRUP)/Office of Drug Evaluation III (ODE III)
Review Completion Date	June 18, 2018
Established Name	Desmopressin acetate sublingual tablets
(Proposed) Trade Name	NOCDURNA
Pharmacologic Class	Vasopressin analogue
Code name	FE 992026, FE 999912
Applicant	Ferring Pharmaceuticals
Formulation(s)	Sublingual tablets
Dosing Regimen	Women – 27.7 microgram (mcg) desmopressin acetate (equivalent to 25 mcg) once daily, one hour before bedtime, administered sublingually without water Men – 55.3 mcg desmopressin acetate (equivalent to 50 mcg desmopressin) once daily, one hour before bedtime, administered sublingually without water
Applicant Proposed Indication(s)/Population(s)	Treatment of nocturia due to nocturnal polyuria in adults who awoken two or more times each night to void
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as above.

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 OSE= Office of Surveillance and Epidemiology
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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DPMH = Divison of Maternal and Pediatric Health
PLLR = Pregnancy and lactation labeling
COA = Clinical Outcomes Assessment Staff
OSI=Office of Scientific Investigations
OSIS = Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AE	Adverse Event
AUC	Area Under the Curve
CDF	Cumulative Distribution Function
CMC	Chemistry, Manufacturing, and Controls
COA	Clinical Outcome Assessment
CSR	Clinical Study Report
eCTD	Electronic Common Technical Document
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
IND	Investigational New Drug
ISS	Integrated Summary of Safety
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NDA	New Drug Application
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OSI	Office of Scientific Investigation
PD	Pharmacodynamics
PK	Pharmacokinetics
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSRIs	Selective Serotonin Reuptake Inhibitors
TEAE	Treatment Emergent Adverse Event
USP	United States Pharmacopeia

1 Executive Summary

1.1. Product Introduction

Desmopressin acetate sublingual tablets (referred to as “desmopressin” or by the proposed tradename NOCDURNA throughout this review) is a synthetic analogue of the endogenous human anti-diuretic hormone, 8-vasopressin. The proposed indication is treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void.

Desmopressin stimulates reabsorption of water from the lumen of the renal collecting ducts, which results in more concentrated urine and less water excretion. On March 3, 2017, NOCTIVA (NDA 201656), a nasal spray formulation of desmopressin, became the first and only product approved by the FDA for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void. Hyponatremia is the most significant risk of desmopressin.

NOCDURNA is a sublingual tablet formulation containing 27.7 microgram (mcg) or 55.3 mcg of desmopressin acetate, equivalent to 25 mcg or 50 mcg of desmopressin, respectively.¹ The proposed daily dose is 27.7 mcg in women and 55.3 mcg in men, to be taken one hour before bedtime. The product disintegrates and releases the drug when placed under the tongue, and is administered without water.

The inactive ingredients are fish gelatin, mannitol, and anhydrous citric acid.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NOCDURNA is proposed for the treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times per night to void. Nearly 90% of the enrolled population in the Phase 3 trials had nocturia, awoke two or more times per night to void, and had nocturnal polyuria (nighttime overproduction of urine).

¹ Throughout this document, we use 25 mcg and 27.7 mcg interchangeably and use 50 mcg and 55.3 mcg interchangeably. However, labeling will consistently refer to the dosage strengths as 27.7 mcg desmopressin acetate and 55.3 mcg desmopressin acetate.

The sponsor conducted three controlled Phase 3 efficacy and safety trials. In the first Phase 3 trial, CS29, desmopressin 100 mcg was statistically superior to placebo with respect to the two prespecified co-primary efficacy endpoints: change from baseline to final visit (Day 28) in mean number of nocturnal voids and the proportion of subjects with a >33% reduction in the mean number of nocturnal voids. A post-hoc sex-based analysis of CS29 efficacy data suggested that in males, from Day 8 to Day 28 NOCDURNA 50 mcg appeared to be beneficial relative to placebo with respect to both co-primary efficacy endpoints except for the 33% responder status at Day 28. In females, from Day 8 to Day 28, NOCDURNA 25 mcg and 50 mcg appeared to be beneficial relative to placebo with respect to both co-primary efficacy endpoints. However, these additional analyses were not controlled at the overall 5% level of significance and could not alone serve as substantial evidence of efficacy for these lower dose regimens. Therefore, the Applicant conducted two new Phase 3 trials, one in women (CS40) and the other in men (CS41), described below, to confirm the post-hoc findings in CS29.

In Phase 3 trial CS40 which enrolled only women, NOCDURNA 25 mcg administered for three months was statistically significantly superior to placebo in reducing the mean number of nocturnal voids (by 0.2 voids per night) and increasing the odds of achieving at least a 33% reduction in nocturia episode frequency (1.9 times greater odds than placebo). In trial CS41, which enrolled only men, NOCDURNA 50 mcg was also statistically significantly superior to placebo with respect to both pre-specified primary endpoints (0.4 fewer voids per night and 2.0 times greater odds of a 33% response).

Although CS40 and CS41 successfully met their prespecified co-primary efficacy endpoints, the mean reduction in nocturnal voids in both trials was small compared to placebo, raising questions about the clinical meaningfulness of the results. This submission includes additional analyses of data from trials CS40 and CS41 that clarifies the clinical meaningfulness of the observed treatment effects. These descriptive analyses showed that compared to placebo, NOCDURNA increased the percentage of patients with at least a 50% reduction from baseline in nocturia episodes (by 12% in men, 17% in women) and increased the percentage of nights with no nocturnal voids (by 9% in men, 4% in women) and at most one nocturnal void (by 11% in men, 13% in women) in patients with nocturnal polyuria.

In addition, cumulative distribution function (CDF) plots of the range of individual changes from baseline in nocturia episode frequency, showed that compared to placebo, NOCDURNA increased the percentage of men experiencing at least one and two fewer voids per night compared to baseline by approximately 22% and 11%, respectively, and the percentage of women experiencing at least one fewer voids per night by 8%.

The totality of the data, taking into account the additional analyses of clinical meaningfulness (the responder analyses combined with the analyses of the percentage of nights with no nocturic voids or only one nocturic void), support the clinical benefit of NOCDURNA in treating adults with nocturia due to nocturnal polyuria who awaken two or more times per night to void. The percentage of nights with no nocturic voids reflects, for those nights, a complete resolution of the symptom being treated. Having one or fewer nocturic episodes per night reflects for those nights, a reduction in nocturia below the threshold for which the drug is indicated.

Based on these considerations, we conclude that the Applicant has met the statutory requirements for establishing the efficacy of NOCDURNA for the proposed indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant is proposing NOCDURNA, 25 mcg for women and 50 mcg for men, for the treatment of nocturia due to nocturnal polyuria (nighttime over-production of urine) in adults who awaken two or more times per night to void. Nocturia is defined as awakening at night to urinate, with each void preceded by and followed by sleep in an otherwise continent patient. Epidemiologic data suggest that having at least two voids per night is associated with impaired health-related quality of life, and we consider this the minimum threshold for pharmacologic therapy.

There are numerous underlying causes of nocturia that must be thoroughly evaluated to identify the proper course of treatment. The Applicant's proposed narrowed indication for nocturia due to nocturnal polyuria is supported by the clinical trial population - nearly 90% of the enrolled population in the Phase 3 trials had nocturia, awoke two or more times per night to void, and had nocturnal polyuria.

Although the Phase 3 trials successfully met their prespecified co-primary efficacy endpoints, the mean reduction in nocturnal voids in both trials was small compared to placebo, raising questions about the clinical meaningfulness of the results. Therefore, this submission includes additional analyses of data from the confirmatory Phase 3 trials intended to clarify the clinical meaningfulness of the observed treatment effects. These descriptive analyses showed that compared to placebo, NOCDURNA increased the percentage of patients with at least a 50% reduction from baseline in nocturia episodes (by 12% in men, 17% in women) and increased the percentage of nights with no nocturnal voids (by 9% in men, 4% in women) and at most one nocturnal void (by 11% in men, 13% in women) in patients with nocturnal polyuria.

The totality of the data, taking into account the additional analyses of clinical meaningfulness (the responder analyses combined with the analyses of the percentage of nights with no nocturic voids or only one nocturic void), support the clinical benefit of NOCDURNA in treating adults with nocturia due to nocturnal polyuria who awaken two or more times per night to void. The percentage of nights with no nocturic voids reflects, for those nights, a complete resolution of the symptom being treated. Having one or fewer nocturic episodes per night reflects for those nights, a reduction in nocturia below the threshold for which the drug is indicated.

Hyponatremia is the most significant risk of all desmopressin products including NOCDURNA. This risk increases with age. Nocturia due to nocturnal polyuria, also increases with age and is most prevalent in older individuals.

Warnings and Precautions mitigate the risk of hyponatremia for currently approved desmopressin products for other indications. Those products have more narrow uses, such as diabetes insipidus. In contrast, NOCDURNA will be used in a diverse, older patient population that likely has multiple co-morbidities and concomitant medications that can predispose to hyponatremia. A Boxed Warning for hyponatremia is necessary to ensure that the modest benefits of the drug outweigh the risks. A Boxed Warning is appropriate because severe hyponatremia can be life-threatening and is very serious in proportion to the benefit of the drug, and because hyponatremia can be mitigated with interventions (e.g., periodic monitoring of serum sodium). In addition, NOCDURNA will be approved with a medication guide because there are actions patients can take to reduce their risk of severe hyponatremia, such as recognizing the symptoms of hyponatremia and avoiding excessive fluid intake.

Labeling will include important information on how to mitigate the risk of hyponatremia, including sex-specific dosing (25 mcg for women, 50 mcg for men), limiting fluid intake for nine hours starting one hour prior to administration, ensuring serum sodium is normal before starting treatment, recommending periodic serum monitoring, and contraindicating in patients at increased risk of severe hyponatremia.

Based on the above considerations, we have concluded that the benefits of NOCDURNA, when used according to labeling, outweigh its risks for the treatment of nocturia due to nocturnal polyuria in adults who urinate two or more times per night.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- Nocturia is defined as awakening at night to urinate, with each void preceded by and followed by sleep in an otherwise continent patient. - The prevalence of nocturia increases with age. Epidemiologic data suggest that having at least two voids per night is associated with impaired health-related quality of life, and the Division considers this the minimum threshold for pharmacologic therapy. - Nocturia is a symptom of one or more conditions or disease processes. One cause of nocturia is nocturnal polyuria which is an increase in nighttime urine production with a corresponding decrease in daytime urine production. The proposed indication for this application is treatment of nocturia due to nocturnal polyuria.	Nocturia can be a bothersome condition associated with impaired quality of life. There are numerous underlying causes that must be thoroughly evaluated to identify the proper course of treatment.
<u>Current Treatment Options</u>	- NOCTIVA, an intranasal formulation of desmopressin, is the only product approved in the U.S. for the treatment of nocturia due to nocturnal polyuria. - Hyponatremia is the most significant risk with all desmopressin products, including NOCTIVA.	An additional therapy with an alternative method of administration and favorable benefit-risk assessment would expand the treatment options for nocturia due to nocturnal polyuria.
<u>Benefit</u>	- The efficacy of NOCDURNA was confirmed in two Phase 3 placebo-controlled trials (CS40 and CS41) that enrolled adults with nocturia, approximately 90% of whom had nocturnal polyuria. These trials were conducted after a post-hoc analysis of an earlier Phase 3 trial suggested that the 50 mcg dose may be beneficial in men and the 25 mcg dose may be beneficial in women. - In CS40 which enrolled only women, NOCDURNA 25 mcg administered for three months significantly reduced the mean number of nocturnal voids compared to placebo (by 0.2 voids per night) and increased the odds of achieving at least a 33% reduction in nocturia episode frequency (1.9 times greater odds than placebo). - In CS41, which enrolled only men, NOCDURNA 50 mcg administered for three months significantly reduced the mean number of nocturnal voids compared to placebo (by 0.4 voids per night) and	The totality of the data supports the clinical benefit of NOCDURNA for the treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times per night to void. Nearly 90% of enrolled subjects in the Phase 3 trials

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	increased the odds of achieving at least a 33% reduction in nocturia episode frequency (2.0 times greater odds than placebo). • Although CS40 and CS41 successfully met their prespecified co-primary efficacy endpoints, the mean reduction in nocturnal voids in both trials was small compared to placebo, raising questions about the clinical meaningfulness of the results. • Additional analyses of data from trials CS40 and CS41 clarified the clinical meaningfulness of the observed treatment effects. These descriptive analyses showed that compared to placebo, NOCDURNA increased the percentage of patients with at least a 50% reduction in nocturia episodes (by 12% in men, 17% in women) and increased the percentage of nights with no nocturnal voids (by 9% in men, 4% in women) and at most one nocturnal void (by 11% in men, 13% in women) in patients with nocturnal polyuria. The percentage of nights with no nocturic voids reflects, for those nights, a complete resolution of the symptom being treated. Having one or fewer nocturic episodes per night reflects for those nights, a reduction in nocturia below the threshold for which the drug is indicated.	had nocturnal polyuria. The trial exclusion criteria limits generalizability, supporting a narrowed indication only for patients with nocturia due to nocturnal polyuria. Although the mean decrease in nocturia episodes is small, in some patients, the response will be more pronounced. Nocturia is symptomatic so each patient will be able to assess the extent of improvement and whether those benefits outweigh the risks.
<u>Risk and Risk Management</u>	• Desmopressin has a long marketing history for various indications, in multiple formulations, with several routes of administration at a range of doses. In general, the safety profile of desmopressin is well characterized and the safety data reviewed for this NDA did not reveal any new safety signals for the drug. Hyponatremia is a known and potentially serious risk of desmopressin drugs that increases with age. Nocturia due to nocturnal polyuria, the indication proposed by the Applicant, also increases with age and is most prevalent in older individuals. • The table below summarizes the incidence of hyponatremia by age and sex in patients with nocturia due to nocturnal polyuria in the three NOCDURNA Phase 3 placebo-controlled trials.	Hyponatremia is the most important risk with all desmopressin products, including NOCDURNA. NOCDURNA will be used in a diverse, older patient population that likely has multiple co-morbidities and

Dimension	Evidence and Uncertainties								Conclusions and Reasons	
	Serum Sodium (mmol/L)	Women <65 years		Women ≥ 65 years		Men < 65 years		Men ≥ 65 years		concomitant medications that can predispose to hyponatremia. A Boxed Warning for hyponatremia is necessary to ensure that the modest benefits of the drug outweigh the risks. A Boxed Warning is appropriate because severe hyponatremia can be life-threatening and is very serious in proportion to the benefits of the drug, and because hyponatremia can be mitigated with interventions (e.g., periodic monitoring of serum sodium). In addition, the drug will be approved with a medication guide because there are actions patients can take to reduce their risk of severe hyponatremia, such as recognizing the symptoms of hyponatremia and avoiding excessive fluid intake.
		Placebo (N=95)	NOCDURNA 25 mcg/day (N=113)	Placebo (N=76)	NOCDURNA 25 mcg/day (N=78)	Placebo (N=95)	NOCDURNA 50 mcg/day (N=98)	Placebo (N=112)	NOCDURNA 50 mcg/day (N=94)	
	130-134	2 (2%)	4 (4%)	5 (7%)	9 (12%)	5 (5%)	11 (11%)	1 (<1%)	22 (23%)	
	126-129	0 (0%)	2 (2%)	0 (0%)	5 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
	≤125	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)	
Three years of post-marketing data from outside the United States (U.S) where NOCDURNA is approved for nocturia due to nocturnal polyuria with 25 mcg dosing in women and 50 mcg dosing in men has not identified new safety concerns.										

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
	☒ Patient reported outcome (PRO)	Section 3.2
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

2 Therapeutic Context

The International Continence Society defines nocturia as having to awaken at night one or more times to void. Each void must be preceded by and followed by sleep in an otherwise continent patient.² Epidemiologic data suggest that having at least two voids per night is associated with impaired health-related quality of life, and the Division considers this the minimum threshold for pharmacologic therapy.³

Nocturia is a symptom of one or more underlying conditions or disease processes, and is not in-and-of-itself, a disease. It is a result of one of three pathophysiologic processes, acting alone or in combination:

Polyuria (increase in 24-hour urine volume): Causes include uncontrolled diabetes mellitus; diabetes insipidus; hypokalemia; medication side effects.

Nocturnal polyuria (increase in nighttime urine production with a corresponding decrease in daytime urine production, resulting in a normal 24-hour urine volume) is defined as a nocturnal urine volume that exceeds 20% of the total 24-hour volume in adults younger than 35 years and 33% of the total 24-hour volume in adults older than 65 years.² Causes include excessive evening fluid intake, medications, and nighttime mobilization of fluid in edematous states, such as congestive heart failure. In addition, reduced nocturnal secretion of the anti-diuretic hormone arginine vasopressin –which can occur with aging -- may contribute to the development of nocturnal polyuria.⁴

Bladder storage problems: Decreases in bladder compliance or changes in neuronal input can reduce the threshold volume for voiding, for example, in patients with overactive bladder (OAB), benign prostatic hyperplasia (BPH), or hypotonic bladder.

The prevalence of nocturia increases with age with greater than two-thirds of men and women older than 70 years reporting one or more void per night. A recent systematic review suggests that the annual incidence of nocturia is 12% among adults older than 60 years of age. Observational and cross-sectional studies have suggested a possible association between nocturia and sleep disruption, decreased quality of life, falls and fracture.

² From uptodate Nocturia: Clinical presentation, evaluation, and management in adults.

³ Tikkinen KA, Johnson TM 2nd, Tammela TL, Sintonen H, et. al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol.* 2010; 57 (3): 488.

⁴ From uptodate Nocturia: Clinical presentation, evaluation, and management in adults.

2.1. **Analysis of Current Treatment Options**

Management of nocturia focuses first on identifying and treating the suspected underlying cause(s) – for example, management of volume overload in a patient with congestive heart failure – as well as behavioral modifications (e.g., fluid restriction before bedtime). In March 2017, NOCTIVA (SER120), a nasal spray formulation of desmopressin, became the first FDA approved treatment in the U.S. for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NOCDURNA is a sublingual formulation of desmopressin. Other desmopressin formulations have been approved in the U.S. for a variety of indications as shown in **Table 3-1**. NOCTIVA is the only product approved in the U.S. for treating nocturia due to nocturnal polyuria.

Table 3-1: FDA Approved Desmopressin Products

Application No. (trade name)	Sponsor	Formulation, dose	Indication(s)	status
NDA 017922 (DDAVP), NDA 021333 (Minirin)	Ferring	0.01% nasal solution; 0.1 - 0.4 mL daily (qd)	Central diabetes insipidus (CDI), primary nocturnal enuresis (PNE)*	Approved
NDA 018938 (DDAVP)	Ferring	Injectable solution, 4 mcg/mL	Hemostasis in patients with hemophilia A and type 1 von Willebrand's disease; CDI	Approved
NDA 019955 (DDAVP), NDA 021795 (desmopressin acetate)	Ferring	0.1 mg and 0.2 mg Tablet, dose range 0.1 mg - 0.8 mg qd	CDI, PNE, renal concentrating capacity test	Approved
NDA 020355 (Stimate)	CSL Behring LLC	1.5 mcg/mL nasal spray	Hemophilia A and mild-moderate von Willebrand's disease	Approved
NDA 201656	Serenity	Nasal spray, 0.75 mcg and 1.5 mcg nightly (qhs)	Nocturia in adults who awaken ≥ 2 times each night to void	Approved

*In 2007, FDA withdrew the PNE indication for intranasal desmopressin formulations due to post-marketing reports of severe hyponatremia in children.

3.2. Summary of Presubmission/Submission Regulatory Activity

First Review Cycle (2009)

In support of the initial marketing application for NOCDURNA, Ferring conducted Phase 3 study CS29 which was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, two-part trial. Trial CS29 enrolled adult male and female patients with nocturia having on average, ≥ 2 voids per night documented in a 3-day voiding diary during screening.

A total of 799 subjects were randomized to one of four doses of desmopressin (10, 25, 50, or 100 mcg) or placebo. In Part I, subjects completed 28 days of treatment. Enrollment was

stratified by age (<65 and ≥65 years) and absence or presence of nocturnal polyuria (ratio of nighttime urine volume/24-hour urine volume ≥33%).⁵ Nearly 90% of enrolled subjects had nocturnal polyuria at baseline.

Upon completion of Part I, subjects on active treatment continued the same treatment for 1 to 6 months and subjects assigned to placebo were randomized to one of the four active treatments for 1 to 6 months. Subjects completing Part II could roll-over into an open-label safety extension study (CS31), which was planned to continue until enrolled subjects had completed a maximum of 2 years and 2.5 months of treatment.

The co-primary efficacy endpoints in Part I of trial CS29 were change from baseline to final visit (Day 28) in mean number of nocturnal voids and the proportion of subjects with a >33% reduction in the mean number of nocturnal voids. The Division of Metabolism and Endocrinology Products (DMEP) agreed to those endpoints at an end-of-Phase 2 meeting with Ferring held on March 26, 2007, and indicated that the 33% responder endpoint is one that measures a clinically significant response.⁶ The 100 mcg NOCDURNA dose was statistically superior to placebo for both co-primary efficacy endpoints at the pre-specified primary efficacy time point of Day 28 as shown in **Table 3-2**.

Table 3-2: Co-Primary Efficacy Endpoints (ITT), Part I of Trial CS29

	Desmopressin				
	Placebo (N=156)	10 mcg (N=155)	25 mcg (N=152)	50 mcg (N=148)	100 mcg (N=146)
Day 28					
Nocturnal voids					
Mean (SD)	2.4 (1.2)	2.4 (1.3)	2.4 (1.4)	2.2 (1.2)	1.8 (1.4)
Mean change (SD)	-0.9 (1.1)	-0.8 (1.1)	-1.0 (1.1)	-1.2 (1.2)	-1.4 (1.2)
Difference vs. placebo		0.0	-0.1	-0.3	-0.6
p-value vs. placebo		p=0.9303	p=0.3104	p=0.0207	p<0.0001
>33% Responder					
N (%)	73 (47%)	73 (47%)	76 (50%)	79 (53%)	103 (71%)
p-value vs. placebo		p=0.9420	p=0.5527	p=0.2662	p<0.0001

Source: NDA 022517 (seq 0000), Module 5.3.5.1, fe992026cs29-report-body-1.pdf Table 21 on page 60 and Table 22 on page 64 ; Module 2.7.3., summary-clin-efficacy-nocturia.pdf Table 5 on pages 18-19

Although the 100 mcg dose was effective, DMEP had concerns with the incidence of hyponatremia at that dose. The Applicant conducted a post-hoc analysis of the co-primary efficacy endpoints with respect to sex. In males, from Day 8 to Day 28 NOCDURNA 50 mcg

⁵ NDA 22517 eCTD Seq 000 DMEP CDTL review finalized in DARRTS on April 9, 2010.

⁶ IND 65890 end-of-phase 2 meeting minutes finalized in DARRTS on June 18, 2007.

appeared to be beneficial relative to placebo with respect to both co-primary efficacy endpoints (see Table 3-3) except for the 33% responder status at Day 28. In females, from Day 8 to Day 28, NOCDURNA 25 mcg and 50 mcg appeared to be beneficial relative to placebo with respect to both co-primary efficacy endpoints (see Table 3-4).

These findings suggested that lower doses of NOCDURNA might be efficacious and warranted confirmation in an additional trial. The sex-specific observations also suggested that women were more sensitive than men to desmopressin activity.

Table 3-3: Co-Primary Efficacy Endpoints (ITT), Part I of Trial CS29 of NOCDURNA, Males

	Placebo	Desmopressin			
		10 mcg	25 mcg	50 mcg	100 mcg
Change from Baseline in Nocturnal voids to Day 28					
	(N=90)	(N=82)	(N=87)	(N=77)	(N=80)
Day 8					
Mean change (SD)	-0.6 (1.1)	-0.5 (0.9)	-0.8 (1.0)	-1.1 (1.2)	-1.2 (1.2)
Day 15					
Mean change (SD)	-0.7 (1.0)	-0.5 (1.0)	-1.0 (1.0)	-1.1 (1.2)	-1.5 (1.1)
Day 22					
Mean change (SD)	-0.8 (1.0)	-0.6 (1.1)	-0.9 (1.1)	-1.3 (1.1)	-1.5 (1.1)
Day 28					
Mean change (SD)	-0.8 (1.1)	-0.5 (0.9)	-0.8 (1.0)	-1.1 (1.2)	-1.4 (1.2)
>33% Responder					
Day 8					
N (%)	30 (33%)	28 (34%)	37 (43%)	38 (49%)	43 (54%)
Day 15					
N (%)	31 (34%)	25 (30%)	43 (49%)	40 (52%)	51 (64%)
Day 22					
N (%)	39 (43%)	34 (41%)	45 (52%)	46 (60%)	55 (69%)
Day 28					
N (%)	45 (50%)	32 (39%)	36 (41%)	37 (48%)	52 (65%)

Source: Clinical Review of NDA 022517 (seq 0000), finalized in DARRTS April 7, 2010, Tables 11 and 12, pp. 36-7.

Table 3-4: Co-Primary Efficacy Endpoints (ITT), Part I of Trial CS29 of NOCDURNA, Females

	Placebo	Desmopressin			
		10 mcg	25 mcg	50 mcg	100 mcg
Change from Baseline in Nocturnal voids to Day 28					
	(N=66)	(N=73)	(N=65)	(N=71)	(N=66)
Day 8					
Mean change (SD)	-0.7 (1.0)	-1.0 (1.1)	-1.0 (1.2)	-1.1 (1.0)	-1.3 (1.2)
Day 15					
Mean change (SD)	-1.0 (1.0)	-1.1 (1.2)	-1.2 (1.3)	-1.3 (1.0)	-1.5 (1.1)
Day 22					
Mean change (SD)	-1.0 (1.0)	-1.3 (1.1)	-1.2 (1.1)	-1.3 (1.0)	-1.6 (1.1)
Day 28					
Mean change (SD)	-0.9 (1.0)	-1.2 (1.1)	-1.2 (1.1)	-1.2 (1.1)	-1.5 (1.1)
>33% Responder					
Day 8					
N (%)	17 (26%)	34 (47%)	33 (51%)	35 (49%)	45 (68%)
Day 15					
N (%)	26 (39%)	37 (51%)	35 (54%)	41 (58%)	49 (74%)
Day 22					
N (%)	27 (41%)	44 (60%)	34 (52%)	41 (58%)	51 (77%)
Day 28					
N (%)	28 (42%)	41 (56%)	40 (62%)	42 (59%)	51 (77%)

Source: Clinical Review of NDA 022517 (seq 0000), finalized in DARRTS April 7, 2010, Tables 11 and 12, pp. 36-7.

On April 22, 2010, DMEP issued a complete response letter where it noted the following:

“The placebo-controlled portion of your pivotal trial, FE992026 CS029, demonstrated efficacy on two co-primary endpoints with only NOCDURNA 100 mcg daily doses for 28 days, as determined by the pre-specified sequential testing procedure for controlling type 1 error across the 4 doses. However, this dose was also associated with a high incidence of hyponatremia, a known side-effect of desmopressin that may have a serious clinical consequence outweighing any perceived benefit of reducing frequency of nocturnal voids. Post-hoc analyses of different subgroups at different time points in this trial suggest differential efficacy by gender at lower doses which may have a more acceptable safety profile. However, these additional analyses were not controlled at the overall 5% level of significance and cannot serve as sufficient evidence of efficacy for a different proposed dosing regimen. In order to address this deficiency, you must conduct a clinical trial to confirm that a lower dosing regimen is a safe and effective treatment of adult nocturia. This trial should be a placebo-controlled trial with a

minimum duration of 3 months to evaluate a longer period of durability and safety relative to placebo.”

At the end-of-review meeting between DMEP and Ferring on September 14, 2010, DMEP advised the sponsor that the risk of hyponatremia in elderly men is too high with a starting dose of 100 mcg (based on data from study CS29). Therefore, DMEP recommended that Ferring instead compare doses of 50 mcg and 75 mcg daily to placebo in a double-blind study using parallel group design followed by an extension during which all subjects escalate to 100 mcg for 4 weeks.

*Second Review Cycle (2012)*⁷

In response to the CR, the sponsor conducted confirmatory trials CS40 and CS41 to further assess sex-specific dosing.

CS40 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, 3-month study in adult females with nocturia, and CS41 was the male counterpart. Trial designs were virtually identical except that CS41 included a 1-month extension phase during which all subjects received desmopressin 100 mcg nightly. These trials were longer than Part I of CS29 and were prospectively designed to evaluate efficacy separately for men and women.

In both studies CS40 and CS41, the randomization was stratified by age (age <65 years, age ≥65 years). In study CS40, female subjects were randomized in a 1:1 ratio within each age category to receive either desmopressin 25 mcg or placebo every night for 3 months. In CS41, males were randomized, aiming for a treatment balance within each age category, to receive placebo, 50 mcg or 75 mcg desmopressin nightly for three months. Dose selection in both trials took into account the sex-specific observations in CS29 described above that suggested that women were more sensitive than men to desmopressin activity, and avoided the 100 mcg dose because of the hyponatremia concerns with that dose. The doses selected by the Applicant were consistent with advice FDA gave at the end-of-review meeting.

To qualify for study participation, subjects had to document at least 2 nocturnal voids per night in a voiding diary that was collected on 3 consecutive days during screening. Subjects were to have no more than 2 episodes per day of urge incontinence or urgency and less than 8 daytime voids per day. Subjects with overt bladder pathology (e.g., urinary retention, bladder cancer) or medical conditions that could contribute to nocturia (e.g., obstructive sleep apnea, heart failure, uncontrolled diabetes mellitus, BPH) were also excluded. A full list of study eligibility criteria is found in Section 16.4.

⁷ Ibid.

Loop diuretics were prohibited during the study. Selective serotonin reuptake inhibitors (SSRIs), NSAIDs, chlorpropamide, carbamazepine and amiodarone were permitted if the subject had been on a stable dose for three months prior to screening.

Subjects were advised to limit fluid intake for nine hours, starting one hour prior to study drug administration. The protocol also required that subjects urinate before bedtime, and that treatment be interrupted during acute inter-current illnesses to minimize the risk of hyponatremia.

The pre-specified primary efficacy endpoints in both trials were:

- Change from baseline (Visit 2) in mean number of nocturnal voids during 3 months of treatment using a longitudinal analysis as assessed by a 3-day voiding diary. The mean number of voids at each visit was calculated as the average over 3 consecutive 24-hour periods immediately prior to the respective visits.
- 33% responder status during 3 months of treatment using a longitudinal analysis as assessed by the 3-day diary. A 33% responder was defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids at each visit relative to baseline (Visit 2).

In the overall population, desmopressin 25 mcg nightly in women and both 50 mcg and 75 mcg nightly in men met both co-primary efficacy endpoints, producing statistically significantly greater reductions in the mean number of nocturnal voids, and increasing the odds of being a 33% responder compared to placebo. Results are shown in **Table 3-5**.

Table 3-5: Co-Primary Efficacy Endpoints in CS40 and CS41 (Full Analysis Set[†])

Change from Baseline, Averaged over a 3-Month Period:	Desmopressin versus placebo		
	CS40	CS41	
	25 mcg	75 mcg	50 mcg
Mean number of nocturnal voids ^a	p=0.0280*	p<0.0001*	p=0.0003*
Adjusted means (nocturnal voids)	-1.46 vs. -1.24	-1.29 vs. -0.88	-1.25 vs. -0.88
Treatment contrast	-0.22	-0.41	-0.37
Proportion of 33% responders ^b	p=0.0061*	p=0.0004*	p=0.0009*
Odds	3.23 vs. 1.75	2.08 vs. 1.02	2.01 vs. 1.02
Odds ratio	1.85	2.04	1.98

Source: NDA 022517 (seq 0017), Module 2.5 clinical-overview.pdf, Table 4, p.24.

*Statistically significant analysis of covariance (ANCOVA) difference versus placebo, p<0.05
 a--repeated measures of change from baseline at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit and baseline nocturnal voids

b--GEE Method for 33% responder status at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit and baseline nocturnal voids

†--Full analysis set consisted of all randomized subjects who received at least one dose of study drug and had at least one efficacy assessment after dosing initiation.

The resubmission received a CR action on January 30, 2013, noting that the treatment effect size of NOCDURNA relative to placebo was modest and of unclear clinical benefit. There were also concerns about the risk of hyponatremia. To resolve the clinical deficiencies, DMEP advised the sponsor to conduct a trial demonstrating a clinically meaningful impact of NOCDURNA on reducing the frequency of nocturnal voids.

Formal Dispute and Proposed Path Forward⁸

On November 21, 2013, Ferring filed a Formal Dispute Resolution Request (FDRR) arguing that it had demonstrated the effectiveness and safety of NOCDURNA. FDA denied the appeal in a letter dated January 14, 2014. In that letter, FDA proposed that the company re-submit the application with additional data Ferring considered appropriate, which would be taken to an advisory committee (AC) meeting. DMEP would then consider the information in the application and discussions at the AC meeting in reaching an action decision.

Third Cycle Review⁹

Ferring submitted a CR response to DMEP on July 31, 2014. The submission contained no new clinical trial data. The proposed indication was modified from nocturia regardless of etiology, to nocturia due to nocturnal polyuria.

⁸ See note 1 above.

⁹ See note 1.

On January 12, 2015, DMEP convened a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) to consider whether the observed effects sizes in the data were clinically meaningful and the benefits of NOCDURNA outweighed its risks. The majority of the EMDAC panel concluded that the data were insufficient to establish clinically meaningful effects for NOCDURNA that outweighed the risk of hyponatremia.

The application received a CR letter from DMEP on January 30, 2015, stating that Ferring had provided insufficient evidence to conclude that the effect of NOCDURNA relative to placebo on the number of nocturnal voids in adults with nocturia due to nocturnal polyuria is clinically meaningful and outweighs the risks of hyponatremia associated with use of the drug. DMEP advised the sponsor to conduct a trial to demonstrate that NOCDURNA provides a meaningful clinical benefit that is associated with the reduction in nocturnal voids in adults with nocturia due to nocturnal polyuria and to prospectively evaluate hyponatremia monitoring strategies that might be incorporated into the post-marketing setting.

Post-Third Cycle Activity

After the EMDAC panel and the issuance of the January 30, 2015 CR, and in accordance with an administrative decision by the Office of New Drugs to assign applications with indications of nocturia resulting from urologic disorders to DBRUP, the NOCDURNA application was transferred to DBRUP on July 6, 2015.

In 2016, DBRUP received the NOCTIVA application, which was discussed at an October 19, 2016 meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC). The BRUDAC considered certain endpoints that could be persuasive of a clinical benefit for the desmopressin drug, including percentage of nights with none or at most one nocturic episode, and voted in favor of approval. In light of these public scientific discussions with relevant experts and comprehensively considering the data presented for the NOCDURNA application in this context, FDA was open to considering whether the Sponsor's existing data could be used to demonstrate a clinically meaningful benefit for NOCDURNA without an additional trial. DBRUP discussed options with the Sponsor for moving the NOCDURNA NDA forward during a March 6, 2017 Type C teleconference.

During the teleconference, DBRUP clarified the following:

- An indication for the treatment of nocturia due to nocturnal polyuria is an acceptable indication for desmopressin products that have clinically meaningful benefits that outweigh their risks.
- One approach to provide convincing evidence of benefit is the approach Ferring discussed with the Division at the July 2015, End-of-review meeting: Use of a PRO measure as a co-primary efficacy endpoint and an enrichment strategy that excludes non-responders.
- Since the July 2015, end-of-review meeting with Ferring, FDA's thinking has expanded about data that could be used to demonstrate a clinically meaningful benefit for

desmopressin drugs to treat nocturia due to nocturnal polyuria (e.g., assessing the percentage of nights with no nocturia and the percentage of nights with one or fewer nocturic voids).

- If Ferring believes it does not need to use a PRO assessment in a new trial and that it can conduct additional analyses of its existing data to show a clinically meaningful benefit for the treatment of nocturia due to nocturnal polyuria, the Division is willing to consider such an approach.
- If Ferring believes it can conduct additional analyses of its existing data to show a clinically meaningful benefit in its two pivotal trials (CS40 and CS41) the next step would be for Ferring to request a meeting with the Division to discuss the proposed Statistical Analysis Plan (SAP).

In written responses to a June 14, 2017, Type A meeting, DBRUP commented on Ferring's proposed SAP for the additional analyses of data from phase 3 trials CS40 and CS41. The Division recommended that Ferring analyze the following:

- Mean change from baseline in nocturnal voids per night during the treatment period;
- Percentage of patients with $\geq 33\%$ reduction in the mean number of voids per night between baseline and the treatment period;
- Percentage of patients with $\geq 50\%$ reduction in the mean number of voids per night between baseline and the treatment period;
- Percentage of nights during the treatment period with at most one nocturnal void;
- Percentage of nights during the treatment period with no nocturnal voids.

Mean change from baseline in nocturnal voids and the 33% responder status were assessed in the original analysis as repeated measurements in a longitudinal manner. The 33% responder status was also assessed in the original analysis as an odds ratio (i.e., likelihood of achieving at least a 33% reduction) rather than the percentage of patients achieving at least a 33% reduction.

DBRUP stated that the efficacy analysis population should be patients who were randomized and took at least one dose of the study drug.

DBRUP also requested that Ferring submit cumulative distribution function (CDF) plots for mean change from baseline in nocturnal voids during the treatment period per treatment arm.

Ferring acknowledged the written comments and agreed to incorporate them into the SAP.

On October 18, 2017, Ferring presented the results from the new analyses according to the SAP to DBRUP at a Type C meeting. DBRUP confirmed that no additional analyses were needed to support NDA resubmission. Ferring submitted a response to the complete response letter of NDA 22517 on December 21, 2017.

Fourth (Current) Cycle Review (2018)

On December 17, 2017, the Sponsor resubmitted its NDA for NOCDURNA in response to the January 30, 2015, CR letter. For the current submission to support clinical benefit of NOCDURNA, the Applicant performed the additional analyses the Division recommended as described above using the clinical trial data from CS40 and CS41.

As noted above, these trials met their prespecified co-primary efficacy endpoints. The intent of these additional analyses was to help interpret the clinical meaningfulness of the observed treatment effects in patients with nocturia due to nocturnal polyuria.

Analyses were conducted for the subgroup of patients with nocturnal polyuria, which represented nearly 90% of the total population. The Applicant proposes to market only the NOCDURNA 50 mcg dose for use in men because it considers the 50 mcg dose to have a more favorable benefit-risk profile. Therefore, the Applicant did not conduct additional analyses of CS41 trial data for the 75 mcg dose.

3.3. Foreign Regulatory Actions and Marketing History

Overseas, desmopressin tablets and a sublingual formulation (containing 60 mcg, 120 mcg or 240 mcg desmopressin, tradename MINIRIN MELT) have been approved for the treatment of nocturia due to nocturnal polyuria since 2005. NOCDURNA (desmopressin 25 mcg in females and 50 mcg in males) is currently approved in 79 countries for “symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults.”

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

4.1. Office of Scientific Investigations (OSI)

Not applicable to this resubmission, which does not include new clinical trials. OSI completed their inspections of the existing trials during a prior review cycle.

4.2. Product Quality

Three strengths of desmopressin sublingual tablets were described in the original NDA submission: 25 mcg; 50 mcg; and 100 mcg desmopressin (as the free base). The application was recommended for approval from the chemistry, manufacturing and controls (CMC) perspective. However, the Office of Compliance had not made an overall CGMP recommendation and

NDA Multi-Disciplinary Review and Evaluation
NDA 022517 Class 2 Resubmission, NOCDURNA (desmopressin acetate sublingual tablets)

labeling had not been finalized. A Complete Response (CR) Letter was issued at the end of the first review cycle due to clinical/statistical, clinical pharmacology, and nonclinical deficiencies. The application subsequently received two additional Complete Response Letters due to clinical issues. No significant CMC changes have been made since the original submission.

Desmopressin acetate continues to be synthesized by PolyPeptide Laboratories (PPL; Sweden). Drug substance CMC is documented in Type II DMF 8396. The information on the drug substance provided in the DMF and in the NDA is adequate to support approval of the application.

Ferring now intends to only market the sublingual tablets containing the equivalent of 25 mcg and 50 mcg desmopressin. The inactive ingredients are gelatin (fish source), mannitol, and anhydrous citric acid. All inactive ingredients comply with USP/NF, and EP monograph requirements.

The product is formed by (b) (4). The blisters are then sealed with (b) (4) lidding.

The drug product specification includes tests for (b) (4). The product is rapidly dissolving and desmopressin is highly soluble throughout the physiological range. Three degradation products have been identified and qualified (see Section 5, Nonclinical Pharmacology / Toxicology). [Gly⁹-OH]desmopressin, [Asp⁵]desmopressin, and [Glu⁴]desmopressin are limited to not more than (b) (4) %, respectively. Unidentified impurities are limited to not more than (b) (4) %, and total degradation products are limited to not more than (b) (4) %.

An expiration dating period (shelf-life) of 48 months has been established for product stored at 25°C in its original package to protect it from light and moisture.

The facilities associated with the manufacture, packaging, and testing of NOCDURNA have acceptable CGMP status. The OPF Division of Inspectional Assessment issued an overall inspection recommendation of Approve on May 22, 2018.

See Unireview Section 11 for CMC comments on the labeling, including revisions to nomenclature and product strength.

The application is recommended for approval from the Office of Product Quality (OPQ) perspective. See the OPQ Integrated Quality Assessment dated June 11, 2018 and Addendum dated June 15, 2018 for details.

4.3. **Clinical Microbiology**

Not Applicable

4.4. **Devices and Companion Diagnostic Issues**

Not Applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. **Executive Summary**

The submitted nonclinical studies were designed to test the safety and comparability of the new product and its impurities to DDAVP (desmopressin acetate) as well as its potential for local reactions. The Applicant also referenced its own nonclinical data in NDA 019955 for DDAVP tablets, which are approved for central diabetes insipidus and primary nocturnal enuresis.

5.2. **Brief Discussion of Nonclinical Findings**

In a 1-month bridging toxicology study in dogs, toxicological findings and toxicokinetic (TK) data with NOCDURNA were similar to DDAVP and were consistent with desmopressin's known pharmacological effects. In general, there were no signs of systemic toxicity in any treated animals. Decreased urinary volumes in treated animals were related to the pharmacological effect of the compound. Serum bilirubin increased in two desmopressin treated females with no other related changes. Findings from the TK data suggested no sex differences and similarity in desmopressin concentrations with two compounds (2 × 200 mcg DDAVP tablets vs. 1 × 240 mcg desmopressin sublingual tablets).

Desmopressin acetate was previously reviewed under Ferring's NDA 019955. The Applicant conducted the following new studies to characterize the local toxicity and qualify the new impurity profile of NOCDURNA:

- A 13-week study in rats by subcutaneous administration that achieved levels of the 3 relevant impurities ([Glu4]desmopressin, [Gly9-OH]desmopressin and [βAsp5]desmopressin) present in the new sublingual tablet formulation. Findings were consistent with desmopressin's pharmacological effects. Absolute kidney weights were significantly increased for mid and high dose animals, with no microscopic findings. The increased kidney weights were attributed to the pharmacological effects of the test article in maximizing tubular reabsorption. The NOAEL was 10 mcg/kg/day, at which only pharmacological effects of desmopressin were noted.

- *In vitro* genotoxicity studies (Ames test, mouse lymphoma assay) showed no genotoxic potential for desmopressin spiked with the 3 relevant impurities present in the new sublingual tablet formulation.
- A 28-day local tolerability study in Syrian hamsters (once daily, cheek pouch) showed no evidence of test article related local reactions or histopathological changes.

Based on these data, the toxicological profile of desmopressin sublingual tablets is consistent with that of desmopressin tablets.

5.3. ADME/PK

The Pharmacokinetics (PK) characteristics of desmopressin are well understood based on previous extensive nonclinical and clinical experience with desmopressin. PK studies conducted in rats and domestic pigs to evaluate the bioavailability of desmopressin when administered via the sublingual route suggested that desmopressin sublingual tablets had a greater bioavailability (C_{max} , T_{max} , AUC, and AUC/dose) of about two-fold, compared to orally administered desmopressin tablets. Plasma levels of desmopressin were detected by radioimmunoassay (RIA) under GLP conditions.

See P. Espandiari reviews for NDA 22517 in DARRTS, dated July 30, 2012 and June 19, 2009.

5.4. Toxicology

5.4.1. General Toxicology

General toxicology studies were previously reviewed under NDA 22517. See P. Espandiari reviews for NDA 22517 in DARRTS, dated July 30, 2012 and June 19, 2009.

5.4.2. Genetic Toxicology

Genetic toxicology studies were previously reviewed under NDA 22517. See P. Espandiari reviews for NDA 22517 in DARRTS, dated July 30, 2012 and June 19, 2009.

5.4.3. Carcinogenicity

No carcinogenicity studies were conducted for this NDA.

5.4.4. **Reproductive and Developmental Toxicology**

Here, we summarize the fertility and embryo-fetal studies that the Applicant cross-references from its DDAVP tablet NDA.

In a non-GLP fertility study in 22 rats, desmopressin acetate, administered subcutaneously to males and females prior to and during mating and to females during early gestation, showed no effects on estrus cycling, copulation rate, or conception rate, with maternal, paternal, and fetal no effect levels greater than 200 mcg/kg/day.

In a non-GLP embryo-fetal study in 20 rats, desmopressin acetate administered intravenously from Days 7 to 17 and through weaning at doses of 0, 9, 47, and 238 mcg/kg/day, showed no drug related reproductive effects, although pharmacologic effects were observed at all doses.

In rats, fetal transfer of labeled DDAVP administered subcutaneously was 4% of maternal blood levels after 1 hour and 39% of maternal blood levels at 4 hours.

In a non-GLP embryo-fetal study in three Dutch belted rabbits, desmopressin acetate administered subcutaneously from Days 6 to 18 at doses of 0, 1, 3, and 10 mcg/kg/day, showed no drug related reproductive effects.

5.4.5. **Prenatal and Postnatal Development**

Here we summarize the prenatal and postnatal development studies that the Applicant cross-references from its DDAVP tablet NDA.

No treatment-related effects on clinical signs, gestation index, delivery, lactation, or implantation sites, were observed. In F₁ offspring, decreased body weight gain and delayed vaginal opening were observed at 200 mcg/kg, attributed to decreased nursing. No treatment-related effect was observed on birth index, viability index on Day 4, weaning index, clinical signs, reflex and motility (righting reflex, negative geotaxis, pupillary reflex, Preyer reflex, pain response), morphological differentiation (pinna detachment, incisor eruption, eyelids opening, testes descent), external appearance, visceral effects, skeletal effects, general behavior, learning (by open field test, water maze test), or reproductive performance.

In F₂ offspring, no treatment-related effects on birth index, viability index, body weight, external appearance, visceral effects, or skeletal effects were observed at any dose level.

No adverse effect levels were judged to be more than 200 mcg/kg/day for F₀ dams, 20 mcg/kg/day for F₁ offspring and more than 200 mcg/kg/day for F₂ offspring.

5.4.6. Other Toxicology Studies

None.

6 Clinical Pharmacology

6.1. Executive Summary

Clinical pharmacology data were submitted with the original NDA and no clinical pharmacology information was newly submitted with the current resubmission. We find the application to be acceptable and recommend approval from the clinical pharmacology standpoint, pending agreement on labeling.

The key clinical pharmacology issues are summarized below:

Key review issues	Comments and (or) recommendations
Sex difference	The pharmacodynamic response (decrease in nocturnal urine volume) following sublingual administration of desmopressin tablets appeared to be more sensitive in female than males. Females with nocturia demonstrated better efficacy responses (change from baseline in mean number of nocturnal voids and 33% responder rate) compared to males at the same doses (Study CS29). In the pivotal Phase 3 trials (Studies CS40 and CS41), females were administered 25 mcg while males were administered 50 or 75 mcg desmopressin.
Hyponatremic event	Given that there is a risk of clinically significant hyponatremia at the proposed doses, the proposed sodium monitoring strategy (serum sodium level should be checked in the first week after initiation and again at one month) for elderly patients (65 years and older) and patients at risk due to concomitant medication should be implemented for all treated patients to reduce the risk of hyponatremia. More frequent serum sodium monitoring is recommended for elderly patients.
Dosing regimen for the general patient population	The Applicant proposed fixed daily doses of 25 mcg for females and 50 mcg for males one hour before bedtime. The conducted studies demonstrated that the overall efficacy and safety profiles support a positive benefit-risk profile in patients with nocturia due to nocturnal polyuria if serum sodium monitoring is appropriately performed. The proposed doses are acceptable from the clinical pharmacology standpoint.

Therapeutic individualization for subpopulations	No dose individualization was proposed based on intrinsic or extrinsic factors, other than sex-specific dosing. Hyponatremic events are more prevalent in patients 65 years or older. The Applicant proposed additional risk mitigation plans (more frequent serum sodium monitoring) in elderly patients. More frequent serum sodium monitoring is recommended for patients treated concomitantly with drugs that can cause water retention and lower serum sodium concentrations. The Applicant proposed a contraindication for patients with fluid overload conditions requiring treatment with diuretics (i.e., loop diuretics). Given that the use of systemic corticosteroids increases the risk for hyponatremia when used in combination with desmopressin, desmopressin should also be contraindicated for patients on concomitant systemic or inhaled corticosteroids.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Onset of the antidiuretic effect (changes in urine osmolality and urine production) following sublingual administration of 60 mcg desmopressin is observed within approximately 30 minutes and lasts approximately 6 hours after dosing in healthy subjects in the water-loaded state (Study CS30; refer to **Section 14.3.1** for more details). The pharmacodynamic response (decrease in nocturnal urine volume) following sublingual administration of desmopressin tablets appeared to be more sensitive in females than males (Study CS29; refer to CLINICAL PHARMACOLOGY REVIEW (03/30/2010) of the original submission).

The PK of desmopressin following sublingual administration of the proposed desmopressin tablets (25 mcg and 50 mcg desmopressin) in humans has not been characterized. The mean absolute bioavailability of desmopressin following sublingual administration of desmopressin tablets (200, 400, and 800 mcg) is 0.25% (Study CS04). The volume of distribution of desmopressin after intravenous administration (2 mcg) is 26.5 L. Desmopressin is mainly excreted in urine. The mean terminal half-life of desmopressin following intravenous administration of desmopressin is 2.8 hours.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed doses are 25 mcg once daily for females and 50 mcg once daily for men, one hour before bedtime. The drug is administered sublingually without water intake.

The Phase 3 trials (Studies CS40 and CS41) showed clinical benefit of 25 mcg desmopressin for females and 50 mcg for males compared to placebo in patients with nocturia due to nocturnal polyuria. However, the trials demonstrated that the proposed doses still have a risk of hyponatremia, particularly in elderly subjects ≥ 65 years of age. Specific warnings and strategies to prevent the risk of hyponatremia should be implemented. The Applicant proposed serum sodium monitoring before starting treatment for all patients and follow-up monitoring (the first week (4-8 days) after initiation and again at one month) for elderly patients (65 years and older) and patients at risk due to concomitant medication(s). Given that hyponatremia with desmopressin can occur in any subject, the proposed post-dose sodium monitoring strategy should be considered for all treated patients to mitigate the risk. More frequent serum sodium monitoring should be recommended for elderly patients. The Applicant also proposed restriction of fluid intake during the treatment period beginning at least 1 hour before and for 8 hours after desmopressin administration, consistent with what was done in the pivotal Phase 3 trials. Given that fluid intake before and during bedtime may lead to a higher risk of hyponatremia during the duration of antidiuretic effect following administration of desmopressin, the proposed restriction of fluid consumption before and after administration of desmopressin may reduce the risk of hyponatremia.

Therapeutic Individualization

A dose-response study in male and female subjects with nocturia demonstrated that the pharmacodynamic response following sublingual administration of desmopressin tablets is more sensitive in female than males (Study CS29). The weight-corrected dose that induced 50% maximum achievable drug effect on nocturnal urine volume (ED_{50}) was significantly different between females and males (2.7-fold higher in males). In the study, female patients with nocturia appeared to have larger efficacy responses (change from baseline in mean number of nocturnal voids and 33% responder rate) compared to males in the dose range from 25 mcg to 100 mcg. The pivotal Phase 3 trials confirmed the efficacy and safety of the 25 mcg dose for females (Study CS40) and the 50 mcg dose for males (Study CS41), respectively. Based on the efficacy and safety data from the pivotal studies, the Applicant proposed sex-specific daily doses, 25 mcg and 50 mcg desmopressin for females and males, respectively.

The Applicant proposed a contraindication for patients with fluid overload conditions which require treatment with loop diuretics. Intranasal desmopressin spray for the treatment of nocturia due to nocturnal polyuria is contraindicated in patients using loop diuretics, systemic, or inhaled glucocorticoids (NOCTIVA[®] prescribing information). Given that systemic corticosteroids increase the risk for hyponatremia when used in combination with desmopressin, the use of desmopressin should be contraindicated in patients on concomitant treatments of systemic or inhaled corticosteroids. After the glucocorticoid is discontinued, NOCDURNA should be started or resumed taking into consideration the time required for the glucocorticoid to be eliminated from the body (e.g., its five half-lives).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. 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 reduction in urine production.
QT Prolongation	Literature search did not yield any case reports of adverse events related to QT prolongation following use of the approved desmopressin products.
Clinical PK	
The PK profile of desmopressin following sublingual administration of NOCDURNA	The PK of desmopressin following sublingual administration of 25 mcg and 50 mcg desmopressin tablets has not been characterized. The PK profile of desmopressin following sublingual administration of higher dose strengths or intravenous administration was characterized using a radioimmunoassay. The Applicant requested a waiver for PK studies of the proposed doses because the analytical method was not sensitive to measure desmopressin of lower strengths (refer to Section 14.3.2 for more details).
Bioavailability	Bioavailability of three different doses (200, 400, and 800 mcg desmopressin) was compared to that of a 2 mcg injection in 24 healthy subjects (Study CS04). The mean absolute bioavailability was 0.25 % (95% confidence interval = 0.21-0.31%) (refer to CLINICAL PHARMACOLOGY REVIEW (3/30/2010) of the original submission).
Distribution	After intravenous administration, the mean volume of distribution was 26.5 L
Elimination	Desmopressin is mainly excreted in urine. The mean terminal half-life and total clearance of desmopressin following intravenous administration of desmopressin is 2.8 hours and 7.6 L/hour, respectively.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, refer to **Section 6.2** regarding the supportive evidence of effectiveness provided by the clinical pharmacology program.

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

Yes, as noted above, we recommend that the proposed sodium monitoring strategy (the first week after initiation and again at one month) for elderly patients (65 years and older) and patients at risk due to concomitant medications be applied to all treated patients, and that more frequent monitoring of serum sodium be recommended for the elderly.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. See our comments in **Section 6.2** regarding serum sodium monitoring for all treated patients, and more frequent monitoring in the elderly.

The Applicant proposed a contraindication for patients with creatinine clearance (CrCL) below 50 ml/min, which is consistent with the labeling for approved desmopressin products. Desmopressin is mainly eliminated via the kidneys. Patients with mild, moderate, and severe renal impairment showed 1.5-fold, 2.4-fold, and 3.6-fold increases, respectively, in drug exposure (area under the plasma drug concentration over time curve, AUC) compared to healthy subjects (Study FE992026; refer to CLINICAL PHARMACOLOGY REVIEW to the original submission, March 30, 2010). The conducted Phase 3 studies enrolled patients with CrCL > 50 mL/min. This circumstance supports the Applicant's proposal.

The currently approved desmopressin products do not have any restriction for use in patients with hepatic impairment. The Applicant has not evaluated the effect of hepatic impairment on the PK of desmopressin and the conducted Phase 3 studies excluded patients with evidence of hepatic and/or biliary diseases. The Applicant has not proposed any contraindication or dose modification for the use of NOCDURNA in patients with hepatic impairment.

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

Yes. More frequent serum sodium monitoring is recommended for patients treated concomitantly with drugs that may cause water retention and lower serum sodium concentrations. The Applicant proposed a contraindication for patients with fluid overload conditions which require treatment with loop diuretics. We agree with the Applicant's proposal that concomitant administration or increase of dosage of drugs such as tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, opiate analgesics, diuretics, carbamazepine, lamotrigine, some antidiabetics of the sulfonylurea group, particularly chlorpropamide, and NSAIDs, which may increase the risk of hyponatremia, should be performed with caution and additional monitoring of serum sodium be recommended. The listed drugs, other than diuretics and sulfonylurea antidiabetics, are consistent with those in the approved desmopressin products. Diuretics such as thiazides can cause hyponatremia. The use of sulfonylureas (e.g., chlorpropamide) may lead to hyponatremia by increasing the secretion of

anti-diuretic hormone (Kadowaki et al., 1983). Thus, the Applicant's proposal appears to be acceptable.

The use of systemic or inhaled corticosteroids may cause fluid retention and hyponatremia. Concomitant treatment of desmopressin with systemic corticosteroids may synergistically lower serum sodium concentrations. Intranasal desmopressin spray for the treatment of nocturia due to nocturnal polyuria is contraindicated in patients using systemic or inhaled glucocorticoids (NOCTIVA prescribing information) because of severe cases of hyponatremia in the Phase 3 trials among some patients also receiving corticosteroids. In the pivotal Phase 3 trials (Studies CS40 and CS41), while there were no cases with a serum sodium value ≤ 125 mmol/L in patients with concomitant corticosteroid use at the proposed doses (25 mcg in females and 50 mcg in males), the incidence of subjects who showed a shift from a normal value of serum sodium concentration at baseline to an abnormal value (< 135 mmol/L) appeared to be higher in the treatment groups (4 out of 8 subjects) than the placebo group (0 out of 5 subjects) when concomitantly treated with inhaled corticosteroids (**Table 6-1**). This finding suggests that concomitant administration of corticosteroids may contribute to the occurrence of hyponatremia in patients who are taking desmopressin. Therefore, the use of NOCDURNA should be contraindicated in patients on systemic or inhaled corticosteroids. The (re)use of NOCDURNA after discontinuation of a glucocorticoid should take into account the time required for the glucocorticoid to be eliminated from the body. Five half-lives of the glucocorticoid can be considered as a washout period before using NOCDURNA.

Table 6-1: The Number of Cases with Hyponatremia at any Post-Baseline Visit in Relation to the Concomitant use of Corticosteroids by Sex and Age at the Proposed Doses (25 mcg for Women and 50 mcg for Men) in Studies CS 40 and CS 41 (Captured from Summary of Clinical Safety).

Serum Sodium (mmol/L)	Females				Males			
	Placebo		25 mcg		Placebo		50 mcg	
	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
Inhaled Glucocorticoid								
Observed N	3	1	1	1	0	1	3	3
<135	0	0	0	1	0	0	1	2
130-134	0	0	0	1	0	0	1	2
126-129	0	0	0	0	0	0	0	0
≤125	0	0	0	0	0	0	0	0
Systemic Glucocorticoid								
Observed N	2	0	0	0	0	4	1	1
<135	0	0	0	0	0	0	0	0
Observed N = number of subjects reporting concomitant use of inhaled or systemic glucocorticoid								

Given that desmopressin is metabolized by proteolytic degradation (Janaky et al., 1984) and has no inhibitory potential on CYP enzymes (Study FE992026 DS PHA0102; refer to CLINICAL PHARMACOLOGY REVIEW (3/30/2010) of the original submission), a clinically significant PK interaction following sublingual administration of desmopressin with concomitant drugs is unlikely to occur.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No new efficacy trials were conducted for the current resubmission. The Applicant included additional exploratory analyses to help interpret the clinical meaningfulness of the observed treatment effects using data from two previously completed Phase 3 trials – CS40 and CS41 - as discussed in **Section 3.2**. The Applicant analyzed those endpoints for the nocturnal polyuria sub-group which is the target patient population for NOCDURNA. Data on durability of effect beyond three months come from Study CS29 and its long-term safety extension CS31. Study designs are summarized in **Table 7-1**.

Table 7-1: Design of Phase 3 Trials of Desmopressin Sublingual Tablets

Trial ID/Country	Trial Design	Treatment	Population
CS29	Two-part, randomized, double-blind, placebo-controlled, parallel group Part I: 4 weeks Part II: 1-6 months	Part I: Desmopressin 10 mcg, 25 mcg, 50 mcg or 100 mcg or placebo Part II: placebo subjects re-randomized to active drug Desmopressin 10 mcg, 25 mcg, 50 mcg or 100 mcg	Part I: 799 adult men and women with nocturia (≥ 2 voids/night required each of 3 nights) Part II: 665 subjects who completed Part I
CS31	Open-label safety extension of CS29 Trial continued until enrolled subjects completed a maximum of 2 years and 2.5 months of treatment	Desmopressin 10 mcg, 25 mcg 50 mcg or 100 mcg	Subjects who enrolled in study CS29 and completed at least Visit 3E in Part II (Day 15)
CS40 US and Canada	3-month randomized, double-blind, placebo-controlled	Desmopressin 25 mcg, placebo	268 adult females (≥ 18 years) with nocturia (≥ 2 voids/night required each of 3 nights)
CS41 US and Canada	3-month randomized, double-blind, placebo-controlled (Part I) followed by 12-month open-label extension phase (Part II)	Part I: desmopressin 50 mcg or 75 mcg, placebo Part II: desmopressin 100 mcg desmopressin (Part II)	395 adult males (≥ 18 years) with nocturia (≥ 2 voids/night required each of 3 nights)

Source: Adapted from Tabular Listing of all Clinical Studies found in NDA 022517 (seq 0039), Module 5.2.

7.2. Review Strategy

Results from Phase 3 trials CS29, CS40, and CS41 were previously reviewed by DMEP.¹⁰ The clinical efficacy review of the current submission will focus on the new, additional analyses of data from trials CS40 and CS41.

¹⁰ NDA 22517 clinical review finalized in DARRTS on April 7, 2010 and January 23, 2013.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial CS29

The first pivotal efficacy and safety trial was CS29, results of which are discussed in **Section 3.2**, Summary of Presubmission/Submission Regulatory Activity.

8.1.2. Trials FE 992026 CS40 and CS41

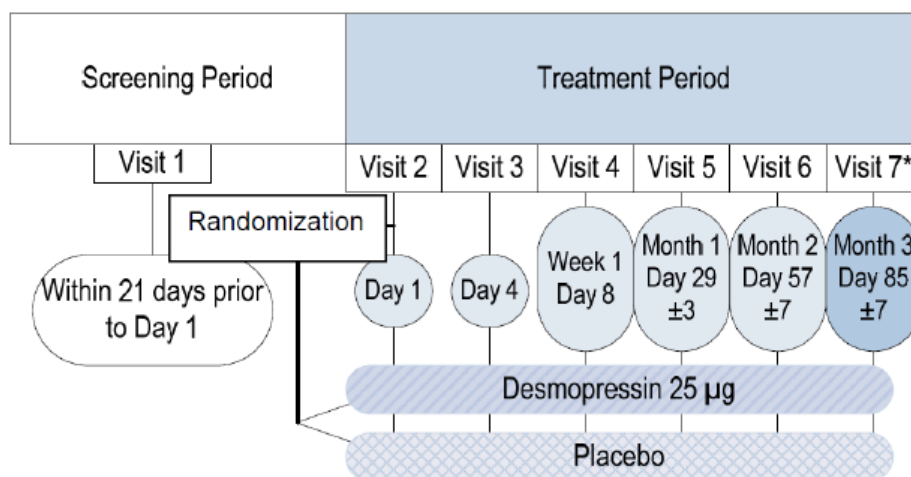
FE 992026 CS40: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Females, and

FE 992026 CS41: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Males.

Trial Designs

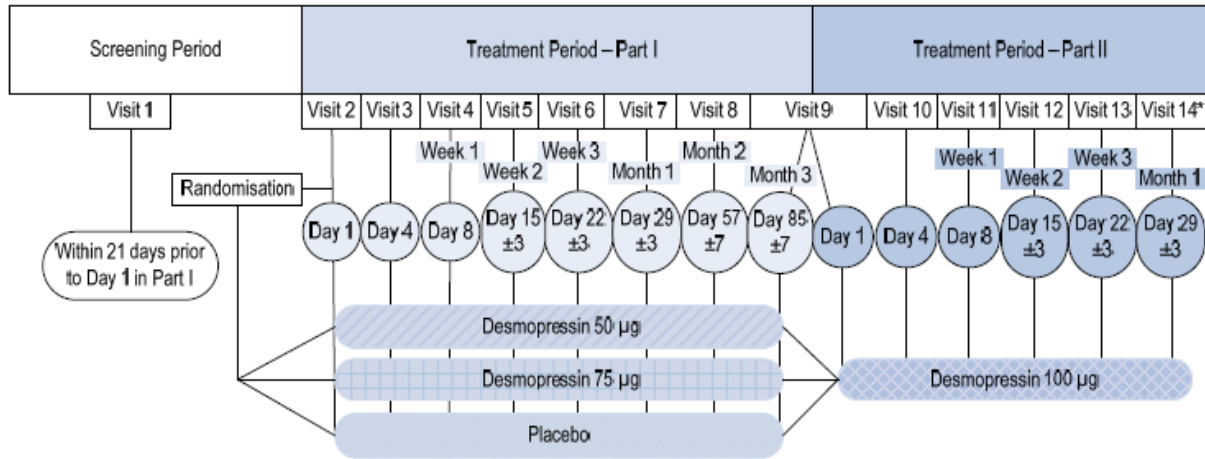
Design of trials CS40 and CS41 is discussed in detail in **Section 3.2**, and depicted in **Figure 8-1** and **Figure 8-2**, respectively. The schedule of assessments for the two trials is found in **Figure 8-3** and **Figure 8-4**.

Figure 8-1: Design of Trial CS40



Source: NDA 022517 (seq 0017), Module 5.3.5.1. CS40 study report, Figure 6-1, p. 19.

Figure 8-2: Design of Trial CS41



Source: NDA 022517 (seq 0017), Module 5.3.5.1. CS41 study report, Figure 6-1, p. 22.

Figure 8-3: Schedule of Assessments, Trial CS40

	Screening	Treatment Period					
Visit	1	2	3	4	5	6	7/EoT ^c
Assessment	-	Week 1			Month 1	Month 2	Month 3
Day of Treatment	^a	1 ^b	4	8	29±3	57±7	85±7
Informed consent	X ^d						
Inclusion and exclusion criteria	X	X					
Randomization		X					
Dispense IMP		X		X	X	X	
Accountability of IMP			X	X	X	X	X
Demographics	X						
Medical history	X						
Physical examination	X						X
Vital signs (BMI, blood pressure, and heart rate)	X						X
Clinical chemistry, hematology, urinalysis	X						X
Serum sodium ^e	X		X	X	X	X	X
Urine pregnancy test ^f	X						
Dispense sleep and voiding diary	X	X	X	X	X	X	
Collect sleep and voiding diary		X	X	X	X	X	X
Dispense fluid intake diary	X	X					
Collect fluid intake diary		X	X				
Dispense urine volume diary	X	X		X		X	
Collect urine volume diary		X	X		X		X
Nocturia Quality of Life (NQoL) questionnaire		X			X		X
Work Productivity and Activity Impairment (WPAI) questionnaire		X					X
Adverse events		X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X

Source: NDA 022517 (seq 0017), Module 5.3.5.1. CS40 study report, Table 6-2, p. 28.

Figure 8-4: Schedule of Assessments, Trial CS41

Visit	Screening		Treatment Period – Part I						
	1	2	3	4	5	6	7	8	9
Assessment	-	Week 1		Week 2	Week 3	Month 1	Month 2	Month 3	
Day	a	1 ^b	4	8	15±3	22±3	29±3	57±7	85±7
Informed consent	X ^d								
Inclusion and exclusion criteria	X	X							
Randomization		X							
Dispense IMP		X		X			X	X	X ^f
Accountability of IMP			X	X			X	X	X
Demographics	X								
Medical history	X								
Physical examination	X								X
Vital signs (blood pressure, heart rate) and BMI	X								X
Clinical chemistry, hematology, urinalysis	X								X
Serum sodium ^e	X		X	X	X	X	X	X	X
Dispense sleep and voiding diary	X	X	X			X	X	X	
Collect sleep and voiding diary		X	X	X			X	X	X
Dispense fluid intake diary	X	X							
Collect fluid intake diary		X	X						
Dispense urine volume diary	X	X				X		X	
Collect urine volume diary		X	X				X		X
Nocturia Quality of Life questionnaire		X					X		X
Work Productivity and Activity Impairment questionnaire		X							X
Adverse events		X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

Source: NDA 022517 (seq 0017), Module 5.3.5.1. CS41 study report, Table 6-2, p. 32.

Study Endpoints

For a discussion of endpoints in the current submission, refer to **Section 3.2**.

All efficacy endpoints for the additional analyses were calculated using the average over the entire treatment period, not as repeated measures as was done in previous review cycles.

Analysis Population

The analysis population was the modified intent-to-treat population (mITT) which included all randomized subjects that took at least one dose of study drug. Data from subjects randomized to desmopressin 75 mcg in Study CS41 were not considered in the analysis because the proposed therapeutic dose in men is 50 mcg desmopressin. Additional efficacy analyses were conducted on the subgroup of patients with nocturia due to nocturnal polyuria. The nocturnal polyuria sub-population included all randomized subjects with baseline nighttime urine production exceeding 33% of the 24-hour total urine volume production

Handling of Missing and Incomplete Data

Efficacy endpoints for the additional analyses were derived from observed diary data only. If subjects did not return a paper diary at a visit, diary data were considered missing. In addition, if bedtime or time of awakening was not recorded, the number of voids on the night in question was considered missing. Sensitivity analyses were performed to assess the impact of the missing data (see below).

Efficacy Analysis Methods

Continuous efficacy endpoints for the additional analyses, i.e., change from baseline in nocturnal voids, percentage of nights with at most one nocturnal void and the percentage of nights with zero void, were analyzed using an ANCOVA model including treatment group, baseline number of voids and age (<65 or ≥65 years). Results reported are least squares means estimates of the treatment differences and the associated 95 % confidence intervals (CIs). Least squares means estimates of the individual treatment effects were also reported.

The 33% responder status as well as the 50% responder status were derived from the mean change during the treatment period, and were analyzed using the Cochran-Mantel-Haenszel (CMH) method, stratified by age (<65 or ≥65 years). Treatment differences in responder status were expressed as percentages with associated 95% CIs.

Cumulative distribution function plots for the change from baseline in mean number of nocturnal voids per night, with a separate plot for each trial, showing the data for each treatment arm were presented.

Sensitivity Analysis for Missing Data

To evaluate the impact of missing data on the efficacy assessment of all efficacy endpoints, the Applicant proposed different approaches for imputation:

1. Placebo-based pattern imputation (PBPI), where missing data were imputed using the observed data from subjects treated with placebo;
2. Baseline observation carried forward (BOCF);
3. Last observation carried forward (LOCF). If there were no post-baseline data, the baseline observation was carried forward.

8.1.3. Study Results

Patient Disposition

A total of 268 subjects enrolled in study CS40 and 395 subjects enrolled in study CS41. Nearly 90% of enrolled subjects had nocturnal polyuria at baseline.

Disposition for the overall population is discussed in the medical officer review finalized in DARRTS on January 23, 2013.

Most nocturnal polyuria subjects completed the trials. The most common reason for premature discontinuation in CS41 was subject withdrawal and in CS40 was protocol violation. Disposition for the nocturnal polyuria population in trials CS40 and CS41 is shown in **Table 8-1**.

Table 8-1: Patient Disposition, Nocturnal Polyuria Population, Studies CS41 and CS40

Disposition	CS41 (Males)		CS40 (Females)	
	Desmopressin 50 mcg	Placebo	Desmopressin 25 mcg	Placebo
Randomized	102	128	121	116
Completed, n (%)	83 (81)	112 (88)	105 (87)	102 (88)
Prematurely withdrawn, n (%)	19 (19)	16 (12)	16 (13)	14 (12)
Withdrawal by subject	7 (7)	5 (4)	1(1)	3 (3)
Protocol violation	5 (5)	3 (2)	6 (5)	6 (5)
Lost to follow-up	3 (3)	3 (2)	4 (3)	0
Adverse event	4 (4)	5 (4)	4 (3)	1 (1)
Other	0	0	1(1)	4 (3)

Source: NDA 022517 (seq 0039), Module 5.3.5.3. CS40-CS41 Clinical Benefit Tables, Table 1.2.1 and 1.2.3, p.10 and p.12.

Protocol Violations/Deviations

Major protocol violations occurred in a small number of subjects in both desmopressin and placebo groups. In study CS40, the most common violation in the desmopressin group was reporting less than two voids per night in the 3-day voiding diary at baseline. In all cases this occurred in only one of the three nights, with all other nights having ≥ 2 voids. In study CS41, low compliance with study medication was the most common major protocol violation, but incidence was similar in the placebo and desmopressin 50 mcg groups.

FDA conducted additional sensitivity analyses in the nocturnal polyuria population excluding patients who had < 2 voids on any night in the 3-day voiding diary at baseline. Results were similar to the analysis results including the patients.

Demographic Characteristics

In the nocturnal polyuria population in the two Phase 3 confirmatory trials, the median age ranged from 62 to 65 years across treatment groups. The majority were white, not Hispanic or Latino. Demographic characteristics of the nocturnal polyuria population in studies CS40 and CS41 are shown in **Table 8-2**.

Table 8-2: Demographic Characteristics of Nocturnal Polyuria Population, Studies CS41 and CS40

Demographic Parameters	CS41 (Males)		CS40 (Females)	
	Desmopressin 50 mcg	Placebo	Desmopressin 25 mcg	Placebo
Sex (N)				
Male	102	128	0	0
Female	0	0	118	114
Age				
Mean years (SD)	60 (14)	61 (14)	59 (15)	60 (14)
Median (years)	63	65	62	65
Min, Max (years)	20, 81	21, 87	19, 81	23, 87
Age Group				
< 65 years	57 (56)	63 (49)	64 (54)	57 (50)
≥ 65 years	45 (44)	65 (51)	43 (46)	57 (50)
Race				
White	81 (79)	100 (78)	96 (81)	90 (79)
Black or African American	19 (19)	26 (20)	21 (18)	22 (19)
Asian	2 (2)	1 (1)	1 (1)	1 (1)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (1)
American Indian or Alaska native	0	1 (1)	0	0
Ethnicity				
Hispanic or Latino	17 (17)	19 (15)	23 (20)	16 (14)
Not Hispanic or Latino	85 (83)	109 (85)	95 (81)	98 (86)

Source: NDA 022517 (seq 0039), Module 5.3.5.3.CS40-CS41 Clinical Benefit Tables, Table 3.2.1, p.26 and Table 3.2.2, p.28.

Other Baseline Characteristics

Trial subjects in both treatment groups reported, on average, approximately 3 nocturnal voids per night at baseline. The majority had no more than four voids per night. Baseline voiding parameters are shown in **Table 8-3**.

Table 8-3: Baseline Voiding Parameters, Nocturnal Polyuria Population, Studies CS41 and CS40

Void parameter	CS41 (Males)		CS40 (Females)	
	Desmopressin 50 mcg (N=102)	Placebo (N=128)	Desmopressin 25 mcg (N=118)	Placebo (N=114)
Mean Nocturnal voids at baseline				
Mean (SD)	3.0 (0.9)	3.0 (0.8)	2.9 (1)	2.9 (1)
Mean number of nocturnal voids category, n (%)				
≥2-3	54 (53)	60 (47)	63 (53)	61 (54)
≥3-4	32 (31)	45 (35)	45 (38)	42 (37)
≥4-5	11 (11)	19 (15)	9 (8)	9 (8)
≥6-7	2 (2)	0	0	1 (1)
≥7	0	0	1 (1)	1 (1)
Percentage of nights with no nocturnal voids at baseline				
Mean (SD)	0	0	0	0
Percentage of nights with at most one nocturnal void at baseline				
Mean (SD)	0.3 (3)	1.0 (9)	0.3 (3)	0.7 (5)

Source: NDA 022517 (seq 0039), Module 5.3.5.3.CS40-CS41 Clinical Benefit Tables, Table 3.2.3 p.30 and Table 3.2.4, p.33

8.1.4. Assessment of Efficacy Trials

Efficacy results from CS40 and CS41 are examined together because the trials had identical study designs except for sex.

As noted in the clinical and statistical reviews from the prior review cycles as well as the briefing documents and slides from the January 12, 2015 Advisory Committee meeting, both trials met their prespecified co-primary efficacy endpoints using the prespecified statistical population and prespecified analyses. However, the observed treatment effects were small, raising questions about the clinical meaningfulness of the findings. The additional analyses that are discussed in this section were conducted to help interpret the clinical meaningfulness of the observed treatment effects, taking into account public scientific discussions among relevant experts about data and analyses that could be used to demonstrate a clinically meaningful benefit for desmopressin drugs to treat nocturia due to nocturnal polyuria.

Nocturnal Polyuria Population

During the fourth (current) review cycle, DBRUP requested the Applicant to reanalyze the prespecified co-primary efficacy endpoints in Studies CS40 and CS41 (see **Section 3.2**) for the

nocturnal polyuria population using the pre-specified methods outlined in the original study analysis plan, i.e., repeated measures ANCOVA and generalized estimation equations (GEE).

The results for the co-primary efficacy endpoints among patients with nocturia due to nocturnal polyuria in each study (see **Table 8-4**) are very similar to the results for the overall nocturia population (see **Table 3-5**).

Table 8-4: Summary of Efficacy Results for Pre-Specified Co-Primary Endpoints, Studies CS41 and CS40, Nocturnal Polyuria Population (mITT)

Pre-specified Co-Primary Efficacy Endpoints (Repeated Measures)	CS41 (Males)		CS40 (Females)	
	50 mcg (N=102)	Placebo (N=128)	25 mcg (N=118)	Placebo (N=114)
	Change from Baseline^a			
Baseline	3.0	3.0	2.9	2.9
Mean change	-1.3	-0.9	-1.5	-1.2
Difference vs. Placebo (95% CI)	-0.4 (-0.6, -0.2)		-0.3 (-0.5, -0.1)	
Proportion of 33% responders^b				
Estimated Probability	0.67	0.50	0.78	0.62
Odds	2.0	1.0	3.5	1.6
Odds ratio	2.0 (1.3, 3.1)		2.2 (1.4, 3.4)	

Source: NDA 022517 (seq 0057), Module 1 response-to-june-14-2018-ir-attachment1-mitt-tables-pdf.pdf

a--repeated measures of change from baseline at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit and baseline nocturnal voids

b--GEE Method for 33% responder status at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit and baseline nocturnal voids

Results for the additional analyses are shown in **Table 8-5**. In subjects with nocturia due to nocturnal polyuria, desmopressin produced on average 0.4 fewer nocturia episodes per night compared to placebo in men, and 0.3 fewer episodes per night in women. The percentage of desmopressin-treated subjects experiencing at least a 33% reduction in nocturia episode frequency during three months of treatment increased by 21% over placebo in men, and by 12% in women. During three months of treatment with desmopressin, the percentage of nights with at most one nocturnal void increased by 11% over placebo in men, and by 13% in women. The percentage of nights with no nocturnal voids increased by 9% in men compared to placebo, and by 4% in women. Finally, the percentage of patients experiencing a 50% reduction in nocturia episode frequency compared to baseline during three months of treatment with desmopressin increased by 12% compared to placebo in men, and by 17% over placebo in women.

Table 8-5: Summary of Additional Analysis Results, Studies CS41 and CS40, Nocturnal Polyuria

Endpoint/Statistic	Population (mITT)			
	CS41 (Males)		CS40 (Females)	
	Desmopressin 50 mcg N=102	Placebo N=128	Desmopressin 25 mcg N=118	Placebo N=114
Change from baseline in number of nocturnal voids				
Baseline	3.0	3.0	2.9	2.9
Change from baseline	-1.3	-0.9	-1.5	-1.2
Difference (95% CI)	-0.4 (-0.6, -0.2)		-0.3 (-0.5, -0.1)	
33% responder[#]				
Proportion (%)	70	47	76	63
Difference (95% CI)	21 (9, 34)		12 (0, 24)	
Percentage of nights with at most one nocturnal void*				
Baseline	0.3	1.0	1.1	0.3
Percentage	44	32	58	45
Difference (95% CI)	11 (3, 20)		13 (4, 21)	
Percentage of nights with no nocturnal voids*				
Baseline	0	0	0	0
Percentage	15	7	19	15
Difference (95% CI)	9 (4, 14)		4 (-3, 11)	
50% responder[#]				
Proportion (%)	41	28	58	43
Difference (95% CI)	12 (0, 25)		17 (4, 30)	

Source: NDA 022517 (seq 0039), Module 5.3.5.3. clinical-benefit-report.pdf, Table 6-2, p.38

*--The percentage was over the entire treatment period and adjusted for baseline number of voids and age category (<65 or ≥65 years old)

--33% and 50% responder statuses analyzed using the Cochran-Mantel-Haenszel method adjusting for age category (<65 or ≥65 years old).

†-- mITT population – all randomized subjects that took at least one dose of study drug.

The Applicant explored the patterns of missing night-time diary data and conducted sensitivity analyses using placebo-based pattern imputation, baseline observation carried forward and last observation carried forward approaches. The missing data were mostly monotonic and mainly

due to withdrawal. All the sensitivity analyses results were consistent with the primary analysis results. FDA analyses confirmed the sponsor's analyses.

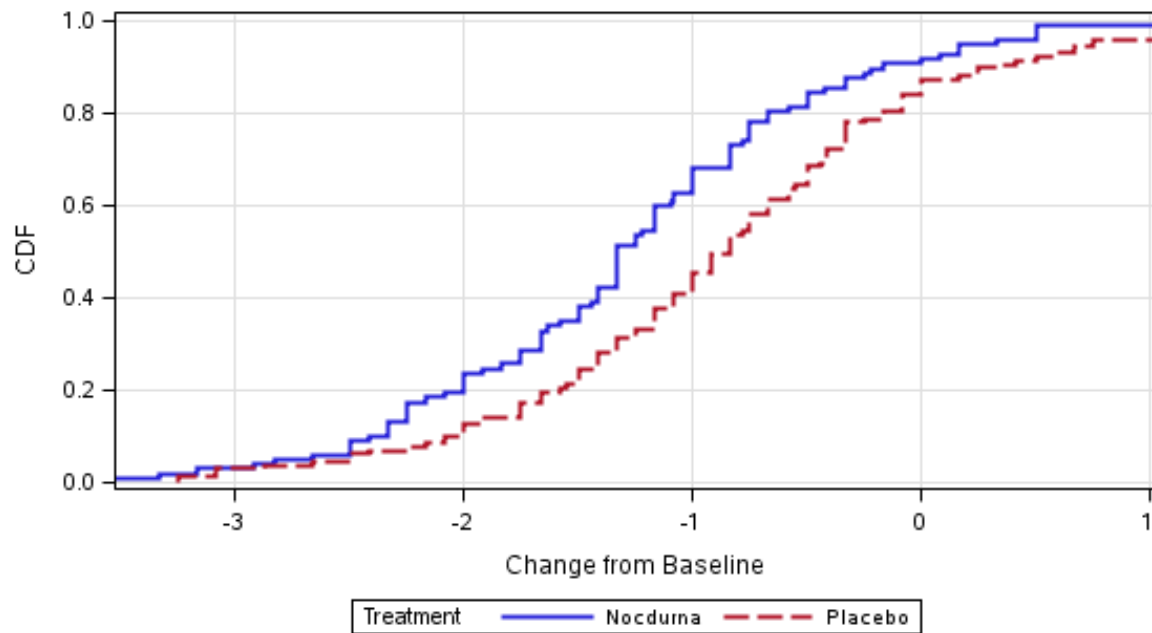
8.1.5. Additional Efficacy Considerations

CDF Plots - Nocturnal Polyuria Subpopulation

The cumulative distribution function (CDF) curves for the mean change from baseline in number of nocturnal voids by treatment group are presented below for studies CS40 and CS41. The CDF shows a continuous plot of the proportion of patients who experienced a mean reduction from baseline in nocturnal voids at that level or greater at each point along the scale score continuum. In the context of responder assessment, the y-axis also represents the proportion of patients who are considered responders at that threshold value on the x-axis. The CDF shows the proportion of responders at every value along the change in nocturnal voids.

As shown in **Figure 8-5**, in males with nocturia due to nocturnal polyuria, there was a clear separation of treatment effect between NOCDURNA and placebo. Approximately 68% of NOCDURNA-treated subjects reported at least one less void per night compared to approximately 46% of subjects receiving placebo. Approximately 24% of subjects receiving NOCDURNA reported at least two less voids per night compared to approximately 13% of subjects receiving placebo.

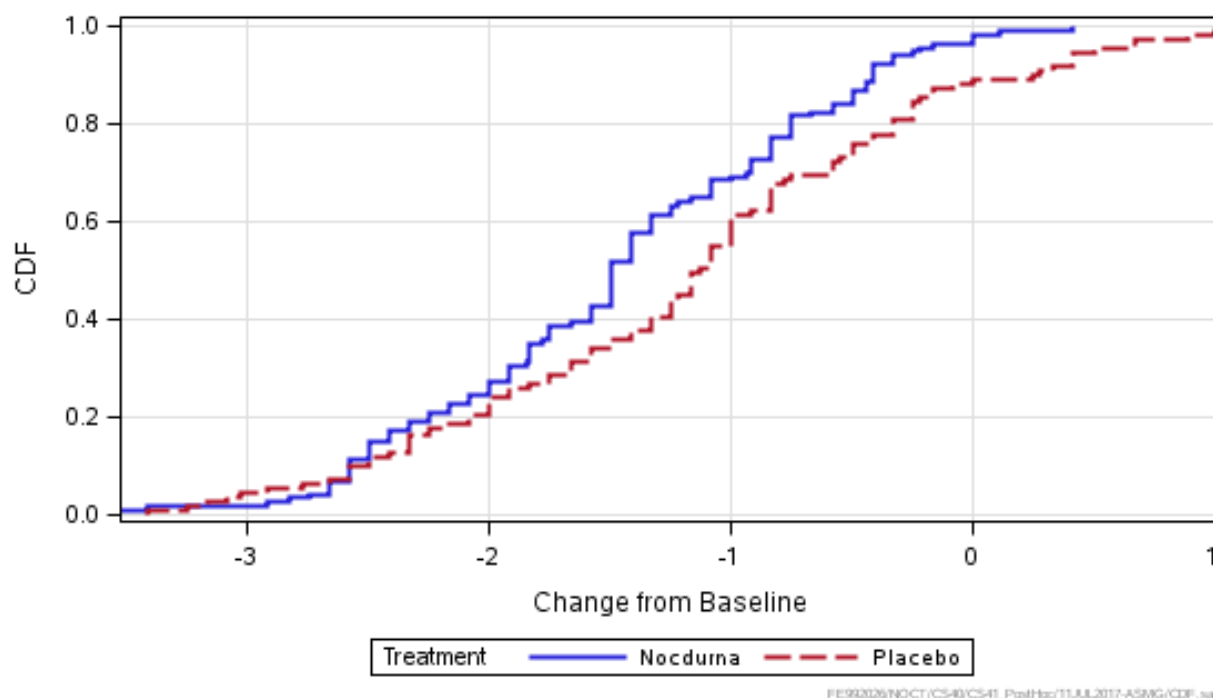
Figure 5: Cumulative Distribution Function plot for Mean Change from Baseline in Number of Nocturnal Voids, Study CS41 (Males), Nocturnal Polyuria Population (mITT)



Source: NDA 022517 (seq 0039), Module 5.3.5.3.CS40-CS41 Clinical Benefit Figures, Figure 6.2.3.3, p.15

In females with nocturnal polyuria, the placebo response was greater than males. However, there is still separation of curves (see **Figure 8-6**). Approximately 69% of women receiving NOCDURNA had at least one less void per night during treatment compared to baseline compared to 61% of women receiving placebo.

Figure 8-6: Cumulative Distribution Function Plot for Mean Change from Baseline in Number of Nocturnal Voids, Study CS40 (Females), Nocturnal Polyuria Population (mITT)



Source: NDA 022517 (seq 0039), Module 5.3.5.3.CS40-CS41 Clinical Benefit Figures, Figure 6.2.3.4, p.16

The CDF plots show that consistently more patients treated with desmopressin experienced at least one fewer void per night.

8.1.6. Dose and Dose-Response

Dose selection was thoroughly addressed in the DMEP primary clinical review of the NDA 22517 Complete Response application submitted on July 30, 2012 (finalized in DARRTS on January 23, 2013). The proposed doses of 25 mcg for women and 50 mcg for men reasonably balance the efficacy and safety of desmopressin.

8.1.7. Onset, Duration, and Durability of Effect

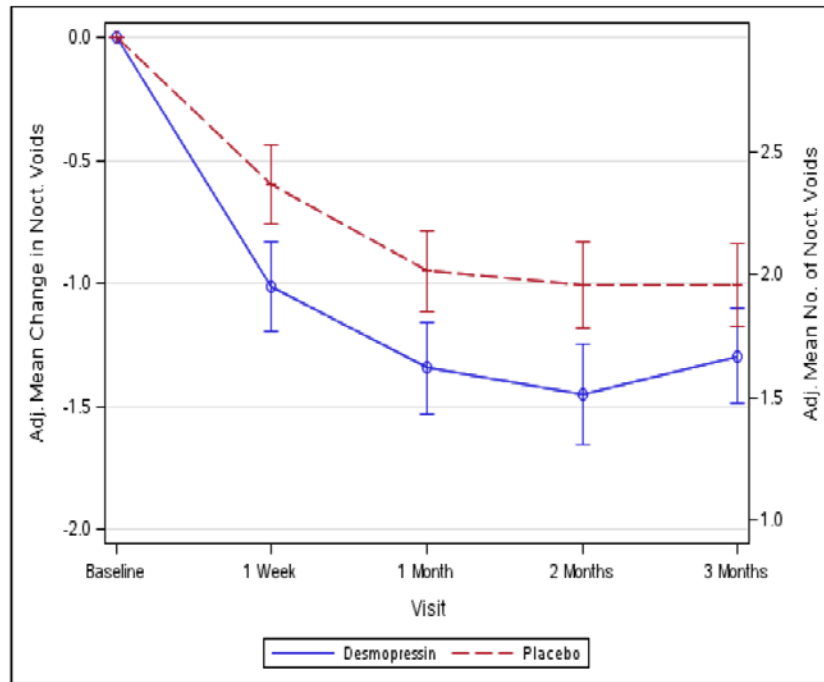
In Studies CS40 and CS41, the first efficacy assessment occurred at treatment week 1. The Applicant plotted the change from baseline in nocturia episode frequency by each visit over the course of the three-month treatment period.

In men with nocturnal polyuria, these descriptive analyses show that nocturia episode frequency progressively decreases for both the desmopressin and placebo groups from week 1

to month 2. The mean decrease is larger for desmopressin than for placebo at each treatment visit (see **Figure 8-7**).

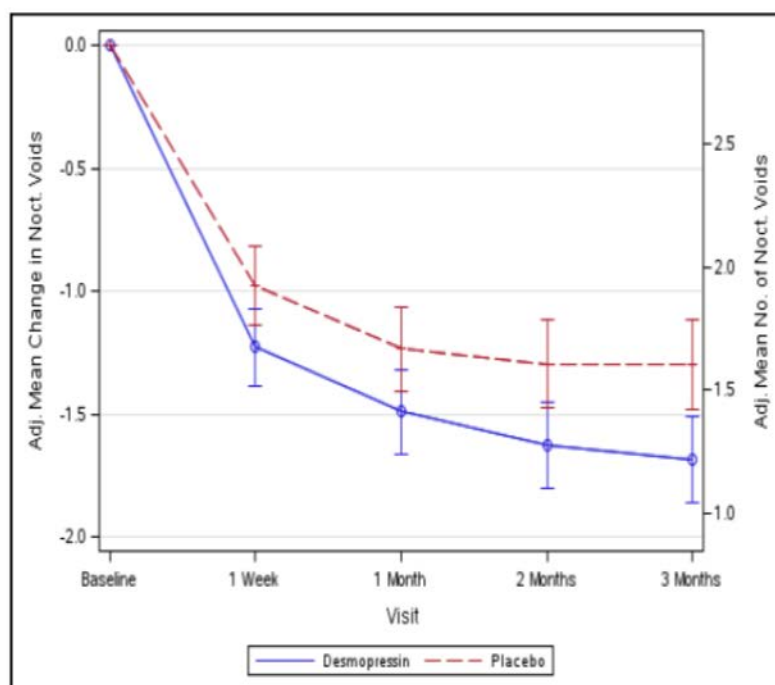
In women with nocturnal polyuria, these descriptive analyses show that nocturia episode frequency progressively decreases for both treatment groups from week 1 to month 3 (see **Figure 8-8**). The mean decrease is larger for desmopressin than for placebo at each time point.

Figure 8-7: Change from Baseline in Mean Number of Nocturnal Voids by Visit over Three Month Treatment Period, Study CS41 (Males), Nocturnal Polyuria Population



Source: NDA 022517 (seq 0039), Module 5.3.5.3.ISE Addendum Figures, Figure 6.2.1.1

Figure 8 8: Change from Baseline in Mean Number of Nocturnal Voids by Visit over Three Month Treatment Period, Study CS40 (Females), Nocturnal Polyuria Population



Source: NDA 022517 (seq 0039), Module 5.3.5.3.ISE Addendum Figures, Figure 6.1.1.1

8.1.8. Summary of Efficacy Findings from Four Review Cycles

- Desmopressin is proposed as a treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times per night to void. Although the population studied in the Phase 3 trials was not required to have nocturnal polyuria, nearly 90% of enrolled subjects did. An effort was made to exclude patients with other intrinsic factors that could contribute to nocturia, such as obstructive sleep apnea and overactive bladder. The exclusion criteria in CS29, 40, and 41 limit generalizability of the results to all patients with nocturia, supporting the more narrowed indication only in the subpopulation of patients with nocturia due to nocturnal polyuria.
- In trial CS29, only desmopressin 100 mcg was statistically superior to placebo with respect to the two prespecified co-primary efficacy endpoints. The mean reduction from baseline in nightly voids was 0.6 fewer voids per night compared to placebo and 24% more patients achieved a greater than 33% reduction in nocturia episode frequency than those on placebo. A post-hoc sex-based analysis of CS29 efficacy data suggested that, in males, from Day 8 to Day 28, NOCDURNA 50 mcg appeared to be beneficial relative to placebo with respect to both co-primary efficacy endpoints (see **Table 3-3**) except for the 33% responder

status at Day 28. In females, from Day 8 to Day 28, NOCDURNA 25 mcg and 50 mcg appeared to be beneficial relative to placebo with respect to both co-primary efficacy endpoints (see **Table 3-4**).

- In trial CS40 which enrolled only women, desmopressin 25 mcg – the proposed dose for marketing – administered for three months was statistically significantly superior to placebo in reducing the mean number of nocturnal voids (by 0.2 voids per night) and increasing the odds of achieving at least a 33% reduction in nocturia episode frequency (1.9 times greater odds than placebo).
- In trial CS41 which enrolled only men, desmopressin 50 mcg – the proposed dose for marketing – was statistically significantly superior to placebo on both co-primary efficacy endpoints. Men on desmopressin 50 mcg had a mean of 0.4 fewer voids per night and had higher odds of achieving at least a 33% reduction in nocturia episode frequency (2.0 times greater odds than placebo).
- Although CS40 and CS41 successfully met their prespecified co-primary efficacy endpoints, the mean reduction in nocturnal voids in both trials was small compared to placebo, raising questions about the clinical meaningfulness of the results.
- In the current resubmission, the Applicant included additional analyses that explored the clinical meaningfulness of the observed treatment effects in trials CS40 and CS41. These descriptive analyses showed that compared to placebo, desmopressin increased the 50% responder rate (by 12% in men, 17% in women) and the percentage of nights with no nocturnal voids (by 9% in men, 4% in women) and at most one nocturnal void (by 11% in men, 13% in women) in patients with nocturnal polyuria.
- In patients with nocturnal polyuria, CDF plots showed that compared to placebo, desmopressin increased the percentage of men experiencing at least one and two fewer voids per night compared to baseline by approximately 22% and 11%, respectively, and the percentage of women experiencing at least one fewer voids per night by 8%.
- In conclusion, the trials met their pre-specified co-primary efficacy endpoints. The totality of the data, taking into account the exploratory analyses of clinical meaningfulness (the responder analyses combined with the analyses of the percentage of nights with no nocturic voids or only one nocturic void), support the clinical benefit of NOCDURNA in treating adults with nocturia due to nocturnal polyuria who awaken two or more times per night to void. The percentage of nights with no nocturic voids reflects, for those nights, a complete resolution of the symptom being treated. Having one or fewer nocturic episodes per night reflects, for those nights, a reduction in nocturia below the threshold for which the drug will be indicated.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety data for desmopressin for the nocturia due to nocturnal polyuria indication are derived from the results of four Phase 3 trials – CS29, CS31, CS40, and CS41. These trials enrolled 1,443 unique subjects with nocturia who received at least one dose of trial drug. The target population for the four trials consisted of nocturia subjects with two or more voids per night. Approximately 88% (n=1,274) of subjects at baseline met the standard criterion for nocturnal polyuria (>33% of 24-hour urine production occurring at nighttime).

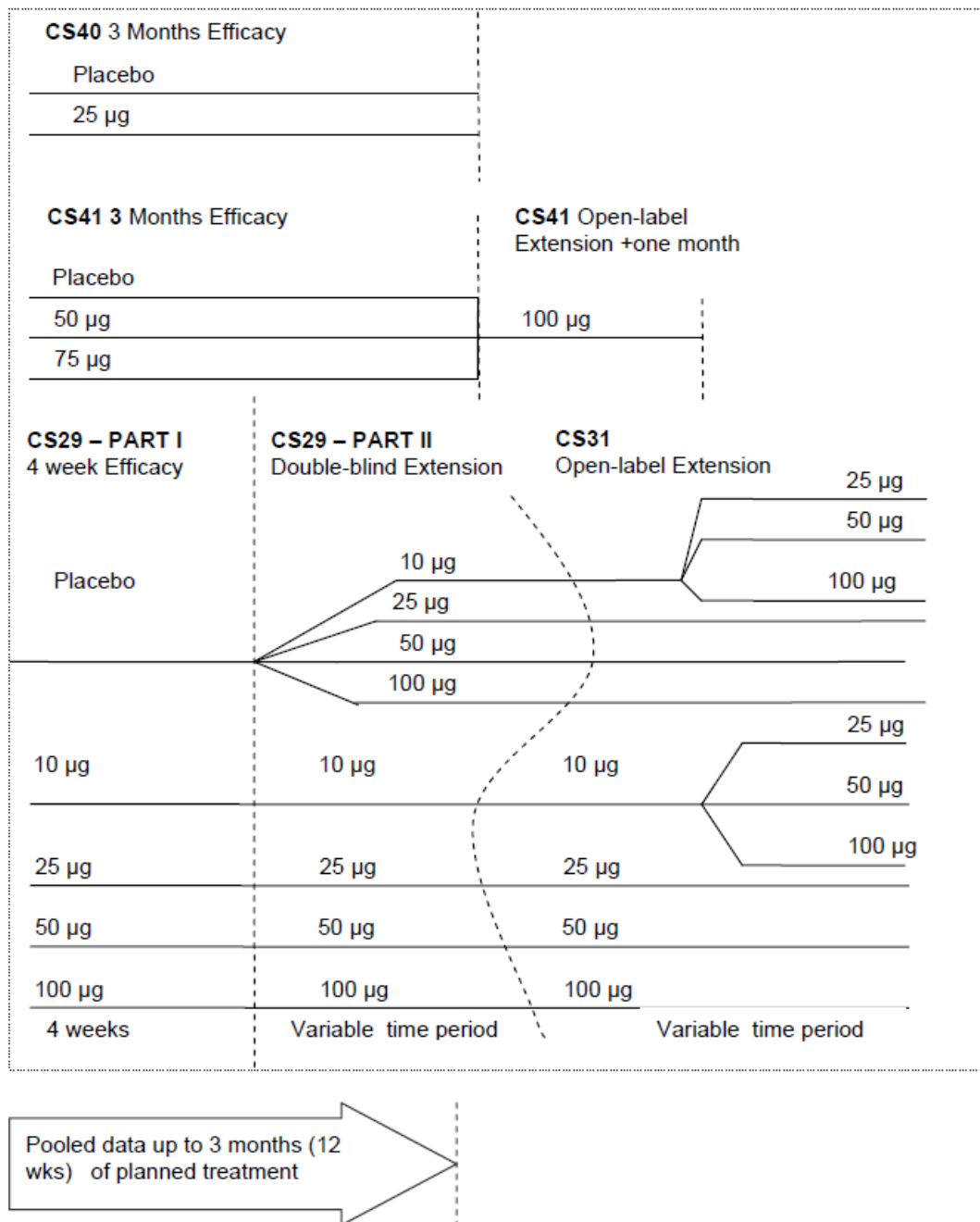
As discussed previously, CS29 was conducted in two parts. Part I was a randomized, double-blind, placebo-controlled, parallel-group, multi-center trial investigating the efficacy and safety of four doses (10 mcg, 25 mcg, 50 mcg, and 100 mcg) of desmopressin or placebo administered for 28 days for the treatment of nocturia in adults. Immediately upon completion of Part I of the trial, all subjects on active treatment could continue into Part II on the same treatment until results were available for Part I (approximately one to six months). Subjects assigned to placebo in Part I were randomly assigned to one of the four active treatments in Part II. To ensure that the trial remained fully blinded during the full extent of both Parts I and II, re-randomization of subjects assigned to placebo after four weeks of treatment was predetermined at the time of initial randomization.

CS31 was a long-term, open-label efficacy and safety extension trial. After results of Part I of CS29 were available, subjects enrolled in Part II who had completed at least Visit 3E (Day 15 of Part II or Day 43 of the trial) were eligible to roll over into CS31. All subjects were to be rolled-over within 4 weeks from the date the Applicant notified site personnel in writing that they could begin rolling over subjects. Subjects were initially assigned in a blinded manner to the same treatment they received in Part II of CS29. Once the database for CS29 was locked, subjects in CS31 were unblinded. Based on the results of CS29, which demonstrated that the 10 mcg dose is a sub-therapeutic dose for the primary efficacy parameters, subjects assigned to the 10 mcg dose were evenly assigned to the other doses of desmopressin (i.e., 25 mcg, 50 mcg, or 100 mcg). The long-term, continued use safety dataset (CS29 Part II + CS31), designated as the S.II analysis dataset, included subjects who had been on active treatment during CS29 Part I, who continued into Part II, and could have continued into CS31. Therefore, S.II included data from CS29 Part II and CS31 up to the time that a subject's dose was changed.

CS40 and CS41 are described in detail in **Section 8.1.2**. After the first 3 months of treatment in CS41, all subjects switched to a higher (100 mcg) desmopressin dose for a period of one month for further evaluation of safety in an open-label extension phase (Part II).

The primary focus of the safety review is the pooled Safety Analysis Dataset, which pooled data from the four Phase 3 desmopressin trials (CS29, CS31, CS40, and CS41) for up to 3 months of treatment. For CS29 and CS31, only data up to 3 months of (planned) treatment was pooled. The pooled analyses focused only on data up to 3 months because subjects in CS40 and CS41 were only exposed in a double-blind manner up to 3 months for the indicated doses. **Figure 8-9** shows the composition of the pooled Safety Analysis Dataset.

Figure 8-9: Composition of Pooled Safety Analysis Dataset



Source: NDA 022517 (seq 0017), Module 5.3.5.3, ISS Statistical Analysis Plan, Figure 1, p. 10.

The duration of placebo treatment varied between the pooled studies. Subjects were treated with placebo for four weeks in CS29 and three months in CS40 and CS41. After the first four weeks of treatment during CS29, the placebo subjects were re-randomized to one of the active treatment groups (10 mcg, 25 mcg, 50 mcg, or 100 mcg desmopressin) according to a pre-specified randomization schedule. Therefore, some subjects were treated with both placebo and an active dose.

To capture this, all post-baseline data was reported under the treatment that the subject was on when the respective event occurred or the value was measured. Hence, some subjects are included more than once in the summary tables, because they were included in the safety dataset for both placebo and the active dose. Since demographics tables presented in the integrated summary are supportive of the actual integrated safety analyses, these tables are also presented using similar treatment group allocation, i.e., including double (and an incidental triple) counting.

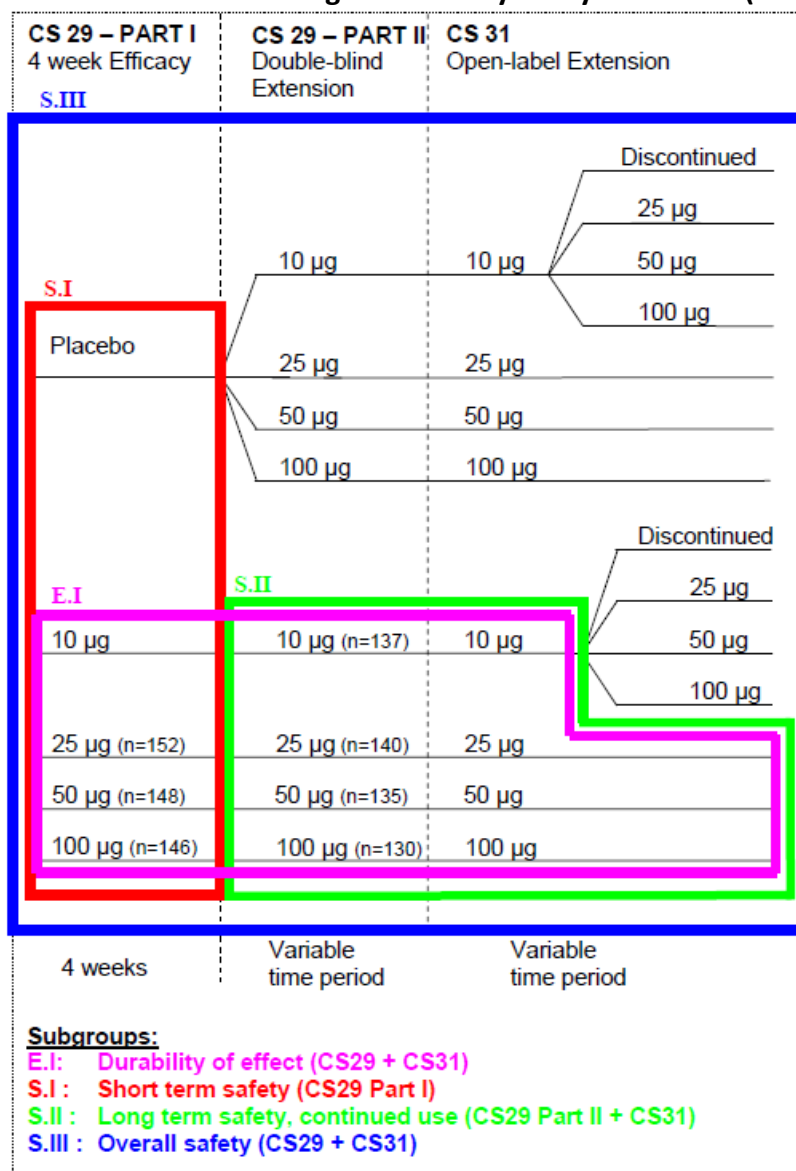
In addition to the three-month pooled data from the four Phase 3 trials, long-term safety was assessed using the S.II and S.III Safety Analysis Datasets for CS29/31. As noted above, the S.II dataset (N=542) assessed long-term, continued use safety and included subjects who had been on active treatment during CS29 Part I, who continued into Part II, and could have continued into CS31. Data from CS31 was included up to the time that a subject's dose was changed. Of the 542 subjects in this dataset, 137 subjects were in the 10 mcg dose group, 140 were in the 25 mcg group, 135 were in the 50 mcg group, and 130 in the 100 mcg group. Subjects who rolled over into CS31 remained on the same treatment they received in Part II of CS29. After the 10 mcg dose was determined to be sub-therapeutic, subjects being treated with this dose were re-randomized to one of the three remaining dose groups. Since the S.II dataset assessed safety with continued use of a single dose, adverse events that occurred after a change in dose were not included in this dataset. Therefore, the exposure for subjects in the 10 mcg dose group was less than that of the other dose groups. The total exposure for the 10, 25, 50, and 100 mcg dose groups was 91, 222, 202, and 191 patient-years, respectively. The S.II dataset was used for the long-term analyses of adverse events and hyponatremia.

The S.III dataset assessed overall long-term safety (CS29 and CS31) and included all subjects who received at least one dose of study drug (placebo or desmopressin). The S.III population counted subjects according to their study drug exposure and, therefore, subjects could be included in more than one treatment group. Thus, of the 1023 subjects in the dataset, 799 were unique subjects who enrolled in CS29, 222 were subjects who were re-randomized from placebo or the 10 mcg desmopressin dose to other dose groups, and 2 were subjects whose dose was decreased. This dataset was used for the baseline to end of study analysis of vital sign measurements and laboratory values.

Figure 8-10 shows the composition of the S.II (outlined in green) and S.III (outlined in blue)

Long-Term Safety Analysis Datasets from CS29/31.

Figure 8-10: S.II and S.III Long-Term Safety Analysis Dataset (CS29/31)



Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report, Figure 1, p. 38.

8.2.2. Review of the Safety Database

Overall Exposure

Three-Month Exposure (Pooled Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

The pooled Safety Analysis Dataset (pooled data from CS29, CS31, CS40, and CS41) was used in the pooled safety analyses. This dataset is defined as all randomized subjects who received at

least 1 dose of study drug. If a subject was given an experimental regimen other than that to which he/she was randomized, he/she is included in the group receiving the therapy.

A total of 1,443 unique subjects received at least 1 dose of trial drug in the Phase 3 trials (CS29, CS31, CS40, and CS41). A total of 1,188 (82%) subjects completed 3 months of treatment; a similar percentage of subjects completed treatment in the desmopressin dose groups (83-88%) and the placebo group (84%) except for the 10 mcg and 100 mcg dose groups which had a slightly lower completion rate (77%). Of the 1,443 subjects, 255 (18%) were prematurely withdrawn; the most common reason for premature discontinuation in the desmopressin dose groups (3-10%) and the placebo group (6%) was withdrawal of consent. Adverse Events (AEs) led to premature discontinuation in 2-6% of subjects across desmopressin dose groups. A summary of subject disposition in the Phase 3 trials in nocturia subjects is presented in **Table 8-6**.

**Table 8-6: Subject Disposition – Pooled 3-Month Data
 (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)**

Disposition	Placebo	10 µg	25 µg	50 µg	75 µg	100 µg	Total
Safety Analysis Dataset	429	194	331	311	122	194	1,443
Completed 3 months, n (%)	360 (84)	149 (77)	283 (85)	259 (83)	107 (88)	149 (77)	1,188 (82)
Prematurely withdrawn, n (%):							
Adverse event	12 (3)	6 (3)	7 (2)	12 (4)	7 (6)	9 (5)	49 (3)
Serum sodium ≤125 mmol/L	3 (<1)	0	0	6 (2)	0	6 (3)	13 (<1)
Lost to follow-up	8 (2)	5 (3)	8 (2)	9 (3)	1 (<1)	4 (2)	34 (2)
Subject withdrew consent	25 (6)	20 (10)	20 (6)	17 (5)	4 (3)	15 (8)	93 (6)
Protocol violation	9 (2)	2 (1)	5 (2)	2 (<1)	3 (2)	2 (1)	23 (2)
Other	12 (3)	12 (6)	8 (2)	6 (2)	0	9 (5)	43 (3)

Note: Some subjects received different doses and are included in more than 1 dose group. The total represents unique subjects only.

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 22, p. 63.

Of the 255 subjects who prematurely discontinued, 119 (47%) discontinued at 0-1 month, 90 (35%) discontinued at 1-2 months, and 46 (18%) discontinued at 2-3 months. Of the 13 subjects who prematurely discontinued due to a serum sodium value ≤125 mmol/L, the majority (10/13; 76.9%) discontinued at 0-1 month.

Most (90%) subjects received only one dose regimen of desmopressin during the 3-month treatment period across all trials (CS29, CS31, CS40, and CS41) (**Table 8-7**). A similar percentage (11-18%) of subjects in the desmopressin 10 mcg, 25 mcg, 50 mcg, and 100 mcg groups received placebo during the 3-month treatment period.

Table 8-7: Subjects Who Received 1 or >1 Dose Regimen During the 3-Month Treatment Period (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)	Total (N=1443) n (%)
1 dose regimen	291 (100)	162 (84)	293 (89)	277 (89)	122 (100)	160 (82)	1,305 (90)
Placebo ^a followed by:	0	32 (16)	38 (11)	34 (11)	0	34 (18)	138 (10)

^aSubjects on placebo in the CS29 trial were re-randomized after 4 weeks to 10 µg, 25 µg, 50 µg, or 100 µg (double counted).

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 23, p. 63.

The number of desmopressin subjects with >8-12 weeks of exposure was 127 (65%) in the 10 mcg group, 256 (77%) in the 25 mcg group, 236 (76%) in the 50 mcg group, 110 (90%) in the 75 mcg group, and 125 (64%) in the 100 mcg group. **Table 8-8** summarizes exposure during the 3-month treatment period.

Table 8-8: Extent of Exposure During the 3-Month Treatment Period (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Duration (weeks)	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)
Missing	0	1 (<1)	0	0	0	0
0 - 1	9 (2)	7 (4)	8 (2)	11 (4)	2 (2)	16 (8)
>1 - 2	7 (2)	5 (3)	6 (2)	4 (1)	3 (2)	7 (4)
>2 - 4	112 (26)	15 (8)	13 (4)	12 (4)	2 (2)	13 (7)
>4 - 8	52 (12)	39 (20)	48 (15)	48 (15)	5 (4)	33 (17)
>8 - 12 ^a	249 (58)	127 (65)	256 (77)	236 (76)	110 (90)	125 (64)

Note: Some subjects received different doses and are in more than 1 dose group.

^aIncludes all Month 3 scheduled assessments regardless of actual day for CS40/CS41.

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 24, p. 64.

Long-Term Continued Use Exposure (S.II Safety Analysis Dataset-CS29/31)

Of the 542 subjects in the S.II Safety Analysis Dataset, 256 (47%) prematurely discontinued, 67 (12%) were re-randomized from the 10 mcg group, and 171 (32%) completed CS31. The most common reasons for discontinuation overall were withdrawal of consent (24%), adverse event (8%), and lost to follow-up (6%). A slightly higher proportion of males than females prematurely discontinued (49% vs. 45%). The proportion of male subjects who withdrew due to adverse events was also slightly higher than the proportion of female subjects who withdrew due to adverse events (9% vs. 5%). One male subject in the 50 mcg dose group discontinued due to decreased serum sodium $\leq$ 125 mmol/L, compared to no female subjects in the 25 mcg dose. A summary of subject disposition for the S.II Safety Analysis Dataset is presented in **Table 8-9**.

**Table 8-9: Subject Disposition – Long-Term Continued Use Data
(S.II Safety Analysis Dataset-CS29/31)**

Stratum: Overall	10 ug* N (%)	25 ug N (%)	50 ug N (%)	100 ug N (%)	Total N (%)
Safety	137 (100.0%)	140 (100.0%)	135 (100.0%)	130 (100.0%)	542 (100.0%)
Re-randomized Subjects	67 (48.9%)				67 (12.4%)
Completed CS31		59 (42.1%)	59 (43.7%)	53 (40.8%)	171 (31.5%)
Withdrawn	56 (40.9%)	72 (51.4%)	60 (44.4%)	68 (52.3%)	256 (47.2%)
Adverse Event	5 (3.6%)	13 (9.3%)	13 (9.6%)	10 (7.7%)	41 (7.6%)
Decreased serum sodium <= 125 mmol/L	1 (0.7%)	0	2 (1.5%)	2 (1.5%)	5 (0.9%)
Use of Exclusionary Medication	1 (0.7%)	2 (1.4%)	1 (0.7%)	0	4 (0.7%)
Protocol Violation	3 (2.2%)	5 (3.6%)	2 (1.5%)	2 (1.5%)	12 (2.2%)
Patient Withdrew Consent	29 (21.2%)	31 (22.1%)	33 (24.4%)	37 (28.5%)	130 (24.0%)
Lost to Follow-up	7 (5.1%)	14 (10.0%)	2 (1.5%)	10 (7.7%)	33 (6.1%)
Other	7 (5.1%)	6 (4.3%)	7 (5.2%)	6 (4.6%)	26 (4.8%)
Not Reported	3 (2.2%)	1 (0.7%)	0	1 (0.8%)	5 (0.9%)
Did not consent to entering CS31	14 (10.2%)	9 (6.4%)	16 (11.9%)	9 (6.9%)	48 (8.9%)

N = Number of subjects; % = Percentage of subjects.

*The 10 ug group includes subjects on 10 ug up to the point they were re-randomized or withdrawn.

S.II: Long term safety, continued use (CS29 Part II + CS31)

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.1.1.5, p. 13.

Of the 542 subjects in the S.II Safety Analysis Dataset, during CS29 Part II and CS31, 286 (53%) received the drug for at least one year, 215 (40%) received the drug for at least 1.5 years, 187 (35%) received the drug for at least two years, and 96 (18%) received the drug for at least 2.5 years. **Table 8-10** summarizes long-term continued use exposure during CS29/31.

**Table 8-10: Extent of Long-Term Continued Use Exposure
(S.II Safety Analysis Dataset-CS29/31)**

Exposure Category	10 ug N (%)	25 ug N (%)	50 ug N (%)	100 ug N (%)	Total N (%)
Safety	137 (100.0%)	140 (100.0%)	135 (100.0%)	130 (100.0%)	542 (100.0%)
Subjects With At Least 1 Year Exposure	35 (25.5%)	92 (65.7%)	82 (60.7%)	77 (59.2%)	286 (52.8%)
Subjects With At Least 1.5 Year Exposure	0	78 (55.7%)	70 (51.9%)	67 (51.5%)	215 (39.7%)
Subjects With At Least 2 Year Exposure	0	67 (47.9%)	62 (45.9%)	58 (44.6%)	187 (34.5%)
Subjects With At Least 2.5 Year Exposure	0	34 (24.3%)	34 (25.2%)	28 (21.5%)	96 (17.7%)
Total Patient-Years	91.40	221.56	202.42	191.09	706.48

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.6.3, p. 565-566.

The extent of long-term continued use exposure (S.II Safety Analysis Dataset-CS29/31) at the sex-specific doses proposed for marketing (25 mcg in females and 50 mcg in males) is summarized in **Table 8-11**.

**Table 8-11: Extent of Long-Term Continued Use Exposure – Gender Specific Doses
 (S.II Safety Analysis Dataset-CS29/CS31)**

Extent of Exposure	Females	Males
	25 mcg (N=58)	50 mcg (N=73)
Subjects with: n (%)		
≥ 1 year exposure	42 (72%)	49 (67%)
≥ 1.5 years' exposure	36 (62%)	42 (58%)
≥ 2 years' exposure	31 (53%)	38 (52%)
≥ 2.5 years' exposure	18 (31%)	19 (26%)
Total Patient Years	99	119

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.6.4, p. 567-570.

Relevant characteristics of the safety population:

Three-Month Pooled Safety Database (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)
 Except for sex, the demographic characteristics for patients included in the pooled three-month database (CS29, CS31, CS40, and CS41) were similar across treatment groups. Though 57% of subjects were male; 66% of subjects receiving desmopressin 25 mcg were female. The race of most subjects was White (81%), 16% were Black, and 2% were Asian. Hispanics or Latinos comprised 12% of the trial population. The mean age of the subjects was 61.1 years (median age: 64 years), and age ranged from 19 to 89 years. Mean weight was 86.2 kg and mean body mass index was 29.5 kg/m². The demographic characteristics of the safety analysis dataset are summarized in **Table 8-12**.

**Table 8-12: Demographic Characteristics – Pooled 3-Month Data
(Safety Analysis Dataset-CS29, CS31, CS40, and CS41)**

Demographic Characteristic	Placebo (N=429)	10 µg (N=194)	25 µg (N=331)	50 µg (N=311)	75 µg (N=122)	100 µg (N=194)
Age (years)						
Mean (SD)	60.9 (13.9)	61.4 (14.1)	61.3 (13.7)	61.1 (12.4)	60.1 (11.7)	62 (13)
Median	64	64	64	63	64	65
Minimum, maximum	20, 87	23, 85	19, 89	20, 88	29, 80	24, 85
Age category, n (%)						
<65 years	224 (52)	103 (53)	167 (50)	165 (53)	63 (52)	92 (47)
≥65 years	205 (48)	91 (47)	164 (50)	146 (47)	59 (48)	102 (53)
Gender, n (%)						
Female	193 (45)	93 (48)	219 (66)	89 (29)	0	89 (46)
Male	236 (55)	101 (52)	112 (34)	222 (71)	122 (100)	105 (54)
Race, n (%)						
White	355 (83)	158 (81)	269 (81)	257 (83)	98 (80)	152 (78)
Black/African American	65 (15)	24 (12)	53 (16)	46 (15)	22 (18)	33 (17)
Asian	6 (1)	3 (2)	4 (1)	6 (2)	2 (2)	7 (4)
American Indian/ Alaskan Native	1 (<1)	2 (1)	0	0	0	0
Native Hawaiian/ Pacific Islander	1 (<1)	1 (<1)	2 (<1)	0	0	0
Other	1 (<1)	6 (3)	3 (<1)	2 (<1)	0	2 (1)
Ethnic origin, n (%)						
Hispanic or Latino	50 (12)	18 (9)	38 (11)	40 (13)	29 (24)	10 (5)
Not Hispanic or Latino	379 (88)	176 (91)	293 (89)	271 (87)	93 (76)	184 (95)
Height (m)						
Mean (SD)	1.71 (0.098)	1.7 (0.101)	1.67 (0.1)	1.72 (0.095)	1.78 (0.073)	1.71 (0.105)
Median	1.71	1.70	1.66	1.73	1.78	1.72
Minimum, maximum	1.49, 1.93	1.24, 1.93	1.4, 1.96	1.38, 1.96	1.57, 1.96	1.42, 1.96
Weight (kg)						
Mean (SD)	85.7 (20)	84.7 (18)	84.4 (19.5)	87.4 (19.6)	92.3 (17.7)	86.6 (20)
Median	84	83.1	82.2	85.8	89.8	84
Minimum, maximum	47.7, 155	42.3, 149	45, 178	46.3, 177	50.8, 153	42.9, 152
BMI (kg/m ²)						
Mean (SD)	29.4 (6.25)	29.4 (6.29)	30.2 (6.7)	29.4 (6.41)	29.2 (4.81)	29.6 (6.62)
Median	28.4	28.4	28.9	28.2	28.6	28.1
Minimum, maximum	16.6, 53.1	16.5, 53.1	16.8, 59.7	16.6, 67.1	16.1, 47	17.5, 58.1

Source: NDA 022517 (seq 0017), Module 5.3.5.3, Integrated Summary of Safety, Table 20, p. 65.

The Phase 3 trials enrolled subjects reporting nocturia with two or more voids per night. Approximately 88% (n=1,274) of subjects met the standard definition for nocturnal polyuria of nocturnal polyuria index >33%. The number of subjects <65 years and ≥65 years in the nocturia due to nocturnal polyuria population is presented by sex and overall in **Table 8-13**.

Table 8-13: Subjects with Nocturia due to Nocturnal Polyuria by Gender and Age – Pooled 3-Month Data (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Females N=549		Males N=725		Total N=1,274	
<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
313	236	323	402	636	638

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 25, p. 64.

Long-Term, Continued Use Safety Database (S.II Safety Analysis Dataset-CS29/31)

The demographic characteristics for patients included in the long-term safety database (S.II CS29/CS31) (N=542) were similar across treatment groups. The race of most subjects was White (80%), 16% were Black, and 2% were Asian. Hispanics or Latinos comprised 6% of the trial population. The mean age of the subjects was 62 years (median age: 65 years), and age ranged from 22 to 89 years. Mean weight was 85.9 kg and mean body mass index was 29.6 kg/m². The demographic characteristics of the long-term continued use S.II safety analysis dataset are summarized in **Table 8-14**.

**Table 8-14: Demographic Characteristics – Long-Term Continued Use Data
(S.II Safety Analysis Dataset-CS29/31)**

Subgroup: Overall	10 ug	25 ug	50 ug	100 ug	Total
Intent to Treat Dataset	137 (100.0%)	140 (100.0%)	135 (100.0%)	130 (100.0%)	542 (100.0%)
Age (Y)					
N	137	140	135	130	542
Mean (SD)	61.5 (14.08)	62.2 (13.51)	61.7 (11.99)	62.4 (11.48)	62.0 (12.80)
Median	64.0	65.0	64.0	65.0	65.0
Min, Max	(23, 84)	(22, 89)	(28, 88)	(24, 82)	(22, 89)
Age Categories					
<65	70 (51.1%)	69 (49.3%)	70 (51.9%)	61 (46.9%)	270 (49.8%)
≥65	67 (48.9%)	71 (50.7%)	65 (48.1%)	69 (53.1%)	272 (50.2%)
Total	137 (100.0%)	140 (100.0%)	135 (100.0%)	130 (100.0%)	542 (100.0%)
Sex, N (%)					
Female	64 (46.7%)	58 (41.4%)	62 (45.9%)	59 (45.4%)	243 (44.8%)
Male	73 (53.3%)	82 (58.6%)	73 (54.1%)	71 (54.6%)	299 (55.2%)
Total	137 (100.0%)	140 (100.0%)	135 (100.0%)	130 (100.0%)	542 (100.0%)
Race, N (%)					
Caucasian	113 (82.5%)	109 (77.9%)	109 (80.7%)	100 (76.9%)	431 (79.5%)
Black/African American	17 (12.4%)	27 (19.3%)	21 (15.6%)	24 (18.5%)	89 (16.4%)
Asian	2 (1.5%)	1 (0.7%)	3 (2.2%)	5 (3.8%)	11 (2.0%)
American Indian/Alaskan Native	0	0	0	0	0
Native Hawaiian/other Pacific Islander	1 (0.7%)	1 (0.7%)	0	0	2 (0.4%)
Other	4 (2.9%)	2 (1.4%)	2 (1.5%)	1 (0.8%)	9 (1.7%)
Total	137 (100.0%)	140 (100.0%)	135 (100.0%)	130 (100.0%)	542 (100.0%)
Ethnic Origin, N (%)					
Hispanic	9 (6.6%)	8 (5.7%)	12 (8.9%)	4 (3.1%)	33 (6.1%)
Not Hispanic	128 (93.4%)	132 (94.3%)	123 (91.1%)	126 (96.9%)	509 (93.9%)
Total	137 (100.0%)	140 (100.0%)	135 (100.0%)	130 (100.0%)	542 (100.0%)
Height (m)					
N	137	140	135	130	542
Mean (SD)	1.70 (0.109)	1.71 (0.104)	1.70 (0.093)	1.71 (0.111)	1.71 (0.104)
Median	1.7	1.7	1.7	1.7	1.7
Min, Max	(1.2,1.9)	(1.5,2.0)	(1.4,1.9)	(1.4,2.0)	(1.2,2.0)
Weight (kg)					
N	137	140	135	130	542
Mean (SD)	84.15 (17.945)	85.92 (19.613)	87.09 (20.036)	86.31 (19.364)	85.86 (19.230)
Median	82.8	84.0	84.0	84.0	84.0
Min, Max	(42.3,148.7)	(45.0,178.0)	(46.7,170.4)	(42.9,151.7)	(42.3,178.0)
BMI (kg/m²)					
N	137	140	135	130	542
Mean (SD)	29.22 (6.286)	29.42 (6.610)	30.22 (7.670)	29.47 (6.436)	29.58 (6.764)
Median	28.44	28.36	28.78	28.04	28.46
Min, Max	(16.52, 52.92)	(17.45, 59.66)	(16.61, 67.15)	(17.51, 58.09)	(16.52, 67.15)

(1) Totals for each categorical variable within treatment group included.

(2) Percentages are calculated within each categorical variable.

(3) Age is truncated before summary calculation.

Note: Only subjects on active treatment in CS29 Part II and CS31 are included.

S.II: Long term safety, continued use (CS29 Part II + CS31)
 Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.1.3.5, p. 43-46.

Approximately 90% (n=489) of subjects in the long-term, continued use safety database had nocturnal polyuria at baseline (nocturnal polyuria index >33%). The number of subjects <65 years and ≥65 years in the nocturia due to nocturnal polyuria population included in the S.II dataset is presented by sex and overall in **Table 8-15**.

Table 8-15: Subjects with Nocturia due to Nocturnal Polyuria by Gender and Age – (Long-Term Safety Dataset-S.II CS29/31)

Female N=217		Males N=272		Total N=489	
<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
130	87	104	168	234	255

Source: Reviewer Analysis: Data Analysis Dataset ADSL (CS31) NDA 022517 (seq 0017), Module 5.3.5.1.

Adequacy of the safety database:

The size of the safety database is adequate and includes enough subjects treated with the doses proposed for approval or with higher doses. A total of 1,443 unique subjects comprised the three-month safety dataset, of which 1,188 (82%) completed three months of treatment. The long-term, continued use dataset included 542 subjects, of which 286 (53%) completed one year of treatment.

Both datasets included subjects who are representative of the target population likely to use the drug: 1,274 (88%) subjects in the three-month safety dataset and 489 (90%) in the long-term continued use dataset had nocturia due to nocturnal polyuria (the patient population for which the Applicant is requesting approval). Approximately 50% of the subjects in each of the datasets were aged 65 years or older.

In addition to the clinical trial data, the Applicant also submitted postmarketing data for oral formulations of desmopressin based on 3.7 million patient years (PY) of exposure for desmopressin tablets (all indications) and 2.3 million PY of exposure for desmopressin sublingual tablets approved outside the U.S. (all indications). Postmarketing data for NOCDURNA (sex-specific dosing of 25 mcg for females and 50 mcg for males) based on approximately 3,548 PY (25 mcg: 1,807 PY; 50 mcg: 1,741 PY) of exposure was also submitted (see **Section 8.2.10** Safety in the Postmarket Setting).

8.2.3. Adequacy of Applicant’s Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No new Phase 3 studies were submitted during the current review cycle. Therefore, the Office of Scientific Investigations was not consulted.

Categorization of Adverse Events

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. The AEs reported during CS29 and CS31 were recoded using this version (13.1); the same version was also used during CS40 and CS41. All AEs that occurred after initiation of treatment (placebo or active) were included in the integrated analyses of CS29, CS31, CS40, and CS41.

Missing event start dates were imputed in the most conservative way (i.e., the event should have started as early as possible based on the (partially) missing start date while remaining treatment-emergent). The crude incidence of treatment-emergent AEs and adverse drug reactions in each dose group was summarized in tables by MedDRA system organ class and preferred term. For the number of subjects experiencing an event, counting was done by subject and not by event. This was done for both system organ class and preferred term (i.e., a subject was only counted once in each system organ class and once within each preferred term within a dose group).

Routine Clinical Tests

All laboratory measurements were performed by a central laboratory using appropriately validated methods. Investigators assessed all out-of-range values as being either clinically significant or not clinically significant.

During CS29, blood samples for assessment of clinical chemistry and hematology and urine samples for urinalysis were collected at the Screening Visit and at the End-of-Study Visits for Part I (Visit 7) and Part II (Visit 9E or sooner). Laboratory results from the End of Study Visit for Part II of CS29 were carried over as the initial results in CS31. Thereafter, blood samples for assessment of clinical chemistry and hematology and urine samples for urinalysis were collected at each study visit, beginning with Visit 2.

During CS40, blood samples for assessment of clinical chemistry and hematology and urine samples for urinalysis were collected at the Screening Visit and at the End-of-Study Visit (Visit 7). During CS41, samples were collected at the Screening Visit and at the End-of-Study Visits for Part I (Visit 9) and Part II (Visit 14).

Serum sodium levels were monitored at the Screening Visit and Visits 3 through 7 of Part I and at all visits (Visits 1E through 9E) of Part II during CS29 and at all visits during CS31. During CS40 and CS41, serum sodium levels were monitored at each visit throughout the trials except for

Visit 2. Subjects with values ≤ 125 mmol/L were to have study drug stopped and were to be withdrawn from the study immediately.

The laboratory tests performed during CS40 and CS41 are summarized in **Table 8-16**. Similar tests were performed during CS29/31.

Table 8-16: Clinical Laboratory Tests Performed CS40 and CS41

Clinical Chemistry	Hematology	Urinalysis
ALT	Hemoglobin	Bilirubin
Albumin	Hematocrit	Blood
Alkaline phosphatase	Platelet count	Glucose
AST	Red blood cell (RBC) count	Ketones
Calcium	Mean corpuscular volume (MCV)	Leukocytes
Chloride	Mean corpuscular hemoglobin (MCH)	Nitrite
Carbon dioxide	Mean corpuscular haemoglobin concentration (MCHC)	pH
Creatinine	White blood cell (WBC) count with differential count	Protein
Gamma-glutamyl transferase (GGT)		Urobilinogen
Glomerular filtration rate (GFR)		Dipstick assessment and microscopic examination (a culture was obtained in case of an abnormal value)
Globulin		
Glucose		
Magnesium		
Potassium		
Phosphorus		
Sodium		
Total bilirubin		
Direct/indirect bilirubin		
Total protein		
Blood urea nitrogen (BUN)		
Uric acid		

Source: NDA 022517 (seq 0017), Module 5.3.5.1, CSR CS40, Table 6-3, p. 35.

8.2.4. Safety Results

Deaths

Four subjects had treatment-emergent adverse events that led to death in the four Phase 3 desmopressin nocturia trials. All four deaths occurred during CS31, the open-label extension trial. None occurred during CS29, CS40, and CS41.

- Subject # (b) (6), a 66-year-old Caucasian male with hypertension, was assigned to placebo in CS29 Part I and was re-randomized to desmopressin 50 mcg in Part II of that trial. On Day 688 of treatment (Day 660 from start of desmopressin), the subject experienced an aortic aneurysm rupture and died the same day. The investigator considered the serious adverse event unrelated to study drug. The cause of death stated in his death certificate is hemopericardium. No additional information was provided. Although it is not possible to reach a definitive conclusion due to missing

information (e.g., autopsy report or medical records), it is unlikely that the study drug had a role in this subject's death.

- Subject # (b) (6), a 73-year-old Caucasian female with a history of breast cancer, was assigned to desmopressin 10 mcg in CS29 and was re-randomized to 25 mcg. According to the safety database, the subject was erroneously given 50 mcg and stayed on that dose. On Day 743 of treatment (Day 288 of the 50 mcg dose), the subject was diagnosed with metastatic breast cancer; study drug was discontinued and she died 151 days later. The investigator considered the serious adverse event unrelated to study drug. It is unlikely that the study drug had a role in this subject's death.
- Subject # (b) (6), a 78-year-old Caucasian male with a history of hypertension, was assigned to desmopressin 25 mcg during CS29 and CS31. On Day 634 of treatment, he experienced a subarachnoid hemorrhage and ruptured cerebral aneurysm; study drug was discontinued and he died 9 days later due to the subarachnoid hemorrhage. The investigator considered the serious adverse event unrelated to study drug. The subject's systolic blood pressure was 140 mmHg at baseline and ranged from 126 to 176 mmHg during treatment; his diastolic blood pressure was 70 mmHg at baseline and ranged from 57 to 86 mmHg during treatment. At his last clinic visit before the event (Day 603), his blood pressure was 151/62 mmHg. A cerebral angiogram done at the time of the event showed advanced atherosclerotic disease in the vertebra-basilar system and both internal carotid arteries, as well as a recently ruptured posterior inferior cerebellar artery aneurysm. Based on the subject's untreated hypertension and atherosclerotic vascular disease, both of which appear to pre-date exposure to the study drug, it is unlikely that the study drug had a role in this subject's death.
- Subject # (b) (6), a 71-year-old Caucasian male with a history of hypertension and hypercholesterolemia, was assigned to desmopressin 50 mcg in CS29 and CS31. On Day 639 of treatment, the subject died due to severe atherosclerotic heart disease. The death certificate stated that the subject had suspected arteriosclerotic heart disease for years. The investigator considered the serious adverse event unrelated to study drug. The death certificate states that the cause of death was cardiac arrest secondary to severe atherosclerotic heart disease present for years. An autopsy was not performed. No additional information was provided. Although it is not possible to reach a definitive conclusion due to missing information (e.g., medical records), it is unlikely that the study drug had a role in this subject's death.

Two additional subjects had adverse events after study drug ended that led to death.

- Subject # (b) (6), a 71-year-old Caucasian male, was assigned to the desmopressin 100 mcg group in CS29 Part I and continued this dose for 849 days in CS29 Part II and CS31. On Day 851, 2 days after treatment was stopped, he experienced a gastrointestinal hemorrhage and the subject was discontinued from the study on Day 856. The subject died 3 days later. The investigator considered the serious adverse

event unrelated to study drug. Concomitant medications included etodolac 200 mg daily, which the subject started one year and nine months before starting the study drug and was taking throughout the trial. Based on the subject's long-term treatment with etodolac, a NSAID known to increase the risk of gastrointestinal bleeding, it is unlikely that the study drug had a role in the adverse event that resulted in this subject's death.

- Subject # (b) (6), a 52-year-old Caucasian male assigned to desmopressin 50 mcg, withdrew consent and discontinued the study after 43 days of treatment in CS31 (total duration of treatment in CS29 and CS31 was 184 days). The site subsequently learned that the subject had developed acute respiratory failure of 3 days' duration and died 52 days after discontinuing study drug. The acute respiratory failure that led to death was considered a complication of HIV. The adverse event was considered by the Investigator to be unrelated to study drug. The subject's death certificate states that the cause of death was acute respiratory failure secondary to multi-organ system failure, sepsis, and acquired immunodeficiency syndrome (present for years). An autopsy was not performed. No additional information was provided. Based on the subject's underlying disease and the duration of time between discontinuing the study drug and the adverse event, it is unlikely that the study drug had a role in this subject's death.

Serious Adverse Events

Three-Month Safety Analysis – Pooled Data (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

The percentage of subjects with any serious adverse event (SAE) ranged from <1% to 4% across the desmopressin groups and was <1% in the placebo group in the three-month safety analysis dataset of Phase 3 trials. The only treatment-emergent SAE that occurred in more than one subject treated with desmopressin was for the preferred term 'hyponatremia', which occurred in 2 (<1%) subjects in the desmopressin 50 mcg dose group and 4 (3%) subjects in the 75 mcg group (see below). SAEs reported during three-months of treatment in the four Phase 3 desmopressin nocturia trials are summarized in **Table 8-17**.

**Table 8-17: Summary of Treatment-Emergent Serious Adverse Events
During 3-Months of Treatment
(Safety Analysis Dataset-CS29, CS31, CS40, and CS41)**

System Organ Class MedDRA Preferred Term	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)
Any serious adverse event	4 (<1)	3 (2)	2 (<1)	5 (2)	5 (4)	3 (2)
Cardiac Disorders						
Acute myocardial infarction	0	0	0	1 (<1)	0	0
Atrial fibrillation	0	1 (<1)	0	0	0	0
General Disorders and Administration Site Conditions						
Pyrexia	1 (<1)	0	0	0	0	0
Infections and Infestations						
Appendicitis	0	0	1 (<1)	0	0	0
Cellulitis	1 (<1)	0	0	0	0	1 (<1)
Diverticulitis	0	1 (<1)	0	0	0	0
Metabolism and Nutrition Disorders						
Hyponatremia	0	0	0	2 (<1)	4 (3)	0
Musculoskeletal and Connective Tissue Disorders						
Myalgia	0	0	1 (<1)	0	0	0
Osteoarthritis	0	0	0	1 (<1)	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)						
Adenosquamous cell lung cancer	0	1 (<1)	0	0	0	0
Bladder transitional cell carcinoma	0	0	0	0	0	1 (<1)
Prostate cancer	1 (<1)	0	0	0	0	1 (<1)
Nervous System Disorders						
Transient global amnesia	0	0	0	0	1 (<1)	0
Respiratory, Thoracic and Mediastinal Disorders						
Asthma	0	0	0	1 (<1)	0	0
Pulmonary embolism	1 (<1)	0	0	0	0	0

Note: Some subjects received different doses and are in more than 1 dose group.

N:number of subjects; n:number of subjects with adverse event; %:percentage of subjects; MedDRA:Medical Dictionary for Regulatory Activities

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 32, p. 74.

In CS40 and CS41, investigators were to report serum sodium values of ≤ 125 mmol/L as SAEs, while in CS29/31, reporting of hyponatremia was based on the investigator's clinical judgement. This may have affected the number of SAEs reported for 'hyponatremia'. An analysis of hyponatremia based on serum sodium laboratory values is presented in **Section 8.2.5** Analysis of Submission-Specific Safety.

Narratives for the SAEs were reviewed. Except for hyponatremia, a role for the study drug in the other SAEs is assessed as unlikely.

In the population of subjects with nocturnal polyuria (N=1,274), the percentage of subjects reporting a SAE was similar to the percentage in the overall nocturia population (<1% to 4%

across the desmopressin groups and <1% in the placebo group). The percentage of subjects in this population reporting a SAE in the to-be-marketed sex specific doses (25 mcg females and 50 mcg males) was 1% for females treated with the 25 mcg dose and 1% for males treated with the 50 mcg dose.

Long-Term Safety Analysis – (S.II Safety Analysis Dataset-CS29/31)

In the long-term, continued use dataset (S.II, N=542) 52 (10%) subjects across all dose groups reported a SAE: 7 (5%) in the 10 mcg dose group; 13 (9%) in the 25 mcg group; 18 (13%) in the 50 mcg group; and 14 (11%) in the 100 mcg group. The only preferred terms reported by more than two desmopressin-treated subjects were atrial fibrillation and osteoarthritis, each reported by three (0.6%) subjects.

Two of the subjects reporting atrial fibrillation had medical histories that could increase the risk of atrial fibrillation (myocardial infarction in one, atrial fibrillation in the other). It is unlikely the events were related to the study drug for these two subjects although it is not possible to definitively exclude a contributory effect of fluid retention related to the pharmacologic effect of the drug. For the third subject (without contributory history) a role for the drug cannot be ruled out.

All three of the subjects who reported the SAE of osteoarthritis had a history of osteoarthritis and underwent joint replacement surgery during the trial. It is unlikely these events were related to the study drug.

Narratives for the other SAEs were reviewed. Two SAEs were assessed by the investigator as possibly related to the study drug.

Subject (b) (6) (PT= cardiac failure congestive): 84-year-old male being treated with the 25 mcg dose was hospitalized for congestive heart failure on study day 496. Medical history includes coronary artery disease, hypertension, and hypercholesterolemia. The drug was temporarily discontinued and restarted after the event. The subject recovered and continued in the trial. It is not possible to rule out an adverse effect of the study drug due to fluid retention related to the pharmacologic effect of the drug.

Subject (b) (6) (PT=coordination abnormality): 84-year-old male being treated with the 50 mcg dose fell backwards and hit his head due to balance difficulty on study day 208. There were no residue effects from the fall, but he was admitted for testing. At that time his serum sodium was 132 mmol/L. His serum sodium ranged from 129-134 mmol/L since starting treatment. The subject recovered but was withdrawn from the trial due to the event. It is possible that his decreased serum sodium may have contributed to his coordination abnormality and resultant fall.

A role for the study drug in the other SAEs is assessed by the reviewer as unlikely.

In the population of subjects who met the criteria for nocturnal polyuria (N=481), 44 (9%) subjects reported a SAE: 7 (6%) in the 10 mcg dose group; 12 (10%) in the 25 mcg group; 14 (12%) in the 50 mcg group; and 11 (10%) in the 100 mcg group. For the to-be-marketed sex specific doses: 25 mcg females (N=53) and 50 mcg males (N=68); 3 (6%) females treated with the 25 mcg dose and 8 (12%) males treated with the 50 mcg dose reported a SAE.

Dropouts Due to Adverse Effects

Three-Month Safety Analysis – Pooled Data (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

The percentage of subjects who prematurely discontinued due to adverse events ranged from 3% to 7% across the desmopressin groups and was 3% in the placebo group in the Phase 3 desmopressin nocturia trials. The preferred terms ‘hyponatremia’ (2% and 3% in the 50 mcg and 75 mcg desmopressin dose groups, respectively) and ‘blood sodium decreased’, ‘headache’, ‘nausea’, and ‘fatigue’ (2% each in the desmopressin 100 mcg dose group) were the only preferred terms that led to premature discontinuation in $\geq 2\%$ of subjects in any treatment group. Treatment-emergent adverse events (TEAEs) leading to discontinuation are summarized in **Table 8-18**.

Table 8-18: Summary of Treatment-Emergent Adverse Events Leading to Premature Discontinuation in >1 Subject in Any Treatment Group – During 3-Months of Treatment (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

System Organ Class MedDRA Preferred Term	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)
Any adverse event leading to premature discontinuation ^a	12 (3)	7 (4)	9 (3)	18 (6)	7 (6)	13 (7)
Eye Disorders						
Dry eye	0	2 (1)	0	0	0	0
Gastrointestinal Disorders						
Nausea	0	0	1 (<1)	0	0	3 (2)
Dry mouth	0	1 (<1)	0	2 (<1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	0	0	0	0	0	3 (2)
Investigations						
Blood sodium decreased	1 (<1)	0	0	4 (1)	1 (<1)	4 (2)
Metabolism and Nutrition Disorders						
Hyponatremia	0	0	1 (<1)	5 (2)	4 (3)	2 (1)
Nervous System Disorders						
Headache	1 (<1)	0	1 (<1)	0	0	4 (2)
Dizziness	0	1 (<1)	0	2 (<1)	0	1 (<1)
Vascular Disorders						
Hypertension	2 (<1)	0	1 (<1)	0	0	0

Note: Some subjects received different doses and are in more than 1 dose group.

N:number of subjects; n:number of subjects with adverse event; %:percentage of subjects

MedDRA:Medical Dictionary for Regulatory Activities

^aIn CS29/CS31, all AEs with identification of trial drug stopped were used for flagging for probability of leading to discontinuation.

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 33, p. 75.

The TEAEs leading to premature discontinuation in the nocturnal polyuria population were consistent with those observed in the overall population. For the nocturnal polyuria population, the incidence of TEAEs that resulted in discontinuation was 3%, 4%, 3%, 6%, 6%, and 8% for the placebo, 10 mcg, 25 mcg, 50 mcg, 75 mcg, and 100 mcg treatment groups, respectively. The preferred terms ‘hyponatremia’ (2% and 4% in the 50 mcg and 75 mcg desmopressin dose groups, respectively) and ‘blood sodium decreased’, ‘headache’, ‘nausea’, and ‘fatigue’ (2% each in the desmopressin 100 mcg dose group) were the only preferred terms that led to premature discontinuation in ≥2% of subjects in any treatment group.

The percentage of subjects in this population discontinuing due to a TEAE in the to-be-marketed sex specific doses (25 mcg females and 50 mcg males) was 3% for females treated with the 25 mcg dose (N=196) and 4% for males treated with the 50 mcg dose (N=195). There were no preferred terms that led to premature discontinuation in ≥2% of subjects in either of these treatment groups.

Long-Term Safety Analysis – (S.II Safety Analysis Dataset-CS29/31)

A total of 44 subjects (8%) in the long-term, continued use dataset (S.II, N=542) discontinued because of an adverse event: 6 (4%) were being treated with the 10 mcg dose, 9 (6%) with the 25 mcg dose, 16 (12%) with the 50 mcg dose, and 13 (10%) with the 100 mcg dose. The most common AEs leading to study discontinuation across all dose groups were hyponatremia and dry mouth. Of the five subjects (0.9%) who discontinued due to hyponatremia, one was in the 25 mcg dose group, two were in the 50 mcg group, and two were in the 100 mcg group. Of the four subjects (0.7%) who discontinued due to dry mouth, two were in the 10 mcg dose group and two were in the 50 mcg group.

In the population of subjects who met the criteria for nocturnal polyuria (N=481), 40 (8%) subjects discontinued due to an AE: 6 (5%) in the 10 mcg dose group, 8 (6%) in the 25 mcg group, 14 (12%) in the 50 mcg group, and 12 (10%) in the 100 mcg group. For the to-be-marketed sex-specific doses: 25 mcg females (N=53) and 50 mcg males (N=68); 3 (6%) females treated with the 25 mcg dose and 8 (12%) males treated with the 50 mcg dose discontinued due to an AE.

Significant Adverse Events

Hyponatremia is a known and significant risk of desmopressin drugs. See **Section 8.2.5** Analysis of Submission-Specific Safety Issues for a detailed discussion of hyponatremia based on serum sodium laboratory values.

Treatment Emergent Adverse Events and Adverse Reactions

Three-Month Safety Analysis – Pooled Data (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

For the pooled three-month data from the four Phase 3 trials, the incidence of common (>2%) TEAEs ranged from 40% to 69% across the desmopressin groups and was 46% in the placebo group. The most frequently reported adverse event was 'dry mouth'. The high incidence of this event may have been due to specific query about dry mouth in CS29/31. In the two studies (CS40 and CS 41) where the adverse event was spontaneously reported, the incidence was ≤4% in the desmopressin groups.

Hyponatremia could be reported as the MedDRA preferred term 'hyponatremia' or 'blood sodium decreased'. There was a dose dependent increase in the combined incidence of these two terms. Hyponatremia is discussed in detail in Section **8.2.5** Analysis of Submission-Specific Safety Issues. Dose dependency was not demonstrated in the other events. **Table 8-19** summarizes the incidence of common (≥2%) TEAEs for the pooled three-month data.

Table 8-19: Incidence of Common ($\geq 2\%$) Treatment-Emergent Adverse Events – During 3-Months of Treatment (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

System Organ Class MedDRA Preferred Term	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)
Any adverse event	196 (46)	122 (63)	181 (55)	180 (58)	49 (40)	133 (69)
Eye Disorders						
Dry eye	0	4 (2)	2 (<1)	0	0	0
Gastrointestinal Disorders						
Dry mouth ^a	55 (13)	65 (34)	60 (18)	64 (21)	1 (<1)	56 (29)
Diarrhoea	10 (2)	5 (3)	13 (4)	12 (4)	4 (3)	3 (2)
Constipation	7 (2)	5 (3)	10 (3)	4 (1)	1 (<1)	2 (1)
Nausea	4 (<1)	5 (3)	8 (2)	9 (3)	3 (2)	9 (5)
Abdominal discomfort	2 (<1)	5 (3)	4 (1)	2 (<1)	0	4 (2)
Gastroesophageal reflux disease	0	0	1 (<1)	1 (<1)	1 (<1)	4 (2)
General Disorders and Administration Site Conditions						
Fatigue	3 (<1)	9 (5)	2 (<1)	6 (2)	2 (2)	4 (2)
Oedema peripheral	4 (<1)	3 (2)	2 (<1)	4 (1)	5 (4)	5 (3)
Infections and Infestations						
Nasopharyngitis	12 (3)	6 (3)	10 (3)	5 (2)	4 (3)	7 (4)
Upper respiratory tract infection	11 (3)	4 (2)	10 (3)	8 (3)	2 (2)	7 (4)
Urinary tract infection	11 (3)	3 (2)	6 (2)	7 (2)	0	4 (2)
Sinusitis	4 (<1)	7 (4)	2 (<1)	2 (<1)	0	2 (1)
Investigations						
Blood sodium decreased	1 (<1)	2 (1)	2 (<1)	5 (2)	2 (2)	8 (4)
Metabolism and Nutrition Disorders						
Hyponatremia	3 (<1)	2 (1)	5 (2)	9 (3)	5 (4)	11 (6)
Musculoskeletal and Connective Tissue Disorders						
Back pain	2 (<1)	2 (1)	9 (3)	4 (1)	2 (2)	3 (2)
Arthralgia	5 (1)	2 (1)	7 (2)	2 (<1)	0	2 (1)
Muscle spasms	5 (1)	4 (2)	6 (2)	5 (2)	0	5 (3)
Nervous System Disorders						
Headache	18 (4)	14 (7)	18 (5)	22 (7)	7 (6)	15 (8)
Dizziness	2 (<1)	7 (4)	5 (2)	11 (4)	1 (<1)	7 (4)
Psychiatric Disorders						
Insomnia	2 (<1)	7 (4)	2 (<1)	9 (3)	0	5 (3)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	2 (<1)	1 (<1)	6 (2)	5 (2)	0	7 (4)
Oropharyngeal pain	4 (<1)	5 (3)	2 (<1)	4 (1)	0	1 (<1)

Note: Some subjects received different doses and are in more than 1 dose group.

N: number of subjects; n: number of subjects with adverse event; %: percentage of subjects; MedDRA: Medical Dictionary for Regulatory Activities

^aSubjects were specifically queried about dry mouth in CS29/CS31 but not in CS40/CS41.

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 28, p. 69.

In the population of subjects who met the criteria for nocturnal polyuria, the overall incidence of subjects with at least one common ($\geq 2\%$) TEAEs was lower than the incidence in the overall nocturia population (29% to 56% across the desmopressin groups and 31% in the placebo

group).

The incidence of common ($\geq 2\%$) TEAEs for subjects with nocturnal polyuria treated with the to-be-marketed sex-specific doses (25 mcg for females and 50 mcg for males) or placebo is summarized in **Table 8-20**.

Table 8-20: Incidence of Common ($\geq 2\%$) Treatment-Emergent Adverse Events – Nocturnal Polyuria Population at Gender Specific Doses (25 mcg Females, 50 mcg Males) (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Adverse Reactions	Women		Men	
	Placebo (N=173)	25 mcg (N=196)	Placebo (N=213)	50 mcg (N=195)
Dry mouth	21 (12%)	25 (13%)	28 (13%)	30 (15%)
Headache	8 (5%)	7 (4%)	8 (4%)	11 (6%)
Diarrhea	4 (2%)	8 (4%)	6 (3%)	5 (3%)
Hyponatremia	2 (1%)	5 (3%)	1 (<1%)	5 (3%)
Urinary tract infection	8 (5%)	5 (3%)	0	5 (3%)
Dizziness	0	3 (2%)	1 (<1%)	6 (3%)
Upper respiratory tract infection	6 (3%)	5 (3%)	2 (<1%)	4 (2%)
Muscle spasms	2 (1%)	4 (2%)	2 (<1%)	3 (2%)
Back pain	2 (1%)	6 (3%)	0	2 (1%)
Constipation	3 (2%)	6 (3%)	3 (1%)	2 (1%)
Arthralgia	3 (2%)	5 (3%)	2 (<1%)	1 (<1%)
Insomnia	1 (<1%)	1 (<1%)	1 (<1%)	6 (3%)
Nausea	3 (2%)	5 (3%)	1 (<1%)	1 (<1%)
Cough	0	2 (1%)	2 (<1%)	3 (2%)
Blood sodium decreased	1 (<1%)	1 (<1%)	0	3 (2%)
Fatigue	1 (<1%)	1 (<1%)	2 (<1%)	4 (2%)

Source: NDA 022517 (seq 0047), Module 1.11.3, Clinical Information Amendment.

Long-Term Safety Analysis – (S.II Safety Analysis Dataset-CS29/31)

Of the 542 subjects in the S.II dataset, 374 (69%) reported a TEAE: 85 (62%) in the 10 mcg dose group, 97 (69%) in the 25 mcg group, 102 (76%) in the 50 mcg group, and 90 (69%) in the 100 mcg group. Across all dose groups, the most frequently reported adverse events were dry mouth (17%), upper respiratory tract infection (9%), hypertension (8%), headache (7%), and urinary tract infection (7%).

None of the most frequently reported adverse events appeared to be dose related.

A total of 481 subjects in the S.II dataset met the criteria for nocturnal polyuria. Of these, 366 (76%) reported a TEAE: 83 (70%) in the 10 mcg dose group, 91 (73%) in the 25 mcg group, 101 (83%) in the 50 mcg group, and 91 (79%) in the 100 mcg group. Across all dose groups, the most frequently reported adverse events were dry mouth (16%), upper respiratory tract infection (8%), hypertension (8%), headache (7%), and urinary tract infection (7%).

Laboratory Findings

Three-Month Safety Analysis – Pooled Data (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Laboratory Values Over Time

Minor mean changes from baseline to the last visit (within the three-month period) were observed in hematology and clinical chemistry variables in all treatment groups. None of the mean changes were considered clinically meaningful.

Individual Subject Changes

Hematology

Shifts in hematology parameters were generally similar across the treatment groups, with no indication of a dose-related trend. None of the shifts were considered clinically meaningful.

The incidence of markedly abnormal changes in hematology variables was generally similar across the desmopressin dose groups, with no indication of a dose-related trend in abnormal changes.

Clinical Chemistry

Except for serum sodium, shifts in clinical chemistry parameters were generally similar across the treatment groups. The incidence of shifts to low sodium was greater in the desmopressin 50 mcg and 100 mcg dose groups (7% and 12%, respectively) than in the 10 mcg, 25 mcg, 75 mcg, and placebo groups (2%, 4%, 2%, and 1%, respectively). Otherwise, there was no indication of a dose-related trend in clinical chemistry shifts. Except for sodium shifts to low, none of the shifts in clinical chemistry parameters were considered clinically meaningful.

The incidence of markedly abnormal changes in clinical chemistry variables was generally similar across the desmopressin dose groups, with no indication of a dose-related trend in abnormal changes.

A detailed analysis of hyponatremia based on serum sodium laboratory values is presented in **Section 8.2.5** Analysis of Submission-Specific Safety.

Long-Term Safety Analysis – (S.III Safety Analysis Dataset-CS29/31)

Laboratory Values Over Time

Minor mean changes from baseline to the last visit were observed in hematology and clinical chemistry variables in all treatment groups. None of the mean changes were considered clinically meaningful.

Individual Subject Changes

Hematology

Higher proportions of subjects in the desmopressin groups than in the placebo group shifted to

high or low values; however, the duration of exposure to placebo was shorter (maximum of 4 weeks) than it was for the active treatment groups. Shifts in hematology parameters across the desmopressin treatment groups were generally similar, with no indication of a dose-related trend. None of the shifts were considered clinically meaningful.

Clinical Chemistry

In general, higher proportions of subjects in the desmopressin groups than in the placebo group shifted to high or low values; however, the duration of exposure to placebo was shorter (maximum of 4 weeks) than for the active treatment groups. The incidence of shifts to low sodium increased with dose: 3%, 8%, 18%, 28%, and 31% for the placebo, 10 mcg, 25 mcg, 50 mcg and 100 mcg desmopressin dose groups. Except for serum sodium, none of the shifts in chemistry parameters were clinically meaningful.

A detailed analysis of hyponatremia based on serum sodium laboratory values is presented in **Section 8.2.5** Analysis of Submission-Specific Safety.

Vital Signs

Three-Month Safety Analysis – Pooled Data (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Minor mean changes from baseline to the last visit were observed in blood pressure and heart rate in all treatment groups. None of the mean changes were clinically meaningful. The incidence of markedly abnormal changes in vital signs was <1% in all treatment groups.

Long-Term Safety Analysis – (S.III Safety Analysis Dataset-CS29/31)

Minor mean increases and decreases from baseline were observed in vital sign variables in all treatment groups, with no consistent pattern. None of the mean changes in blood pressure or heart rate were clinically meaningful.

Electrocardiograms (ECGs)

Electrocardiogram data were not included in this submission.

QT

QT data were not included in this submission.

Immunogenicity

Immunogenicity data were not included in this submission.

8.2.5. Analysis of Submission-Specific Safety Issues

Hyponatremia

Hyponatremia is a known risk of desmopressin drugs. In the pooled three-month data from CS29, CS31, CS40, and CS41; 51 (4%) subjects in the desmopressin treatment groups reported an AE of either 'blood sodium decreased' or 'hyponatremia' compared to 4 (1%) subjects in the placebo group. Six of the events (two in the 50 mcg dose group and four in the 75 mcg dose group) met the criteria for a SAE and 22 (one in the 25 mcg dose group, nine in the 50 mcg dose group, five in the 75 mcg dose group, six in the 100 mcg dose group, and one in the placebo group) led to discontinuation from the study.

In the Phase 3 trials, investigators reported the preferred terms of 'hyponatremia' or 'blood sodium decreased' based on their judgement of whether the event was clinically significant. Except for CS40 and CS41, where serum sodium values of ≤ 125 mmol/L were to be reported as SAEs, there were no prespecified criteria for the definition of clinically significant hyponatremia. Not all serum sodium laboratory values < 135 mmol/L were judged as clinically significant and therefore might not have been reported as AEs by the investigators.

In addition to AE reporting, serum sodium concentrations were also assessed throughout CS29, CS31, CS40, and CS41. These data provide a more comprehensive and consistent assessment of desmopressin's effect on serum sodium levels. The following categorical analyses are based on serum sodium laboratory values.

Three-Month Safety Analysis – Pooled Data (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

For the pooled three-month data from the four Phase 3 trials, an increased incidence of nadir serum sodium values < 130 mmol/L, was observed in all desmopressin dose groups (10 mcg [1%], 25 mcg [3%], 50 mcg [4%], 75 mcg [7%], and 100 mcg [10%]) compared to placebo ($< 1\%$). The incidence of a nadir value ≤ 125 mmol/L was 0%, 0%, 2%, 3%, and 1% in the desmopressin 10 mcg, 25 mcg, 50 mcg, 75 mcg, and 100 mcg dose groups, respectively, and $< 1\%$ in the placebo group. The results of a categorical analysis of nadir serum sodium values for the pooled three-month data are shown in **Table 8-21**.

**Table 8-21: Categorical Analysis of Nadir Serum Sodium Values
 At Any Post-Baseline Visit Up To 3-Months
 (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)**

Serum Sodium (mmol/L)	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg ^a (N=311) n (%)	75 µg (N=122) n (%)	100 µg ^b (N=194) n (%)
Observed N	421	181	319	301	122	180
<135	15 (4)	24 (13)	37 (12)	58 (19)	21 (17)	61 (34)
130-134	14 (3)	22 (12)	29 (9)	47 (16)	12 (10)	43 (24)
126-129	0	2 (1)	8 (3)	4 (1)	5 (4)	16 (9)
≤125	1 (<1)	0	0	7 (2)	4 (3)	2 (1)

Note: Some subjects received different doses and are in more than 1 dose group.

Observed N: number of subjects with at least one value recorded in time interval; n: number of subjects with low sodium value; %: n/observed N x 100

^aTwo additional 50 µg subjects (b) (6) had a serum sodium value ≤125 mmol/L 1 day after the last dose of desmopressin ODS1 in [CS31] and were not included in the table.

^bTwo additional 100 µg subjects (b) (6) had a serum sodium value ≤125 mmol/L 1 day after the last dose of desmopressin ODS1 in [CS29] and were not included in the table.

Source: NDA 022517 (seq 0039), Module 5.3.5.3, Safety Update, Table 4-20, p. 53.

It should be noted that two subjects (b) (6) in the desmopressin 50 mcg dose group in CS31 and two subjects (b) (6) in the 100 mcg dose group in CS29 had a serum sodium value ≤125 mmol/L and were not included in the above table. The reason for this inconsistency is due to the data cut-off date (date of last desmopressin administration or Day 84, whichever was first) used for CS29 and CS31. These four subjects had a serum sodium value ≤125 mmol/L one day after their last dose of desmopressin; therefore, they were not included in Table 8-21 (see footnotes a and b in Table 8-21). If these four subjects are included, the incidence of serum sodium ≤125 for the 50 mcg dose group would be 3% and the incidence in the 100 mcg group would be 2%.

Most subjects who developed hyponatremia did so within the first month of active treatment. Table 8-22 is categorical analysis of serum sodium by month during the first three months of treatment.

Table 8-22: Categorical Analysis of Serum Sodium by Month (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Serum Sodium (mmol/L)	Placebo N=429	10 mcg N=194	25 mcg N=331	50 mcg N=311	75 mcg N=122	100 mcg N=194
Month 0-1:						
130-134	13 (3%)	18 (10%)	24 (8%)	38 (13%)	11 (9%)	35 (19%)
126-129	0	1 (<1%)	6 (2%)	5 (2%)	5 (4%)	15 (8%)
≤125	1 (<1%)	0	0	6 (2%)	4 (3%)	2 (1%)
Month 1-2:						
130-134	3 (1%)	11 (7%)	15 (6%)	22 (9%)	2 (2%)	19 (13%)
126-129	0	1 (<1%)	2 (<1%)	0	1 (1%)	5 (3%)

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≤125	0	0	0	1 (<1%)	0	0
Month 2-3:						
130-134	1 (<1%)	1 (<1%)	10 (4%)	10 (5%)	3 (3%)	8 (8%)
126-129	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0
≤125	0	0	0	0	0	0

Source: NDA 022517 (seq 0017), Module 5.3.5.3, Integrated Summary of Safety, Table 7.1.2.1, p. 489-490.

One 74-year-old male subject in the 50 mcg dose group had a serum sodium value of 125 mmol/L at the two-month visit. His serum sodium values were 135, 133, 131, 129, and 127 mmol/L at Day 4, Week 1, Week 2, Week 3, and Month 1, respectively. Under the Applicant's proposed monitoring plan, the subject's hyponatremia would have been identified during the first week of treatment and desmopressin would have been temporarily or permanently discontinued.

Subgroup Analysis of Serum Sodium Levels

Age

The incidence of serum sodium values <135 mmol/L was increased in subjects >65 years of age compared to subjects <65 years of age in all desmopressin dose groups (range: of 17-44% for subjects >65 years of age compared to 7-23% for subjects <65 years of age). This was also the case for the incidence of serum sodium values <130 mmol/L (range: 2-17% for subjects ≥65 years of age compared to 0-3% for subjects <65 years of age).

The incidence of serum sodium values ≤125 mmol/L in the placebo 10 mcg, 25 mcg, 50 mcg, 75 mcg, and 100 mcg groups for subjects >65 years of age was <1%, 0%, 0%, 3%¹¹, 5%, and 2%¹², compared to 0%, 0%, 0%, 2%, 2%, and 0%, respectively, for subjects <65 years of age. The results of a categorical analysis of nadir serum sodium values by age are shown in **Table 8-23**.

¹¹ The two subjects in the 50 µg dose group with serum sodium values ≤125 mmol/L one day after their last dose were both ≥65 years of age. If both are included, the percentage changes to 4%.

¹² The two subjects in the 100 µg dose group with serum sodium values ≤125 mmol/L one day after their last dose were both ≥65 years of age. If both are included, the percentage changes to 4%.

Table 8-23: Categorical Analysis of Nadir Serum Sodium Values – Any Post-Baseline Visit up to 3 Months by Age – (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg ^a n (%)		75 µg n (%)		100 µg ^b n (%)	
	<65 years (N=224)	≥65 years (N=205)	<65 years (N=103)	≥65 years (N=91)	<65 years (N=167)	≥65 years (N=164)	<65 years (N=165)	≥65 years (N=146)	<65 years (N=63)	≥65 years (N=59)	<65 years (N=92)	≥65 years (N=102)
Observed N	221	200	98	83	162	157	162	139	63	59	86	94
<135	8 (4)	7 (4)	7 (7)	17 (20)	11 (7)	26 (17)	20 (12)	38 (27)	10 (16)	11 (19)	20 (23)	41 (44)
130-134	8 (4)	6 (3)	7 (7)	15 (18)	9 (6)	20 (13)	16 (10)	31 (22)	8 (13)	4 (7)	18 (21)	25 (27)
126-129	0	0	0	2 (2)	2 (1)	6 (4)	1 (<1)	3 (2)	1 (2)	4 (7)	2 (2)	14 (15)
≤125	0	1 (<1)	0	0	0	0	3 (2)	4 (3)	1 (2)	3 (5)	0	2 (2)

Note: Some subjects received different doses and are in more than 1 dose group.

Observed N: number of subjects with at least one value recorded in time interval; n: number of subjects with low sodium value; %: n/observed N x 100

^aTwo subjects (b) (6) ≥65 years of age in the 50 µg dose group had a serum sodium value ≤125 mmol/L 1 day after the last dose of desmopressin ODST in [CS31] and were not included in the table.

^bTwo subjects (b) (6) ≥65 years of age in the 100 µg dose group had a serum sodium value ≤125 mmol/L 1 day after the last dose of desmopressin ODST in [CS29] and were not included in the table.

Source: NDA 022517 (seq 0039), Module 5.3.5.3, Safety Update, Figure 4-22, p. 57.

Gender

Among males, the incidence of serum sodium values <135 mmol/L ranged from 12% in the desmopressin 25 mcg dose group to 30% in the 100 mcg group. The incidence of serum sodium values <130 mmol/L increased from 0%, 1%, <1%, and 2% in the placebo, 10 mcg, 25 mcg, and 50 mcg groups, respectively, to 7% and 9% in the 75 mcg and 100 mcg groups. Three (1%¹³) male subjects in the 50 mcg group, 4 (3%) male subjects in the 75 mcg group, and 2 (2%) male subjects in the 100 mcg group had a serum sodium value ≤125 mmol/L.

Among females, the incidence of serum sodium values <135 mmol/L ranged from 11% in the desmopressin 10 mcg and 25 mcg dose groups to 24% and 39% in the 50 mcg and 100 mcg groups. The incidence of serum sodium values <130 mmol/L increased from <1%, 1%, and 3% in the placebo, 10 mcg, and 25 mcg groups, respectively, to 9% and 11% in the 50 mcg and 100 mcg groups. The only desmopressin dose group with a serum sodium value ≤125 mmol/L in female subjects was 50 mcg (4 subjects; 5%)¹⁴. The results of a categorical analysis of nadir serum sodium values by sex are shown in Table 8-24.

¹³ One male subject in the 50 mcg dose group had a serum sodium value ≤125 mmol/L one day after his last dose. If he is included, the percentage changes to 2%.

¹⁴ If the three female subjects who had a serum sodium value ≤125 mmol/L one day after their last dose (one in the 50 µg dose group and two in the 100 µg dose group) are included, the percentages for the 50 mcg and 100 mcg dose groups change to 6% and 2%, respectively.

Table 8-24: Categorical Analysis of Nadir Serum Sodium Values – Any Post-Baseline Visit up to 3-Months by Gender (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg ^a n (%)		75 µg n (%)		100 µg ^b n (%)	
	Males (N=236)	Females (N=193)	Males (N=101)	Females (N=93)	Males (N=112)	Females (N=219)	Males (N=222)	Females (N=89)	Males (N=122)	Females (N=0)	Males (N=105)	Females (N=89)
Observed N	230	191	94	87	105	214	219	82	122	0	97	83
<135	7 (3)	8 (4)	14 (15)	10 (11)	13 (12)	24 (11)	38 (17)	20 (24)	21 (17)	0	29 (30)	32 (39)
130-134	7 (3)	7 (4)	13 (14)	9 (10)	12 (11)	17 (8)	34 (16)	13 (16)	12 (10)	0	20 (21)	23 (28)
126-129	0	0	1 (1)	1 (1)	1 (<1)	7 (3)	1 (<1)	3 (4)	5 (4)	0	7 (7)	9 (11)
≤125	0	1 (<1)	0	0	0	0	3 (1)	4 (5)	4 (3)	0	2 (2)	0

Note: Some subjects received different doses and are in more than 1 dose group.

Observed N: number of subjects with at least one value recorded in time interval; n: number of subjects with low sodium value; %: n/observed N x 100

^aOne male subject (b) (6) and 1 female subject (b) (6) in the 50 µg dose group had a serum sodium value ≤125 mmol/L 1 day after the last dose of desmopressin ODS in [CS31] and were not included in the table.

^bTwo female subjects (b) (6) in the 100 µg dose group had a serum sodium value ≤125 mmol/L 1 day after the last dose of desmopressin ODS in [CS29] and were not included in the table.

Source: NDA 022517 (seq 0039), Module 5.3.5.3, Safety Update, Figure 4-21, p. 55.

Gender and Age

Among female subjects, the incidence of serum sodium values <135 mmol/L ranged from 5% and 6% in the desmopressin 10 mcg and 25 mcg dose groups to 17% and 28% in the 50 mcg and 100 mcg groups in subjects <65 years, and from 24% and 19% in the desmopressin 10 mcg and 25 mcg dose groups to 38% and 53% in the 50 mcg and 100 mcg groups in subjects ≥65 years. The incidence of serum sodium values <130 mmol/L increased from none in the 10 mcg group to 2%, 8%, and 4% in the 25 mcg, 50 mcg and 100 mcg groups, respectively, for subjects <65 years, and from 3% in the 10 mcg group to 6%, 10%, and 19% in the 25 mcg, 50 mcg, and 100 mcg groups, respectively, for subjects ≥65 years.

The only desmopressin dose group with a serum sodium value ≤125 mmol/L in females was 50 mcg (3 subjects [6%] <65 years and 1 subject [3%] ≥65 years)¹⁵. The results of a categorical analysis of nadir serum sodium values by sex and age for female subjects are shown in Table 8-25.

¹⁵ If the three female subjects who were ≥65 years and had a serum sodium value ≤125 mmol/L one day after their last dose (one in the 50 mcg dose group and two in the 100 mcg dose group) are included, the percentages for the 50 mcg ≥65 years and 100 mcg ≥65 years dose-age groups change to 6% and 5%, respectively.

Table 8-25: Categorical Analysis of Nadir Serum Sodium Values – Any Post-Baseline Visit up to 3-Months by Gender and Age – Females (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		100 µg n (%)	
	<65 years (N=109)	≥65 years (N=84)	<65 years (N=61)	≥65 years (N=32)	<65 years (N=126)	≥65 years (N=93)	<65 years (N=56)	≥65 years (N=33)	<65 years (N=50)	≥65 years (N=39)
Observed N	108	83	58	29	125	89	53	29	47	36
<135	2 (2)	6 (7)	3 (5)	7 (24)	7 (6)	17 (19)	9 (17)	11 (38)	13 (28)	19 (53)
130-134	2 (2)	5 (6)	3 (5)	6 (21)	5 (4)	12 (13)	5 (9)	8 (28)	11 (23)	12 (33)
126-129	0	0	0	1 (3)	2 (2)	5 (6)	1 (2)	2 (7)	2 (4)	7 (19)
≤125	0	1 (1)	0	0	0	0	3 (6)	1 (3)	0	0

Note: Some subjects received different doses and are in more than 1 dose group.

Observed N: number of subjects with at least one value recorded in time interval; n: number of subjects with low sodium value; %: n/observed N x 100

Source: NDA 022517 (seq 0039), Module 5.3.5.3, Safety Update, Figure 4-23, p. 59.

Among males, the incidence of serum sodium values <135 mmol/L ranged from 10%, 11%, and 10% in the desmopressin 10 mcg, 25 mcg, and 50 mcg dose groups to 16% and 18% in the 75 mcg and 100 mcg groups in subjects <65 years; and from 19% and 13% in the desmopressin 10 mcg and 25 mcg dose groups to 25%, 19%, and 38% in the 50 mcg, 75 mcg, and 100 mcg groups in subjects ≥65 years. The only desmopressin dose group with a serum sodium value <130 mmol/L in males <65 years was 75 mcg (2 subjects [3%]). In males ≥65 years, the incidence of serum sodium values <130 mmol/L increased from 2% and 1% in the desmopressin 10 mcg and 25 mcg dose groups to 4%, 12%, and 16% in the 50 mcg, 75 mcg, and 100 mcg groups, respectively. The only desmopressin dose group with a serum sodium value ≤125 mmol/L in males <65 years was 75 mcg (1 subject [2%]). In males ≥65 years, the incidence of serum sodium values ≤125 mmol/L ranged from none in the 10 mcg and the 25 mcg groups to 3%¹⁶, 5%, and 3% in the 50 mcg, 75 mcg, and 100 mcg dose groups, respectively. The results of a categorical analysis of nadir serum sodium values by sex and age for male subjects are shown in **Table 8-26**.

¹⁶ One male subject ≥65 years in the 50 µg dose group had a serum sodium value ≤125 mmol/L one day after his last dose. If he is included, the percentage changes to 4%.

Table 8-26: Categorical Analysis of Nadir Serum Sodium Values – Any Post-Baseline Visit up to 3 Months by Gender and Age – Males (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		75 µg n (%)		100 µg n (%)	
	<65 years (N=115)	≥65 years (N=121)	<65 years (N=42)	≥65 years (N=59)	<65 years (N=41)	≥65 years (N=71)	<65 years (N=109)	≥65 years (N=113)	<65 years (N=63)	≥65 years (N=59)	<65 years (N=42)	≥65 years (N=63)
Observed N	113	117	40	54	37	68	109	110	63	59	39	58
<135	6 (5)	1 (<1)	4 (10)	10 (19)	4 (11)	9 (13)	11 (10)	27 (25)	10 (16)	11 (19)	7 (18)	22 (38)
130-134	6 (5)	1 (<1)	4 (10)	9 (17)	4 (11)	8 (12)	11 (10)	23 (21)	8 (13)	4 (7)	7 (18)	13 (22)
126-129	0	0	0	1 (2)	0	1 (1)	0	1 (<1)	1 (2)	4 (7)	0	7 (12)
≤125	0	0	0	0	0	0	0	3 (3)	1 (2)	3 (5)	0	2 (3)

Note: Some subjects received different doses and are in more than 1 dose group.
 Observed N: number of subjects with at least one value recorded in time interval; n: number of subjects with low sodium value; %: n/observed N x 100
 Source: NDA 022517 (seq 0039), Module 5.3.5.3, Safety Update, Figure 4-24, p. 59.

Nocturnal Polyuria Population – With Gender Specific Dosing

Among females with nocturnal polyuria, the incidence of serum sodium values <135 mmol/L was 18% in the desmopressin 25 mcg dose group in subjects >65 years and 5% in subjects <65 years. The incidence of serum sodium values <135 mmol/L in the placebo group was 8% in subjects >65 years and 2% in subjects <65 years. The incidence of serum sodium values <130 mmol/L was 6% in the desmopressin 25 mcg dose group in female subjects >65 years and 2% in female subjects <65 years. There were no female subjects treated with desmopressin 25 mcg with a serum sodium value ≤125 mmol/L.

Among males with nocturnal polyuria, the incidence of serum sodium values <135 mmol/L was 28% in the desmopressin 50 mcg dose group in subjects ≥65 years and 11% in subjects <65 years. The incidence of serum sodium values <135 mmol/L in the placebo group was <1% in subjects ≥65 years and 5% in subjects <65 years. The incidence of serum sodium values <130 mmol/L was 4% in the desmopressin 50 mcg dose group in subjects ≥65 years and 0% in subjects <65 years. There were 3 (3%) male subjects ≥65 years treated with desmopressin 50 mcg¹⁷, and no subjects <65 years, with a serum sodium value ≤125 mmol/L. The results of a categorical analysis of nadir serum sodium values for female subjects treated with desmopressin ODST 25 mcg and male subjects treated with desmopressin 50 mcg are shown in **Table 8-27**.

¹⁷ One male subject ≥65 years (with nocturnal polyuria) in the 50 mcg dose group had a serum sodium value ≤125 mmol/L one day after his last dose. If he is included, the percentage changes to 4%.

Table 8-27: Incidence of Hyponatremia – Any Post-Baseline Visit up to 3-Months by Gender and Age at Proposed Doses – Nocturnal Polyuria Population (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Serum Sodium (mmol/L)	Females				Males			
	Placebo n (%)		25 µg n (%)		Placebo n (%)		50 µg n (%)	
	<65 years (N=96)	≥65 years (N=77)	<65 years (N=114)	≥65 years (N=82)	<65 years (N=97)	≥65 years (N=116)	<65 years (N=98)	≥65 years (N=97)
Observed N	95	76	113	78	95	112	98	94
<135	2 (2)	6 (8)	6 (5)	14 (18)	5 (5)	1 (<1)	11 (11)	26 (28)
130-134	2 (2)	5 (7)	4 (4)	9 (12)	5 (5)	1 (<1)	11 (11)	22 (23)
126-129	0	0	2 (2)	5 (6)	0	0	0	1 (1)
≤125	0	1 (1)	0	0	0	0	0	3 (3)

Note: Some subjects received both placebo and desmopressin and are in more than 1 treatment group.

Observed N: number of subjects with at least one value recorded in time interval; n: number of subjects with low sodium value; %: n/observed N x 100

Source: NDA 022517 (seq 0039), Module 5.3.5.3, Safety Update, Figure 4-28, p. 63.

For female subjects treated with the sex specific dose of 25 mcg, the incidence of a serum sodium value between 126-129 mmol/L was 2% and 6%, for the younger (<65 years) and older (≥65 years) age groups, respectively, and no subject had a serum sodium value ≤125 mmol/L in either age group. For male subject treated with the sex specific dose of 50 mcg, the incidence of a serum sodium value between 126-129 mmol/L was 0% and 1%, for the younger and older age groups, respectively. Though no subject in the younger age group had a serum sodium value ≤125 mmol/L, the incidence in the older age group was 3%. These results were similar for both the nocturia and nocturnal polyuria populations.

Applicant's Proposed Serum Sodium Monitoring Plan

The Applicant submitted a sodium monitoring plan to minimize the risk of hyponatremia and especially hyponatremia with serum sodium less than 125 mmol/L in patients treated with NOCDURNA. The Applicant believes that the monitoring plan will lead to early identification of cases of hyponatremia while the serum sodium values are still within the 130-134 mmol/L range and will help prevent at-risk patients developing hyponatremia.

Under the proposed monitoring plan all patients will be required to have a baseline serum sodium of at least 135 mmol/L (the lower limit of the reference range). In addition, patients at least 65 years of age and patients at risk for hyponatremia (due to concomitant medication) should be monitored during the first week of treatment and again approximately 4 weeks after treatment initiation and have a serum sodium of at least 135 mmol/L.

When the proposed serum sodium monitoring plan was applied retrospectively to subjects with nocturnal polyuria treated at the sex-specific doses proposed for marketing (25 mcg for females and 50 mcg for and males) all (11 out of 11) subjects with a serum sodium value <130 mmol/L were captured by the monitoring plan. These results are summarized in **Table 8-28**.

Table 8-28: Incidence of Hyponatremia not Captured by the Proposed Serum Sodium Monitoring Plan by Gender and Age at Gender Specific Doses – Nocturnal Polyuria Population (Safety Analysis Dataset-CS29, CS31, CS40, and CS41)

Serum Sodium (mmol/L)	Females				Males			
	Placebo n (%)		25 µg n (%)		Placebo n (%)		50 µg n (%)	
	<65 years (N=94)	≥65 years (N=69)	<65 years (N=112)	≥65 years (N=70)	<65 years (N=94)	≥65 years (N=110)	<65 years (N=95)	≥65 years (N=81)
Observed N	93	68	111	66	92	106	95	78
<135	2 (2)	1 (1)	4 (4)	2 (3)	3 (3)	0	8 (8)	10 (13)
130-134	2 (2)	1 (1)	4 (4)	2 (3)	3 (3)	0	8 (8)	10 (13)
126-129	0	0	0	0	0	0	0	0
≤125	0	0	0	0	0	0	0	0

Observed N: number of subjects with at least one value recorded in time interval; n: number of subjects with low sodium value; %: n/observed N x 100
 Note: Some subjects received both placebo and desmopressin and are in more than 1 treatment group.

A subject was defined as 'captured' if the laboratory value of the serum sodium was <135 mmol/L at baseline, Week 1 (Week 1 value), or Month 1. A subject was also considered as 'captured' if he or she reported a co-incident adverse event that could be associated with an low serum sodium level (<135 mmol/L).

Source: NDA 022517 (seq 0039), Module 5.3.5.3, Safety Update, Figure 4-29, p. 64.

The Applicant's proposed monitoring plan captured all subjects with a serum sodium value <130 mmol/L. It should be noted that subjects were also considered captured if they reported a co-incident AE associated with a low serum sodium level.

Because hyponatremia also occurred in some younger patients who did not appear to be at increased risk for hyponatremia, we have concluded that the Applicant's proposed monitoring plan should be applied to all treated patients, rather than to only those ≥65 years or those at increased risk for hyponatremia. The Applicant has agreed to modify the monitoring plan to include all patients.

Long-Term Safety Analysis – (S.II Safety Analysis Dataset-CS29/31)

Of the 542 subjects with long-term, continued treatment with desmopressin (S.II dataset), across all treatment groups (10, 25, 50, and 100 mcg desmopressin), 112 (21%) had a nadir serum sodium value that was <135 mmol/L; 87 (16%) had a value between 130-134 mmol/L; 23 (4%) had a value between 125-129 mmol/L; and 2 (0.4%) had a value that was <125 mmol/L. Of the 140 subjects treated with the 25 mcg dose, 30 (21%) had a nadir serum sodium value that was <135 mmol/L; 28 (20%) had a value between 130-134 mmol/L; 2 (1%) had a value between 125-129 mmol/L; and none had a value that was <125 mmol/L. Of the 135 subjects treated with the 50 mcg dose, 33 (24%) had a nadir serum sodium value that was <135 mmol/L; 23 (17%) had a value between 130-134 mmol/L; 9 (7%) had a value between 125-129 mmol/L; and one (1%) had a value that was <125 mmol/L. The overall incidence of hyponatremia with long-term continuous use of desmopressin during CS29/31 is summarized in **Table 8-29**.

Table 8-29: Incidence of Hyponatremia [S.II] Analysis Dataset

	10 ug		25 ug		50 ug		100 ug		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Safety	137	(100.0%)	140	(100.0%)	135	(100.0%)	130	(100.0%)	542	(100.0%)
Serum Sodium										
Observed N	94	(68.6%)	112	(80.0%)	104	(77.0%)	98	(75.4%)	408	(75.3%)
>= 135 mmol/l	79	(57.7%)	82	(58.6%)	71	(52.6%)	64	(49.2%)	296	(54.6%)
< 135 mmol/l	15	(10.9%)	30	(21.4%)	33	(24.4%)	34	(26.2%)	112	(20.7%)
130-134 mmol/l	13	(9.5%)	28	(20.0%)	23	(17.0%)	23	(17.7%)	87	(16.1%)
125-129 mmol/l	1	(0.7%)	2	(1.4%)	9	(6.7%)	11	(8.5%)	23	(4.2%)
< 125 mmol/l	1	(0.7%)	0		1	(0.7%)	0		2	(0.4%)

N = Number of subjects with lowest observed serum sodium in the given category.

% = Percentage of subjects.

S.II: Long term safety, continued use (CS29 Part II + CS31)

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.8.1.4, p. 1239.

Subgroup Analysis – Gender and Age

In the group of female subjects treated with the 25 mcg dose who were younger than 65 years, one subject had a nadir sodium value between 125-129 mmol/L and none had a value <125 mmol/L. For female subjects treated with the 25 mcg dose who were 65 years or older, none had a nadir sodium value <130 mmol/L. The incidence of hyponatremia with long-term, continued use of desmopressin during CS29/31 is summarized by age for female subjects in **Table 8-30** and **Table 8-31**.

**Table 8-30: Incidence of Hyponatremia [S.II] Analysis Dataset: By Gender/Age
 Females <65 years**

Subgroup: Female, < 65 years										
	10 ug		25 ug		50 ug		100 ug		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Safety	40	(100.0%)	37	(100.0%)	41	(100.0%)	33	(100.0%)	151	(100.0%)
Serum Sodium										
Observed N	25	(62.5%)	29	(78.4%)	29	(70.7%)	26	(78.8%)	109	(72.2%)
>= 135 mmol/l	22	(55.0%)	22	(59.5%)	25	(61.0%)	18	(54.5%)	87	(57.6%)
< 135 mmol/l	3	(7.5%)	7	(18.9%)	4	(9.8%)	8	(24.2%)	22	(14.6%)
130-134 mmol/l	3	(7.5%)	6	(16.2%)	3	(7.3%)	7	(21.2%)	19	(12.6%)
125-129 mmol/l			1	(2.7%)	1	(2.4%)	1	(3.0%)	3	(2.0%)
< 125 mmol/l			0		0		0		0	

N = Number of subjects with lowest observed serum sodium in the given category.

% = Percentage of subjects.

S.II: Long term safety, continued use (CS29 Part II + CS31)

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.8.1.6, p. 1244.

**Table 8-31: Incidence of Hyponatremia [S.II] Analysis Dataset: By Gender/Age
 Females $\geq$ 65 years**

Subgroup: Female, $\geq$ 65 years										
	10 ug		25 ug		50 ug		100 ug		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Safety	24	(100.0%)	21	(100.0%)	21	(100.0%)	26	(100.0%)	92	(100.0%)
Serum Sodium										
Observed N	18	(75.0%)	18	(85.7%)	15	(71.4%)	20	(76.9%)	71	(77.2%)
$\geq$ 135 mmol/l	14	(58.3%)	13	(61.9%)	10	(47.6%)	11	(42.3%)	48	(52.2%)
< 135 mmol/l	4	(16.7%)	5	(23.8%)	5	(23.8%)	9	(34.6%)	23	(25.0%)
130-134 mmol/l	3	(12.5%)	5	(23.8%)	3	(14.3%)	5	(19.2%)	16	(17.4%)
125-129 mmol/l	1	(4.2%)	0		1	(4.8%)	4	(15.4%)	6	(6.5%)
< 125 mmol/l			0		1	(4.8%)	0		1	(1.1%)

N = Number of subjects with lowest observed serum sodium in the given category.

% = Percentage of subjects.

S.II: Long term safety, continued use (CS29 Part II + CS31)

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.8.1.6, p. 1245.

For male subjects treated with the 50 mcg dose who were younger than 65 years, none had a nadir sodium value less than 130 mmol/L. For male subjects who were 65 years or older, seven subjects (16%) had a nadir sodium value between 125-129 mmol/L and none had a value < 125 mmol/L. The incidence of hyponatremia with long-term, continued use of desmopressin during CS29/31 is summarized by age for male subjects in **Table 8-32** and **Table 8-33**.

**Table 8-32: Incidence of Hyponatremia [S.II] Analysis Dataset: By Gender/Age
 Males <65 years**

Subgroup: Male, < 65 years										
	10 ug		25 ug		50 ug		100 ug		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Safety	30	(100.0%)	32	(100.0%)	29	(100.0%)	28	(100.0%)	119	(100.0%)
Serum Sodium										
Observed N	22	(73.3%)	22	(68.8%)	25	(86.2%)	15	(53.6%)	84	(70.6%)
>= 135 mmol/l	20	(66.7%)	18	(56.3%)	17	(58.6%)	12	(42.9%)	67	(56.3%)
< 135 mmol/l	2	(6.7%)	4	(12.5%)	8	(27.6%)	3	(10.7%)	17	(14.3%)
130-134 mmol/l	2	(6.7%)	4	(12.5%)	8	(27.6%)	3	(10.7%)	17	(14.3%)
125-129 mmol/l			0		0		0		0	
< 125 mmol/l			0		0		0		0	

N = Number of subjects with lowest observed serum sodium in the given category.

% = Percentage of subjects.

S.II: Long term safety, continued use (CS29 Part II + CS31)

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.8.1.6, p. 1242.

**Table 8-33: Incidence of Hyponatremia [S.II] Analysis Dataset: By Gender/Age
 Males ≥65 years**

Subgroup: Male, >= 65 years										
	10 ug		25 ug		50 ug		100 ug		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Safety	43	(100.0%)	50	(100.0%)	44	(100.0%)	43	(100.0%)	180	(100.0%)
Serum Sodium										
Observed N	29	(67.4%)	43	(86.0%)	35	(79.5%)	37	(86.0%)	144	(80.0%)
>= 135 mmol/l	23	(53.5%)	29	(58.0%)	19	(43.2%)	23	(53.5%)	94	(52.2%)
< 135 mmol/l	6	(14.0%)	14	(28.0%)	16	(36.4%)	14	(32.6%)	50	(27.8%)
130-134 mmol/l	5	(11.6%)	13	(26.0%)	9	(20.5%)	8	(18.6%)	35	(19.4%)
125-129 mmol/l			1	(2.0%)	7	(15.9%)	6	(14.0%)	14	(7.8%)
< 125 mmol/l	1	(2.3%)	0		0		0		1	(0.6%)

N = Number of subjects with lowest observed serum sodium in the given category.

% = Percentage of subjects.

S.II: Long term safety, continued use (CS29 Part II + CS31)

Source: NDA 022517 (seq 0017), Module 5.3.5.1, Clinical Study Report CS31 (Statistical Tables), Table 14.8.1.6, p. 1243.

Two subjects had a serum sodium value <125 mmol/L during long-term, continued use treatment in CS29/31. One subject was a 70 year old female being treated with the 50 mcg dose. The subject had serum sodium values of 122 and 125 mmol/L on Study Days 331 and 333, respectively. On Study Days 4, 8, and 15, the subject's serum sodium was 134, 130, and 131 mmol/L, respectively. Under the proposed monitoring plan, the subject would have been identified during the first week of treatment and desmopressin would have been temporarily or permanently discontinued. In addition, the Applicant is not seeking approval of the 50 mcg dose in females.

The second subject was a 78-year-old male being treated with the 10 mcg dose. The subject had serum sodium values of 125 and 123 mmol/L on Study Days 124 and 327, respectively. One day prior to the Day 124 assessment, the subject had started prednisone 4 mg daily by mouth for asthmatic bronchitis. On Study Days 4, 15, 22, and 29, the subject's serum sodium was 137, 136, 135, and 133 mmol/L, respectively. Under the proposed monitoring plan, the subject would have been identified during the first month of treatment and desmopressin would have been temporarily or permanently discontinued. After Study Day 29, all sodium values were <135 mmol/L, except for Day 36 when it was 137 mmol/L. While the subject's hyponatremia on Day 124 could have resulted from starting prednisone, the cause of the Day 327 event is not clear.

Nocturnal Polyuria Population – With Sex Specific Dosing

Among female subjects with nocturnal polyuria treated with the 25 mcg dose (N=53), four subjects who were ≥ 65 years had serum sodium values <135 mmol/L and none had a value <130 mmol/L. For subjects <65 years of age, six had serum sodium values <135 mmol/L. Of these, one had serum sodium between 126 and 129 mmol/L and none had a value ≤ 125 mmol/L.

Among male subjects with nocturnal polyuria treated with the 50 mcg dose (N=68), 15 subjects who were ≥ 65 years had serum sodium values <135 mmol/L. Of these, 9 had serum sodium between 130 and 134, 6 had serum sodium between 126 and 129 mmol/L, and none had a value ≤ 125 mmol/L. For subjects <65 years of age, seven had serum sodium values <135 mmol/L and none had a value <130 mmol/L.

Applicant's Proposed Serum Sodium Monitoring Plan

When the proposed serum sodium monitoring plan was applied retrospectively to subjects with nocturnal polyuria in the long-term, continued use dataset (S.II) treated with the sex-specific doses proposed for marketing (25 mcg for females and 50 mcg for and males), the one female subject with serum sodium between 126 and 129 was captured by the monitoring plan as were four of the six male subjects with serum sodium between 126 and 129 mmol/L.

The Applicant has agreed to modify the monitoring plan to include serum sodium assessment during the first week, after one month, and then periodically thereafter for all patients.

8.2.6. **Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

No COA data were submitted that would inform the safety/tolerability of NOCDURNA.

8.2.7. **Safety Analyses by Demographic Subgroups**

Age

Treatment-emergent adverse events with an incidence of at least 2% and a 2-fold difference in incidence between age groups (<65 years, ≥65 years) in any treatment group are displayed in **Table 8-34**. Of these events, blood sodium decreased and hyponatremia showed a consistent difference in incidence across the desmopressin 75 mcg and 100 mcg dose groups (greater incidence among subjects ≥65 years of age).

Table 8-34: Treatment-Emergent Adverse Events With At Least a 2% Incidence and Two-Fold Difference in Incidence Between Age Groups in Any Treatment Group (Safety Analysis Dataset)

System Organ Class MedDRA Preferred Term	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		75 µg n (%)		100 µg n (%)	
	Age Group in Years											
	<65 (n=224)	≥65 (n=205)	<65 (n=103)	≥65 (n=91)	<65 (n=167)	≥65 (n=164)	<65 (n=165)	≥65 (n=146)	<65 (n=63)	≥65 (n=59)	<65 (n=92)	≥65 (n=102)
Any adverse event	95 (42)	101 (49)	64 (62)	58 (64)	90 (54)	91 (55)	97 (59)	83 (57)	20 (32)	29 (49)	59 (64)	74 (73)
Eye Disorders												
Dry eye	0	0	1 (<1)	3 (3)	0	2 (1)	0	0	0	0	0	0
Gastrointestinal Disorders												
Diarrhoea	4 (2)	6 (3)	4 (4)	1 (1)	6 (4)	7 (4)	6 (4)	6 (4)	2 (3)	2 (3)	3 (3)	0
Nausea	2 (<1)	2 (<1)	2 (2)	3 (3)	7 (4)	1 (<1)	5 (3)	4 (3)	2 (3)	1 (2)	2 (2)	7 (7)
Abdominal discomfort	0	2 (<1)	3 (3)	2 (2)	3 (2)	1 (<1)	1 (<1)	1 (<1)	0	0	1 (1)	3 (3)
General Disorders and Administration Site Conditions												
Fatigue	1 (<1)	2 (<1)	2 (2)	7 (8)	1 (<1)	1 (<1)	0	6 (4)	1 (2)	1 (2)	1 (1)	3 (3)
Oedema peripheral	0	4 (2)	1 (<1)	2 (2)	0	2 (1)	3 (2)	1 (<1)	1 (2)	4 (7)	3 (3)	2 (2)
Infections and Infestations												
Nasopharyngitis	8 (4)	4 (2)	5 (5)	1 (1)	3 (2)	7 (4)	3 (2)	2 (1)	2 (3)	2 (3)	4 (4)	3 (3)
Upper respiratory tract infection	7 (3)	4 (2)	1 (<1)	3 (3)	8 (5)	2 (1)	6 (4)	2 (1)	1 (2)	1 (2)	5 (5)	2 (2)
Urinary tract infection	7 (3)	4 (2)	1 (<1)	2 (2)	2 (1)	4 (2)	1 (<1)	6 (4)	0	0	1 (1)	3 (3)
Investigations												
Blood sodium decreased	0	1 (<1)	0	2 (2)	1 (<1)	1 (<1)	0	5 (3)	0	2 (3)	1 (1)	7 (7)
Metabolism and Nutrition Disorders												
Hyponatraemia	1 (<1)	2 (<1)	1 (<1)	1 (1)	1 (<1)	4 (2)	5 (3)	4 (3)	2 (3)	3 (5)	3 (3)	8 (8)
Musculoskeletal and Connective Tissue Disorders												
Arthralgia	1 (<1)	4 (2)	1 (<1)	1 (1)	1 (<1)	6 (4)	1 (<1)	1 (<1)	0	0	0	2 (2)
Muscle spasms	2 (<1)	3 (1)	1 (<1)	3 (3)	3 (2)	3 (2)	2 (1)	3 (2)	0	0	0	5 (5)
Nervous System Disorders												
Headache	11 (5)	7 (3)	9 (9)	5 (5)	6 (4)	12 (7)	10 (6)	12 (8)	5 (8)	2 (3)	7 (8)	8 (8)
Dizziness	1 (<1)	1 (<1)	2 (2)	5 (5)	2 (1)	3 (2)	5 (3)	6 (4)	1 (2)	0	1 (1)	6 (6)
Psychiatric Disorders												
Insomnia	1 (<1)	1 (<1)	3 (3)	4 (4)	1 (<1)	1 (<1)	6 (4)	3 (2)	0	0	2 (2)	3 (3)
Respiratory, Thoracic and Mediastinal Disorders												
Cough	0	2 (<1)	0	1 (1)	2 (1)	4 (2)	4 (2)	1 (<1)	0	0	2 (2)	5 (5)

Note: Some subjects received different doses and are in more than 1 dose group.

Source: NDA 022517 (seq 0017), Module 5.3.5.3, Integrated Summary of Safety), Table 40, p. 100.

See “Section 8.2.5 Analysis of Submission-Specific Safety Issues” for analyses of hyponatremia based on serum sodium levels by age groups.

Gender

Treatment-emergent adverse events with an incidence of at least 2% and a 2-fold difference in incidence between males and females in any treatment group are displayed in **Table 8-35**. No consistent differences in the incidence of AEs between male and female subjects across the desmopressin dose groups were observed.

Table 8-35: Treatment-Emergent Adverse Events With At Least a 2% Incidence and Two-Fold Difference in Incidence Between Males and Females in Any Treatment Group (Safety Analysis Dataset)

System Organ Class MedDRA Preferred Term	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		100 µg n (%)	
	Males (n=236)	Females (n=193)	Males (n=101)	Females (n=93)	Males (n=112)	Females (n=219)	Males (n=222)	Females (n=89)	Males (n=105)	Females (n=89)
Any adverse event	104 (44)	92 (48)	65 (64)	57 (61)	70 (63)	111 (51)	116 (52)	64 (72)	71 (68)	62 (70)
Eye Disorders										
Dry eye	0	0	3 (3)	1 (1)	0	2 (<1)	0	0	0	0
Gastrointestinal Disorders										
Dry mouth	29 (12)	26 (13)	37 (37)	28 (30)	31 (28)	29 (13)	35 (16)	29 (33)	31 (30)	25 (28)
Diarrhoea	6 (3)	4 (2)	2 (2)	3 (3)	4 (4)	9 (4)	6 (3)	6 (7)	1 (<1)	2 (2)
Nausea	1 (<1)	3 (2)	2 (2)	3 (3)	2 (2)	6 (3)	2 (<1)	7 (8)	5 (5)	4 (4)
Abdominal discomfort	0	2 (1)	4 (4)	1 (1)	1 (<1)	3 (1)	2 (<1)	0	4 (4)	0
Gastroesophageal reflux disease	0	0	0	0	0	1 (<1)	0	1 (1)	1 (<1)	3 (3)
Infections and Infestations										
Urinary tract infection	0	11 (6)	0	3 (3)	1 (<1)	5 (2)	6 (3)	1 (1)	1 (<1)	3 (3)
Upper respiratory tract infection	3 (1)	8 (4)	2 (2)	2 (2)	4 (4)	6 (3)	4 (2)	4 (4)	3 (3)	4 (4)
Nasopharyngitis	7 (3)	5 (3)	2 (2)	4 (4)	5 (4)	5 (2)	4 (2)	1 (1)	3 (3)	4 (4)
Metabolism and Nutrition Disorders										
Hyponatraemia	1 (<1)	2 (1)	1 (<1)	1 (1)	0	5 (2)	5 (2)	4 (4)	6 (6)	5 (6)
Musculoskeletal and Connective Tissue Disorders										
Muscle spasms	3 (1)	2 (1)	1 (<1)	3 (3)	2 (2)	4 (2)	3 (1)	2 (2)	2 (2)	3 (3)
Nervous System Disorders										
Headache	10 (4)	8 (4)	7 (7)	7 (8)	8 (7)	10 (5)	11 (5)	11 (12)	6 (6)	9 (10)
Psychiatric Disorders										
Insomnia	1 (<1)	1 (<1)	5 (5)	2 (2)	1 (<1)	1 (<1)	6 (3)	3 (3)	3 (3)	2 (2)
Respiratory, Thoracic and Mediastinal Disorders										
Cough	2 (<1)	0	0	1 (1)	4 (4)	2 (<1)	3 (1)	2 (2)	1 (<1)	6 (7)
Oropharyngeal pain	3 (1)	1 (<1)	1 (<1)	4 (4)	0	2 (<1)	2 (<1)	2 (2)	0	1 (1)

Note: Some subjects received different doses and are in more than 1 dose group.

Note: The 75 µg dose group is not presented since it was administered to male subjects only.

Source: NDA 022517 (seq 0017), Module 5.3.5.3, Integrated Summary of Safety), Table 39, p. 98.

See “**Section 8.2.5** Analysis of Submission-Specific Safety Issues” for analyses of hyponatremia based on serum sodium levels by sex.

Race

Within each treatment group, there were too few non-Caucasian subjects (24 to 74 subjects) compared with Caucasian subjects (98 to 355 subjects) to draw meaningful conclusions with respect to the difference in the incidence of adverse events by race.

8.2.8. Specific Safety Studies/Clinical Trials

A Phase 1/2 trial (CS001) evaluated the effect of renal impairment on the safety and pharmacokinetics (PK) of desmopressin. In this trial, a single IV bolus injection of desmopressin was administered to subjects with normal renal function and subjects with varying degrees of renal impairment.

In patients with moderately and severely impaired renal function, clearance and terminal half-life changed significantly resulting in a clinically relevant increase in terminal half-life from 3 hours in healthy subjects to 9 hours in patients with severely impaired renal function. Because of the increased risk of hyponatremia with these PK changes, NOCDURNA will be contraindicated in patients with an estimated glomerular filtration rate below 50 mL/min/1.73 m².

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No studies to assess the carcinogenic potential of NOCDURNA were submitted. Labeling for the currently marketed desmopressin acetate products states that studies have not been performed to evaluate carcinogenic potential.

Human Reproduction and Pregnancy

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

Pediatrics and Assessment of Effects on Growth

NOCDURNA is indicated for adults with nocturia due to nocturnal polyuria and has not been

evaluated in patients younger than 18 years of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

No formal abuse potential studies or studies to evaluate withdrawal or rebound were necessary nor conducted as part of the clinical research program for NOCDURNA.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The first desmopressin product, an intranasal formulation for diabetes insipidus, was approved in 1972. The first oral formulation (a desmopressin tablet) was approved in 1987 for diabetes insipidus, in 1989 for nocturnal enuresis, and in 2001 for nocturia due to nocturnal polyuria (daily dose 0.1-0.4 mg). The desmopressin sublingual tablet formulation was first approved in 2005 for the indications of diabetes insipidus, nocturnal enuresis, and nocturia (daily dose 60-240 mcg). In 2012, NOCDURNA was approved outside the U.S. for nocturia due to nocturnal polyuria with sex-specific dosing (daily dose 25 mcg for females and 50 mcg for males).

Post-marketing safety data for desmopressin is available from the Applicant's global safety database. This database contains all reported cases for all desmopressin formulations marketed by the Applicant, since the first approval in 1972. The information in the safety database comprises all cases reported by health professionals, consumers, and regulatory authorities, cases reported in the scientific literature, and SAEs occurring during clinical trials and other studies.

These postmarketing data are consistent with the known safety profile of desmopressin. Here we focus on the hyponatremia data, which is the most important safety concern with these products.

Hyponatremia

There have been 1,214 postmarketing reports of hyponatremia till August 31, 2017 for the Applicant's desmopressin formulations. Most postmarketing hyponatremia cases were reported with the intranasal desmopressin formulations (47%), with the tablet (14%) (DDAVP in the U.S.; Minirin outside the U.S.), and with the MINIRIN MELT sublingual tablet approved outside the U.S. (16%).

The following data described below summarizes the cases of hyponatremia from post-

marketing safety experiences, excluding cases from clinical trials, but including other studies such as non-interventional studies, market research programs, and patient support programs.

Hyponatremia and the Desmopressin Tablet (DDAVP in the U.S.; Minirin Outside the U.S.)

A total of 179 hyponatremia cases have been reported. Most of the cases (129) involved adults, of which 91 cases were reported for elderly patients (≥ 65 years). The remaining 50 cases were either in an unknown age group or children.

Most hyponatremia cases (61%) in adults were reported as serious and the patients were reported to recover in most cases; 1 case was fatal and in 40 cases the outcome was unknown.

The fatal case is a literature report from the U.S. describing an 80-year-old female with a history of breast cancer with mastectomy, hypertension, cardiac arrhythmia, and nocturnal polyuria, who was treated with 0.2 mg. The patient experienced hyponatremia and seizure after 3 days of treatment, and was hospitalized. Blood sodium level was 108 mmol/L. According to autopsy results, her death was attributed to retroperitoneal hemorrhage from an unidentified area. Confounding factors for the hyponatremia event included her daily intake of eight 6-oz. glasses of water, unknown baseline electrolyte state and the patient's cardiovascular condition.

Hyponatremia and the MINIRIN MELT Sublingual Tablet (60, 120, and 240 mcg dose)

A total of 202 hyponatremia cases have been reported. Most cases involved adults (N=155), of which 106 cases were reported for elderly patients (≥ 65 years). The reported indication for the adult cases is presented in **Table 8-36**.

Table 8-36: Distribution of Hyponatremic Cases by Indication for Adult Patients by Age – MINIRIN MELT Sublingual Tablet

Indication Preferred Term	>18 years to <65 years	≥ 65 years
Diabetes Insipidus	12	11
Enuresis	4	7
Nocturia	2	16
Other/not reported	31	72
Total	49	106

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 50, p. 101.

Most hyponatremia cases (85%) in adults were reported as serious and the patients were reported to recover in most cases; 1 case was fatal and in 32 cases the outcome was unknown.

The fatal case was reported from Norway describing an 82-year-old female who experienced hyponatremia (serum sodium 115 mmol/L) after 2 months of treatment with desmopressin sublingual tablet for urinary frequency. The daily dose was 60 mcg and confounding factors included concomitant medications (antidepressants and diuretics), which are known to interact with desmopressin and cause hyponatremia.

There were three reports of coma together with hyponatremia in adults:

- The first case was reported by a nurse in Norway. The patient, a 63-year-old female, experienced water intoxication, hyponatremia and coma while being treated with 120 mcg daily for nocturnal polyuria. The case is confounded by the patient's excessive alcohol consumption (drinking 4-5 beers a day).
- The second case was a literature case report from Italy describing a drug-drug interaction between the 240 mcg daily dose and NSAIDs in a 50-year-old male, who was treated for central diabetes insipidus and experienced coma and seizures. The case was confounded by several factors and the patient was previously treated with desmopressin for approximately 40 years without any episodes of hyponatremia. The third case reported concomitant use with amitriptyline and ibuprofen, where the interactive anti-diuretic effects were believed to be the cause of hyponatremia, cramps and coma in a 41-year-old man. Approximately two months before event onset, the patient started using amitriptyline and ibuprofen. Two to three days after desmopressin (120 mcg) was added due to suspicion of diabetes insipidus, he developed serious hyponatremia, cramping and coma. Intensive care treatment was initiated and serum-sodium gradually returned to normal. Desmopressin and ibuprofen were discontinued. The initiation of desmopressin coincided with the patient's development of hyponatremia, cramping, and coma. The three suspected drugs probably contributed to the event.

NOCDURNA

Patient Exposure

NOCDURNA (sex-specific dosing 25 mcg for females and 50 mcg for males) was first launched in Canada in August 2014. Calculation of patient exposure NOCDURNA is based on sales figures from the first launch in 2014 up to August 31, 2017. The cumulative patient-years of exposure is estimated to be approximately (b) (4) (25 mcg: (b) (4); 50mcg (b) (4)).

Overall Safety Profile

As of August 31, 2017, a total of 28 post-marketing cases (55 reactions) NOCDURNA have been received by the Applicant. The most commonly reported events were 'Drug ineffective' and 'Hyponatremia'. The most commonly reported reactions for NOCDURNA are presented in **Table 8-37**.

Table 8-37: Most Common Adverse Reactions Spontaneously Reported with NOCDURNA

Adverse Reaction (Preferred Term)	Number of Reactions
Hyponatremia	12
Drug ineffective	4
Nausea	3
Headache	3
Asthenia	2
Decreased appetite	2
Off label use	2

^aHyponatremia is defined using these MedDRA PT: Hyponatremia and Blood sodium decreased.
Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 51, p. 103.

In 78% of the post-marketing NOCDURNA cases, the indication was nocturia. In the remaining cases, NOCDURNA was used for enuresis (4%), urine output decreased (6%), or the indication was not reported (13%).

The age distribution for NOCDURNA cases was 46% for elderly patients ≥ 65 years, 7% for patients >18 to <65 years and 7% for patients <18 years. In the remaining cases the age was not reported (39%).

The sex distribution for NOCDURNA cases was 21% for female elderly patients ≥ 65 years and 25% for male elderly patients ≥ 65 years. For adults >18 to <65 years, there were 2 female cases (7%). For children <18 years, there were 2 male cases. In the remaining cases (no age reported) 14% were female, 18 % were male and in the two last cases sex was not reported.

Overall, 6 cases were serious and 22 cases non-serious. For the majority of cases (64%) the patient outcome was either recovered or recovering. No fatal outcomes were reported. In 10 cases, the outcome was unknown. The 6 serious cases had the following events reported: hyponatremia (4) (**Table 8-38**), anuria (1), and seizure (1).

Table 8-38: Serious Hyponatremia Cases with NOCDURNA

Case number	Age	Gender	Sodium value	Other information
2014FE02799	Unknown	Female	Unknown	None
2015FE00355	84	Male	Baseline – 142 1 week – 134 10 days – 126	None
2017FE01890	78	Female	Baseline – 138 10 day – 129 1 month – 126	None
2017FE03828	75	Male	Unknown	After the first week of medication, sodium level was around the lower level of the reference value, but because the patient felt that he was getting benefit from the treatment, it was decided to continue and to measure sodium again after one week. When this was done, sodium level was clearly under the reference value. There were no symptoms associated with hyponatremia.

Source: NDA 022517 (seq 0039), Module 2.7.4, Summary of Clinical Safety, Table 52, p. 104.

The reports of seizure and anuria are discussed below:

2015FE01573 is a serious report of seizure in a female patient. She had received treatment with MINIRIN MELT 120 mcg daily for 8 months with no issues. Treatment was switched to NOCDURNA 25 mcg daily for 21 days, but was not effective. The patient returned to treatment with MINIRIN MELT 120 mcg. After two weeks, the patient experienced convulsions and hyponatremia, with a serum sodium of 115 mmol/L. The patient was admitted to the hospital and spent three days in the Intensive Care Unit. Based on the time sequence of exposure to NOCDURNA, it is unlikely that NOCDURNA was the cause of the event.

2015FE00894 is a serious report of anuria in an 86-year-old male with a history of

prostatitis who experienced complete anuria for 72 hours during treatment with NOCDURNA (desmopressin) 50 mcg daily for nocturia. After taking NOCDURNA, 50 mcg at bedtime for 2 nights, the patient experienced complete anuria for 72 hours. Treatment with NOCDURNA was permanently discontinued and the patient was administered 3 months of Avodart. The patient recovered after NOCDURNA was discontinued. The event appears to be related to treatment with NOCDURNA.

Expectations on Safety in the Postmarket Setting

No new safety concerns were identified from the postmarketing experience with NOCDURNA outside the U.S. or with the Applicant's other approved desmopressin products.

8.2.11. Integrated Assessment of Safety

Desmopressin has a long marketing history for various indications, in multiple formulations, with several routes of administration at a range of doses. In general, the safety profile of desmopressin is well characterized and the safety data reviewed for this NDA did not reveal any new safety signals for the drug. Hyponatremia is a known and potentially serious risk of desmopressin drugs that increases with age. Nocturia due to nocturnal polyuria, the indication proposed by the Applicant, also increases with age and is most prevalent in older individuals. Therefore, the focus of this safety review was on hyponatremia.

Most of the NOCDURNA-treated patients who developed hyponatremia in the clinical trials had mild hyponatremia. The incidence of serum sodium concentrations below 130 mmol/L was low. Available post-marketing data with NOCDURNA from outside the U.S. did not identify new or worrisome concerns.

Warnings and Precautions help mitigate the risk of hyponatremia for desmopressin products approved for other indications. Those products have more narrow uses, such as diabetes insipidus, hemostasis during surgery for patients with Hemophilia A or von Willebrand's disease, and primary nocturnal enuresis in children. In contrast, NOCDURNA will be used in a diverse, older patient population that likely has multiple co-morbidities and concomitant medications that can predispose to hyponatremia. A Boxed Warning for hyponatremia is necessary to ensure that the modest benefits of the drug outweigh the risks. A Boxed Warning is appropriate because severe hyponatremia can be life-threatening and is very serious in proportion to the benefit of the drug, and because hyponatremia can be mitigated with interventions (e.g., periodic monitoring of serum sodium).

The key measures for minimizing the risk of hyponatremia are described in labeling and include:

- Gender-specific dosing (25 mcg for women, 50 mcg for men);
- Limiting fluid intake for nine hours starting one hour before taking NOCDURNA;
- Ensuring serum sodium is normal prior to initiating or resuming NOCDURNA;

- Monitoring serum sodium within 1 week and approximately one month after initiating therapy and periodically thereafter, with more frequent monitoring recommended in patients 65 years of age and older and in patients at increased risk of hyponatremia (e.g., those on concomitant medications that can contribute to hyponatremia);
- Contraindications for conditions that increase the risk of severe hyponatremia.

In addition, the drug will be approved with a medication guide, that by law, must be dispensed to patients each time they obtain a new prescription or refill of the medication. The medication guide conveys important information on actions patients can take to reduce their risk of severe hyponatremia, such as recognizing the symptoms of hyponatremia, avoiding excessive fluid intake, and checking with their health care provider before starting new medications that may increase the risk of hyponatremia.

SUMMARY AND CONCLUSIONS

See the benefit-risk assessment in **Section 1**. We have concluded that the benefits of NOCDURNA 50 mcg nightly in men and 25 mcg in women for the treatment of nocturia due to nocturnal polyuria in patients who awaken at least twice per night to void outweigh the risks when used according to labeling, and recommend approval.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was required during this review cycle.

10 Pediatrics

NOCDURNA is indicated for adults with nocturia due to nocturnal polyuria and has not been evaluated in patients less than 18 years of age. During the first cycle NDA review, the Pediatric Review Committee (PeRC) granted a full waiver of pediatric studies because the condition is present almost exclusively in adults.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Key issues pertaining to labeling include the following. See the approved labeling for details.

- Ferring's proposed NOCDURNA dosage form, 'orally disintegrating sublingual tablet', is incorrect. The drug product is administered by placement under the tongue, where the product disintegrates, drug is released and is presumably absorbed. The dosage form is thus, 'sublingual tablet'. See USP General Chapter <1121> *Nomenclature* and the USP Nomenclature Guidelines, March 2016, referenced therein.
- Desmopressin acetate is currently available as nasal solutions, metered nasal sprays, injections, and oral tablets. The strength of these products is expressed in terms of the salt, desmopressin acetate. The OPQ Office of Policy for Pharmaceutical Quality (OPPQ) Product Quality Labeling (PQL) team recommends that, for consistency with these approved products, the strength of NOCDURNA be expressed based on the acetate salt. The strengths of NOCDURNA are thus, 27.7 mcg of desmopressin acetate (equivalent to 25 mcg of desmopressin) and 55.3 mcg of desmopressin acetate (equivalent to 50 mcg of desmopressin).
- NOCDURNA will be indicated for patients with nocturia due to nocturnal polyuria in patients who awaken at least two times per night to void, and will not receive a broad nocturia indication. Approximately 90% of the patients with nocturia in the Phase 3 trials had nocturnal polyuria, and the trials had numerous exclusion criteria that limited generalizability to all patients with nocturia.
- NOCDURNA will have a Boxed Warning and medication guide because of the risk of hyponatremia. Labeling will state that NOCDURNA can cause severe hyponatremia and will include important information on how to mitigate this risk, including sex-specific dosing, limiting fluid intake for nine hours starting one hour prior to administration, ensuring serum sodium is normal before starting treatment, recommending periodic serum monitoring, and contraindicating in patients at increased risk of severe hyponatremia. The hyponatremia data will be included in the Adverse Reactions section of labeling.
- The Clinical Studies section will focus on the patients with nocturnal polyuria, consistent with the narrowed indication, and include the results from the exploratory analyses that helped interpret the clinical meaningfulness of the observed treatment effects. No p-values will be reported for these exploratory analyses.

11.2 Carton and Container Labeling

The Division of Medication Error Prevention and Analysis and the Product Quality Review Team have worked with the Applicant on the carton and container labeling. Agreement has been reached and there are no outstanding issues from a CMC and medication error perspectives. See the separate consults in DARRTS and the OPQ Integrated Quality Assessment and associated addendum in Panorama for further details.

11.3 Proprietary Name Assessment

The proposed proprietary name, NOCDURNA, is acceptable. See the Proprietary Name Request Conditionally Acceptable letter dated April 30, 2018.

12 Risk Evaluation and Mitigation Strategies (REMS)

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

13 Postmarketing Requirements and Commitment

None

14 Appendices

14.1. References

Janaky T, Laszlo FA, and Morgan J-L. Titration of vasopressin analogues and their metabolic fate after intravenous injection in the rat. *Acta Medica Hungarica* 1984; 41:43-54.

Kadowaki T, Hagura R, Kajinuma H, Kuzuya N, Yoshida S. Chlorpropamide-induced hyponatremia: incidence and risk factors. *Diabetes Care*. 1983;6:468-71.

14.2. Financial Disclosure

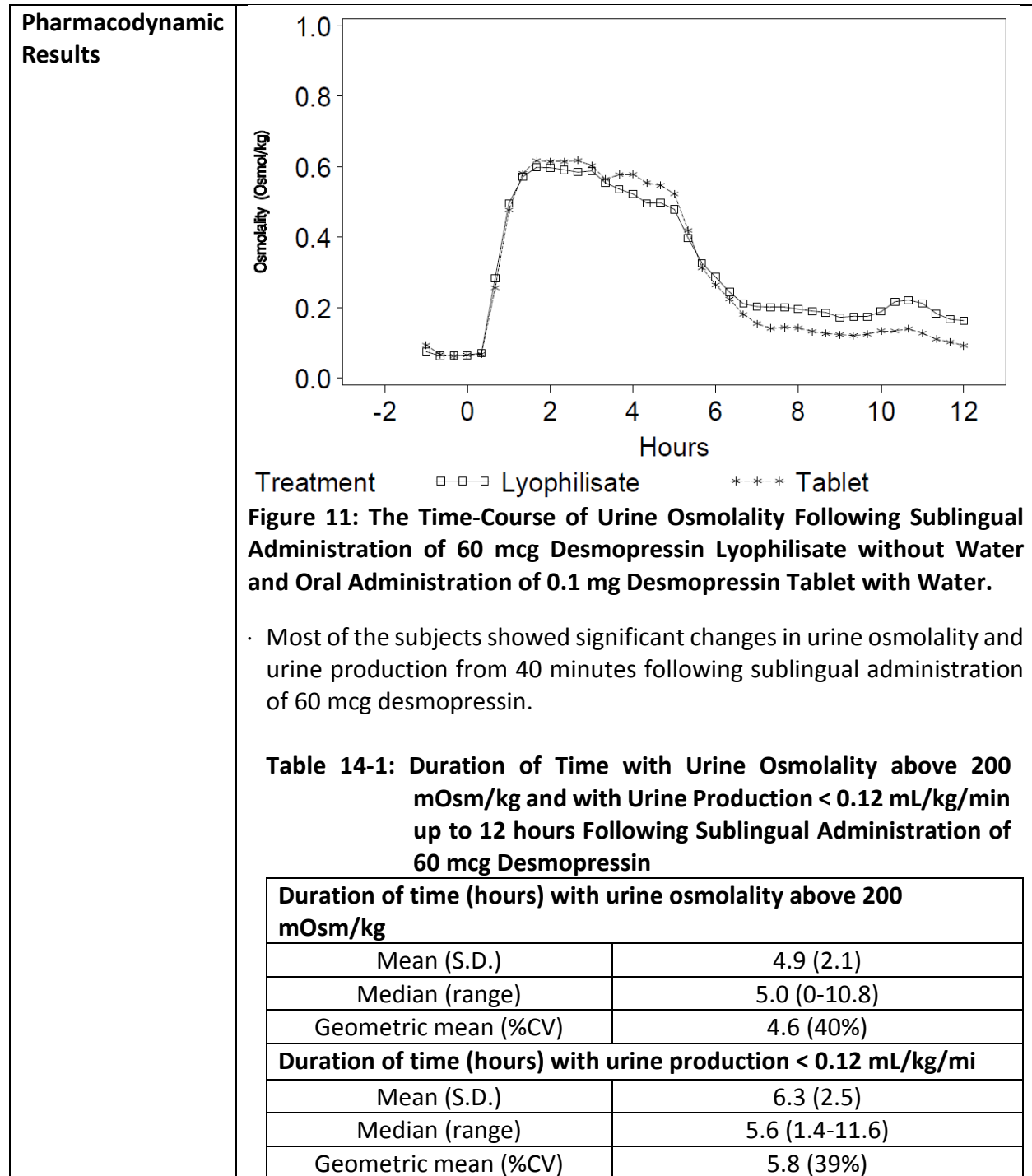
Financial disclosure information was submitted and reviewed during the previous review cycles (please refer to reviews by William Lubas, M.D., Ph.D. archived in DARRTS on April 7, 2010 and January 23, 2013). No new studies were submitted in the current resubmission.

14.3. OCP Appendices (Technical documents supporting OCP recommendations)

14.3.1. Pharmacodynamics of desmopressin following sublingual administration of desmopressin tablet

The pharmacodynamics of desmopressin following sublingual administration of lyophilized 60 mcg desmopressin was compared to swallowing a 100 mcg desmopressin tablet in healthy water-loaded subjects (Study CS30). The study design and pharmacodynamic results are summarized as follows:

Design	· An open-labelled, randomized, two-sequence, two-treatment, cross-over study · 34 males and 26 females aged between 18 and 50 years · A wash-out period: >3 days between the periods · Sublingual administration of 60 mcg desmopressin lyophilisate without water and oral administration of 0.1 mg desmopressin tablet with 200 mL water · Urine osmolality and volume measurement every 20 minutes up to 12 hours post-dose



Based on the changes in both pharmacodynamic parameters, onset of antidiuretic effect is likely to be observed between 20 and 40 minutes following sublingual administration of 60 mcg desmopressin. When considering onset and duration of time with urine osmolality above 200 mOsm/kg and time with urine production < 0.12 mL/kg/min, antidiuretic effect appeared to last approximately 6 hours following sublingual dosing of desmopressin in healthy, water-loaded

subjects. However, in the proposed labeling, (b) (4)

We recommend revising this description as follows: “The mean time to onset of action was observed within 30 minutes and lasted approximately 6 hours after dosing following sublingual administration of desmopressin.”

14.3.2. Waiver of PK Studies of Sublingual Desmopressin Administration

The PK of desmopressin following sublingual administration of the proposed doses, 25 mcg and 50 mcg desmopressin tablets, has not been characterized. The Applicant requested a waiver for PK studies of doses lower than 60 mcg, including the proposed clinical doses of 25 and 50 mcg, during the end of Phase 2 meeting (IND 065890, March 26, 2007) because of the following reasons: 1) availability of PK data at doses of 60 mcg, 120 mcg and 240 mcg; and 2) the analytical method was not sensitive to measure desmopressin of lower strengths. The Biopharmaceutics team agreed to waive the PK studies (December 7, 2007), if: 1) desmopressin PK is linear over the proposed dose range; 2) the different formulation strengths are proportionally similar in their active and inactive ingredients; and 3) their dissolution profiles are comparable to those of the higher strength(s) used in previous PK studies.

The Applicant submitted a formal biowaiver request during the Pre-NDA meeting (October 20, 2008: submission date – September 19, 2008) with the following information: 1) Study CS21: a PK linearity study of 60 mcg, 120 mcg and 250 mcg sublingual tablets; 2) The analytical method used for the quantitative determination of desmopressin in human plasma and the validation report; and 3) Dissolution report of 10-240 mcg sublingual tablets.

Regarding PK linearity, while the Applicant concluded that exposure showed a dose-proportional increase with increasing dose following sublingual administration of 60, 120, and 240 mcg, the biopharmaceutics team noted that “The PK study showed a trend rather than a conclusive evidence of dose linearity and also noted that this study had many deficiencies including missing data, extrapolated PK parameters, high variability, and unacceptable bioanalytical method” (Biopharmaceutics Review, DARRTS date: December 05, 2008). The Applicant provided the following justification of the linearity requirement of desmopressin PK over the tested dose range (10 to 100 mcg) at that time: “We are not planning, nor are we able, to carry out pharmacokinetic studies with the lower strengths of MINIRIN MELT due to the fact that analytical methods are not sufficiently sensitive to measure desmopressin in blood following administration of these lower strengths. For this reason, it is not feasible to demonstrate pharmacokinetic linearity over the proposed range.”

Regarding dosage strength composition proportionality, the Applicant submitted information showing that the inactive ingredients in all doses including 60, 120, and 240 mcg strengths used in the PK linearity study are qualitatively and quantitatively the same, which are also the same as the proposed and to-be-marketed dose strengths, 25 and 50 mcg.

Regarding dissolution similarity, the Applicant submitted the dissolution test reports of the four strengths (10, 25, 50, and 100 mcg) used in the U.S. clinical program and the three strengths

(60, 120, and 240 mcg) registered in Europe. The results showed that approximately 100% dissolution is achieved after 6 minutes and there was no difference between the different dissolution media or the different tablet strengths.

The biopharmaceutics review team within the then Office of New Drug Quality Assessment (ONDQA), concluded that the provided information and justification were acceptable and granted the biowaiver at the proposed clinical dose strengths under IND 065890 (Dr. Houda Mahyni; January 14, 2009).

14.3.3. Sex Differences in the PK of Desmopressin Following Sublingual Administration

The clinical studies showed that women may respond to lower desmopressin doses than men (refer to **Section 1.3 and 3.2**) Although cross-study comparison of two PK studies (CS21 and CS20) showed that sex differences in drug exposure were not statistically significant when adjusted for body weight, those PK studies used an invalid bioanalytical method to measure the plasma concentrations of desmopressin (refer to CLINICAL PHARMACOLOGY REVIEW [3/30/2010] of the original submission). Therefore, this PK comparison to assess sex effect is inconclusive.

14.4. Eligibility Criteria for Trials CS40 and CS41

Inclusion Criteria:

1. Male (trial CS41) or Female (trial CS40) 18 years of age or older,
2. At least two nocturnal voids every night in a consecutive three-day period during screening (as determined by diary dispensed at Visit 1 and collected at Visit 2).

Exclusion Criteria:

1. Evidence of severe daytime voiding dysfunction defined as:
 - Urge urinary incontinence (more than one episode/day in the three-day diary period);
 - Urgency (more than one episode/day in the three-day diary period);
 - Frequency (more than eight daytime voids/day in the three-day diary period)
2. Interstitial cystitis
3. Chronic prostatitis (trial CS41 only)/chronic pelvic pain syndrome (CPPS)
4. Suspicion of bladder outlet obstruction (BOO) or a urine flow of less than 5 mL/s as confirmed by uroflowmetry performed after suspicion of BOO
5. Surgical treatment, including transurethral resection, for BOO or benign prostatic hyperplasia within the past six months (trial CS41 only)

5. Urinary retention or a post void residual volume in excess of 150 mL as confirmed by bladder ultrasound performed after suspicion of urinary retention
6. Habitual or psychogenic polydipsia (fluid intake resulting in a urine production exceeding 40 mL/kg/24 hours)
7. Central or nephrogenic diabetes insipidus
8. Syndrome of inappropriate antidiuretic hormone
9. Current or a history of urologic malignancies e.g. bladder cancer
10. Genito-urinary tract pathology e.g., infection or stone in the bladder and urethra causing symptoms
11. Neurogenic detrusor activity (detrusor overactivity)
12. Suspicion or evidence of cardiac failure
13. Uncontrolled hypertension
14. Uncontrolled diabetes mellitus
15. Hyponatremia:
 - Serum sodium level must be within normal limits
16. Renal insufficiency:
 - Serum creatinine must be within normal limits and estimated glomerular filtration rate must be more than or equal to 50 mL/min
17. Hepatic and/or biliary diseases:
 - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels must not be more than twice the upper limit of normal range
 - Total bilirubin level must not be more than 1.5 mg/dL
18. History of obstructive sleep apnea
19. Previous desmopressin treatment for nocturia
20. Treatment with another investigational product within three months prior to screening
21. Concomitant treatment with any prohibited medication (see below)
22. Pregnancy, breastfeeding, or a plan to become pregnant during the period of the clinical trial (Trial CS40 only).
23. Subjects of reproductive age must have documentation of a reliable method of contraception.
24. All pre-and peri-menopausal subjects must perform pregnancy tests. Amenorrhea of more than 12 months' duration based on the reported date of the last menstrual period is sufficient documentation of post-menopausal status and does not require a pregnancy test (Trial CS40 only).
25. Known alcohol or substance abuse
26. Work or lifestyle that may interfere with regular night-time sleep e.g. shift workers
27. Any other medical condition, laboratory abnormality, psychiatric condition, mental incapacity, or language barrier which, in the judgement of the Investigator, would impair participation in the trial

Prohibited medications: any investigational drug, loop diuretics, phosphodiesterase (PDE)-5 inhibitors restricted to sildenafil (Viagra), one dose per week only and no dosing in the five days immediately preceding a scheduled visit.

The following medications were permitted provided the subject had been on a stable dose for the three months prior to screening:

Alpha-blockers, 5-alpha reductase inhibitors, anti-muscarinic therapy for overactive bladder, sedative/hypnotic medications for sleep disorders, selective serotonin reuptake inhibitors (SSRIs), chronic use of non-steroidal anti-inflammatory agents (NSAIDs), chlorpropamide, carbamazepine and amiodarone.

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/s/

NENITA I CRISOSTOMO
06/18/2018

SURESH KAUL
06/18/2018

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06/18/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRMCG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22517
Supporting document/s: 44 (eCTD 0039)
Applicant's letter date: 21 December 2017
CDER stamp date: 21 December 2017
Product: Nocdurna™ (Desmopressin) ; TABLET,
ORALLY DISINTEGRATING
Indication: Treatment of nocturia in adults
Applicant: Ferring Pharmaceuticals Inc.
Review Division: Division of Bone, Reproductive and Urologic
Products
Reviewer: Laurie McLeod-Flynn, Ph.D., D.A.B.T.
Supervisor/Team Leader: Mukesh Summan, Ph.D., D.A.B.T.
Division Director: Hylton V. Joffe, M.D., M.M.Sc.
Project Manager: Nenita Crisostomo

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22517 are owned by Ferring Pharmaceuticals Inc. or are data for which Ferring Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22517 that Ferring Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22517.

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1 Executive Summary

1.1 Introduction

NOCDURNA is being developed by Ferring Pharmaceuticals for the treatment of nocturia in adults. It is a new orally disintegrating tablet formulation of desmopressin for sublingual use.

The submitted nonclinical studies were designed to test the safety and comparability of the new product and its impurities as well as its potential for any local reactions. These nonclinical studies were submitted in conjunction with reference to NDA 19955 data for desmopressin tablets for treatment of nocturia in adults at pharmacologically equivalent doses.

1.2 Brief Discussion of Nonclinical Findings

In a 1-month bridging toxicology study in dogs, toxicological findings and toxicokinetic data with NOCDURNA were similar to DDAVP and were consistent with known pharmacological effects of desmopressin. In general, there were no signs of systemic toxicity in any treated animals. Decreased urinary volumes in treated animals were noted, related to the pharmacological effect of the compound. The values of serum bilirubin were increased in two desmopressin treated females with no other related changes. Findings from the TK data suggested no sex differences and similarity in level of desmopressin levels in two compounds (2 × 200 mcg DDAVP tablets vs. 1 × 240 mcg desmopressin orally disintegrating tablets).

Desmopressin acetate was previously reviewed under NDA 19955 (Ferring). To characterize the local toxicity and qualify the new impurity profile of NOCDURNA, new studies were conducted.

In a 13-week study in rats by subcutaneous administration, three impurities of desmopressin were included at relevant levels. Findings in this study were consistent with the pharmacological effects of desmopressin. Absolute kidney weights were significantly increased for mid and high dose animals, with no microscopic findings. The increased kidney weights were considered due to the pharmacological effects of the test article in maximizing tubular reabsorption. The NOAEL was considered to be 10 mcg/kg/day, at which only pharmacological effects of desmopressin were noted.

In *in vitro* genotoxicity studies (Ames test, mouse lymphoma assay) no genotoxic potential was observed for desmopressin spiked with the 3 relevant impurities.

The toxicological profile of desmopressin orally disintegrating tablets was considered to be consistent with desmopressin tablets.

A 28-day local tolerability study was conducted in Syrian hamsters (once daily, cheek pouch.) No evidence of test article related local reactions or histopathological changes were observed.

A fertility study in rats, embryo-fetal studies in rats and rabbits, and a pre-and post-natal study in rats were performed under NDA 19955.

In a non-GLP fertility study in rats, sc desmopressin acetate, administered to males and females prior to and during mating and to females during early gestation, showed no effects on estrus cycling, copulation rate, conception rate, with maternal, paternal, and fetal no effect levels greater than 200 mcg/kg/day.

In a non-GLP embryo-fetal study in rats, iv desmopressin acetate, administered from Days 7 to 17 and through weaning at doses of 0, 9.47, 47.4, and 238 mcg/kg/day, showed no drug related reproductive effects, although pharmacology was observed at all doses.

In rats, fetal transfer of labeled DDAVP (sc) was 4% of maternal blood level after 1 hour and 39% of maternal blood levels at 4 hours

In a non-GLP embryo-fetal study in Dutch belted rabbits, sc desmopressin acetate, administered from Days 6 to 18 at doses of 0, 1, 3, and 10 mcg/kg/day, showed no drug related reproductive effects.

In a pre- and post-natal development study, desmopressin acetate had no effect on clinical signs, gestation index, delivery, lactation, or implantation sites. In F₁ offspring, proposed to be due to decreased nursing. No treatment related effect was observed, on birth index, viability index on day 4, weaning index, clinical signs, reflex and motility (righting reflex, negative geotaxis, pupillary reflex, Preyer reflex, pain response), morphological differentiation (pinna detachment, incisor eruption, eyelids opening, testes descent), external appearance, visceral effects, skeletal effects, general behavior, learning (by open field test, water maze test) or reproductive performance. In F₂ offspring, no treatment related effects on birth index, viability index on days 4 and 7, body weight, external appearance, visceral effects or skeletal effects were observed at any dose level. No adverse effect levels (sc) were judged to be more than 200 mcg/kg/day for F₀ dams, 20 mcg/kg /day for F₁ offspring and more than 200 mcg/kg/day for F₂ offspring.

1.3 Recommendations

1.3.1 Approvability

Pharmacology Toxicology recommends approval.

My review is complete and a summary of my review has been added to the multidisciplinary review and evaluation document. My review is based on the

information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

1.3.3 Labeling

DBRUP and the sponsor have agreed on the following label:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

NOCDURNA is not recommended for the treatment of nocturia in pregnant women. Nocturia is usually related to normal, physiologic changes during pregnancy that do not require treatment with NOCDURNA.

(b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Desmopressin acetate, administered during organogenesis did not cause fetal harm in teratology studies in rats at intravenous doses up to 238 mcg/kg/day or in rabbits at subcutaneous doses up to 10 mcg/kg/day, representing 92- and 8-times, respectively, the maximum recommended human dose in women of 27.7 mcg, based on body surface area (mg/m²).

8.2 Lactation

Risk Summary

Desmopressin is present in small amounts in human milk (see Data).

There is no information on the effects of desmopressin on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's need for NOCDURNA and any potential adverse effects on the breastfed child from NOCDURNA or from the underlying maternal condition.

Data

Human Data

The breast milk of lactating women was collected over 8 hours following desmopressin (300 mcg) administration using nasal spray. Based on the measured concentrations of desmopressin, the amounts of

desmopressin that may be transferred to a breastfed infant correspond to 0.0001-0.0005% of the dose administered.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Desmopressin acetate, administered during organogenesis did not cause fetal harm in teratology studies in rats at intravenous doses up to 238 mcg/kg/day or in rabbits at subcutaneous doses up to 10 mcg/kg/day, representing 92- and 8-times, respectively, the maximum recommended human dose in women of 27.7 mcg, based on body surface area (mg/m²).

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10 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with desmopressin have not been performed to evaluate carcinogenic potential.

Desmopressin has shown no potential for mutagenesis in bacterial mutagenicity (Ames) and mouse lymphoma assays.

Animal studies with desmopressin have shown no impairment of fertility in male and female rats at doses up to 200 mcg/kg/day.

2 Drug Information

2.1 Drug

CAS Registry Number: 16679-58-6

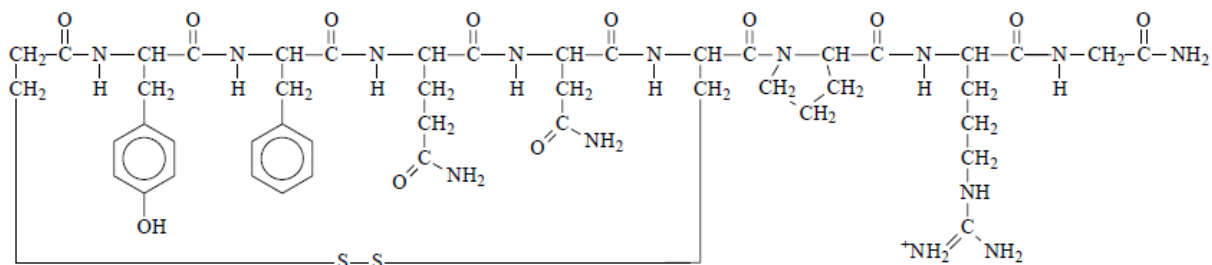
Generic Name: Desmopressin, arginine vasopressin

Code Name: DDAVP, KW-8008

Chemical Name: 1-Desamino-8-D-arginine vasopressin acetate; 1-(3-Mercaptopropranoic acid)-8-D-arginine- vasopressin monoacetate (*1-desamino-8-D-arginine vasopressin*)

Molecular Formula/Molecular Weight: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$ / 1183.34

Structure or Biochemical Description:



Desmopressin acetate is a nonapeptide which differs from endogenous antidiuretic hormone (ADH) at position 1 where it is deaminated and position 8 where L-arg is replaced by D-arg.

Pharmacologic Class: Arginine vasopressin (synthetic anti-diuretic hormone, vasopressin analog)

2.2 Relevant INDs, NDAs, BLAs and DMFs

DDAVP® Desmopressin Acetate Tablets (NDA19-955), Desmopressin Acetate Nasal Spray (NDA 21-333), Desmopressin Acetate Tablets (NDA 21-795) and DMF 8396.

2.3 Drug Formulation

Each orally disintegrating tablet contains desmopressin acetate equivalent to 25 mcg and 50 mcg of desmopressin as free base. The inactive ingredients are gelatin, mannitol, and anhydrous citric acid. The proposed dosing regimens are for women 25 mcg daily and for men 50 mcg daily.

Desmopressin Orally Disintegrating Tablet 25 mcg:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.050 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 50 µg desmopressin free base.

2.4 Comments on Novel Excipients

No novel excipients were used.

2.5 Comments on Impurities/Degradants of Concern

Sponsor's Table: Comparison of Impurity Profiles for DDAVP Tablets and Desmopressin Orally Disintegrating Tablet

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

NOCDURNA is indicated for the treatment of nocturia in adults. It is an orally disintegrating tablet formulation of 27.7 mcg or 55.4 mcg desmopressin acetate for daily sublingual administration.

2.7 Regulatory Background

Desmopressin has been marketed since 1972 as intranasal, intravenous, and oral formulations for the treatment of diabetes insipidus and primary nocturnal enuresis.

3 Studies Submitted**3.1 Studies Reviewed****Single Dose Toxicity Studies**

- 1) Desmopressin: Pharmacokinetics and oral bioavailability in the rat and domestic pig
- 2) Pharmacokinetics in the domestic pig following administration of two different dosage forms and a pig PK study (Tablet vs. orally disintegrating tablet administration).

Repeat Dose Toxicity Studies

- 1) 13 -week Subcutaneous Toxicity Study in Rats
- 2) 1-month bridging toxicity study in dogs

Genetic Toxicology Studies

- 1) Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 100, TA 1537 and TA 98 and *Escherichia coli* WP2uvrA
- 2) EF992026 Mouse Lymphoma Cell Mutation Assay

Local tolerance Study:

- 1) Oral Irritation in the Syrian Hamster

3.2 Studies Not Reviewed: none

3.3 Previous Reviews Referenced

July 30, 2012 and June 19, 2009 NDA reviews by Parvaneh Espandiari

4 Pharmacology

Desmopressin is a synthetic analogue of the antidiuretic hormone vasopressin (ADH.) Its antidiuretic effects are mediated by stimulation of vasopressin 2 (V2) receptors in renal collecting ducts, increasing water re-absorption by the kidney, and consequently reducing urine production. Desmopressin has a more potent, prolonged duration of action as well as decreased pressor activity compared to ADH.

The demonstration of pharmacological activity of desmopressin orally disintegrating tablet is based on referenced data; no additional pharmacology studies were conducted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

PK studies in rats and domestic pigs to evaluate the bioavailability of desmopressin when administered via sublingual route suggested that desmopressin orally disintegrating tablets had a greater bioavailability (C_{max}, T_{max}, AUC and AUC/dose) of about two-fold, compared to tablets. Plasma levels of desmopressin were detected by radioimmunoassay (RIA) under GLP conditions.

As reviewed by Parvaneh Espandiari:

Study Title: Pharmacokinetics in the domestic pig following administration of two different dosage forms.

Study report #: FE992026 DS PHA 0501 - Final and CRO study code: (b) (4)
1475/090

Volume # and page#: Electronic submission

Conducting laboratory and location: (b) (4)

Date of initiation: Date: 22 May 2006

Background: This study was designed to investigate the absorption of desmopressin by orally disintegrating tablet administration to pigs.

Methods:

The absorption of the test article was investigated with a 3-way-cross-over study in six female pigs:

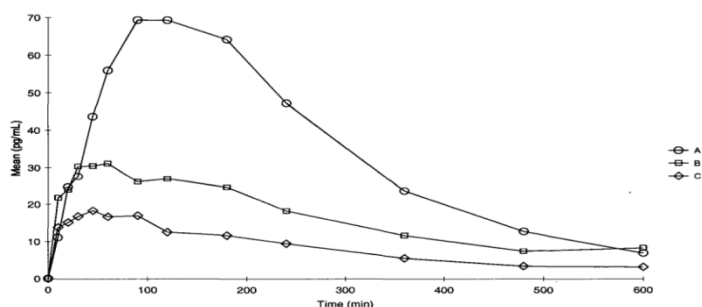
Group A: Minirin (240 mcg) was administered sublingually to anaesthetized pigs (for 2 hours). To prevent swallowing, the esophagus of pigs in this group was occluded using an endotracheal tube.

Group B: Minirin (240 mcg) was administered sublingually to conscious pigs.

Group C: Orally disintegrating tablet (2 x 200 mcg) was administered orally. Blood samples were collected pre dose and at 10, 20, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8 and 10 hours after treatment and analyzed by radioimmunoassay for desmopressin.

Results:

Figure 1. Sponsor's Figure: Mean plasma concentration vs. time curves of desmopressin after administration of orally disintegrating tablet to anaesthetized pigs



Mean plasma concentration vs. time curves of desmopressin after administration of orally disintegrating tablet to anaesthetized pigs with occluded esophagus (A) or conscious pigs with non-occluded esophagus (B) and administration of orally disintegrating tablet to conscious pigs (C).

In Group A (anaesthetized pigs), the plasma level of desmopressin was detected after 10 minutes of treatment, indicating that desmopressin was absorbed sublingually. In this group, C_{max} occurred at 1.93 hrs. In Group B (conscious pigs, passage through the esophagus was not prevented), C_{max} was observed at 0.82 hrs. In Group C, (oral administration) C_{max} occurred at 0.67 hrs. The results showed that desmopressin orally disintegrating tablet increased the absorption compared to desmopressin tablets. When corrected for administered doses, the mean AUC value for Group A was greater than the other group's values. Mean AUC/mcg administrated values were 1.49, 0.67 and 0.20 hr.pg/mL, for Groups A, B, and C, respectively. The prolonged absorption time of the test article in pigs with occluded esophagus is presumed related to the longer time that test article remains in the sublingual cavity.

Conclusion: Results of this study showed that the bioavailability of desmopressin orally disintegrating tablet was several-fold (~2-fold) higher than desmopressin tablets under the conditions of this study.

As reviewed by Parvaneh Espandiari:

Study Title: Desmopressin: Pharmacokinetics and oral bioavailability in the rat and domestic pig

Study report #: FE 992026 DS PHA 03 02; FE 992026 DS PHA 03 03

Volume # and page#: Electronic submission

Conducting laboratory and location: (b) (4)

Date of initiation: 08 July 2004

Background: This study was designed to investigate the oral bioavailability of different doses of desmopressin in rats.

Methods: Desmopressin was administered (i.v. at 0.445 mcg/kg or orally at 20, 50 and 100 mcg/kg) to rats (n=40) and domestic pigs (i.v. at 0.1 mcg/kg or orally at 200 and 500 mcg (n=6). Desmopressin plasma levels were detected by radioimmunoassay up to 480 minutes.

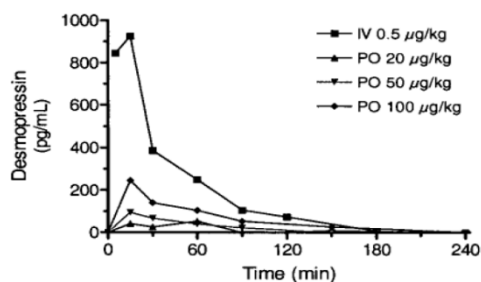
Sponsor's Table: Doses of desmopressin in the rat study

Group	Route	Dose ¹⁾ (µg/kg)	Animal nos.
1	Intravenous	0.445	1-10
2	Oral	20	11-20
3	Oral	50	21-30
4	Oral	100	31-40

Sponsor's Table: Doses of desmopressin in the pig study

Route	Dose ¹⁾
Intravenous	0.1 µg/kg
Oral	200 µg
Oral	500 µg

Figure 2. Sponsor's figure: Plasma levels of Desmopressin in rats after i.v. and p.o. administration:



Mean plasma levels of desmopressin after i.v. and p.o. administration to rats (N= 4 or 5.)

Table 1. Sponsor's table: Mean pharmacokinetic parameters of desmopressin after oral administration to rats (free base)

Dose (ug/kg)	T _{max} (min)	C _{max} (pg/mL)	AUC ₀₋₁₁ (min*pg/mL)	AUC _{0-inf} (min*pg/mL)	AUC ₀₋₂₄ (%)	T _{1/2} (min)	F* (%)
20	60	52.9	3468.2	NA	NA	NA	0.19
50	15	95.1	5114.4	5663.8	21.9	37.3	0.12
100	15	246.8	14169.4	14836.7	12.6	48.5	0.16

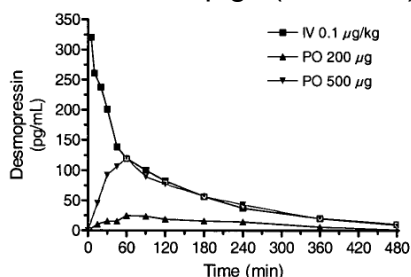
* For 20 ug/kg AUC₀₋₁₁ was used for the calculation of F. For 50 and 100 ug/kg AUC₀₋₂₄ was used for the calculation of F.

Table 2. Sponsor's table: Mean pharmacokinetic parameters of desmopressin after intravenous administration to rats (dose of 0.445 mcg/kg free base)

AUC ₀₋₁₁ (min*pg/mL)	AUC _{0-inf} (min*pg/mL)	AUC ₀₋₂₄ (%)	Cl (mL/min/kg)	λ _z (1/min)	T _{1/2} (min)	V _d (mL/kg)	V _{ss} (mL/kg)
41335.9	41379.8	0.6	10.8	0.0274	25.3	392.0	427.0

In pigs:

Figure 3. Sponsor's figure: Mean plasma levels of Desmopressin after i.v. and p.o. administration to pigs (N=5 or 6):



In pigs:

Table 3. Pharmacokinetic parameters of desmopressin acetate after oral administration to pigs:

Dose	Pig	T _{max} (min)	C _{max} (pg/mL)	AUC ₀₋₁₁ (min*pg/mL)	AUC _{0-inf} (min*pg/mL)	AUC ₀₋₂₄ (%)	T _{1/2} (min)	F (%)
200	1	15	18.5	3663	NA	NA	NA	0.21
	2	60	24.2	4295	NA	NA	NA	NA
	3	90	51.3	9515	NA	NA	NA	0.50
	4	90	20.7	4386	5120	20.9	132.3	0.30
	5	60	33.5	9116	11644	21.7	228.8	0.61
	6	90	20.7	3364	4192	30.7	116.5	0.23
	NObs	6	6	6	6	6	6	5
	Mean	67.5	28.2	5723.0	6985.5	24.4	159.2	0.37
	SD	29.6	12.5	2811.4	4061.2	5.4	60.8	0.18
	Min	15	18.5	3364	4192	20.9	116.5	0.21
	Max	90	51.3	9515	11644	30.7	228.8	0.61
CV%	43.9	44.5	49.1	58.1	22.3	38.2	47.4	
500	1	60	121.0	19679	20905	5.9	113.9	0.55
	3	60	144.0	20420	22685	10.0	137.7	0.54
	4	45	44.2	8537	9783	18.0	142.5	0.28
	5	45	187.0	39760	41891	5.1	113.6	1.15
	6	15	126.0	22084	23515	6.1	111.4	0.65
	NObs	5	5	5	5	5	5	5
	Mean	45.0	124.4	22096.1	23755.7	9.0	123.8	0.63
	SD	18.4	51.8	11230.8	11548.5	5.4	15.0	0.32
	Min	15	44.2	8537	9783	5.1	111.4	0.28
	Max	60	187.0	39760	41891	18.0	142.5	1.15
	CV%	40.8	41.7	50.8	48.6	59.7	12.1	50.9

NA: Not applicable

Table 4. Pharmacokinetic parameters of desmopressin acetate after intravenous administration to pigs (0.1 mcg/kg):

Pig	AUC ₀₋₁₁ (min*pg/mL)	AUC _{inf} (min*pg/mL)	AUC ₀₋₂₄ (%)	Cl (mL/min/kg)	T _{1/2} (min)	λ _z (1/min)	V _z (mL/kg)	V _{ss} (mL/kg)
1	30728	33030	7.0	2.75	126.6	0.0055	502.2	474.7
3	33198	34907	4.9	2.50	109.7	0.0063	396.2	353.2
4	28886	30321	4.7	2.86	102.5	0.0068	423.2	399.2
5	29362	30909	5.0	2.84	113.5	0.0061	465.0	441.7
6	28224	29421	4.1	3.03	110.3	0.0063	481.4	415.8
NObs	5	5	5	5	5	5	5	5
Mean	30079.7	31717.7	5.1	2.80	112.5	0.0062	453.6	416.9
SD	1970.3	2223.4	1.1	0.19	8.9	0.0005	43.2	45.6
Min	28224	29421	4.1	2.50	102.5	0.0055	396.2	353.2
Max	33198	34907	7.0	3.03	126.6	0.0068	502.2	474.7
CV%	6.6	7.0	21.2	6.8	7.9	7.6	9.5	10.9

Results and Discussion:

The PK and bioavailability of the test article were investigated in two species (rat and pig) with different route of administration (i.v. and oral). The bioavailability of desmopressin in rats was close to human values and its elimination was faster than in human. In pigs: bioavailability at 500 mcg was higher than 200 mcg which was higher than in humans; however, the PK of desmopressin after i.v. treatment was close to human values. Results suggested that both models are appropriate for testing oral peptide delivery system for desmopressin.

Table 5. Sponsor's table: Comparative pharmacokinetics of desmopressin in different species.

	Rat	Dog*	Pig	Human**
T _{1/2} (min)	25.3	61.1	112.5	55 min-3.62 h
Clearance (mL/min/kg)	10.8	7.4	2.8	1.7-2.6
V _{ss} (mL/kg)	427	499	417	206-373
T _{max} (min)	15	26	45-68	60-71
F (%)	0.12-0.19	0.83	0.37-0.63	0.1-0.24

Table 6. Sponsor's table: clinical pharmacokinetics of desmopressin orally disintegrating tablet

Parameter	Unit	Desmopressin Melt (200 µg)		Desmopressin Melt (400 µg)		Desmopressin Melt (800 µg)	
		Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI
AUC	hr*pg/mL	64	[52-78]	150	[122-184]	283	[205-389]
AUC _t	hr*pg/mL	47	[36-60]	119	[86-164]	259	[186-362]
C _{max}	pg/mL	14	[11-18]	30	[23-41]	65	[46-92]
t _{max}	hr	1.5 ⁺	0.5-2.0 ⁺⁺	1.0 ⁺	0.75-2.0 ⁺⁺	1.5 ⁺	0.75-2.0 ⁺⁺
t _{1/2}	hr	2.8	27.9 ⁺⁺⁺	3.0	24.7 ⁺⁺⁺	2.9	16.3 ⁺⁺⁺

⁺: median, ⁺⁺: range, ⁺⁺⁺: CV% geo. mean

Discussion and Conclusions

Results suggest the bioavailability of desmopressin orally disintegrating tablet was about 2 fold higher than desmopressin tablets.

Tabulated summary in pigs:

Table 7. Sponsor's table: Absorption in pigs after a single dose

Test Article: Desmopressin
Location in CTD: 4.2.2.2
Study No.: [FE 992026 DS PHA 0501]

Species	Domestic pig			Domestic pig			Domestic pig		
Number of Animals/Gender (M/F)	6 F (Anaesthetised)			6 F (Conscious)			6 F (Conscious)		
Feeding Condition	Overnight fasting			Overnight fasting			Overnight fasting		
Vehicle/Formulation	Orally disintegrating tablet			Orally disintegrating tablet			Tablet		
Method of Administration	Sublingual, oesophagus occluded			Sublingual, oesophagus not occluded			Oral		
Dose ($\mu\text{g}/\text{animal}$)	240			240			2 x 200		
Sample (e.g., whole blood, plasma, serum etc)	Plasma			Plasma			Plasma		
Analyte	Desmopressin			Desmopressin			Desmopressin		
Assay	RIA			RIA			RIA		
PK Parameters:	Mean	SD	N	Mean	SD	N	Mean	SD	N
$T_{\max}$ (h)	1.93	1.18	5	0.82	0.56	6	0.67	0.47	6
$C_{\max}$ (pg/mL)	73.7	54.4	6	37.4	23.2	6	21.2	11.1	6
AUC_{0-4} (h $\times$ pg/mL)	342	242	6	162	96.3	6	80.7	27.5	6
AUC_{0-8} (h $\times$ pg/mL)	442	196	5	276	69.8	2	131	27.8	2
$AUC_{\%Ext}$ (%)	8.90	5.55	5	8.75	1.05	2	15.5	4.63	2
$T_{1/2}$ (h)	2.32	0.380	5	2.24	0.412	2	2.17	0.454	2
AUC/dose	1.49	1.03	6	0.67	0.41	6	0.20	0.07	6

Additional information: RIA : Radioimmunoassay

6 General Toxicology

6.2 Repeat-Dose Toxicity

As reviewed by Parvaneh Espandiari:

Study title: DDAVP Tablets & Desmopressin Orally Disintegrating Tablets (ODT)-1-Month Bridging Toxicity Study in Dogs

Study no.: 72837
 Study report location: (b) (4)
 Conducting laboratory and location: (b) (4)
 Date of study initiation: January 24, 2011
 GLP compliance: yes
 QA statement: yes
 Drug, lot #, and % purity: DDAVP tablets (batch number: BE1891A); orally disintegrating desmopressin tablets (batch number 952458, 95.5%); placebo (batch number 1033643)

Key Study Findings

The values of serum bilirubin were increased in two ODT desmopressin treated females (2/4) with no other-related changes. One of these females had a high bilirubin at baseline.

TK data suggested no sex differences and similarity in level of desmopressin levels for both compounds (2 × 200 mcg DDAVP tablets vs. 1 × 240 mcg desmopressin orally disintegrating tablets).

Methods

Doses:	0 mcg/animal (placebo orally disintegrating tablets); 400 mcg/animal DDAVP (2 tablets of 200 mcg); 240 mcg/animal desmopressin (orally disintegrating tablet)
Frequency of dosing:	daily for at least 28 days
Route of administration:	DDAVP tablets: orally Desmopressin and placebo (orally disintegrating tablets): sublingually
Dose volume:	NA
Formulation/Vehicle:	orally disintegrating placebo tablet
Species/Strain:	Beagle dogs
Number/Sex/Group:	4/sex/group
Age:	6 to 7 months old
Weight:	Males: 6.5 and 9.7 kg; Females: 6.1 and 7.9 kg

Observations and Results

Mortality

Animals were observed for any visible signs of ill health daily.
All animals survived to the end of the study.

Clinical Signs

Animals were observed daily for any visible signs of ill health or behavioral changes.
Results were not remarkable.

Body Weights

Animals were weighed once weekly, including first and last days of the study.
The groups mean body weight gain during the study was comparable across treatment groups.

Feed Consumption

From Day -7 to the end of the study, the consumption of food was estimated daily for each animal by weighing unconsumed diet ~2 hours after feeding.
Results were not remarkable.

Hematology

Blood samples were taken from all fasted overnight animals through jugular vein.

Table 2 Haematology and coagulation parameters

Parameter	Method/Equipment	Unit
Haemoglobin (Hb)	Direct measurement/ABX Pentra DX120SPS	mmol/l
Red blood cell count (RBC)	Direct measurement/ABX Pentra DX120SPS	10 ¹² /l
Reticulocyte count (RETIC)	Direct measurement/ABX Pentra DX120SPS	% and 10 ¹² /l
Haematocrit (HT)	Direct measurement/ABX Pentra DX120SPS	ml/100 ml
Mean cell volume (MCV)	Calculated/ABX Pentra DX120SPS	fl
Mean cell haemoglobin (MCH)	Calculated/ABX Pentra DX120SPS	fmol
Mean cell haemoglobin concentration (MCHC)	Calculated/ABX Pentra DX120SPS	mmol/l
White blood cell count (WBC)	Direct measurement/ABX Pentra DX120SPS	10 ⁹ /l
Differential leucocyte count (NEUTRO, LYMPHO, EOS, BASO, MONO)	Direct measurement/ABX Pentra DX120SPS	% and 10 ⁹ /l
Platelet count (Plt)	Direct measurement/ABX Pentra DX120SPS	10 ⁹ /l
Activated partial thromboplastin time (APTT)	IL Test™/ACL™(*)	sec.
Prothrombin time modified (Pt-m)	Modified IL Test™/ACL™(*)	sec.
Fibrinogen (Fib)	IL Test™/ACL™(*)	g/l

(* Instrumentation Laboratories, Automated Coagulation Laboratory)

Results were not remarkable.

Clinical Chemistry

In females treated with desmopressin, total bilirubin levels significantly increased in 2 females with no other related changes in injury markers for liver or renal.

Table 8. Sponsor’s Table: Total Bilirubin, Means and Standard Deviations in Dogs

GROUP (Dose)	TBILI			
	Mean	S.D.	N	P
1 (Placebo, 0 µg)	<0.95	>0.39	4	
2 (DDAVP, 400 µg)	1.08	0.35	4	
3 (Desmopressin, 240 µg)	1.85	0.47	4 *	

Table 9. Sponsor’s Table: Total Bilirubin, Individual Values in Dogs

Individual values	Females		
	ANIMAL NO	Before start	At termination
		TBILI	TBILI
1 (Placebo, 0 µg)	5	(b) (4)	(b) (4)
	6		
	7		
	8		
2 (DDAVP, 400 µg)	13		
	14		
	15		
	16		
3 (Desmopressin, 240 µg)	21		
	22		
	23		
	24		

In desmopressin treated females, serum levels of bilirubin were normal in 2/4 and high in 2/4. One of the two females with elevated bilirubin had a baseline elevation prior to drug exposure. The higher serum levels of bilirubin in these two animals were not related to the higher level of exposure of compound. In this study, females had a higher level of exposure because they had lower mean body weights compared to males. However, drug exposure was variable in this study. The elevated serum bilirubin in high dose female dogs given desmopressin ODT appears to be incidental because:

1. It occurred in 1/4 female dogs given desmopressin ODT at 240 mcg but not with DDAVP tablets at 400 mcg of either gender despite similar AUC values across dosage forms. One of the 2 female dogs with the bilirubin elevation has a high background total bilirubin at baseline. This observation occurs at 240 mcg after 28 days in a female dogs which has systemic exposure >20X higher than anticipated at the MRHD=50 mcg
2. Parameters that were evaluated in the bridging dog toxicology study, including TK were quite variable (limited animal numbers n=4)
3. In the 13 week rat study, the qualitative increase in conjugated bilirubin in urine was observed in some males (4) and one female rat given SC desmopressin; however, there were no elevations in unconjugated bilirubin (plasma) in this study
4. Neither the dog or rat toxicity study showed any correlative histopathology (bile duct/liver), transaminase elevations or hematology parameters (hemolysis/anemia)

Table 10. Sponsor's Table: Total Bilirubin in the 13-Week Rat Study

Males TBILL															
ANIMAL Before termination															
GROUP (Dose)	NO	Day 1		Day 28		Day 1		Day 28		Day 1		Day 28			
		<LOD	<LOD	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (hr*pg/ml)	Loss correlated AUC _{0-∞} ¹	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (hr*pg/ml)	Loss correlated AUC _{0-∞} ¹
1 (Placebo, 0 µg)	1	<LOD	<LOD												
	102	<LOD	0.7												
	3	0.7	1.0												
	4	0.5	0.8												
2 (DDAVP, 400 µg)	9	0.9	1.4	9	675	0.5	1.20	1,041	990	9	324	0.5	1.33 ²	648	672
	10	<LOD	1.1	10	54.8	0.5	1.19 ²	107	118	10	344	1.0	1.01 ³	544	618
	11	0.8	0.9	11	251	1.0	1.16	387	353	11	122	1.0	1.28 ³	255	258
	12	<LOD	0.6	12	121	1.0	0.89 ²	218	205	12	281	0.5	1.31 ³	418	434
3 (Desmopressin, 240 µg)	17	1.4	1.0	17	242	0.5	1.25 ²	386	723	17	300	0.5	1.15 ³	489	966
	18	1.0	0.5	18	257	0.5	1.14 ³	450	694	18	252	0.5	1.18 ³	407	695
	19	0.5	1.0	19	392	0.5	1.46 ³	875	1,222	19	313	1.0	1.34 ³	701	1,007
	20	0.5	0.5	20	118	0.5	1.57 ³	393	777	20	103	2.0	1.18 ³	247	504

Females TBILL															
ANIMAL Before termination															
GROUP (Dose)	NO	Day 1		Day 28		Day 1		Day 28		Day 1		Day 28			
		<LOD	<LOD	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (hr*pg/ml)	Loss correlated AUC _{0-∞} ¹	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (hr*pg/ml)	Loss correlated AUC _{0-∞} ¹
1 (Placebo, 0 µg)	5	0.8	1.1												
	6	1.2	0.8												
	7	0.8	<LOD												
	8	0.6	1.4												
2 (DDAVP, 400 µg)	13	0.7	1.2	13	160	0.5	1.42	241	190	13	150	0.5	0.89 ⁴	231	179
	14	1.4	1.5	14	110	1.0	0.84 ²	218	221	14	656	0.5	1.23 ³	892	959
	15	0.8	0.7	15	533	0.5	0.94	798	789	15	246	0.5	0.93 ²	262	262
	16	0.6	0.9	16	376	0.5	1.16	540	446	16	283	0.5	1.46 ³	384	336
3 (Desmopressin, 240 µg)	21	1.6	2.2	21	176	0.5	0.84 ²	288	414	21	661	0.5	1.19 ²	944	1,457
	22	0.9	2.3	22	96.5	0.5	0.98 ²	144	207	22	180	0.5	1.11 ³	422	634
	23	0.9	1.5	23	143	0.5	1.15 ²	180	278	23	226	1.0	1.09 ³	389	640
	24	1.4	1.4	24	371	1.0	0.98 ³	593	901	24	241	0.5	1.31 ³	403	654

Urinalysis

Urine samples were collected from all animals (housed individually in metal cages) for a period of 18 hours (±30 minutes) from early afternoon to the following morning.

Sponsor's Table: Urinalysis Parameters

Parameter	Method/Equipment	Unit/Range
Volume		ml
Specific gravity (SG)	Ames Multistix 10SG/Clinitek 500	No unit
pH	Ames Multistix 10SG/Clinitek 500	No unit
Colour (COLOUR)	Visual examination	No unit
Protein (PROTEIN)	Ames Multistix 10SG/Clinitek 500	g/l
Leucocytes (LEUC)	Ames Multistix 10SG/Clinitek 500	Cells/ μ l
Nitrite (NITRITE)	Ames Multistix 10SG/Clinitek 500	No unit
Blood (BLOOD)	Ames Multistix 10SG/Clinitek 500	Erythrocytes/ μ l
Glucose (GLUCOSE)	Ames Multistix 10SG/Clinitek 500	mmol/l
Ketones (KETONES)	Ames Multistix 10SG/Clinitek 500	mmol/l
Bilirubin (BILI)	Ames Multistix 10SG/Clinitek 500	No unit
Urobilinogen (UROBIL)	Ames Multistix 10SG/Clinitek 500	μ mol/l

Decreased urinary volume was noted in treated animals compared to control animals (more pronounced in Desmopressin treated animals compared to DDAVP treated animals). The sponsor reported that no statistical analysis was performed for the urine volume due to small number of animals in the control group (n=2). No significant differences were noted for other urinary parameters.

Table 11. Sponsor's Table: Urine Volumes in Male Dogs

Before start of treatment		Males				At termination of treatment			
GROUP (Dose)	VOLUME				GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p		MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	78.7	85.2	3		1 (Placebo, 0 μ g)	128.5	14.8	2	
2 (DDAVP, 400 μ g)	83.5	65.9	4		2 (DDAVP, 400 μ g)	120.5	80.9	4	
3 (Desmopressin, 240 μ g)	63.8	68.1	4		3 (Desmopressin, 240 μ g)	104.8	59.0	4	

Group mean values Statistical group test not valid for groups with N<3

Table 12. Sponsor's Table: Urine Volumes in Female Dogs

Before start of treatment		Females				At termination of treatment			
GROUP (Dose)	VOLUME				GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p		MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	59.5	39.6	4		1 (Placebo, 0 μ g)	115.0	7.1	2	
2 (DDAVP, 400 μ g)	59.5	35.4	4		2 (DDAVP, 400 μ g)	103.8	30.5	4	
3 (Desmopressin, 240 μ g)	29.3	26.8	4		3 (Desmopressin, 240 μ g)	47.5	41.2	4	

Group mean values Statistical group test not valid for groups with N<3

No significant changes were reported with levels of the urinary bilirubin in females.

Table 13. Sponsor's Table: Urinary Bilirubin in Dogs

Before start of treatment				At termination of treatment					
GROUP (Dose)	BILIRUBIN			p	GROUP (Dose)	BILIRUBIN			p
	No trace	Total				No trace	Small amounts	Total	
1 (Placebo, 0 µg)		4	4		1 (Placebo, 0 µg)	4	0	4	
2 (DDAVP, 400 µg)		4	4		2 (DDAVP, 400 µg)	4	0	4	
3 (Desmopressin, 240 µg)		4	4		3 (Desmopressin, 240 µg)	3	1	4	
Total		12	12		Total	11	1	12	

Gross Pathology

Necropsy was performed on all animals and all macroscopic evaluation was reported. No remarkable differences were reported.

Organ Weights

On the day of necropsy, all animal total body weights as well as weights of organs/tissues were recorded. In addition, paired organs were weighed together. The only significant changes were reported in desmopressin treated males for spleens. In this group, the spleen relative weight (% of body weight) were lower (ss) compared to control animals (with no other related changes).

Table 14. Sponsor's Table: Absolute (g) and Relative (% of Body Weight and Brain Weight) Organ Weights

Males

GROUP (Dose)	SPLEEN				SPLEEN				SPLEEN			
	ABSOLUTE				% of BODY WT				% OF BRAIN WT			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1 (Placebo, 0 µg)	50.65	13.83	4		0.572	0.124	4		64.2	13.0	4	
2 (DDAVP, 400 µg)	43.31	10.45	4		0.501	0.115	4		56.8	15.7	4	
3 (Desmopressin, 240 µg)	30.89	7.30	4		0.355	0.058	4	*	41.1	9.5	4	

* means p<0.05, versus control group

Histopathology

Adequate Battery: yes

Peer Review: yes

Histological Findings

All tissues were fixed in phosphate buffered neutral 4% formaldehyde with the exception of the eyes and testes (Modified Davidson's fixative). The lungs were infused with fixative at necropsy. Histological alterations were graded on a 5-grade system as follows: Grade 1-Minimal/Very few/Very small; Grade 2-Slight/Few/Small; Grade 3 Moderate/ Moderate number/Moderate size; Grade 4-Marked/Many/Large; Grade 5-Massive/Extensive number/Extensive size.

Sponsor's Table: Organs/Tissues Evaluated

Organs and tissues	W e i g h	F i x	M i c r o	Organs and tissues	W e i g h	F i x	M i c r o
Abnormalities (gross lesions)		x	x	Pancreas		x	x
Adrenals	x	x	x	Pituitary	x	x	x
Aorta (thoracic)		x	x	Prostate	x	x	x
Brain	x	x	x	Salivary gland (right parotid, sublingual and submandibular)		x	x
Bone marrow smear		x		Sciatic nerve		x	x
Bones (medial condyl of right femur)		x	x	Skeletal muscle		x	x
Epididymides		x	x	Skin		x	x
Eyes with lens/optic nerve		x	x	Spinal cord (thoracic, lumbar)		x	x
Gall bladder		x	x	Spleen	x	x	x
Heart with aortic arch	x	x	x	Sternum (for bone marrow)		x	x
Intestine small (duodenum, jejunum, ileum)		x	x	Stomach		x	x
Intestine large (caecum, colon, rectum)		x	x	Testes	x	x	x
Joint (knee)		x	x	Thymus	x	x	x
Kidneys	x	x	x	Thyroid (incl. parathyroids)	x	x	x
Larynx		x	x	Tongue		x	x
Liver (all main lobes)	x	x	x	Trachea		x	x
Lungs (cranial and caudal lobes, both sides)		x	x	Ureters		x	x
Lymph nodes (right mandibular and mesenteric)		x	x	Urinary bladder		x	x
Mammary gland		x	x	Uterus (horn, cervix and oviducts)	x	x	x
Oesophagus		x	x	Vagina		x	x
Ovaries	x	x	x				

Treatment-related findings were reported in all dose groups (more incidences in the RLD treated groups). According to the Sponsor, these changes were well known as incidental background changes in laboratory Beagle dogs of this age (historical control data was not submitted).

Table 15. Histopathology in dogs

ORGAN/FINDING	DOSE GROUP:	01		02		03	
		SEX: M	F	M	F	M	F
:	ANIM.EXAM.:	4	4	4	4	4	4
LARGE INTESTINE	:	-	-	-	1	-	-
- nodule	:	-	-	-	1	-	-
HEART	:	4	4	4	4	4	4
- Mononucl cells focal	:	1	-	-	-	-	-
Grade 1:	:	1	-	-	-	-	-
AORTA	:	4	4	4	4	4	4
- Mineralisation focal	:	-	-	-	-	1	-
Grade 2:	:	-	-	-	-	1	-
LUNG	:	4	4	4	4	4	4
- Subpl fibr/alv metap	:	-	1	-	1	-	-
Grade 1:	:	-	-	-	1	-	-
Grade 2:	:	-	1	-	-	-	-
- Inflam cells focal	:	2	4	1	2	2	2
Grade 1:	:	2	4	-	1	2	2
Grade 2:	:	-	-	1	1	-	-
- Macrophages alveolar	:	2	1	3	2	1	1
Grade 1:	:	2	1	3	2	1	1

ORGAN/FINDING	DOSE GROUP:	01		02		03	
		SEX: M	F	M	F	M	F
:	ANIM.EXAM.:	4	4	4	4	4	4
TONGUE	:	4	4	4	4	4	4
- Ulceration focal	:	-	-	-	-	-	1
Grade 1:	:	-	-	-	-	-	1
- Mononucl cells focal	:	-	-	1	-	-	-
Grade 1:	:	-	-	1	-	-	-
CECUM	:	4	4	4	4	4	4
- Inflammation multifo	:	-	-	-	1	-	-
Grade 3:	:	-	-	-	1	-	-
LIVER	:	4	4	4	4	4	4
- EMH/mononucl cells	:	1	1	2	1	2	-
Grade 1:	:	1	1	2	1	2	-
PANCREAS	:	4	4	4	4	4	4
- Atrophy exocrine	:	1	-	2	-	-	-
Grade 1:	:	-	-	1	-	-	-
Grade 2:	:	1	-	-	-	-	-
Grade 3:	:	-	-	1	-	-	-
KIDNEYS	:	4	4	4	4	4	4
- Basophilic tubules	:	-	-	2	-	1	-
Grade 1:	:	-	-	2	-	1	-
- Hyaline casts focal	:	-	-	-	1	-	-
Grade 1:	:	-	-	-	1	-	-

CODES AND SYMBOLS USED AT FINDING LEVEL:

 GRADE 1 = Minimal / very few / very small
 GRADE 2 = Slight / few / small
 GRADE 3 = Moderate / moderate number / moderate size
 (= Finding unilateral in paired organs
 * = Comment in text of individual animal data

Toxicokinetics

Blood samples were taken on Day 1 and Day 28, from all animals at different time points: Pre-treatment, and 30 min, 1, 2, 4, 6, and 8 hours.

TK data are summarized below:

Table 16. Toxicokinetics in Dogs

Summary of average toxicokinetic parameters after dosing of male and female dogs for 1 and 28 days with desmopressin

Group	Day		Dose (ug/animal)	Rsq	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} ¹ (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF}	AUC _{%Extrap} (%)	AUC _{0-8hr} (hr*pg/ml)	Dose correlated AUC _{0-8hr}	Cl _F (ml/hr/kg)	Vz _F (ml/kg)	Lambda _z (1/hr)	R _{acc}	R _A
2	1	N	400	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		0.99	285	0.7	1.10	444	414	1.24	440	410	191,309	307,461	0.65		
		Sd		0.00	223	0.3	0.19	328	315	0.89	326	313	125,225	224,278	0.12		
		CV%		0.47	78.34	37.64	17.69	73.82	76.21	72.14	73.94	76.35	65.46	72.95	18.18		
2	28	N	400	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		1.00	301	0.6	1.18	454	465	1.04	450	461	141,981	232,339	0.61	1.00	1.80
		Sd		0.00	163	0.2	0.21	230	266	0.29	227	263	76,696	106,890	0.11	0.00	1.80
		CV%		0.46	54.34	37.03	17.71	50.61	57.15	27.67	50.49	57.06	54.02	46.01	18.70	0.00	100.45
3	1	N	240	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		0.99	224	0.6	1.17	414	652	1.50	409	644	105,570	167,796	0.61		
		Sd		0.01	112	0.2	0.25	236	339	0.92	232	332	70,930	98,160	0.13		
		CV%		0.71	49.84	31.43	21.23	57.11	51.99	61.23	56.71	51.55	67.19	58.50	20.87		
3	28	N	240	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		1.00	285	0.8	1.19	500	820	0.99	495	811	67,581	115,629	0.58	1.00	1.58
		Sd		0.00	166	0.5	0.09	220	310	0.38	218	307	20,798	34,561	0.04	0.00	1.06
		CV%		0.46	58.37	65.27	7.42	43.93	37.81	38.05	43.94	37.90	30.77	29.89	7.03	0.00	67.27

¹ Average T_{1/2} is based on both T_{1/2} calculation intervals

Females were exposed to the higher level of compounds due the lower mean body weights (400 mcg of DDAVP in males was ~47-51 mcg/kg/day and in females ~53-56 mcg/kg/day; and 240 mcg of desmopressin was ~28-29 mcg/kg/day in males and ~32-34 mcg/kg/day in females). According to the sponsor, the human bioavailabilities of desmopressin were used for adjusting the anticipated exposure, which, for the tablets was ~0.15%, and in the orally disintegrating tablet was ~0.25%. In dogs, the bioavailability of desmopressin for DDAVP tablets was ~0.85% and for the desmopressin orally disintegrating tablet was not known.

Dosing Solution Analysis

The LC-MS/MS method was used to analyze desmopressin in dog plasma (K3EDTA). Results were reproducible (28 or 82.4% out of 34 repeat analyses) and met acceptance criteria.

As reviewed by Parvaneh Espandiari:

Study title: Oral Irritation in the Syrian Hamster

Study no.: 52338 (b) (4) ;

Ferring Ref. No: FE992026DSTOX0301

Study report location: (b) (4)

Conducting laboratory and location: (b) (4)

Date of study initiation: 08 January 2004

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: 23006FBG; sum of impurity 0.4%

Background: The study was conducted for 28 days in Syrian Hamsters (10/sex, 1 application/ day) to determine the local reaction of desmopressin orally disintegrating tablet

Key Study Findings

Oral lyophilisates containing 360 mcg desmopressin or placebo (both packed in oil) showed similar effects when administered to the cheek pouches of Syrian hamsters daily for 28 days. Results showed no cheek pouch irritation after 28 days with the test article.

The test article and placebo were treated in the cheek pouch of each animal in different groups: The animals were treated as follows:

Animal No	Sex	Group No	Treatment	Colour code
1 - 3	M	1	Untreated	White
4 - 6	F			
7 - 9	M	2	Placebo	Blue
10 - 12	F			
13 - 16	M	3	Test article	Green
17 - 20	F			

The pouches were examined macroscopically and microscopically were graded as:

Reaction	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4

The microscopic findings were graded according to the following system:

Reaction	Numerical grading
1. Epithelium	
Normal, intact	0
Cell degeneration or flattening	1
Metaplasia	2
Focal erosion	3
Generalised erosion	4
2. Leucocyte infiltration (per high power field)	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked	4
3. Vascular congestion	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked, with disruption of vessels	4
4. Oedema	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked	4

The test article was classified by the five response categories in the table below:

Irritation Index	
0	None
1 to 4	Minimal
5 to 8	Mild
9 to 11	Moderate
12 to 16	Severe

Observations and Results

Results:

In general, there were no microscopic findings in any group (averages were 0).

Sponsor's summary:

Clinical signs and body weight gain

Animal No 3 had a wound on the nose from Day 15 to Day 29. Animal No 11 had a wound on the neck from Day 4 to Day 15, probably due to the collar; from Day 15 until termination on Day 29 the skin was red, but intact. Animal No 12 had a wound on the neck from Day 2 to Day 11, probably due to the collar. Animal No 19 had oedema in both cheek pouches from Day -5 to -3. No other abnormalities were observed during the study period. All animals had normal and similar body weight gain during the study period.

Table 17. Sponsor’s Table: Body Weights in Hamsters

FE992026
ORAL IRRITATION TEST IN
THE SYRIAN HAMSTER
Individual body weight(g)
All groups (untreated, placebo and test article group)

Animal No	Sex	Day -11	Day -6	Day -5	Day -4	Day -3	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Weight gain (Day -11 to 29)
1	M	(b) (4)											
2	M												
3	M												
4	F												
5	F												
6	F												
7	M												
8	M												
9	M												
10	F												
11	F												
12	F												
13	M												
14	M												
15	M												
16	M												
17	F												
18	F												
19	F												
20	F												

Table 18. Sponsor’s Tables: Macroscopic Findings in Hamsters

The average of macroscopic scores were 0.1 for males and 0.0 for females for control groups (untreated and placebo groups). For the test article treated groups, the average macroscopic scores were 0.1 for males and 0.1 for females. For the recovery animals, on Day 36, only the female hamster showed very slight erythema.

ORAL IRRITATION TEST IN
THE SYRIAN HAMSTER
Macroscopic findings. Scores for erythema – Untreated group (colour code: white)

Animal No	Sex	Treatment	Check Pouch	Mean Score	Left - right	Group Average
1	Male	Untreated	Left	0.1	0.1	0.1
			Right	0.0		
2			Left	0.2	0.2	
			Right	0.0		
3			Left	0.0	0.0	
			Right	0.0		
4	Female	Untreated	Left	0.0	0.0	0.0
			Right	0.0		
5			Left	0.0	0.0	
			Right	0.0		
6			Left	0.2	-0.1	
			Right	0.3		

Animal No	Sex	Treatment	Cheek Pouch	Mean Score	Left - right	Group Average
7	Male	Placebo	Left	0.0	0.0	0.1
			Right	0.0		
8			Left	0.1	0.1	
			Right	0.0		
9			Left	0.2	0.1	
			Right	0.1		
10	Female	Placebo	Left	0.1	-0.1	0.0
			Right	0.2		
11			Left	0.0	0.0	
			Right	0.0		
12			Left	0.3	0.1	
			Right	0.2		

Macroscopic findings. Scores for erythema– Test article group (colour code: green)

Animal No	Sex	Treatment	Cheek Pouch	Mean Score	Left - right	Group Average
13	Male	Test article	Left	0.1	0.1	0.1
			Right	0.0		
14			Left	0.1	0.1	
			Right	0.0		
15			Left	0.2	0.1	
			Right	0.1		
16	Left	0.1	-0.1			
	Right	0.2				
17	Female	Test article	Left	0.1	0.1	0.1
			Right	0.0		
18			Left	0.2	0.1	
			Right	0.1		
19			Left	0.4	0.2	
			Right	0.2		
20	Left	0.1	0.1			
	Right	0.0				

Recovery score Day 36		
Animal No	Cheek pouch	Day 36 Score before termination
13	Left	0
	Right	0
20	Left	1
	Right	0

Table 19. Sponsor's Table: Microscopic Findings in Hamsters

FE992026

ORAL IRRITATION TEST IN
THE SYRIAN HAMSTER

Grading of Microscopic Findings for Oral Irritation Studies

Group No. 1 - Untreated

Reaction	Animal No 1		2		3		4		5		6	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Epithelium	0	0	0	0	0	0	0	0	0	0	0	0
Leucocyte infiltration	0	0	0	0	0	0	0	0	0	0	0	0
Vascular congestion	0	0	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0	0	0
Individual Primary Irritation Index	0		0		0		0		0		0	

Group No. 2 - Placebo

Reaction	Animal No 7		8		9		10		11		12	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Epithelium	0	0	0	0	0	0	0	0	0	0	0	0
Leucocyte infiltration	0	0	0	0	0	0	0	0	0	0	0	0
Vascular congestion	0	0	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0	0	0
Individual Primary Irritation Index	0		0		0		0		0		0	

Group No. 3 - Test article

Reaction	Animal No 14		15		16		17		18		19	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Epithelium	0	0	0	0	0	0	0	0	0	0	0	0
Leucocyte infiltration	0	0	0	0	0	0	0	0	0	0	0	0
Vascular congestion	0	0	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0	0	0
Individual Primary Irritation Index	0		0		0		0		0		0	

Recovery animals

Reaction	Animal No 13		20	
	Left	Right	Left	Right
Epithelium	0	1	0	0
Leucocyte infiltration	0	2	0	0
Vascular congestion	0	0	0	0
Oedema	0	0	0	0
Individual Primary Irritation Index	- 3		0	

Conclusion:

There were no significant differences in the average macroscopic scores for treated animals compared to control animals (average of 1 for all treated animals and 0.1 for males and 0.0 for females in control animals). Results showed no local reactions with desmopressin after 28 days suggesting the test article is safe to use sublingually.

As reviewed by Parvaneh Espandiari:

Study title: 13 -week Subcutaneous Toxicity Study in Rats

Study no.: (b) (4) : 58881 and Ferring Ref No: FE992026DSTOX0501

Study report location: (b) (4)

Conducting laboratory and location: (b) (4)

Date of study initiation: 20 March 2006

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: Batch#: CRS-MIX-Desmopressin-2005:1; 102% of label claim (the test article was spiked with 3 impurities: ([Glu4] desmopressin, Gly9- OH] desmopressin, and [βAsp5] desmopressin, at concentrations of (b) (4) %, respectively).

Background:

The toxicity of desmopressin 3 impurities ([Glu4]desmopressin, [Gly9-OH]desmopressin and [βAsp5]desmopressin at a level of (b) (4) % for each impurity) was investigated by daily subcutaneous injection in 13 week rat study.

Key Study Findings

Significant pharmacological changes in urine samples were noted in all treated animals at the high dose (females and males) (Decreased volume, reduced pH and higher concentrations of sodium, potassium and chloride, specific gravity and protein concentration. In addition, the urinary color was darker in high dose female rats.

At all dose levels, absolute and relative kidney weights increased with no macroscopic findings (significant at MD and HD with relative kidney weights).

Histopathology showed an increased incidence of cystic/cleft-like spaces and granulomatous inflammation at sc injection site in all treated males and at HD with females (not clinically relevant to clinical sublingual route).

NOAEL= 10 mcg/kg/day (the high dose)

Reviewer: *The purpose of this study was to evaluate the toxicological profile of desmopressin with 3 impurities ([Glu4]desmopressin,[Gly9-OH]desmopressin and [βAsp5]desmopressin at a level of (b) (4) % for each impurity) by daily s.c. for 13 weeks in rats. In general the toxicological profile is similar to desmopressin, suggesting no significant effect of 3 impurities at tested concentration levels. The incidences of cystic/cleft-like spaces and granulomatous inflammation at sc injection site are not clinically relevant since the test article is proposed for sublingual formulation for marketing and there was no irritation sublingually in the local irritation in hamster study. Findings were attributed to the pharmacological effect of the test article and were not*

considered to be adverse. Based on the ICH Q3A Guidance for Industry for impurities, the sponsor performed this study as one of the requirements for qualification of impurities. Results of this study showed no safety concerns. However, the TK data of this study were not presented; therefore, there is not sufficient data with this study to bridge to the clinical exposure or to determine therapeutic dose safety margins.

Methods

Doses: Control vehicle or 0.1, 1.0, 10.0 mcg desmopressin/kg/day
 Route of administration: subcutaneous
 Dose volume: 1 ml/kg
 Species/Strain: SD rats / (b) (4)
 Number/Sex/Group: 10/sex/group
 Age: 5 weeks old
 Weight: Males: 103-135 g; females; 103-129 g

Observations and Results

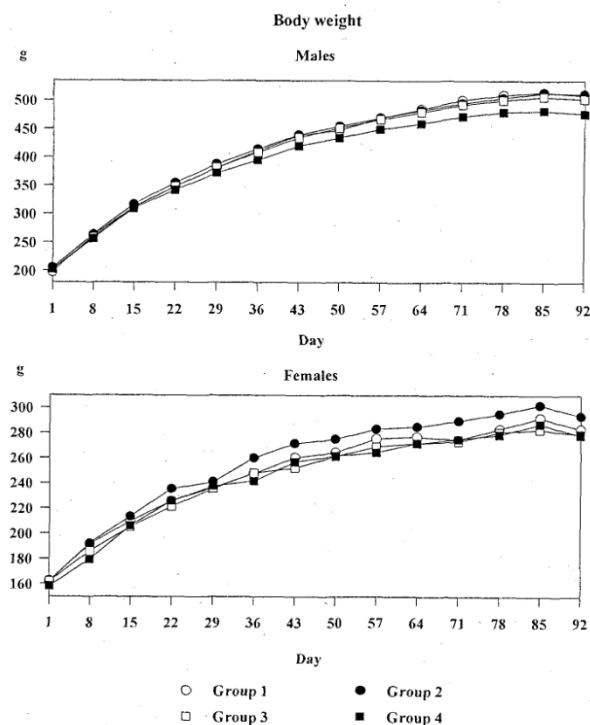
Mortality/ Clinical Signs

Not remarkable

Body Weights

No significant changes were detected in mean body weight or mean body weight gain in treated animals to control animals.

Figure 4. Sponsor's Figure: Body Weights in Rats



Feed Consumption

Not remarkable

Hematology

Table 19. Hematology Parameters in Rats

In males: Platelets were significantly decreased only in the LD treated males.

Males

GROUP	Hb				RBC				HT				MCV				MCH			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	9.60	0.28	10		9.14	0.33	10		47.4	1.7	10		52.0	1.2	10		1.06	0.05	10	
2	9.47	0.33	10		9.24	0.37	10		47.1	2.1	10		50.8	2.2	10		1.03	0.07	10	
3	9.48	0.37	10		9.11	0.33	10		46.9	1.7	10		51.4	1.2	10		1.04	0.05	10	
4	9.67	0.34	10		9.21	0.33	10		47.7	1.8	10		51.8	1.1	10		1.07	0.05	10	

GROUP	MCHC				WBC				% NEUTRO				NEUTRO				% LYMPHO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	20.2	0.2	10		14.80	2.27	10		5.3	2.9	10		0.81	0.47	10		93.6	3.0	10	
2	20.2	0.2	10		14.03	2.43	10		8.1	4.2	10		1.11	0.65	10		90.5	4.5	10	
3	20.3	0.2	10		13.57	2.55	10		6.2	3.0	10		0.80	0.29	10		91.4	4.0	10	
4	20.3	0.2	10		14.79	2.83	10		4.7	2.5	10		0.71	0.42	10		94.3	2.3	10	

Males

GROUP	LYMPHO				% EOS				EOS				% BASO				BASO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	13.83	2.09	10		0.5	0.7	10		0.06	0.10	10		0.0	0.0	10		0.00	0.00	10	
2	12.71	2.40	10		0.8	0.9	10		0.11	0.14	10		0.0	0.0	10		0.00	0.00	10	
3	12.48	2.76	10		1.4	1.3	10		0.17	0.16	10		0.0	0.0	10		0.00	0.00	10	
4	13.91	2.60	10		0.7	0.8	10		0.11	0.14	10		0.0	0.0	10		0.00	0.00	10	

GROUP	% MONO				MONO				Plt				APTT				Pt			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	0.6	0.7	10		0.09	0.11	10		579	43	10		17.6	3.8	10		15.4	0.6	10	
2	0.6	0.5	10		0.08	0.08	10		495	73	10	*	18.8	5.2	9		15.5	0.6	9	
3	1.0	0.9	10		0.12	0.12	10		515	79	10		20.1	5.9	10		15.3	0.8	10	
4	0.3	0.5	10		0.06	0.10	10		514	43	10		16.2	3.3	10		15.3	0.5	10	

Males

GROUP	FIB			
	Mean	S.D.	N	p
1	3.21	0.36	10	
2	3.26	0.37	9	
3	2.83	0.87	10	
4	3.34	0.31	10	

In Females: No changes were observed.

females

GROUP	Hb				RBC				HT				MCV				MCH			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	9.29	0.41	10		8.47	0.41	10		45.5	2.4	10		53.8	1.3	10		1.10	0.00	10	
2	9.11	0.20	10		8.51	0.30	10		44.6	1.2	10		52.7	1.4	10		1.08	0.04	10	
3	9.32	0.48	10		8.44	0.50	10		45.4	2.7	10		53.9	2.0	10		1.11	0.03	10	
4	9.18	0.32	10		8.47	0.23	10		45.1	1.5	10		53.2	0.9	10		1.10	0.00	10	

GROUP	MCHC				WBC				% NEUTRO				NEUTRO				% LYMPHO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	20.4	0.3	10		12.39	2.88	10		8.0	4.6	10		0.98	0.58	10		90.2	5.3	10	
2	20.4	0.2	10		11.84	1.57	10		8.1	3.7	10		0.95	0.41	10		90.2	4.5	10	
3	20.5	0.2	10		12.39	2.55	10		7.7	5.0	10		0.93	0.63	10		91.2	5.3	10	
4	20.5	0.2	10		11.97	1.79	10		6.6	3.2	10		0.78	0.41	10		92.1	3.4	10	

Females

GROUP	LYMPHO				% EOS				EOS				% BASO				BASO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	11.20	2.74	10		1.5	1.6	10		0.18	0.21	10		0.0	0.0	10		0.00	0.00	10	
2	10.70	1.70	10		1.5	1.6	10		0.18	0.19	10		0.0	0.0	10		0.00	0.00	10	
3	11.32	2.61	10		1.0	0.9	10		0.12	0.12	10		0.0	0.0	10		0.00	0.00	10	
4	11.04	1.74	10		1.0	0.7	10		0.12	0.10	10		0.0	0.0	10		0.00	0.00	10	

GROUP	% MONO				MONO				Pit				APTT				Pt			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	0.3	0.7	10		0.04	0.08	10		532	97	10		14.5	2.2	10		14.5	0.6	10	
2	0.2	0.4	10		0.02	0.04	10		511	95	10		14.9	5.5	10		15.9	3.0	10	
3	0.1	0.3	10		0.01	0.03	10		535	78	10		14.6	3.1	10		14.7	0.3	10	
4	0.3	0.5	10		0.03	0.05	10		519	61	10		15.1	2.2	10		14.9	0.8	10	

Females

GROUP	FIB			
	Mean	S.D.	N	p
1	2.54	0.18	10	
2	2.49	0.38	10	
3	2.34	0.26	10	
4	2.30	0.35	10	

Clinical Chemistry

Table 20. Clinical Chemistry Parameters in Rats

In males: The levels of magnesium were significantly decreased only in the HD animals.

Males

GROUP	ALAT				ASAT				ALKPH				BILI				GGT			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	1.72	0.25	10		1.53	0.24	10		2.72	0.51	10		1.45	0.66	10		0.00	0.01	10	
2	1.72	0.25	10		1.59	0.25	10		2.55	0.25	10		1.11	0.66	10		0.01	0.01	10	
3	1.78	0.31	10		1.68	0.32	10		2.69	0.45	10		1.11	0.32	10		0.01	0.01	10	
4	1.73	0.36	10		1.54	0.27	10		2.74	0.47	10		1.16	0.52	10		0.01	0.00	10	

GROUP	CHOL				TRIG				UREA				CREAT				GLUC			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	2.95	0.46	10		1.91	0.54	10		7.19	0.94	10		30.1	3.7	10		9.15	2.34	10	
2	2.87	0.28	10		2.12	0.56	10		7.27	0.99	10		32.0	5.9	10		9.41	3.18	10	
3	2.82	0.38	10		2.24	0.82	10		7.08	0.60	10		32.9	9.5	10		10.27	3.20	10	
4	2.99	0.43	10		2.04	0.69	10		7.77	0.52	10		32.5	7.1	10		7.55	0.97	10	

GROUP	Na				K				Ca				Mg				P			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	154.6	3.6	10		6.58	0.87	10		3.16	0.15	10		1.20	0.09	10		3.08	0.24	10	
2	154.7	2.5	10		6.27	0.69	10		3.07	0.24	10		1.11	0.16	10		3.01	0.40	10	
3	155.2	3.6	10		6.27	0.63	10		3.11	0.18	10		1.20	0.16	10		3.07	0.45	10	
4	155.7	3.4	10		6.47	0.61	10		3.10	0.09	10		1.09	0.07	10	**	2.78	0.41	10	

GROUP	Cl				PROTEIN				ALB				GLOBULIN				ALB/G Ratio			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	107.2	3.0	10		72.4	3.3	10		44.2	2.6	10		28.2	2.0	10		1.57	0.14	10	
2	107.4	1.2	10		71.2	4.7	10		43.1	2.1	10		28.1	3.4	10		1.55	0.15	10	
3	107.5	2.8	10		72.6	3.6	10		43.8	1.4	10		28.8	2.7	10		1.53	0.12	10	
4	107.6	2.9	10		71.3	2.1	10		43.4	2.7	10		27.9	2.5	10		1.57	0.23	10	

In Females: no changes were noted.

Females

GROUP	ALAT				ASAT				ALKPH				BILI				GGT			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	1.18	0.26	10		1.53	0.21	10		2.06	0.48	10		1.77	0.48	10		0.01	0.01	10	
2	1.45	0.33	10		1.72	0.29	10		2.16	0.42	10		1.23	0.63	10		0.01	0.01	10	
3	1.38	0.22	10		1.66	0.24	10		2.10	0.47	10		1.56	0.65	10		0.01	0.01	10	
4	1.27	0.25	10		1.62	0.21	10		1.78	0.14	10		1.40	0.37	10		0.01	0.01	10	

GROUP	CHOL				TRIG				UREA				CREAT				GLUC			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	3.31	0.63	10		0.95	0.31	10		6.92	0.68	10		33.9	4.1	10		8.63	2.64	10	
2	3.07	0.46	10		0.96	0.42	10		6.90	0.74	10		35.9	8.9	10		9.82	1.71	10	
3	2.78	0.72	10		1.03	0.39	10		6.32	0.99	10		30.7	5.4	10		8.30	1.33	10	
4	2.79	0.43	10		1.00	0.46	10		7.34	0.88	10		31.0	4.4	10		9.62	1.59	10	

Females

GROUP	Na				K				Ca				Mg				P			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	156.4	5.0	10		6.78	0.95	10		3.13	0.13	10		1.31	0.22	10		2.63	0.37	10	
2	154.7	4.6	10		6.24	0.95	10		3.10	0.20	10		1.32	0.18	10		2.79	0.58	10	
3	156.3	4.4	10		6.19	0.55	10		3.08	0.20	10		1.22	0.09	10		2.67	0.27	10	
4	155.1	4.8	10		5.89	0.64	10		3.12	0.18	10		1.32	0.07	10		2.78	0.17	10	

GROUP	Cl				PROTEIN				ALB				GLOBULIN				ALB/G Ratio			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	109.7	2.0	10		73.3	5.8	10		47.1	4.4	10		26.2	3.7	10		1.83	0.28	10	
2	108.9	4.1	10		72.3	2.8	10		47.5	2.6	10		24.8	1.9	10		1.93	0.21	10	
3	109.9	2.8	10		72.4	4.5	10		48.9	3.2	10		23.5	2.8	10		2.11	0.32	10	
4	108.5	4.2	10		72.1	2.3	10		47.9	2.0	10		24.2	3.2	10		2.02	0.34	10	

Urinalysis

At the high dose, in all treated animals, changes in urine samples were noted: significantly lower volume, reduced pH, higher concentrations of electrolytes (sodium, potassium, and chloride), and higher specific gravity/protein concentration (attributed to the pharmacological effect of the desmopressin).

The darker color of urine samples was noted at the high dose in females (not attributed to blood in urine).

At the high dose, all animals had an increased concentration of sodium, K, Cl in urine.

Microscopic findings of spun sediment showed a higher protein content at the high dose in males.

Table 21. Urinalysis Parameters in Rats

In Males:

males

GROUP	VOLUME				Na				K				Cl			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	15.0	4.4	10		28.1	10.3	10		140.1	32.4	10		39.6	24.5	10	
2	17.9	7.7	10		42.6	13.7	10	*	126.7	46.5	10		39.0	17.6	10	
3	19.7	5.3	10	*	34.6	12.9	10		106.7	24.2	10		26.4	12.3	10	
4	8.2	0.9	10	**	82.4	25.7	10	**	243.7	45.0	10	**	104.9	26.8	10	**

GROUP	SPECIFIC GRAVITY					Total	p
	1.010	1.015	1.020	1.025	≥1.030		
1	5	2	3	0	0	10	
2	3	6	1	0	0	10	
3	6	4	0	0	0	10	
4	0	0	2	7	1	10	**
Total	14	12	6	7	1	40	

GROUP	pH				Total	p
	7.0	7.5	8.0	8.5		
1	0	4	5	1	10	
2	2	5	3	0	10	
3	0	5	5	0	10	
4	8	2	0	0	10	**
Total	10	16	13	1	40	

GROUP	COLOUR			Total	p
	Light yellow	Yellow	Dark yellow		
1	2	8	0	10	
2	3	7	0	10	
3	5	5	0	10	
4	0	7	3	10	
Total	10	27	3	40	

GROUP	PROTEIN				Total	p
	Trace	0.3 g/l	1.0 g/l	>3.0 g/l		
1	1	6	2	1	10	
2	0	4	6	0	10	
3	0	7	3	0	10	
4	0	0	6	4	10	**
Total	1	17	17	5	40	

GROUP	LEUCOCYTES			Total	p
	No trace	15 cells/ μ l	70 cells/ μ l		
1	1	2	5	2	10
2	0	0	8	2	10
3	0	3	6	1	10
4	0	3	5	2	10
Total	1	8	24	7	40

GROUP	BLOOD			Total	p
	No trace	25 cells/ μ l	200 cells/ μ l		
1	10	0	0	10	
2	9	1	0	10	
3	10	0	0	10	
4	9	0	1	10	
Total	38	1	1	40	

GROUP	GLUCOSE		Total	p
	No trace	Total		
1	10	10		
2	10	10		
3	10	10		
4	10	10		
Total	40	40		

GROUP	KETONES				Total	p
	No trace	Trace	1.5 mmol/l	3.9 mmol/l		
1	0	2	8	0	10	
2	1	4	5	0	10	
3	0	2	8	0	10	
4	0	0	9	1	10	
Total	1	8	30	1	40	

GROUP	BILIRUBIN		Total	p
	No trace	Small amounts		
1	10	0	10	
2	10	0	10	
3	10	0	10	
4	6	4	10	
Total	36	4	40	

GROUP	UROBILI-NOGEN		Total	p
	3.2 μmol/l			
1	10		10	
2	10		10	
3	10		10	
4	10		10	
Total	40		40	

GROUP	ERYTHROCYTES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	8	1	1	0	0	10	
2	5	3	2	0	0	10	
3	8	1	1	0	0	10	
4	7	2	0	1	0	10	
Total	28	7	4	1	0	40	

GROUP	LEUCOCYTES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	7	3	0	0	0	10	
2	6	4	0	0	0	10	
3	5	2	3	0	0	10	
4	1	5	3	0	1	10**	
Total	19	14	6	0	1	40	

GROUP	EPITHELIAL CELLS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	4	3	3	0	0	10	
2	0	5	5	0	0	10	
3	4	1	5	0	0	10	
4	0	2	7	1	0	10	
Total	8	11	20	1	0	40	

GROUP	CRYSTALS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	0	0	7	3	10	
2	0	1	0	8	1	10	
3	0	0	2	7	1	10	
4	0	0	0	9	1	10	
Total	0	1	2	31	6	40	

GROUP	URATES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	0	9	1	0	10	
2	1	1	8	0	0	10	
3	2	1	6	1	0	10	
4	0	3	7	0	0	10	
Total	3	5	30	2	0	40	

GROUP	HYALINE CASTS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	10	0	0	0	0	10	
2	10	0	0	0	0	10	
3	10	0	0	0	0	10	
4	10	0	0	0	0	10	
Total	40	0	0	0	0	40	

GROUP	GRANULAR CASTS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	10	0	0	0	0	10	
2	10	0	0	0	0	10	
3	10	0	0	0	0	10	
4	10	0	0	0	0	10	
Total	40	0	0	0	0	40	

GROUP	BACTERIA					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	0	0	8	2	10	
2	0	0	0	10	0	10	
3	0	0	0	10	0	10	
4	0	0	0	10	0	10	
Total	0	0	0	38	2	40	

In Females:

GROUP	VOLUME				Na				K				Cl			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	14.6	4.2	10		31.1	8.8	10		97.7	43.4	10		34.6	24.4	10	
2	12.0	3.0	10		42.6	13.3	10	*	119.3	36.5	10		54.8	15.7	10	
3	15.0	7.7	10		41.3	18.9	10		92.2	43.2	10		35.3	22.3	10	
4	4.5	1.0	10	**	92.4	38.6	10	**	247.2	55.3	10	**	126.9	37.6	10	**

GROUP	SPECIFIC GRAVITY							Total	p
	≤1.005	1.010	1.015	1.020	1.025	≥1.030			
1	1	3	2	2	2	0	10		
2	0	0	7	0	2	1	10		
3	0	4	4	1	1	0	10		
4	0	0	0	0	0	10	10	**	
Total	1	7	13	3	5	11	40		

GROUP	pH					Total	p
	6.0	6.5	7.0	7.5			
1	0	1	8	1	10		
2	0	3	7	0	10		
3	0	3	4	3	10		
4	3	7	0	0	10	**	
Total	3	14	19	4	40		

GROUP	COLOUR			Total	p
	Light yellow	Yellow	Dark yellow		
1	5	5	0	10	
2	2	8	0	10	
3	4	6	0	10	
4	0	0	10	10	**
Total	11	19	10	40	

GROUP	PROTEIN					Total	p
	No trace	Trace	0.3 g/l	1.0 g/l	>3.0 g/l		
1	6	2	1	1	0	10	
2	2	2	5	1	0	10	
3	4	3	2	1	0	10	
4	0	0	1	7	2	10	**
Total	12	7	9	10	2	40	

GROUP	LEUCOCYTES				Total	p
	No trace	15 cells/μl	70 cells/μl	125 cells/μl		
1	6	3	1	0	10	
2	4	5	0	1	10	
3	4	5	1	0	10	
4	9	1	0	0	10	
Total	23	14	2	1	40	

GROUP	BLOOD		p
	No trace	Total	
1	10	10	
2	10	10	
3	10	10	
4	10	10	
Total	40	40	

GROUP	GLUCOSE		p
	No trace	Total	
1	10	10	
2	10	10	
3	10	10	
4	10	10	
Total	40	40	

GROUP	KETONES			Total	p
	No trace	Trace			
1	10	0		10	
2	10	0		10	
3	10	0		10	
4	9	1		10	
Total	39	1		40	

GROUP	BILIRUBIN			Total	p
	No trace	Small amounts			
1	10	0		10	
2	10	0		10	
3	10	0		10	
4	9	1		10	
Total	39	1		40	

GROUP	UROBILINOGEN			Total	p
	3.2 $\mu\text{mol/l}$	16 $\mu\text{mol/l}$			
1	10	0		10	
2	10	0		10	
3	10	0		10	
4	9	1		10	
Total	39	1		40	

GROUP	ERYTHROCYTES						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	8	2	0	0	0	0	10	
2	9	1	0	0	0	0	10	
3	9	1	0	0	0	0	10	
4	9	1	0	0	0	0	10	
Total	35	5	0	0	0	0	40	

GROUP	LEUCOCYTES						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	6	2	2	0	0	0	10	
2	7	3	0	0	0	0	10	
3	9	1	0	0	0	0	10	
4	7	3	0	0	0	0	10	
Total	29	9	2	0	0	0	40	

GROUP	ERYTHROCYTES						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	8	2	0	0	0	0	10	
2	9	1	0	0	0	0	10	
3	9	1	0	0	0	0	10	
4	9	1	0	0	0	0	10	
Total	35	5	0	0	0	0	40	

GROUP	LEUCOCYTES						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	6	2	2	0	0	0	10	
2	7	3	0	0	0	0	10	
3	9	1	0	0	0	0	10	
4	7	3	0	0	0	0	10	
Total	29	9	2	0	0	0	40	

GROUP	EPITHELIAL CELLS						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	2	4	4	0	0	0	10	
2	1	3	6	0	0	0	10	
3	1	3	6	0	0	0	10	
4	1	3	6	0	0	0	10	
Total	5	13	22	0	0	0	40	

GROUP	CRYSTALS						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	0	3	2	5	0	0	10	
2	0	1	3	6	0	0	10	
3	0	1	3	5	1	0	10	
4	0	1	6	3	0	0	10	
Total	0	6	14	19	1	0	40	

GROUP	URATES						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	2	3	4	1	0	0	10	
2	3	4	3	0	0	0	10	
3	4	2	3	1	0	0	10	
4	1	5	4	0	0	0	10	
Total	10	14	14	2	0	0	40	

GROUP	HYALINE CASTS						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	10	0	0	0	0	0	10	
2	10	0	0	0	0	0	10	
3	10	0	0	0	0	0	10	
4	10	0	0	0	0	0	10	
Total	40	0	0	0	0	0	40	

GROUP	GRANULAR CASTS					Total	p	GROUP	BACTERIA					Total	p
	No trace	Traces	Slight	Moderate	Marked				No trace	Traces	Slight	Moderate	Marked		
1	10	0	0	0	0	10		0	0	0	7	3	10		
2	10	0	0	0	0	10		0	0	0	8	2	10		
3	10	0	0	0	0	10		0	0	0	5	5	10		
4	10	0	0	0	0	10		0	0	0	10	0	10		
Total	40	0	0	0	0	40		0	0	0	30	10	40		

Organ Weights

Relative kidney weights increased in the mid- and high-dose males and females. No other organ changes were noted.

Table 22. Organ Weights in Rats

In males:

MALES

GROUP	BODY WT, g				ADRENALS				ADRENALS				BRAIN				BRAIN			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE							
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	508.7	53.8	10		46.9	7.8	10		0.0093	0.0015	10		2253	91	10		0.446	0.036	10	
2	510.4	25.4	10		51.5	5.8	10		0.0101	0.0014	10		2262	80	10		0.444	0.021	10	
3	503.8	42.1	10		50.8	10.9	10		0.0101	0.0022	10		2213	89	10		0.441	0.029	10	
4	477.5	31.9	10		48.4	11.0	10		0.0102	0.0023	10		2230	157	10		0.468	0.029	10	

GROUP	EPIDIDYMIDES				EPIDIDYMIDES				HEART				HEART				KIDNEYS			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	1500	141	10		0.298	0.039	10		1600	137	10		0.316	0.026	10		2916	300	10	
2	1413	67	10		0.278	0.019	10		1580	152	10		0.309	0.025	10		3158	275	10	
3	1439	140	10		0.287	0.029	10		1688	217	10		0.335	0.031	10		3240	336	10	
4	1401	100	10		0.295	0.035	10		1563	135	10		0.328	0.026	10		3146	265	10	

GROUP	KIDNEYS				LIVER				LIVER				PITUITARY				PITUITARY			
	RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	0.575	0.050	10		16557	1659	10		3.26	0.17	10		13.5	2.5	10		0.00266	0.00048	10	
2	0.618	0.027	10		17532	1971	10		3.43	0.24	10		13.6	2.9	10		0.00266	0.00051	10	
3	0.643	0.041	10	**	16578	1410	10		3.30	0.22	10		15.9	5.0	10		0.00317	0.00106	10	
4	0.660	0.044	10	**	16014	1555	10		3.35	0.22	10		14.0	5.1	10		0.00294	0.00109	10	

GROUP	PROSTATE				PROSTATE				SPLEEN				SPLEEN				TESTES			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	622	112	10		0.123	0.021	10		1075	134	10		0.212	0.024	10		3980	377	10	
2	666	92	10		0.131	0.019	10		1071	228	10		0.209	0.037	10		3793	176	10	
3	746	183	10		0.149	0.039	10		980	130	10		0.195	0.022	10		3954	298	10	
4	649	100	9		0.138	0.025	9		1021	180	10		0.213	0.029	10		3972	213	10	

GROUP	TESTES				THYMUS				THYMUS				THYROIDES				THYROIDES			
	RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	0.79	0.12	10		412	91	10		0.081	0.013	10		24.4	5.2	10		0.00485	0.00120	10	
2	0.74	0.05	10		428	104	10		0.084	0.018	10		28.1	7.2	10		0.00548	0.00126	10	
3	0.79	0.07	10		432	81	10		0.086	0.013	10		25.4	4.1	10		0.00507	0.00086	10	
4	0.84	0.08	10		403	85	10		0.085	0.020	10		26.5	6.6	10		0.00557	0.00142	10	

In Females:

GROUP	BODY WT, g				ADRENALS				ADRENALS				BRAIN				BRAIN			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE							
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	283.0	17.7	10		68.0	7.6	10		0.0241	0.0032	10		2019	66	10		0.717	0.058	10	
2	294.2	18.0	10		72.6	10.1	10		0.0247	0.0034	10		2070	105	10		0.705	0.036	10	
3	280.6	22.7	10		71.0	6.5	10		0.0254	0.0023	10		2049	67	10		0.735	0.066	10	
4	278.0	12.9	10		73.4	6.9	10		0.0264	0.0023	10		2046	75	10		0.737	0.040	10	

GROUP	HEART				HEART				KIDNEYS				KIDNEYS				LIVER			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	1029	80	10		0.365	0.035	10		1679	103	10		0.595	0.048	10		8937	1223	10	
2	1053	80	10		0.359	0.027	10		1849	110	10	*	0.629	0.029	10		9077	790	10	
3	1024	119	10		0.365	0.033	10		1882	177	10	**	0.672	0.048	10	**	8651	879	10	
4	990	119	10		0.356	0.037	10		1990	135	10	**	0.716	0.038	10	**	8825	1059	10	

GROUP	LIVER				PITUITARY				PITUITARY				OVARIES				OVARIES			
	RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE			
	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p
1	3.17	0.50	10		16.3	3.4	10		0.00577	0.00112	10		103.1	11.1	10		0.0364	0.0026	10	
2	3.09	0.26	10		17.1	3.8	10		0.00581	0.00119	10		107.2	13.9	10		0.0366	0.0057	10	
3	3.09	0.22	10		15.4	4.9	10		0.00544	0.00144	10		99.1	13.4	10		0.0353	0.0035	10	
4	3.17	0.31	10		16.8	4.3	10		0.00603	0.00146	10		105.6	15.2	10		0.0380	0.0048	10	

GROUP	SPLEEN				SPLEEN				THYMUS				THYMUS				THYROIDS			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p
1	632	88	10		0.224	0.037	10		314	53	10		0.111	0.020	10		19.0	3.7	10	
2	705	100	10		0.240	0.033	10		321	72	10		0.109	0.024	10		19.1	5.5	10	
3	695	59	10		0.249	0.024	10		315	37	10		0.113	0.016	10		21.2	5.6	10	
4	685	118	10		0.246	0.037	10		301	71	10		0.108	0.023	10		19.4	4.2	10	

GROUP	THYROIDS				UTERUS				UTERUS			
	RELATIVE				ABSOLUTE				RELATIVE			
	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p
1	0.00673	0.00130	10		644	134	10		0.227	0.038	10	
2	0.00646	0.00166	10		710	138	10		0.244	0.060	10	
3	0.00753	0.00175	10		728	167	10		0.260	0.063	10	
4	0.00697	0.00146	10		697	273	10		0.254	0.113	10	

Histopathology

Adequate Battery: yes
Peer Review: yes

Histological Findings

At the injection site, hemorrhage was reported in all treated animals (including controls). Incidences and severity of cystic/cleft-like spaces and granulomatous inflammation were dose-related. However, this effect was not considered clinically relevant to the new product (orally disintegrating tablet formulation is proposed for marketing).

Table 23. Histopathology in Rats

GROUP	Inflammation, granulomatous					Total	p
	No findings	Minimal	Slight	Moderate			
1	9	1	0	0	0	10	
2	5	3	2	0	0	10	
3	3	4	2	1	0	10	*
4	2	2	4	2	0	10	**
Total	19	10	8	3	0	40	

Females

GROUP	Inflammation, granulomatous				Total	p
	No findings	Minimal	Slight	Moderate		
1	3	1	5	1	10	
2	2	3	3	2	10	
3	2	3	4	1	10	
4	1	1	3	5	10	
Total	8	8	15	9	40	

* means p<0.05 versus control group
 ** means p<0.01 versus control group

Males

GROUP	Mononuclear cells, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	5	5	0	0	10	
2	5	5	0	0	10	
3	7	3	0	0	10	
4	9	1	0	0	10	
Total	26	14	0	0	40	

Females

GROUP	Mononuclear cells, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	7	3	0	0	10	
2	8	2	0	0	10	
3	8	2	0	0	10	
4	10	0	0	0	10	
Total	33	7	0	0	40	

Males

GROUP	Haemorrhage, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	6	4	0	0	10	
2	6	2	2	0	10	
3	5	3	2	0	10	
4	7	3	0	0	10	
Total	24	12	4	0	40	

Females

GROUP	Haemorrhage, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	7	1	2	0	10	
2	8	0	2	0	10	
3	6	3	1	0	10	
4	7	3	0	0	10	
Total	28	7	5	0	40	

Males

GROUP	Cystic/cleftlike space				Total	p
	No findings	Minimal	Slight	Moderate		
1	7	2	1	0	10	
2	2	7	1	0	10	
3	3	6	1	0	10	
4	2	4	4	0	10	
Total	14	19	7	0	40	

Females

GROUP	Cystic/cleftlike space				Total	p
	No findings	Minimal	Slight	Moderate		
1	2	7	1	0	10	
2	3	6	1	0	10	
3	2	7	1	0	10	
4	1	7	2	0	10	
Total	8	27	5	0	40	

Conclusion: The toxicology profile of desmopressin with 3 impurities ([Glu4]desmopressin, Gly9-OH]desmopressin, and [β Asp5]desmopressin, at concentration levels of (b) (4) %, respectively) was consistent with desmopressin suggesting no significant toxicological effects of these 3 impurities.

As previously reviewed for NDA 19955:

Study title: Toxicological Studies of DDAVP (Desmopressin Acetate, 180 days in rats)((b) (4) , 1986)

DDAVP was administered intravenously to Wistar rats at doses of 0, 9.47, 47.4, and 238 mcg/kg (daily, N=10.) No premature deaths or test article related effects on clinical signs, or food consumption were observed. A reversible increase in blood urea nitrogen was seen at 47.4 mcg/kg and above. A reversible slight increase in kidney weight was also observed at these doses, along with increased protein casts. At 238 mcg/kg, hyaline droplets were observed in tubular epithelia; reversibility of kidney effects was observed after discontinuation of drug. A no adverse effect level was estimated to be 9.47 mcg/kg.

Study title: Toxicity Studies of KW-8008 (Desmopressin Acetate): 6-Month Subcutaneous Toxicity Study in Dogs ((b) (4) 1991)

DDAVP was administered subcutaneously to dogs at doses of 0, 1, 10, and 100 mcg/kg (daily, N=3.) No premature deaths or test article related effects on clinical signs, ECG, ophthalmology, body weight, food consumption, hematology or urinalysis were observed. Increases in cholesterol and phospholipid were observed in 3 females at 10 mcg/kg and 2 females at 100 mcg/kg. An increase in blood urea nitrogen was seen in 2

males and 2 females at 100 mcg/kg early in the administration period. Increases in absolute and relative kidney weights were observed in 1 male at 10 mcg/kg and 1 male at 100 mcg/kg. Kidney histopathology included thickening of Bowman's capsule, swelling of papillar epithelium, and focal inflammatory cell infiltration and interstitial fibrosis in the cortex, at 10 mcg/kg and above. A no adverse effect level was estimated to be 1 mcg/kg.

7 Genetic Toxicology

As reviewed by Parvaneh Espandiari:

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

As reviewed by Parvaneh Espandiari:

7.2 *In Vitro* Assays in Mammalian Cells

Study Title: FE992026 Mouse Lymphoma Cell Mutation Assay

Study no.: (b) (4) study #: 776744; (b) (4) report #: 25517; Ferring Ref. #: FE992026DSMUT0502

Volume # and page #: Vol. 1, p 1-60

Conducting laboratory and location:

(b) (4)

Date of study initiation: 25 February 2005

GLP compliance: yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: U25017/125/16; 102% of label claim (the test article was spiked with 3 impurities: ([Glu4]desmopressin, Gly9-OH]desmopressin, and [βAsp5]desmopressin, at concentration levels of (b) (4) %, respectively).

Key study findings:

In the mouse lymphoma L5178Y/TK+/- cell line FE992026 was not genotoxic in the absent or presence S9-mix.

Methods:

Strains/species/cell line:

Mouse lymphoma L5178Y/TK+/- cell line was used to detect gene mutation and chromosomal damage (clastogenicity and /or aneuploidy).

Doses used in definitive study:

Mutagenicity assays were performed (+/- S9 mix) with up to 5000 mcg/mL.

The concentrations of FE 992026 tested were as follows (mcg/mL):

- Assay 1 (in the absence of S9 mix¹): 156, 313, 625, 1250, 2500 and 5000
- Assay 2 (in the presence of S9 mix¹): 156, 313, 625, 1250, 2500 and 5000
- Assay 3 (in the absence of S9 mix²): 125, 250, 500, 1000, 2000, 3000, 4000 and 5000
- Assay 4 (in the presence of S9 mix¹): 250, 500, 1000, 2000, 3000 and 4000

¹ Experiment using a 4 h exposure period
² Experiment using a 24 h exposure period

Each dose range selection was based on all available results at the time the selection was made.

Basis of dose selection:

The highest practical concentration limited by the solubility or pH of the test item
 Negative controls;

The control cultures were treated with the basic culture medium (R0P).

Positive controls:

Ethyl methanesulphonate (EMS), methyl methanesulphonate (MMS) and 3-methylcholanthrene (3-MC)

Incubation and sampling times:

The assay was carried out with cultures of 3X10⁵ (for 4 hours) or 3X10⁵ (for 24 hours) cells, a dose range of test compound (156, 313, 626, 1250, 2500 and 5000 mcg/mL for 3 hours or 125, 250, 500, 1000, 2000, 3000, 4000 and 5000 mcg/mL 24 hours) as well as positive/negative controls and +/- S9. After incubation (at 370 C with different exposure time), followed with an expression period (2 days with daily adjusted cell population), the mutagenic potential of test compound (for TK-/-) was evaluated.

Study validity:

All positive and negative controls gave appropriate responses.

Results:

Maximum concentrations of test compound were limited to 5000 mcg/mL (+/-S9, respectively) for 3 hours or 24 hours of treatment.

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Absence of S9 Mix (4 h Exposure)
Summary of Means of Data (Assay 1)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁷)	MF (Induced Mutant Fraction x10 ⁷)	Ratio of Small to Large Colonies	Statistical Comparison
R/P	(4 ml added)	100	54	-	0.77	-
EMS	250	89	454	400	0.33	*
MMS	10	45	857	803	2.00	*
FE 992026	156	NPS	NPS	-	-	-
	313	NPS	NPS	-	-	-
	625	101	52	-	1.83	-
	1250	88	54	10	0.82	-
	2500	100	52	-	1.03	-
	5000	77	63	8	0.86	-

MF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P < 0.05)
 Test for mean level of mutant fraction with concentration of FE 992026 = not significant (P = 0.58)
 NPS = Not Plated - Surplus

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Presence of S9 Mix (4 h Exposure)
Summary of Means of Data (Assay 2)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁻⁷)	IMF (Induced Mutant Fraction x10 ⁻⁷)	Ratio of Small to Large Colonies	Statistical Comparison
R ₁ P	(4 ml added)	100	48	-	0.64	-
3-MC	2.5	23	1208	1158	1.71	*
FE 992026	156	NPT/P	NPT/P	-	-	-
	313	121	69	11	0.69	-
	625	139	65	17	0.29	-
	1250	121	36	-	0.50	-
	ppth 2500	62	43	-	1.08	-
	ppth 5000	NPT/P	NPT/P	-	-	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P < 0.05)
 Test for linear trend of mutant fraction with concentration of FE 992026 = not reported - slope negative
 NPT/P = Not Plated - Spillage
 NPT/P = Not Plated - Toxic/Dense precipitation
 ppth = Precipitation

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Absence of S9 Mix (24 h Exposure)
Summary of Means of Data (Assay 3)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁻⁷)	IMF (Induced Mutant Fraction x10 ⁻⁷)	Ratio of Small to Large Colonies	Statistical Comparison
R ₁ P	(4 ml added)	100	55	-	0.66	-
EMS	150	29	1359	1304	0.27	*
MMS	5	38	1028	971	1.71	*
FE 992026	125	79	66	1	0.61	-
	250	60	43	-	0.71	-
	500	84	52	-	1.46	-
	1000	72	72	17	0.56	-
	ppth 2000	18	41	-	0.49	-
	ppth 3000	NPT/P	NPT/P	-	-	-
	ppth 4000	NPT/P	NPT/P	-	-	-
	ppth 5000	NPT/P	NPT/P	-	-	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P < 0.05)
 Test for linear trend of mutant fraction with concentration of FE 992026 = not reported - slope negative
 NPT/P = Not Plated - Spillage
 NPT/P = Not Plated - Toxic/Dense precipitation
 ppth = Precipitation

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Presence of S9 Mix (4 h Exposure)
Summary of Means of Data (Assay 4)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁻⁷)	IMF (Induced Mutant Fraction x10 ⁻⁷)	Ratio of Small to Large Colonies	Statistical Comparison
R ₁ P	(4 ml added)	100	65	-	0.77	-
3-MC	2.5	45	977	913	0.98	*
FE 992026	250	135	47	-	0.82	-
	500	110	54	-	1.03	-
	1000	85	67	2	0.73	-
	ppth 2000	46	43	-	0.35	-
	ppth 3000	17	58	-	0.92	-
	ppth 4000	NPT/P	NPT/P	-	-	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P < 0.05)
 Test for linear trend of mutant fraction with concentration of FE 992026 = not reported - slope negative
 NPT/P = Not Plated - Spillage
 NPT/P = Not Plated - Toxic/Dense precipitation
 ppth = Precipitation

Summary: Results of this study showed that FE992026, which contains (b) (4) levels of 3 impurities ([Glu₄]desmopressin, Gly₉-OH]desmopressin, and [βAsp₅]desmopressin, at concentration levels of (b) (4) %, respectively) than the reference product, was devoid of mutagenic or clastogenic activity.

8 Carcinogenicity

Ferring Pharmaceuticals Inc. (Ferring) requested a waiver for carcinogenicity studies under 21CFR314.90, and provided the following nonclinical data as justification:

1. Mechanisms of Action

Desmopressin ([1-mercaptopropionic acid, 8 D Arg] vasopressin), is a cyclic nonapeptide synthetic analogue of the naturally occurring antidiuretic hormone arginine vasopressin (AVP). It is structurally similar to endogenous AVP, differing only by the

absence of an N-terminal amino group and substitution of D-arginine for L-arginine at position 8 (ensuring that it is longer-acting than AVP and vasopressin-2 [V₂] receptor specific). Desmopressin is enzymatically degraded by endopeptidases, and about half is excreted unchanged in the urine ([FE 992026 CS001]). The resulting intermediates following enzymatic cleavage has been shown to degrade further by consecutive reactions to intermediate peptides and essential or substituted amino acids, including phenylalanine.

2. Clinical and Non-Clinical Data

Carcinogenicity studies have not been performed with desmopressin, because it is very closely related to the naturally occurring peptide hormone AVP, its selective activity is mediated through one of the same receptors as AVP (V₂), and its metabolic degradation products are benign peptides and amino acids. In addition, desmopressin has no mutagenic potential, and in none of the long term toxicology studies by both oral and systemic routes has there been any evidence of histopathological risk factors for neoplasia (absence of hyperplasia, cellular hypertrophy, or foci of cellular alterations). A literature search revealed no carcinogenic, hyperplastic or neoplastic liability for desmopressin and there are no indications for cancer-related pharmacological properties of desmopressin based on other members in this class.

In addition, the following clinical information was submitted:

3. Post-Marketing Safety Data

Cumulatively, a total of 16 cases, containing events under the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) 'neoplasms benign, malignant and unspecified (incl. cysts and polyps)' have been reported spontaneously up to August 31, 2017 with all formulations of desmopressin. Two cases were non-serious and 14 cases were serious. The cumulative patient exposure of desmopressin (all formulations) up to August 31, 2017, is estimated to (b) (4) patients.

4. Cases by Formulation

Eight cases were reported for desmopressin nasal spray or nasal drop solutions, 5 cases were reported for oral formulations (3 oral lyophilisate, 2 tablets), and for 3 cases, the formulation was unknown.

5. Cases by Age group

Six cases were reported for children/adolescents, 5 cases for adult, 2 cases for elderly patients and 3 cases were of unknown age.

6. Cases by Events

Three cases were reported with benign neoplasms (of which 2 cases were non-serious), 3 cases were reported with malignant neoplasms and 10 cases were reported without

specification of malignancy. The neoplasms were distributed among different SOCs, 6 events were within 'nervous system', 3 events within 'blood system', 2 events within 'endocrine system', 2 events within 'gastrointestinal system', 1 event within 'skin and cutaneous system', 1 event within 'renal and urinary system', and 1 event was without body site specification.

7. Cases by causality

In 3 of the cases patients had a medical history of tumors or neoplasm related history, and causality (both by the reporter and by Ferring) was ruled out. Nine cases had no reporter causality assessment, of which 2 cases had a reported medical history of tumors or neoplasm related history. Two cases had un-assessable causality due to limited information. Two cases were assessed by the reporter as related to desmopressin. In one of these cases, the patient was concomitantly treated with 11 different drugs, of which all were considered as suspected drugs by the reporter. In addition, the patient was a long-term smoker (since approximately 30 years) which was considered a risk factor by the reporter. Ferring has assessed the causality as un-assessable. In the other case, the reporter was the consumer and very limited information was provided. Furthermore, the patient had a history of 3 recurrences of craniopharyngioma, and the case was assessed as not related by Ferring. The above-mentioned 16 cases have not established a proven causal relationship between desmopressin treatment and carcinogenic potential. The cases are reported with limited information and in most cases, reporter's causality assessment is missing. In addition, several cases had reported medical history of tumors or neoplasms. Considering the large cumulative patient exposure and the very few cases reported with events under MedDRA SOC 'neoplasms benign, malignant and unspecified', no carcinogenetic potential in humans has been identified based on the post-marketing safety data. Nearly 40 years of therapeutic use in the USA and 45 years of therapeutic use globally of desmopressin in the treatment of a number of conditions has failed to indicate any oncogenic or carcinogenic potential in humans.

9 Reproductive and Developmental Toxicology

Summary of fertility and embryo-fetal studies, as reviewed for NDA 19955:

In a non-GLP fertility study in rats (1991), KW-8008 (desmopressin acetate)(sc, N=22) administered to males and females prior to and during mating and to females during early gestation, showed no effects on estrus cycling, copulation rate, conception rate, with maternal, paternal, and fetal no effect levels greater than 200 mcg/kg/day. No pharmacokinetic study was performed. A human therapeutic dose by a subcutaneous route of administration is 2 mcg or 0.03 mcg/kg. A sublingual dose of 27.7 mcg was chosen to be pharmacodynamically equivalent to the therapeutic sc dose.

In a non-GLP embryo-fetal study in rats (1986), desmopressin acetate (iv, N = 20), administered from Days 7 to 17 and through weaning at doses of 0, 9.47, 47.4, and 238

mcg/kg/day, showed no drug related reproductive effects, although pharmacology was observed at all doses. No pharmacokinetic study was performed. A human therapeutic dose by an intravenous route of administration is 2 mcg or 0.03 mcg/kg. A sublingual dose of 27.7 mcg was chosen to be pharmacodynamically equivalent to the therapeutic iv dose.

In rats, fetal transfer of labeled DDAVP (sc) was 4% of maternal blood level after 1 hour and 39% of maternal blood levels at 4 hours

In a non-GLP embryo-fetal study in Dutch belted rabbits (1972, (b) (4)), desmopressin acetate (sc, N = 3), administered from Days 6 to 18 at doses of 0, 1, 3, and 10 mcg/kg/day, showed no drug related reproductive effects. No pharmacokinetic study was performed. A human therapeutic dose by a subcutaneous route of administration is 2 mcg or 0.03 mcg/kg. A sublingual dose of 27.7 mcg was chosen to be pharmacodynamically equivalent to the therapeutic sc dose.

Prenatal and Postnatal Development, as reviewed for NDA 19955:

Study title: Study of the Effects of KW-8008 Administered Subcutaneously to Rats during Perinatal and Lactation Periods

Conducting laboratory and location:

(b) (4)

Date of study initiation: 14 February 1992

GLP compliance:

(b) (4)

QA statement: yes

Drug, lot #, and % purity: Lot No.920212, 97.7 % pure

Key Study Findings

No treatment related effects on clinical signs, gestation index, delivery, lactation, or implantation sites, were observed. In F₁ offspring, decreased body weight gain and delayed vaginal opening were observed at 200 mcg/kg, proposed to be due to decreased nursing. No treatment related effect was observed, on birth index, viability index on day 4, weaning index, clinical signs, reflex and motility (righting reflex, negative geotaxis, pupillary reflex, Preyer reflex, pain response), morphological differentiation (pinna detachment, incisor eruption, eyelids opening, testes descent), external appearance, visceral effects, skeletal effects, general behavior, learning (by open field test, water maze test) or reproductive performance.

In F₂ offspring, no treatment related effects on birth index, viability index on days 4 and 7, body weight, external appearance, visceral effects or skeletal effects were observed at any dose level.

No adverse effect levels (sc) were judged to be more than 200 mcg/kg/day for F₀ dams, 20 mcg/kg /day for F₁ offspring and more than 200 mcg/kg/day for F₂ offspring.

No pharmacokinetic study was performed. A human therapeutic dose by a subcutaneous route of administration is 2 mcg or 0.03 mcg/kg. A sublingual dose of 27.7 mcg was chosen to be pharmacodynamically equivalent to the therapeutic sc dose.

Methods

Doses:	0, 2, 20, and 200 mcg/kg/day
Frequency of dosing:	daily
Dose volume:	1 ml/kg
Route of administration:	subcutaneous
Formulation/Vehicle:	saline
Species/Strain:	S1c:SD rats
Number/Sex/Group:	24
Study design:	Daily administration from day 17 of pregnancy to day 21 after delivery

11 Integrated Summary and Safety Evaluation

NOCDURNA, a new formulation of desmopressin (desmopressin orally disintegrating tablet), was submitted as a 505(b)(1) application. The active ingredient desmopressin is a structural analog of the natural human antidiuretic hormone (8-arginine vasopressin). There is extensive international clinical experience with marketed desmopressin (oral-Minirin; IV injection, intranasal spray).

In a 1-month bridging toxicology study in dogs, toxicological findings and toxicokinetic data with NOCDURNA were very similar to DDAVP tablets and were consistent with known pharmacological effects of desmopressin. In general, there were no other signs of systemic toxicity in any treated animals. Decreased urinary volumes in treated animals were noted, related to the pharmacological effect of the compound. The values of serum bilirubin were increased in two desmopressin treated females with no other related changes. Findings from the TK data suggested no sex differences and similarity in level of desmopressin levels in two compounds (2 × 200 mcg DDAVP tablets vs. 1 × 240 mcg desmopressin orally disintegrating tablets).

Desmopressin acetate was previously reviewed under NDA 19955 (Ferring). To characterize the local toxicity and qualify the new impurity profile of NOCTURNA, new studies were conducted.

In a 13-week study in rats by subcutaneous administration, the three impurities of desmopressin, [Glu4]desmopressin, [Gly9-OH]desmopressin and [βAsp5]desmopressin, were included at relevant levels of (b) (4) %, respectively. Findings in this study were consistent with the pharmacological effects of desmopressin. Absolute kidney weights were significantly increased for mid and high dose animals, with no microscopic findings. The increased kidney weights were considered due to the pharmacological effects of the test article in maximizing tubular reabsorption. The NOAEL was considered to be 10 mcg/kg/day, at which only pharmacological effects of desmopressin were noted.

In *in vitro* genotoxicity studies (Ames test, mouse lymphoma assay) no genotoxic potential was observed for desmopressin spiked with the 3 relevant impurities at higher concentrations than proposed for CMC specifications.

The effects of desmopressin in recent animal studies were similar to those observed in chronic animal studies for NDA 19955 and include effects on urinary volume and pH, specific gravity and concentration of sodium, potassium, chloride and protein, and increased absolute kidney weights.

A 28-day local tolerability study was conducted in Syrian hamsters (once daily, cheek pouch.) No evidence of test article related local reactions or histopathological changes were observed.

A fertility study in rats, embryo-fetal studies in rats and rabbits, and a pre-and post-natal study in rats were performed under NDA 19955.

In a non-GLP fertility study in rats, sc desmopressin acetate, administered to males and females prior to and during mating and to females during early gestation, showed no effects on estrus cycling, copulation rate, conception rate, with maternal, paternal, and fetal no effect levels greater than 200 mcg/kg/day.

In a non-GLP embryo-fetal study in rats, iv desmopressin acetate, administered from Days 7 to 17 and through weaning at doses of 0, 9.47, 47.4, and 238 mcg/kg/day, showed no drug related reproductive effects, although pharmacology was observed at all doses.

In rats, fetal transfer of labeled DDAVP (sc) was 4% of maternal blood level after 1 hour and 39% of maternal blood levels at 4 hours

In a non-GLP embryo-fetal study in Dutch belted rabbits, sc desmopressin acetate, administered from Days 6 to 18 at doses of 0, 1, 3, and 10 mcg/kg/day, showed no drug related reproductive effects.

In a pre- and post-natal development study, desmopressin acetate had no effect on clinical signs, gestation index, delivery, lactation, or implantation sites. In F₁ offspring, decreased body weight gain and delayed vaginal opening were observed at 200

mcg/kg, proposed to be due to decreased nursing. No treatment related effect was observed, on birth index, viability index on day 4, weaning index, clinical signs, reflex and motility (righting reflex, negative geotaxis, pupillary reflex, Preyer reflex, pain response), morphological differentiation (pinna detachment, incisor eruption, eyelids opening, testes descent), external appearance, visceral effects, skeletal effects, general behavior, learning (by open field test, water maze test) or reproductive performance. In F₂ offspring, no treatment related effects on birth index, viability index on days 4 and 7, body weight, external appearance, visceral effects or skeletal effects were observed at any dose level. No adverse effect levels (sc) were judged to be more than 200 mcg/kg/day for F₀ dams, 20 mcg/kg /day for F₁ offspring and more than 200 mcg/kg/day for F₂ offspring.

Pharmacokinetics were not measured in the original chronic toxicity studies for NDA19955. Intravenous and subcutaneous doses in rats and dogs were compared to the therapeutic i.v. or s.c. dose of 2 mcg or about 0.03 mcg/kg in humans by body surface area.

In rats, a 200 mcg/kg dose is approximately 1100 fold the human effective dose (HED) of 0.03 mcg/kg, by body surface area, using a correction factor of 6 for rats vs. humans. A single dose pharmacokinetic study in rats suggested that exposures in rats by AUC may exceed the estimated multiples of exposure using body surface area.

In dogs, a 100 mcg/kg dose is approximately 1800 fold the HED, by body surface area, using a correction factor of 1.8 for dogs vs. humans. In the 1-month bridging study, a 240 mcg (about 24 mcg/kg) dose of orally disintegrating tablet was shown to have an AUC of about 500 pghr/ml in dogs. A human dose of 200 mcg/kg (about 3.3 mcg/kg) was shown to have an AUC of about 64 pghr/ml (or approximately 16 pghr/ml for a 50 mcg dose); the dose in dogs in the bridging study is therefore about 17 fold the HED.

Exposure to desmopressin acetate from orally disintegrating tablets was designed to be similar to that of safe and effective doses from previously marketed dosage forms. The dose of desmopressin acetate contained in an orally disintegrating table is 27.7 or 55.4 mcg or about 1 mcg/kg, which is expected to have a lower bioavailability than i.v. or s.c. administration.

Table 24. Sponsor's tabulated summaries:

Desmopressin FE992026, FE999912;
2.6.7.1 Toxicology: Overview
DN-OVERVIEW-103;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
Page 1 of 1

2.6.7.1 Toxicology: Overview

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (µg/kg/day) ^a	GLP Compliance	Testing Facility	Study Number	Location in CTD
Single-Dose Toxicity	No new data							
Repeat-Dose Toxicity	No new data							
13-week toxicity study in rats	Sprague Dawley, Niac:SD rats	Subcutaneous injection	13 weeks	0, 0.1, 1, 10	Yes	(b) (4)	[58881]	4.2.3.2
Genotoxicity	No new data							
Ames test	<i>S. typhimurium</i> TA 1535, 100, 1537, 98 & <i>E. coli</i> WP2uvrA	Direct plating & Pre-incubation	2 or 3 days	17-5000 µg/plate	Yes	(b) (4)	[775739]	4.2.3.3.1
Mouse lymphoma assay	L5178Y clone 3.7.2.C	Assay 1 – S9 Assay 2 + S9 Assay 3 – S9 Assay 4 + S9	4 hours 4 hours 24 hours 4 hours	150-5000 150-5000 125-5000 250-4000 µg/mL	Yes	(b) (4)	[775744]	4.2.3.3.1
Carcinogenicity	No new data							
Reproductive and Developmental Toxicity	No new data							
Local Tolerance	No new data							
Oral irritation in hamsters	Syrian hamster	Orally in the cheek pouch	28 days	0, 0, 360 µg/day	Yes	(b) (4)	[52338]	4.2.3.6
Other Toxicity Studies	No new data							

^a Unless otherwise specified. For Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined.

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Desmopressin FE992026, FE999912;
2.6.7.7 Repeat-Dose Toxicity
DN-SUMMARY-276;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
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2.6.7.7 Repeat-Dose Toxicity

Report Title: Desmopressin: 13-week subcutaneous toxicity study in rats				Test Article: Desmopressin			
Species/Strain:	Rat/Sprague Dawley Niac:SD	Duration of Dosing:	13 weeks	Study No.:	[58881]		
Initial Age:	5 weeks	Duration of Postdose:	None	Location in CTD:	4.2.3.2		
Date of First Dose:	W/b 28 Feb 2005	Method of Administration:	Subcutaneous injection	GLP Compliance:	Yes		
Special Features:	None	Vehicle/Formulation:	0.9 % NaCl	No Observed Adverse Effect Level:	10 µg/kg/day		
Daily Dose (µg/kg)	0 (Control)		0.1		1		10
Number of Animals	10M	10F	10M	10F	10M	10F	10M 10F
Toxicokinetics: AUC	ND	ND	ND	ND	ND	ND	ND ND
Noteworthy Findings							
Died or Sacrificed Moribund	0	0	0	0	0	0	0 0
Body Weight Gain (g, % ^a)	311.9	120.8	98	109	96	97	88 99
Food Consumption (g, % ^a)	2364.0	1549.6	100	106	101	101	97 101
Water Consumption (% ^a)	ND	ND	ND	ND	ND	ND	ND ND
Clinical Observations	-	-	-	-	-	-	- -
Ophthalmoscopy	-	-	-	-	-	-	- -
Hematology	-	-	-	-	-	-	- -
Serum Chemistry	-	-	-	-	-	-	- -
Urinalysis							
Volume (mL)	15.0	14.6	17.9	12.0	19.7*	15.0	8.2** 4.5**
Sodium (mmol/L)	28.1	31.1	42.6*	42.6*	34.6	41.3	82.4** 92.4**
Potassium (mmol/L)	140.1	97.7	126.7	119.3	106.7	92.2	243.7*** 247.2***
Chloride (mmol/L)	39.6	34.6	39.0	54.8	26.4	35.3	104.9** 126.9**
Specific gravity (no unit)	1.014	1.016	1.014	1.019	1.012	1.015	1.025*** 1.030***
pH (no unit)	7.9	7.0	7.6	6.9	7.8	7.0	7.1** 6.4**

Ferring Pharmaceuticals

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Desmopressin FE992026, FE999912;
2.6.7.7 Repeat-Dose Toxicity
DN-SUMMARY-276;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
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Daily Dose (µg/kg)	0 (Control)		0.1		1		10	
Organ Weights^a								
Absolute Kidney Weight (mg, %)	2916	1679	108	110*	111	112**	108	119**
Relative Kidney Weight (% , %)	0.575	0.595	107	106	112**	113**	115**	120**
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology								
Injection site changes	+	+	+	+	+	+	++	++
Postdose Evaluation:	ND	ND	ND	ND	ND	ND	ND	ND

- No noteworthy findings + Mild ++ Moderate +++ Marked

* - p<0.05 ** - p<0.01

^aAt end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

ND Not done

Desmopressin FE992026, FE999912;
2.6.7.8 Genotoxicity: *In Vitro*
DN-SUMMARY-277;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
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2.6.7.8 Genotoxicity: *In Vitro*
2.6.7.8A Study No. 775739

Report Title: FE 992026: Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537 and TA 98 and <i>Escherichia coli</i> WP2uvrA				Test Article: Desmopressin	
Test for Induction of:	Reverse mutation in bacterial cells	No. of Independent Assays:	2	Study No.:	[775739]
Strains:	<i>S. typhimurium</i> : TA 1535, TA 100, TA 1537, TA 98. <i>E. coli</i> : WP2uvrA	No. of Replicate Cultures:	3	Location in CTD:	4.2.3.3.1
Metabolising System:	Aroclor 1254-induced rat liver S-9 mix	No. of Cells Analysed/Culture:	Not applicable	GLP Compliance:	Yes
Vehicles: For Test Article:	Sterile, ultrapure water	For Positive Controls:	DMSO	Date of Treatment:	15 Mar – 11 Apr 2005
Cytotoxic Effects:	Thinning of back ground lawn with all strains at 5000 µg/plate both in the presence and absence of S9 mix	Genotoxic effects:	None		

Ferring Pharmaceuticals

CONFIDENTIAL

Desmopressin FE992026, FE999912;
2.6.7.16 Local Tolerance
DN-SUMMARY-278;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
Page 1 of 1

2.6.7.16 Local Tolerance

Test Article: Desmopressin

Species/ Strain	Method of Administration	Doses (µg/animal/day)	No. and Gender per Group	Noteworthy Findings	Study Number
Syrian hamster	Insertion of an orally disintegrating tablet into the left cheek pouch	0 (untreated) 0 (placebo) 360	3 M + 3 F 3 M + 3 F 4 M + 4 F	There were no noteworthy findings in any group	Scantox [52338] in 4.2.3.6

2.6.7.1 Toxicology: Overview

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (µg/kg/day)*	GLP Compliance	Testing Facility	Study Number	Location in CTD
Single-Dose Toxicity	No new data							
Repeat-Dose Toxicity	13-week toxicity study in rats							
	Sprague Dawley, Ntac:SD rats	Subcutaneous injection	13 weeks	0, 0.1, 1, 10	Yes	(b) (4)	[58881]	4.2.3.2
Genotoxicity								
Ames test	<i>S. typhimurium</i> TA 1535, 100, 1537, 98 & <i>E. coli</i> WP2uvrA	Direct plating & Pre-incubation	2 or 3 days	17-5000 µg/plate	Yes		[775739]	4.2.3.3.1
Mouse lymphoma assay	L5178Y clone 3.7.2.C	Assay 1 - S9 Assay 2 + S9 Assay 3 - S9 Assay 4 + S9	4 hours 4 hours 24 hours 4 hours	156-5000 156-5000 125-5000 250-4000 µg/mL	Yes		[775744]	4.2.3.3.1
Carcinogenicity	No new data							
Reproductive and Developmental Toxicity	No new data							
Local Tolerance	Oral irritation in hamsters							
	Syrian hamster	Orally in the cheek pouch	28 days	0, 0, 360 µg/day	Yes		[52338]	4.2.3.6
Other Toxicity Studies	No new data							

* Unless otherwise specified. For Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined.

Ferring Pharmaceuticals

CONFIDENTIAL

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Desmopressin acetate, a vasopressin analog, has been marketed since 1972 in multiple formulations and its safety profile well studied in humans. Additional studies submitted with the current application include a 13-week subcutaneous toxicity study in rats and two genotoxic studies (Ames assay, mouse lymphoma assay) using desmopressin acetate spiked with relevant concentration of 3 new impurities found in the new formulation, a 1-month bridging study in dogs with pharmacokinetics, and a 28-day local tolerability assay in Syrian hamster cheek pouches.

No treatment related local toxicity was observed in the Syrian hamster assay. No notable differences in the toxicity of oral and sublingual formulations were observed in the 1-month dog bridging study. No additional effect of the three new impurities ([Glu₄]desmopressin, [Gly₉-OH]desmopressin and [βAsp₅]desmopressin) were observed in a 13-week toxicity study in rats of desmopressin spiked with relevant concentrations of these impurities. No evidence of additional genotoxicity was observed in an Ames assay or in a mouse lymphoma assay of desmopressin spiked with the 3 impurities.

The effects of desmopressin orally disintegrating tablets in the animal studies submitted were similar to those observed in chronic animal studies for NDA 19955 and include decreased urinary volume and pH, increased specific gravity and concentration of sodium, potassium, chloride and protein, and increased kidney weights at high doses. There is no impediment to approval of this drug from a Pharmacology/ Toxicology perspective.

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/s/

LAURIE L MCLEOD FLYNN
06/18/2018

MUKESH SUMMAN
06/18/2018
Nonclinical supports AP

Summary Review for Regulatory Action

Date	(see electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA #	022517
Supplement #	
Applicant Name	Ferring Pharmaceuticals, Inc.
Date of Submission	July 31, 2014
PDUFA Goal Date	January 31, 2014
Proprietary Name / Established (USAN) Name	Nocdurna/desmopressin
Dosage Forms / Strength	Orally disintegrating tablets / 25 ucg and 50 ucg
Proposed Indication(s)	1. Treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer DMEP, Medical Officer DPP, Medical Officer DBRUP, DEPI and DRISK Reviews and Consults	Lubas William MD PhD; Farchione, Tiffany MD; Wiederhorn, Roger MD; Bright, Patricia PhD; Vega, Amarilys, MD;
SEALD Consult	Kovacs, Sarrit M, PhD

OND=Office of New Drugs
 DSI=Division of Scientific Investigations
 CDTL=Cross-Discipline Team Leader

1. Introduction

On July 31st, 2014 Ferring Pharmaceuticals, Inc. submitted a Class 2 resubmission of the new drug application for Nocdurna under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act. The resubmission is a complete response to the Complete Response Letter issued by the Agency on January 30th 2014.

Regulatory History

The application received a complete response in two previous cycles of review because the risks were deemed to outweigh the demonstrated benefits of the therapy for the proposed indication. It is important to note that the proposed indication for the first two cycles of reviews was different than the currently proposed indication. In the first two cycles of review, the applicant had proposed to indicate Nocdurna for the treatment of adults with nocturia regardless of age or cause(s). For this resubmission the applicant proposes to indicate NOCDURNA for the treatment of nocturia due to nocturnal polyuria in all adult patients who awaken at least twice per night to void.

First Review Cycle¹

The pivotal study in the first cycle of review (**Trial-CS029**) was a 28 day study comparing the effect of four doses of NOCDURNA (10, 25, 50 and 100 mcg) to placebo. The primary objective of the trial was to demonstrate that participants randomized to NOCDURNA would have a significant reduction in the mean number of nocturnal voids **and** would be more likely to experience a 33% reduction in the number of nocturnal voids. Use of a two component co-primary endpoint was recommended to ensure that significant differences based on mean changes were not driven by the response of a few outliers.

Only the 100 mcg dose group demonstrated a statistically significant effect over placebo at Day 28. In this dose group, the placebo adjusted mean (95% CI) reduction from baseline in the number of voids per night was -0.61 (-0.85, -0.38) void per night and the odds of experiencing a 33% reduction from baseline in the number of nocturnal voids was greater on NOCDURNA than placebo [Odds ratio (95% CI); 2.9 (1.8, 4.7)].

Hyponatremia, including severe hyponatremia, was identified as a risk associated with the use of NOCDURNA in this trial. More people on active therapy withdrew due to hyponatremia and a clear dose-response relationship between incident cases of hyponatremia and NOCDURNA dose was observed. Furthermore, questions were raised with regard to the generalizability of the safety findings because specific patient populations with certain medical conditions common to patients with nocturia and known to predispose patients to

¹ Refer to Dr. Parks' April 22, 2010 Division Director Memorandum in DARRTS.

hyponatremia were specifically excluded from pivotal trial participation (e.g., renal impairment, use of loop diuretic, congestive heart failure).

Post hoc analyses suggested a differential effect by gender and the possibility that lower, gender specific, dosing could yield a more favorable benefit risk profile. In the Complete Response Letter the applicant was instructed to conduct an additional trial. The Division also voiced a concern regarding interpretability of the clinical meaningfulness of the small effect size absent a demonstrated effect on a patient reported or clinical outcome. The applicant was advised to develop an instrument to capture the patient-perceived benefit of using NOCDURNA as a treatment for nocturia.

Second Review Cycle²

The applicant conducted two new 3-month, placebo-controlled studies to address the deficiencies in the Complete Response Letter. **Trial-CS40** evaluated the 25 mcg dose of Nocdurna in women and **Trial-CS41** evaluated a 50 and 75 mcg dose in men. Both studies employed similar designs and relied on the same two co-primary efficacy endpoints as **Trial-CS029**.

In women, NOCDURNA 25 mcg (**Trial-CS40**) resulted in a placebo-adjusted mean (95% CI) reduction from baseline in the number of voids per night of -0.24 (-0.44, -0.04) void per night and increased odds of experiencing a 33% reduction from baseline in the number of nocturnal voids [Odds ratio (95% CI); 1.8 (1.2, 2.8)].

In men, NOCDURNA 75 mcg and 50 mcg (**Trial-CS41**) resulted in a placebo-adjusted mean (95% CI) reduction from baseline in the number of voids per night of -0.40 (-0.60, -0.20) and -0.37 (-0.57, -0.17) void per night respectively and increased odds of experiencing a 33% reduction from baseline in the number of nocturnal voids [Odds ratio (95% CI); 2.0 (1.4, 3.0) and 2.0 (1.3, 3.0 for the 75 and 50 mcg dose respectively)].

The Division again had difficulties interpreting the clinical meaningfulness of the small reported mean reduction in nocturnal voids (~ 1.7 voids per week in women and 2.8 voids per week in men). Although a patient reported instrument [e.g., Nocturia Quality of Life questionnaire (NQoL)] was used in the pivotal trial to measure the impact of nocturia and its treatment on the patient's quality of life, results derived from this instrument were not compelling because the instrument lacked validity³, relied on a long recall period (i.e., average symptoms over two-weeks) and analyses were post-hoc, exploratory, unadjusted for multiplicity and results lacked consistence across time points and populations.

² refer to Dr. Parks' January 30, 2013 Division Director Memorandum in DARRTS.

³ The instrument was noted to lack content validity because it failed to include all the dimensions of the impact of nocturia on a patient's quality of life and included dimensions not related to the concept the instrument was intended to measure. For example, the NQoL instrument was noted to lack an assessment of the psychological/emotional impact of nocturia, to include measurements of general concepts which could be impacted by non-nocturia related aspects of life (e.g., economic well-being), to include items not related to assessing the impact of nocturia treatment (e.g., worried about lack of available therapy).

Hyponatremia for both sexes and at all doses was again noted as the most important risk associated with the use of NOCDURNA and questions regarding the generalizability of the trial derived hyponatremia risk estimates to the care setting for whom this drug were again raised.

In the overall benefit-risk assessment, the magnitude of the demonstrated treatment effect was deemed insufficient to justify the risk of hyponatremia and the application received a second Complete Response. The Division requested the sponsor carry out another trial with the objective of establishing the clinical meaningfulness of the demonstrated effect on the reduction in nocturnal voids using a patient reported instrument the applicant had been developing with input from the Study Endpoints Development team at FDA (i.e., the Nocturia Impact Diary).

Dispute and Proposed Path Forward

The applicant appealed the Division's decision through a formal dispute resolution request (FDRR) and asked that the application be approved on the grounds that they had successfully demonstrated safety and efficacy of NOCDURNA 25 and 50 mcg. The appeal was denied. As a proposed path forward the applicant was asked to re-submit the application with additional data to support the robustness of the efficacy findings along with any data they viewed as relevant to informing the clinical importance of the demonstrated effect size (e.g., sleep data) and the Division was asked to convene an Advisory Committee for the purpose of presenting the totality of evidence to subject matter experts and publically discussing the issues raised in the first two cycles of reviews and more broadly, the benefit risk of NOCDURNA for the proposed indication.

2. Background

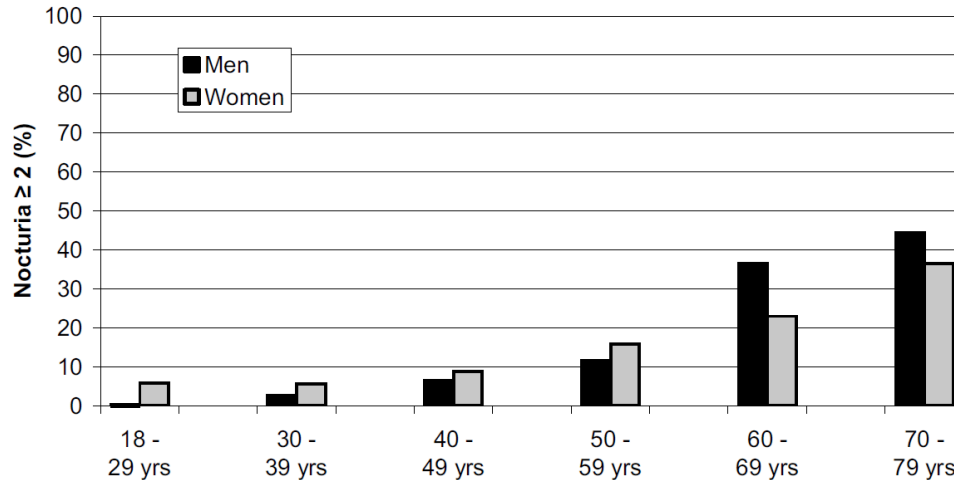
Desmopressin is a synthetic analog of the neurohypophyseal nonapeptide hormone arginine vasopressin (AVP). Compared to arginine vasopressin, desmopressin has a longer duration of action, greater anti-diuretic properties and lower blood pressure raising effects. In the US, desmopressin is approved to treat central diabetes insipidus, hemophilia A, type 1 von Willebrand's disease, nocturnal enuresis in children and as a diagnostic test to measure renal concentrating abilities. Desmopressin reduces urinary volume through reabsorption of free water.

Nocturia

Clinically meaningful nocturia has been defined based on expert opinion as waking-up 2 or more times per night to void where each voiding episode is preceded and followed by sleep. The applicant relied on this criterion to select patients for participation in their pivotal trials. Risk factors for nocturia identified from cross-sectional and case-control data include advanced age, obesity, hypertension, snoring, diuretic use, anti-depressant use, diabetes,

benign prostatic hypertrophy, prostate cancer and congestive heart failure. Prevalence of nocturia increases with age and as defined above is highly prevalent in older age groups.

Figure 1: Prevalence of Nocturia By Age and Sex (Tikkinen et al. 2006)⁴



Observational and cross-sectional questionnaire-based studies have suggested a possible association between nocturia and abnormal sleep onset and maintenance⁵, depression, decreased quality of life, and in patients older than 75 years old, falls and fracture⁶.

Nocturia can result from disorders that cause frequent, low volume, nighttime voids (e.g., overactive bladder, bladder obstruction) or frequent, high volume, nighttime voids [e.g., nocturnal polyuria, global polyuria (diabetes insipidus or mellitus)] or a combination of both. Patients with sleep disorders (e.g., obstructive sleep apnea, restless leg syndrome, and periodic limb movements) also complain of nocturia. Whether these patients wake-up because of a true need to urinate or as a result of an unrecognized sleep disturbance (an apneic episode or a limb movement) which they falsely attribute to the need to urinate has been raised by some studies.

Nocturnal polyuria

Nocturnal polyuria is a subset of nocturia characterized by excessive volume of urine produced at night. The diagnosis is age-dependent as has been defined as a nocturnal urine volume that exceeds 20% of the total 24-hour volume in adults younger than 35 years and 33% of the total 24-hour volume in adults older than 65 years respectively⁷. It has been attributed to abnormalities in the diurnal variation of AVP secretion, to abnormalities in the diuresis of solutes (e.g., urea, sodium, potassium) and to nighttime mobilization of

⁴ J Urol. 2006 Feb; 175(2):596-600.

⁵ J Gerontol A Biol Sci Med Sci. 1996;51(3):M108.

⁶ J Am Geriatr Soc. 1992;40(12):1217; Int J Clin Pract. 2010;64(5):577; Neurourol Urodyn. 2009;28(8):949

⁷ Neurourol Urodyn. 2002; 21(2):179-83.

edematous fluid in conditions such as congestive heart failure, nephrotic syndrome, or venous insufficiency.

Therapeutic Approach

There are currently no FDA approved products for the treatment of nocturia or nocturnal polyuria. Desmopressin, at doses approved for other indications, is sometimes used off-label to treat patients with nocturia who have not responded to lifestyle/behavioral and therapeutic interventions that address the more immediate cause(s) of nocturia. Desmopressin is marketed in Europe and Canada for the treatment of nocturia in adults under the age of 65 years.

Hyponatremia

Acute and chronic dilutional hyponatremia are recognized risks associated with the use of desmopressin. Acute, severe, hyponatremia can cause neurologic dysfunction due to cerebral edema and result in loss of consciousness, seizure, coma, respiratory arrest and death. Recent observational, cross sectional and experimental studies suggest a possible association between mild chronic hyponatremia and neurocognitive impairment, gait disturbances⁸ and predisposition to falls⁹, osteoporosis¹⁰, fractures in elderly and mortality¹¹. Advanced age, female gender, medications (e.g., thiazide and loop diuretics, NSAIDs, anti-depressants), and specific disease states (e.g., renal impairment, congestive heart failure, nephrotic syndrome) predispose to hyponatremia.

3. CMC/Device

No new data were submitted in this resubmission.

4. Nonclinical Pharmacology/Toxicology

No new data were submitted in this resubmission.

5. Clinical Pharmacology/Biopharmaceutics

No new data were submitted in this resubmission.

6. Clinical Microbiology

No new data were submitted in this resubmission.

7. Clinical/Statistical-Efficacy

⁸ Am J Med. 2006;119(1):71.e1.

⁹ QJM. 2008;101(7):583.

¹⁰ J Bone Miner Res. 2010;25(3):554

¹¹ Am J Med. 2009;122(9):857 and Kidney Int. 2013 Apr;83(4):700-6.

The applicant re-submitted the application without new clinical trial data on July 31st 2014. In the re-submission the applicant presents post-hoc analyses from exploratory endpoints of existing trial data and selected literature to make the case that use of Nocdurna in the proposed population should meaningfully impact quality of life.

The Division of Metabolism and Endocrinology Products consulted the Division of Psychiatry Products to assess the claim made by the applicant that the increased time to first awakening (~40-50 minutes longer on NOCDURNA) will meaningfully impact the patient's quality of life through its impact on sleep (See full review by Dr. Farchione in DARRTS dated 12/04/2014). Dr. Farchione concludes:

“Although there is some face validity to the sponsor’s argument that a placebo-subtracted increase of 39-49 minutes in FUSP may improve health-related quality of life, the means by which that conclusion is reached requires several inferential steps, each based on limited direct evidence. The sponsor is making an argument based on a proxy in the absence of objective evidence. The argument would be more compelling if the sponsor had polysomnographic data to support the claim that improvements in FUSP are related to increases in SWS; even in that case, there would still be an additional inferential leap required before one could conclude that Nocdurna improves health-related quality of life or reduces the risk of long-term consequences of chronic sleep disturbance.”

The Division of Metabolism and Endocrinology Products consulted the Study Endpoints team to address whether the Nocturia Quality of Life Questionnaire (NQoL) or the Nocturia Impact Diary (NI Diary) used in the post-hoc analyses could support a claim that Nocdurna meaningfully impacts quality of life (see full review by Dr. Sarrits in DARRTS and dated 12/23/2015). Dr. Sarrit concludes:

“that the clinical trial evidence submitted by the applicant is inadequate to support labeling claims on the basis of the NI Diary or NQoL because of the exploratory nature of the data. Therefore, these clinical trial results do not meet standards for inclusion in labeling claims. However, the NI Diary was developed specifically for use in clinical trials and may be able to support labeling claims if it demonstrates a clinically meaningful and statistically significant treatment effect in adequate and well-controlled trials.”

Finally the Division of Metabolism and Endocrinology Products consulted the Division of Bone, Reproductive and Urologic Products to provide a perspective on the disease (i.e., adults with nocturia due to nocturnal polyuria), the population evaluated in clinical trials, the effect size and the risks associated with NOCDURNA (see full review by Dr. Wiederhorn in DARRTS and dated 12/10/2014). Dr. Wiederhorn summarizes DBRUP's perspective as follows:

“We have the following three comments from the urologic perspective:

- 1. The demonstrated effect of NOCDURNA on the frequency of nocturia in patients with nocturnal polyuria is small when compared to placebo. The clinical meaningfulness of*

this small effect is not interpretable in the absence of a validated measure of the clinical benefit of reduction of nocturia episodes.

2. *In the pivotal studies, homogenous urologic populations were not studied, making the efficacy study results difficult to interpret. Based on the Sponsor's proposed target patient group (nocturia secondary to nocturnal polyuria), patients eligible for Nocturna studies should have had: 1) overproduction of urine at night (nocturnal polyuria), 2) a normal capacity bladder, and 3) little or no symptoms of the two most commonly occurring lower urinary tract voiding dysfunctions, overactive bladder (OAB) and benign prostatic hypertrophy (BPH). Included in the completed studies were patients with lower urinary tract symptoms (LUTS) due to BPH and OAB. In addition, patients with small bladder capacities were neither identified nor eliminated. Responders to lifestyle modification during the run-in period were also not eliminated. Elimination of these subgroups would have allowed for a urologically homogenous study population, free of confounding intrinsic urologic factors that may reasonably be expected to have independent effects on nighttime voids, the primary efficacy endpoint. By grouping these disparate conditions into one trial, no or minimal treatment effects in some populations may have masked clinically meaningful benefits seen in other populations, yielding the observed overall small treatment effect of unknown clinical relevance.*
3. *Hyponatremia is a significant safety concern. It would appear that a large segment of the target population (patients with nocturia secondary to nocturnal polyuria) is over 65 years of age. This is also the age group of patients who had a disproportionate incidence of hyponatremia due to Nocturna. While it may be ultimately possible to label this risk with appropriate monitoring, additional information should be presented clarifying the hyponatremia risk, especially in regard to potential of hyponatremia at times distant from initiating therapy, the increased risk in geriatric patients, and the justification for proposed monitoring."*

8. Safety

No new clinical trial data were submitted in this resubmission.

9. Advisory Committee Meeting

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) met on January 12, 2015 to discuss the safety and efficacy of NOCDURNA (desmopressin), orally disintegrating tablets, submitted by Ferring Pharmaceuticals, Inc. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Ferring Pharmaceuticals Inc. The committee members were asked to vote on the following question.

VOTE: Does the demonstrated benefit of NOCDURNA outweigh the risks and support approval for nocturia due to nocturnal polyuria?

Provide a rationale for your vote. If you believe additional studies are needed, explain whether these studies are needed pre-approval or whether they can be conducted post-approval. Provide specific recommendations on ways to identify patients who may be candidates for this drug in clinical practice or in additional trials

The outcome of the vote was: **Yes = 5 No = 10 Abstain = 2**

The committee discussion from the draft minutes is reproduced below:

“The majority of the committee voted “No” and most committee members who voted “No” along with the two members that abstained from the vote, stated that while both co-primary endpoints achieved statistically significant differences from placebo in the two Phase III trials, the clinical benefit of the observed treatment effect remained unclear, particularly given the large placebo effect seen in the trials. One committee member stated that the sponsor is heading in the right direction exploring the time to first awakening (time to first nocturnal void), but more objective clinical efficacy data, such as data from a validated PRO instrument and/or polysomnography (e.g., slow wave sleep), is needed in pre-approval studies. Others also stated that pre-approval trials linking the currently demonstrated effect on nocturnal voids to a clinically meaningful outcome should be completed. The committee members that voted “Yes” expressed that while the benefit was not that impressive over placebo, it was in fact present and with proper labeling the benefit outweighs the risks, in their opinions. Additionally, some committee members expressed that the risk of hyponatremia was still a concern. One member stated that a postmarketing risk mitigation program may be an appropriate way to address the risk of hyponatremia. One member stated that additional prospective studies may be needed to validate the proposed serum sodium monitoring strategy. Please see the transcript for details of the committee discussion.”

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend a Complete Response.

- Risk Benefit Assessment

The additional information submitted by the applicant in the resubmission was considered and the totality of the evidence for benefit(s) and risk(s) available from the application was presented and publicly discussed at the Endocrinologic and Metabolic Drugs Advisory Committee on January 12th 2015. The committee recommended against approving Nocurna for nocturia due to nocturnal polyuria. The advisors who abstained and voted against approval did so because they were not certain that Nocurna’s impact on the reduction in nocturnal voids relative to placebo represented a meaningful therapeutic benefit. Most advisors remained concerned about the risks of hyponatremia associated with use of the drug and in light of the uncertainty surrounding clinical benefit voted against approval. I

concur with this general view. The analyses related to measures of sleep quality or bother were retrospective, exploratory and derived from instruments which would not support a quality of life claim for this condition. Although select analyses trended in the direction of a benefit no direct, robust evidence of benefit is available from the data in the application. Finally, there are no data in the application to support a conclusion that Nocdurna would provide a benefit through lowering risks of important outcomes (e.g., falls and fractures) that have been identified as associated with nocturia in observational studies.

The risk of hyponatremia (mild and severe) is real as there is a great amount of overlap between the populations at risk for hyponatremia and nocturia. Some risks associated with mild chronic hyponatremia identified from observational studies appear diametrically opposed to purported benefits of nocturia treatment (reduction in falls and fractures) and render an estimate of net benefit difficult absent outcomes data. Although severe hyponatremia was not frequently observed in the program, generalizability of the trial findings to the broader population of patients with nocturia due to nocturnal polyuria remains a concern. Finally, the applicant in this resubmission has proposed a very proscriptive mitigation strategy to prevent the risk of severe hyponatremia and ensure the benefits of the drug outweighs this risk in the care setting. I am concerned that such a strategy, if deemed absolutely required for benefit risk balance, would be difficult to implement in the care setting given the size of the population for whom this drug would be indicated.

To address the deficiency, the applicant will need to conduct a trial to demonstrate that Nocdurna provides a meaningful clinical benefit that is associated with the reduction in number of nocturnal voids in adults with nocturia due to nocturnal polyuria. To meet this objective, the trial should employ efficacy endpoint(s) that directly capture patient benefit related to the treatment of nocturia due to nocturnal polyuria; for example, a validated patient-reported outcome instrument that captures the clinical impact of the changes in nocturnal voids on quality of sleep or bother. Such an instrument (Nocturnal Impact Diary) has been in development.

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/s/

JEAN-MARC P GUETTIER
01/30/2015



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

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA/BLA #: NDA 22517

Drug Name: Nocdurna (desmopressin melt)

Indication(s): Treatment of Nocturia in Adults

Applicant: Ferring Pharmaceutical Ltd.

Date(s): Submitted on July 31, 2014

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Anna Kettermann, Dipl. Math, MA

Concurring Reviewers: Mark Rothmann, Ph.D., Statistical Team Leader
Thomas Permutt, Ph.D., Division Director

Medical Division: Division of Metabolism and Endocrinology Products

Clinical Team: William Lubas, MD

Project Manager: Jennifer Johnson

Keywords: NDA review, clinical studies, missing data, quality of life

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1 EXECUTIVE SUMMARY

On January 12, 2015, the efficacy and safety findings from the Nocdurna clinical development program were discussed publicly at a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. After considering the information in the submission and discussions at the advisory committee meeting, the advisory committee voted 10-5 against recommending approval of Nocdurna (desmopressin) for the indication of nocturnal polyuria.

This is a review of studies CS40 and CS41 submitted by Ferring Pharmaceutical Inc. These studies were submitted as a part of the package for Nocdurna (Desmopressin). The proposed indication for Nocdurna is adult nocturia due to nocturnal polyuria. These studies were previously reviewed by Dr. Wei Liu. This review examines issues of missing data and patient reported outcomes data (PRO). Both of those topics were not covered in the previous reviews.

Studies CS40 (in women) and CS41 (in men) utilized gender-specific doses in men and women. Both studies had similar protocols and were designed to test Nocdurna for 3 months. Study CS40 included two arms (Desmopressin 25 mcg and placebo). In contrast, study CS41 included three study arms (Desmopressin 50mcg, Desmopressin 70 mcg, and placebo).

Previously, based on the outcomes of longitudinal data modelling, a 1.23 ± 0.07 voids per night reduction was achieved in the placebo arm of study CS40. A slightly larger reduction of 1.47 ± 0.07 voids per night was achieved in the treatment arm of this study. A similar reduction was achieved in the study CS41 (Desmopressin 70 mcg arm 1.28 ± 0.07 , Desmopressin 50 mcg arm 1.27 ± 0.08 , and placebo arm 0.88 ± 0.07).

The analyses presented in this review identified that 17.9% of subjects in study CS40 discontinued the study prematurely. Additionally, subjects that discontinued the study early demonstrated a smaller reduction in number of nocturnal voids than subjects who stayed in the study. The situation was very different in study CS41, where the reductions in nocturnal voids were similar among subjects who stayed and subjects who discontinued the study. Overall, 15.4% of subjects prematurely discontinued study CS41.

Sensitivity analysis was conducted for CS40 since the pattern of reduction in voids was different between those who discontinued study participation early and those who completed the study. Taking the difference between first and last visits for all subjects including those who did not complete the study through 3 months, e.g., treating those who dropped out as having plateaued, the reduction in voids was 1.53 ± 1.04 for the treatment arm and 1.26 ± 1.13 for the placebo arm. Instead, assuming that those who dropped out returned to their baseline number of voids, the reduction was 1.39 ± 1.1 voids per night for the treatment arm. Similarly, when placebo subjects who prematurely discontinued study participation were removed from the analysis, the reduction was 1.38 ± 1.13 . These results imply that the worst case scenario for treatment (those who discontinued their study participation prior to 3-month visit were assumed to have no benefit at all) has similar outcomes to the best case scenario for placebo (only those who felt they were benefitting enough to continue through the completion of the study period were retained in the sample).

Here are the highlights from the PRO analyses:

In study CS 40, over 60% of subjects in each arm reported to have no improvements or worsening in quality of life (QOL) scores at month 1 visit. The percentage of subjects with no improvements reduced to approximately 55.7% at 3-months visit. The percent of subjects with no improvements was almost identical in both placebo and treatment arms. Similarly, in study CS41, more than half of subjects reported no improvement or worsening QOL scores in both months 1 and 3. At month 3, the largest percent of subjects who did not experience changes in QOL or got worse was among subjects on placebo (94 subjects, 74.02%) followed by Desmopressin 75 (66 subjects, 62.26%) and Desmopressin 50 (60 subjects, 57.69%).

I was concerned about the possibility that subjects who discontinued participation did so because they were not satisfied. To examine this, I stratified the PRO data by completion status. In study CS41, the fraction of subjects who showed worsening or unchanged QOL scores at month 1 was higher among those who discontinued study participation before month 3 than among those who had voiding data at month 3. In contrast, the fraction of subjects in study CS40 who showed worsening or unchanged QOL scores at month 1 was the same among those who discontinued the study at month 3 as among those who completed the study. These findings may only be considered to be preliminary since the number of subjects who did not complete the study was too small to subdivide and obtain robust results. Further studies will be needed to provide more definitive findings.

My conclusions: the systematic pattern in subjects with missing data in study CS40 should be stated when the outcomes are presented. Sensitivity analyses involving different scenarios (e.g. return to the baseline void count, etc.) for the subjects who discontinued study participation early may be able to provide more insight into understanding of the data. Although efficacy was shown to be statistically significant in a previous review, I defer to clinicians regarding its clinical significance.

The PRO survey would have provided more insight into reasons that subjects discontinued participation if there had been further follow-up to specifically ascertain those reasons. That information would help inform the extent to which apparent efficacy was affected by how the missing data were handled.

INTRODUCTION

This is a review of studies CS40 and CS41 submitted by Ferring Pharmaceutical Inc. on July 30, 2012 as a part of review package for Nocdurna (desmopressin). These studies were previously reviewed by Dr. Wei Liu. Since July 30 2012, there were no new studies submitted by the sponsor. The focal points of my review are the issues of missing data and analysis of patient-reported outcomes (PROs).

1.1 Overview

Desmopressin is a synthetic analogue of the naturally occurring antidiuretic hormone vasopressin which is the primary physiologic determinant of free water excretion by promoting free water reabsorption and reducing urine production.

The proposed indication for Nocdurna is adult nocturia due to nocturnal polyuria. This refers to a condition, in which increased urine production at night, mostly in elderly patients, results in them having to get up out of bed multiple times to void. The sponsor is seeking the treatment of patients, who do not have other treatable medical causes for nocturia, or if they have such causes, that they have been adequately addressed by current standard of care.

For all the details of the regulatory history of this submission please see Dr. Liu's review from January 25, 2013.

This review is focused on two studies CS40 (Title: A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Females) and CS41 (Title: A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension to Demonstrate the Efficacy and Safety of Desmopressin Oral Disintegrating Tablet for the Treatment of Nocturia in Adult Males). Specifically (as it was mentioned in the previous section), this review is focused on missing data and Patient Reported Outcomes (PRO).

Studies CS40 (in women) and CS41(in men) utilized gender-specific doses in men and women.

Table 1. List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
CS40	Phase 3. A Multi-center, Randomized (stratified by age, <65, ≥65), Double-blind, Placebo-controlled, Parallel-group Trial	3 months		Desmopressin: 25 µg 137 Placebo: 131	Adult Females with nocturia
CS41	Phase 3. A Multi-center, Randomized (stratified by age, <65, ≥65), Double-blind, Placebo-controlled, Parallel-group Trial	3 months	1 month open-label extension with all patients on desmopressin 100 µg	Desmopressin: 75 µg 129 50 µg 123 Placebo: 143	Adult Males with nocturia

1.2 Data Sources

The sponsor submitted this NDA including electronic study data to the FDA CDER Electronic Document Room (EDR). All documents are located in the folder \\CDSESUB1\evsprod\NDA022517

This submission is in electronic common technical document (eCTD) format. Study datasets were provided as SAS XPORT transport files. The datasets were joinable by unique identifier (SUBJID). The datasets were in good organization. Define.pdf file was clear enough. The reported analysis results were in good quality.

2 STATISTICAL EVALUATION

Primary endpoints:

- 1) change from baseline in mean number of nocturnal voids
- 2) proportion of subjects with > 33% reduction in the mean number of nocturnal voids

In order to succeed in the trial, the sponsor had to test both co-primary endpoints and win on both endpoints. Nocturnal voids were recorded in a diary on 3 consecutive 24 hour periods at baseline, Week 1, Month 1, Month 2 and Month 3.

Additionally, PROs were collected by the sponsor in the following domains: Quality of Life, bother/concern, and sleep/energy. Two criteria were used to define responders:

1. Reduction of ≥ 2 nocturnal voids from baseline to Month 3
2. Increase of ≥ 2 hours in time to first nocturnal void from baseline to Month 3

This definition was very different from the definition of responder in the main analysis (as indicated in the primary endpoints section).

2.1 Data and Analysis Quality

Study datasets were provided as SAS XPORT transport files. The analysis datasets were joinable by unique identifier (SUBJID). The datasets were in good organization. Define.pdf file was clear enough.

2.2 Evaluation of Efficacy

2.2.1 Study Design and Endpoints

The studies CS40 (women) and CS41 (men) were similar in design and duration except that women were only randomized to a single desmopressin dose (25mcg) or placebo, while men were randomized to two possible desmopressin doses (50 and 75mcg) or placebo. The schema for these two clinical trials is presented below. While trial CS40 employed a standard parallel group design, trial CS41 included, in addition to the placebo-controlled parallel group design phase, an extension phase during which a 100mcg dose was evaluated. The purpose of this extension was to see if there was any benefit in titrating men who had safely been exposed to lower doses to a higher dose. The extension part of this trial is not covered by this review.

Figure 1. Study scheme Study CS40 (women)

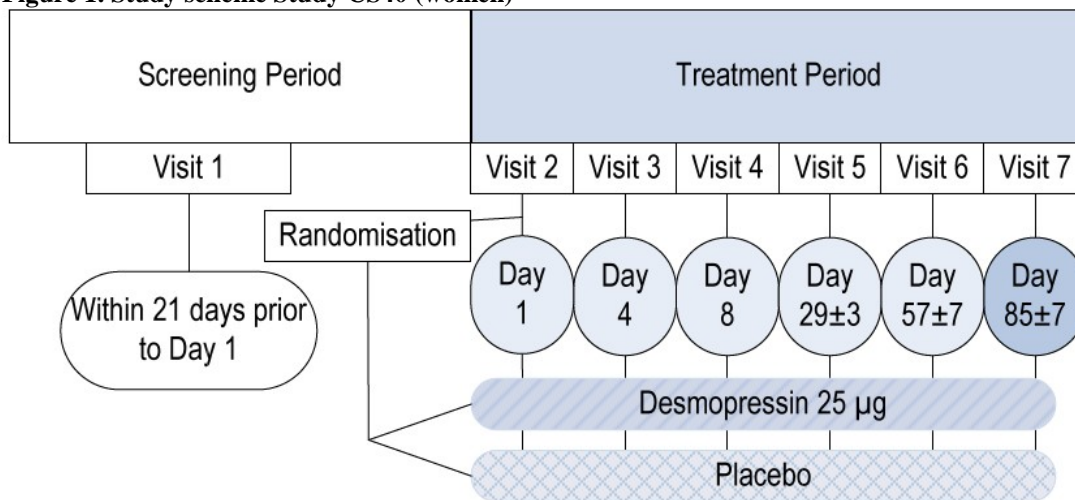
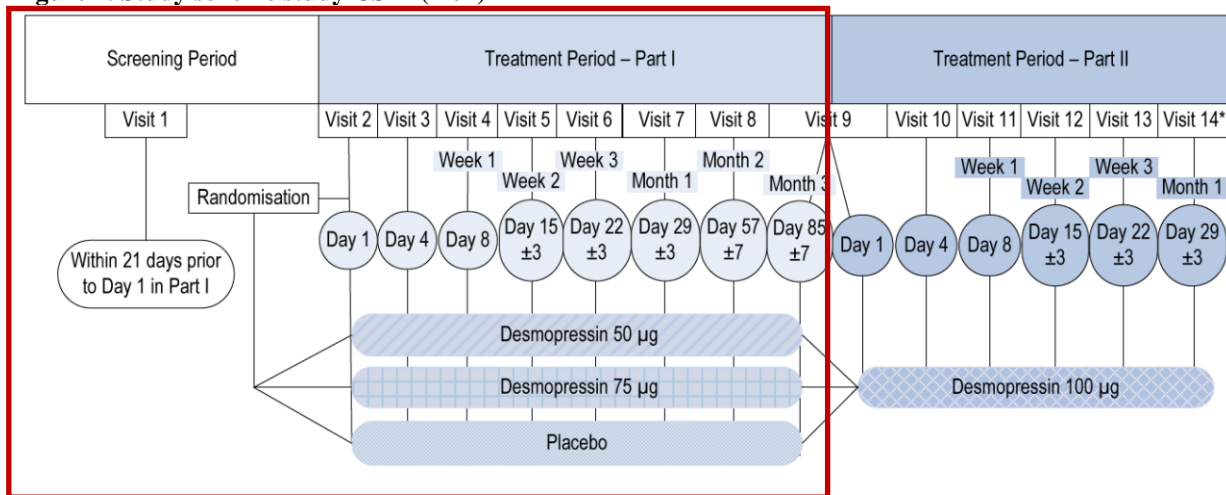


Figure 2. Study scheme study CS41 (men)



The red rectangle delineates the main study period that is being evaluated in this review. The follow-up period (Part II) is not a part of this review.

2.2.2 Statistical Methodologies

The inclusion criteria identified an adult patient population with frequent nighttime voids:

1. Subjects provided written informed consent prior to performance of any trial-related activity
2. ≥ 18 years of age (at the time of written consent)
3. Subjects reported at least 2 nocturnal voids every night in a consecutive 3-day period during the screening period (as determined by the diary dispensed at Visit 1 and collected at Visit 2).

For the detailed demographic characteristics, description of analysis conducted by the sponsor for the primary endpoint, please see Dr. Liu's review. This review is focused on evaluation of missing data patterns and their potential impact on the trial outcome.

2.2.3 Results and Conclusions

I conducted my own analysis of patterns of missing data and here are the outcomes:

Missing data

Study CS40

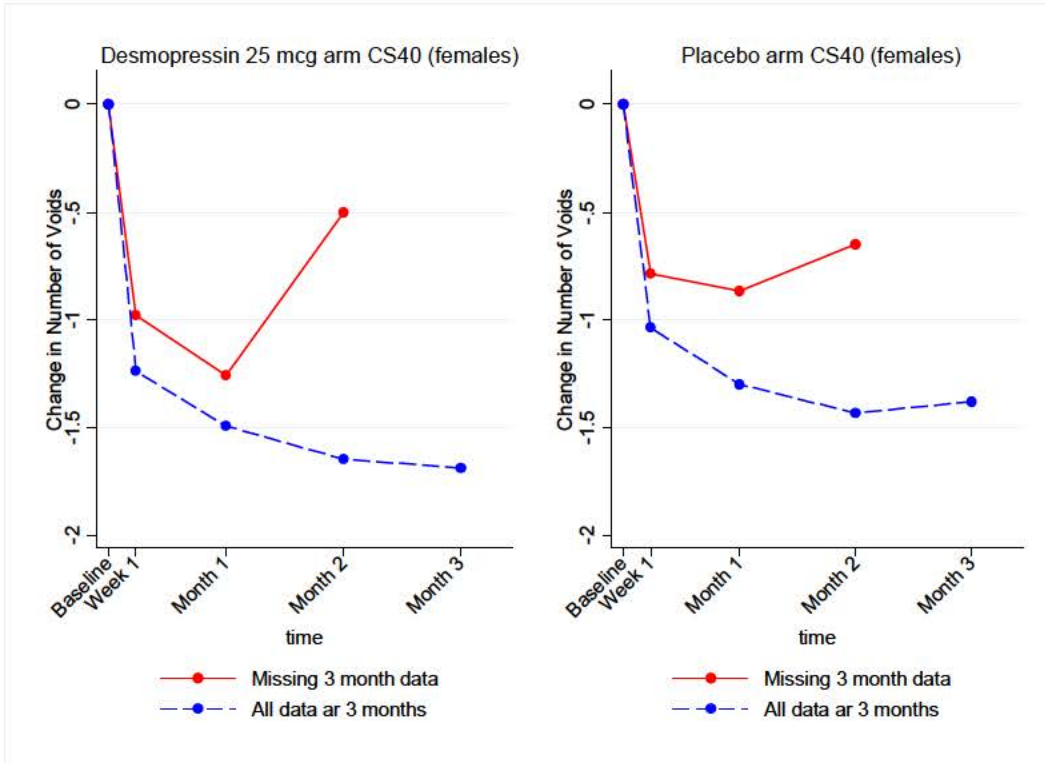
Overall, per randomized analysis set (ITT), 17.9% of subjects did not have data on number of voids at the 3-months visit. As a result of that, only 220 subjects contributed data to the primary analysis. The number of subjects with missing information at 3 months was slightly smaller when FAS was considered (15.7%). A detailed distribution of missing data is presented in the table below. A careful examination of missing data patterns revealed that among subjects in the FAS dataset, 43.9% of subjects who did not have voiding data at 3-months visit had provided 1-

months data, i.e. those subjects contributed to 1-months analyses but were not evaluated at the end of the study.

Table 2. Study CS40 missing data

Dataset	Treatment		Placebo		Total	
	All subjects	Missing at month 3	All subjects	Missing at month 3	All subjects	Missing at month 3
ITT						
By randomization	137	24 (17.5%)	131	24(18.3%)	268	48(17.9%)
By treatment	139	24 (17.3%)	129	24(18.6%)		

Figure 3. Change in number of voids study CS40



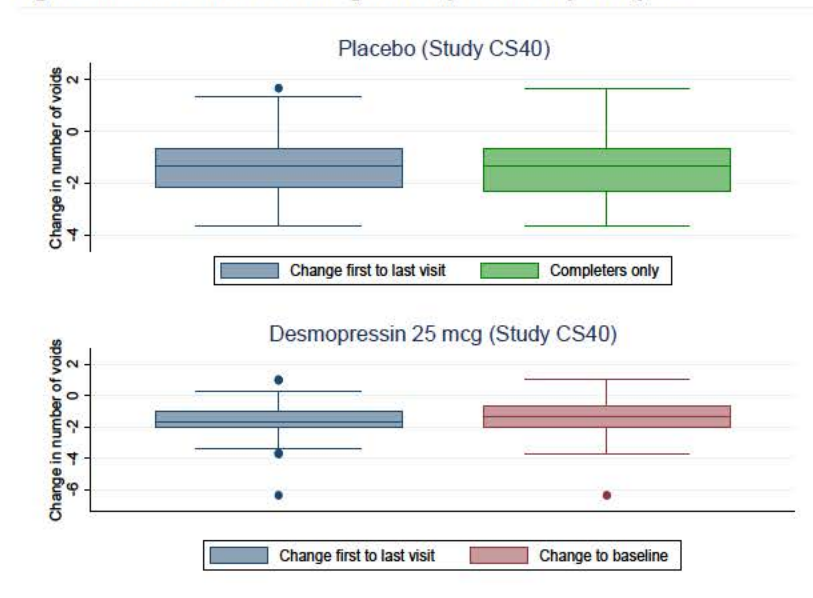
A graphical comparison between subjects who had and did not have data at 3-months visit is presented above. The graph consists of two panels. Observations for the treatment arm are plotted on the left side and data for the placebo arm are presented on the right. Values on the y-axis indicate a mean change in number of voids per night; values on the x-axis indicate the visit. For both graphs, the solid line represents subjects who provided data on the number of voids at 3-months visit; the dashed line represents subjects who did not have data at month 3.

An examination of the trends depicted on the graph reveals that the rate of change in number of voids was higher among subjects who did not leave the study prematurely, those women who had data at 3-months visit. This observation is true for both trial arms. Specifically, at month one of the study, subjects on the desmopressin arm who did not have a measurement for voids at month 3 had a mean reduction of 1.26 (sd 0.71) voids per night while subjects on the

desmopressin arm who had a measurement for voids at month 3 had a mean reduction of 1.49 (sd 1.03) voids per night. So, among those subjects with a month 1 measurement for voids on the desmopressin arm, subjects who did not have a month 3 measurement for voids had a smaller mean reduction at month 1 (by 0.23 voids per night) than those subjects who had a month 3 measurement for voids. At month one of the study, subjects on the placebo arm who did not have a measurement for voids at month 3 had a mean reduction of 0.87 (sd 1.29) voids per night while subjects on the placebo arm who had a measurement for voids at month 3 had a mean reduction of 1.30 (sd 1.09) voids per night. So, among those subjects with a month 1 measurement for voids on the placebo arm, subjects who did not have a month 3 measurement for voids had a smaller mean reduction at month 1 (by 0.43 voids per night) than those subjects who had a month 3 measurement for voids. The missing data do not seem to have created any bias favoring desmopressin.

An exploratory sensitivity analysis was conducted for CS40 since the pattern of reduction in voids was different between those who discontinued study participation early and those who completed the study. Taking the difference between first and last visits for all subjects including those who did not complete the study through 3 months, e.g., treating those who dropped out as having plateaued, the reduction in voids was 1.53 ± 1.04 for the treatment arm and 1.26 ± 1.13 for the placebo arm. Instead, assuming that those who dropped out returned to their baseline number of voids, the reduction was 1.39 ± 1.1 voids per night for the treatment arm. Similarly, when placebo subjects who prematurely discontinued study participation were removed from the analysis, the reduction was 1.38 ± 1.13 . These results imply that the worst case scenario for treatment (those who discontinued their study participation prior to 3-month visit were assumed to have no benefit at all) has similar outcomes to the best case scenario for placebo (only those who felt they were benefitting enough to continue through the completion of the study period were retained in the sample). The results of the exploratory sensitivity analysis are presented in the figure below.

Figure 4: The results of the exploratory sensitivity analysis



Study CS41

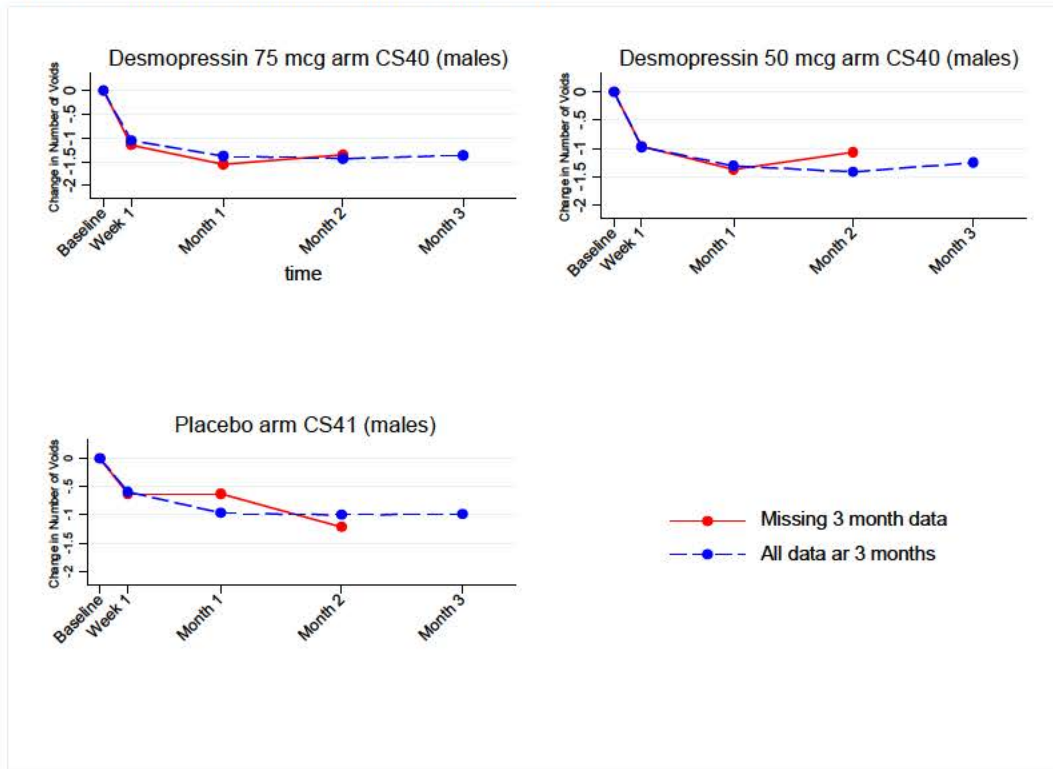
Overall, per ITT, 15.4% of subjects did not have data on number of voids at 3-months visit. As a result of that, only 334 subjects contributed data to the primary analysis. Similar to the study CS40, the number of subjects with missing information at 3 months was slightly smaller when FAS was considered (13.3%). A detailed distribution of missing data is presented in the table below.

A careful examination of missing data patterns revealed that among subjects in the FAS dataset, 39.2% of subjects who did not have voiding data at 3-months visit had provided 1-months data, i.e. those subjects contributed to 1-months analyses but were not evaluated at the end of the study. The percentages of subjects with missing 3-month visit and non-missing 1-month visit were: 31.2% in Desmopressin 50 mcg arm, 38.9% in Desmopressin 75, and 47.6% in placebo.

Table 3. Study CS41 missing data

Dataset	Desmopressin 50 mcg		Desmopressin 75 mcg		Placebo		Total	
	All subjects	Missing at month 3	All subjects	Missing at month 3	All subjects	Missing at month 3	All subjects	Missing at month 3
ITT								
By randomization	123	20(16.3%)	129	23(17.3%)	143	18(12.6%)	395	61(15.4%)
By treatment	124	20(16.1%)	127	22(17.3%)	144	19(13.2%)		

Figure 5. Change in number of voids study CS41



Similar to before, a graphical comparison between subjects who had and those who did not have data at 3-months visit is presented above.

At month one of the study, subjects on the desmopressin 50 mcg arm who did not have a measurement for voids at month 3 had a mean reduction of 1.37 (sd 0.94) voids per night while subjects on the desmopressin 50 mcg arm who had a measurement for voids at month 3 had a mean reduction of 1.30 (sd 1.02) voids per night. So, among those subjects with a month 1 measurement for voids on the desmopressin 50 mcg arm, subjects who did not have a month 3 measurement for voids had a larger mean reduction at month 1 (by 0.07 voids per night) than those subjects who had a month 3 measurement for voids. At month one of the study, subjects on the desmopressin 75 mcg arm who did not have a measurement for voids at month 3 had a mean reduction of 1.56 (sd 0.82) voids per night while subjects on the desmopressin 75 mcg arm who had a measurement for voids at month 3 had a mean reduction of 1.38 (sd 1.03) voids per night. So, among those subjects with a month 1 measurement for voids on the desmopressin 75 mcg arm, subjects who did not have a month 3 measurement for voids had a larger mean reduction at month 1 (by 0.18 voids per night) than those subjects who had a month 3 measurement for voids.

At month one of the study, subjects on the placebo arm who did not have a measurement for voids at month 3 had a mean reduction of 0.62 (sd 0.92) voids per night while subjects on the placebo arm who had a measurement for voids at month 3 had a mean reduction of 0.96 (sd 1.05) voids per night. So, among those subjects with a month 1 measurement for voids on the placebo arm, subjects who did not have a month 3 measurement for voids had a smaller mean reduction at month 1 (by 0.34 voids per night) than those subjects who had a month 3 measurement for voids. The missing data does not seem to have created any bias favoring either desmopressin arm.

A detailed list of missing observations for both studies is presented in the appendix (Tables 6-10). Descriptive statistics for subjects who completed and those who discontinued early are located in the appendix (Tables 8 and 11).

Patient reported outcomes (PRO)

The NQoL is a 13-item questionnaire that assesses the impact of nocturia on QoL and treatment outcomes. It was initially developed from study questionnaires given to men at urology clinics in the United Kingdom, and more recently has been shown to be applicable to women as well. The NQoL was developed to measure the impact of nocturia on quality of life. It is divided into two sections: a Sleep/Energy Domain and a Bother/Concern domain each consisting of 6 questions, and a global quality of life question which is scored separately. The recall period for the test was two weeks. Subjects were asked to score 12 items on a 0-4 scale and the global question on a scale ranging from very good to very poor. Higher numbers indicate a better impact on QoL.

For the submission, the sponsor conducted post-hoc longitudinal analyses (repeated measures ANCOVA adjusting for baseline as a covariate and age stratification factor, treatment, visit, and treatment-by-visit interaction term as factor) to investigate the treatment effect of desmopressin versus placebo on the change from baseline in NQoL domain scores and total score and 3-day average quality-of-sleep score.

In this review, I focused on absolute changes in scores from baseline to the end of study without adjustment for other covariates. The changes in scores were also examined with respect to the

data on nocturnal voids, i.e. comparing PRO results between subjects who prematurely discontinued and those who stayed in the study. Since the number of subjects was small, no formal testing was performed.

Study CS40

The sponsor conducted patient-reported outcomes in the following domains:

1. Quality of Life
2. bother and concern
3. sleep and energy questionnaires

Quality of life, bother and concern, sleep and energy were assessed at two time points, month 1 and 3 months. The number of women who participated in those questionnaires was the same across all domains.

In both arms, the number of subjects at 3-months visit was smaller than the number of subjects at 1-month visit. Only one person in the placebo arm had QOL data available and no nocturnal void data at the 3-months visit.

Table 4. Relationship between PRO outcomes and nocturnal voids data. Study CS40

	Study arm	Study completion status (availability of nocturnal void data at 3-months visit)	
		Void data available	Void data not available
Subjects with available PRO data at <i>month 1</i>	Desmopressin 25	115	13
	Placebo	105	15
Subjects with available PRO data at <i>month 3</i>	Desmopressin 50	115	-
	Placebo	105	1

I examined the scores in all of the domains. Here are my findings (the tables with detailed outcomes on each of the domains are presented in the appendix Tables 12-14).

Quality of life (QOL)

Over 60% of subjects in each arm reported to have no improvements or worsening in quality of life (QOL) scores at month 1 visit. The percentage of subjects with no improvements reduced to approximately 55.7% at 3-months visit. The percent of subjects with no improvements was almost identical in both placebo and treatment arms.

Women in Desmopressin arm who did not have voiding data at 3 months-visit seemed to be more likely not to have improved their QOL score (69.23% of subjects with missing data at 3-months visit compared to 63.48% with of the subjects without missing data at 3 months in the Desmopressin arm). In the placebo arm, the percentages were identical when subjects with and without data at 3-months visit were compared.

Bother/concern score

Overall, bother scores were slightly higher among subjects with no improvement in the placebo arm when compared to the Desmopressin arm (18.75% versus 23.33% at month 1 and 13.04% versus 17.92% at month 3). At month 1, subjects who did not have void data at month 3 visit showed a higher level of subjects with no improvements in bother scores (30.77% in Desmopressin arm and 33.33% in placebo arm versus 17.39% in Desmopressin arm and 21.9% in placebo subjects who had no missing data at visit 3). These results might not be very reliable since the number of subjects with missing data was small.

Sleep/energy score

At month 1, 26.56% of subjects on Desmopressin and 16.67% on placebo did not have improvements in their sleep score. Among subjects in the treatment arm who had missing data at 3-months visit, 46% were women who did not have improvements in the sleep/energy score. In the placebo arm, only 26.67% of the subjects who did not have data at 3-months visit did not report improvements in the sleep score.

At the end of the trial (3 months), the percentages of subjects with no improvements in sleep/energy scores were similar in both arms (16.52% in the treatment arm and 19.81% in the placebo arm).

Study CS41

Similar to study CS40, quality of life, bother and concern, sleep and energy were assessed at two time points, month 1 and 3 months. The number of men who participated in those questionnaires was the same across all domains.

In all three study arms, the number of subjects at the 3-months visit was smaller than the number of subjects at the 1-month visit. Two subjects in the Desmopressin 75 mg arm and 3 subjects in the placebo arm had QOL data available but no nocturnal void data at the 3-months visit.

Table 5. Relationship between PRO outcomes and nocturnal voids data. Study CS41

	Study arm	Study completion status (availability of nocturnal void data at 3-months visit)	
		Void data available	Void data not available
Subjects with available PRO data at <i>month 1</i>			
	Desmopressin 50	104	9
	Desmopressin 75	115	10
	Placebo	125	13
Subjects with available PRO data at <i>month 3</i>	Desmopressin 50	104	-
	Desmopressin 75	104	2
	Placebo	124	3

Quality of life (QOL)

At month 1, the fraction of subjects who discontinued study participation before month 3 and showed worsening or unchanged QOL scores was larger than the fraction of subjects who experienced no improvements in those scores among subjects who had voiding data at 3-months visit.

At month 3, the largest percent of subjects who did not experience changes in QOL or got worse was among subjects on placebo (94 subjects, 74.02%) followed by Desmopressin 75 (66 subjects, 62.26%) and Desmopressin 50 (60 subjects, 57.69%).

Overall, in all treatment arms and in all categories of study participation, more than 50% of subjects showed worsening or no improvement in quality of life.

Bother/concern score:

Overall, the percentage of subjects who showed no improvement or worsening in their bother/concern score was around 30% at month 1, and 26% at month 3.

At month 1, the percentage of subjects who did not have improvements in their bother/concern scores was larger among the subjects who had no voiding data at month 3. In this situation, the calculated percentages might not provide reliable results since the numbers of subjects in those categories was very small.

Sleep/energy score:

At month 1, an overall trend in sleep/energy score showed that the largest fraction of subjects who did not have an improvement was in placebo (34.78%), followed by Desmopressin 75 (33.91%) and Desmopressin 50 (24.78%). At month 3 the percentages of subjects who did not improve were similar in the Desmopressin 75 and placebo arms (33.02% and 30.71%).

At month 1, the trends for subjects who did not have voiding data at month 3 were similar to the overall trends, but since the numbers of those subjects were very small, it is difficult to make any reliable conclusions.

The tables with detailed outcomes on each of the domains are presented in the appendix (Tables 15-17).

2.3 Evaluation of Safety

An evaluation of the safety of desmopressin presented in this submission is included in the clinical review by Dr. William Lubas.

3 SUMMARY AND CONCLUSIONS

3.1 Statistical Issues

Missing data

Lack of improvement in the primary efficacy endpoint (number of nocturnal voids) may have been a factor in some women discontinuing participation in the study CS40 before the 3-months

visit. Efficacy may be overstated when that population is excluded from the analysis. Therefore, interpretation of the study results should recognize the amount of missing data. In my evaluation, the study CS41 which included only male participants did not have similar patterns of missing data.

Patient reported outcomes

The sponsor's definitions of the responder in PRO analysis and in primary analysis were different.

Surprisingly, although QOL scores were worse among men who discontinued the study in CS41 than among those who completed the study, the change in nocturnal voids was the same for each completion status. Either the perceived and actual outcomes are not aligned or the survey did not fully capture the subjects' perceptions of their experience during the study.

3.2 Conclusions and Recommendations

As it was mentioned in the paragraph above, the lack of improvement could have been a contributing factor to the early study discontinuation. Therefore the issue of missing data should be addressed when the outcomes of this study are going to be presented. Sensitivity analyses involving different scenarios (e.g. return to the baseline void count etc) for the subjects who left the study prematurely might be able to provide more insight into understanding of the data.

I recommend additional studies that include a placebo run-in period and then has those subjects with inadequate changes in the number of voids randomized to placebo or desmopressin. Such studies were mentioned at the advisory committee meeting by advisory committee members. All randomized subjects should be followed for outcomes including those who have discontinued their assigned treatment.

APPENDICES

Study CS40

Table 6. Study CS40: Numbers of missing subjects per visit

Visit	ITT(per randomization)		
	Desmopressin 25 mcg	Placebo	Total
Day 4	6	3	9
Week 1	9	7	16
Month 1	11	10	21
2 Months	16	15	31
3 Months	24	24	48
Total	66	59	125

The columns of the table show the number of subjects who had missing data at each specific visit. The numbers presented in the rows are not mutually exclusive, i.e. a subject could have discontinued participation in the study at month1, therefore, her data will show as missing at 2-months and at 3-months visits. The red rectangle delineates the number of subjects missing at the end of the study.

Table 7. Study CS40 Last data available by visit (Visit at which the subject finished her study participation)

VISIT	ITT (per randomization)		
	Desmopressin 25 mcg	Placebo	Total
Baseline	5	3	8
Day 4	2	3	5
Week 1	4	3	7
Month 1	5	5	10
2 Months	8	10	18
3 Months	113	107	220
Total	137	131	268

The columns of the table show the visit at which study participants discontinued their participation in the trial. The numbers presented in the rows are mutually exclusive, i.e. 220 subjects completed the study, 18 subjects discontinued after the 2-months visit, etc. The red rectangle delineates the number of subjects who completed the study, i.e. had their last study visit at 3 months.

B. Second co-primary endpoint (33% responder status during the three months of treatment)

The missing data rate was similar across all arms and across all nights.

Comparison between subjects who had observations available at 3 month visit and those who had no observations at 3 months.

Baseline data: the baseline age and initial number of voids per night were similar among subjects who had measurements at 3 months and those who did not complete the study. Height, weight and BMI were statistically different only in the treatment arm: $p=0.0008$, $p=0.0208$, and $p=0.2026$.

Table 8. Study CS40: Baseline data

Desmopressin 25 mcg no missing data at visit 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
Baseline # of voids	113	2.7	2.0	9.7	2.8	0.9
AGE	113	62.0	19.0	81.0	58.9	14.3
BMI	113	31.1	18.2	50.5	31.8	7.2
WEIGHT	113	80.1	51.2	135.8	83.7	19.5
HEIGHT	113	1.6	1.5	1.8	1.6	0.1

Desmopressin 25 mcg those who had data missing at month 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
Baseline # of voids	20	2.8	2.0	4.3	2.8	0.7
AGE	20	66.0	28.0	80.0	62.9	14.1
BMI	20	28.8	19.2	42.1	29.6	5.9
WEIGHT	20	73.2	47.4	117.3	72.9	16.3
HEIGHT	20	1.6	1.4	1.7	1.6	0.1

Placebo no missing data at visit 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
Baseline # of voids	107	2.7	2.0	7.0	2.9	0.8
AGE	107	63.0	23.0	87.0	59.6	14.5
BMI	107	28.6	17.9	46.6	29.2	6.6
WEIGHT	107	73.4	49.7	139.5	78.1	19.6
HEIGHT	107	1.6	1.5	1.8	1.6	0.1

Placebo those who had data missing at month 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
Baseline # of voids	21	2.7	2.0	4.0	2.8	0.7
AGE	21	65.0	41.0	85.0	62.7	11.5
BMI	21	28.0	18.2	43.3	28.4	6.6
WEIGHT	21	76.2	51.5	114.4	77.0	18.3
HEIGHT	21	1.7	1.5	1.8	1.6	0.1

Study CS41

Numbers of missing subjects per visit (subject might have only skipped a visit and came back for the next visit, therefore the total number should be equal or less than the number of subjects who exited the study at that particular visit)

Table 9. Study CS41 Numbers of missing subjects per visit

Visit	ITT(per randomization)			
	Desmopressin 50 mcg	Desmopressin 75 mcg	Placebo	Total
Day 4	4	7	3	14
Week 1	7	9	2	18
Month 1	11	12	4	27
2 Months	16	16	11	43
3 Months	20	23	18	61
Total	58	67	38	163

The columns of the table show the number of subjects who had missing data at each specific visit. The numbers presented in the rows are not mutually exclusive, i.e. a subject could have discontinued participation in the study at month1, therefore, his data will show as missing at 2-months and at 3-months visits. The red rectangle delineates the number of subjects missing at the end of the study.

Table 10. Study CS41 Last data available by visit (Visit at which the subject finished her study participation)

VISIT	ITT(per randomization)			
	Desmopressin 50 mcg	Desmopressin 75 mcg	Placebo	Total
Baseline	4	7	1	12
Day 4	3	0	0	3
Week 1	4	5	3	12
Month 1	4	4	6	14
2 Months	5	7	8	20
3 Months	103	106	125	334
Total	123	129	143	395

The columns of the table show the visit at which study participants discontinued their participation in the trial. The numbers presented in the rows are mutually exclusive, i.e. 334 subjects completed the study, 20 subjects discontinued after the 2-months visit, etc. The red rectangle delineates the number of subjects who completed the study, i.e. had their last study visit at 3 months.

Comparison between subjects who had observations available at 3 month and those who had no observations at 3 months visit.

Table 11. Stdy CS41: Baseline data

Desmopressin 50 mcg no missing data at visit 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
base	103	2.7	2.0	6.0	2.8	0.8
AGE	103	64.0	20.0	81.0	60.3	13.4
BMIBL	103	28.9	19.9	41.7	29.2	4.5
WEIGHTBL	103	90.0	56.5	139.1	91.7	17.0
HEIGHTBL	103	1.8	1.6	2.0	1.8	0.1

Desmopressin 50 mcg those who had data missing at month 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
base	16	3.0	2.0	5.5	3.2	1.0
AGE	16	63.0	39.0	79.0	64.6	11.6
BMIBL	16	29.5	23.5	50.1	30.0	6.4
WEIGHTBL	16	93.1	67.6	176.9	93.6	25.8
HEIGHTBL	16	1.8	1.6	1.9	1.8	0.1

Desmopressin 75 mcg no missing data at visit 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
base	106	2.7	2.0	6.3	2.9	0.9
AGE	106	64.0	29.0	80.0	59.7	11.9
BMIBL	106	27.9	16.1	47.0	28.7	4.6
WEIGHTBL	106	88.3	50.8	147.9	90.9	16.9
HEIGHTBL	106	1.8	1.6	1.9	1.8	0.1

Desmopressin 75 mcg those who had data missing at month 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
base	18	3.3	1.7	4.7	3.4	0.8
AGE	18	65.0	44.0	77.0	62.4	9.9
BMIBL	18	31.7	19.6	43.3	31.8	5.4
WEIGHTBL	18	97.0	63.6	152.8	100.2	20.5
HEIGHTBL	18	1.8	1.7	2.0	1.8	0.1

Placebo no missing data at visit 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
base	125	2.7	2.0	5.7	2.9	0.8
AGE	125	64.0	21.0	87.0	60.8	14.2
BMIBL	125	28.5	18.0	48.5	29.4	5.3
WEIGHTBL	125	88.6	47.7	155.3	91.8	18.7
HEIGHTBL	125	1.8	1.6	1.9	1.8	0.1

Placebo those who had data missing at month 3

Variable	N	Median	Minimum	Maximum	Mean	Std Dev
base	17	2.7	1.0	4.3	2.8	0.8
AGE	17	64.0	35.0	83.0	60.4	14.7
BMIBL	17	28.9	19.9	39.1	28.3	4.7
WEIGHTBL	17	93.2	57.6	128.7	91.5	17.7
HEIGHTBL	17	1.8	1.7	1.9	1.8	0.0

When compared within each arm, the baseline characteristics were similar in subjects with and without observations at month 3. The only differences that were statistically significant were the variables weight and BMI in the 75 mcg arm, with p-values $p=0.0389$ and $p=0.0116$ respectively.

PRO Study CS40

Table 12. Study CS40: Quality of life domain: results with respect to nocturnal voids.

	ARM	Nocturnal voids data status at 3-months visit (missing yes/no)	Unchanged or worse		better	
			n	%	n	%
baseline to month 1	Desmopressin 25	No	73	63.48	42	36.52
		Yes	9	69.23	4	30.77
	Placebo	No	63	60.00	42	40.00
		Yes	9	60.00	6	40.00
Baseline to month 3	Desmopressin 25	No	64	55.65	51	44.35
	Placebo	No	58	55.24	47	44.76
		Yes	1	100.00	-	-
baseline to month 1	Desmopressin 25	All	82	64.06	46	35.94
	Placebo	All	72	60.00	48	40.00
baseline to month 3	Desmopressin 25	All	64	55.65	51	44.35
	Placebo	All	59	55.66	47	44.34

Table 13. Study CS40: Bother/concern domain: results with respect to nocturnal voids.

bother/concern questionnaire	ARM	Nocturnal voids data status at 3-months visit (missing yes/no)	Unchanged or worse		better	
			n	%	n	%
baseline to month 1	Desmopressin 25	No	20	17.39	95	82.61
		Yes	4	30.77	9	69.23
	Placebo	No	23	21.90	82	78.10
		Yes	5	33.33	10	66.67
baseline to month 3	Desmopressin 25	No	15	13.04	100	86.96
	Placebo	No	19	18.10	86	81.90
		Yes	1	100.00	-	-
baseline to month 1	Desmopressin 25	All	24	18.75	104	81.25
	Placebo	All	28	23.33	92	76.67
baseline to month 3	Desmopressin 25	All	15	13.04	100	86.96
	Placebo	All	19	17.92	87	82.08

Table 14. Study CS40 Sleep/energy domain: results with respect to nocturnal voids.

Sleep/energy questionnaire	ARM	Nocturnal voids data status at 3-months visit (missing yes/no)	Unchanged or worse		better	
			n	%	n	%
baseline to month 1	Desmopressin 25	No	28	24.35	87	75.65
		Yes	6	46.15	7	53.85
	Placebo	No	16	15.24	89	84.76
		Yes	4	26.67	11	73.33
Baseline to month 3	Desmopressin 25	No	19	16.52	96	83.48
	Placebo	No	21	20.00	84	80.00
		Yes	1	100.00	-	-
baseline to month 1	Desmopressin 25	All	34	26.56	94	73.44
	Placebo	All	20	16.67	100	83.33
baseline to month 3	Desmopressin 25	All	19	16.52	96	83.48
	Placebo	All	21	19.81	85	80.19

PRO Study 41

Table 15. Study CS41: Quality of life domain: results with respect to nocturnal voids.

QOL questionnaire	ARM	Nocturnal voids data status at 3-months visit (missing yes/no)	Unchanged or worse		better	
			n	%	n	%
baseline to month 1	Desmopressin 50	No	61	58.65	43	41.35
		Yes	6	66.67	3	33.33
	Desmopressin 75	No	72	68.57	33	31.43
		Yes	8	80.00	2	20.00
	Placebo	No	91	72.80	34	27.20
		Yes	12	92.31	1	7.69
Baseline to month 3	Desmopressin 50	No	60	57.69	44	42.31
	Desmopressin 75	No	65	62.50	39	37.50
		Yes	1	50.00	1	50.00
	Placebo	No	91	73.39	33	26.61
		Yes	3	100.00	-	-
baseline to month 1	Desmopressin 50	All	67	59.29	46	40.71
	Desmopressin 75	All	80	69.57	35	30.43
	Placebo	All	103	74.64	35	25.36
baseline to month 3	Desmopressin 50	All	60	57.69	44	42.31
	Desmopressin 75	All	66	62.26	40	37.74
	Placebo	All	94	74.02	33	25.98

Table 16. Study CS41: Bother/concern domain: results with respect to nocturnal voids.

Bother/concern questionnaire	ARM	Nocturnal voids data status at 3-months visit (missing yes/no)	Unchanged or worse		better	
			n	%	n	%
baseline to month 1	Desmopressin 50	No	33	31.73	71	68.27
		Yes	3	33.33	6	66.67
	Desmopressin 75	No	30	28.57	75	71.43
		Yes	4	40.00	6	60.00
	Placebo	No	37	29.60	88	70.40
		Yes	5	38.46	8	61.54
Baseline to month 3	Desmopressin 50	No	27	25.96	77	74.04
		Yes	25	24.04	79	75.96
	Desmopressin 75	No	-	-	2	100.00
		Yes	32	25.81	92	74.19
	Placebo	No	32	25.81	92	74.19
		Yes	1	33.33	2	66.67
baseline to month 1	Desmopressin 50	All	36	31.86	77	68.14
	Desmopressin 75	All	34	29.57	81	70.43
	Placebo	All	42	30.43	96	69.57
baseline to month 3	Desmopressin 50	All	27	25.96	77	74.04
	Desmopressin 75	All	25	23.58	81	76.42
	Placebo	All	33	25.98	94	74.02

Table 17. Study CS41: Sleep/energy domain: results with respect to nocturnal voids.

Sleep/energy questionnaire	ARM	Nocturnal voids data status at 3-months visit (missing yes/no)	Unchanged or worse		better	
			n	%	n	%
baseline to month 1	Desmopressin 50	No	26	25.00	78	75.00
		Yes	2	22.22	7	77.78
	Desmopressin 75	No	34	32.38	71	67.62
		Yes	5	50.00	5	50.00
	Placebo	No	41	32.80	84	67.20
		Yes	7	53.85	6	46.15
Baseline to month 3	Desmopressin 50	No	26	25.00	78	75.00
		Yes	34	32.69	70	67.31
	Desmopressin 75	No	1	50.00	1	50.00
		Yes	39	31.45	85	68.55
	Placebo	No	39	31.45	85	68.55
		Yes	-	-	3	100.00
baseline to month 1	Desmopressin 50	All	28	24.78	85	75.22
	Desmopressin 75	All	39	33.91	76	66.09
	Placebo	All	48	34.78	90	65.22
baseline to month 3	Desmopressin 50	All	26	25.00	78	75.00
	Desmopressin 75	All	35	33.02	71	66.98
	Placebo	All	39	30.71	88	69.29

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/s/

ANNA E KETTERMANN
01/30/2015

MARK D ROTHMANN
01/30/2015
I concur

Division Director's Memo

Date	January 30, 2013
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA #	22-517
Supplement #	
Applicant Name	Ferring Laboratories
Date of Submission	30 July 2012
PDUFA Goal Date	30 January 2013
Proprietary Name / Established (USAN) Name	Nocdurna
Dosage Forms / Strength	25 and 50 mcg orally disintegrating tablets
Proposed Indication(s)	Adult nocturia
Action/Recommended Action for NME:	Complete Response

Introduction

Ferring Pharmaceuticals has submitted its response to a Complete Response (CR) letter issued on 22 April 2010 for NDA 22-517 in which the applicant is seeking approval of Nocdurna for the treatment of nocturia in adults. Nocturia is defined by the International Continence Society as the complaint by an individual who has to awake at night one or more times to void. Please see my memo dated 22 April 2010 for a discussion of the original application.

Vasopressin is a hypothalamic neuropeptide synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and stored in the posterior pituitary where it is released in response to osmotic and non-osmotic stimuli. For purposes of this application, the function of vasopressin as an anti-diuretic hormone to maintain normal plasma osmolality is the primary focus for efficacy and safety, as it is this action of the hormone that Ferring is making use of for the treatment of nocturia. Vasopressin binds to the vasopressin-2 (V2) receptors located on the renal collecting tubules where their stimulation results in renal water conservation to maintain plasma osmolality with a narrow range of 280 to 285 mEq/L.

Nocdurna or desmopressin is a synthetic vasopressin analogue. Unlike the endogenous neurohormone, the vasopressin analogues have a longer half-life and greater V2 receptor selectivity, minimizing the vasoconstrictive effects of vasopressin on V1 receptors.

In this resubmission, the results of two placebo-controlled clinical trials (CS40 and CS41) were provided to specifically address the clinical deficiency identified in the CR letter. In

addition, data from an extension study evaluating quality of life measures and a 4-week comparative toxicology study were provided. This memo will focus predominantly on the findings from CS40 and CS41. The reader is referred to Dr. Dragos Roman's cross-discipline team leader (CDTL) memo and the specific discipline reviews for a complete review of this resubmission.

Background

The original NDA relied on the findings from a single trial comprised of a 28-day randomized, double-blind, placebo-controlled period evaluating 4 doses of Nocdurna (10, 25, 50 and 100 mcg) followed by an open-label extension. The study employed two co-primary efficacy endpoints: the change in the mean number of nocturnal voids from baseline to Day 28 and the proportion of subjects with > 33% reduction in the mean number of nocturnal voids from baseline to Day 28. A statistically significant finding was only obtained with Nocdurna 100 mcg; however, this dose was accompanied by a high rate of hyponatremia. Several post-hoc subgroup analyses were performed by dose and gender, lending to different conclusions on efficacy and safety by different review disciplines but all suggesting that a lower dose and differential effect by gender should be further investigated to determine if a safe and effective regimen could be identified. The CR letter outlined this deficiency as follows:

In order to address this deficiency, you must conduct a clinical trial to confirm that a lower dosing regimen is a safe and effective treatment of adult nocturia. This trial should be a placebo-controlled trial with a minimum duration of 3 months to evaluate a longer period of durability and safety relative to placebo.

The CR letter also outlined other discipline-specific deficiencies which have been addressed in Dr. Roman's CDTL memo and I will not reiterate in my memo. However, I would note that the following comment was relayed under a subsection titled "Clinical Comments Not Related to Approvability"

1. Your clinical development program did not provide any direct evidence that reduced frequency of nocturnal voids is associated with a clinical benefit. References to increased risk of fractures in patients with nocturia are examples of an association and no conclusion can be made that treating nocturia will reduce the incidence of fractures. Similarly, you were not able to determine if reduced frequency in nocturnal voids would provide a meaningful benefit in the individual's health-related quality of life. Although improved health-related quality of life does not form the basis for approval of this product, demonstration of such an improvement utilizing a tool that is acceptable to the Agency's Study Endpoints and Labeling Development (SEALD) team will provide supportive evidence for treating nocturia.

The CR letter did not identify the absence of an acceptable patient-reported outcome (PRO) measure as an absolute deficiency to be addressed with this resubmission although it did

express the uncertainty of clinical benefit associated with numeric reductions in nocturnal void. An acceptable PRO for which demonstration of a positive effect of Nocturna could be established through this tool would certainly help in the setting of marginal benefit or concerning risks associated with the drug. With this resubmission, reliance on a PRO has moved to the forefront of necessary data for an approval consideration.

Clinical/Statistical-Efficacy

The applicant conducted two new 3-month, placebo-controlled clinical studies to address the CR letter. Study CS40 evaluated the 25 mcg dose of Nocturna in women and Study CS41 evaluated the 50 and 75 mcg doses in men. Both studies employed similar designs and relied on two co-primary efficacy endpoints: change from baseline in the average number of nocturnal voids over 3 months and 33% responder status over 3 months. The protocols for both studies were reviewed as special protocol assessments (SPA) with input from FDA to address the shortcomings of the single trial reviewed in the original NDA submission. Please see Dr. Lubas' primary medical review and Dr. Liu's statistical review as well as Dr. Roman's CDTL memo for a thorough discussion of the trial design, execution, and analysis plans.

The following table from Dr. Liu's review summarizes the overall findings from both studies for the primary efficacy endpoints.

Table 1. 1. Efficacy Summary in Desmopressin and Placebo Treated Patients during 3 Months (ITT/FAS)¹

CS40, Females	Placebo		Desmopressin 25 µg		p-value
Mean number of nocturnal voids	n	# voids	n	# voids	
Baseline mean ± SE	128	2.88 ± 0.07	133	2.84 ± 0.08	
Adj. Mean Change from baseline ±SE	128	-1.23 ± 0.07	133	-1.47 ± 0.07	
Adj. LS Mean Treatment Difference (95% CI)				-0.24 (-0.44, -0.04)	0.0194
33% responder status	n		n		
Adjusted Mean Probability	128	0.63	133	0.76	
Odds		1.72		3.12	
Odds ratio, adj. LS Mean (95% CI)				1.81 (1.16, 2.82)	0.0095
CS41, Males	Placebo		Desmopressin 75 µg		p-value
Mean number of nocturnal voids	n	# voids	n	# voids	
Baseline mean ± SE	142	2.90 ± 0.07	124	2.99 ± 0.08	
Adjusted Mean Change from baseline ±SE	142	-0.88 ± 0.07	124	-1.28 ± 0.07	
Adj. LS Mean Treatment Difference (95% CI)				-0.40 (-0.60, -0.20)	< .0001
33% responder status	n		n		
Adjusted Mean Probability	142	0.50	124	0.67	
Odds		1.00		2.02	
Odds ratio, adjusted LS Mean (95% CI)				2.02 (1.36, 3.00)	0.0005
CS41, Males	Placebo		Desmopressin 50 µg		
Mean number of nocturnal voids	n	# voids	n	# voids	
Baseline mean ± SE	142	2.90 ± 0.07	119	2.88 ± 0.08	
Adj. Mean Change from baseline ±SE	142	-0.88 ± 0.07	119	-1.27 ± 0.08	
Adj. LS Mean Treatment Difference (95% CI)				-0.37 (-0.57, -0.17)	0.0003
33% responder status	n		n		
Adjusted Mean Probability	142	0.50	119	0.67	
Odds		1.00		2.00	
Odds ratio, adjusted LS Mean (95% CI)				2.00 (1.33, 3.01)	0.0008

¹ average of week-1, month-1, month-2, and month-3, with treatment-by-visit interaction term in the model (interaction term pre-specified)

Efficacy in Women

Statistically significant differences in treatment effect on each co-primary endpoint were demonstrated in women treated with Nocdurna 25 mcg over placebo; however, the continuous co-primary endpoint for mean change from baseline was only nominally significant (p=0.019). Furthermore, the results were not robust as sensitivity analyses based on the per protocol population and “as treated” population no longer yielded statistically significant results (p>0.05). For example, two patients randomized to placebo were identified as receiving desmopressin in error. Re-analysis of the primary endpoint was not significant (p>0.06).

To describe the non-robustness of the treatment effect in a clinical setting, one can consider the mean reduction in number of nocturnal voids in both Nocdurna and placebo groups. Both treatment groups had a baseline mean of approximately 2.8 voids per night. At the end of treatment, the mean change from baseline in number of voids was approximately 1.46 in Nocdurna versus 1.24 in placebo with a treatment difference of -0.22 voids per night. Since it is difficult to conceptualize what a fraction of a void means clinically, Dr. Roman presents these differences as it might appear over the course of a week. In his memo he extrapolates the findings from CS40 wherein a patient with 20 baseline weekly nocturnal voids has a reduction to 10 voids per week while on Nocdurna versus a reduction to about 12 voids per week while on placebo.

Even describing the treatment difference in actual whole number of voids, the clinical relevance of ~2 fewer voids in a week is open to subjective interpretation. For example, the argument that fewer episodes of nocturnal voids may reduce the risk of fall and fractures in the elderly can be countered by one's position that any one of the remaining nocturnal voids can still be the index fracture event for the patient. In other words, not having some means of attributing clinical relevance to this small treatment effect leaves the conclusion of benefit very open to interpretation.

Efficacy in Men

Statistically significant differences in treatment effect on each co-primary endpoint were demonstrated in men treated with Nocdurna 50 and 75mcg over placebo. Unlike the findings in CS40, statistically significant differences on both co-primary endpoints were observed and unaltered by sensitivity analyses. There was little difference in efficacy between the two doses.

Despite the consistent statistically significant effect of Nocdurna in men across different analyses, the clinical relevance of a placebo-subtracted difference of ~ 0.4 voids per night remains questionable. A similar exercise of extrapolating these findings to one week's duration was undertaken by Dr. Roman wherein a male patient treated with 50 mcg of Nocdurna might experience a reduction from 20 nocturnal voids to 9 within a week versus 13 in the placebo group is still subject to interpretation.

In the primary medical officer's review, Dr. Lubas is impressed with the change from baseline in both studies. Indeed, one can easily conclude that a 50% reduction from baseline in the number of times one is awoken at night is relevant but when one takes into consideration what can also be achieved in the placebo group, that change from baseline with Nocdurna seems less impressive. In his review, Dr. Lubas argues for the approval of Nocdurna by discounting the placebo effect because "the placebo response overestimates what can be achieved in a usual care setting, where patients may be less likely to strictly follow dietary recommendations and may be less compliant with filling out 3-day voiding diaries and measuring fluid intake and urine output. That said, there is no current available therapy for this indication and a placebo is not a viable option."

While I appreciate Dr. Lubas' position, I am not in agreement with his arguments for the following reasons:

- While it may be that a greater response (i.e., reduction in nocturnal voids) in the placebo group can be attributed to the lifestyle interventions imposed by the clinical protocols, these same interventions were applied to the Nocdurna groups as these were double-blinded, randomized trials and there was no evidence that the groups were treated differently throughout the trial. Hence it could also be argued that the lifestyle intervention in the clinical trials 'overestimates what can be achieved with Nocdurna' and that in a usual care setting where patients become more complacent with fluid restriction and record-keeping, the change from baseline for Nocdurna may not be as impressive.

- Placebo in the form of a sugar-pill prescribed by a healthcare provider may not be a viable option but in these trials we should view the placebo pill as a means to maintaining the double-blind so that behaviors are not altered based on one's knowledge of treatment assignment. With that in mind, what is being prescribed in the trial was lifestyle intervention, which is certainly a viable option for the treatment of nocturia.

As stated under the Background section, the applicant was informed that having an acceptable quality of life measure may provide supportive evidence to better interpret the clinical relevance of small changes in frequency of nocturnal voids. The applicant provided data from the Nocturia Quality of Life (NQoL) questionnaire, the Work Productivity and Activity Index (WPAI), and a recently developed Nocturnal Impact Diary. The first two tools were deemed unacceptable measures after review by the Study Endpoints and Labeling Development (SEALD) team during the first review cycle. Deficiencies of these two tools were conveyed to the applicant. The Nocturnal Impact Diary was developed with advice from SEALD and while it appears promising, the one study evaluating its use was not adequately powered to show an effect on quality of life measures. Please see the reviews of Dr. James Stanbury from SEALD for details. In short, no patient-reported outcome measures supporting clinical benefit of Nocdurna could be gleaned from this resubmission.

Safety

The primary safety concern with this product is hyponatremia. This risk was observed in the original submission at the higher proposed dose of Nocdurna 100 mcg and formed the basis for a complete response action. As has already been described in previous memos, hyponatremia is an expected outcome based on the pharmacologic effect of the drug inhibiting free water clearance. Other factors contribute to this risk including inappropriate intake of fluids, medications, and loss of sodium (e.g., renal or GI losses) out of proportion to free water excretion, which would be impaired because of this drug.

Hyponatremia is more often a laboratory finding but clinical signs and symptoms may arise if the degree of hyponatremia is marked or the decrease is acute. Inappropriate correction of hyponatremia, particularly rapid correction of chronic hyponatremia, may also result in serious and permanent neurologic damage. While such events may be rare the consequences are devastating.

The applicant has proposed a lower dosing regimen for men and women and while no serious adverse events due to hyponatremia occurred, the incidence of hyponatremia was still higher with Nocdurna 25 and 50 mcg than placebo. In CS40, three women receiving Nocdurna 25 mcg versus none on placebo had serum sodium levels between 126 and 129 mmol/L. In CS41, severe hyponatremia (serum sodium $\leq$ 125 mmol/L) was seen in two men receiving Nocdurna 50 mcg and four men receiving Nocdurna 75 mcg versus none on placebo. No serious adverse events were reported as a result of these laboratory abnormalities but this is not unexpected given the closer monitoring in a clinical trial prompting treatment discontinuation.

Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

In its resubmission, Ferring followed the advice of FDA to prospectively evaluate lower doses of Nocdurna in males and females with nocturia for a longer period of assessment than originally done in CS29. The two studies conducted in response to the CR letter provided a thorough and adequate assessment of the efficacy of Nocdurna.

The most concerning risk associated with Nocdurna is dilutional hyponatremia, which if severe can result in serious neurologic damage and death. In this resubmission, the risk of hyponatremia with Nocdurna is evident; however, there were no serious adverse events attributed to any reports of hyponatremia. This finding is reassuring but there is an element of false security given the protocol-imposed patient screening and monitoring. It remains to be seen if patients will be amenable to return to their doctor's office or a laboratory facility to have a serum sodium level measured and whether reports of these values will reach the patient in a timely fashion. Furthermore, the risk of hyponatremia isn't entirely dependent on the dose of Nocdurna but on the behavior and concurrent medical conditions of the patient. Laxity in adherence to fluid restriction while on Nocdurna will increase the risk of hyponatremia. Similarly, changes in medications or medical conditions may also increase this risk.

At issue here is weighing this risk of hyponatremia and the potential for serious cases observed postmarketing with the modest reductions in nocturnal voids associated with Nocdurna. Dr. Roman has suggested identifying a patient population who despite lifestyle intervention, still presents with nocturia and might be a population to evaluate any added treatment effect of Nocdurna. A prospective evaluation of the Nocturia Index Diary could also be tested in this patient population. I concur with his recommendation to require further studies of Nocdurna to better define the clinical benefit of reducing frequency of nocturnal voids to offset the potential for hyponatremia.

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/s/

MARY H PARKS
01/30/2013

Cross-Discipline Team Leader Review

Date	1/28/2013
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-517 (supplement 17)
Supplement#	
Applicant	Ferring Pharmaceuticals
Date of Submission	July 30, 2012
PDUFA Goal Date	January 30, 2013
Proprietary Name / Established (USAN) names	Nocdurna (desmopressin)
Dosage forms / Strength	Orally disintegrating tablets 25 mcg and 50 mcg
Proposed Indication(s)	Nocturia
Recommended:	Complete Response

1. Introduction

On July 30, 2012 Ferring Pharmaceuticals submitted the current NDA efficacy supplement (Supplement 17) as a response to the Complete Response letter issued by the Agency on April 22, 2010, to NDA 22-517, a 505(b)(2) application in support of Nocdurna (desmopressin acetate) for the treatment adult nocturia. The original NDA (SN 0000) was submitted on 6/19/2009; it included a newly developed orally disintegrating formulation, a sublingual tablet that referenced desmopressin tablets as the listed drug for the non-clinical toxicology program.

The April 22, 2010 Complete Response letter highlighted the following deficiencies:

- 1) Clinical/statistical: The 100 mcg Nocdurna dose, although effective, was associated with an unacceptable risk of severe hyponatremia. The Division advised the applicant to evaluate lower desmopressin doses in a new placebo-controlled clinical trial. The basis for this recommendation was the observation that the risk of hyponatremia was less with lower doses, but that such doses had not been formally evaluated in a hypothesis driven trial. The letter also pointed out that there were gender-specific differences in efficacy and that this observation should be addressed in future trials.
- 2) Clinical Pharmacology: Because the pharmacokinetic information of the to-be-marketed formulation was obtained with an analytical method that was not properly validated¹, the applicant was asked to reanalyze the data from the bioequivalence study CS019 with a validated analytical method, and to collect and analyze pharmacokinetic samples in future clinical trials.

¹ The Applicant used a radioimmunoassay for the analysis of plasma samples in several clinical pharmacology studies, but the assay was rejected by FDA.

3) Nonclinical: the applicant was informed of the need to conduct a comparative toxicology study of one month duration comparing Nocdurna to the listed drug product in order to “bridge” the orally disintegrating formulation to the data obtained with the listed desmopressin.

Additional comments (i.e. not related to approvability) were provided stressing the following: 1) the lack of any direct evidence that the reduced frequency of nocturnal voids seen with Nocdurna was associated with a clinical benefit; 2) the absence of an acceptable, validated tool to be used for evaluation of the effect of Nocdurna on health-related quality of life endpoints (the applicant was advised to develop such an instrument with advice from the Agency’s Study Endpoints and Labeling Development (SEALD) team); 3) the need to formally evaluate the proposed monitoring scheme for hyponatremia, a scheme that was proposed after analyzing the data obtained in the Phase 3 trial, but which has not been tested prospectively or confirmed independently in another clinical trial; 4) the applicant was advised to collect pharmacokinetic samples in future trials in order to conduct exposure-response analyses, and to improve and validate the bioanalytical methods used to analyze such samples.

There were multiple interactions between the FDA (specifically, the Division and the SEALD team) and the applicant:

- An End-of-Review meeting took place on 10/14/2010. The meeting covered a broad range of issues related to dose selection, choice of endpoints and design of the new phase 3 clinical trials, development and validation of a patient reported outcomes (PRO) questionnaire, content of a complete response NDA supplement.
- Two SPA assessments for two new clinical studies, one to explore a dose of 25 mcg in females, and one to evaluate the 50 mcg and 75 mcg desmopressin doses in males.
- Advice was provided regarding the development and qualification of a new PRO, the Nocturia Impact Diary (NI Diary), and how to implement it in the existing Nocdurna clinical program.
- Agreement was reached regarding the submission of a comparative toxicokinetic study protocol for review.

As a result of these discussions, Ferring Pharmaceuticals has submitted the current supplement that includes the following:

- Two clinical trials, studies CS40 and CS41, which evaluate lower dosing regimens of Nocdurna, thus addressing the clinical deficiency identified in the Complete Response letter.
- A four-week toxicology study comparing Nocdurna with the reference listed drug (this was a response to the non-clinical deficiency identified in the Complete Response letter).
- A study (CS000034) that evaluated the newly developed PRO (the Nocturia Impact Diary) in women and men with nocturia treated with Nocdurna.

2. Background

General background information was presented in the CDTL review associated with the original Nocurna submission. Briefly, desmopressin is a synthetic analogue of the pituitary hormone arginine-vasopressin, a nonapeptide designed to extend the duration of action of the native hormone. The chemical modifications to endogenous vasopressin include desamination of a cysteine residue and replacement of L-arginine by D-arginine in position 8 in the peptide sequence. Like vasopressin, desmopressin, binds to V2 receptors in the distal and collecting tubules of the kidney and enhances water reabsorption. Ferring Pharmaceuticals developed a new desmopressin formulation for the nocturia indication, an orally disintegrating tablet for sublingual administration. The drug product, to be marketed under the name NOCDURNA, contains the active ingredient desmopressin as desmopressin acetate, along with gelatin, mannitol and citric acid as excipients. NOCDURNA is formulated in two dosage strengths: 25 mcg and 50 mcg of desmopressin. The original NDA submission contained information for the 25, 50, and 100 mcg doses and proposed to market only the 25 and 100 mcg doses. In the complete response the 100 mcg is withdrawn and the applicant proposes to market the 25 mcg and 50 mcg doses. Nocurna is to be administered once daily at bedtime.

The active ingredient, desmopressin, has been approved in a variety of dosage forms, strengths, and routes of administration (subcutaneous injection, nasal spray, and oral tablets) and is currently approved for the following indications:

- treatment of patients with diabetes insipidus
- treatment of children with primary nocturnal enuresis
- treatment of patients with type I von Willebrand's disease and hemophilia A
- measurement of the kidney's ability to concentrate urine for patients with suspected renal disease

Nocturia refers to a condition prevalent particularly in the elderly in which individuals regularly need to wake up from sleep to void multiple times at night². It is associated with decrease in quality of sleep followed by daytime fatigue and sleepiness and a 2-fold increase in risk of falls, with subsequent risk of fractures; for more detail on the condition refer to Dr.Lubas's original Medical Review, Section 2.6. At present there are no pharmacologic therapies approved for this condition.

Desmopressin has a well characterized mechanism of action and a long record of use (desmopressin has been approved in the US in 1978). The safety profile of desmopressin has been relatively well characterized over more than three decades of use. The main safety issue associated with this drug, dilutional hyponatremia, can be anticipated based on its mechanism of action, and has been seen across different patient populations, with different degrees of severity depending on the specific dose and patient susceptibility, the elderly being more vulnerable to hyponatremia due to reduced kidney function and ability to reabsorb sodium. Therefore, central to this submission is the question whether it has provided sufficient

² Van Kerrebroeck et al.: The standardisation of Terminology in Nocturia: Report from the Standardisation Subcommittee of the International Continence Society. *Neurourology and Urodynamics*, 21:179-183 (2002).

evidence of efficacy in the intended population (adults with nocturia), and whether the dose regimens that demonstrate efficacy are reasonably safe with respect to the hyponatremic risk.

3. CMC/Device

The CMC review (DARRTS, 12/7/12 and 1/7/13) recommends approval without any additional studies. Based on the stability data provided, it grants a 48-month expiry at room temperature. The manufacturing process and site are the same as those of in the original submission. The review notes that “all facilities involved in the manufacture, testing and packaging of the drug substance and drug product requested for inspection have been found acceptable by the Office of Compliance (acceptable overall recommendation given on December 27, 2012).”

4. Nonclinical Pharmacology/Toxicology

The nonclinical/pharmacology/toxicology review (DARRTS, 11/29/2012) recommends approval and it does not request any additional non-clinical studies.

In response to the non-clinical deficiency listed in the April 22, 2010, Complete Response letter, the applicant submitted a 1-month toxicology study in dogs in order to qualify impurities specific to the new formulation and to provide a “bridge” to the listed desmopressin product (such a bridge was supposed to be provided in the original NDA by a clinical bioequivalence study, but the analytical method used for measuring the drug was not properly validated – see Section 5 of this memorandum for details).

The review concludes that the toxicological findings and the toxicokinetic data observed with the orally disintegrating formulation of desmopressin are very similar to those of the listed drug, and are consistent with the pharmacological effects of desmopressin in general. No signs of systemic toxicity were observed in any of the treated animals. Finally, previously reviewed animal studies support the safety of the new sublingual route (i.e. no evidence of any local reactions or any histopathological changes related to the test article were found).

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review (DARRTS, 1/16/2013) finds the resubmission “acceptable from a Clinical Pharmacology standpoint.” The review addresses the clinical pharmacology deficiencies that were communicated in the Complete Response letter, which requested that the applicant 1) re-analyze the samples used in the bioequivalence study CS019³ with a validated analytical method, and 2) collect blood samples in future clinical trials that explore newly recommended doses. However, at the End-of-Review meeting the applicant informed the FDA that pharmacokinetic (PK) samples from the relative bioavailability study CS019

³ The study compared Desmopressin melt (240 µg) and Desmopressin tablets (Minirin®) (400 µg).

were not available. Of note, the biopharmaceutics reviewer in the Office of New Drug Quality Assessment had granted a biowaiver for the PK evaluation of lower dose strengths⁴. Therefore, the FDA agreed that the clinical pharmacology recommendations included in the Complete Response letter were no longer relevant (need to demonstrate bioequivalence for lower strengths) or feasible (repeat analysis of CS019 data). However, without a bioequivalence study between the proposed formulation and the listed desmopressin, the applicant could not rely on the findings of the listed drug. To address this issue the FDA requested that a 1-month bridging toxicity and toxicokinetics study in dogs be conducted (see Section 4 of this memorandum for the nonclinical pharmacology/toxicology conclusions). In this review, the clinical pharmacology reviewer concludes that

Although there is no PK information with the current formulation at the proposed clinical doses, sponsor did provide the PK at higher dose strengths of a formulation very similar to the proposed to be marketed formulation. Please see Clinical Pharmacology review of the original submission DARRTS date 03/30/2010 for detailed discussion on the difference in two formulations. In addition, in this NDA Sponsor used to be marketed formulation in their pivotal Phase 3 trials and demonstrated a clear dose response relationship suggesting that the drug is bioavailable at the proposed dose strengths. Thus, the efficacy and clear dose response in the Phase 3 trials with the to be marketed formulation can be used as surrogate for the bioavailability of the drug.

A biopharmaceutics review (DARRTS, 1/8/13) recommends approval. The biopharmaceutics review finds the disintegration data, the proposed disintegration test and acceptance criteria satisfactory. The orally disintegrating desmopressin tablet is highly soluble throughout the physiological range, and the drug product dissolves rapidly with a dissolution > ^(b)₍₄₎ % in 15 minutes.

6. Clinical Microbiology

The microbiology review (DARRTS, 1/3/13) does not identify any deficiencies and recommends approval without any additional studies.

7. Clinical/Statistical- Efficacy

In his clinical review (DARRTS, 01/24/13) Dr. Lubas recommends approval of the 25 mcg Nocturna dose for women and the 50 mcg dose for men. He also recommends against approval of the 75 mcg Nocturna dose in men because it did not provide additional benefit over the 50 mcg dose while, at the same time, it was associated with an increased risk of severe hyponatremia. These recommendations are based on the results of the two clinical trials submitted in this supplement, studies CS40 and CS41, as well as Study CS29, which has been analyzed during the first review cycle. Therefore, studies CS40 and CS41 are also the focus of both the efficacy and safety section of this memorandum.

⁴ The Applicant requested a biowaiver to conduct pharmacokinetics studies on the proposed lower dosage strengths (10, 25, 50, and 100 mcg; IND 65,890) because the assay was below the detection limits for desmopressin at proposed lower doses, and FDA granted the waiver on March 11, 2009.

Study CS40 was conducted in females who received either placebo or 25 mcg of desmopressin. Study CS41 enrolled only males who were administered placebo or desmopressin at either the 50 mcg or the 75 mcg dose. Both studies have been designed as randomized, placebo-controlled, double-blind clinical trials with input from the Division (both were reviewed as Special Protocol Assessments). Both were multicenter studies conducted in the US and Canada, and enrolled approximately 130 patients per arm (268 females in CS40 and 395 males in CS41). In both trials patients were stratified by age (<65 and >65 years); as such, each treatment arm enrolled approximately equal proportions of patients in each of these two strata. Both studies were 3 months in duration, and Study CS41 had a 1-month extension in which patients who completed the first 3 months were escalated to a 100 mcg daily dose regardless of the previous dose or treatment. Subjects received the study medication once a day at bedtime. They were specifically instructed to limit water intake other than necessary for satisfying thirst, and to avoid caffeinated or other diuretic beverages.

Both studies enrolled only adult patients (mean age 60 years) that had to have ≥ 2 voids per night. The mean number of nocturnal voids at baseline was approximately 2.9; most patients, 80-90%, had between 2 and 4 voids per night. Measurements of the number of nocturnal voids and the time to the first void were based on information obtained from patient diaries. Such information was collected over 3 consecutive days at specified time points: baseline, Week 1, Months 1, 2 and 3. Excluded from the trials were patients who had conditions that increased the risk of hyponatremia (e.g. pre-existing hyponatremia, renal insufficiency), conditions that could affect the metabolism of water and sodium (e.g. diabetes insipidus,) or urological conditions that may affect the normal flow of urine such as those that result in urinary retention (quantitative criteria were put in place for post void residuals)⁵. Subjects could be enrolled if they had been on stable doses of alpha blockers or 5-alpha-reductase inhibitors for prostatic hypertrophy, or on antispasmodics for overactive bladder.

Studies CS40 and CS41 had similar efficacy assessment plans. The primary efficacy endpoint was a composite of two co-primary endpoints: 1) change in mean number of nocturnal voids using a longitudinal analysis⁶ and 2) the proportion of patients who exhibited > 33% reduction from baseline in the mean number of nocturnal voids. Of note, the statistical approach taken for these two studies was somewhat different from that of the original NDA. In the original study (CS29) the primary efficacy analyses were conducted at the last time point of the trial (Month 1) and did not account for any intermediate time points. Of note, desmopressin's pharmacological effect is apparent with the first dose, and the drug does not need to reach a steady state to exhibit full pharmacological activity; in fact it is excreted almost entirely before the next dose, having a $T_{1/2}$ of only 2.8 hours. Given this fact and the observation that some doses evaluated in Study CS29 failed to achieve statistical significance at one month while doing so at prior time points,⁷ the FDA reviewers and statisticians agreed that measuring the

⁵ > 150mL in women and > 250 mL in men.

⁶ The mean number of voids for each arm was the average of the number of voids collected at four time points: baseline, Week 1, Months 1, 2 and 3. End each time point was an average of voids obtained over a 3-day period.

⁷ The Month 1 results were statistically significant for the 25 mcg dose in women and for the 100 mcg dose in men. The 50 mcg dose would have been statistically significant on Days 8 and 22 in men if that had been the prespecified endpoint but not on Days 15 and Month 1, the latter being the prespecified endpoint.

drug-to-placebo difference across the whole duration of the trial was clinically more relevant and informative than any one single time point. Efficacy analyses of the last time point of the trial (Month 3 in Studies CS40 and CS41) were relegated as secondary efficacy endpoints and were assessed as part of a pre-specified hierarchical order aiming to minimize type 1 error. The secondary efficacy endpoints were: mean change from baseline, 33% responders, change from baseline in the time to first void, and change from baseline in mean nocturnal and 24-hour urine volume. Finally, both CS40 and CS41 had high completion rates (around 80%) and excellent compliance with study medication (97-100%).

7.1 Evidence of efficacy of the 25 mcg dose in females (Study CS40)

The primary efficacy analysis demonstrated nominal superiority of the 25 mcg desmopressin dose over placebo for each of the co-primary endpoints (p-value<0.05; see Table 1 modifying Table 1 of the Statistical Review, DARRTS 1/25/13). Patients in both the desmopressin and placebo groups started with a mean baseline of 2.8 voids and had mean reductions relative to baseline of 1.5 and 1.2 voids, respectively. However, the placebo-subtracted effect was small: approximately 0.22 voids. The Statistical Reviewer conducted a series of sensitivity analyses and concludes that the statistical result is not robust. While statistical significance was achieved for the Intent-to-Treat/Full Analysis Set (ITT/FAS) patient population (p-value=0.019 with interaction term, p-value=0.028 without interaction) and for the completer populations (p=0.02), it was not confirmed for the per protocol population (p-value=0.07) (refer to Table 3.2 of the statistical review, page 19).

Table 1. Primary Efficacy Analysis-Study CS40 (ITT/FAS Population)

	Placebo		Desmopressin 25 mcg		p-value
	n		n		
Mean number of nocturnal voids					
Baseline mean ± SE	128	2.88 ± 0.07	133	2.84 ± 0.08	
Adj. Mean Change from baseline ±SE1	128	-1.23 ± 0.07	133	-1.47 ± 0.07	
T-C, adjusted LS Mean (95% CI) 1				-0.24 (-0.44, -0.04)	0.0194
33% responder status					
Adjusted Mean¹	128	0.63	133	0.76	
Probability Odds		1.72		3.12	
Odds ratio, adj. LS Mean (95% CI)				1.81 (1.16, 2.82)	0.0095

¹ average of week-1, month-1, month-2, and month-3, with visit-by-treatment interaction term in the model (interaction term pre-specified)

ITT= intent-to-treat' FAS=full analysis set.

Source: table 1 of the statistical review modified.

Of additional interest, both the clinical and the statistical reviews point out that two patients randomized to the placebo arm received desmopressin in error. The primary analysis maintained these patients to their randomized treatments; however, when a sensitivity analysis was conducted assigning these two patients to the actual treatment received (desmopressin), the results of the primary efficacy analysis were no longer statistically significant (p=0.06). I

am in agreement with the statistical reviewer who interprets this finding as an indication that the treatment effect was not particularly robust, and that relatively small numerical changes can either preserve statistical significance (as was the case of the completer population) or not (see the per protocol analysis and the example above). It is also interesting to note the direction of change in statistical significance of treatment effect. In general, drop-in by placebo patients wherein an effective investigational treatment is prescribed to some in the placebo group leads to a diminished treatment effect of the investigational agent. In this situation, the opposite is observed further supporting the conclusion that the efficacy of desmopressin 25 mcg is modest and non-robust.

The secondary efficacy analysis pre-specified a hierarchical order of endpoints to be statistically evaluated at the end of the trial (Month 3) in the following sequence: mean number of nocturnal voids, proportion of 33% responders, mean time to first void, mean nocturnal urine volume, mean 24-hour urine volume. Statistical significance could only be claimed if the previous endpoint in the statistical sequence was <0.05. As summarized in Table 7 on page 31 of the Clinical Review, only the change in number of nocturnal voids could be claimed because the proportion of 33% responders did not reach statistical significance. It is worth mentioning that although P values for the mean time to first void and mean nocturnal volume could not be formally claimed as statistically significant, the calculated P value for each of them was <0.05. With this limitation in mind, they indicate changes consistent with the pharmacological activity of desmopressin.

7.2 Evidence of efficacy of the 50 and 75 mcg doses in males (Study CS41)

The primary efficacy analysis demonstrated superiority for the 50 mcg and 75 mcg desmopressin doses over placebo (Table 2). Patients began treatment with a mean of 2.9 voids per night and the placebo-subtracted effect size was -0.40 and -0.37 voids/night for the 75 and 50 mcg doses, respectively. Sensitivity analyses in several patient populations were consistent with, and supported, the results of the primary efficacy analysis (see tables 3.4 and 3.5 of the statistical review). Although the 50 mcg and 75 mcg doses were not formally compared they seem to yield similar efficacy results.

Table 2. Primary Efficacy Analysis-Study CS41 (ITT/FAS Population)

CS41, Desmopressin 75 mcg	Placebo		Desmopressin		p-value
Mean number of nocturnal voids	n		n		
Baseline mean ± SE	142	2.90 ± 0.07	124	2.99 ± 0.08	< .0001
Adjusted Mean Change from baseline ±SE	142	-0.88 ± 0.07	124	-1.28 ± 0.07	
T-C, adjusted LS Mean (95% CI)				-0.40 (-0.60, -0.20)	
33% responder status					
Adjusted Mean	142	0.50	124	0.67	0.0005
Probability		1.00		2.02	
Odds ratio, adjusted LS Mean (95% CI)				2.02 (1.36, 3.00)	
CS41, Desmopressin 50 mcg					

Mean number of nocturnal voids					
Baseline mean ± SE	142	2.90 ± 0.07	119	2.88 ± 0.08	
Adjusted Mean Change from baseline ±SE T-C, adjusted LS Mean (95% CI)	142	-0.88 ± 0.07	119	-1.27 ± 0.08 -0.37 (-0.57, -0.17)	0.0003
33% responder status					
Adjusted Mean Probability	142	0.50	119	0.67	
Odds ratio, adjusted LS Mean (95% CI)		1.00		2.00 2.00 (1.33, 3.01)	0.0008

¹ average of week-1, month-1, month-2, and month-3, with visit-by-treatment interaction term in the model (interaction term pre-specified)

ITT= intent-to-treat’ FAS=full analysis set.

Source: table 1 of the statistical review modified.

All but one⁸ of the secondary efficacy analyses included in the pre-specified sequence were statistically significant for the 75 mcg dose (p<0.05). Because the prespecified testing procedure required that changes in all endpoints in the 75 mcg sequence reach statistical significance before proceeding to testing the 50 mcg dose, none of the secondary analyses for the 50 mcg dose could be claimed as statistically significant, although all but one had P values below 0.05 (they included mean nocturnal void, proportion of responders, time to first nocturnal void, and nocturnal urine volume).

8. Safety

To date, the Nocdurna Phase 3 trials include safety information obtained from over 1,000 patients exposed to desmopressin doses ranging from 10 mcg to 100 mcg, with a large proportion of patients having been treated for up to 3 months and some beyond. The safety profile of desmopressin in patients with nocturia has largely been characterized in the clinical trials analyzed during the first review cycle (please refer to the Medical Officer’s Review, CDTL’s review and Division Director’s review, all in DARRTS). Hyponatremia has emerged as the main safety signal in both males and females and has been discussed extensively during the first review cycle. In fact, the Complete Response letter affirms the Division’s concern with hyponatremia when it refers to “the Nocdurna dose of 100 mcg which demonstrated efficacy [but] was associated with an unacceptable risk of severe hyponatremia”.

Hyponatremia is an adverse event that was anticipated on the basis of the mechanism of action of desmopressin (renal reabsorption of water) and was confirmed during clinical trials. It is critical that any Nocdurna dose(s) that is proposed to be marketed be supported by evidence that it is not associated with an unreasonable risk of severe hyponatremia. Therefore, this section of the memorandum will focus on the issue of hyponatremia in general and severe hyponatremia in particular, severe hyponatremia being defined as serum sodium < 125 mmol/L. Emphasis will be placed, where possible, on discussing hyponatremia in patient populations at risk, in particular the elderly because they have intrinsically a higher risk of

⁸ Mean 24-hour urine volume at Month 3, the last endpoint in the sequence (Table 7 of the Clinical Review)

developing hyponatremia due to age related decline in renal function and limited ability to preserve sodium renally, and because most elderly tend to have comorbid conditions that may predispose or contribute to electrolyte imbalances.

It is important to understand that clinical trials CS40 and CS41 excluded patients at risk for hyponatremia. Subjects had to have a normal screening sodium serum concentration and an estimated GFR above 50mL/min. A sodium monitoring plan was incorporated in the trial design and consisted in two measurements in the first week of treatment (days 4 and 8) and monthly thereafter. Per protocol, desmopressin was to be discontinued and patients withdrawn from the trial if they developed severe hyponatremia. Moreover, serum sodium values >125 but ≤ 130 mmol/L required that subjects be evaluated with a follow up measurement to assess if there was progression or resolution of hyponatremia.

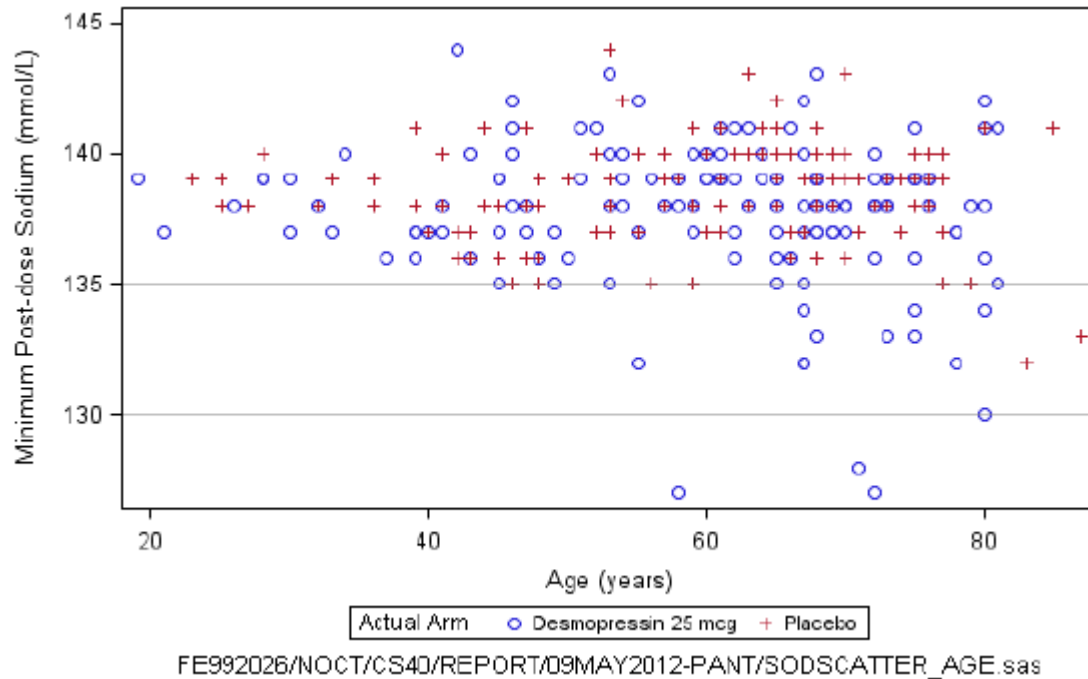
8.1 Hyponatremia in women treated with the 25 mcg daily dose (Clinical trial CS40)

There were no cases of severe hyponatremia in women treated with 25 mcg of desmopressin (and none in the placebo group), and no subject discontinued study drug due to low serum sodium or to an adverse event that could be linked to hyponatremia. Three desmopressin-treated women had serum sodium levels between 126 and 129 mmol/L (they represent 2% of all measurements; none had such values in the placebo group). All improved, apparently, without any additional intervention; most normalized and some returned to >130 mmol/l values.⁹ Mild declines in serum sodium in the range of 130-134 mmol/L were seen four times more frequently in the desmopressin group relative to placebo (8% vs. 2%).

Figure 8 of the Clinical Review (reproduced below) is a scatter plot of post-dose” minimum” serum sodium levels. Not surprisingly, given the pharmacological effect of desmopressin, most of the sodium levels below the lower limit of the normal range were in the desmopressin group, albeit not exclusively. The declines in serum sodium seem to affect preferentially older patients.

⁹ These levels were 127 mmol/L (2 subjects) and 128 mmol/L (1 subject), and all occurred during the first month of treatment (two occurred in women >65 years of age and one in a 58 year-old).

Figure 1 Plot of Minimum Post-Dose Serum Sodium Levels in study CS40 (women only)



Of note, in the Phase 3 clinical trial CS29/CS31 which was reviewed during the first cycle, among women treated with 25 mcg dose, none developed severe hyponatremia (4 women had serum sodium levels between 126 and 129 mmol/L, but none below 125 mmol/L). I am in agreement with Dr. Lubas’s conclusion that based on observations made from these two datasets (current NDA supplement and previous NDA), the 25 mcg dose does not appear to pose a significant risk of severe hyponatremia in women. I also recognize the fact that the patients that would be treated in clinical practice are likely to be more diverse than those studied in clinical trials, and therefore the Nocturna label will need to anticipate and warn about particular conditions or clinical situations that may increase the hyponatremia risk.

8.2 Hyponatremia in men treated with the 50 mcg and 75 mcg daily dose (Clinical trial CS41)

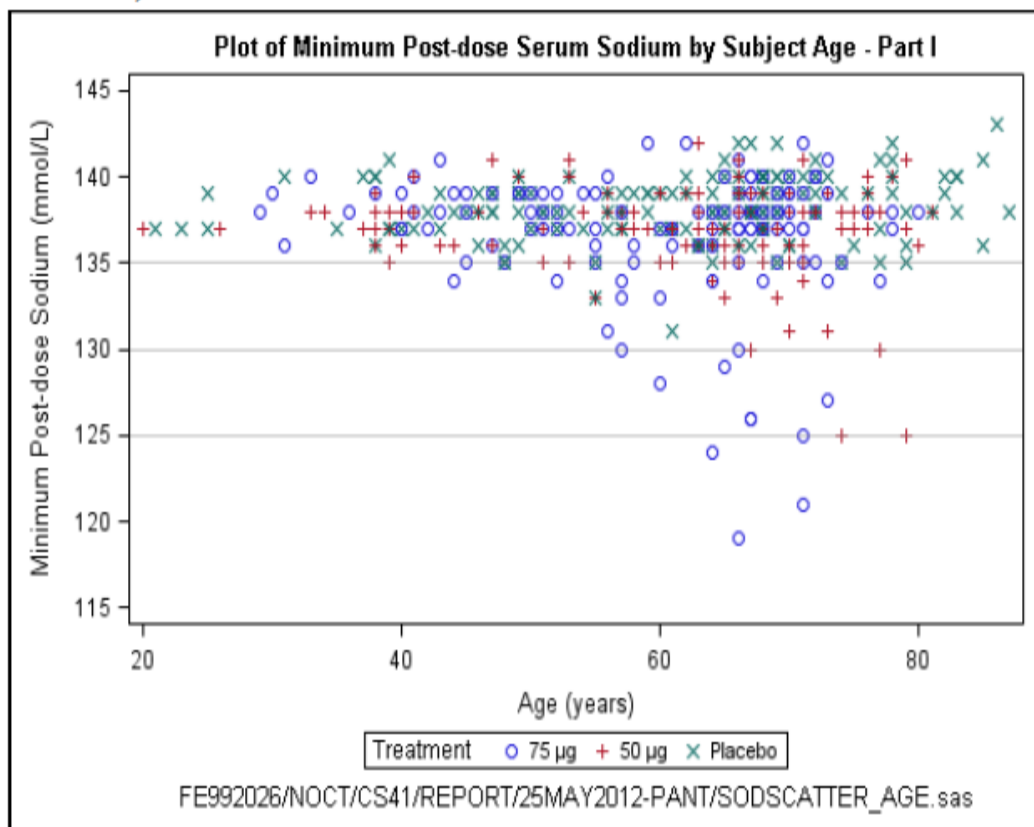
In trial CS41, severe hyponatremia was seen in two men in the 50 mcg dose arm (2%, both in the >65 age group) and four men treated with the 75 mcg dose (3%, not restricted to any age stratum). It is possible that both subjects in the 50 mcg arm would have been identified with the sponsor’s proposed monitoring scheme which calls for evaluations of serum sodium at days 4, 8 and 1 month in patients >65 years of age, assuming follow-up for abnormal values¹⁰. The proposed monitoring scheme would not have been able to identify all patients in the 75 mcg since one of them was <65 years.

¹⁰ The two subjects who had severe hyponatremia in the 50 mcg arm were 74 and 79 years old, respectively; they had sodium levels of 125 mmol/L, one on Day 7 and one at Month 2; the latter had a sodium level of between 130 and 125 mmol/L at the one month visit that required follow-up which, in turn, led to the identification of a Month 2 level consistent with severe hyponatremia.

Mild declines in serum sodium (i.e. 130-134 mmol/L) were seen about 8 times more frequently than placebo for the 50 mcg dose (8% vs. 1%) and 10 times more for the 75mcg dose (10% vs. 1%). There were no patients with sodium levels between 126-129 mmol/L in the 50 mcg dose, while 4% of patients in the 75 mcg had sodium levels within this range.

Figure 11-1, reproduced below provides a scatterplot that illustrates the “minimum” post-dose serum sodium levels in study CS40 for both doses and placebo. It shows that most of the below normal sodium concentrations were seen with the 75 mcg dose, a dose regimen that the applicant does not seek to market. As seen in the companion graph in women previously, most declines below the lower limit of normal occurred in older patients.

Figure 11-1 Minimum Post-Dose Serum Sodium Levels by Subject Age (Safety Analysis Set) – Part I



Cross-reference: [\[Figure 7.1.1.39\]](#)

Dr Lubas mentions in his review that there were two cases of severe hyponatremia in men at doses of 50 µg or lower during the CS29/CS31 study, but none of them should have been treated with desmopressin according to the currently proposed label which excludes patients with renal impairment and recommends temporary discontinuation of treatment during acute illnesses. These two cases underscore the fact that use of desmopressin will take place in more diverse clinical circumstances in clinical practice. Therefore, the Nocurna label should identify and warn about specific conditions and situations of hyponatremic risk. I am in

agreement with Dr. Lubas that the 50 mcg dose is reasonably safe with respect to hyponatremia risk and that the 75 mcg dose is associated with an undesirable safety profile.

Finally, there were no safety issues of significance, other than hyponatremia, that Dr. Lubas identified in his review. Several adverse events were seen with higher frequency relative to placebo (e.g. dry mouth, headache) but they do not raise approvability issues.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

10. Pediatrics

Nocturna was granted a full waiver for pediatric studies during the previous review cycle.

11. Other Relevant Regulatory Issues

In response to a request from the Division of Metabolism and Endocrinology Products, the Study Endpoint and Labeling Development (SEALD) team reviewed the results generated with the Nocturia Quality of Life (NQoL) and the Work Productivity and Activity Index (WPAI) questionnaires as measurements of changes in health-related quality of life in studies CS 40 and CS 41 (DARRTS 9/27/12 and 1/7/13). The review concludes that neither the NQoL nor the WPAI results from these trials should be used for labeling claims. The fact that these PRO instruments failed to demonstrate a clear benefit is of significance because the applicant has not been able to date to provide any clear evidence that the reduction in the number of nighttime voids is associated with any additional clinical benefit.

NQoL, a questionnaire that measured the impact of nocturia on quality of life, was reviewed during the previous cycle by the SEALD reviewer and was not found acceptable for a variety of reasons including the fact that it failed to address the psychological and emotional impact of nocturia. Following the original submission, the applicant worked with the agency to develop a new PRO, the Nocturia Impact (NI) diary which, however, was not ready for use when studies CS40 and CS41 were initiated. These trials still utilized the NQoL questionnaire with mixed results. Specifically, the current SEALD consult is critical of the robustness of the PRO findings obtained with the NQoL instrument in studies CS40 and CS41. The SEALD reviewer points out that this PRO was an exploratory analysis and was not incorporated in the hierarchy of secondary endpoints. More importantly, I believe, some parts of the questionnaire performed inconsistently in different trials, and even when consistent and statistically significant results were seen, they were modest in size and of unclear significance. For instance, in the addendum to the original consult, the SEALD reviewer note that

....inconsistent positive results shown for use of the questionnaire in these two trials [...] appeared in post-hoc analyses rather than planned statistical procedures. In CS40, the global item shows no significant difference between placebo and treatment and is actually better for placebo on average at

Month 1, while the global results show a clear advantage for drug in CS41. The bother/concern domain results show no significant advantage for drug in CS41, with evidence for a significant advantage at 3 months in Trial CS40.

The clinical review contains similar observations, pointing out to some results that suggest clinical benefit but also highlighting internal inconsistencies in some of the results (e.g. the observation of demonstration of efficacy at the lower dose of 50 mcg but not at the higher dose of 75 mcg at the month 3 evaluation). It concludes that

...while it is positive that there are some signs that suggest clinical benefit in the post hoc analysis specifically in “total score” and “sleep quality” these results are exploratory and would need to be repeated”.

Finally, the new PRO that was developed with advice from the agency, the Nocturia Impact (NI) Diary, was evaluated prospectively in a small study (Study 00034). In this randomized, placebo-controlled, double-blind, 1-month trial, 26 women and 26 men who completed studies CS40 and CS41 received either placebo or desmopressin (25 mcg for females and 75 mcg for males) for one month. This small and probably underpowered study failed to show efficacy in either men or women with respect to changes in PROs.

12. Labeling

Since this reviewer does not recommend approval, no specific comments regarding labeling will be made.

The proprietary name “Nocdurna” has been reviewed and found acceptable from a safety and promotional perspective by the Office of Medication Error Prevention and Risk Management (DARRTS 10/25/12)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response.

- Risk Benefit Assessment

During this second review cycle the applicant has made significant steps in characterizing the use of desmopressin in adult patients with nocturia. First and foremost, the applicant has been able to demonstrate prospectively, in well-controlled studies that the dose regimens of 25 mcg in women and 50 mcg men result in statistically significant reductions in the number of nocturnal voids when compared to placebo. This provides important information that was missing in the initial review cycle wherein some of the doses proposed for marketing were

based to a large extent on observations made from dose and gender subgroup analyses in a clinical trial that explored higher doses and did not anticipate the significant gender differences that were observed. Although there remains a higher rate of hyponatremia associated with Nocturna even at these doses relative to placebo, the majority of patients had serum sodium concentrations > 130 mmol/L and for those who had levels below 130 mmol/L, no serious adverse event ensued. The applicant proposes the above-mentioned doses for marketing in the US.

Although the primary efficacy analyses in both females and males reached nominal statistical significance (with the caveat that in females this result had only limited support from the sensitivity analyses, as already discussed), one has to ask the question whether this statistically significant result is also clinically relevant.

One way to put in a practical context the results of studies CS40 and CS41 is to conceptualize the treatment effect size over a period of time that is easy to relate to clinically, such as **one week**. Extrapolated to this clinical situation, the observations and results of Study CS 40 indicate that a female patient who experienced 20 nocturnal voids per week prior to initiating treatment, had a reduction of 10 voids over seven days of 25 mcg of desmopressin treatment, but only a reduction of about 1.7 voids compared to placebo. In probabilistic terms a desmopressin treated patient has a 13% absolute probability over placebo of becoming a responder (defined as someone who had a reduction in nocturnal voids >33%). For a male patient starting with 20 voids over a one-week period, 50 mcg of desmopressin resulted in a reduction to 9 voids over the following week, 3.5 voids more than placebo (and 17% absolute probability over placebo of meeting the definition of responder). These numbers indicate quite a striking difference in the impact of the desmopressin treatment when assessed as a change from baseline or as change relative to placebo. The difference between the baseline-subtracted and the placebo-subtracted reduction in number of voids in both males and females has received considerable attention in the Clinical Review (Section 6.1.4, pages 29-30). Dr. Lubas comments that

In the present situation it seems unlikely that a placebo could affect the release of endogenous vasopressin in patients with nocturia, although that has not been clinically tested, but it seems more likely that the large observed placebo effect has to do with behavioral changes in the study population as a result of the study protocol recommendations. Specifically, patients were instructed to empty their bladder before going to bed and to limit fluid intake to satisfy thirst only. Evening intake of liquids with diuretic effect, such as coffee, tea, caffeinated soft drinks, and alcoholic beverages, was especially discouraged. Patients were instructed on how to measure urine volume and fluid intake and to document this information in a voiding diary for 3 consecutive days during multiple times during the study.

I am in full agreement with Dr. Lubas that the efficacy changes seen in the placebo arms of studies CS40 and CS41 are likely to represent the effect of modifications in lifestyle and behavior, although I make a clear distinction between the effect of lifestyle changes and a “placebo effect.” Lifestyle changes were specific, prospectively implemented and protocol-specified interventions. They have a clear rationale for use: reduction of water intake is expected to reduce urine output in patients who can secrete vasopressin¹¹ and have largely

¹¹ Although elderly patients with nocturia have been proposed to have a loss of the cyclicality in vasopressin secretion or a blunting of vasopressin response, they are not vasopressin deficient per se.

conserved renal function and, as such, they are expected to elicit a clinical response at least in some patients. Evidence from the placebo arms of trials CS40 and CS41 shows that lifestyle changes, a non-pharmacological intervention, had an important clinical impact, resulting in greater than 1/3 reductions in number of voids relative to baseline. The small difference in effect size between the desmopressin arm and the placebo arm argue that in this particular patient population that includes any patient with nocturia, lifestyle intervention was quite successful in reducing the number of nocturnal voids without any added risk of hyponatremia. I believe that the efficacy results of studies CS40 and CS41 indicate that the potential effect of lifestyle intervention was underappreciated in the planning stages of the trials. This unexpected response to lifestyle changes poses a labeling dilemma. As proposed, the Nocdurna indication is solely for desmopressin and not for desmopressin AND lifestyle intervention, and therefore labeling it with the results of studies CS40 and CS41 would be misleading.

With these observations in mind, it is conceivable that the applicant has not identified the most appropriate patient population with nocturia for treatment with desmopressin. Given the response to non-pharmacological interventions observed in both Study CS40 and CS41, it could be that a more appropriate patient population targeted for desmopressin use would consist of patients with nocturia who have failed lifestyle modification interventions. Such a subgroup of patients (which may still be considerable given the size of the nocturia patient population) has currently no therapeutic option. Unfortunately, there are no data in the Nocdurna Phase 3 program to support and label Nocdurna for use in such a population. To do this, the applicant would need to re-evaluate the effect of the 25 mcg dose (females) and 50 mcg dose (males) in clinical trials that exclude during the run-in periods patients who respond to lifestyle changes.

Finally, given that the overall effect size of desmopressin relative to placebo was small, I do not think that such a an effect supports approval for Nocdurna treatment alone, especially in absence of an additional clinical benefit. As I indicated in the previous CDTL review, the applicant has failed to provide evidence of clinical benefit that goes beyond a reduction in the number of nocturnal voids (see PRO data as an example).

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None at this time given that the recommendation is for a Complete Response.

- Recommended Comments to Applicant

The applicant should be informed that:

- 1) The effect size of Nocdurna relative to placebo is modest in the currently studied patient population and much of the treatment effect associated with Nocdurna was due to a concomitant behavior and lifestyle intervention.
- 2) The confounding effect of lifestyle intervention was underappreciated in the planning stages of the trials.

- 3) The information provided by patient reported outcome evaluations does not strongly support a clinical benefit beyond the small reduction of the number of nocturnal voids relative to placebo.
- 4) The applicant could consider identifying a patient population for which the observed nocturnal void reduction has a greater impact. Such a population may consist of patients with nocturia who have failed lifestyle modification intervention.
- 5) Alternatively, the applicant needs to provide convincing evidence of clinical benefit that goes beyond the reduction in number of nocturnal voids. Using the newly validated PRO in a clinical trial seems at this time to be the most direct way of providing such evidence.

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/s/

DRAGOS G ROMAN
01/28/2013

MARY H PARKS
01/28/2013



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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA #: 22517
Sequence #: 0017
Drug Name: Nocurna (desmopressin melt)
Indication(s): Treatment of Nocturia in Adults
Applicant: Ferring Pharmaceutical Ltd.
Date(s): Submitted July 30, 2012
Review Priority: Standard (6-months for Complete Response)

Biometrics Division: Division of Biometrics 2 (HFD-715)
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Concurring Reviewers: J. Todd Sahlroot, Ph.D. (Deputy Director)

Medical Division: Metabolism and Endocrinology Products (HFD-510, DMEP)
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Keywords: NDA review, clinical studies, robustness of evidence, effect size

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1. EXECUTIVE SUMMARY

The applicant seeks the indication of Nocdurna (desmopressin melt) for the treatment of nocturia in adult males and females. The applicant conducted two similarly-designed, placebo-controlled studies, one in each gender. Doses studied were 50 and 75 mcg in males, and 25 mcg in females.

The efficacy data in Study CS41 (males) support the superiority of desmopressin at both planned doses over placebo based on statistical results for the two co-primary efficacy endpoints, change from baseline in the average number of nocturnal voids over 3 months and 33% responder status over 3 months (p-value <0.001 for both doses, both co-primary endpoints) (Table 1). Mean effect sizes were -0.40 and -0.37 voids/night for 75 and 50 mcg, respectively, from mean baselines of about 3 voids/night. The primary analysis results were supported by statistically significant results for sensitivity analyses of the co-primary endpoints and for key secondary endpoints.

Data in females (Study CS40) showed nominal significance (p-value<0.05) on both co-primary endpoints for desmopressin 25 mcg vs. placebo. However, results for the continuous co-primary endpoint based on change from baseline were not robust. Although the primary analysis was nominally significant (ITT/FAS; p-value=0.019 with treatment-by-visit interaction term, p-value=0.028 without the interaction term), sensitivity analysis based on per protocol population was not statistically significant (p-value=0.07). Two patients randomized to placebo received desmopressin 25 mcg in error. When the primary analysis was repeated, but assigning these two patients to the desmopressin group instead of the placebo group (“as treated”), the results were not statistically significant (p-value=0.06). The observed effect size (-0.24 voids/night with treatment-by-visit interaction term, -0.22 voids/night without interaction) was less than half the target effect size used for the sample size calculation (-0.50 voids/night) and small relative to the observed mean placebo change from baseline (-1.23 voids/night).

Table 1. 1. Efficacy Summary in Desmopressin and Placebo Treated Patients during 3 Months (ITT/FAS)¹

CS40, Females	Placebo		Desmopressin 25 µg		p-value
Mean number of nocturnal voids	n	# voids	n	# voids	
Baseline mean ± SE	128	2.88 ± 0.07	133	2.84 ± 0.08	
Adj. Mean Change from baseline ±SE	128	-1.23 ± 0.07	133	-1.47 ± 0.07	
Adj. LS Mean Treatment Difference (95% CI)				-0.24 (-0.44, -0.04)	0.0194
33% responder status	n		n		
Adjusted Mean	128	0.63	133	0.76	
Probability		1.72		3.12	
Odds ratio, adj. LS Mean (95% CI)				1.81 (1.16, 2.82)	0.0095
CS41, Males	Placebo		Desmopressin 75 µg		p-value
Mean number of nocturnal voids	n	# voids	n	# voids	
Baseline mean ± SE	142	2.90 ± 0.07	124	2.99 ± 0.08	
Adjusted Mean Change from baseline ±SE	142	-0.88 ± 0.07	124	-1.28 ± 0.07	
Adj. LS Mean Treatment Difference (95% CI)				-0.40 (-0.60, -0.20)	< .0001
33% responder status	n		n		
Adjusted Mean	142	0.50	124	0.67	
Probability		1.00		2.02	
Odds ratio, adjusted LS Mean (95% CI)				2.02 (1.36, 3.00)	0.0005
CS41, Males	Placebo		Desmopressin 50 µg		
Mean number of nocturnal voids	n	# voids	n	# voids	
Baseline mean ± SE	142	2.90 ± 0.07	119	2.88 ± 0.08	
Adj. Mean Change from baseline ±SE	142	-0.88 ± 0.07	119	-1.27 ± 0.08	
Adj. LS Mean Treatment Difference (95% CI)				-0.37 (-0.57, -0.17)	0.0003
33% responder status	n		n		
Adjusted Mean	142	0.50	119	0.67	
Probability		1.00		2.00	
Odds ratio, adjusted LS Mean (95% CI)				2.00 (1.33, 3.01)	0.0008

¹ average of week-1, month-1, month-2, and month-3, with treatment-by-visit interaction term in the model (interaction term pre-specified)

Statistical Issues:

The Statistical Analysis Plan pre-specified that the treatment-by-visit interaction term would be included in the primary statistical model. In the final report, the sponsor omitted the interaction term from the primary analysis because “the treatment-by-visit interaction was found to be non-significant at the 5% level”. The sponsor included the interaction term in a sensitivity analysis. It is not standard OB practice to identify non-significant (p>.05) terms using results from a pre-specified model and then re-run the model without these terms. The type 1 error properties of such a procedure are not well understood. On the other hand, one could argue that including the treatment-by-visit interaction term in the model would be most appropriate, and only necessary, when conducting a repeated measures analysis whose goal is to evaluate the response at a single time point. Including the interaction term would not be necessary, or advisable, when evaluating a mean response across multiple time points (which is the continuous primary efficacy endpoint here).

This reviewer calculated p-values from models with and without the interaction term. This reviewer confirmed that the primary efficacy results were similar regardless of the presence or absence of the treatment-by-visit interaction term in the statistical model.

The pre-specified primary treatment estimate was the average response across the 4 time points at Week 1, Month 1, Month 2 and Month 3. This estimate was agreed to between the Agency and the sponsor as part of the Special Protocol Assessment. The primary analysis for Study CS29 in the original NDA submission was based on the treatment difference at the last time point of the study, Day 28, which ignored post-randomization data prior to that time point. The data from trial CS29 suggested that the effects of desmopressin were seen well before Day 28 and possibly as early as Week 1. To correct what was thought to be a shortcoming of the CS29 statistical analysis plan, the sponsor based the treatment difference in Studies CS40 and CS41 on the average response across the four time points. The change from baseline in the number of voids at the Month 3 time point and corresponding 33% responder endpoint – identical to the co-primary endpoints but measured solely at the Month 3 time point -- were designated as the first two key secondary endpoints and included in the hierarchical testing procedure for controlling type 1 error across the primary and key secondary endpoints. Results showed that, in the female study (CS40), the change from baseline in the number of voids at Month 3 was statistically significant ($p < 0.05$), but the 33% responder status endpoint at Month 3 was not statistically significant ($p > 0.05$). This latter result again points to the lack of robustness of the 25 mcg dose in females.

Labelling Recommendations:

Recommendations for the proposed label are included in Section 5.3.

2. INTRODUCTION

2.1 Overview

Desmopressin is a synthetic analogue of the naturally occurring antidiuretic hormone vasopressin which is the primary physiologic determinant of free water excretion by promoting free water reabsorption and reducing urine production. Desmopressin is modified with increased and prolonged antidiuretic effect while minimizing the effect on smooth muscle vasoconstriction. Desmopressin binds to V2 receptors in the distal and collecting tubules of the kidney and increases the permeability of these tissues to water which, in turn, decreases urine production while concomitantly enhancing water reabsorption. Other attributes include greater V2 receptor selectivity (the antidiuretic-to-vasopressor ratio is 3000-fold greater than vasopressin) enabling a more potent anti-diuretic effect than vasopressin. Desmopressin is available as a subcutaneous injection (1984, FDA), nasal spray (1978, FDA), and oral tablets (1995, FDA) and has been approved by the FDA for the following indications:

- treatment of central diabetes insipidus
- diagnostic in performing renal concentration capacity testing

- treatment of primary nocturnal enuresis in children (6 and above and in adults up to 46 years of age at doses of 0.2mg to 0.6mg, 5/2008)
- treatment for type 1 von Willebrand's disease (bleeding disorder, coagulation abnormality) and hemophilia A (bleeding disorder caused by a lack of blood clotting factor VIII)

Ferring Pharmaceuticals Inc. originally submitted NDA022517/0000, study FE992026 CS29 and extension CS31, on June 22, 2009, seeking an indication for Nocturna, an orally disintegrating tablet formulation of desmopressin, for the treatment of adults with nocturia. This product has been approved in Europe for the treatment of nocturia at doses of 60 mcg, 120 mcg, and 240 mcg but is limited to patients under the age of 65 years due to the risk of hyponatremia (low serum sodium). The efficacy data in Study CS29 were reviewed by this reviewer. This application was not approved by FDA primarily due to the finding that the only dose shown to be efficacious according to the pre-specified efficacy rule (100 mcg) was associated with a high incidence of hyponatremia. In order to address this deficiency, the sponsor was advised to conduct two clinical trials to confirm that a lower dosing regimen was a safe and effective treatment of adult nocturia. The trials should be placebo-controlled with a minimum duration of 3 months to evaluate a longer period of durability and safety relative to placebo. In response, the sponsor submitted two Special Protocols under IND 65890 which were reviewed by this statistical reviewer.

On July 30, 2012, the sponsor submitted its Complete Response submission to NDA 22-517, Nocturna (desmopressin) Orally Disintegrating Tablets. In this NDA resubmission, the sponsor included study results of the confirmatory trials for studies CS40 (females) and CS41 (males), as well as for extension study CS000034 (Nocturia Impact Study using the Nocturia Impact Diary to support QoL labeling claims), and a four-week comparative toxicology study.

The study CS40 was entitled:

A Multi-centre, Randomised, Double-blind, Placebo-controlled, Parallel-group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Females

The study CS41 was entitled:

A Multi-centre, Randomised, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Males

The study CS000034 was entitled:

A Double-blind, Randomized, Placebo-controlled Study, Investigating the Impact Burden of Nocturia Using the Nocturia Impact Diary

The trial CS000034 was a phase 3b study with the primary objective to assess the psychometric properties of the Nocturia Impact (NI) diary and the trends on the impact burden of nocturia following treatment with desmopressin orally disintegrating tablets and would be reviewed by SEALD. This reviewer reviewed the two pivotal efficacy clinical trials CS40 and CS41.

Table 2.1 shows an overview of studies CS40 and CS41

Table 2.1. Trial Overview

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
CS40	<i>Phase 3. A Multi-centre, Randomised (stratified by age, <65, ≥65), Double-blind, Placebo-controlled, Parallel-group Trial</i>	<i>3 months</i>	<i>NA</i>	<i>Desmopressin: 25 µg 137 Placebo: 131</i>	<i>Adult Females with Nocturia</i>
CS41	<i>Phase 3. A Multi-centre, Randomised (stratified by age, <65, ≥65), Double-blind, Placebo-controlled, Parallel-group Trial</i>	<i>3 months</i>	<i>1 month open-label extension with all patients on desmopressin 100 µg</i>	<i>Desmopressin: 75 µg 129 50 µg 123 Placebo: 143</i>	<i>Adult Males with Nocturia</i>

2.2 Data Sources

The sponsor submitted this NDA including electronic study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. The data were submitted in SAS Xport transport format.

Application:	NDA022517
Company	Ferring
Drug	Nocdurna (desmopressin) Orally Disintegrating Tablets
CDER EDR link	\\CDSESUB1\EVSPROD\NDA022517\0017
Letter date	7/30/2012

The applicant's electronic submission was well-organized. Parallel structure in the presentation of the results across all studies was well-done and appreciated by the reviewer.

All graphs and tables in the review were created by this reviewer unless otherwise noted.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

I reviewed the quality and integrity of the submitted data. Relevant issues include:

- Whether it is possible to reproduce the primary analysis dataset from tabulation or “raw” datasets : [yes](#)
- Whether it is possible to trace how the primary endpoint was derived from the original data source (e.g., case report form): [yes](#).
- Whether it is possible to verify the randomized treatment assignments: [yes](#)
- Findings from the Division of Scientific Investigation or other source(s) that question the usability of the data: NA

I had no difficulty processing the data.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The confirmatory trials were multi-centre, randomized, double-blind, placebo-controlled, parallel-group trials to demonstrate the efficacy and safety of desmopressin orally disintegrating tablet for the treatment of nocturia in adult females (Study CS40) and males (Study CS41) with a treatment period of 3 months. Study CS41 was followed with an open-label extension for one month. The main treatment periods consisted of 7 visits.

The primary objective for CS40/CS41 was to demonstrate the safety and efficacy of desmopressin orally disintegrating tablets against placebo for the treatment of patients with nocturia during three months of treatment.

The studies were carried out in USA and Canada with 45 trial sites in CS40 and 50 in CS41, respectively.

In study CS40, a total of 649 patients were screened and 268 patients were randomized in a 1:1 ratio to treatment. 137 patients received desmopressin 25 µg and 131 received placebo.

In study CS41, a total of 1013 patients were screened and 395 patients were randomized in a 1:1:1 ratio to treatment. 123 patients received desmopressin 50 µg, 129 received desmopressin 75 µg, and 143 received placebo

The randomizations for both CS40 and CS41 were stratified by age (<65, and ≥65)

In CS40/CS41, there were 2 co-primary endpoints:

- The first co-primary endpoint was the change from baseline (Visit 2) in mean number of nocturnal voids during three months of treatment (across Visits 4, 5, 6, and 7) using a longitudinal analysis as assessed by the three-day diary. The mean number of voids at each visit will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits
- The second co-primary endpoint was the 33% responder status during the three months of treatment (across Visits 4, 5, 6, and 7) using a longitudinal analysis as assessed by the three-day diary. A 33% responder is defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids relative to baseline (Visit 2)

The secondary efficacy endpoints of the two studies were:

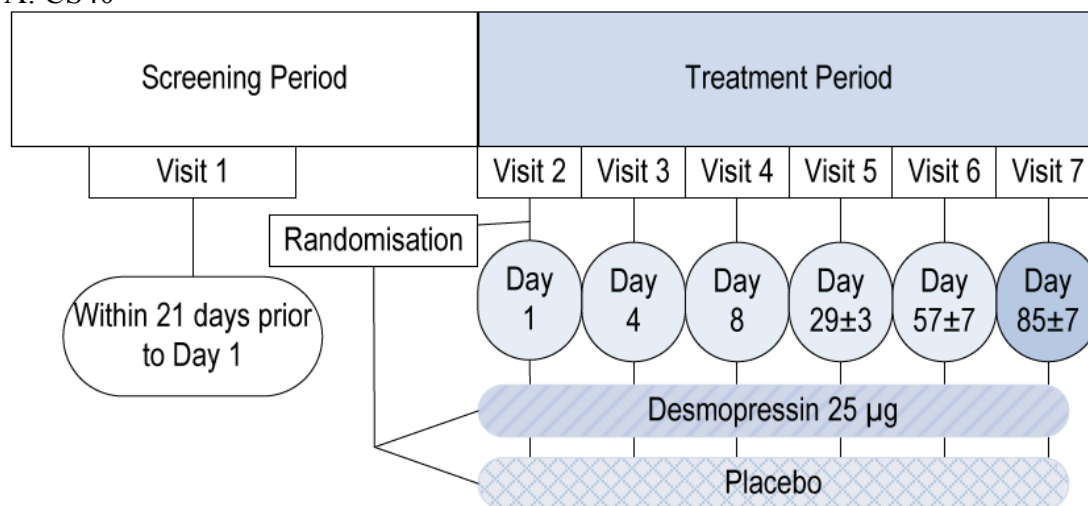
1. Change from baseline (Visit 2) in mean number of nocturnal voids at Month 3 (85 days) as assessed by the three-day diary
2. Proportion of 33% responders at Month 3 (85 days) as assessed by the three-day diary
3. Change from baseline (Visit 2) in mean time to first void at Month 3 (85 days) as assessed by the three-day diary. The time to first void is defined as the time from going to bed with the intention of sleeping until first void or until waking in the morning in the case where there is no nocturnal void. The mean time to first void will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits
4. Change from baseline (Visit 2) in mean nocturnal urine volume and mean 24-hour urine volume at Month 3 (85 days) as assessed by the three-day diary. The nocturnal urine volume will include the volume of the first morning void. The mean urine volumes will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits

The key safety parameters include frequency and severity of adverse events and incidence of hyponatraemia as measured by serum sodium level throughout the trial.

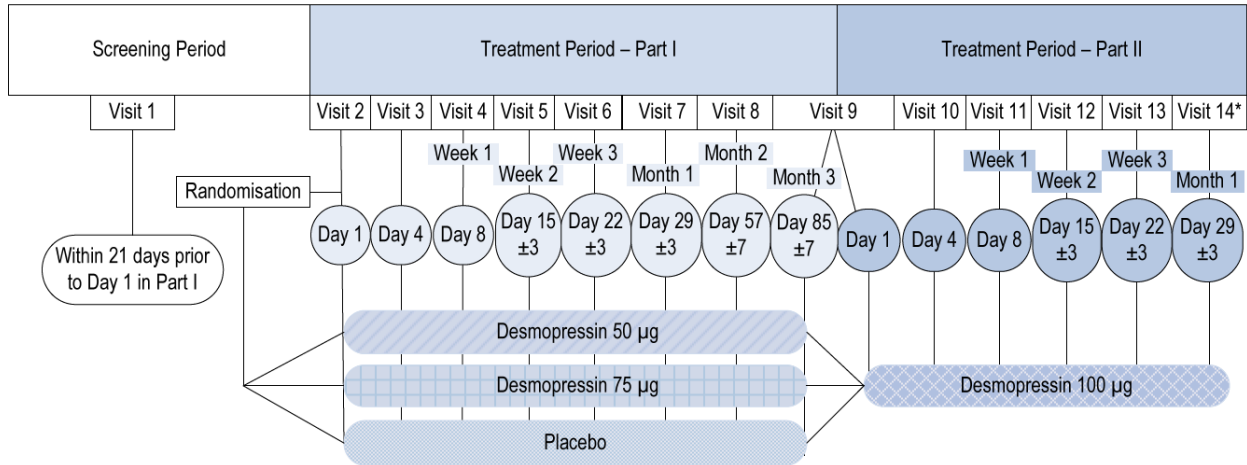
The sponsor's design diagram of the studies CS40 and CS41 is shown in Figure 3.1.

Figure 3.1. Overview of the study design.

A: CS40



B: CS41



3.2.2 Statistical Methodologies

The efficacy objective of both CS40 and CS41 was to demonstrate superiority of desmopressin to placebo simultaneously on the two co-primary endpoints, the change from baseline in mean number of nocturnal voids and the 33% responder status during three months of treatment. Both co-primary endpoints were to be assessed using a two-sided alpha of 5%. Study CS41 used a step-down approach from high (75 µg) to low dose (50 µg) at the 5% significance level.

The sample sizes were determined by the sponsor via simulation based on estimates derived from NDA 22-517 trial CS29 using female patients on a dose of 25 µg for CS40 and male patients on doses 50 µg and 75 µg for CS41. Assuming a difference of 0.5 voids per night in a *non-enriched* population of female patients at level $\alpha=0.05$ with the sponsor's estimates for means across time and the variance-covariance matrix (see fe992026cs40-protocol-1.pdf), the study CS40 needs 130 subjects per arm to achieve at least 95% power for testing superiority to placebo on both co-primary endpoints. Similarly, the study CS41 needs 130 subjects per arm for the high dose (75 µg) to achieve at least 95% power for testing superiority to placebo on both co-primary endpoints with a treatment effect of 0.3 mean nocturnal voids at level $\alpha=0.05$ (two-sides). The sample size of 130 subjects per arm for the low dose (50 µg) with a treatment effect of 0.2 mean nocturnal voids, however, would yield 67% of power on both co-primary endpoints. The sample size determinations were based on the sponsor's estimates for means across time and the variance-covariance matrix (see fe992026cs41-protocol-1.pdf).

The sponsor defined the following analysis datasets:

- Safety Analysis Set (SAS): The safety analysis dataset will include all subjects who received at least one dose of treatment (desmopressin or placebo) and have at least one safety assessment. In particular, if a subject was ineligible but had at least one administration of treatment, data will be included in the safety dataset. All safety analyses will be done based on the actual treatment.

- Intention-to-Treat (ITT) Analysis Set: All randomised subjects will be included in the ITT analysis dataset.
- Full Analysis Set (FAS): All randomised and exposed subjects with at least one efficacy assessment after dosing initiation comprises the Full Analysis dataset.
- Per-Protocol (PP) Analysis Set: The PP analysis set was defined as data from all randomised and exposed subjects except those excluded as a result of major protocol violations.

All efficacy analyses would be done based on the FAS population.

The sponsor's primary analysis approach for the two co-primary endpoints was a longitudinal analysis of efficacy data collected during the three months of treatment. The first co-primary endpoint would be analyzed with repeated measures using an analysis of covariance (ANCOVA) with the change in mean nocturnal voids as the dependent variable and baseline mean nocturnal voids as a covariate, treatment and visit as factors including a treatment-by-visit interaction term, and with the stratification factor (age <65, age ≥65). The second co-primary endpoint would be analyzed with generalized estimation equation (GEE) methodology with the responder status as a dependent variable and baseline mean nocturnal voids as a covariate, treatment and visit as factors including a treatment-by-visit interaction term, and with the stratification factor (age <65, age ≥65). The two co-primary analyses were based on the full analysis set (FAS) of the intention-to-treat (ITT) dataset, and sensitivity analysis would be based on the per protocol (PP population).

Note that the primary treatment estimate is an average response across the 4 time points (Week 1, Month 1, Month 2 and Month 3). This estimate was agreed to between the Agency and the sponsor as part of the Special Protocol Assessment. The primary analysis for Study CS29 was not based on an average across time points. It was based on the treatment contrast at Day 28 which ignored post-randomization data prior to that time point and was felt to be a shortcoming of the previous analysis plan.

Treatment-by-visit interaction

The Statistical Analysis Plan pre-specified that the treatment-by-visit interaction term be included in the primary statistical model. In the final report, the sponsor omitted the interaction term from the primary analysis because "the treatment-by-visit interaction was found to be non-significant at the 5% level". The sponsor included the interaction term in a sensitivity analysis. It is not standard OB practice to identify non-significant ($p > .05$) terms using results from a pre-specified model and then re-run the model without these terms. The type 1 error properties of such a procedure are not well understood. On the other hand, one could argue that including the treatment-by-visit interaction term in the model would be most appropriate, and only necessary, when conducting a repeated measures analysis whose goal is to evaluate the response at a single time point. Including the interaction term would not be necessary, or advisable, when evaluating a mean response across multiple time points (which is the primary efficacy endpoint here). This reviewer calculated p-values from models with and without the interaction term.

Missing data

The average number of voids per night over the three consecutive days prior to each visit was used as an estimate for each visit. That is, if at least one measurement was available for one of the three consecutive days, then the average over the available information was used. However,

if no data were available for a given visit, then no data were imputed at that visit for the primary (repeated measures) analysis. Using observed cases without imputation (e.g., no LOCF) is “standard operating procedure” for repeated measures analyses.

In the sponsor’s analysis of the study CS41 data, the superiority to placebo would be tested simultaneously on the two co-primary endpoints in a step-down approach from the highest 75 µg to the lowest 50 µg dose to control the type 1 error rate at the 5% significant level. More precisely, only if the 75 µg group demonstrated a statistically significant reduction in the mean number of nocturnal voids and 33% responder rate during three months of treatment compared to placebo would the trial be declared positive for that dose. If the 75 µg demonstrated significance, then the 50 µg could be claimed superior to placebo, if it showed a statistically significant improvement over placebo.

The four key secondary endpoints were tested by the sponsor, each at alpha=5%, in a hierarchical testing procedure if a dose demonstrated statistical significance on both co-primary endpoints. The secondary endpoints would be tested in the following order:

1. Mean change in nocturnal voids at Month 3 (85 days)
2. Proportion of 33% responders at Month 3 (85 days)
3. Mean time to first void at Month 3 (85 days)
4. Pharmacodynamic response at Month 3 (85 days)

In study 41, testing for key secondary endpoints for 50 mcg was conducted only after testing was completed for all key secondary endpoints for 75 mcg. Therefore, the family-wise error rate (FWE) was controlled across the co-primary and key secondary endpoints in both studies. The secondary endpoints would be analyzed using ANCOVA with main effects for treatment and the stratification factor (age <65, age ≥65), and a covariate for the baseline variable using LOCF on the FAS and PP analysis sets.

This reviewer did additional sensitivity analyses to efficacy endpoints using MMRM and ANCOVA on completers.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In study CS40, two randomized subjects (subjid= (b) (6) and (b) (6)) received the wrong treatment kits by error. Subject (b) (6) was randomized to kit#1078 (placebo) but received kit #0078 (desmopressin 25 mcg) in error. Subject (b) (6) was randomized to kit#1001 (placebo) but received kit #0001 (desmopressin 25 mcg) in error. The two female patients, who were white elderly (ages of 76 and 78 years, respectively), both completed the trial. This reviewer also identified two subjects, in study CS41, who were both randomized to desmopressin 75 mcg. One subject (subjid= (b) (6)) received desmopressin 50 mcg and the other (subjid= (b) (6)) received placebo. The efficacy analyses by this reviewer were based on the randomized arm as performed by the sponsor. Analyzing by treatment actually received (“as treated”) is a sensitivity analysis.

A description of the patient populations in the review is shown in Table 3.1.

Table 3.1. Patient disposition, demographic and baseline information (ITT/FAS)

A: CS40

Study population	Desmopressin	Placebo	Total
Randomized (ITT)	137 (100%)	131 (100%)	268 (100%)
SAFETY	135 (99%)	126 (96%)	261 (97%)
FAS	133 (97%)	128 (98%)	261 (97%)
Per Protocol (PP)	122 (89%)	115 (88%)	237 (88%)
Completers	119 (87%)	114 (87%)	233 (87%)
Age (years)			
Mean(SE)	59.6 (1.2)	60.0 (1.2)	59.8 (0.9)
Range	19-81	23-87	19-87
% >=65 yrs	60 (44%)	61 (47%)	121 (45%)
Race			
% White	111 (81%)	106 (81%)	217 (81%)
Baseline BMI <30	63 (46%)	86 (66%)	149 (56%)
Baseline # of nocturnal voids <3	81 (59%)	73 (56%)	154 (57%)

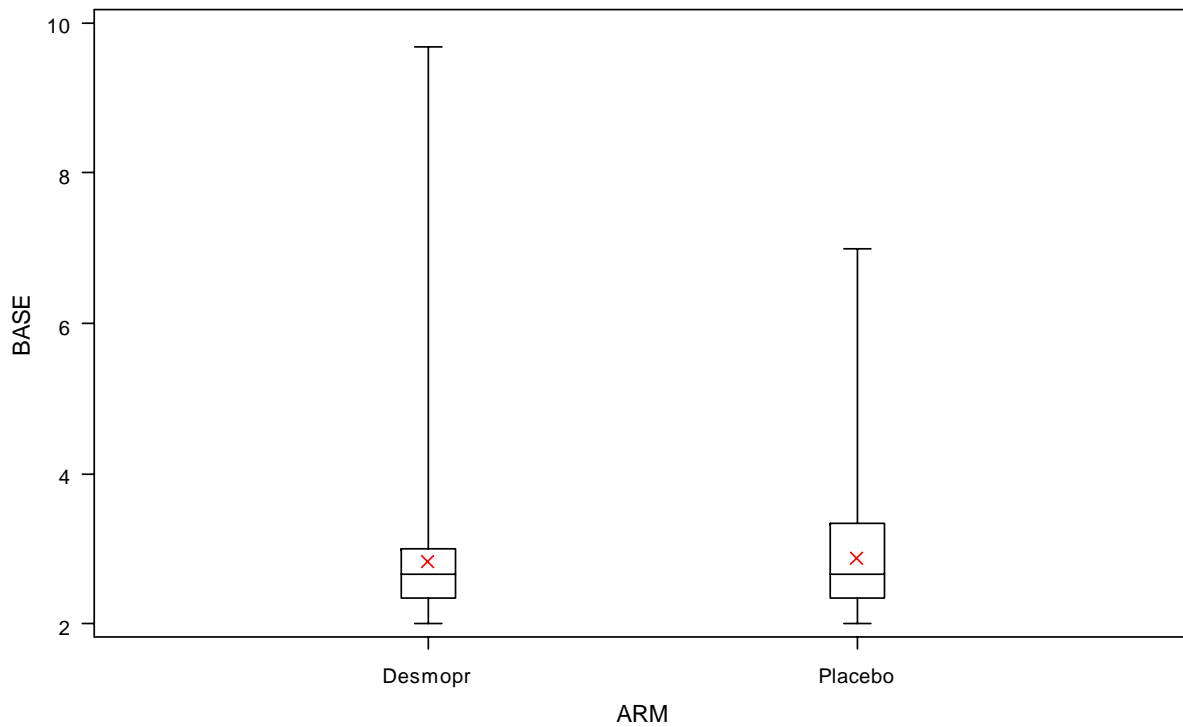
B: CS41

Study population	Desmopressin		Placebo	Total
Dose	75 µg	50 µg		
Randomized (ITT)	129 (100%)	123 (100%)	143 (100%)	395 (100%)
Safety	122 (95%)	119 (96%)	143 (99%)	384 (97%)
FAS	124 (96%)	119 (97%)	142 (99%)	385 (97%)
Per Protocol (PP)	115 (89%)	112 (91%)	136 (95%)	363 (92%)
Completers	98 (76%)	97 (79%)	120 (84%)	315 (80%)
Age (years)				
Mean(SE)	59.4 (1.1)	60.4 (1.2)	60.8 (1.2)	60.6 (0.7)
Range	27-80	20-81	21-87	20-87
% >=65 yrs	59 (48%)	59 (50%)	68 (48%)	186 (48%)
Race				
% White	102 (79%)	101 (82%)	113 (79%)	310 (80%)
Baseline BMI <30	77 (60%)	73 (59%)	91 (64%)	241 (61%)
Baseline # of nocturnal voids<3	65 (50%)	72 (59%)	74 (52%)	211 (53%)

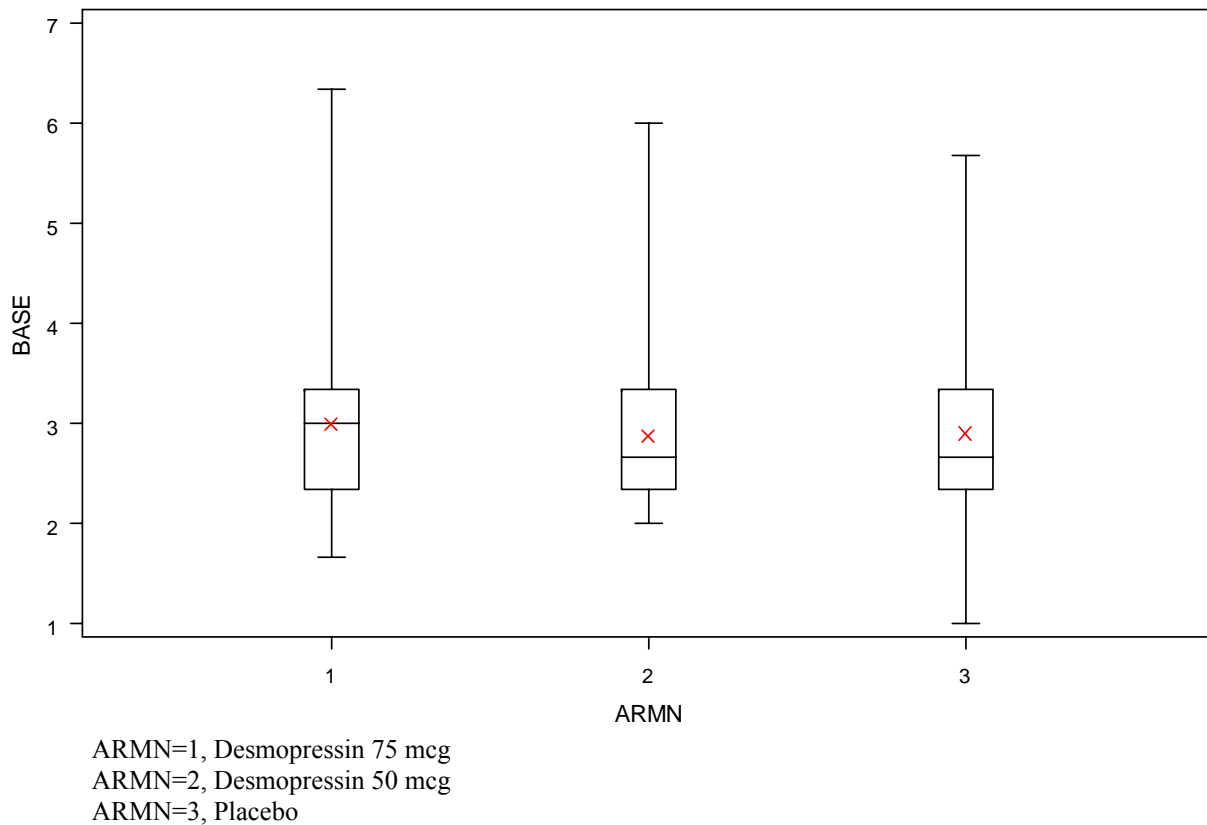
Figures 3.2A (Study CS40) and 3.2B (Study CS41) show the distributions of the mean number of baseline nocturnal voids by treatment arm. In each boxplot the bottom and top of the box are the 25th and 75th percentiles, respectively; the “x” and the line near the middle of the box are the mean and median (50th percentile), respectively; the top line above the box is the maximum observation; and the bottom line below the box is the minimum observation. Across the different treatment groups, baseline levels appear to have similar means and comparable variations.

Figure 3.2. Baseline Numbers of Nocturnal Voids in Different Treatment Groups (ITT/FAS).

A: CS40



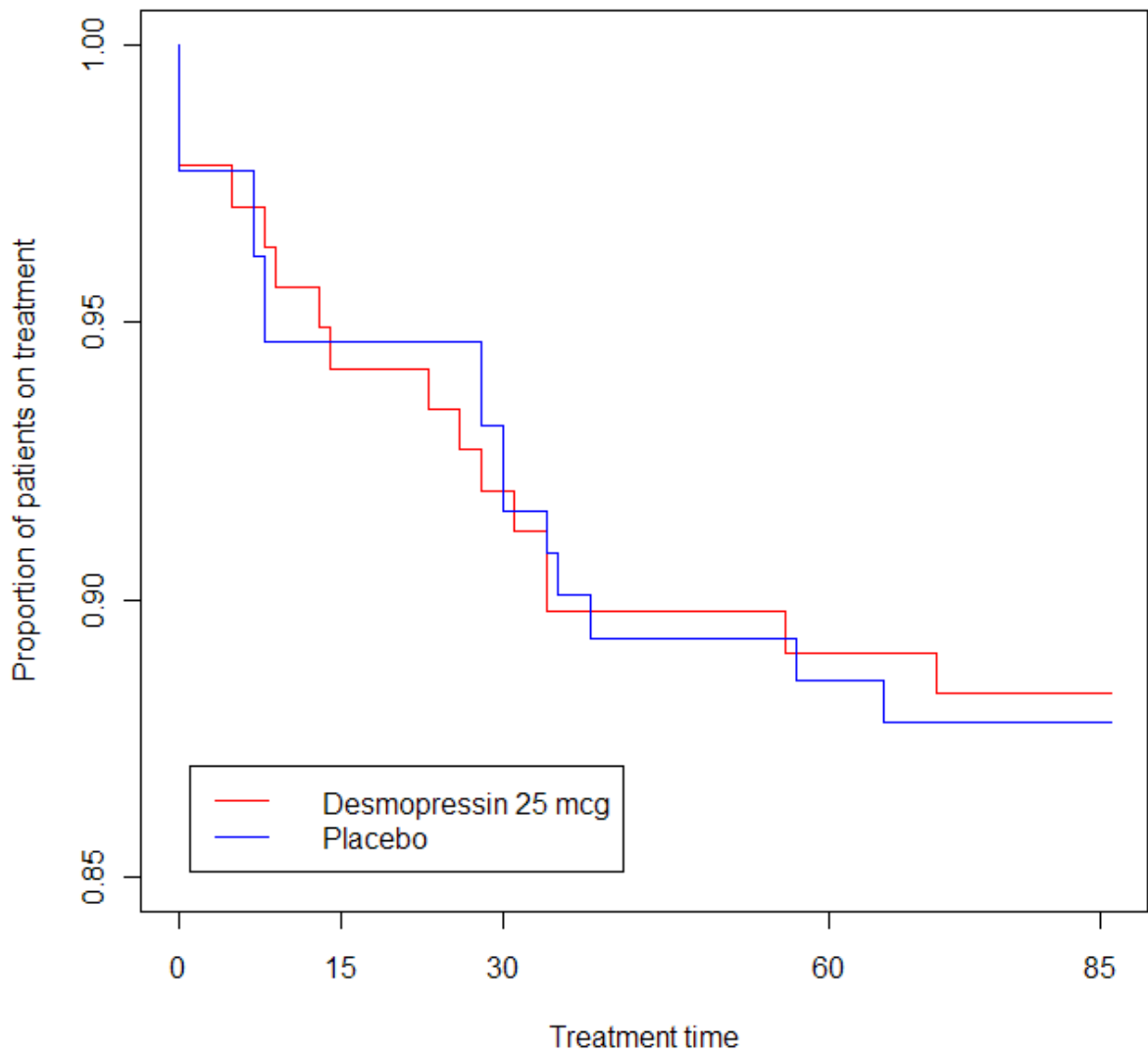
B: CS41



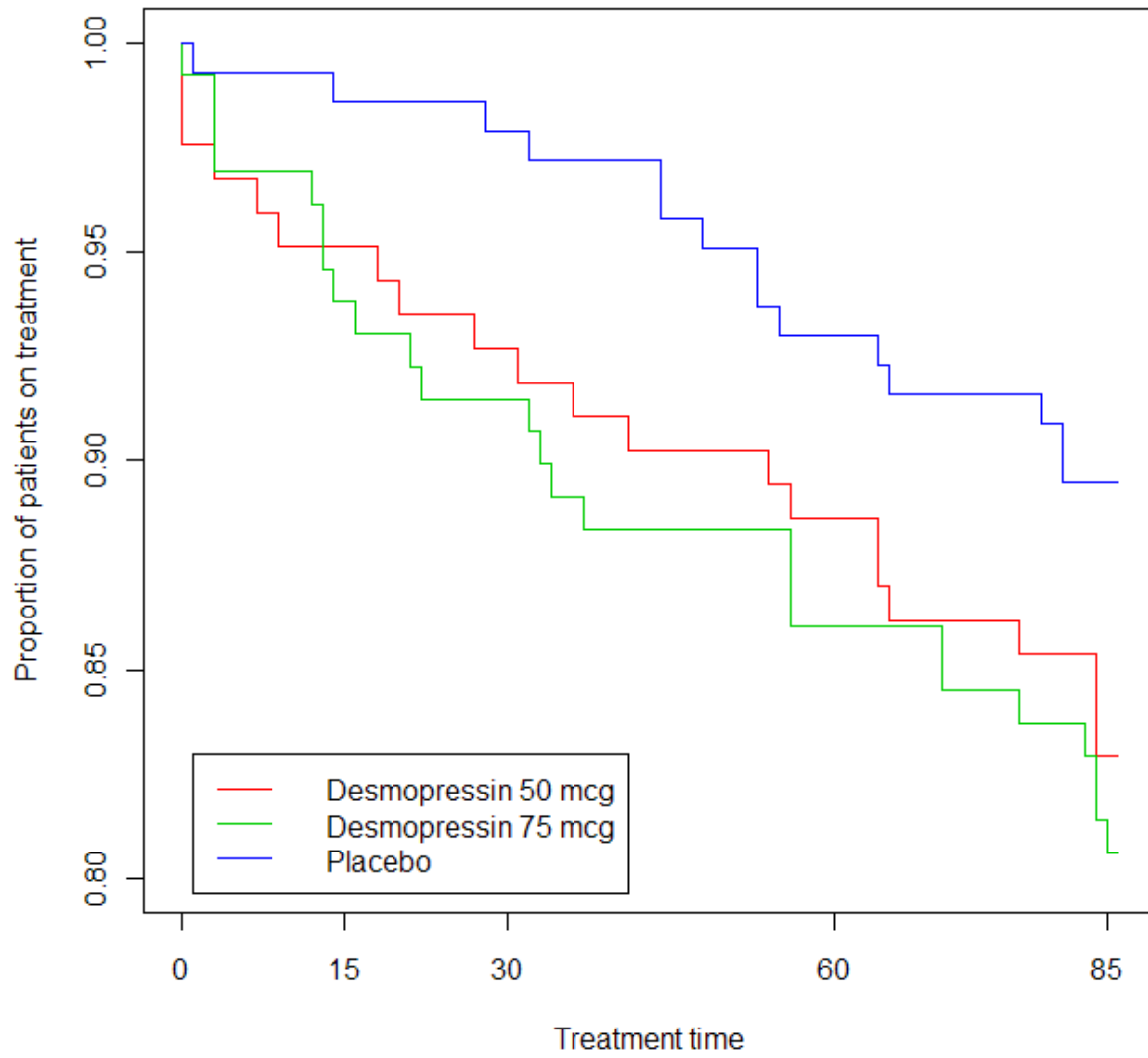
The time to dropout is plotted using Kaplan-Meier curves (Figures 3.3). The dropout rates were comparable across treatment arms, desmopressin 25 mcg and placebo, in study CS40 (Figure 3.3 A). According to the sponsor, most dropouts in CS40 were due to protocol violations in both arms and more patients in the desmopressin 25 μ g arm dropped out due to adverse events (n=4) and “Lost to follow-up” (n=4) than the placebo arm (1 in each category). For study CS41 as shown in Figure 3.3 B, however, the dropout rates differ between treatment arms. The dropout rate increased with increasing desmopressin dose. The placebo arm has the lowest rate, the 75 mcg arm the highest, and the 50 mcg arm was in between. The sponsor reported that the largest number of dropouts was due to personal choice (termed by the sponsor as “Withdrawal by subjects”). More patients in the desmopressin 75 mcg arm dropped due to “Adverse event” in the desmopressin 75 mcg arm (6%) than the desmopressin 50 mcg arm (3%) and placebo arm (4%). Dropout rates due to protocol violations were higher in the two desmopressin arms (both 5%) than the placebo arm (2%). At the end of study, the dropout rates did not differ statistically between each dose and placebo for both studies CS40 and CS41.

Figure 3.3. Time to Dropout during the Treatment Period between Treatment Groups (ITT/FAS).

A: CS40



B: CS41



3.2.4 Efficacy Results and Conclusions

Study 40

This reviewer's results are summarized in Tables 3.2 and 3.3. The sponsor's results are also shown. This reviewer confirmed the sponsor's analysis results.

Table 3.2. Change from Baseline in Mean Number of Nocturnal Voids in Desmopressin 25 µg and Placebo Treated Female Patients for 3-Months Period (ITT/FAS)

	Desmopressin 25 µg		Placebo		p-value
	n	void	n	void	
Baseline mean ± SE	133	2.84 ± 0.08	128	2.88 ± 0.07	
Adjusted Mean Change from baseline ±SE					
FAS ^{1*} (sponsor)	128	-1.46 ± 0.07	124	-1.24 ± 0.07	
FAS ¹ (as treated)	130	-1.44 ± 0.07	122	-1.26 ± 0.07	
PP ¹ (sponsor)	118	-1.48	111	-1.30	
PP ¹	118	-1.49 ± 0.07	111	-1.29 ± 0.08	
FAS ^{2*} (sponsor)	128	-1.47 ± 0.07	124	-1.23 ± 0.07	
FAS ² (as treated)	130	-1.44 ± 0.07	122	-1.25 ± 0.07	
PP ² (sponsor)	118	-1.49	111	-1.30	
PP ²	118	-1.49 ± 0.07	111	-1.29 ± 0.08	
Completers ²	118	-1.49 ± 0.07	113	-1.25 ± 0.08	
Adjusted LS Mean Treatment Difference (95% CI)					
FAS ^{1*} (sponsor)				-0.22 (-0.42, -0.02)	0.0280
FAS ¹ (as treated)				-0.18 (-0.38, 0.02)	0.0794
PP ¹ (sponsor)				-0.18 (-0.39, 0.03)	0.0899
PP ¹				-0.19 (-0.40, 0.01)	0.0677
FAS ^{2*} (sponsor)				-0.24 (-0.44, -0.04)	0.0194
FAS ² (as treated)				-0.19 (-0.40, 0.01)	0.0591
PP ² (sponsor)				-0.19 (-0.40, 0.03)	0.0856
PP ²				-0.20 (-0.41, 0.01)	0.0662
Completers ²				-0.24 (-0.45, -0.04)	0.0220

¹ average of week-1, month-1, month-2, and month-3, no treatment-by-visit interaction term in the mixed model

² average of week-1, month-1, month-2, and month-3, with treatment-by-visit interaction term in the mixed model

* This reviewer obtained the same results as the sponsor

Table 3.3. Odds Ratio of 33% Responder Status in Desmopressin 25 µg and Placebo Treated Female Patients for 3-Months Period (ITT/FAS)

		Desmopressin 25 µg		Placebo		p-value
		n		n		
FAS ¹ (sponsor)	Probability	128	0.76	124	0.63	
	Odds		3.23		1.75	
FAS ¹	Probability	128	0.76	124	0.63	
	Odds		3.16		1.71	
FAS ¹ (as treated)	Probability	130	0.75	122	0.64	
	Odds		3.04		1.75	
PP ¹ (sponsor)	Probability	118	0.77	111	0.66	
	Odds		3.33		1.94	
PP ¹	Probability	118	0.76	111	0.65	
	Odds		3.24		1.85	
FAS ² (sponsor)	Probability	128	0.76	124	0.63	
	Odds		3.12		1.72	
FAS ² (as treated)	Probability	130	0.75	122	0.64	
	Odds		2.99		1.77	
PP ² (sponsor)	Probability	118	0.76	111	0.67	
	Odds		3.23		1.99	
PP ²	Probability	118	0.76	111	0.65	
	Odds		3.17		1.88	
Completer ²	Probability	118	0.75	113	0.64	
	Odds		3.07		1.79	
Odds ratio, adjusted LS Mean (95% CI)						
FAS ¹ (sponsor)					1.85 (1.19, 2.86)	0.0061
FAS ¹					1.85 (1.19, 2.86)	0.0061
FAS ¹ (as treated)					1.74 (1.13, 2.69)	0.0127
PP ¹ (sponsor)					1.71 (1.08, 2.73)	0.0229
PP ¹					1.76 (1.11, 2.78)	0.0161
FAS ² (sponsor)					1.81 (1.16, 2.82)	0.0095
FAS ² (as treated)					1.76 (1.13, 2.73)	0.0127
PP ² (sponsor)					1.63 (1.01, 2.62)	0.0458
PP ²					1.69 (1.05, 2.70)	0.0291
Completers ²					1.72 (1.08, 1.11)	0.0220

¹ average of week-1, month-1, month-2, and month-3, no treatment-by-visit interaction term in the GEE model

² average of week-1, month-1, month-2, and month-3, with treatment-by-visit interaction term in the GEE model

Although the nominal superiority of desmopressin over placebo was achieved for both co-primary endpoints in CS40, results for the continuous co-primary endpoint based on change from baseline were not robust. The primary analysis was nominally significant (ITT/FAS; p=0.019 with treatment-by-visit interaction term, p=0.028 without interaction); however, sensitivity analysis based on per protocol population was not statistically significant (p=0.07). Two patients randomized to placebo received desmopressin 25 mcg in error. When the primary analysis was repeated, but assigning these two patients to the desmopressin group instead of the placebo group (“as treated”), the results were not statistically significant (p≥0.06).

Furthermore, the observed effect size (-0.24 voids/night with treatment-by-visit interaction term, -0.22 voids/night without interaction) was less than half the target effect size used for the sample size calculation (-0.50 voids/night) and small relative to the observed mean placebo change from baseline (-1.23 voids/night). The totality of results suggests that this desmopressin dose for females was associated with a effect size which produced efficacy results which were not very robust.

The efficacy data (averaged nocturnal voids) for the two patients who received erroneous treatments are shown below (both completers):

SUBJID	ARM	ARMA	VISIT	Baseline	Value	Change
(b) (6)	Pl acebo	Desmopressi n 25 mcg	Week 1	3. 6667	4. 6667	1
	Pl acebo	Desmopressi n 25 mcg	1 Month	3. 6667	5	1. 3333
	Pl acebo	Desmopressi n 25 mcg	2 Months	3. 6667	5	1. 3333
	Pl acebo	Desmopressi n 25 mcg	3 Months	3. 6667	5	1. 3333
	Pl acebo	Desmopressi n 25 mcg	Week 1	3. 3333	2. 3333	-1
	Pl acebo	Desmopressi n 25 mcg	1 Month	3. 3333	1. 6667	-1. 6667
	Pl acebo	Desmopressi n 25 mcg	2 Months	3. 3333	2	-1. 3333
	Pl acebo	Desmopressi n 25 mcg	3 Months	3. 3333	2. 3333	-1

ARM: randomized arm

ARMA: actual treatment received

Study 41

This reviewer's results for study 41 are summarized in Tables 3.4 and 3.5. The sponsor's are also shown. This reviewer confirmed the sponsor's analysis results.

Table 3.4. Change from Baseline in Mean Number of Nocturnal Voids in Desmopressin 75 µg, 50 µg, and Placebo Treated Male Patients for 3-Months Period (ITT/FAS)

	Desmopressin 75 µg			Desmopressin 50 µg			Placebo	
	n	# void	p-value	n	# void	p-value	n	# void
Baseline mean ± SE	124	2.99 ± 0.08		119	2.88 ± 0.08		142	2.90 ± 0.07
Adjusted Mean Change from baseline ±SE				116	-1.25		141	-0.88
FAS (sponsor) ^{1*}	120	-1.29		117	-1.25 ± 0.07		142	-0.87± 0.07
FAS (as treated) ¹	118	-1.30 ± 0.07		111	-1.27 ± 0.08		135	-0.88± 0.07
PP (sponsor) ^{1*}	113	-1.31 ± 0.08		116	-1.26 ± 0.08		141	-0.88± 0.07
FAS (sponsor) ^{2*}	120	-1.28 ± 0.07		117	-1.26 ± 0.08		142	-0.87± 0.07
FAS(as treated) ²	118	-1.29 ± 0.07		111	-1.28 ± 0.08		135	-0.89± 0.07
PP (sponsor) ^{2*}	113	-1.30 ± 0.08		97	-1.27 ± 0.08		119	-0.86± 0.07
Completers ²	96	-1.27 ± 0.08						
Adj. LSmean Treatment Difference (95% CI)								
FAS (sponsor) ^{1*}		-0.41 (-0.61, -0.22)	< .0001		-0.37 (-0.57, -0.17)	0.0003		
FAS(as treated) ¹		-0.43 (-0.63, -0.23)	< .0001		-0.38 (-0.57, -0.18)	0.0002		
PP (sponsor) ^{1*}		-0.41 (-0.62, -0.21)	< .0001		-0.39 (-0.60, -0.19)	0.0002		
FAS (sponsor) ^{2*}		-0.40 (-0.60, -0.20)	< .0001		-0.37 (-0.57, -0.17)	0.0003		
FAS(as treated) ²		-0.42 (-0.61, -0.22)	< .0001		-0.38 (-0.58, -0.18)	0.0002		
PP (sponsor) ^{2*}		-0.41 (-0.62, -0.21)	< .0001		-0.39 (-0.60, -0.19)	0.0002		
Completers ²		-0.42 (-0.63, -0.20)	0.0002		-0.41 (-0.63, -0.19)	0.0003		

¹ no treatment-by-visit interaction term in the model, average of week-1, month-1, month-2, and month-3

² with treatment-by-visit interaction term in the model, average of week-1, month-1, month-2, and month-3

* This reviewer obtained the same results as the sponsor

Table 3.5. Odds Ratio of 33% Responder Status in Desmopressin 75 µg, 50 µg, and Placebo Treated Male Patients for 3-Months Period (FAS)

	Desmopressin 75 µg			Desmopressin 50 µg			Placebo	
	n		p-value	n		p-value	n	
Adjusted Mean								
FAS (sponsor) ¹								
Probability	120	0.67		116	0.67		141	0.50
Odds		2.08			2.01			1.02
FAS ¹								
Probability	120	0.67		116	0.67		141	0.50
Odds		2.05			1.99			1.00
FAS (as treated) ¹								
Probability	118	0.68		117	0.66		142	0.50
Odds		2.10			1.96			1.00
PP (sponsor) ¹								
Probability	113	0.68		116	0.68		135	0.49
Odds		2.11			2.08			0.97
PP ¹								
Probability	113	0.68		111	0.67		135	0.49
Odds		2.08			2.05			0.97
FAS (sponsor) ²								
Probability	120	0.67		116	0.67		141	0.50
Odds		2.05			2.03			1.01
FAS ²								
Probability	120	0.67		116	0.67		141	0.50
Odds		2.02			2.00			1.00
FAS (as treated) ²								
Probability	118	0.67		117	0.66		142	0.50
Odds		2.06			1.98			1.00
PP (sponsor) ²								
Probability	113	0.67		111	0.68		135	0.49
Odds		2.06			2.11			0.97
PP ²								
Probability	113	0.67		111	0.68		135	0.49
Odds		2.03			2.08			0.96
Completers ²								
Probability	96	0.66		97	0.68		119	0.50
Odds		1.95			2.14			0.98
Odds ratio, adjusted LS Mean (95% CI)								
FAS (sponsor) ¹		2.04 (1.38, 3.03)	0.0004		1.98 (1.32, 2.96)	0.0009		
FAS ¹		2.04 (1.38, 3.03)	0.0002		1.98 (1.32, 2.96)	0.0009		
FAS(as treated) ¹		2.10 (1.41, 3.12)	0.0003		1.96 (1.31, 2.92)	0.0010		
PP (sponsor) ¹		2.16 (1.44, 3.24)	0.0002		2.13 (1.42, 3.21)	0.0003		
PP ¹		2.16 (1.44, 3.24)	0.0002		2.13 (1.42, 3.21)	0.0003		
FAS (sponsor) ²		2.02 (1.36, 3.00)	0.0005		2.00 (1.33, 3.01)	0.0008		
FAS ²		2.02 (1.36, 3.00)	0.0005		2.00 (1.33, 3.01)	0.0008		
FAS(as treated) ²		2.05 (1.38, 3.06)	0.0004		1.98 (1.32, 2.97)	0.0009		
PP (sponsor) ²		2.11 (1.41, 3.18)	0.0003		2.17 (1.43, 3.27)	0.0002		
PP ²		2.11 (1.41, 3.18)	0.0003		2.17 (1.43, 3.27)	0.0002		
Completers ²		1.98 (1.29, 3.05)	0.0019		2.18 (1.40, 3.38)	0.0005		

¹ no treatment-by-visit interaction term in the model, average of week-1, month-1, month-2, and month-3

² with treatment-by-visit interaction term in the model, average of week-1, month-1, month-2, and month-3

Both 75 mcg and 50 mcg showed statistically larger reductions in the number of voids per night compared to placebo as measured by the two co-primary endpoints. Sensitivity analyses (also shown in Tables 3.4 and 3.5) supported the primary analysis results. In particular, the statistical superiority of desmopressin at either dose versus placebo at the 0.05 significance level was not altered by analyses based on treatment actually received (“as treated”). There was a negligible dose response; for example, without the treatment-by-visit interaction term the mean number of nocturnal voids at 75 mcg dose was -0.41 voids/night vs placebo), only slightly larger than that at the 50 mcg (-0.37 voids/night).

The results for the secondary endpoints, the mean change from baseline in the number of nocturnal voids and the 33% responder status at the Month 3 time point, are listed in Tables 3.6-3.9 for CS40 and CS41. These two endpoints were the first and second endpoints, respectively, in the pre-specified hierarchy of secondary endpoints designated for type 1 error control in the Statistical Analysis Plan. Results indicated that both endpoints were statistically significant in males at both doses. In females, the continuous endpoint was statistically significant, but the 33% responder status endpoint was not significant.

Table 3.6. Change from Baseline in Mean Number of Nocturnal Voids in Desmopressin 25 µg and Placebo Treated Female Patients at Month 3 (ANCOVA, ITT/FAS)

	Desmopressin 25 µg		Placebo		p-value
	n	voids	n	voids	
Baseline mean ± SE	133	2.84 ± 0.08	128	2.88 ± 0.07	
Adjusted Mean Change from baseline ±SE					
FAS (LOCF)	132	-1.59 ± 0.08	128	-1.29 ± 0.08	
PP	107	-1.69 ± 0.09	100	-1.44 ± 0.09	
Completers	113	-1.69 ± 0.09	107	-1.37 ± 0.09	
FAS (MMRM) ¹	113	-1.66 ± 0.09	107	-1.34 ± 0.09	
Adjusted LS Mean Treatment Difference (95% CI)					
FAS (LOCF)				-0.30 (-0.54, -0.07)	0.0104
PP				-0.25 (-0.50, -0.00)	0.0486
Completers				-0.32 (-0.57, -0.08)	0.0102
FAS (MMRM) ¹				-0.32 (-0.56, -0.07)	0.0115

¹ with treatment-by-visit interaction term in the model.

Table 3.7. Odds Ratio of 33% Responder Status in Desmopressin 25 µg and Placebo Treated Female Patients at Month 3 (ANCOVA, ITT/FAS)

		Desmopressin 25 µg		Placebo		p-value
		n		n		
Adjusted Mean						
FAS (LOCF)	Probability	132	0.79	128	0.68	
	Odds		3.71		2.15	
PP	Probability	107	0.80	100	0.75	
	Odds		3.99		2.98	
Completer	Probability	113	0.79	107	0.72	
	Odds		3.85		2.59	
FAS (MMRM) ¹	Probability	113	0.79	107	0.71	
	Odds		3.75		2.50	
Odds ratio, adjusted LS Mean (95% CI)						
FAS (LOCF)					1.72 (0.98, 3.05)	0.0586
PP					1.34 (0.68, 2.60)	0.3871
Completers					1.48 (0.79, 2.78)	0.2208
FAS (MMRM) ¹					1.50 (0.81, 2.78)	0.1925

¹ with treatment-by-visit interaction term in the model.

Table 3.8. Change from Baseline in Mean Number of Nocturnal Voids in Desmopressin 75 µg, 50 µg and Placebo Treated Female Patients at Month 3 (ANCOVA, ITT/FAS)

	Desmopressin 75 µg			Desmopressin 50 µg			Placebo	
	n		p-value	n		p-value	n	
Baseline mean ± SE	124	2.99 ± 0.08		119	2.88 ± 0.08		142	2.90 ± 0.07
Adjusted Mean Change from baseline ±SE								
FAS (LOCF)	122	-1.35 ± 0.08		119	-1.29 ± 0.09		142	-1.00 ± 0.08
PP	102	-1.36 ± 0.09		101	-1.31 ± 0.09		123	-0.98 ± 0.09
Completers	97	-1.36 ± 0.10		97	-1.28 ± 0.10		118	-0.96 ± 0.09
FAS (MMRM) ¹	97	-1.36 ± 0.10		97	-1.27 ± 0.10		118	-0.96 ± 0.09
Adj. LSmean Treatment Difference (95% CI)								
FAS (LOCF)		-0.35 (-0.57, -0.12)	0.0029		-0.29 (-0.52, -0.06)	0.0128		
PP		-0.39 (-0.64, -0.13)	0.0028		-0.33 (-0.58, -0.08)	0.0100		
Completers		-0.41(-0.66, -0.15)	0.0020		-0.33 (-0.58, -0.07)	0.0126		
FAS (MMRM) ¹		-0.40 (-0.66, -0.14)	0.0023		-0.32 (-0.57, -0.06)	0.0153		

¹ with treatment-by-visit interaction term in the model.

Table 3.9. Odds Ratio of 33% Responder Status in Desmopressin 75 µg, 50 µg and Placebo Treated Female Patients at Month 3 (ANCOVA, ITT/FAS)

	Desmopressin 75 µg			Desmopressin 50 µg			Placebo	
	n		p-value	n		p-value	n	
Adjusted Mean								
FAS (LOCF)								
Probability	122	0.67		119	0.66		142	0.53
Odds		2.06			1.96			1.14
PP								
Probability	102	0.65		101	0.68		123	0.52
Odds		1.89			2.14			1.08
Completers								
Probability	97	0.66		97	0.67		118	0.52
Odds		1.91			2.07			1.09
FAS (MMRM) ¹								
Probability	97	0.66		97	0.67		118	0.53
Odds		1.91			2.01			1.11
Odds ratio, adjusted								
LS Mean (95% CI)								
FAS (LOCF)		1.81 (1.08, 3.02)	0.0233		1.72 (1.03, 2.87)	0.0386		
PP		1.74 (1.00, 3.03)	0.0500		1.98 (1.13, 3.47)	0.0176		
Completers		1.76 (0.99, 3.12)	0.0530		1.91 (1.07, 3.40)	0.0283		
FAS (MMRM) ¹		1.73 (0.99, 3.03)	0.0550		1.82 (1.05, 3.15)	0.0333		

¹ with treatment-by-visit interaction term in the model.

The results for the secondary endpoint, the change from baseline in mean time to the first nocturnal void at the Month 3 timepoint are listed in Tables 3.10 for each study. Because the 33% responder rate did not achieve statistical significance in Study CS40, statistical significance could not be claimed for any of the subsequent endpoints in the hierarchy, including time to first nocturnal void.

Table 3.10. Change from Baseline in Averaged Mean Time of First Nocturnal Voids in Desmopressin and Placebo Treated Patients at Month 3 (ITT/FAS)

A: CS40

	Desmopressin		Placebo		p-value
	n	minutes	n	minutes	
Desmopressin 25 µg					
Baseline mean ± SE	133	147 ± 5	128	143 ± 5	
Adjusted Mean Change from baseline ±SE					
FAS (LOCF) ¹	132	155 ± 12	128	105 ± 12	
FAS (average) ²	128	139 ± 9	124	101 ± 9	
FAS (OC(as treated)) ²	130	159 ± 12	122	112 ± 13	
FAS (LOCF, as treated) ¹	134	153 ± 12	126	107 ± 12	
Adjusted LS Mean Treatment Difference (95% CI)**					
FAS (LOCF) ¹				49 (16, 82)	0.0034
FAS (average) ²				38 (12, 64)	0.0048
FAS (average, as treated) ²				48 (13, 82)	0.007
FAS (LOCF, as treated) ¹				45 (13, 78)	0.0068

** Statistical significance could not be claimed per the pre-specified hierarchical testing procedure

B: CS41

	Desmopressin 75 µg			Desmopressin 50 µg			Placebo	
	n	minutes	p-value	n	minutes	p-value	n	minutes
Baseline mean ± SE	124	143 ± 5		119	146 ± 5		142	147 ± 5
Adjusted Mean Change from baseline ±SE								
FAS (LOCF) ¹	122	118 ± 10		119	112 ± 10		142	73 ± 10
FAS (average) ²	120	105 ± 8		116	103 ± 8		141	58 ± 8
FAS (average, as treated) ²	118	120 ± 11		117	112 ± 11		142	73 ± 10
FAS (LOCF, as treated) ¹	120	117 ± 10		120	111 ± 10		143	72 ± 10
Adj. LSmean Treatment Difference (95% CI)								
FAS (LOCF) ¹			0.0026			0.0064		
FAS (average) ²		43 (15, 71)	<.0001		39 (11, 67)	<.0001		
FAS (average, as treated) ²		48 (26, 70)	0.0016		45 (23, 68)	0.0094		
FAS (LOCF, as treated) ¹		47 (18, 76)	0.0016		39 (10, 68)	0.0058		
		45 (17, 73)			39 (11, 67)			

¹ ANCOVA, at month 3 (visit 7)

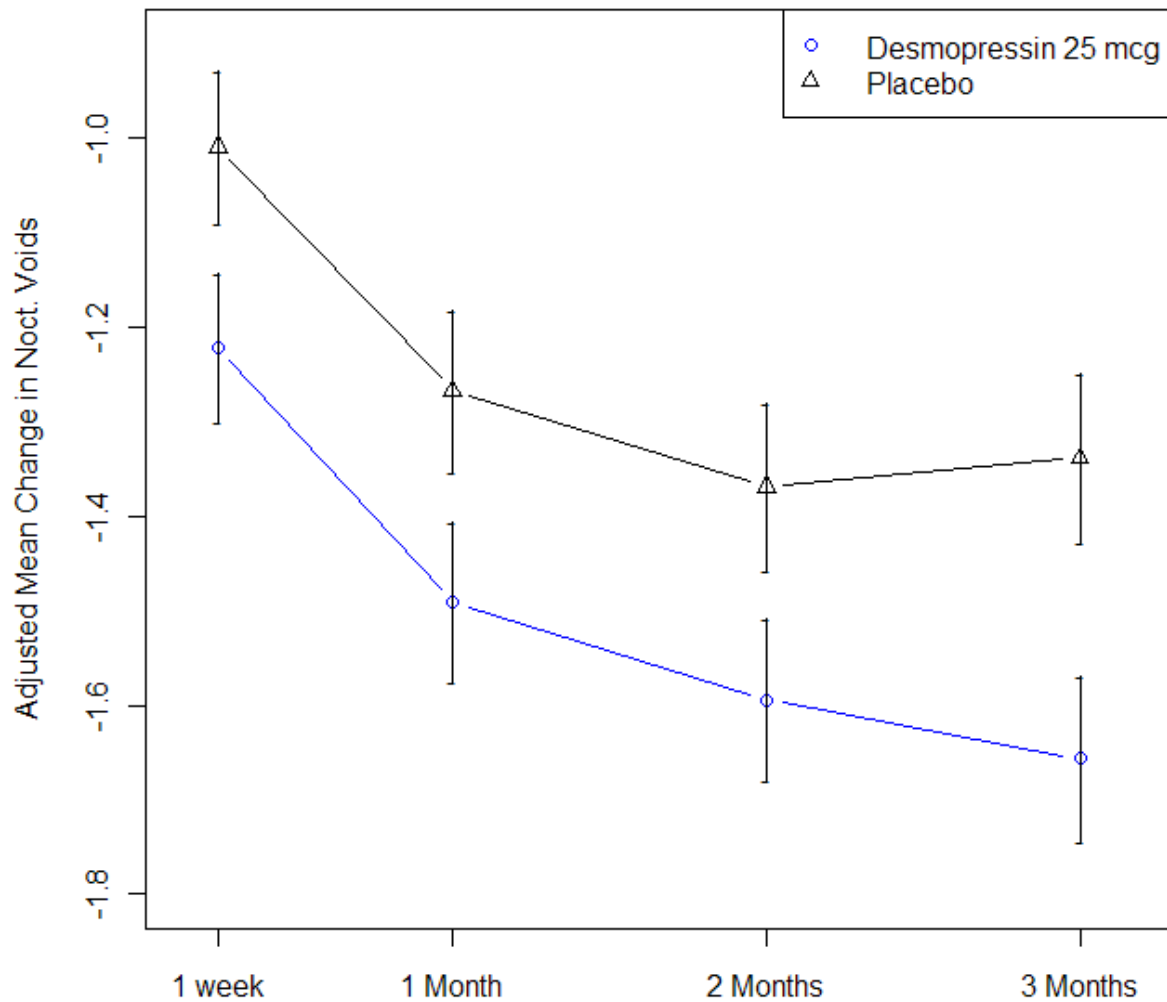
² average of week-1, month-1, month-2, and month-3, with treatment-by-visit interaction term in the model

The results above for CS41 on the first time of nocturnal void are consistent with sponsor's analyses, supporting the efficacy of desmopressin.

The time course of the changes from baseline in the number of voids and the 33% responder status between desmopressin and placebo are shown in Figure 3.4 for CS40 and Figure 3.5 for CS41, respectively, for study completers. Shown at each time point are the model-adjusted mean changes from baseline and corresponding standard errors.

Figure 3.4. The Time Courses over 3 Months for Change from Baseline in Mean Number of Nocturnal Voids and 33% Responder Status in Women. (Study CS40, ITT, Completers)

A. Change from baseline in mean number of nocturnal voids



B. 33% Responder status

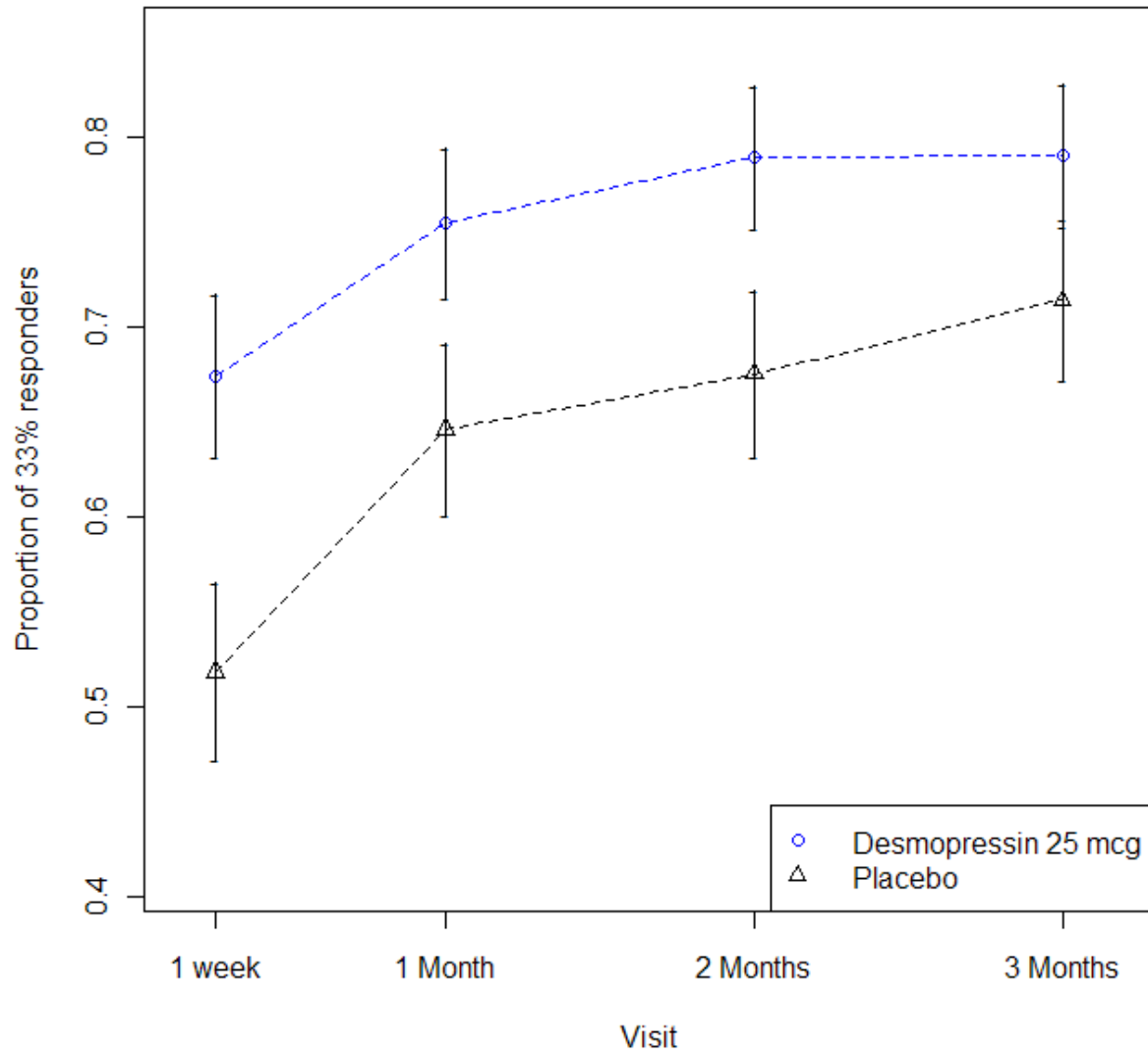
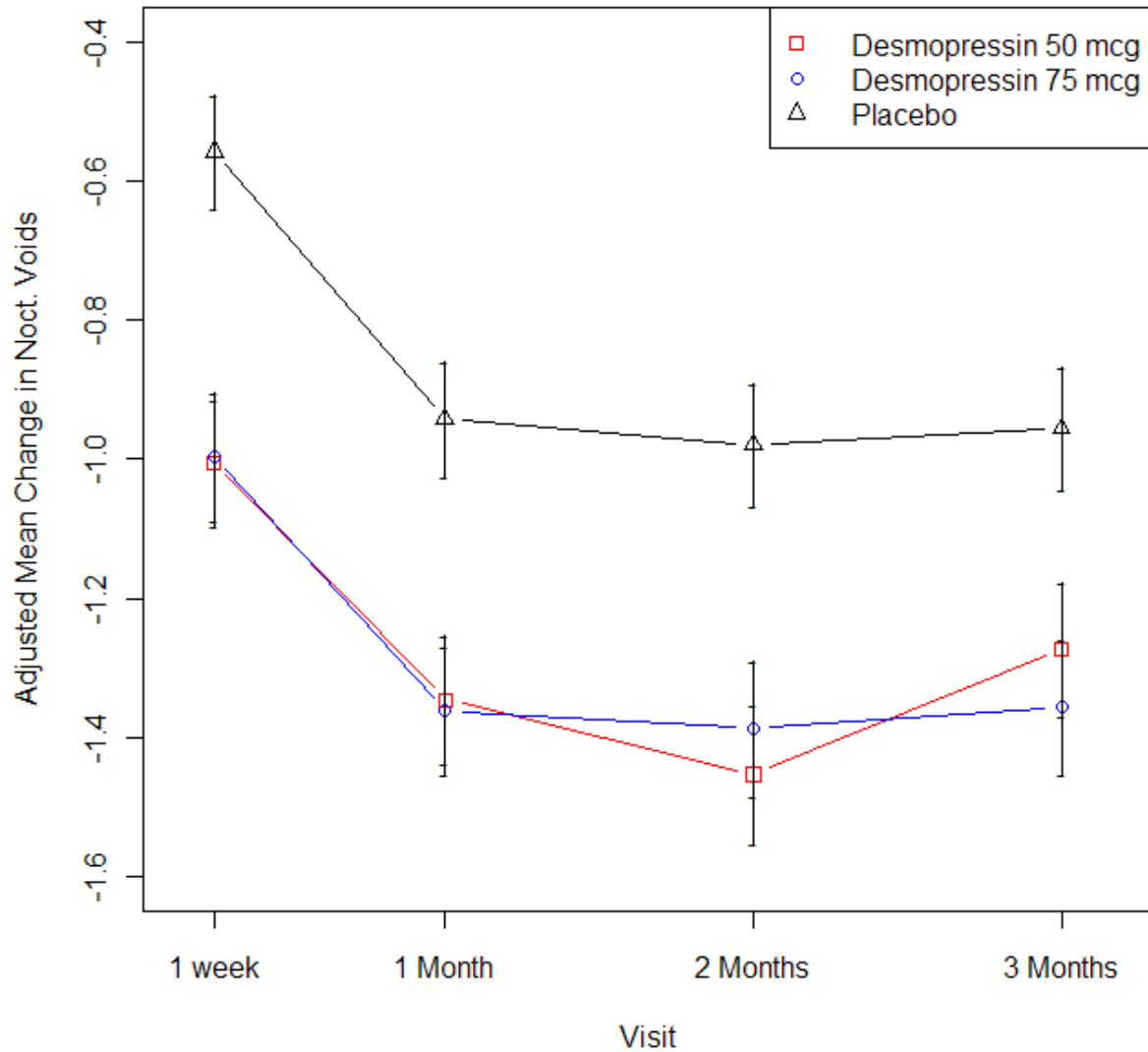
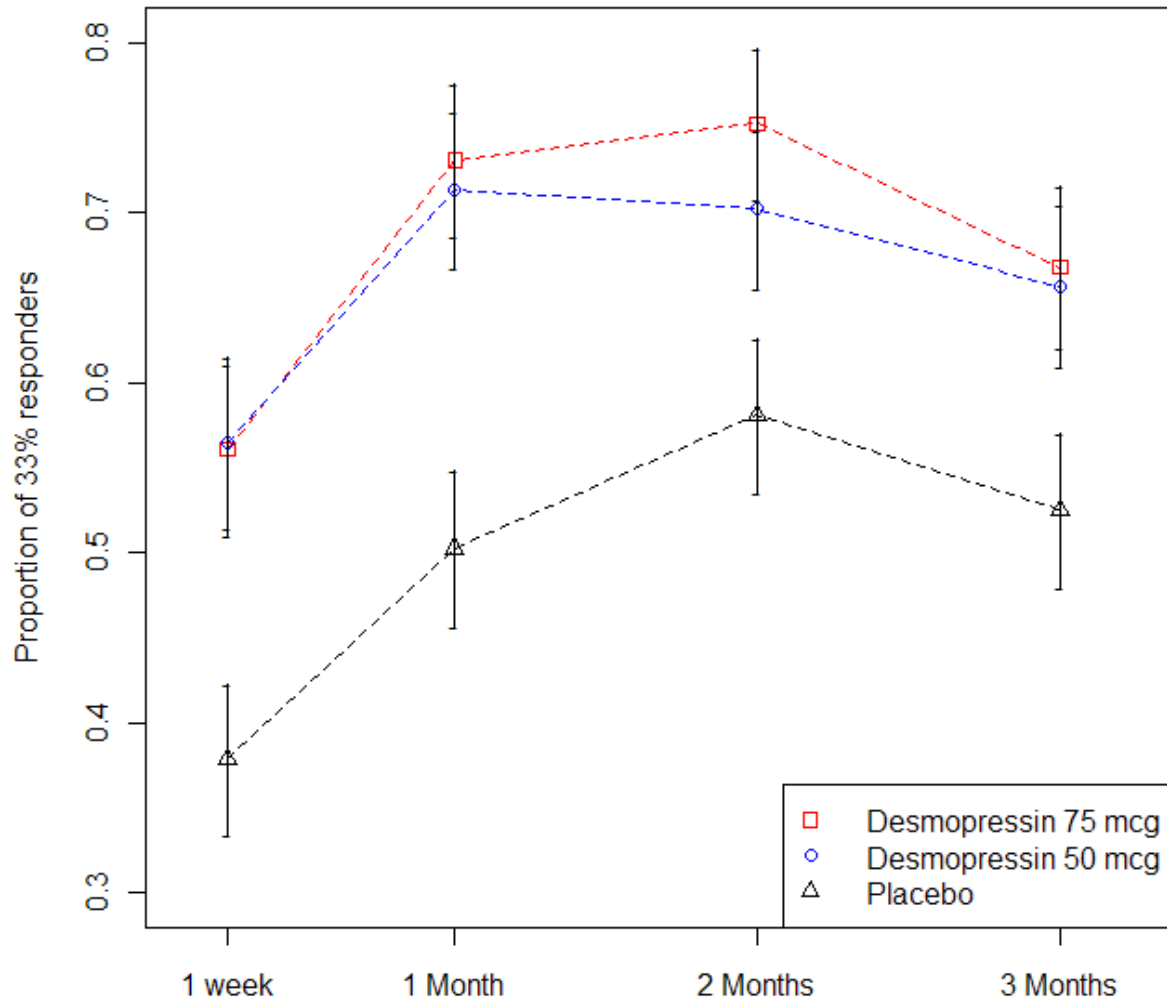


Figure 3.5. The Time Courses over 3 Months for Change from Baseline in Mean Number of Nocturnal Voids and 33% Responder Status in Men. (Study CS41, ITT, Completers)

A. Change from baseline in mean number of nocturnal voids



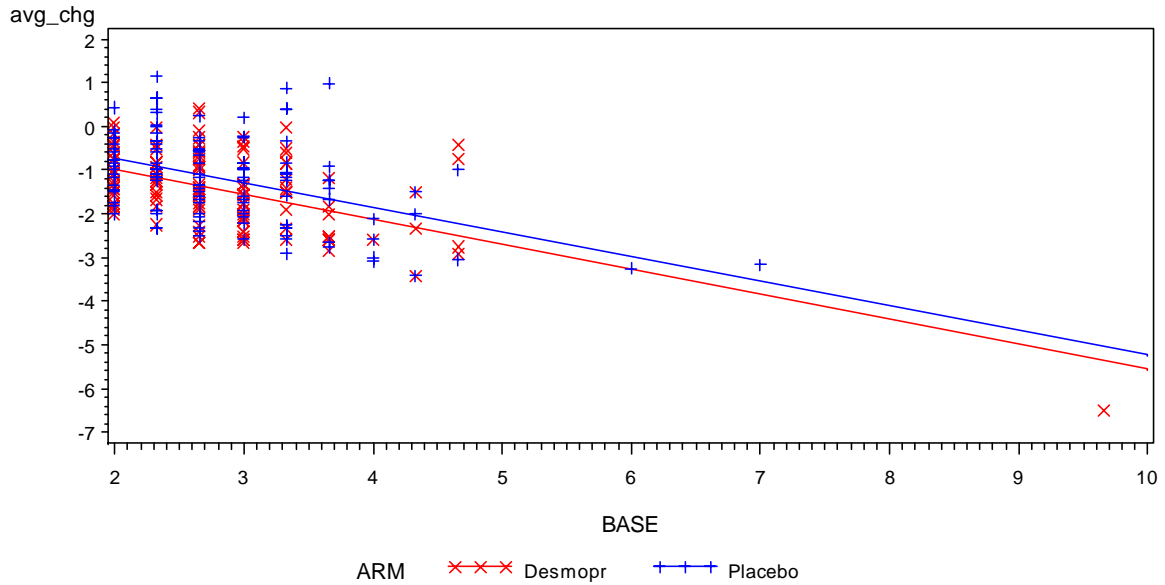
B. 33% Responder status



This reviewer visually examined the relationship between patients' baseline levels in the number of nocturnal voids and their corresponding averaged changes (Week 1, Month 1, Month 2, and Month 3) from baseline after 3 months treatment (LOCF) for studies CS40 and CS41 (at each dose), respectively, as shown in Figures 3.6 A and B. The treatment-baseline interaction is not significant at $\alpha=0.10$ level between desmopressin and placebo.

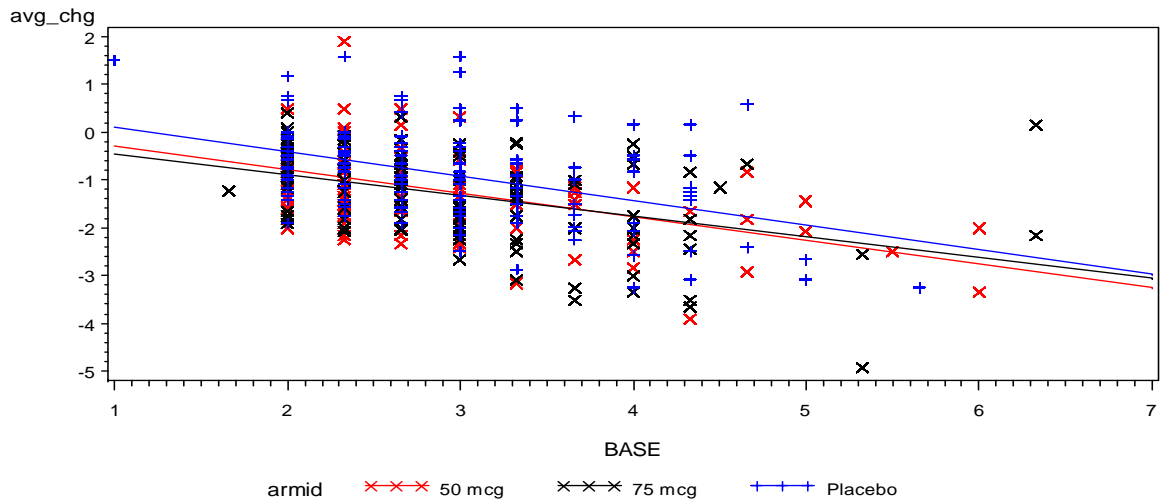
Figure 3.6. The Plot of Changes from Baseline in Averaged Number of Nocturnal Voids versus Baseline Levels During 3 Months Treatments (ITT/FAS, LOCF): A. Study CS40; B. Study CS41.

A: CS40



Regression equation : $\text{avg\_chg}(\text{ARM: Desmopressin 25 mcg}) = 0.18234 - 0.57368 \cdot \text{BASE}$.
 Regression equation : $\text{avg\_chg}(\text{ARM: Placebo}) = 0.399868 - 0.563592 \cdot \text{BASE}$.

B: CS41



Regression equation : $\text{avg\_chg}(\text{armid: 50 mcg}) = 0.188227 - 0.48943 \cdot \text{BASE}$.
 Regression equation : $\text{avg\_chg}(\text{armid: 75 mcg}) = -0.020607 - 0.431616 \cdot \text{BASE}$.
 Regression equation : $\text{avg\_chg}(\text{armid: Placebo}) = 0.616489 - 0.512662 \cdot \text{BASE}$.

In CS40, patient (b) (6) was one of two patients given incorrect treatment. The patient (b) (6) was an outlier (based on the averaged change of nocturnal voids) from others with the same baseline value as shown below. This could explain, at least partially why the p-value doubled based on “as treated” arms as compared to the randomized arms:

SUBJID	avg_chg	ARM	ARMA	BASE
(b) (6)	0.99	Placebo	Desmopressin 25 mcg	3.66
	-1.16	Desmopr	Desmopressin 25 mcg	3.66
	-1.83	Desmopr	Desmopressin 25 mcg	3.66
	-2	Desmopr	Desmopressin 25 mcg	3.66
	-2.5	Desmopr	Desmopressin 25 mcg	3.66
	-2.5	Desmopr	Desmopressin 25 mcg	3.66
	-2.58	Desmopr	Desmopressin 25 mcg	3.66
	-2.58	Desmopr	Desmopressin 25 mcg	3.66
	-2.83	Desmopr	Desmopressin 25 mcg	3.66
	-0.91	Placebo	Placebo	3.66
	-1.22	Placebo	Placebo	3.66
	-1.25	Placebo	Placebo	3.66
	-1.41	Placebo	Placebo	3.66
	-1.66	Placebo	Placebo	3.66
	-2.66	Placebo	Placebo	3.66
	-2.77	Placebo	Placebo	3.66

The averaged number of nocturnal voids appears distributed normally in study CS40.

The sponsor’s efficacy results for the two studies, in female and male subjects, respectively, were verified by this reviewer. In each study, nominal superiority of desmopressin over placebo was observed for both co-primary endpoints at a significant level of 0.05, regardless of the presence of the treatment-by-visit interaction term in the model. However, the results of study CS40 for the continuous co-primary endpoint were not robust. In both studies, two subjects erroneously received treatments different from the randomized treatments. When the primary analysis for Study CS40 was repeated, but assigning the two patients to the desmopressin group instead of the placebo group (“as treated”), the results were not statistically significant (p=0.06). Additional sensitivity analysis for Study CS40 using the per protocol population was also not significant (p=0.07).

Although the superiority of desmopressin 25 mcg over placebo was nominally achieved in Study CS40, the effect size (an average response across Week 1, Month 1, Month 2, and Month 3) was small relative to the average response in the placebo group. The difference from placebo in the mean number of nocturnal voids was -0.22 voids/night (p-value=0.0280) based on the intent-to-treat analysis, but was only -0.19 voids/night for the “as treated” analysis (not statistically significant, p=0.0591). These changes in efficacy were due to results in the two aforementioned patients, suggesting that the efficacy was not very robust.

For males (CS41), efficacy was demonstrated for both doses on the co-primary endpoints, for sensitivity analyses of the co-primary endpoints and for key secondary endpoints. The mean treatment differences were -0.40 voids/night for 75 mcg and -0.37 voids/night for 50 mcg (ITT arms, with treatment-by-visit interaction term). The statistical significance was not altered when

the two subjects who were given the wrong treatment were analyzed according to treatment actually received.

3.3 Evaluation of Safety

An evaluation of the safety of desmopressin presented in this submission is included in the clinical review by Dr. Williams Lubas.

3.4 Benefit:Risk Assessment (Optional)

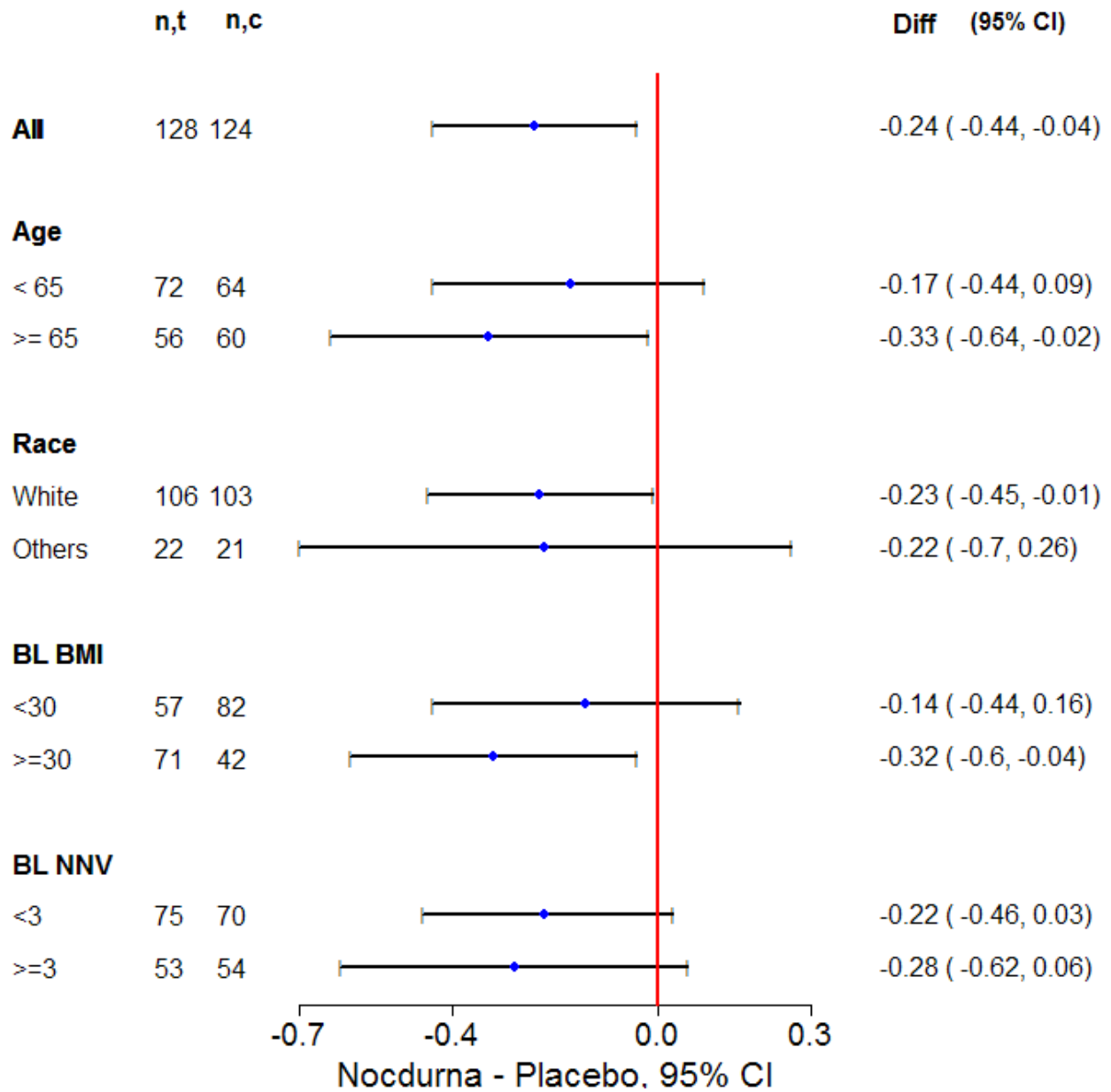
I did not conduct a benefit:risk analysis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses of the continuous co-primary endpoint, the change from baseline in the mean number of nocturnal voids, were performed across categories of age (<65 years, ≥ 65 years), race (Caucasian and non-Caucasian), baseline BMI (<30 Kg/m², ≥ 30 Kg/m²), and baseline number of nocturnal voids (<3 times/night, ≥ 3 times/night). No subgroup analyses were performed by country because these two studies were conducted in US ($\geq 99\%$ in CS40, and $\geq 97\%$ in CS41) and Canada. The forest plots for CS40 and CS41 are shown in Figures 4.1 and 4.2. Shown for each subgroup is the model-adjusted averaged (Week 1, Month 1, Month 2 and Month 3) mean difference in the number of nocturnal voids between desmopressin and placebo.

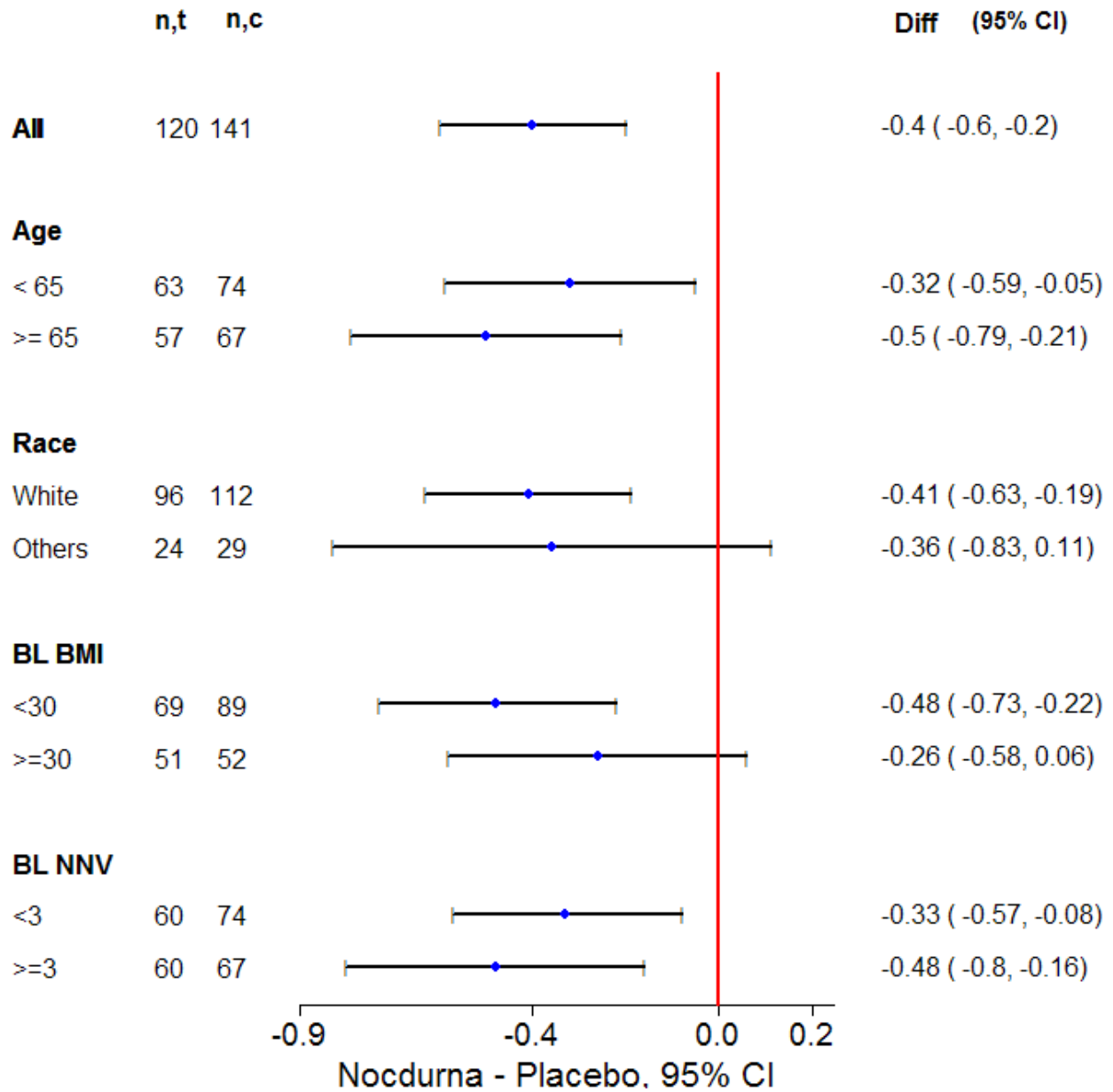
Figure 4.1. The Forest Plot of Changes from Baseline in Mean Number of Nocturnal Voids in Desmopressin 25 µg and Placebo Treated Female Patients for 3-Months Period (ITT/FAS).



NNV- Number of Nocturnal voids

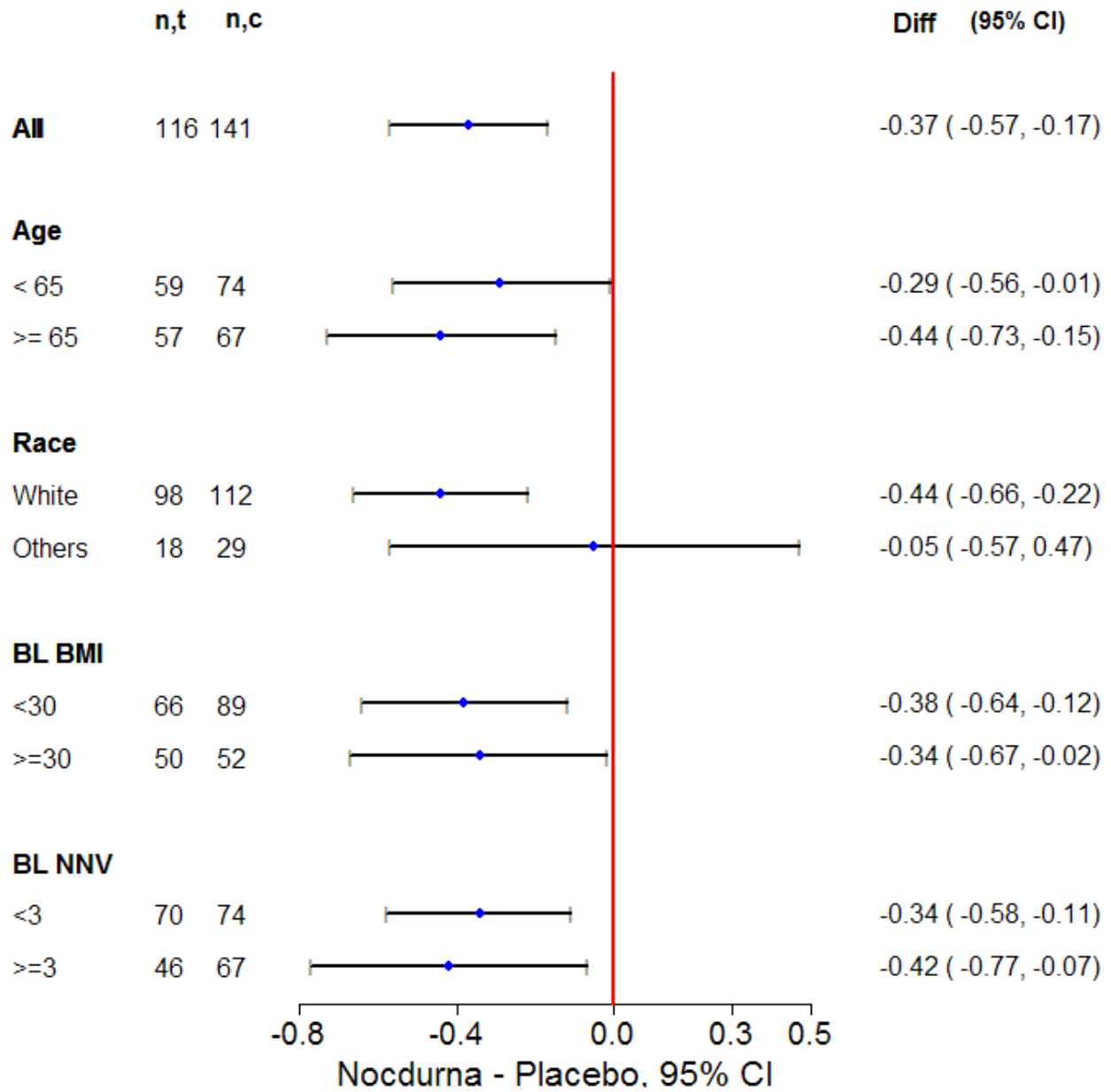
Figure 4.2. The Forest Plot of Changes from Baseline in Mean Number of Nocturnal Voids in Desmopressin 75 µg, 50 µg , and Placebo Treated Male Patients for 3-Months Period (ITT/FAS).

A: 75 µg



NNV- Number of Nocturnal voids

B: 50 µg



NNV- Number of Nocturnal voids

For both studies, desmopressin (at each dose) was numerically superior to placebo for all subgroups examined indicating reasonable consistency of effect across subgroups.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The Statistical Analysis Plan pre-specified that the treatment-by-visit interaction term be included in the primary statistical model. In the final report, the sponsor omitted the interaction term from the primary analysis because “the treatment-by-visit interaction was found to be non-significant at the 5% level”. The sponsor included the interaction term in a sensitivity analysis. It is not standard OB practice to identify non-significant ($p > .05$) terms using results from a pre-specified model and then re-run the model without these terms. The type 1 error properties of such a procedure are not well understood. On the other hand, one could argue that including the treatment-by-visit interaction term in the model would be most appropriate, and only necessary, when conducting a repeated measures analysis whose goal is to evaluate the response at a single time point. Including the interaction term would not be necessary, or advisable, when evaluating a mean response across multiple time points (which are the primary efficacy endpoints here).

The pre-specified primary treatment estimate was the average response across the 4 time points at Week 1, Month 1, Month 2 and Month 3. This estimate was agreed to between the Agency and the sponsor as part of the Special Protocol Assessment. The primary analysis for Study CS29 in the original NDA submission was based on the treatment difference at the last time point of the study, Day 28, which ignored post-randomization data prior to that time point. The data from trial CS29 suggested that the effects of desmopressin were seen well before Day 30 and possibly as early as Week 1. To correct what was thought to be a shortcoming of the CS29 statistical analysis plan, the sponsor decided to base the treatment difference in Studies CS40 and CS41 on the average response across the four time points. The change from baseline in the number of voids at the Month 3 time point and corresponding 33% responder endpoint – identical to the co-primary endpoints but measured solely at the Month 3 time point -- were designated as the first two key secondary endpoints and included in the hierarchical testing procedure for controlling type 1 error across the primary and key secondary endpoints. Results showed that, in the female study (CS40), the change from baseline in the number of voids at Month 3 was statistically significant ($p < 0.05$), but the 33% responder status endpoint at Month 3 was not statistically significant ($p > 0.05$).

5.2 Conclusions and Recommendations

The efficacy data in Study CS41 (males) support the superiority of desmopressin at both planned doses over placebo based on statistical results for the two co-primary efficacy endpoints, change from baseline in the average number of nocturnal voids over 3 months and 33% responder status over 3 months ($p < 0.001$ for both doses, both co-primary endpoints). Mean effect sizes were -0.40 and -0.37 voids/night for 75 and 50 mcg, respectively, from mean baselines of about 3 voids/night.

Data in females (Study CS40) showed nominal significance ($p < .05$) on both co-primary endpoints for desmopressin 25 mcg vs placebo. However, results for the continuous co-primary endpoint based on change from baseline were not robust. Although the primary analysis was nominally significant (ITT/FAS; $p = 0.019$ with interaction term, $p = 0.028$ without interaction), sensitivity analysis based on per protocol population was not statistically significant ($p = 0.07$). Two patients randomized to placebo received desmopressin 25 mcg in error. When the primary analysis was repeated, but assigning these two patients to the desmopressin group instead of the placebo group (“as treated”), the results were not statistically significant ($p = 0.06$). The observed effect size (-0.24 voids/night with treatment-by-visit interaction term, -0.22 voids/night without interaction) was less than half the target effect size used for the sample size calculation (-0.50 voids/night) and small relative to the observed mean placebo change from baseline (-1.23 voids/night).

5.3 Labeling Recommendations (as applicable)

Labeling Recommendations:

The statistical review addresses statements in the label (section 14) concerning:

1. Description of randomization: The sponsor should include the information that the randomization was stratified by age of 65 years old for both studies.
2. Figures: Indicate if they are plots of observed data or completers.
2. Make it clear that the efficacy results as the average of Week 1, Month 1, Month 2, and Month 3.
3. It should also show the results of undisturbed sleep time after 3 months of treatment in the placebo arms.

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CLINICAL REVIEW

Application Type	NDA Type 5
Application Number(s)	22-517 Se17 SDN19
Priority or Standard	Standard Resubmission/Class 2

Submit Date(s)	July 30, 2012
Received Date(s)	July 30, 2012
PDUFA Goal Date	Jan. 30, 2013
Division / Office	DMEP/ODEII
Reviewer Name(s)	William Lubas M.D.,Ph.D.
Review Completion Date	Jan. 18, 2013

Established Name	desmopressin acetate
(Proposed) Trade Name	Nocdurna
Therapeutic Class	vasopressin analogue
Applicant	Ferring Pharmaceuticals Inc.

Formulation(s)	Oral disintegrating sublingual tablet
Dosing Regimen	Single sublingual dose at bedtime
Indication(s)	Adult nocturia
Intended Population(s)	Adults with nocturia

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that Nocdurna be approved for the treatment of adult nocturia at the following doses: women 25 µg and men 50 µg.

1.2 Risk Benefit Assessment

Nocdurna demonstrated efficacy at doses of 25µg in women and at doses of 50 and 75 µg in men. However, because there was no clear benefit in efficacy at the 75 µg dose in men and there was an increased risk of hyponatremia at that dose the maximal recommended doses are 25 µg in women and 50 µg in men.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

The sponsor has submitted a Medication Guide in accordance with 21 CFR 208 as patient labeling rather than a REMS. There is no need for a formal REMS at this time.

1.4 Recommendations for Postmarket Requirements (PMR) and Commitments

It is recommended that the sponsor set up a pharmacovigilance PMR to identify cases of severe hyponatremia requiring hospitalization in patients treated with Nocdurna. The purpose of the PMR is to determine if such cases are occurring despite physicians following the recommendations for serum sodium monitoring, and the contraindications to use in patients with moderate to severe renal failure or cardiac failure to determine if additional strategies may be required to ensure safe use. The PMR may also help to assess the risk for hyponatremia in elderly patients on concomitant medications that have been shown to increase the risk of hyponatremia e.g. tricyclic antidepressants, SSRIs and NSAIDs etc, and whether additional serum sodium monitoring may be required in certain cases during the initiation of such medications or change in medication dosage.

2 Introduction and Regulatory Background

2.1 Product Information

Vasopressin, the naturally occurring antidiuretic hormone, binds to receptors in the collecting duct and distal tubules of the kidney promoting water reabsorption and binds

to receptors on smooth muscle cells in arterioles leading to vasoconstriction and an increase in systemic blood pressure. Desmopressin, a synthetic analogue of vasopressin, is modified to increase and prolong the antidiuretic effect while minimizing the effect on smooth muscle vasoconstriction.

Desmopressin is available as a subcutaneous injection, nasal spray, and oral tablets. It has been approved for the following indications:

- treatment of patients with diabetes insipidus who have a deficiency of endogenous vasopressin
- measurement of the kidney's ability to concentrate urine [i.e. renal concentration capacity testing (RCCT)] for patients with suspected renal disease
- treatment of children with primary nocturnal enuresis (PNE)
- treatment of patients with type I von Willebrand's disease and hemophilia A

The nasal spray is no longer marketed for the PNE indication because of a higher risk of hyponatremic seizures compared to the tablet formulation. The therapeutic dose for the treatment of bleeding disorders is about 15-fold higher than the dose used for the voiding indications, so treatment requires use of a high-dose nasal spray or injection.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently approved medications for the treatment of adult nocturia in the US. According to the sponsor, desmopressin has been approved for the treatment of adult nocturia, in subjects up to 65 years of age, in 70 countries worldwide.

Drugs used to treat over active spastic bladder or underactive flaccid bladder (e.g. oxybutynin, tolterodine, or bladder obstruction due to benign prostatic hypertrophy (e.g. tamsulosin) have been studied for the treatment of adult nocturia but have not been shown to be effective. Currently none of these products are indicated for the treatment of nocturia in the US.

2.3 Availability of Proposed Active Ingredient in the United States

Desmopressin is available in 0.1 and 0.2mg scored tablets for the treatment of PNE, central DI (diabetes insipidus) and Renal Concentration Capacity Testing.

Desmopressin is available as a 4 µg/mL IV injection for the treatment of central DI and to prevent bleeding in patients with hemophilia A or type I von Willebrand's Disease.

Desmopressin is available as a 10 µg/spray nasal spray, and as a 100 µg/mL rhinal tube capable of dispensing doses of 5 µg and above, intranasally, for the treatment of central DI.

Desmopressin is available as a 150 µg/spray nasal spray to prevent bleeding in patients with hemophilia A or type I von Willebrand's Disease.

2.4 Important Safety Issues With Consideration to Related Drugs

There are currently no other V2 receptor agonists approved in the US.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Desmopressin tablets NDA 21-795, originally referred to as Minirin tablets, were approved May 5, 2008 for the treatment of central diabetes insipidus, primary nocturnal enuresis and renal concentration capacity testing. The sponsor has now developed a rapid melting oral lyophilisate, desmopressin melt, for the treatment of adult nocturia. Pharmacokinetic data indicate a linear relationship between the tablet and melt formulations as follows:

60 µg of the melt corresponds to 0.1 mg of the tablet formulation
120 µg of the melt corresponds to 0.2 mg of the tablet formulation
240 µg of the melt corresponds to 0.4 mg of the tablet formulation
360 µg of the melt corresponds to 0.6 mg of the tablet formulation

Desmopressin melt (60 µg, 120 µg, and 240 µg) was first approved in outside the US in February 2005 and is currently approved in 70 countries. In countries where desmopressin melt is currently approved, use is limited to patients <65 years of age and no serum sodium monitoring is required. (Of Note, the two doses evaluated in the current resubmission, 25 and 50 µg of desmopressin melt, would correspond to 0.042mg and 0.084mg of the tablet formulation. Both of which are lower than the lowest currently approved tablet dosage)

On June 19, 2009 Ferring submitted an NDA seeking a new indication, treatment of adults with nocturia, for Nocdurna (desmopressin) orally disintegrating tablets under the following dosing recommendations:

- Women 25 µg qhs
- Men < 65 y/o 100 µg qhs
- Men ≥ 65 y/o 100 µg qhs with serum sodium monitoring at Day 4 and at one month

After a thorough review which resulted in four different recommendations about how to handle the submission the division issued a CR letter on 22 April 2010 with the following Clinical/Stat comments:

The placebo-controlled portion of your pivotal trial, FE992026 CS029, demonstrated efficacy on two co-primary endpoints with only Nocturna 100 mcg daily doses for 28 days, as determined by the pre-specified sequential testing procedure for controlling type 1 error across the 4 doses. However, this dose was also associated with a high incidence of hyponatremia, a known side-effect of desmopressin that may have a serious clinical consequence outweighing any perceived benefit of reducing frequency of nocturnal voids. Post-hoc analyses of different subgroups at different time points in this trial suggest differential efficacy by gender at lower doses which may have a more acceptable safety profile. However, these additional analyses were not controlled at the overall 5% level of significance and cannot serve as sufficient evidence of efficacy for a different proposed dosing regimen.

In order to address this deficiency, you must conduct a clinical trial to confirm that a lower dosing regimen is a safe and effective treatment of adult nocturia. This trial should be a placebo-controlled trial with a minimum duration of 3 months to evaluate a longer period of durability and safety relative to placebo.

Following the issuance of this letter the sponsor engaged in dialogue with the division on the development of a patient reported outcome (PRO) questionnaire to help in assessing the clinical benefit associated with the treatment of adult nocturia. This has resulted in the development of a new PRO the Nocturia Impact (NI) Diary. This new PRO asks 10 specific questions followed by an overall impact question. It retains 7 of 12 specific questions and the final overall impact question originally included in the Nocturia Quality of Life (NQoL) questionnaire previously reported in the literature. However, the wording of these questions is changed and 4 new questions are added as the result of preliminary testing in nocturia patients by this sponsor of a larger instrument containing 14 items.

In October 2010, Ferring submitted Special Protocol Assessments for separate studies in adult males, FE 992026 CS41, and in adult females, FE 992026 CS40, with nocturia. Protocols for these two studies were approved in communications issued from the division on Nov. 19, 2010 and Nov. 22, 2010, respectively.

In response to the CR letter the sponsor is now submitting data from the following confirmatory trials

- CS40 testing safety and efficacy of the 25 µg dose vs. placebo for 3 months in women

- CS41
 - Part I- testing safety and efficacy of 50 and 75µg doses vs. placebo for 3 months in men
 - Part II- follow-up study testing the safety and efficacy of the 100 µg dose for an additional 1 month in men
- 34 IMPACT- PRO study 000034, a preliminary study testing the Nocturia Impact (NI) Diary in women (25µg) and men (75µg) vs. placebo

In this current submission the sponsor is seeking approval of the 25 µg dose in women and the 50 µg dose in men. Sodium monitoring at baseline is recommended for all pts. Repeat monitoring at Day 4 and one month is to be restricted to men ≥ 65 years of age. Treatment with Nocdurna is to be discontinued if serum sodium falls to <130mmol/L. A medication guide, but no formal REMS, has been submitted as part of this resubmission.

2.6 Other Relevant Background Information

See this medical officer's review of the original submission to find a discussion of the difference between the nocturia and primary nocturnal enuresis indications and for a literature review of adult nocturia.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Data quality and completeness were adequate to permit review of this submission.

3.2 Compliance with Good Clinical Practices

Clinical sites from the pivotal trials in the original submission were inspected and found to be acceptable in support of the current indication.

In the current submission, which used many of the same clinical sites, no individual site had more than 10% of the proportion of patients, and an analysis by our statistician Dr. Liu showed that removal of individual sites with the greatest or second greatest efficacy or with the largest number of patients would not have affected the statistical significance of the data. So no one site dominated the efficacy results. Also, no one site had more than one patient with serum sodium < 130mmol/L which might represent a safety concern with respect to hyponatremia. Therefore, additional inspections were not requested from the sites in the current submission.

3.3 Financial Disclosures

The sponsor submitted information that none of the listed clinical investigators in the two pivotal studies, CS40 and CS41, who were required to disclose financial information, had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) nor did any of them receive significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug substance of desmopressin melt 25 and 50 µg is desmopressin acetate, a synthetic analogue of human arginine-vasopressin. This is identical to the drug substance used in 0.1 and 0.2 mg desmopressin tablets (approved in US) and in 60, 120 and 240 µg desmopressin melt (approved in Europe).

Each desmopressin oral disintegrating tablet contains 25 or 50 µg of desmopressin, (b) (4) of gelatin, (b) (4) of mannitol and anhydrous citric acid (b) (4). The gelatin used in the drug product was prepared from fish (b) (4). Therefore, it is possible that subjects allergic to fish may be allergic to the current formulation.

Tablets are packed in blisters consisting of a (b) (4).

4.2 Clinical Microbiology

The applicant carried out verification studies to demonstrate that the stated microbial limits testing methods are suitable for use with the subject drug product. No microbiology deficiencies were identified.

4.3 Preclinical Pharmacology/Toxicology

The sponsor submitted a 1-month bridging toxicity study in dogs with toxicokinetics to fulfill the nonclinical deficiency in the CR letter. This study bridged the 240 µg orally disintegrating tablet to the currently approved 200 µg DDAVP tablets. There was an initial concern over elevations in bilirubin levels in female dogs receiving the orally disintegrating tablet but after further review it was determined that this was an incidental finding. Consistent with this, liver and bile duct histopathology were normal in these animals as were serum transaminases levels and hematology parameters. In Dr.

Parvaneh's final assessment, there were no significant differences in the toxicological findings, including histopathology and TK data, between the different formulations.

In addition, there had been no evidence of local reactions or histopathological changes in the cheek pouch of Syrian Hamsters in a 28-day study previously reviewed by Dr. Parvaneh as part of the original submission.

4.4 Clinical Pharmacology

The sponsor received a biowaiver for PK studies at dose strengths 25 and 50 µg as their analytical method was not sensitive enough to measure serum desmopressin levels following administration of these small doses.

The sponsor submitted PK data at dose strengths of 60, 120 and 240 µg of desmopressin in CS020 to permit extrapolation to data for the lower doses, however the data from this study were not acceptable because of problems with bioanalytical issues. Therefore, exposure data for the 25 and 50 µg dose strengths was extrapolated from reliable data at the higher doses of 200 to 800 µg used in study CS004. This was an open-label, randomized, balanced, four-way cross over study of three doses of sublingual melt (200, 400 and 800 µg) and IV desmopressin (2µg). Following sublingual administration, desmopressin maximum plasma concentrations were observed at 0.5 - 2.0 hours post dose. The maximum plasma concentration was 14, 30 and 65 pg/mL after a sublingual dose of 200, 400 and 800 µg, respectively. After reaching maximum plasma concentration desmopressin was eliminated with a half-life in the range of 2.8 - 3.0 hours.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study ID	No. of Centers	Study Dates (Start-Completion)	No. of Subjects Randomized / Completed / Dropouts	Design / Control	Route and Regimen	Sex (M/F) Mean Age (Range) Race (W/B/O)	Endpoints
[FE992026 CS29] (Part I)	78 enrolled subjects	Part I Start: 04 Jun 2007	799 randomized/ 710 completed/ 89 discontinued	Randomized, double-blind, placebo-controlled, parallel-group	Oral placebo or Oral desmopressin: 10 µg, 25 µg, 50 µg, or 100 µg	416 males/341 females 62.0 years (20-89) 80%White/15% Black/5%Other	<u>Efficacy</u> : change from baseline to final visit (Day 28) in mean number of nocturnal voids and proportion of subjects with >33% reduction in the mean number of nocturnal voids. <u>Safety</u> : serum sodium monitoring on study Days 4, 8, 15, 22, and 28 during Part I and on Days 4, 8, 15, 29, and then monthly during Part II; frequency and severity of AEs, and clinically significant changes in laboratory values and vital signs
		Part II End: 22 Feb 2008	665 randomized/ 566 completed/ 99 discontinued	Placebo subjects re-randomized (at initial randomization) to active drug	Oral desmopressin: 10 µg, 25 µg, 50 µg, or 100 µg	369 males/296 females 61.9 years (22-89) 82%White/14%Black/4%Other	<u>Efficacy</u> : change from baseline to Months 2, 3, 5, and 7 in mean number of nocturnal voids and proportion of subjects with >33% reduction in the mean number of nocturnal voids <u>Safety</u> : same as Part I
[FE992026 CS31] ^a	70 enrolled subjects	06 Dec 2007 21 May 2010	542 enrolled/ 171 completed/ 256 discontinued	Open-label	Oral desmopressin: 10 µg, 25 µg, 50 µg, or 100 µg	299 males/243 females 62.0 years (22-89) 80%White/16%Black/4%Other	<u>Efficacy</u> : change from baseline of CS29 in mean number of nocturnal voids, proportion of subjects with >33% reduction in the mean number of nocturnal voids, duration of first sleep period, total sleep time, and quality of life <u>Safety</u> : serum sodium monitoring; frequency and severity of AEs, and clinically significant changes in laboratory values and vital signs
[FE992026 CS40]	39 enrolled subjects	01 Nov 2010 22 Nov 2011	268 randomized/ 233 completed/ 35 discontinued	Randomized, double-blind, placebo-controlled, parallel-group	Oral placebo or desmopressin: 25 µg	261 females 59.8 years (19-87) 82%White/17%Black/1%Other	<u>Efficacy (primary)</u> : change from baseline in mean number of nocturnal voids, proportion of subjects with at least a 33% reduction in the mean number of nocturnal voids versus baseline <u>Safety</u> : frequency and severity of AEs, clinically significant changes in laboratory values and vital signs, incidence of hyponatraemia as assessed by sodium levels, and fluid intake 3 days before and 3 days after initiation of treatment
[FE992026 CS41] (Part I)	50 enrolled subjects	Part I Start: 15 Feb 2011	395 randomized/ 327 completed/ 68 discontinued	Randomized, double-blind, placebo-controlled, parallel-group	Oral placebo or desmopressin: 50 µg or 75 µg	385 males 60.6 years (20-87) 81%White/17%Black/2%Other	<u>Efficacy (primary)</u> : change from baseline in mean number of nocturnal voids, proportion of subjects with at least a 33% reduction in the mean number of nocturnal voids versus baseline <u>Safety</u> : frequency and severity of AEs, clinically significant changes in laboratory values and vital signs, incidence of hyponatraemia as assessed by sodium levels, and fluid intake 3 days before and 3 days after initiation of treatment
		Part II End: 20 Jan 2012	327 randomized/ 315 completed/ 12 discontinued	Open-label	Oral desmopressin: 100 µg	327 males 60.2 years (20-87) 80%White/18%Black/2%Other	<u>Efficacy</u> : change from baseline in mean number of nocturnal voids at 1 month <u>Safety</u> : same as Part I

^a Study CS31 was an open-label extension of Study CS29. All results presented are for the S.II (CS29 Part II + CS31) analysis dataset.

Clinical Review
 William Lubas M.D., Ph.D.
 NDA 22-517 Se17 SDN19
 Nocturna (desmopressin acetate)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage, Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3b	[000034, IMPACT]	5.3.5.1	The objectives of the study were to assess: psychometric properties (reliability and validity) of the NI Diary, the association between reduction of number of nocturnal voids and the mean changes in NI scores (sensitivity of the NI total score to change in nocturia), and which NI Diary items accounted for the main difference in change in total NI score in treatment versus placebo	Randomized, placebo-controlled, double-blind, parallel-group, comparative	Oral placebo or desmopressin: 25 µg (females) or 75 µg (males)	56 randomized, 56 completed	Male and female subjects with nocturia, aged ≥18 years, previously completed FE992026 CS40 or FE992026 CS41 at least 30 days prior to Screening, an average of at least 2 nocturnal voids every night during 2 consecutive 3-day periods during the Screening period, and a serum sodium level within normal range at Screening.	1 month	Completed full report

AUC=area under the plasma concentration-time curve; CDI=central diabetes insipidus; C_{max}=maximum observed plasma concentration; i.v. or IV =intravenous; NI = Nocturia Impact; PD=pharmacodynamic(s); PK=pharmacokinetic(s); PNE=primary nocturnal enuresis

5.2 Review Strategy

The efficacy review focused on the pivotal trials CS40 in women and CS41 in men. Independent reviews were performed by this medical officer and the statistician, Dr. Wei Liu. The efficacy results were discussed between the medical team and the statisticians before the final assessments were written. Data from the earlier pivotal trial CS029 and open label extension CS031 was used to address the limited robustness of the efficacy data in women and to address long term efficacy and safety.

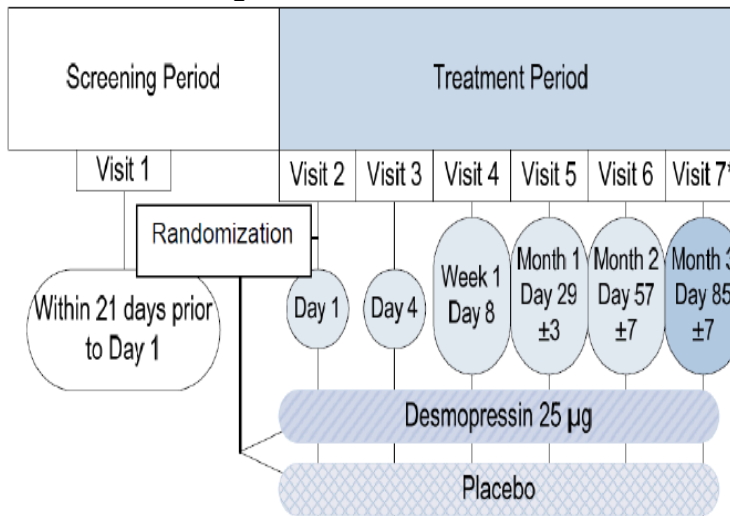
The PRO data in CS40, CS41 and 34 IMPACT study 000034 were also independently reviewed by Dr. Jim Stansbury in the SEALD team, and this information was used to address the efficacy of the PRO endpoints in this review.

5.3 Discussion of Individual Studies/Clinical Trials

Pivotal Clinical Trials

- CS40 randomized 268 women 1:1 to desmopressin 25 µg or placebo.

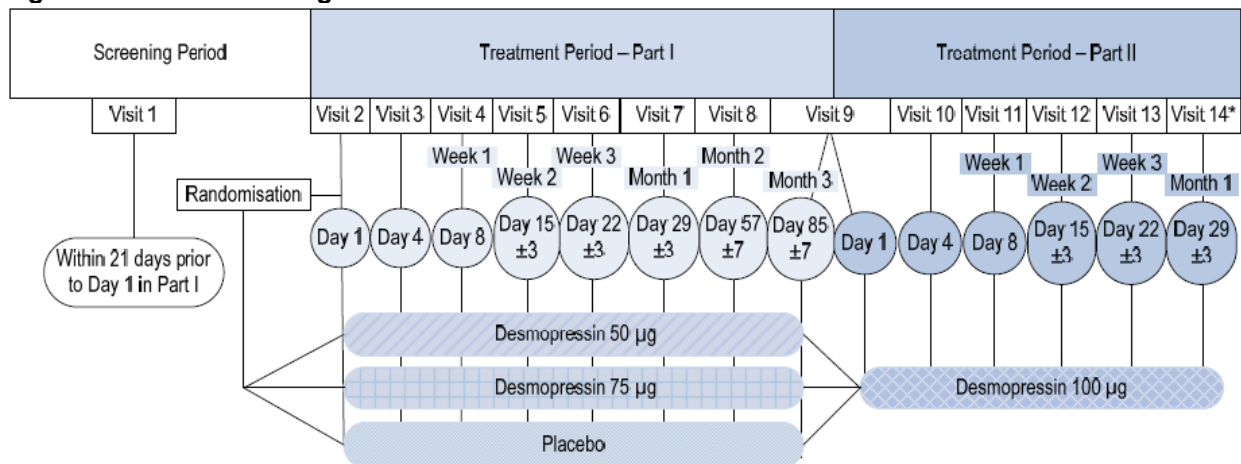
Figure 1 CS 40 Trial Design



*=The End-of-Study Visit (Visit 7) was scheduled for 3 months of treatment (at Day 85±7). Discontinued subjects were to be called in for an End-of-Study Visit, as soon as possible after a decision of discontinuation had been made, for end-of-trial assessments.

- CS41 randomized 395 men 1:1:1 to desmopressin 50 µg, desmopressin 75 µg or placebo

Figure 2 CS 41 Trial Design



*) The End of Trial Visit is scheduled after four months of treatment. Discontinued subjects should be called in for an End of Trial Visit as soon as possible after a decision of discontinuation has been taken for end of trial assessments.

Both studies were stratified by age < 65 and ≥65 y/o (mean age 60 yrs, 13% ≥75yrs)

Inclusion Criteria

- ≥2 nocturnal voids per night as determined by a 3-day voiding diary (most pts had a mean of ≥2 to <3 nocturnal voids (48-60%) or ≥3 to <4 nocturnal voids (27-34%) at baseline)

Exclusion Criteria

- Renal insufficiency
- Diabetes insipidus
- Hyponatremia
- Urinary retention post void residual > 150mL (women) > 250mL (men)

Both studies had the same coprimary endpoints:

- 1) change from baseline in mean number of nocturnal voids
- 2) proportion of subjects with > 33% reduction in the mean number of nocturnal voids

6 Review of Efficacy

Efficacy Summary

The pivotal studies CS40 (in women) and CS41 (in men) were randomized, double-blind, parallel-group, placebo-controlled trials of Nocturna for the treatment of adult nocturia, an indication for which there are currently no approved drug products in the US. The studies enrolled adults 18 years of age and older with an average of ≥2 nocturnal voids demonstrated using a 3-day voiding diary. Subjects with urinary retention and/or a post void residual of >150mL (women) and > 250mL (men) were excluded, although subjects could be enrolled if they had been on stable doses of alpha blockers or 5-alpha-reductase inhibitors for prostatic hypertrophy or antispasmodics for overactive bladder. The primary endpoint was a composite of (1) the mean reduction in the number of nocturnal voids and (2) the proportion of subjects with a > 33% reduction from baseline in the mean number of nocturnal voids. Nocturnal voids were recorded in a diary on 3 consecutive 24 hour periods at baseline, at Week 1 and at Months 1, 2 and 3. The co-primary endpoint was assessed longitudinally over the three-month period of treatment. Among the secondary endpoints mean time to first void at Month 3 was also assessed. Patient Reported Outcomes (PROs) were assessed by the Nocturia Quality of Life (NQoL) questionnaire, 3 questions contained in the subject sleep diaries, and the Work Productivity and Activity Impairment (WPAI) questionnaire. The Nocturia Impact (NI) diary which had been developed by the sponsor in collaboration with the Agency was not available at the time the pivotal trials were initiated. A preliminary trial testing the utility of the NI diary, 34 IMPACT study 000034, was also included in this

submission. However, this study was underpowered to produce any meaningful or useful conclusions (see section 6.1.10).

There was clear evidence of statistical significance with respect to both co-primary endpoints in the pivotal studies for women at the 25 µg dose and men at the 50 and 75 µg doses (see Sections 6.1.4 and 6.1.8). That said, the efficacy in women on the 25 µg dose was not very robust with respect to the measurement of the first co-primary endpoint, mean reduction in the number of nocturnal voids, and there was no clear difference in efficacy between the 50 and 75 µg doses in men. In addition, there was concern as to whether the treatment effect was clinically significant given that the placebo subtracted difference appeared small. It is this medical officer's assessment that the placebo response for the adult nocturia indication in these clinical trials overestimates what can be achieved in a usual care setting, where patients may be less likely to strictly follow dietary recommendations and may be less compliant with filling out 3-day voiding diaries and measuring fluid intake and urine output. That said, there is no current available therapy for this indication and a placebo is not a viable option.

Additional supportive information from a PRO would be helpful in attributing clinical benefit to the use of Nocdurna in the treatment of adult nocturia. In the pivotal trials the NQoL questionnaire did not show a statistically significant improvement in scores using the pre-specified analyses, although post hoc analyses did suggest improvement in sleep quality and the bother/concern domains. Therefore, it would be useful if the sponsor utilized the NI diary they have developed in collaboration with the Agency to confirm a clear clinical benefit in a future study in this study population.

The secondary endpoints were tested in a hierarchical step-down approach and so only the mean number of nocturnal voids at Month 3 in women on the 25 µg dose could be claimed as statistically significant, and none of the secondary endpoints in men on the 50 µg dose, for which the sponsor is also seeking an indication, could be claimed as statistically significant. Nonetheless, it is still worth examining the data from the third secondary endpoint "mean time to first nocturnal void" as a measurement of a potentially clinically relevant endpoint. In study CS40 in women, the mean time to first nocturnal void at baseline at Month 3 was around 145 min (2.4 hrs); with desmopressin there was an additional increase of 155 min (2.6 hrs), which was 49 minutes (0.8hrs) longer in the desmopressin group compared to the placebo group (p=0.0034). In study CS41 in men the mean time to first nocturnal void at baseline at Month 3 was around 146 min (2.4 hrs); with desmopressin 50 µg there was an additional increase of 112 min (1.9 hrs), which was 39 minutes (0.65hrs) longer in the desmopressin group compared to the placebo group (p=0.0064). While again it seems reasonable to question whether such a small placebo subtracted effect, e.g. < 1hr, would have any clinical significance, it has to be understood that it is not known how much of this observed placebo effect would be maintained in an actual use situation. Ignoring this placebo effect the time to first awakening with desmopressin treatment would more than double from about 2.4 hrs to 5.0 hrs in women and almost double from 2.4 hrs to 4.3 hrs in men. It is this

medical officer's assessment that such large effects would likely be beneficial with respect to sleep quality.

In conclusion, it is this medical officer's assessment that there is enough clinical evidence to support the efficacy of Nocdurna in the treatment of adult nocturia at doses of 25 µg in women and 50 or 75 µg in men. However, because of safety concerns with respect to hyponatremia seen at the 75 µg dose in men in study CS41 (see Summary of Safety) only the 50 µg dose will be recommended for final approval.

6.1 Indication

The proposed indication is the treatment of adult nocturia, by decreasing nocturnal urinary frequency and volume and prolonging the time to first nocturnal void.

6.1.1 Methods

This submission contains two double-blind, placebo controlled pivotal trials CS40 (in women) and CS41 (in men) which will be reviewed in detail to support the safety and efficacy of desmopressin sublingual melt for the treatment of adult nocturia.

Additional follow up information from the open-label extension CS031, also included in this submission to support long term efficacy and safety, will be reviewed when relevant to the current indication.

Study 000034, assessing the Nocturia Impact (NI) Diary as a useful tool for investigating the impact of nocturia will be addressed, but as the study was not powered for efficacy the information is of limited value in the final assessment, and so will not be reviewed in detail.

6.1.2 Demographics

The mean age of the subjects in studies CS40 and CS41 was 60 years (median age-64 years). Age ranged from 19 to 87 years, with 35% age 65 to < 75 and 13% ≥75 years of age. All 268 subjects in CS40 were female, and all 395 subjects in CS41 were male. Most subjects were Caucasian 81%, with 17% African American and 1% Asian.

Table 1 Demographics and Subject Characteristics (CS40 and CS41)

Demographic Characteristic	CS40 (females)		CS41 (males)		
	Placebo (N=128)	25 µg (N=133)	Placebo (N=142)	50 µg (N=119)	75 µg (N=124)
Age (years)					
Mean (SD)	60.1 (14.1)	59.5 (14.3)	60.8 (14.2)	60.8 (13.2)	60.1 (11.6)
Median	64	62	64	64	64
Minimum, maximum	23, 87	19, 81	21, 87	20, 81	29, 80
Age (years), N (%)					
<65	65 (51%)	71 (53%)	74 (52%)	62 (52%)	64 (52%)
≥65	63 (49%)	62 (47%)	68 (48%)	57 (48%)	60 (48%)
Sex, N (%)					
Female	(100%)	(100%)	0	0	0
Male	0	0	(100%)	(100%)	(100%)
Race, N (%)					
White	104 (81%)	109 (82%)	112 (79%)	99 (83%)	99 (80%)
Black/African American	22 (17%)	23 (17%)	27 (19%)	18 (15%)	22 (18%)
Asian	1 (<1%)	1 (<1%)	2 (1%)	2 (2%)	3 (2%)
Other	1 (<1%)	0	1 (<1%)	0	0
Ethnic Origin, N (%)					
Hispanic or Latino	17 (13%)	26 (20%)	20 (14%)	25 (21%)	29 (23%)
Not Hispanic or Latino	111 (87%)	107 (80%)	122 (86%)	94 (79%)	95 (77%)
Height (m)					
Mean (SD)	1.63 (0.07)	1.62 (0.07)	1.77 (0.07)	1.77 (0.08)	1.78 (0.07)
Median	1.63	1.62	1.78	1.78	1.78
Minimum, maximum	1.49, 1.83	1.4, 1.78	1.57, 1.93	1.58, 1.96	1.57, 1.96
Weight (kg)					
Mean (SD)	77.9 (19.4)	82.1 (19.3)	91.8 (18.5)	92 (18.3)	92.3 (17.7)
Median	74.1	79.1	89.2	90.7	89.8
Minimum, maximum	49.7, 140	47.4, 136	47.7, 155	56.5, 177	50.8, 153
BMI (kg/m ²)					
Mean (SD)	29.1 (6.58)	31.4 (7.03)	29.2 (5.25)	29.3 (4.77)	29.2 (4.79)
Median	28	30.3	28.7	28.9	28.6
Minimum, maximum	17.9, 46.6	18.2, 50.5	18, 48.5	19.9, 50.1	16.1, 47

Cross Reference: CS40 [Table 3.1] and CS41 [Table 3.1]

Source Table 5 ISE

The mean number of baseline voids was similar across treatment groups. Most pts had a mean of ≥ 2 to < 3 nocturnal voids (48-60%) or ≥ 3 to < 4 nocturnal voids (27-34%) at baseline. The mean time to first nocturnal void ranged from 143 to 147min (2.4 to 2.5hrs).

Table 2 Mean Baseline Void Parameters (CS40 and CS41)

Void Characteristic	CS40		CS41		
	Placebo (N=128)	25 μ g (N=133)	Placebo (N=142)	50 μ g (N=119)	75 μ g (N=124)
Number of Nocturnal Voids					
Mean (SD)	2.88 (0.798)	2.84 (0.887)	2.90 (0.807)	2.88 (0.864)	2.99 (0.897)
Median	2.67	2.67	2.67	2.67	3
Minimum, maximum	2, 7	2, 9.67	1, 5.67	2, 6	1.67, 6.33
Nocturnal Voids Category, N (%)					
< 2	0	0	1 (<1%)	0	1 (<1%)
$\geq 2-3$	71 (55%)	78 (59%)	73 (51%)	71 (60%)	60 (48%)
$\geq 3-4$	44 (34%)	45 (34%)	46 (32%)	32 (27%)	42 (34%)
$\geq 4-5$	11 (9%)	9 (7%)	19 (13%)	11 (9%)	17 (14%)
$\geq 6-7$	1 (<1%)	0	3 (2%)	3 (3%)	2 (2%)
≥ 7	1 (<1%)	1 (<1%)	0	2 (2%)	2 (2%)
Mean Time to First Nocturnal Void (min)					
Mean (SD)	143 (57.6)	147 (56.9)	147 (57.5)	146 (53.0)	143 (56.0)
Median	135	149	137	148	140
Minimum, maximum	32.3, 350	10.7, 299	19, 325	16, 309	49, 262
Mean Nocturnal Urine Volume (mL)					
Mean (SD)	607 (338)	627 (328)	620 (313)	607 (325)	647 (345)
Median	561	617	548	508	586
Minimum, maximum	98.3, 1742	60, 1617	81.7, 1877	60, 1792	75, 1833
Mean 24-Hour Urine Volume (mL)	(N=128)	(N=132)			
Mean (SD)	1343 (688)	1409 (687)	1360 (621)	1373 (636)	1447 (624)
Median	1316	1372	1246	1249	1305
Minimum, maximum	200, 3592	165, 3200	209, 3542	125, 3045	333, 3533
Mean Nocturnal Polyuria Index, (%)	(N=128)	(N=132)			
Mean (SD)	47 (13.8)	45.3 (11.5)	46.6 (12.6)	45.1 (11.0)	44.2 (11.5)
Median	45.2	44.7	44.4	44.8	44.7
Minimum, maximum	21.2, 114	14, 76.7	20.7, 84.1	14.5, 83.1	14, 76.7
Nocturnal Polyuria Index Category, N (%)	(N=128)	(N=132)			
< 33	14 (11%)	15 (11%)	15 (11%)	19 (16%)	17 (14%)
≥ 33	114 (89%)	117 (88%)	127 (89%)	100 (84%)	107 (86%)

Cross-Reference: CS40 [Table 3.4] and CS41 [Table 3.5]

Source Table 7 ISE

6.1.3 Subject Disposition

CS40 (women)

Most patients 233 (87%) completed the study with only 35 (13%) discontinuing prematurely. A similar number of subjects withdrew from the placebo (n=17) and 25 μ g (n=18) treatment arms. The most common reason for withdrawal was “protocol

violation” which occurred in a similar number of subjects in the placebo (n=8) and 25 µg (n=7) treatment arms.

CS41 (men)

Most patients 327 (83%) completed Part I of the study with only 68 (17%) discontinuing prematurely. Slightly more subjects withdrew desmopressin treatment arms 50 µg (n=23) and 75 µg (n=26) compared to the placebo arm (n=19). This was due to a slightly higher rate of “withdrawal by subject” (n=8 and 9 vs. n=6) and “protocol violation” (n=6 and 6 vs. n=3) (see Table 3). It is this medical officer’s assessment that these minor differences probably did not impact on the integrity of the current data as 98% of all subjects had at least one efficacy assessment after dosing initiation and all randomized subjects were included in the ITT analysis dataset.

Table 3 Subject Disposition

Disposition	CS40 (females)		CS41 (males)		
	Placebo	25 µg	Placebo	50 µg	75 µg
Randomized (ITT)	131	137	143	123	129
Completed, N (%)	114 (87%)	119 (87%)	124 (87%)	100 (81%)	103 (80%)
Prematurely Withdrawn	17 (13%)	18 (13%)	19 (13%)	23 (19%)	26 (20%)
Withdrawal by subject	3 (2%)	2 (1%)	6 (4%)	8 (7%)	9 (7%)
Lost to follow-up	1 (<1%)	4 (3%)	4 (3%)	5 (4%)	3 (2%)
Adverse event	1 (<1%)	4 (3%)	6 (4%)	4 (3%)	8 (6%)
Protocol violation	8 (6%)	7 (5%)	3 (2%)	6 (5%)	6 (5%)
Other	4 (3%)	1 (<1%)	0	0	0
Full Analysis Set (FAS)	128	133	142	119	124

Cross-reference: CS40 [Table 1.1] and CS41 [Table 1.1]

Source Table 3 ISE

Of the 327 subjects who completed Part I and entered into Part II, 315 (96%) subjects completed Part II of the trial and only 12 (4%) subjects discontinued prematurely.

6.1.4 Analysis of Primary Endpoint(s)

The prespecified co-primary endpoint consisted of:

1. the change in mean number of nocturnal voids from baseline and
2. the proportion of subjects with a greater than 33% reduction in the number of nocturnal voids.

assessed longitudinally over the 3 months of treatment.

In the original trial CS29 the same co-primary endpoints were prespecified for Day 28 only and were not assessed over a longitudinal period of time. The Day 28 results were statistically significant for:

- the 25µg dose vs. placebo in women
- the 100 µg dose vs. placebo in men

(Note the 50 µg dose would have been statistically significant on Days 8 and 22 in men if that had been the prespecified endpoint but not on Days 15 and 28, the latter being the prespecified endpoint.)

In study CS40 both coprimary endpoints were statistically significant for the 25 µg dose over the 3 month study period (1st coprimary p=0.028 and 2nd coprimary p=0.0061).

In study CS41 both coprimary endpoints were statistically significant for the 50 and 75 µg doses over the 3 month study period (50 µg-1st coprimary p=0.0003 and 2nd coprimary p=0.0009; 75 µg-1st coprimary p<0.0001 and 2nd coprimary p=0.0004).

Table 4 First Coprimary Endpoint-Change from baseline in Mean Number of Nocturnal Voids Averaged over a 3-Month period

CS40 (females)	Desmopressin		Comparison versus Placebo		
	25 µg	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	-1.46	-1.24	-0.22	[-0.42, -0.02]	0.0280*
CS41 (males)					
	75 µg	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	-1.29	-0.88	-0.41	[-0.61, -0.22]	<0.0001*
	50 µg	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	-1.25	-0.88	-0.37	[-0.57, -0.17]	0.0003*

* Statistically significant difference versus placebo, p≤0.05.

Note: Repeated measures ANCOVA of change from baseline at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit, and baseline nocturnal voids.

Cross-reference: [CS40, Table 6.1.1.1] and [CS41, Table 6.1.1.1]

Source table 10 ISE

Table 5 Second Co-Primary Endpoint-Odds Ratio of Patients with >33% Response from baseline Averaged over a 3-Month Period

CS40 (females)	Desmopressin		Comparison versus Placebo		
	25 µg	Placebo	Odds Ratio	95% CI	p-value
Probability	0.76	0.64	1.85	[1.19, 2.86]	0.0061*
Odds	3.23	1.75			
CS41 (males)					
	75 µg	Placebo	Odds Ratio	95% CI	p-value
Probability	0.67	0.50	2.04	[1.38, 3.03]	0.0004*
Odds	2.08	1.02			
	50 µg	Placebo	Odds Ratio	95% CI	p-value
Probability	0.67	0.50	1.98	[1.32, 2.96]	0.0009*
Odds	2.01	1.02			

* Statistically significant difference versus placebo, p≤0.05.

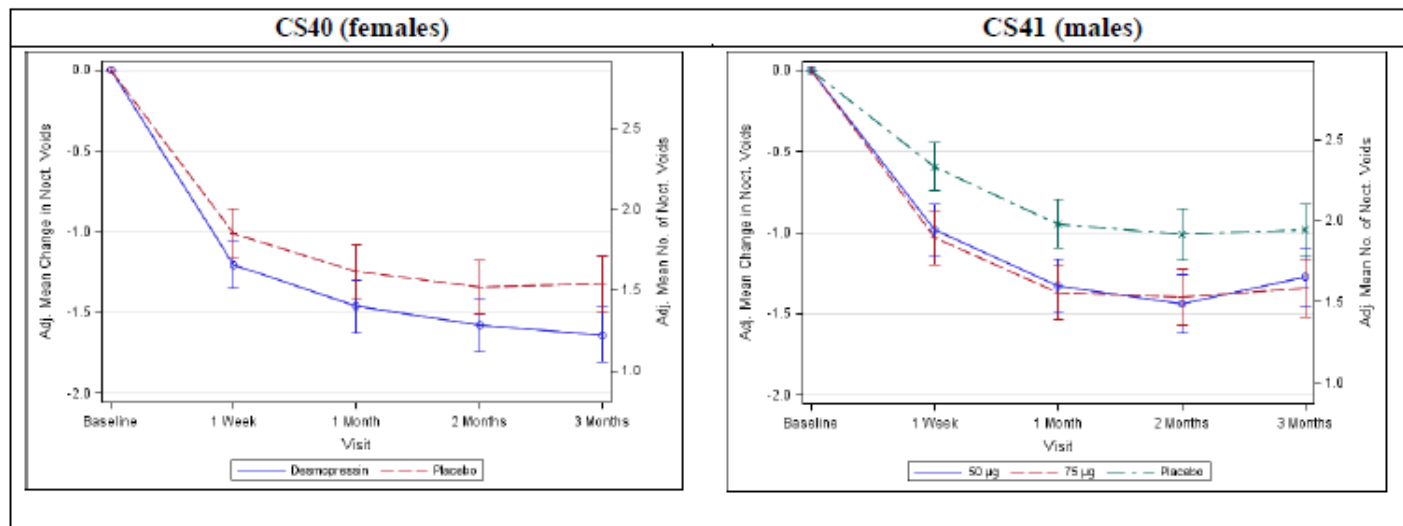
Note: GEE Method for 33% responder status at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit, and baseline nocturnal voids.

Cross-reference: [CS40, Table 6.1.1.2] and [CS41, Table 6.1.1.2]

Source Table 13 ISE

Fig. 3 shows that in both men and women there appears to be an increase in efficacy over the course of the first month of therapy for the first co-primary endpoint which is maintained for the duration of the 3 month study, and that there is no difference in efficacy between the 50 and 75 µg doses in men.

Figure 3 Adjusted Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Voids (CS40 and CS41)



Note: The mean number of nocturnal voids at baseline was 2.88 voids in the placebo group and 2.84 voids in the desmopressin group in CS40 [CS40, Table 3.4] and was 2.90 voids in the placebo group, 2.88 voids in the desmopressin 50 µg group, and 2.99 voids in the desmopressin 75 µg group in CS41 [CS41, Table 3.5]. Although treatment-by-visit interaction was not significant, the adjusted mean changes from baseline depicted in this figure are based on the model including the treatment-by-visit interaction, to demonstrate numerical changes of treatment contrasts in time.

Cross-reference: [CS40, Figure 6.1.1.1] and [CS41, Figure 6.1.1.1]

Source Fig. 4 ISE

Similar results were obtained with respect to the second co-primary endpoint as depicted in Tables 6 and Fig. 4.

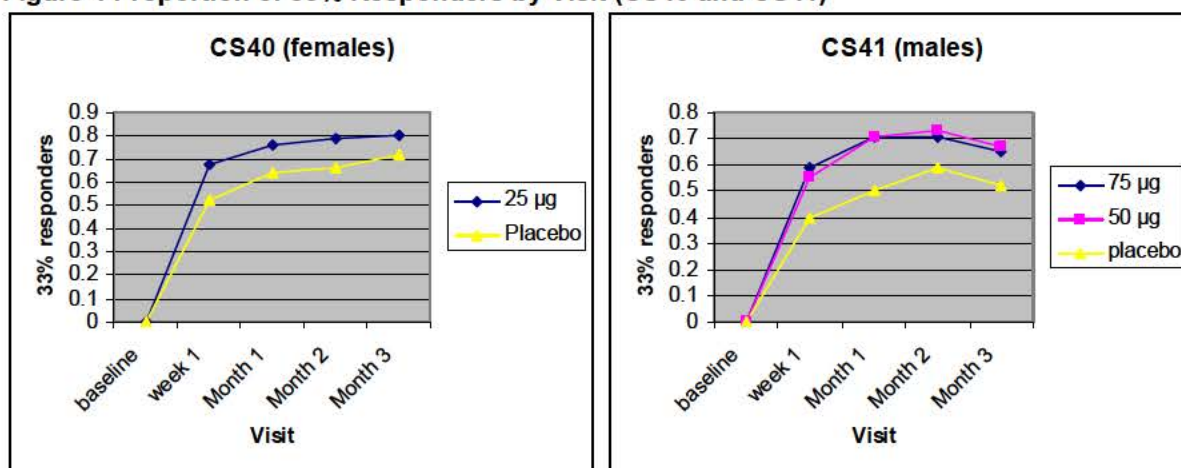
Table 6 Proportion of 33% Responders by Visit (CS40 and CS41)

	CS40 (females)		CS41 (males)		
	Desmopressin 25 µg (N=133)	Placebo (N=128)	Desmopressin 75 µg (N=124)	Desmopressin 50 µg (N=119)	Placebo (N=142)
Week 1	87/128 (68%)	65/124 (52%)	71/120 (59%)	64/116 (55%)	56/141 (40%)
Month 1	96/126 (76%)	77/121 (64%)	83/117 (71%)	79/112 (71%)	69/139 (50%)
Month 2	96/121 (79%)	77/116 (66%)	80/113 (71%)	78/107 (73%)	78/132 (59%)
Month 3	90/113 (80%)	77/107 (72%)	69/106 (65%)	69/103 (67%)	65/125 (52%)
Month 1, open-label (Part II of CS41)	—	—	75/96 (78%)	73/96 (76%)	85/115 (74%)

Cross-reference: [CS40, Table 6.1.3.3] and [CS41, Table 6.1.3.3]

Source Table 24 ISE

Figure 4 Proportion of 33% Responders by Visit (CS40 and CS41)



Source Table 24 ISE

Statistical Analysis

In study CS40 two women were randomized to placebo but received desmopressin 25 µg instead (Subject (b) (6) and Subject (b) (6)). The sponsor's analysis reported in Tables 4 and 5 kept these patients in the placebo group to which they were originally assigned. When the Agency's statistician, Dr. Liu, repeated the efficacy analysis with these two patients assigned to the drug group they actually received, e.g. desmopressin 25 µg, he found that because one of these patients was a significant outlier with results at the top 1 to 2% of the observed data, the first co-primary, the change in the mean number of voids, was no longer statistically significant at the 0.05 level with the p-value going from 0.0280 to 0.0591. If both of these patients had been excluded from the analysis the p-value would still have been statistically significant with an intermediate value of 0.03. In terms of the second co-primary endpoint, proportion of 33% responders, if these two patients were assigned to the drug group they actually received, the p-value would have gone from 0.0061 to 0.0127 so it still would have been statistically significant. However, the fact that one of the co-primary endpoints would have no longer been statistically significant due to a change in data for a single patient, even if it was a significant outlier, suggests the data in women at the 25 µg dose was not very robust.

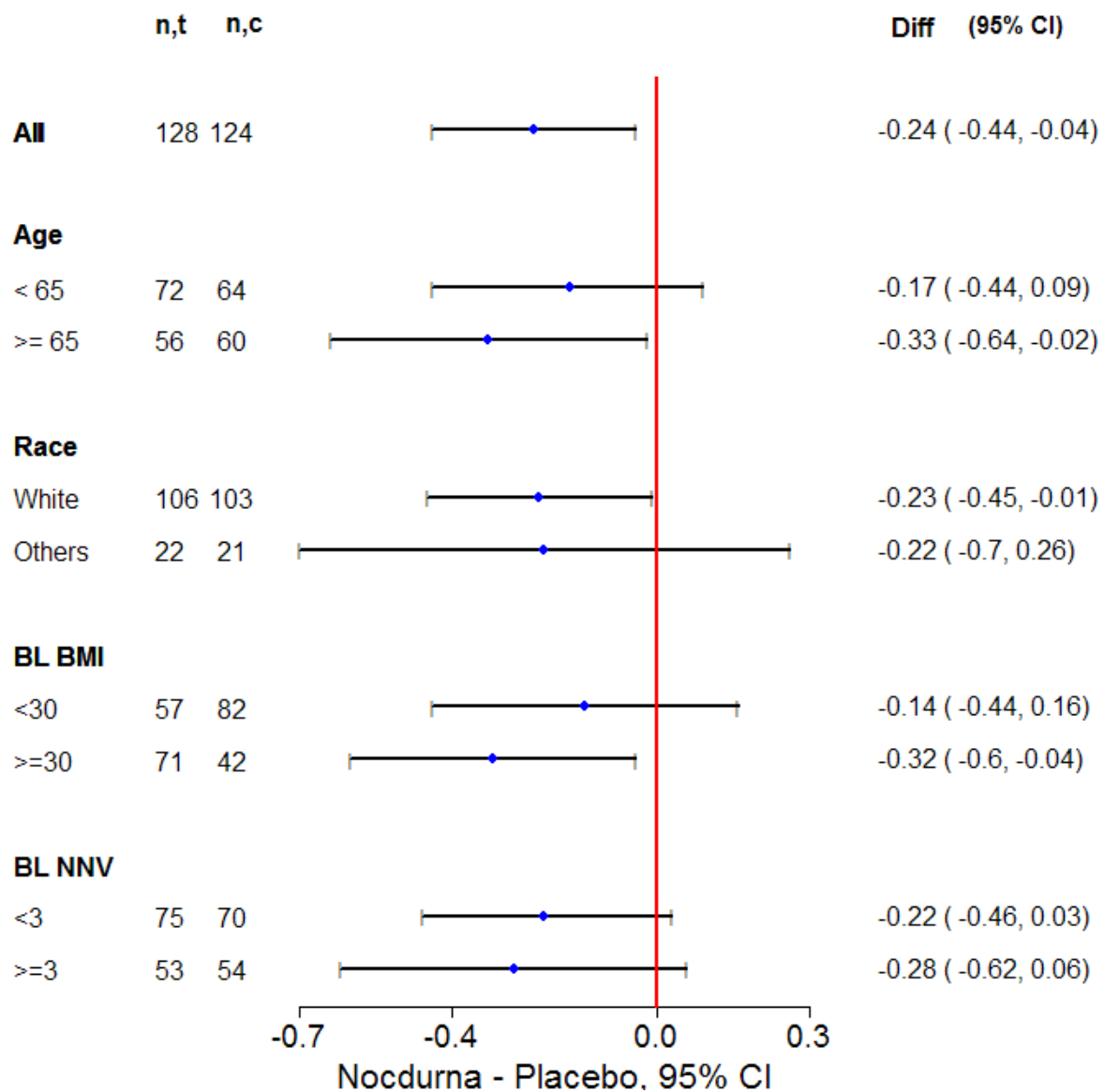
In study CS41 one man randomized to placebo was actually given desmopressin 50 µg and one man randomized to desmopressin 75 µg was given desmopressin 50 µg. In this case there was essentially no change in the p-values for the two co-primary endpoints despite how these patients were assigned in the analysis. When Dr. Liu repeated the efficacy analysis with these two patients assigned to the drug group they actually received the following changes were seen:

50 µg dose- 1st co-primary would have stayed at <0.0001; the second co-primary would have decreased slightly from 0.0003 to 0.0002.

75 µg dose- 1st co-primary would have stayed at 0.0004; the second co-primary would have stayed at 0.0009.

The lack of robustness in the data in women treated with NocduRNA 25 µg is also apparent in the Forest Plot subgroup analysis performed by Dr. Liu. While the point estimate is clearly on the side of efficacy for NocduRNA in all treatment groups only the subgroups of elderly women ≥65 years of age, white women, and obese women with BMIs ≥30 were statistically significant.

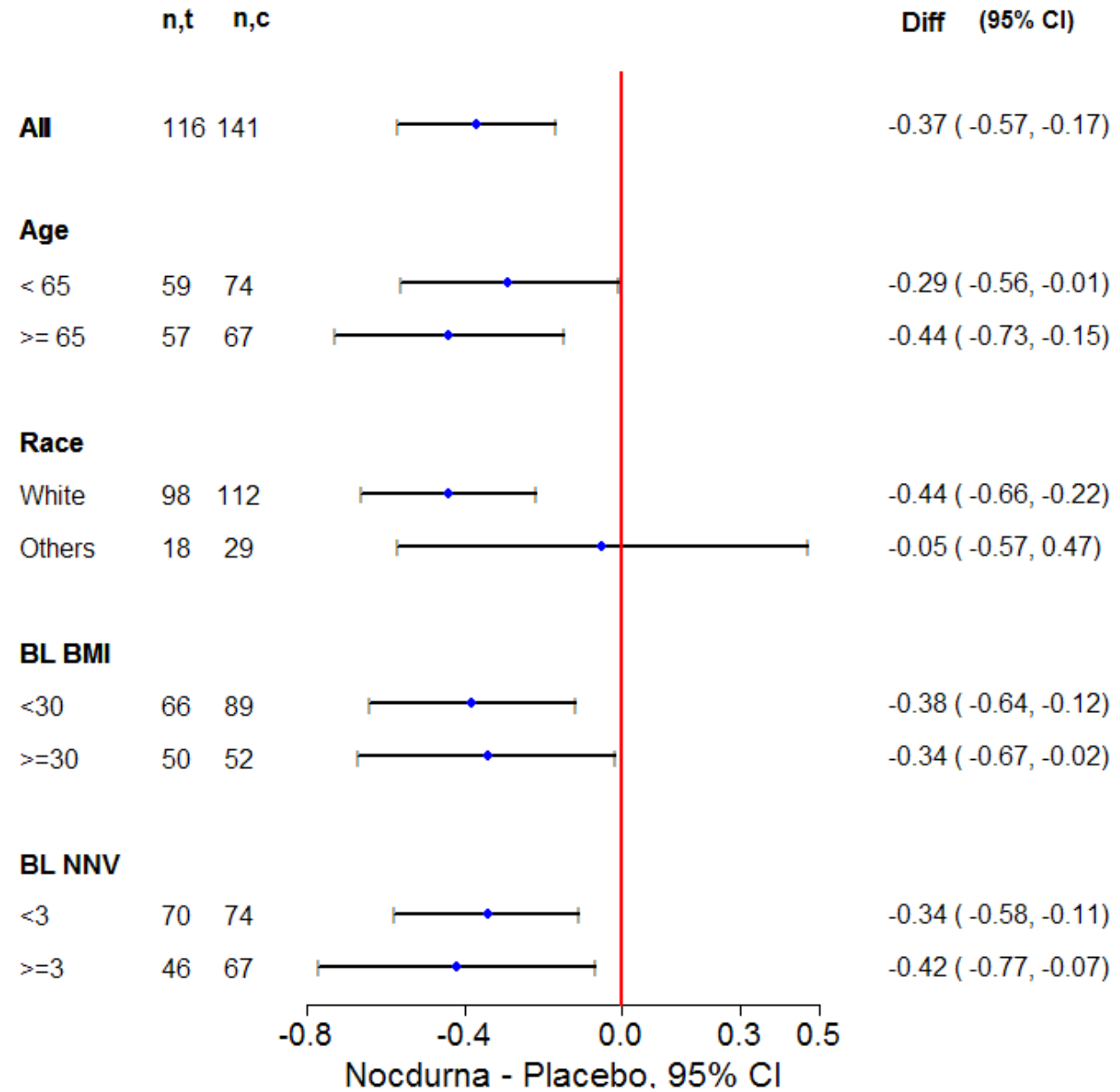
Figure 5 Forest Plot Changes from Baseline in Mean Number of Nocturnal Voids (first co-primary endpoint) in CS41 for Women Treated with NocduRNA 25 µg



NNV-Number of Nocturnal Voids
 Source Dr. Liu's statistical review.

In contrast, all of the subgroups in men treated with Nocdurna 50 µg were statistically significant except for non-Caucasian men and that primarily because of the small number of non-Caucasian men enrolled in the study.

Figure 6 Forest Plot Changes from Baseline in Mean Number of Nocturnal Voids (first co-primary endpoint) in CS41 for Men Treated with Nocdurna 50 µg



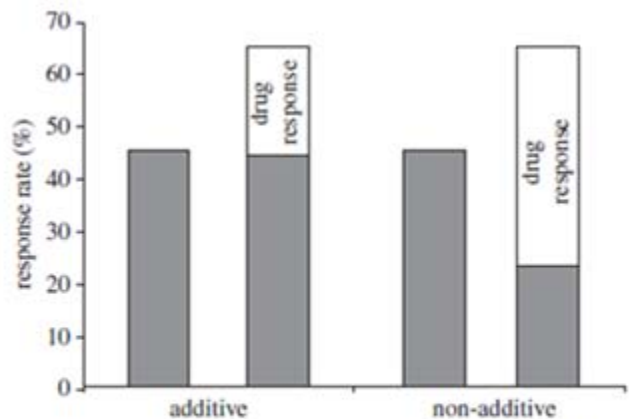
NNV-Number of Nocturnal Voids
 Source Dr. Liu's statistical review.

Placebo Effect

While there is clear evidence of statistical significance with respect to both co-primary endpoints in the new studies, although it can be argued that that data in women treated with Nocdurna 25 µg is not that robust, there is the additional concern that the placebo subtracted difference in the mean number of voids (1st co-primary) appears small. For women the placebo subtracted difference in adjusted mean voids (see Table 4) is -0.22 and for men the difference is -0.41 at the 75 µg dose and -0.37 at the 50 µg dose. It seems reasonable to question whether such a small effect would have any clinical significance.

However, a placebo subtracted analysis assumes that the drug and placebo effects are additive. This is not always the case as demonstrated below¹

Figure 7 Additive Vs. Non-additive Models for the Placebo Effect



the size of the placebo response is assumed to be equal in the drug and in the placebo arm of trials. Alternatively, it could be smaller or greater (as indicated here) in the drug arm when compared with placebo.

Whether the placebo response is additive is a function of a number of factors including whether the drug and placebo affect the primary endpoint by a similar mechanism, the maximal response attributed to the different mechanisms of action of the drug and placebo, and whether the placebo response can be graded i.e. show a dose response. In the present situation it seems unlikely that a placebo could affect the release of endogenous vasopressin in patients with nocturia, although that has not been clinically tested, but it seems more likely that the large observed placebo effect has to do with behavioral changes in the study population as a result of the study protocol recommendations. Specifically, patients were instructed to empty their bladder before going to bed and to limit fluid intake to satisfy thirst only. Evening intake of liquids with diuretic effect, such as coffee, tea, caffeinated soft drinks, and alcoholic beverages, was

¹ Enck P, Weimer K, Horing B, Klosterhalfen S, Zipfel S: **Placebo effects in clinical trials - more questions than answers.** *Phil Trans Roy Soc B* 2011, **366**:1889-1895.

especially discouraged. Patients were instructed on how to measure urine volume and fluid intake and to document this information in a voiding diary for 3 consecutive days during multiple times during the study. While similar instructions could be given by a treating physician in a usual care situation, outside of a clinical trial, it seems unlikely that most patients would follow such recommendations as closely as was the case in these clinical trials. Treatment compliance during the diary recording periods in studies CS40 and CS41 ranged from 97 to 100%. Therefore, it is likely that in a usual care situation the placebo effect would be much lower than observed in this clinical trial. The question then arises how much of the treatment effect would be diminished in a usual care situation. Assuming a non-additive placebo model, all or most of the observed treatment effect could still be retained in such a situation.

As the placebo response has dramatically increased over the past two decades from about 30 to 50% in antidepressant drug trials it has become ever more difficult to run trials that show a benefit relative to placebo. One recent article suggested that the efficacy data for 38 randomized, blinded, placebo-controlled trials used for the initial approval of six of the most widely prescribed antidepressants between 1987 and 1999 showed that 80% of the drug effect was due to placebo. While the results showed a statistical difference favoring active antidepressants over placebo, the authors concluded that the difference was clinically insignificant. This study was criticized because it ignored the fact that research has shown that endpoints in depression are non-additive². The question arises could future drugs be approved for this indication if they have to show what is considered a clinically relevant difference from placebo and not just a statistically relevant difference.

However, there is another serious problem with assuming clinically relevant efficacy only relative to a placebo, when dealing with a condition for which there is no currently approved treatment. The patient's only real options are drug or no treatment as a placebo is not a viable option in a real use situation.

In conclusion, while this medical officer would have no problem recommending that patients have a trial without medication to see if behavioral changes might be sufficient to treat their nocturia in individual cases, medication should be available so that it could be recommended to patients who weren't adequately treated with behavioral modification therapy alone.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints were tested in a pre-specified order using a hierarchical step-down approach (see Table 7). As a result of the hierarchical approach only the mean

² <http://www.bhsiclinics.com/blog/2012/02/29/placebos-and-antidepressants-deceptive-conclusions-about-deceptive-treatments>

number of nocturnal voids at Month 3 in women on the 25 µg dose and the first four endpoints in men treated with the 75 µg dose could be claimed as statistically significant. Since the hierarchical scheme for CS41 required that all of the secondary endpoints in men on the 75 µg dose be statistically significant before the endpoints on the 50 µg dose could be assessed, even though the first four endpoints on the 50 µg dose in men had p-values below 0.05 they could not be claimed as statistically significant.

Table 7 Statistical Significance for Secondary Endpoints, Based on the Pre-Specified Hierarchical Approach

Secondary Endpoint for Change from Baseline in:	p-value: desmopressin versus placebo		
	CS40	CS41	
	25 µg	75 µg	50 µg
Mean number of nocturnal voids at Month 3	0.0104*	0.0029*	0.0128+
Proportion of 33% responders at Month 3	0.0586	0.0233*	0.0386+
Mean time to first nocturnal void at Month 3	0.0034+	0.0026*	0.0064+
Mean nocturnal urine volume at Month 3	0.0031+	0.0034*	0.0086+
Mean 24-hour urine volume at Month 3	0.1829	0.4126	0.7353

* Statistically significant difference versus placebo, $p \leq 0.05$.

+ Statistical significance could not be claimed, based on the hierarchical approach

Cross-reference: CS40 Table [6.2.1.1], [6.2.2.1], [6.2.3.1], and [6.2.4.1]; CS41 Table [6.2.1.1], [6.2.2.1], [6.2.3.1], and [6.2.4.1]

Source Table 15 ISE

Nevertheless, this medical officer believes it is still worth examining the data from the third secondary endpoint “mean time to first nocturnal void” as a measurement of a potentially clinically relevant endpoint. In study CS40 in women, the mean time to first nocturnal void at baseline at Month 3 was around 145 min (2.4 hrs); with desmopressin there was an additional increase of 155 min (2.6 hrs), which was 49 minutes (0.8hrs) longer in the desmopressin group compared to the placebo group ($p=0.0034$). In study CS41 in men the mean time to first nocturnal void at baseline at Month 3 was around 146 min (2.4 hrs); with desmopressin 50 µg there was an additional increase of 112 min (1.9 hrs), which was 39 minutes (0.65hrs) longer in the desmopressin group compared to the placebo group ($p=0.0064$). While again it seems reasonable to question whether such a small placebo subtracted effect, i.e. < 1hr, would have any clinical significance, it has to be understood that it is not known how much of the placebo effect observed in this clinical trial would be observed in an usual care situation compared to how much of the treatment affect might be lost in a usual care situation. That said, with desmopressin treatment the time to first awakening in these trials more than doubles from about 2.4 hrs to 5.0 hrs in women and almost doubles from 2.4 hrs to 4.3 hrs in men. It is this medical officer’s assessment that such large effects would likely be beneficial with respect to sleep quality.

Table 8 Change from Baseline in Mean Time (minutes) to First Nocturnal Void at Month 3 (CS40 and CS 41)

CS40 (females)	Desmopressin		Comparison versus Placebo		
	25 µg	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	154.73	105.70	49.03	[16.35, 81.70]	0.0034 ⁺
CS41 (males)	Desmopressin		Comparison versus Placebo		
	75 µg	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	115.63	72.86	42.76	[15.02, 70.51]	0.0026*
CS41 (males)	Desmopressin		Comparison versus Placebo		
	50 µg	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	111.82	72.86	38.95	[11.03, 66.88]	0.0064 ⁺

* Statistically significant difference versus placebo, $p \leq 0.05$.

+ Statistical significance could not be claimed per hierarchical testing procedure.

Note: ANCOVA of change from baseline adjusted for age (<65, ≥65 years) and baseline time to first nocturnal void, using LOCF.

Cross-reference: [CS40, Table 6.2.3.1] and [CS41, Table 6.2.3.1]

Source Table 18 ISE

6.1.6 Other Endpoints

Quality of life was assessed by the Nocturia Quality of Life (NQoL) questionnaire, 3 questions contained in the subject sleep diaries, and the Work Productivity and Activity Impairment (WPAI) questionnaire. Of these Patient Reported Outcome (PRO) scales, the N-QoL questionnaire is probably the most useful as it was developed specifically to measure the impact of nocturia on quality of life. However a prior review of the validity of this PRO by the SEALD team reviewer, Ann Trentacosti, during the original NocduRNA submission, had determined that this PRO did not adequately address the psychological and emotional impacts of nocturia and thereby could not be used to support a health related claim. Most of the items in the Bother/Concern domain were considered not useful as they did not measure the effectiveness of treatment, and the general quality of life question was considered too general as it could include “non health-related aspects of life”. In addition the data from study CS029 in the original submission did not show statistical significance with respect to the overall score and it was against the PRO guidance to focus on individual questions in an attempt to try to salvage a claim. Following the original submission the sponsor worked with the agency to develop a new PRO the Nocturia Impact (NI) Diary. However, the NI Diary was not available at the time the pivotal trials CS40 and CS41 were performed so the NQoL was reutilized in the current studies. Again the pre-specified analyses were not significant but a post hoc analyses using repeated measures ANCOVA adjusting for baseline as a covariate and age group, treatment, visit, and treatment-by-visit interaction term as factors did show statistical significance.

- In CS40, statistically significant improvements, favoring desmopressin, were observed at Month 3 for total score and both NQoL domain scores.
- In CS41, statistically significant improvements, favoring the total score for both doses of desmopressin, were observed at Month 1, but the total NQoL score at Month 3 in the desmopressin 75 µg group was not statistically significant ($p=0.12$).

It is not clear to this medical reviewer why there would not be efficacy at the higher dose at the Month 3 visit if the finding of efficacy at the lower dose of 50 µg was real.

Looking at the sleep quality sub-scores there were statistically significant improvements at the 25 µg dose compared to placebo for women in CS40 but results were only statistically significant at the lower 50 µg dose compared to placebo in men in CS41. Again it is not clear why there were no significant findings in men at the 75 µg dose if this represented a true finding.

In conclusion, while it is positive that there are some signs that suggest clinical benefit in the post hoc analysis specifically in “total score” and “sleep quality” these results are exploratory and would need to be confirmed in a new study.

Results of the WPAI questionnaires for both CS40 and CS41 were not statistically significant.

6.1.7 Subpopulations

Gender

In the original submission, study CS29 showed that sensitivity to the antidiuretic response to desmopressin was greater in women. These results were confirmed in a PK study by Juul et al.³ which determined the ED50 in men at 43 µg and in women at 16 µg corresponding to a 2.7-fold higher estimated exposure in women vs. men.

In this current submission, study CS40 confirmed the efficacy of the lower dose of desmopressin melt 25 µg in women whereas similar efficacy was seen at the higher doses of 50 and 75 µg in study CS 41 in men (see Tables 4 and 5, and Fig. 3).

Age

Subgroup analysis by age category (i.e. <65 yrs vs. ≥65 yrs) suggests a trend for greater efficacy in the elderly subjects in both men and women (see Forest plots in Fig. 5 and Fig. 6). This would be consistent with why hyponatremia was seen primarily in men over 65 yrs of age. However, tests for the interaction between treatment and age in the mean change from baseline in number of nocturnal voids, the first co-primary endpoint, were not statistically significant (see Table 9) in CS40 (women, p=0.24) or CS41 (men, p=0.57). Similarly, tests for the interaction between treatment and age in 33% responder status, the second co-primary endpoint, were also not statistically significant (see Table 10) in CS40 (women, p=0.60) or CS41 (men, p=0.87). Therefore, there is no need for dose adjustment for age greater than 65 yrs.

³ [Am J Physiol Renal Physiol](#). 2011 May;300(5):F1116-22. doi: 10.1152/ajprenal.00741.2010. Epub 2011 Mar 2. **Gender difference in antidiuretic response to desmopressin.** Juul KV, Klein BM, Sandström R, Erichsen L, Nørgaard JP.

Table 9 Subgroup Analysis: First Co-Primary Endpoint- Repeated Measures ANCOVA of the Change from Baseline in Mean Number of Nocturnal Voids, Averaged over 3 Months of Treatment by Age Group (CS40 and CS41)

Adjusted means	Desmopressin		Comparison versus Placebo			
	CS40 (females)	25 µg	Placebo	Treatment contrast	95% CI	p-value
<65 years	-1.61		-1.49	-0.13	[-0.40, 0.14]	0.3543
≥65 years	-1.31		-0.96	-0.35	[-0.65, -0.05]	0.0215*
Homogeneity of treatment contrast						0.2449
CS41 (males)	75 µg		Placebo	Treatment contrast	95% CI	p-value
	<65 years	-1.44				
≥65 years	-1.16		-0.63	-0.53	[-0.81, -0.24]	0.0004*
	50 µg		Placebo	Treatment contrast	95% CI	p-value
	<65 years	-1.39				
≥65 years	-1.06		-0.63	-0.43	[-0.72, -0.14]	0.0041*
Homogeneity of treatment contrast						0.5690

* Statistically significant difference versus placebo, p≤0.05.

Note: Repeated measures ANCOVA of change from baseline at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit, and baseline nocturnal voids.

Cross-reference: CS40 Tables [6.4.13], [6.4.14], and [6.19]; CS41 Tables [6.4.13], [6.4.14], and [6.19]

Source Table 51 ISE

Table 10 Subgroup Analysis: Second Co-Primary Endpoint- 33% Responder Status Averaged over 3 Months of Treatment by Age Group (CS40 and CS41)

CS40 (females)		Desmopressin		Comparison versus Placebo		
		25 µg	Placebo	Odds Ratio	95% CI	p-value
<65 years	Probability	0.81	0.71	1.69	[0.89, 3.21]	0.1072
	Odds	4.19	2.48			
≥65 years	Probability	0.71	0.55	2.02	[1.11, 3.69]	0.0221*
	Odds	2.50	1.24			
Homogeneity of odds ratio						0.5966
CS41 (males)		75 µg		Comparison versus Placebo		
		Placebo	Odds Ratio	95% CI	p-value	
<65 years	Probability	0.75	0.61	1.90	[1.07, 3.38]	0.0289*
	Odds	2.96	1.56			
≥65 years	Probability	0.59	0.40	2.18	[1.26, 3.76]	0.0052*
	Odds	1.46	0.67			
		50 µg		Comparison versus Placebo		
		Placebo	Odds Ratio	95% CI	p-value	
<65 years	Probability	0.73	0.61	1.75	[0.99, 3.09]	0.0542
	Odds	2.72	1.56			
≥65 years	Probability	0.58	0.40	2.09	[1.19, 3.69]	0.0106*
	Odds	1.40	0.67			
Homogeneity of odds ratio						0.8651

* Statistically significant difference versus placebo, p≤0.05.

Note: GEE Method for 33% responder status at Week 1, Month 1, Month 2, and Month 3, adjusted for age (<65, ≥65 years), visit, and baseline nocturnal voids.

Cross-reference: CS40 Tables [6.4.27], [6.4.28] and [6.4.33]; CS41 Tables [6.4.27], [6.4.28] and [6.4.33]

Source Table 51 ISE

Race

Too few non-Caucasian subjects were enrolled in the pivotal studies CS40 and CS41 to draw any conclusions about differences in efficacy.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

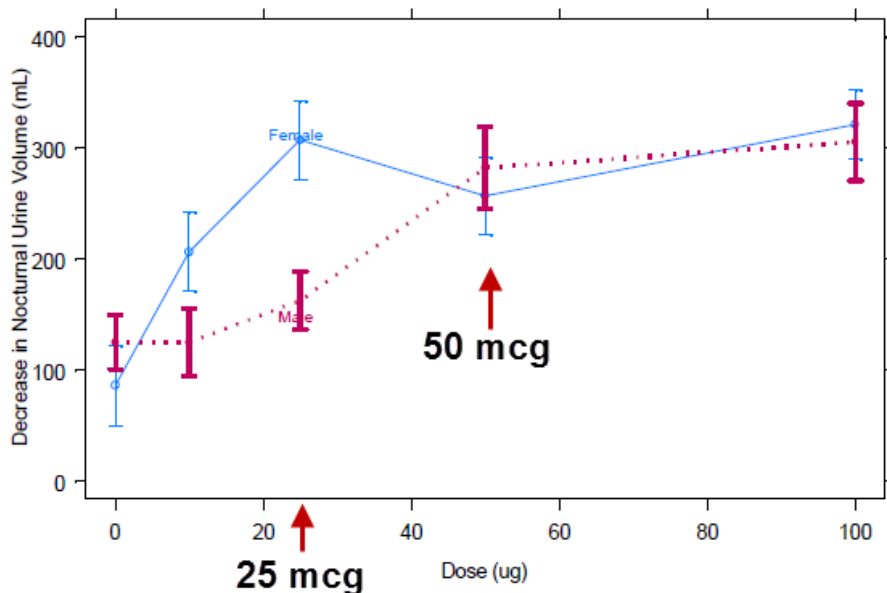
Women

Pivotal study CS40 showed that the 25 µg dose of Nocdurna was statistically significant in women with respect to placebo for both co-primary endpoints 1) change in the mean number of nocturnal voids from baseline, $p=0.028$, and 2) the proportion of subjects with a greater than 33% reduction in the number of nocturnal voids, $p=0.0061$, assessed longitudinally over the 3 months of treatment. However, the effect size was not very robust as a reanalysis of the data showed that reassigning two patients who had been randomized to placebo but actually received Nocdurna 25 µg during the trial would have changed the p-value for the first co-primary from 0.028 to 0.056 and for the second co-primary from 0.0061 to 0.0127. At least part of the reason for this large effect is due to the fact that one of these patients was a significant outlier with results at the top 1 to 2% of the observed data. But another reason for why the study results were not that robust has to do with the large placebo effect (-1.24) seen in this study which is almost 50% higher than what was seen in women in study CS29 (-0.84) and what was seen in men in either CS29 (-0.88) or CS41 (-0.88).

Fig. 3 shows that the change in the mean number of nocturnal voids was clearly statistically significant with respect to baseline at the 25 µg dose in women but then it was also clearly statistically significant with respect to baseline with placebo as well. It is this medical officer's assessment that the large placebo effect seen in these studies would be hard to reproduce in a usual care situation as patients would be less likely to follow the extensive monitoring of fluid intake and urine output which were incorporated into these study protocols for an extended period of time. Therefore, it is important to consider the treatment effect vs. baseline and not just vs. placebo.

There is however, additional evidence to support the efficacy of the 25 µg dose in women. A post hoc analysis of the women subgroup from study CS29 in the original Nocdurna submission had similar results with both co-primary endpoints on Day 28, the prespecified endpoint, being statistically significant with p-values of 0.0200 and 0.0197, respectively. In addition, measurement of the mean decrease in urine volume from CS29 in which both men and women were exposed to Nocdurna doses ranging from 10 to 100 µg, showed that the maximal response with respect to change in urine volume occurred at the 25 µg dose in women and at the 50 µg dose in men. Both of which are the doses the sponsor is currently proposing for this indication.

Figure 8 FE992026 CS029: Mean ($\pm$ SE) observed decrease in nocturnal urine



Females: n=60, 66, 61, 66, 60 ; males: n=80, 71, 83, 71, 75, for doses 0, 10, 25, 50, and 100 μ g, respectively.

Source Fig 3. Modeling Report/Desmopressin Sensitivity in Females and Males. Se0000 6/22/2009
 5.3.5.1 Legacy Study Report

In addition, in the current pivotal studies CS40 and CS41 the placebo subtracted change from baseline in nocturnal volume at Month 3 in women treated with the 25 μ g dose was -84mL ($p=0.0031$) or intermediate with respect to the changes in volume seen in men treated with 50 μ g (-78mL, $p=0.0086$) and 75 μ g (-86mL, $p=0.0034$) again suggesting that the 25 μ g dose in women has similar efficacy to the 50 and 75 μ g doses in men (see Table 11).

Table 11 Change from Baseline to Month 3 in Nocturnal Urine Volume (mL) (CS40 and CS41)

CS40 (females)	Desmopressin		Comparison versus Placebo		
	25 μ g	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	-234.6	-151.0	-83.56	[-138.74; -28.38]	0.0031 ⁺
CS41 (males)	75 μ g	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	-217.1	-130.9	-86.17	[-143.69; -28.64]	0.0034*
	50 μ g	Placebo	Treatment contrast	95% CI	p-value
Adjusted means	-208.7	-130.9	-77.80	[-135.70; -19.89]	0.0086 ⁺

* Statistically significant difference versus placebo, $p \leq 0.05$.

+ Statistical significance could not be claimed per hierarchical testing procedure.

Note: ANCOVA of change from baseline adjusted for age (<65, $\geq$ 65 years) and baseline nocturnal urine volume, using LOCF.

Cross-reference: [CS40, Table 6.2.4.1] and [CS41, Table 6.2.4.1]

Source Table 19 ISE

Men

Pivotal study CS41 showed that the 50 µg dose of NocduRNA was statistically significant in men with respect to placebo for both co-primary endpoints 1) change in the mean number of nocturnal voids from baseline, $p=0.0003$, and 2) the proportion of subjects with a greater than 33% reduction in the number of nocturnal voids, $p=0.0009$, assessed longitudinally over the 3 months of treatment. In men these results appear robust. However, there was little additional increase in efficacy at the higher dose of 75 µg in men (see Fig.3 and Fig. 4). Because of concern over the higher risk of hyponatremia seen with the 75 µg dose (See Section 7.3.4 Hyponatremia in the Safety Review) with no additional benefit with respect to efficacy, only the 50 µg dose will be recommended for approval in men.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Data from the pivotal trial CS40 and CS41 confirm durability of efficacy throughout the 3 month placebo-controlled treatment period (see Fig. 3 and Fig. 4). No formal testing was performed by the sponsor on the data from the long term extension Study CS29/31 as there was no placebo group for comparison after the first month of therapy. The continued dose response out to 92 wks or almost 2 years supports continued efficacy for those that elect to stay on treatment (See Fig. 9 and Fig. 10). However, these figures do not list the number of subjects left at each time point and they cannot rule out the possibility that efficacy could have decreased in some subjects who then discontinued prematurely from the study.

Figure 9 Durability of Effect: First Co-Primary endpoint- Change from Baseline in Mean Number of Nocturnal Voids (E.1 – CS29+CS31)

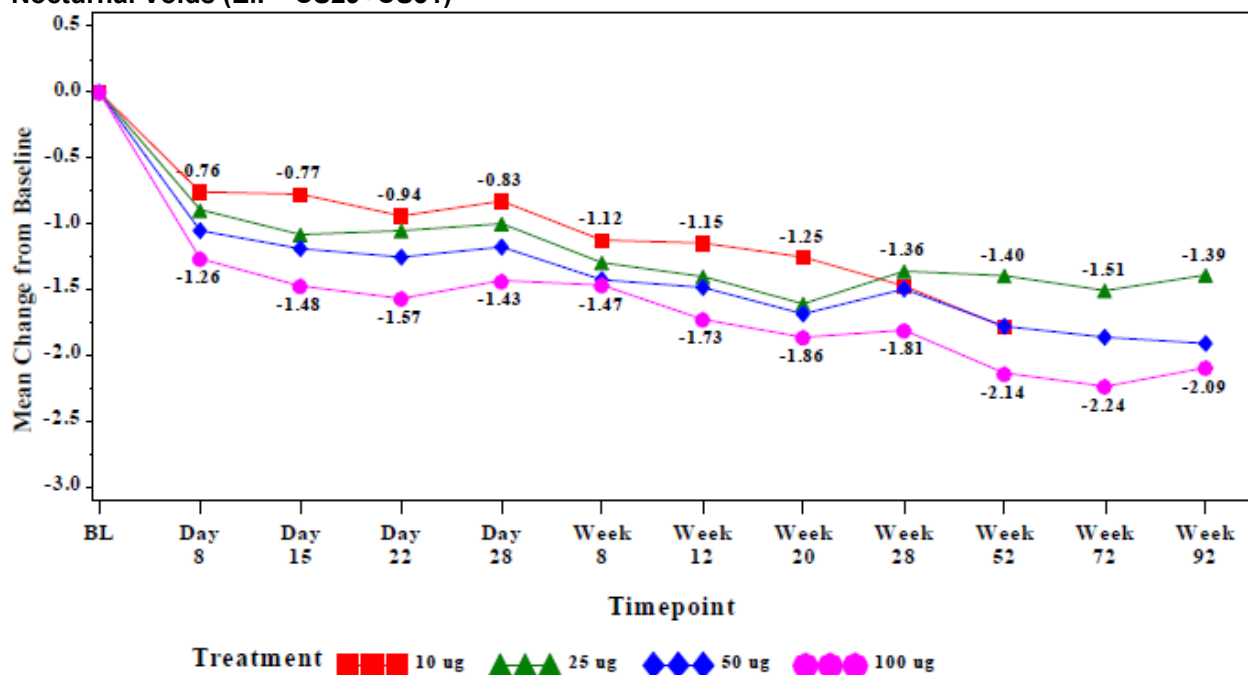
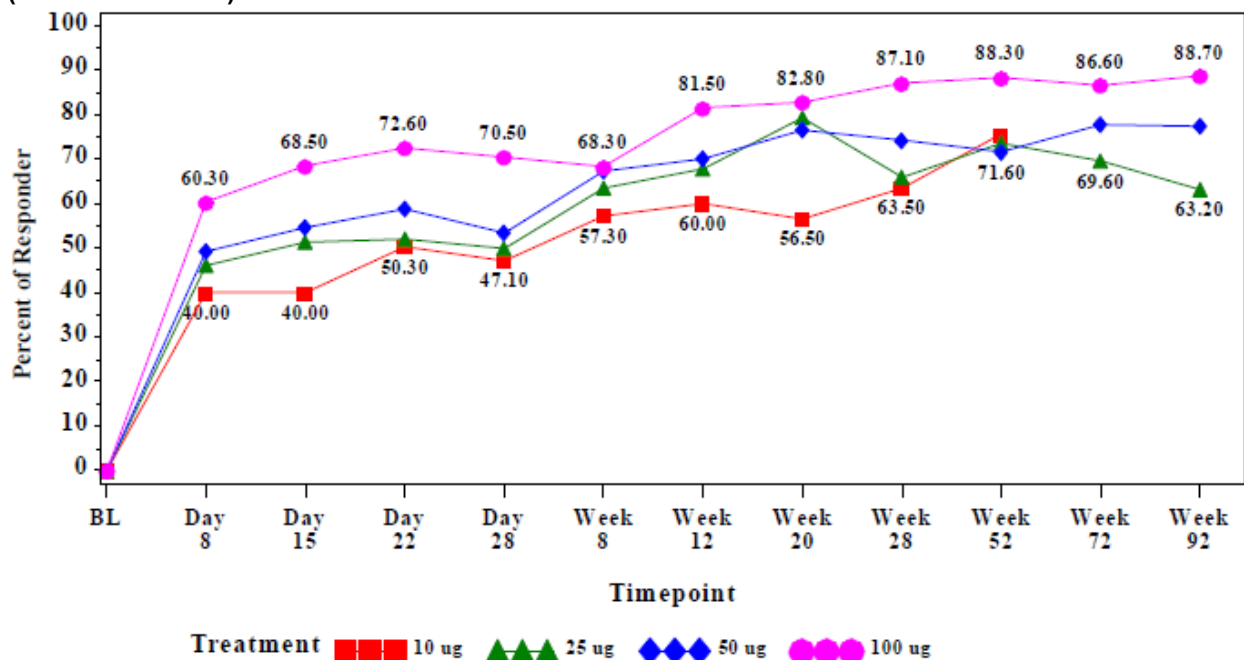


Figure 10 Durability of Effect: Second Co-Primary Endpoint- Proportions of 33% Responders (E.I – CS29+CS31)



6.1.10 Additional Efficacy Issues/Analyses

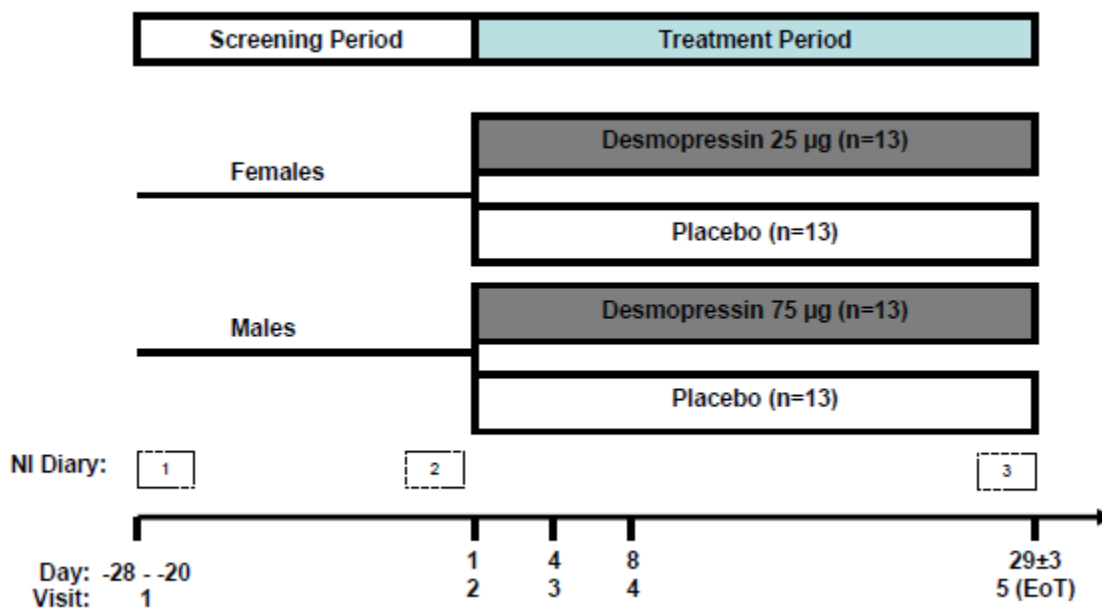
34 IMPACT- PRO study 00034

Following the original submission the sponsor worked with the agency to develop a new PRO the Nocturia Impact (NI) Diary to investigate the burden of nocturia on adult patients. This new PRO asks 10 specific questions followed by an overall impact question. It retains 7 of 12 specific questions and the final overall impact question included in the NQoL questionnaire previously reported in the literature. However, the wording of these questions is changed and 4 new questions are added as the result of preliminary testing of a larger instrument containing 14 items.

Study 00034 was a 1 month, randomized, placebo-controlled, double-blind trial with 26 women and 26 men designed to investigate the utility of the NI Dairy in the adult nocturia population. Subjects were selected from patients who had completed the CS40 and CS41 trials. A washout period of >30 days was used to decrease the risk of any carryover effect. Subjects who received active treatment during CS40 or CS41 were to have been responders (defined as a reduction from Baseline in nocturnal voids at the Month 1 visit of $\geq 33\%$) and subjects who received placebo during these 2 studies were to have been non-responders (defined as a reduction from Baseline in nocturnal voids at the Month 1 visit of $< 33\%$). This subject selection was performed to try to ensure inclusion of the most differentiated subjects, thereby increasing the likelihood of detecting a difference as the study was otherwise not adequately powered for the

proposed endpoints. Subjects were rerandomized in this second study so subjects previously on placebo could have received drug and visa versa. Women were dosed with 25 µg or placebo. Men were dosed with 75 µg or placebo. Note this dose in men is higher than the 50 µg dose which the sponsor is currently proposing.

Figure 11 34 IMPACT- Study 00034 Trial Design



Efficacy was determined by comparing results from two 3-day baseline diaries obtained during the screening period to one 3-day diary obtained at one month at the end of treatment.

Given the small number of patients in this study the sponsor was not able to show efficacy with respect to the pre-specified co-primary endpoints in either men or woman and could not correlate the improvement in NI score to treatment with desmopressin. Instead, the sponsor presented a post hoc analysis comparing the difference in mean change in NI total score from Baseline to the Month 1 visit for responders versus non-responders, where a responder was defined as subject who experienced a reduction from Baseline in nocturnal voids at the Month 1 visit of $\geq 33\%$. While these results suggest the NI Diary may eventually be useful in studying the burden of nocturia in this study population these results cannot be used to support any improvement in patient reported outcomes at the current time. It is recommended that the sponsor repeat an adequately powered trial which first shows efficacy with respect to treatment with desmopressin compared to placebo and then confirm that the efficacy with respect to a decrease in nocturia can be correlated to an improvement in the NI Diary score. Such a trial would provide supportive evidence of a real clinical benefit associated with the improvement in nocturia.

7 Review of Safety

Safety Summary

The pivotal trials CS40 and CS41 studied the safety and efficacy of Nocdurna in the treatment of adult nocturia for a period of 3 months. Additional long term data from earlier trials including CS029 and CS031 resulted in exposure data out to 92 weeks in a limited number of subjects. The most common adverse events reported in any treatment group were hyponatremia, blood sodium increased, headache, dry mouth, diarrhea, dizziness and peripheral edema which occurred primarily in the Nocdurna treatment groups. No cases of hyponatremia or blood sodium decrease were considered serious. In fact only one case of hyponatremia in the pivotal trials was associated with an adverse event, i.e. dizziness, and the patient was discontinued from the study.

Hyponatremia (serum sodium < 130 mmol/L) is a well described adverse reaction associated with the use of all desmopressin formulations. Severe hyponatremia (serum sodium < 125 mmol/L) or a rapid drop in serum sodium from baseline are especially serious as they can lead to cerebral edema and seizures. Elderly patients are more susceptible to the development of hyponatremia because of a decrease in renal function which makes it harder for them to limit sodium excretion and because of the increased frequency of comorbid conditions in the elderly population. Under normal circumstances the elderly can maintain fluid homeostasis, but their ability to respond to external stresses is limited. Conditions that can predispose to the development of hyponatremia include volume depletion (due to vomiting, diarrhea, severe burns, blood loss), medications (e.g. diuretics, SSRIs, NSAIDs, TCAs, antiepileptic drugs, chemotherapy agents), CHF, cirrhosis, renal failure, malignancies, pulmonary disorders (e.g. pneumonia, TB, acute respiratory failure), endocrine disorders (e.g. hypothyroidism, glucocorticoid deficiency) and SIADH (due to head trauma, neurosurgery, CNS infections)⁴. In fact, hyponatremia is the most common electrolyte abnormality seen in the general hospital population with an incidence of about 1% in the US⁵.

Because of the concern for the risk of the development of hyponatremia, all patients were required to have baseline serum sodium levels ≥ 135 mmol/L in order to be enrolled in the Phase 3 studies. In studies CS40 and CS41 6/649=0.9% and 11/1013=1.0% respectively, were screening failures due to baseline hyponatremia. Consistent with this exclusion criterion the sponsor is currently recommending baseline serum sodium screening for all subjects and starting therapy only in patients with normal serum sodium levels at baseline.

⁴ [Causes and management of hyponatremia](#). Palmer BF, Gates JR, Lader M. Ann Pharmacother. 2003 Nov;37(11):1694-702. Review

⁵ [Hyponatremia](#). Al-Salman J, Kemp D, Randall D. West J Med. 2002 May;176(3):173-6.

Because of the concern that patients with renal impairment might be at greater risk for hyponatremia patients, all patients in the clinical trials were also screened for signs of potential renal impairment based on serum creatinine above the normal range and eGFR < 50mL/min. A higher percentage of subjects were screening failures because of the concern over renal impairment i.e. 86/649=13% (CS40) and 159/1013=16% (CS41) than due to baseline hyponatremia. The sponsor is currently recommending a contraindication to use in subjects with moderate to severe renal impairment but is not recommending baseline serum creatinine screening to check for renal impairment.

In these Phase 3 studies serum sodium was monitored regularly throughout the trial. For the 3-month studies, CS40 and CS41, serum sodium was measured at screening, Days 4, 8, 29, 57 and 85. If the value was ≤ 130 mmol/L, the subject was scheduled for a visit as soon as possible for further evaluation. If the serum sodium value was ≤ 125 mmol/L, the subject was withdrawn from the trial and treatment was stopped immediately. Because of the study results the sponsor is currently recommending additional monitoring only for men 65 years of age or older: once during the first week after starting treatment and a second time at one month after starting treatment. The sponsor believes that this monitoring scheme should successfully identify subjects at risk of hyponatremia before they develop any serious adverse reactions due to progression to severe hyponatremia.

In CS40, a parallel group study comparing placebo to 25 μ g of desmopressin in women, three women had serum sodium levels between 126 and 129mmol/L but all normalized their serum sodium on their own without need for intervention. No women had severe hyponatremia with serum sodium levels ≤ 125 mmol/L. Similarly, in the previous trials CS29 and CS31 while there were 4 women with serum sodium levels between 126 and 129mmol/L on the 25 μ g dose again none developed severe hyponatremia (≤ 125 mmol/L). From the current data the 25 μ g dose appears safe for the treatment of nocturia in women with baseline serum sodium monitoring as recommended by the sponsor.

In Part I of CS41, a parallel group study comparing placebo to desmopressin 50 μ g and 75 μ g, 6 men developed severe hyponatremia (≤ 125 mmol/L) at doses of 50 μ g (n=2), and 75 μ g (n=4), and all were discontinued from the trial. The two subjects at the 50 μ g dose were 74 and 79 years of age and so would have been picked up by the sponsor's proposed monitoring scheme for men 65 years of age and older. One subject on the 75 μ g dose was 64 years of age and therefore would not have been picked up under the current monitoring scheme, but the sponsor is not recommending treatment with this higher dose in men.

In Part II of CS41, all subjects were titrated up to the dose of 100 μ g of desmopressin for an additional month of therapy. Two subjects (1 placebo/desmopressin 100 μ g and 1 desmopressin 75 μ g/100 μ g) developed post-baseline serum sodium levels ≤ 125

mmoL/L. Both men were discontinued from the study. One subject on the 100 µg dose was 58 years of age and therefore would not have been picked up under the current monitoring scheme, but the sponsor is not recommending treatment with this higher dose in men.

Similarly in CS29 and CS31 there were four cases of severe hyponatremia (≤ 125 mmoL/L) in men at doses of 100 µg, but only two cases at doses of 50 µg or lower. One was an 81 year old male treated with the 50 µg dose who should have never been enrolled in the study due to moderate renal failure (creatinine clearance of 42 mL/min) and one was a 78 year old male who developed a pulmonary infection on day 327 on the 10 µg dose who did not have the medication discontinued during the intercurrent illness. Because of the mitigating circumstance it is this medical officer's assessment that these two cases do not reflect negatively on the safety of 50 µg or lower doses of Nocdurna in men. Therefore, the current data support the safety of the 50 µg dose for the treatment of nocturia in men as long as there is adequate monitoring at baseline and additional serum sodium monitoring in men over 65 years of age at one week and one month after starting treatment.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Three month data from the pivotal trials CS40 in women and CS41 in men and long term data from the earlier pivotal trial CS029 and open label extension CS031 were used to evaluate safety.

7.1.2 Categorization of Adverse Events

Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. In the ISS, common adverse events were defined as adverse events that occurred with a crude incidence rate (percentage of treated subjects reporting the event) $>2.0\%$ in any treatment group. Hyponatremia was coded "hyponatraemia" under Metabolism and Nutritional Disorders. Decreases in serum sodium or low serum sodium were coded as "blood sodium decreased" under Investigations.

For the purpose of this review, this medical officer defined "hyponatremia" as serum sodium < 130 mmoL/L and "severe hyponatremia" as serum sodium < 125 mmoL/L.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Three month data from the pivotal trials CS40 in women and CS41 in men were pooled with the long term data from the earlier pivotal trial CS029 and open label extension CS031 to evaluate safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1,443 unique subjects were included in the Phase 3 studies of which 429 received placebo and 1,014 received one or more doses of desmopressin. A total of 1188 (82%) subjects completed 3 months of treatment. Similar percentages of subjects completed treatment in the desmopressin dose groups (77-88%) and the placebo group (84%). Premature discontinuation from the studies occurred in 255 (18%) subjects. “Adverse events” (4-6%) and “serum sodium 125mmol/L” (2-3%) were more common at doses of 50 µg and above compared to the respective placebo rates of 3% and < 1%. The most common reason for premature discontinuation was withdrawal of consent which occurred at rates of 3 to 10% in the desmopressin dose groups and at 6% in the placebo group.

Table 12 Subject Exposure (Safety Analyses Dataset)

Disposition	Placebo	10 µg	25 µg	50 µg	75 µg	100 µg	Total
Safety Analysis Dataset	429	194	331	311	122	194	1443
Completed 3 months, n (%)	360 (84)	149 (77)	283 (85)	259 (83)	107 (88)	149 (77)	1188 (82)
Prematurely withdrawn, n (%):							
Adverse event	12 (3)	6 (3)	7 (2)	12 (4)	7 (6)	9 (5)	49 (3)
Serum sodium ≤125 mmol/L	3 (<1)	0	0	6 (2)	0	6 (3)	13 (<1)
Lost to follow-up	8 (2)	5 (3)	8 (2)	9 (3)	1 (<1)	4 (2)	34 (2)
Subject withdrew consent	25 (6)	20 (10)	20 (6)	17 (5)	4 (3)	15 (8)	93 (6)
Protocol violation	9 (2)	2 (1)	5 (2)	2 (<1)	3 (2)	2 (1)	23 (2)
Other	12 (3)	12 (6)	8 (2)	6 (2)	0	9 (5)	43 (3)

Note: Some subjects received different doses and are included in more than 1 dose group. The total represents unique subjects only.

Cross-reference: [Table 1.1]

Source ISS Table 17

In general, the demographic characteristics of age, height, weight and BMI were similar between the placebo and desmopressin treatment groups in the Safety Analyses Dataset (see Table 13). Women were exposed to lower doses of desmopressin with most women treated in the desmopressin 25 µg group while most men were treated in

the desmopressin 50 µg group. Most subjects were Caucasian 78 to 83%, with 12 to 18% African Americans, and 5 to 24 % Hispanic depending on the treatment group.

Table 13 Demographic Characteristics of the Safety Analyses Dataset

Demographic Characteristic	Placebo (N=429)	10 µg (N=194)	25 µg (N=331)	50 µg (N=311)	75 µg (N=122)	100 µg (N=194)
Age (years)						
Mean (SD)	60.9 (13.9)	61.4 (14.1)	61.3 (13.7)	61.1 (12.4)	60.1 (11.7)	62 (13)
Median	64	64	64	63	64	65
Minimum, maximum	20, 87	23, 85	19, 89	20, 88	29, 80	24, 85
Age category, n (%)						
<65 years	224 (52)	103 (53)	167 (50)	165 (53)	63 (52)	92 (47)
≥65 years	205 (48)	91 (47)	164 (50)	146 (47)	59 (48)	102 (53)
Gender, n (%)						
Female	193 (45)	93 (48)	219 (66)	89 (29)	0	89 (46)
Male	236 (55)	101 (52)	112 (34)	222 (71)	122 (100)	105 (54)
Race, n (%)						
White	355 (83)	158 (81)	269 (81)	257 (83)	98 (80)	152 (78)
Black/African American	65 (15)	24 (12)	53 (16)	46 (15)	22 (18)	33 (17)
Asian	6 (1)	3 (2)	4 (1)	6 (2)	2 (2)	7 (4)
American Indian/ Alaskan Native	1 (<1)	2 (1)	0	0	0	0
Native Hawaiian/ Pacific Islander	1 (<1)	1 (<1)	2 (<1)	0	0	0
Other	1 (<1)	6 (3)	3 (<1)	2 (<1)	0	2 (1)
Ethnic origin, n (%)						
Hispanic or Latino	50 (12)	18 (9)	38 (11)	40 (13)	29 (24)	10 (5)
Not Hispanic or Latino	379 (88)	176 (91)	293 (89)	271 (87)	93 (76)	184 (95)
Height (m)						
Mean (SD)	1.71 (0.098)	1.7 (0.101)	1.67 (0.1)	1.72 (0.095)	1.78 (0.073)	1.71 (0.105)
Median	1.71	1.70	1.66	1.73	1.78	1.72
Minimum, maximum	1.49, 1.93	1.24, 1.93	1.4, 1.96	1.38, 1.96	1.57, 1.96	1.42, 1.96
Weight (kg)						
Mean (SD)	85.7 (20)	84.7 (18)	84.4 (19.5)	87.4 (19.6)	92.3 (17.7)	86.6 (20)
Median	84	83.1	82.2	85.8	89.8	84
Minimum, maximum	47.7, 155	42.3, 149	45, 178	46.3, 177	50.8, 153	42.9, 152
BMI (kg/m ²)						
Mean (SD)	29.4 (6.25)	29.4 (6.29)	30.2 (6.7)	29.4 (6.41)	29.2 (4.81)	29.6 (6.62)
Median	28.4	28.4	28.9	28.2	28.6	28.1
Minimum, maximum	16.6, 53.1	16.5, 53.1	16.8, 59.7	16.6, 67.1	16.1, 47	17.5, 58.1

Note: Some subjects received different doses and are in more than 1 dose group.

BMI=body mass index; SD=standard deviation

Cross-reference: [Table 3.1]

Source Table 20 ISS

7.2.2 Explorations for Dose Response

There was a clear dose response for the adverse reactions of “hyponatremia” and “blood sodium decreased” across the dose range 10 to 100 µg/day (See Table 24). No other adverse reactions showed a clear dose response.

7.2.3 Special Animal and/or In Vitro Testing

No new special animal and/or in vitro testing was included in this submission.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new metabolic, clearance and interaction workup data was included in this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Desmopressin is the only currently approved vasopressin 2 (V2) receptor agonist.

(b) (4)
[REDACTED]
[REDACTED]. However, this finding has not been reported with desmopressin.

7.3 Major Safety Results

Table 14 Summary of Adverse Events by Study Dose

	Placebo (N=429)	10 µg (N=194)	25 µg (N=331)	50 µg (N=311)	75 µg (N=122)	100 µg (N=194)
All adverse events, n (%)	196 (46)	122 (63)	181 (55)	180 (58)	49 (40)	133 (69)
Deaths, n (%)	0	0	0	0	0	0
Serious adverse events, n (%)	4 (<1)	3 (2)	2 (<1)	5 (2)	5 (4)	3 (2)
Adverse events leading to discontinuation, ^a n (%)	12 (3)	7 (4)	9 (3)	18 (6)	7 (6)	13 (7)
Severe adverse events, n (%)	7 (2)	10 (5)	9 (3)	18 (6)	2 (2)	8 (4)
ADRs, n (%)	89 (21)	79 (41)	98 (30)	101 (32)	20 (16)	89 (46)
ADRs leading to discontinuation, ^a n (%)	6 (1)	4 (2)	6 (2)	14 (5)	5 (4)	11 (6)

Note: Some subjects received different doses and are in more than 1 dose group.

ADR=adverse drug reaction

^a In CS29/CS31, all AEs with identification of study drug stopped were used for flagging for probability of leading to discontinuation.

Cross-reference: [Table 7.1.1.1]

Source Table 21 ISS

7.3.1 Deaths

There were no deaths observed in the 3-month treatment period during the Phase 3 trials.

7.3.2 Nonfatal Serious Adverse Events

The percentage of subjects with nonfatal serious adverse events ranged from <1% to 4% across the desmopressin groups and was <1% in the placebo group in the Phase 3 desmopressin nocturia studies. The only MedDRA Preferred Term category that had multiple events and looked like it might be dose dependent was “hyponatremia” which occurred at an incidence of <1% at the 50 µg dose and at an incidence of 3% at the 75 µg dose.

Table 15 Summary of Nonfatal Serious Adverse Events by MedDRA Preferred Term

System Organ Class MedDRA Preferred Term	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)
Any serious adverse event	4 (<1)	3 (2)	2 (<1)	5 (2)	5 (4)	3 (2)
Cardiac Disorders						
Acute myocardial infarction	0	0	0	1 (<1)	0	0
Atrial fibrillation	0	1 (<1)	0	0	0	0
General Disorders and Administration Site Conditions						
Pyrexia	1 (<1)	0	0	0	0	0
Infections and Infestations						
Appendicitis	0	0	1 (<1)	0	0	0
Cellulitis	1 (<1)	0	0	0	0	1 (<1)
Diverticulitis	0	1 (<1)	0	0	0	0
Metabolism and Nutrition Disorders						
Hyponatraemia	0	0	0	2 (<1)	4 (3)	0
Musculoskeletal and Connective Tissue Disorders						
Myalgia	0	0	1 (<1)	0	0	0
Osteoarthritis	0	0	0	1 (<1)	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)						
Adenosquamous cell lung cancer	0	1 (<1)	0	0	0	0
Bladder transitional cell carcinoma	0	0	0	0	0	1 (<1)
Prostate cancer	1 (<1)	0	0	0	0	1 (<1)
Nervous System Disorders						
Transient global amnesia	0	0	0	0	1 (<1)	0
Respiratory, Thoracic and Mediastinal Disorders						
Asthma	0	0	0	1 (<1)	0	0
Pulmonary embolism	1 (<1)	0	0	0	0	0

Note: Some subjects received different doses and are in more than 1 dose group.

MedDRA=Medical Dictionary for Regulatory Activities

Cross-reference: [Table 7.1.1.16]

Source Table 24 ISS

7.3.3 Dropouts and/or Discontinuations

In the Phase 3 desmopressin nocturia studies the % of subjects who prematurely discontinued due to adverse events was similar in the 10 and 25 µg desmopressin groups (4 and 3%, respectively) compared to the incidence in the placebo group (3%), but was slightly increased at the higher desmopressin doses 50 µg (6%), 75 µg (6%) and 100 µg (7%). The only MedDRA preferred term the occurred at 2% or greater in multiple treatment groups was hyponatremia: 50 µg (2%), 75 µg (3%). Other adverse reactions that were seen in a single treatment group at the rate of 2% or greater were

only seen at 100 µg dose, and they included: blood sodium increased (2%), nausea (2%), fatigue (2%), and headache (2%).

Table 16 Summary of Discontinuations by MedDRA Preferred Term

System Organ Class MedDRA Preferred Term	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)
Any adverse event leading to premature discontinuation ^a	12 (3)	7 (4)	9 (3)	18 (6)	7 (6)	13 (7)
Eye Disorders						
Dry eye	0	2 (1)	0	0	0	0
Gastrointestinal Disorders						
Nausea	0	0	1 (<1)	0	0	3 (2)
Dry mouth	0	1 (<1)	0	2 (<1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	0	0	0	0	0	3 (2)
Investigations						
Blood sodium decreased	1 (<1)	0	0	4 (1)	1 (<1)	4 (2)
Metabolism and Nutrition Disorders						
Hyponatraemia	0	0	1 (<1)	5 (2)	4 (3)	2 (1)
Nervous System Disorders						
Headache	1 (<1)	0	1 (<1)	0	0	4 (2)
Dizziness	0	1 (<1)	0	2 (<1)	0	1 (<1)
Vascular Disorders						
Hypertension	2 (<1)	0	1 (<1)	0	0	0

Note: Some subjects received different doses and are in more than 1 dose group.

MedDRA=Medical Dictionary for Regulatory Activities

^a In CS29/CS31, all AEs with identification of study drug stopped were used for flagging for probability of leading to discontinuation.

Cross-reference: [Table 7.1.1.21]

Source Table 25 ISS

7.3.4 Significant Adverse Events

Hyponatremia

Hyponatremia (serum sodium <130 mmol/L) is a well described adverse reaction associated with the use of all desmopressin formulations. Severe hyponatremia (serum sodium <125 mmol/L) or a rapid drop in serum sodium from baseline are especially serious as they can lead to cerebral edema and seizures. Elderly patients are especially susceptible to the development of hyponatremia because of a decrease in renal function which makes it harder for them to limit sodium excretion. Under normal circumstance they can maintain fluid homeostasis, but their ability to respond to external stresses is limited. Conditions that can predispose to the development of hyponatremia include volume depletion (due to vomiting, diarrhea, severe burns, blood loss), medications (e.g. diuretics, SSRIs, NSAIDs, TCAs, antiepileptic drugs, chemotherapy agents), CHF,

cirrhosis, renal failure, malignancies, pulmonary disorders (e.g. pneumonia, TB, acute respiratory failure), endocrine disorders (e.g. hypothyroidism, glucocorticoid deficiency) and SIADH (due to head trauma, neurosurgery, CNS infections)⁶. In fact, hyponatremia is the most common electrolyte abnormality seen in the general hospital population with an incidence of about 1% in the US⁷.

Because of the concern for the risk of the development of hyponatremia, all patients were required to have baseline serum sodium levels ≥ 135 mmol/L in order to be included in the Phase 3 studies. In studies CS40 and CS41 6/649=0.9% and 11/1013=1% respectively, were screening failures due to baseline hyponatremia. Consistent with this exclusion criteria the sponsor is currently recommending baseline serum sodium screening for all subjects and starting therapy only in patients with normal serum sodium levels at baseline.

Because of the concern that patients with renal impairment might be at greater risk for hyponatremia patients, all patients in the clinical trials were also screened for signs of potential renal impairment based on serum creatinine above the normal range and eGFR < 50mL/min. A higher percentage of subjects were screening failures because of the concern over renal impairment i.e. 86/649=13% (CS40) and 159/1013=16% (CS41) than due to baseline hyponatremia. The sponsor is currently recommending a contraindication to use in subjects with moderate to severe renal impairment but is not recommending baseline serum creatinine screening to check for renal impairment.

In these Phase 3 studies serum sodium was monitored regularly throughout the trial. For the 3-month studies CS40 and CS41 serum sodium was measured at screening, Days 4, 8, 29, 57 and 85. If the value was ≤ 130 mmol/L, the subject was scheduled for a visit as soon as possible for further evaluation. If judged clinically significant by the Investigator, the low sodium value was recorded as an AE. If the serum sodium value was ≤ 125 mmol/L, the subject was withdrawn from the trial and treatment was stopped immediately. The case was recorded and reported as an SAE. Because of the study results the sponsor is currently recommending additional monitoring only for men 65 years of age or older: once during the first week after starting treatment and a second time at one month after starting treatment. The sponsor believes that this monitoring scheme should successfully identify subjects at risk of hyponatremia before they develop any serious adverse reactions due to progression to severe hyponatremia.

Table 17 lists the incidence rates for hyponatremia at any post baseline visit during the initial 3 months of therapy in the Phase 3 Safety Analysis Dataset. Due to data cut-off

⁶ [Causes and management of hyponatremia](#). Palmer BF, Gates JR, Lader M. Ann Pharmacother. 2003 Nov;37(11):1694-702. Review

⁷ [Hyponatremia](#). Al-Salman J, Kemp D, Randall D. West J Med. 2002 May;176(3):173-6.

dates 4 subjects had serum sodium levels ≤ 125 mmol/L one day after the last dose of desmopressin or after the 3-month visit and therefore were not included in the table. It is not clear why hyponatremia which is such a rare event should have occurred on these dates. Therefore, the table was modified by this medical officer to include the revised percentages in red to show what the results would have been if these pts had been included in the table. Even after including these patients the risk of severe hyponatremia with sodium levels ≤ 125 mmol/L was at most 3% at the higher doses of 50 μ g and above.

Table 17 Incidence of Hyponatremia in the 3-Month Safety Analysis Dataset

Serum Sodium (mmol/L)	Placebo (N=429) n (%)	10 μ g (N=194) n (%)	25 μ g (N=331) n (%)	50 μ g ^a (N=311) n (%)	75 μ g (N=122) n (%)	100 μ g ^b (N=194) n (%)
Observed N	421	181	319	301	122	180
<135	15 (4)	24 (13)	37 (12)	58 (19)	21 (17)	61 (34)
130-134	14 (3)	22 (12)	29 (9)	47 (16)	12 (10)	43 (24)
126-129	0	2 (1)	8 (3)	4 (1)	5 (4)	16 (9)
≤ 125	1 (<1)	0	0	7 (2) (3)	4 (3)	2 (1) (2)

Note: Some subjects received different doses and are in more than 1 dose group.

^a Two additional 50 μ g subjects (b) (6) had a serum sodium value ≤ 125 mmol/L 1 day after the last dose of desmopressin in [CS31] and were not included in the table.

^b Two additional 100 μ g subjects (b) (6) had a serum sodium value ≤ 125 mmol/L 1 day after the last dose of desmopressin in [CS29] and were not included in the table.

Cross-reference: [ISS Table 7.1.2.1]

Source Table 26 ISS

The rate of severe hyponatremia (≤ 125 mmol/L) seen in these trials likely overestimates what will be seen in practice assuming the recommended monitoring is employed. In these studies pts were allowed to continue therapy with low serum sodium levels < 135mmol/L as long as they didn't drop to 125 mmol/L or lower at which point they were discontinued from the study. According to the proposed monitoring schedule any subject whose sodium drops below 130mmol/L is to be discontinued from treatment. In these studies the vast majority of pts with sodium levels <135mmol/L normalized on their own without the need to discontinue the medication, and of the 14 pts in the database with serum sodium levels reported at ≤ 125 mmol/L only four dropped directly from a normal value ≥ 135 to a value of ≤ 125 .

- a 71 y/o female on placebo who went from 137 to 121 in 9 days
- a 56 y/o female on 50 μ g who went from 137 to 120 in 14 days
- a 77 y/o female on 50 μ g who went from 139 to 123 in 14 days
- a 66 y/o male on 75 μ g dose who went from 139 to 119 in 10 days

However, none of these occurred at the currently proposed doses of desmopressin 25 μ g for women and desmopressin 50 μ g for men. The fact that one patient on placebo dropped directly from a normal serum sodium of 137mmol/L to a value of 121mmol/L during the first week of treatment in CS29 could suggest that asymptomatic severe

hyponatremia can occur at a low background rate in the elderly population, or alternatively it may represent an aberrant lab test as the patient had no other adverse reactions associated with the episode and recovered by the next repeat lab test to a value of 138mmol/L.

In CS40, a parallel group study comparing placebo to desmopressin 25 µg in women, three women had serum sodium levels between 126 and 129mmol/L but all normalized their serum sodium on their own without need for intervention. No women had severe hyponatremia with serum sodium levels ≤125mmol/L.

Table 18 Minimum Serum Sodium Values (Safety Analysis Set) in study CS40

Serum Sodium Level	Placebo (N=126)	Desmopressin 25 µg (N=135)
≤125 mmol/L	0	0
126-129 mmol/L	0	3 (2%)
130-134 mmol/L	2 (2%)	11 (8%)
≥135 mmol/L	124 (98%)	121 (90%)

Cross-reference: [Table 7.1.1.1]

Source Table 11-6 fe992026-cs40-report-body

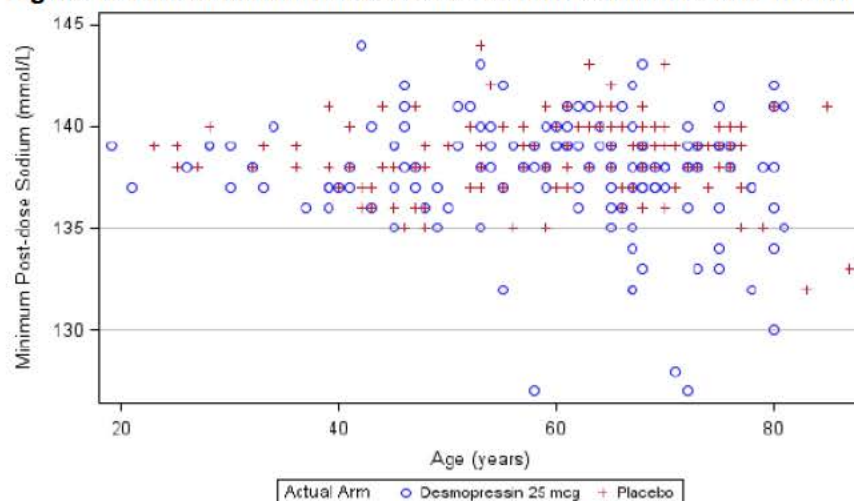
Table 19 Women with Serum Sodium < 130mmol/L in study CS40

Site-Subject # (b) (6)	Age	Baseline Sodium	Low Sodium Level	Study Visit
	58	133 mmol/L	127 mmol/L	Week 1
	71	134 mmol/L	128 mmol/L	Day 4
	72	144 mmol/L	127 mmol/L	Month 1

Cross-reference: [Listing 8.1.2]

Source Table 11-7 fe992026-cs40-report-body

Figure 12 Plot of Minimum Post-Dose Serum Sodium Levels in study CS40 (women only)



FE992026/NOCT/CS40/REPORT/09MAY2012-PANT/SODSCATTER_AGE sas

Source Fig. 11.1 fe992026-cs40-report-body

Similarly in the previous trials CS29 and CS31 while there were 4 women with serum sodium levels between 126 and 129mmol/L on the 25 µg dose no women developed severe hyponatremia (≤ 125 mmol/L). From the current data the 25 µg dose appears safe for the treatment of nocturia in women with baseline serum sodium monitoring.

In Part I of CS41, a parallel group study comparing placebo to desmopressin 50µg and desmopressin 75µg, 6 men had severe hyponatremia (≤ 125 mmol/L) at doses of 50µg (n=2), and 75µg (n=4), and all were discontinued from the trial.

Table 20 Minimum Serum Sodium Values (Safety Analysis Set) in study CS41 Part I

Serum Sodium Level	Placebo (N=143)	Desmopressin 50 µg (N=119)	Desmopressin 75 µg (N=122)
≤ 125 mmol/L	0	2 (2%)	4 (3%)
126-129 mmol/L	0	0	5 (4%)
130-134 mmol/L	2 (1%)	9 (8%)	12 (10%)
≥ 135 mmol/L	141 (99%)	108 (91%)	101 (83%)

Cross-reference: [Table 7.1.1.4]

Source Table 11-11 fe992026-cs41-report-body

Table 21 Men with Serum Sodium < 125mmol/L in Part I of study CS41

Site-Subject # (b) (6)	Treatment	Age	Baseline Sodium	Low Sodium Level	Study Visit
	50 µg	74	137 mmol/L	125 mmol/L	Month 2
	50 µg	79	136 mmol/L	125 mmol/L	Day 7 (End of Trial)
	75 µg	66	139 mmol/L	119 mmol/L	Day 4
	75 µg	64	134 mmol/L	124 mmol/L	Week 1
	75 µg	71	141 mmol/L	125 mmol/L	Week 2
	75 µg	71	139 mmol/L	121 mmol/L	Month 1

a. Subject discontinued due to an SAE of hyponatremia.

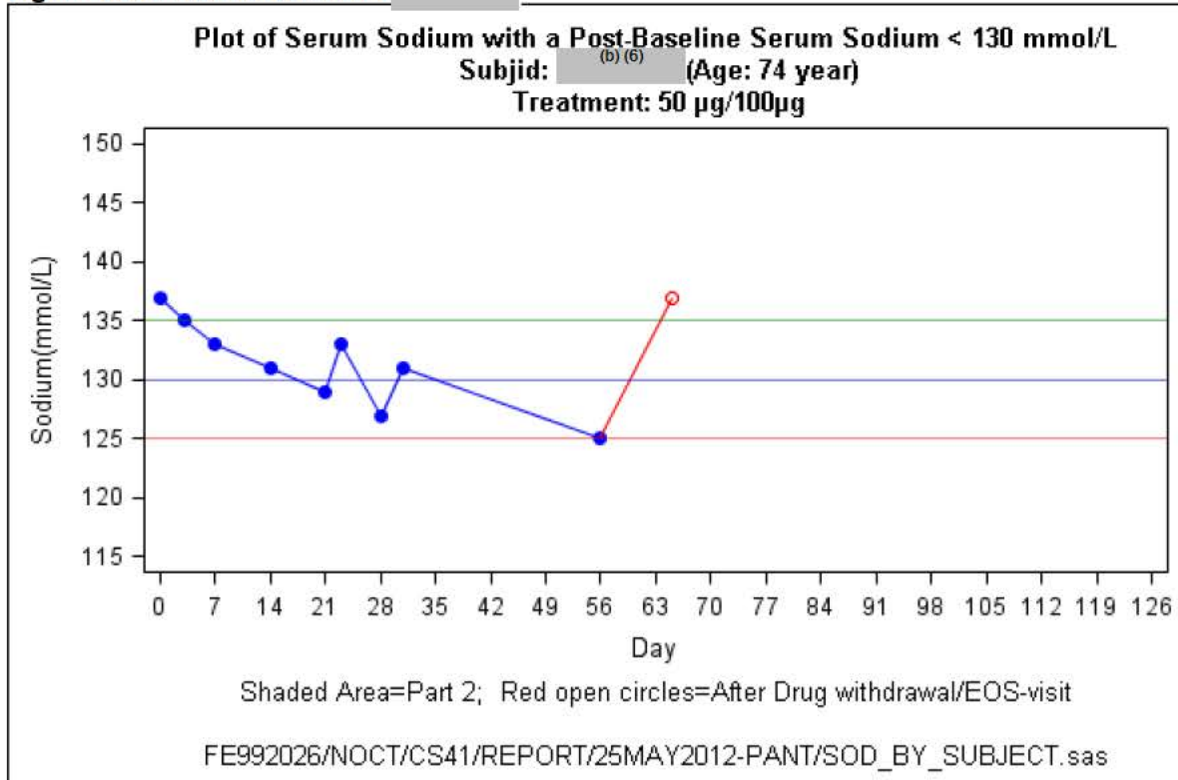
b. Subject discontinued due to an AE of dizziness.

Cross-reference: [Listing 8.1.1]

Source Table 11-13 fe992026-cs41-report-body

For clarification, while subject (b) (6) treated with the 50 µg dose did not reach a sodium level <125mmol/L until the two month visit he already had a sodium level of between 130 and 125mmol/L at the one month visit and as such would have been identified by the sponsor's proposed monitoring scheme and would have been discontinued from further treatment in a real use situation.

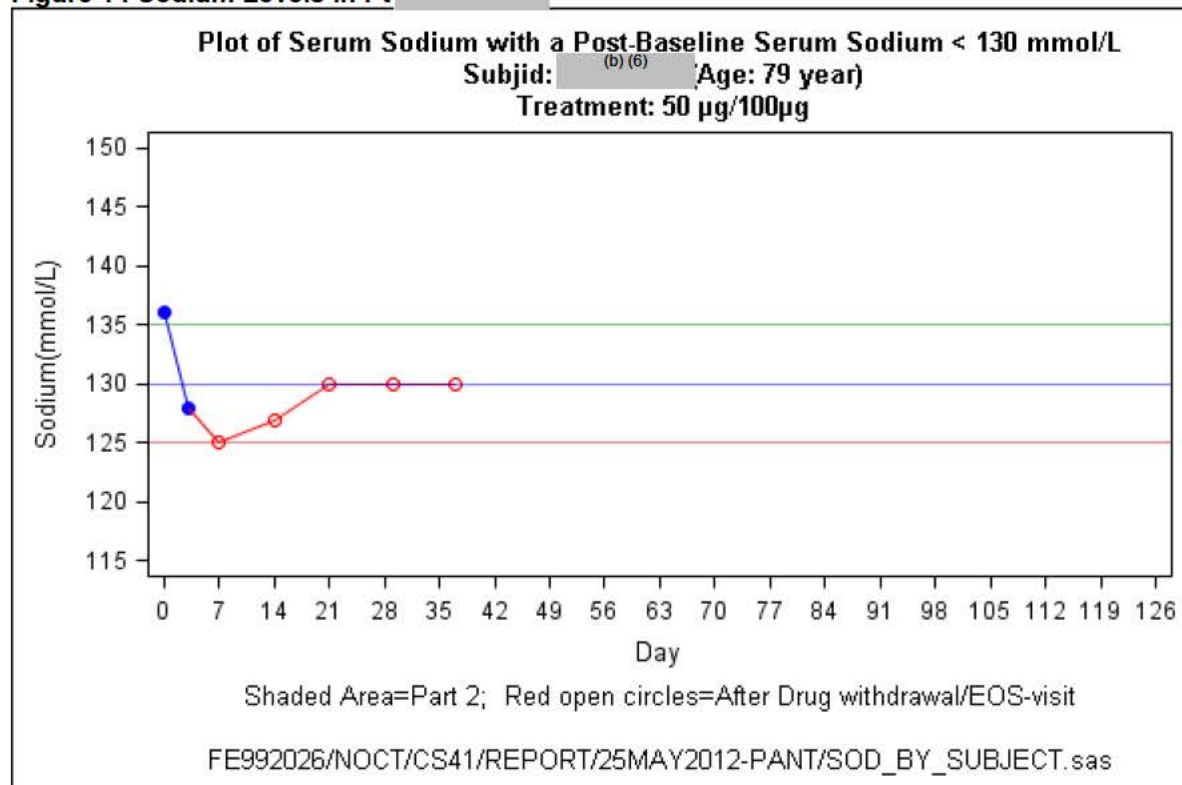
Figure 13 Sodium Levels in Pt (b) (6)



Source Fig. 11-2 fe992026-cs41-report-body (red circles correspond to values after desmopressin was discontinued).

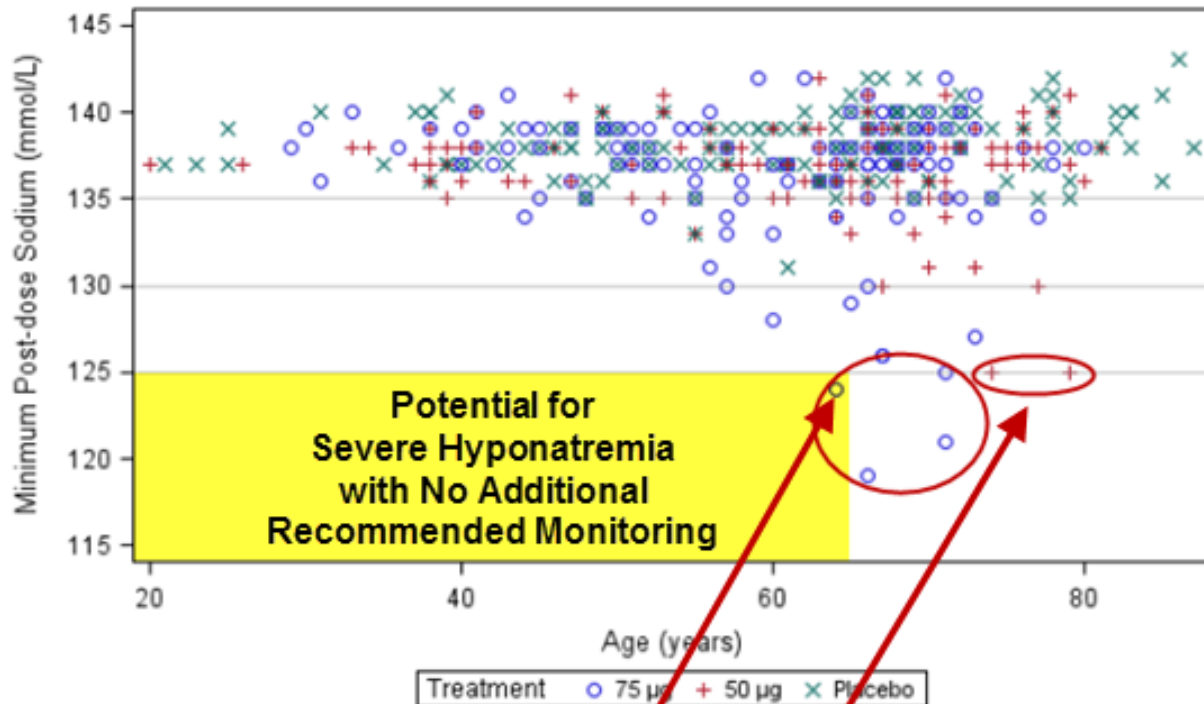
In addition subject (b) (6), the other subject treated with desmopressin 50 µg who went on to have a serum sodium level of < 125mmol/L was discontinued at the 7 day visit because of a complaint of dizziness. At that time the serum sodium was between 130 and 125mmol/L and as such he would have been identified by the sponsor's proposed monitoring scheme. Therefore he should have been discontinued from further treatment in a real use situation even if he had not had symptoms of dizziness. Of note this was the only patient in the Safety Database that had an Adverse Reaction associated with a low serum sodium level. For the rest of the subjects hyponatremia was identified only through the pre-specified monitoring scheme.

Figure 14 Sodium Levels in Pt (b) (6)



Source Fig. 11-2 fe992026-cs41-report-body (red circles correspond to values after desmopressin was discontinued).

Figure 15 Plot of Minimum Post-Dose Serum Sodium Levels in Part I of study CS41 (men only)



FE992026/NOCT/CS41/REPORT/25MAY2012-PANT/SODSCATTER_AGE.sas

Source Fig. 11.1 fe992026-cs41-report-body

The two subjects at the currently proposed 50 µg dose were 74 and 79 years of age and so would have been picked up by the sponsor's proposed monitoring scheme for men ≥ 65 years of age. One male on the 75 µg dose with a serum sodium of 124mmol/L was 64 years of age and so would not have been picked up under the proposed monitoring scheme which recommends monitoring only for men 65 yrs of age and older, but as the sponsor is not recommending treatment with the 75 µg dose the current data support the safety of the 50 µg dose in men with the sponsor's proposed monitoring scheme.

In Part II of CS41, all subjects were titrated up to the dose of 100 µg of desmopressin for an additional month of therapy. Two subjects (1 placebo/desmopressin 100 µg and 1 desmopressin 75 µg/100 µg) had a post-baseline serum sodium level ≤ 125 mmol/L. Both pts were discontinued from the study.

Table 22 Minimum Serum Sodium Values (Safety Analysis Set) in study CS41 Part II

Serum Sodium Level	Desmopressin			
	Placebo/100 µg (N=124)	50 µg/100 µg (N=101)	75 µg/100 µg (N=102)	Total (N=327)
≤125 mmol/L	1 (<1%)	0	1 (<1%)	2 (<1%)
126-129 mmol/L	3 (2%)	1 (<1%)	1 (<1%)	5 (2%)
130-134 mmol/L	10 (8%)	12 (12%)	11 (11%)	33 (10%)
≥135 mmol/L	110 (89%)	88 (87%)	89 (87%)	287 (88%)

Note: The total column was calculated.

Cross-reference: [Table 7.1.1.7]

Source Table 11-15 fe992026-cs41-report-body

Table 23 Men with Serum Sodium < 125mmol/L in Part II of study CS41

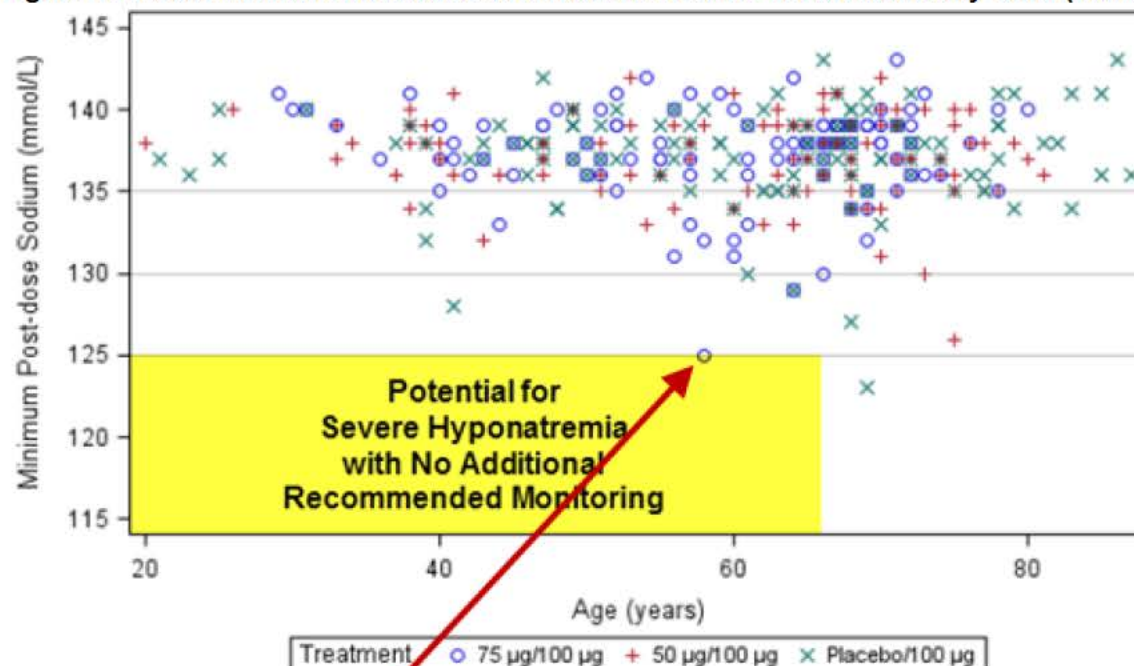
Site-Subject #	Treatment	Age	Baseline Sodium	Low Sodium Level	Study Visit
(b) (6)	Placebo/100 µg	69	144 mmol/L	123 mmol/L	OL Day 4
	75 µg/100 µg	58	138 mmol/L	125 mmol/L	OL Week 2

a. Discontinued due to an SAE of hyponatremia.

Cross-reference: [Listing 8.1.1]

Source Table 11-17 fe992026-cs41-report-body

Figure 16 Plot of Minimum Post-Dose Serum Sodium Levels in Part II of study CS41 (men only)



FE992026/NOCT/CS41/REPORT/25MAY2012-PANT/SODSCATTER_AGE.sas

Source Fig. 11-4 fe992026-cs41-report-body

As subject (b) (6) was under 65 years of age the proposed monitoring scheme would not have identified this case of severe hyponatremia, but as the sponsor is not proposing treatment with the 100 µg dose in men the current data continue to support the safety of the 50 µg dose in men with the current monitoring scheme.

7.3.5 Submission Specific Primary Safety Concerns

See Hyponatremia 7.3.4

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Dose-dependent increases in the incidence of “hyponatremia” and “blood sodium increased” were observed. The incidence of hyponatremia was <1% in the placebo group compared to 1%, 2%, 3%, 4%, and 6% in the 10 µg, 25 µg, 50 µg, 75 µg, and 100 µg desmopressin groups, respectively. The incidence of blood sodium decreased was <1% in the placebo group compared to higher rates at doses of 50 µg and above: 50 µg (2%), 75 µg (2%) and 100 µg (4%).

Table 24 Common Adverse Events Occurring in at Least 2% of Subjects in any Treatment Group

System Organ Class MedDRA Preferred Term	Placebo (N=429) n (%)	10 µg (N=194) n (%)	25 µg (N=331) n (%)	50 µg (N=311) n (%)	75 µg (N=122) n (%)	100 µg (N=194) n (%)
Any adverse event	196 (46)	122 (63)	181 (55)	180 (58)	49 (40)	133 (69)
Eye Disorders						
Dry eye	0	4 (2)	2 (<1)	0	0	0
Gastrointestinal Disorders						
Dry mouth ^a	55 (13)	65 (34)	60 (18)	64 (21)	1 (<1)	56 (29)
Diarrhoea	10 (2)	5 (3)	13 (4)	12 (4)	4 (3)	3 (2)
Constipation	7 (2)	5 (3)	10 (3)	4 (1)	1 (<1)	2 (1)
Nausea	4 (<1)	5 (3)	8 (2)	9 (3)	3 (2)	9 (5)
Abdominal discomfort	2 (<1)	5 (3)	4 (1)	2 (<1)	0	4 (2)
Gastroesophageal reflux disease	0	0	1 (<1)	1 (<1)	1 (<1)	4 (2)
General Disorders and Administration Site Conditions						
Fatigue	3 (<1)	9 (5)	2 (<1)	6 (2)	2 (2)	4 (2)
Oedema peripheral	4 (<1)	3 (2)	2 (<1)	4 (1)	5 (4)	5 (3)
Infections and Infestations						
Nasopharyngitis	12 (3)	6 (3)	10 (3)	5 (2)	4 (3)	7 (4)
Upper respiratory tract infection	11 (3)	4 (2)	10 (3)	8 (3)	2 (2)	7 (4)
Urinary tract infection	11 (3)	3 (2)	6 (2)	7 (2)	0	4 (2)
Sinusitis	4 (<1)	7 (4)	2 (<1)	2 (<1)	0	2 (1)
Investigations						
Blood sodium decreased	1 (<1)	2 (1)	2 (<1)	5 (2)	2 (2)	8 (4)
Metabolism and Nutrition Disorders						
Hyponatraemia	3 (<1)	2 (1)	5 (2)	9 (3)	5 (4)	11 (6)
Musculoskeletal and Connective Tissue Disorders						
Back pain	2 (<1)	2 (1)	9 (3)	4 (1)	2 (2)	3 (2)
Arthralgia	5 (1)	2 (1)	7 (2)	2 (<1)	0	2 (1)
Muscle spasms	5 (1)	4 (2)	6 (2)	5 (2)	0	5 (3)
Nervous System Disorders						
Headache	18 (4)	14 (7)	18 (5)	22 (7)	7 (6)	15 (8)
Dizziness	2 (<1)	7 (4)	5 (2)	11 (4)	1 (<1)	7 (4)
Psychiatric Disorders						
Insomnia	2 (<1)	7 (4)	2 (<1)	9 (3)	0	5 (3)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	2 (<1)	1 (<1)	6 (2)	5 (2)	0	7 (4)
Oropharyngeal pain	4 (<1)	5 (3)	2 (<1)	4 (1)	0	1 (<1)

Note: Some subjects received different doses and are in more than 1 dose group.

MedDRA=Medical Dictionary for Regulatory Activities

^a Subjects were specifically queried about dry mouth in CS29/CS31 but not in CS40/CS41.

Cross-reference: Tables [7.1.1.6] and [7.1.1.26]

Source Table 22 ISS

None of the other adverse reactions showed what appeared to be clear dose-dependent increases. Adverse reaction preferred terms occurring at rate of 5% or greater in multiple treatment groups included

- headache- the placebo subtracted event rate ranged from 1 to 4% and
- dry mouth- the placebo subtracted event rate ranged from 0 to 21%. Of note when subjects were not specifically queried about dry mouth in studies CS40 and CS41 the incidence rate dropped to $\leq 4\%$ in all desmopressin dose groups. Suggesting that while dry mouth may be a common event it was typically not considered serious enough for the patients to mention it on their own without specifically being queried about it.

7.4.2 Laboratory Findings

The incidence of markedly abnormal changes in hematology and clinical chemistry variables other than serum sodium was generally similar across the desmopressin dose groups, with no indication of a dose-related trend in abnormal changes. A summary of markedly abnormal changes is presented in Table 29 in the Appendix.

There was essentially no change in the mean serum sodium concentration from baseline to the last visit for any doses of Nocdurna (10 to 100 μg) in the 3-Month Safety Analysis Dataset (see Table 30 in the Appendix).

7.4.3 Vital Signs

There were no dose response changes with respect to mean or % change from the mean in blood pressure or heart rate. There were no dose response changes with respect to markedly abnormal increases or decreases in blood pressure or heart rate. Overall no clinically significant findings in vital signs or physical exams were identified in these studies.

7.4.4 Electrocardiograms (ECGs)

No information about ECG measurements between treatment groups was included in this submission.

7.4.5 Special Safety Studies/Clinical Trials

No information regarding special safety studies was included in this submission.

7.4.6 Immunogenicity

No information regarding immunogenicity was included in this submission.

7.5 Other Safety Explorations

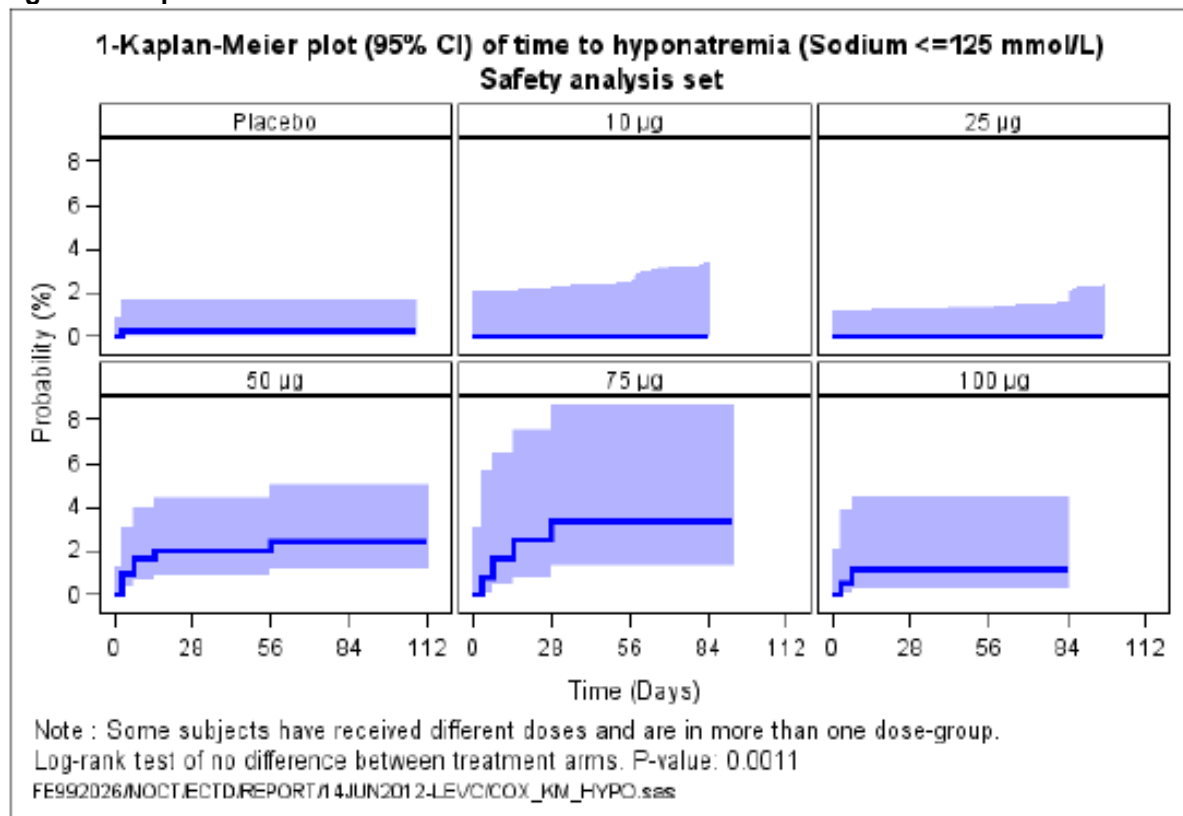
7.5.1 Dose Dependency for Adverse Events

There was a clear dose dependency only with respect to the risk of hyponatremia (see Table 17 and 24). None of the other treatment-related adverse events including: dry mouth, headache, dizziness or gastrointestinal complaints showed dose dependency (See Table 24).

7.5.2 Time Dependency for Adverse Events

The sponsor's analysis confirmed that serum sodium monitoring at Day 4 to 8 of treatment and at 1 month of treatment would identify all cases in which serum sodium fell to 125mmol/L or lower. There was one patient on desmopressin 50 µg who did not reach a reach a sodium level <125mmol/L until the two month visit but he already had a sodium level of between 130 and 125mmol/L at the one month visit and as such would have been identified by the sponsor's proposed monitoring scheme and would have been discontinued from further treatment in a real use situation.

Figure 17 Kaplan-Meier Plot of time to Serum Sodium < 125mmol/L



Source Fig. 7.1.2.19

7.5.3 Drug-Demographic Interactions

Gender

Hyponatremia was seen at lower doses in women than men.

Table 25 Incidence of Hyponatremia by Gender up to the 3-Month Visit (Safety Analysis Dataset)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg ^a n (%)		75 µg n (%)	
	Males (N=236)	Females (N=193)	Males (N=101)	Females (N=93)	Males (N=112)	Females (N=219)	Males (N=222)	Females (N=89)	Males (N=122)	Females (N=0)
Observed N	230	191	94	87	105	214	219	82	122	0
<=135	7 (3)	8 (4)	14 (15)	10 (11)	13 (12)	24 (11)	38 (17)	20 (24)	21 (17)	0
130-134	7 (3)	7 (4)	13 (14)	9 (10)	12 (11)	17 (8)	34 (16)	13 (16)	12 (10)	0
126-129	0	0	1 (1)	1 (1)	1 (<1)	7 (3)	1 (<1)	3 (4)	5 (4)	0
≥125	0	1 (<1)	0	0	0	0	3 (1)	4 (5)	4 (3)	0

Note: Some subjects received different doses and are in more than 1 dose group.

Source Table 27 ISS

Outside of hyponatremia which was seen in lower doses in females than males there was no difference in the rates of treatment emergent adverse reactions (See Table 31 in the Appendix for a more complete listing of the data).

Age

Hyponatremia was seen more frequently in elderly patients ≥65 years of age.

Table 26 Incidence of Hyponatremia by Age < and ≥65 years up to the 3-Month Visit (Safety Analysis Dataset)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg ^a n (%)		75 µg n (%)	
	<65 years (N=224)	≥65 years (N=205)	<65 years (N=103)	≥65 years (N=91)	<65 years (N=167)	≥65 years (N=164)	<65 years (N=165)	≥65 years (N=146)	<65 years (N=63)	≥65 years (N=59)
Observed N	221	200	98	83	162	157	162	139	63	59
<=135	8 (4)	7 (4)	7 (7)	17 (20)	11 (7)	26 (17)	20 (12)	38 (27)	10 (16)	11 (19)
130-134	8 (4)	6 (3)	7 (7)	15 (18)	9 (6)	20 (13)	16 (10)	31 (22)	8 (13)	4 (7)
126-129	0	0	0	2 (2)	2 (1)	6 (4)	1 (<1)	3 (2)	1 (2)	4 (7)
≥125	0	1 (<1)	0	0	0	0	3 (2)	4 (3)	1 (2)	3 (5)

Note: Some subjects received different doses and are in more than 1 dose group.

Source Table 28 ISS

Outside of the treatment emergent adverse reactions of “blood sodium decreased” and “hyponatremia” which was seen more commonly in elderly patients ≥65 years of age there was no difference in the rates of treatment emergent adverse reactions by age (See Table 32 in the Appendix for a more complete listing of the data).

Race

There were too few non-Caucasian patients to be able to draw any clear conclusions about the incidence of hyponatremia by race.

Table 27 Incidence of Hyponatremia by Race Caucasian vs. non Caucasian up to the 3-Month Visit (Safety Analysis Dataset)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg* n (%)		75 µg n (%)	
	Caucasian (N=355)	Non-Caucasian (N=74)	Caucasian (N=158)	Non-Caucasian (N=36)	Caucasian (N=269)	Non-Caucasian (N=62)	Caucasian (N=257)	Non-Caucasian (N=54)	Caucasian (N=98)	Non-Caucasian (N=24)
Observed N	348	73	146	35	259	60	249	52	98	24
≤135	14 (4)	1 (1)	22 (15)	2 (6)	33 (13)	4 (7)	51 (20)	7 (13)	17 (17)	4 (17)
130-134	13 (4)	1 (1)	20 (14)	2 (6)	25 (10)	4 (7)	41 (16)	6 (12)	8 (8)	4 (17)
126-129	0	0	2 (1)	0	8 (3)	0	3 (1)	1 (2)	5 (5)	0
≤125	1 (<1)	0	0	0	0	0	7 (3)	0	4 (4)	0

Note: Some subjects received different doses and are in more than 1 dose group.

Source Table 32 ISS

There were too few non-Caucasian patients to be able to draw any clear conclusions about the incidence of treatment emergent adverse reactions by race.

7.5.4 Drug-Disease Interactions

Liver Function

Desmopressin has not been shown to undergo significant liver metabolism in *in vitro* studies with human microsomes. Formal *in vivo* studies have not been performed. No dose adjustments are being recommended for patients with liver disease.

Renal Function

The half life of desmopressin is greatly increased in subjects with moderate to severe renal impairment, as desmopressin is excreted unchanged via the kidneys. The observed mean terminal half life was 2.8, 4.0, 6.6 and 8.7 hours for patients with no, mild, moderate and severe renal impairment defined as creatinine clearances of > 80, 50-80, 30-49 and 5-29mL/min, respectively. Dose adjustments would be necessary to treat patients with moderate to severe renal function. The sponsor is currently proposing to contraindicate use in such patients.

7.5.5 Drug-Drug Interactions

While there is a potential for drug interactions with drugs that may increase water retention or hyponatremia such as tricyclic antidepressants, SSRIs, chlorpromazine, carbamazepine NSAIDs, diuretics, etc. only the use of loop diuretics was specifically excluded in the pivotal studies. If such medications were initiated during the studies additional sodium measurements were recommended at 3 to 7 days after treatment initiation. Within each treatment group, there were too few subjects with use of selected concomitant medications compared to subjects without such use to draw meaningful conclusions with respect to the difference in the incidence of AEs by selected concomitant medications.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No information regarding carcinogenicity was included in this submission.

7.6.2 Human Reproduction and Pregnancy Data

No information regarding human reproduction or use in pregnancy was obtained from the pivotal trial as females of reproductive age were required to use a reliable method of contraception.

7.6.3 Pediatrics and Assessment of Effects on Growth

No information regarding use in pediatrics was obtained from the pivotal trials. Subjects had to be ≥ 18 years of age to be enrolled in these studies.

A waiver was requested and granted by the PeRC during the first submission because the indication sought in this application is an adult condition. Since the product was already reviewed during the first submission, there was no need to go the PeRC during this resubmission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdosing with desmopressin leads to prolongation of the duration of action with an increased risk of water retention and hyponatremia. Severe hyponatremia, with serum sodium levels ≤ 125 mmol/L was seen in women receiving doses ≥ 50 μ g and in men over age 65 receiving doses ≥ 75 μ g. Decreased renal function is likely to increase the risk for overdose as the drug is primarily excreted unmetabolized in the urine. There is no specific antidote for desmopressin. Patients will need to have fluid intake restricted, have their fluid and electrolyte status followed closely and be treated symptomatically.

No new information regarding drug abuse potential, withdrawal and rebound were obtained from this submission.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a Medication Guide for Nocdurna to be provided to patients with each dispensed NOCDURNA prescription to inform them of the risks of hyponatremia and the need for sodium monitoring.

8 Postmarket Experience

Desmopressin was first approved worldwide as an intranasal formulation for the treatment of diabetes insipidus in 1972. The first oral formulation, a tablet, was approved in 1987 for diabetes insipidus, in 1989 for nocturnal enuresis, and in 2001 for nocturia (dose 0.1-0.4 mg). The oral formulation desmopressin melt was approved in 2005 for the indications diabetes insipidus, nocturnal enuresis, and nocturia (dose 60-240 µg). There is a linear relationship in PK between the tablet and melt formulations:

60 µg Melt corresponds to 0.1 mg Tablet formulation
 120 µg Melt corresponds to 0.2 mg Tablet formulation
 240 µg Melt corresponds to 0.4 mg Tablet formulation

The nocturia indication is currently approved in more than 80 countries for the tablet and more than 70 countries for the melt. In these countries the nocturia indication is limited to patients under 65 years of age, but there has been off label use in elderly patients.

The majority of post-marketing reports were observed with the intranasal formulations of desmopressin (53%), followed by the tablets (19%), and melt (11%).

The most frequently reported adverse reactions were similar for the desmopressin melt and all oral desmopressin formulations and included drug ineffective, followed by hyponatremia, headache, GI symptoms and skin reactions.

Table 28 Most Frequently Reported Spontaneous Adverse Reactions

Adverse Reactions as of 30 April 2012	Oral Desmopressin (n=1891)		Minirin Melt (n=660)	
	Number of reactions	(%)	Number of reactions	(%)
Drug effect decreased/ drug ineffective	207	10.9	100	15.1
Hyponatremia (MedDRA SMQ)	151	8.0	35	5.3
Headache	104	5.5	44	6.7
Abdominal Pain	59	3.1	29	4.4
Nausea	56	3.0	23	3.5
Vomiting	48	2.5	18	2.7
Rash/Urticaria/Skin Reaction	42	2.2	22	3.3
Convulsions	33	1.7	Not listed	
Weight Increased	28	1.5	14	2.1

Source Tables 41 and 44 ISS

The most common indication for the use of desmopressin is primary nocturnal enuresis in children 18 years of age and younger. The sponsor estimates the treatment of adult nocturia constitutes only 10 to 20% of the world wide use of this medication.

The overall age distribution for adverse reactions for oral desmopressin cases is 51% for ≤ 18 years, 16.5% for ≥ 18 to < 65 years, and 15% for ≥ 65 years, which roughly represents the greater use in the younger population.

The adverse reaction of greatest concern is hyponatremia which can lead to seizures and coma or death. Children can tolerate doses of 0.2 to 0.6mg of desmopressin tablets for the treatment of primary nocturnal enuresis with very little risk for hyponatremia assuming proper fluid restriction is employed. Adults, however, primarily those age 50 and older appear to be more sensitive to the risk of hyponatremia. The safety data from the pivotal trials included in this submission support doses no higher than 25 μg of the melt formulation in women or 50 μg of the melt formulation in men with appropriate sodium monitoring.

A total of 780 cases of hyponatremia have been reported to the sponsor's safety database as of April 30, 2012. The majority of the cases were reported with the intranasal desmopressin formulation (60%) followed by the tablet (15%) and melt (4.6%). As a result of the higher observed rate of hyponatremia with the nasal formulation the Agency removed the indication for the treatment of primary nocturnal enuresis in 2007 and added additional safety information to the desmopressin PIs.

A majority of the hyponatremia cases with desmopressin tablets were in adults

- 25/117=21% age 18 to 65 years of age and
- 67/117=57% 65 years of age or older.

Only about 10 cases (9%) were in patients treated for diabetes insipidus, so the majority of cases were probably for the treatment of nocturia/nocturnal enuresis even if no clear indication was listed in the case report. There was one fatal case and 8 cases in which the outcome was not known. The one fatal case was from the US and involved an 80 year old female who experienced a hyponatremic seizure three days after starting 0.2mg of desmopressin tablets for nocturnal polyuria. There was no clear documentation of baseline serum sodium or relevant medical history in the case report to determine if she was an appropriate candidate for this form of treatment. In addition the dose was much higher than should have been recommended from the current safety information.

A majority of the hyponatremia cases with desmopressin melt were in adults

- 7/35=20% age 18 to 65 years of age and
- 19/35=54% age 65 or older.

Only about 4 cases (11%) were in patients treated for diabetes insipidus, so the majority of cases were probably for the treatment of nocturia/nocturnal enuresis even if no clear indication was listed in the case report. There was one fatal case and 2 cases in which the outcome was not known. The one fatal case was from Norway and involved an 82 year old female who developed severe hyponatremia (serum sodium =115mmol/L) after 2 months of treatment with 60 μg of desmopressin melt for urinary frequency (pollakiuria). There was no clear documentation of baseline serum sodium or relevant

medical history in the case report to determine if she was an appropriate candidate for this form of treatment. In addition, she was taking diuretic agents which are currently contraindicated for concomitant use with desmopressin and the dose was much higher than should have been recommended in women from the current safety information.

The cumulative exposure of desmopressin melt (all indications) up to 2011 is estimated to be (b) (4) patient-years, assuming a daily dose of 120 µg. Estimating that the rate of use for the nocturia indication was 10 to 20% that would correspond to a cumulative exposure of (b) (4) million patient-years, and the 22 cases of hyponatremia observed in adults for indications other than diabetes insipidus would correspond to event rates of 1 case per (b) (4) patient-years of treatment, with one death per (b) (4) million patient-years. As with all estimates from spontaneous reports these event rates are probably at least 10 fold underestimates of the true rate but that would still represent a very low rate, and these event rates were seen in patients given much higher doses of the melt formulation than would be currently recommended by this medical officer's analysis of the data in this submission. Note the approved doses in over 70 countries worldwide for nocturia are 60 to 240 µg of the melt formulation or 0.1 to 0.4 mg of the tablet. In addition, there is no current recommendation for measuring baseline serum sodium in such patients nor for additional monitoring in men over age 65, which would further limit the number of events of hyponatremia that are seen. On the other hand, it can be argued that use in pts over 65 years of age may have been significantly restricted by the fact that the nocturia indication was approved only for pts under 65 years of age, assuming most physicians were strictly following the labeling recommendations, and that this may partially explain the low event rate seen in elderly pts. Taking all this information into account it is this medical officer's conclusion that the current post marketing data would support the safety of desmopressin melt for the treatment of adult nocturia at doses of 25 µg in women and 50 µg in men with appropriate serum sodium monitoring.

9 Appendices

9.1 Literature Review/References

See the original NDA submission for a review of the literature with respect to the indication of nocturia.

Placebo effects in clinical trials - more questions than answers. Enck P, Weimer K, Horing B, Klosterhalfen S, Zipfel S: *Phil Trans Roy Soc B* 2011, **366**:1889-1895.

<http://www.bhsiclinics.com/blog/2012/02/29/placebos-and-antidepressants-deceptive-conclusions-about-deceptive-treatments>

Clinical Review
William Lubas M.D., Ph.D.
NDA 22-517 Se17 SDN19
Nocdurna (desmopressin acetate)

Gender difference in antidiuretic response to desmopressin. Am J Physiol Renal Physiol. 2011 May;300(5):F1116-22. doi: 10.1152/ajprenal.00741.2010. Epub 2011 Mar 2. Juul KV, Klein BM, Sandström R, Erichsen L, Nørgaard JP.

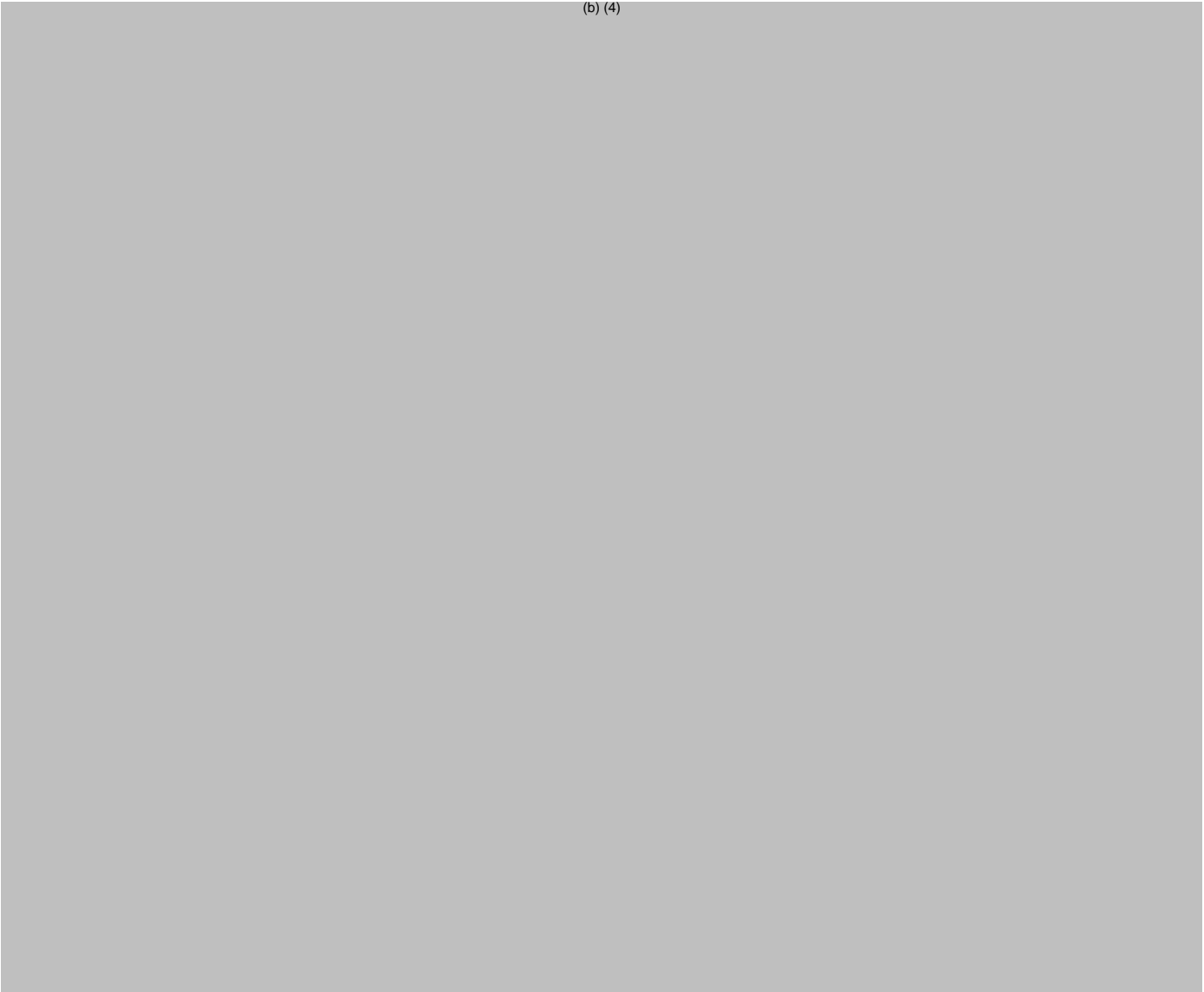
Causes and management of hyponatremia. Palmer BF, Gates JR, Lader M. Ann Pharmacother. 2003 Nov;37(11):1694-702. Review

Hyponatremia. Al-Salman J, Kemp D, Randall D. West J Med. 2002 May;176(3):173-6.

9.2 Labeling Recommendations

The labeling recommendations are currently being negotiated with the sponsor.

(b) (4)



(b) (4)



9.3 Advisory Committee Meeting

There was no advisory committee meeting for this application.

9.4 Additional Tables and Figures

Table 29 Incidence of Markedly Abnormal Changes in Lab Values

Parameter (markedly abnormal criterion)	Placebo (N=429) n/N (%)	10 µg (N=194) n/N (%)	25 µg (N=331) n/N (%)	50 µg (N=311) n/N (%)	75 µg (N=122) n/N (%)	100 µg (N=194) n/N (%)
Hematology						
Eosinophils/Leukocytes (≥10%)	1/378 (<1)	0/135	0/266	0/235	0/118	1/133 (<1)
Hematocrit (≤0.37 for males, ≤0.32 for females) ≥0.55	3/345 (<1) 2/345 (<1)	5/126 (4) 0/126	9/252 (4) 0/252	7/226 (3) 2/226 (<1)	0/110 0/110	4/125 (3) 0/125
Hemoglobin (≤115 g/L for males, ≤95 g/L for females)	0/338	0/129	1/252 (<1)	0/225	0/105	0/125
Lymphocytes/Leukocytes (≤10%)	2/353 (<1)	0/118	2/234 (<1)	0/227	0/117	0/118
MCH (≤25 pg)	0/331	0/124	1/254 (<1)	0/228	0/102	0/123
MCHC (≤18.62 mmol/L)	6/285 (2)	0/136	3/217 (1)	10/211 (5)	7/74 (9)	0/135
MCV (≥105 fL)	9/360 (3)	0/119	2/255 (<1)	7/233 (3)	8/107 (7)	0/118
Monocytes/Leukocytes (≥20%)	0/360	0/126	0/238	1/226 (<1)	1/112 (<1)	0/118
Red blood cells (≤3.5 × 10 ¹² /L)	0/343	1/125 (<1)	0/251	0/233	0/110	0/129
Clinical Chemistry						
Direct Bilirubin (≥8.55 µmol/L)	0/373	1/131 (<1)	1/264 (<1)	0/242	0/118	0/130
Bilirubin (≥1.5 × ULN)	1/386 (<1)	0/137	0/271	0/248	1/119 (<1)	0/135
BUN (≥10.7 mmol/L)	2/359 (<1)	0/135	1/264 (<1)	3/238 (1)	0/112	1/133 (<1)
Chloride (≤90 mmol/L)	0/388	0/138	0/274	1/247 (<1)	0/119	1/135 (<1)
GGT (>3 × ULN)	0/334	0/127	2/253 (<1)	0/221	0/106	0/130
Glucose ≤2.8 mmol/L ≥10 mmol/L	0/321 4/321 (1)	0/99 0/99	0/228 4/228 (2)	1/177 (<1) 7/177 (4)	0/110 4/110 (4)	0/86 0/86
Potassium ≤3.0 mmol/L ≥5.8 mmol/L	0/373 3/373 (<1)	0/138 0/138	1/260 (<1) 0/260	0/235 0/235	0/112 0/112	0/131 1/131 (<1)
Phosphate (≤0.5 mmol/L)	0/385	0/136	0/262	0/233	1/115 (<1)	0/131
Urate (≥0.62 mmol/L for males, ≥0.51 mmol/L for females)	0/368	1/132 (<1)	0/254	2/239 (<1)	0/112	0/133

Note: Some subjects received different doses and are in more than 1 dose group.

Note: Only rows for which at least 1 subject had a markedly abnormal value are presented. Only subjects with a normal baseline value and at least 1 markedly abnormal post-baseline value are included.

BUN=blood urea nitrogen; GGT=gamma-glutamyl transferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; ULN=upper limit of normal

Cross-reference: [Table 7.2.2.11]

Source Table 37 ISS

Table 30 Serum Sodium Values at Baseline and at the Last Visit in the 3-Month Study Period (Safety Analysis Set)

Sodium (mmol/L)

	Placebo		10 µg		25 µg		50 µg		75 µg		100 µg	
	Abs. value	Change from BL	Abs. value	Change from BL	Abs. value	Change from BL	Abs. value	Change from BL	Abs. value	Change from BL	Abs. value	Change from BL
Safety Analysis Set	429		194		331		311		122		194	
Baseline												
N	424		187		322		304		122		189	
Mean	140		139		140		140		140		139	
SD	2.31		2.27		2.24		2.37		2.25		2.24	
Median	140		139		140		139		140		139	
Minimum	133		131		133		133		134		133	
Maximum	151		145		147		148		148		147	
Last Visit**												
N	421		181		318		301		122		180	
Mean	140	0.0641	139	-0.204	139	-0.528	139	-1.07	139	-0.73	138	-1.59
SD	2.36	2.32	2.38	2.48	2.76	2.54	3.48	3.25	2.47	2.48	3.76	3.59
Median	140	0	139	0	139	0	139	-1	140	-1	139	-1
Minimum	121	-16	129	-7	126	-11	120	-17	130	-10	120	-15
Maximum	147	6	144	7	145	6	146	6	145	4	143	8
Mean % change*		0.0449		-0.15		-0.385		-0.784		-0.524		-1.16

BL = Baseline

* Based on the geometric mean of the ratio of the post-baseline to baseline value

** Last scheduled post-baseline measurement within 3 months study period

Note : Some subjects have received different doses and are in more than one dose-group.

FE992026/NOCT/ECTD/REPORT/14JUN2012-LEVC/LB_BY_VISIT.sas

Source Table 7.2.11 ISS

Table 31 Treatment Emergent AEs by Gender

Treatment-Emergent Adverse Events With At Least a 2% Incidence and Two-Fold Difference in Incidence Between Males and Females in Any Treatment Group (Safety Analysis Dataset)

System Organ Class MedDRA Preferred Term	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		100 µg n (%)	
	Males (n=236)	Females (n=193)	Males (n=101)	Females (n=93)	Males (n=112)	Females (n=219)	Males (n=222)	Females (n=89)	Males (n=105)	Females (n=89)
Any adverse event	104 (44)	92 (48)	65 (64)	57 (61)	70 (63)	111 (51)	116 (52)	64 (72)	71 (68)	62 (70)
Eye Disorders										
Dry eye	0	0	3 (3)	1 (1)	0	2 (<1)	0	0	0	0
Gastrointestinal Disorders										
Dry mouth	29 (12)	26 (13)	37 (37)	28 (30)	31 (28)	29 (13)	35 (16)	29 (33)	31 (30)	25 (28)
Diarrhoea	6 (3)	4 (2)	2 (2)	3 (3)	4 (4)	9 (4)	6 (3)	6 (7)	1 (<1)	2 (2)
Nausea	1 (<1)	3 (2)	2 (2)	3 (3)	2 (2)	6 (3)	2 (<1)	7 (8)	5 (5)	4 (4)
Abdominal discomfort	0	2 (1)	4 (4)	1 (1)	1 (<1)	3 (1)	2 (<1)	0	4 (4)	0
Gastroesophageal reflux disease	0	0	0	0	0	1 (<1)	0	1 (1)	1 (<1)	3 (3)
Infections and Infestations										
Urinary tract infection	0	11 (6)	0	3 (3)	1 (<1)	5 (2)	6 (3)	1 (1)	1 (<1)	3 (3)
Upper respiratory tract infection	3 (1)	8 (4)	2 (2)	2 (2)	4 (4)	6 (3)	4 (2)	4 (4)	3 (3)	4 (4)
Nasopharyngitis	7 (3)	5 (3)	2 (2)	4 (4)	5 (4)	5 (2)	4 (2)	1 (1)	3 (3)	4 (4)
Metabolism and Nutrition Disorders										
Hyponatraemia	1 (<1)	2 (1)	1 (<1)	1 (1)	0	5 (2)	5 (2)	4 (4)	6 (6)	5 (6)
Musculoskeletal and Connective Tissue Disorders										
Muscle spasms	3 (1)	2 (1)	1 (<1)	3 (3)	2 (2)	4 (2)	3 (1)	2 (2)	2 (2)	3 (3)
Nervous System Disorders										
Headache	10 (4)	8 (4)	7 (7)	7 (8)	8 (7)	10 (5)	11 (5)	11 (12)	6 (6)	9 (10)
Psychiatric Disorders										
Insomnia	1 (<1)	1 (<1)	5 (5)	2 (2)	1 (<1)	1 (<1)	6 (3)	3 (3)	3 (3)	2 (2)
Respiratory, Thoracic and Mediastinal Disorders										
Cough	2 (<1)	0	0	1 (1)	4 (4)	2 (<1)	3 (1)	2 (2)	1 (<1)	6 (7)
Oropharyngeal pain	3 (1)	1 (<1)	1 (<1)	4 (4)	0	2 (<1)	2 (<1)	2 (2)	0	1 (1)

Note: Some subjects received different doses and are in more than 1 dose group.

Note: The 75 µg dose group is not presented since it was administered to male subjects only.

MedDRA=Medical Dictionary for Regulatory Activities

Cross-reference: [Table 1.1.1.]

Source Table 39 ISS

Table 32 Treatment Emergent AEs by Age

Treatment-Emergent Adverse Events With At Least a 2% Incidence and Two-Fold Difference in Incidence Between Age Groups in Any Treatment Group (Safety Analysis Dataset)

System Organ Class MedDRA Preferred Term	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		75 µg n (%)		100 µg n (%)	
	Age Group in Years:											
	<65 (n=224)	≥65 (n=105)	<65 (n=103)	≥65 (n=91)	<65 (n=167)	≥65 (n=164)	<65 (n=165)	≥65 (n=146)	<65 (n=63)	≥65 (n=59)	<65 (n=92)	≥65 (n=102)
Any adverse event	95 (42)	101 (49)	64 (62)	58 (64)	90 (54)	91 (55)	97 (59)	83 (57)	20 (32)	29 (49)	59 (64)	74 (73)
Eye Disorders												
Dry eye	0	0	1 (<1)	3 (3)	0	2 (1)	0	0	0	0	0	0
Gastrointestinal Disorders												
Diarrhoea	4 (2)	6 (3)	4 (4)	1 (1)	6 (4)	7 (4)	6 (4)	6 (4)	2 (3)	2 (3)	3 (3)	0
Nausea	2 (<1)	2 (<1)	2 (2)	3 (3)	7 (4)	1 (<1)	5 (3)	4 (3)	2 (3)	1 (2)	2 (2)	7 (7)
Abdominal discomfort	0	2 (<1)	3 (3)	2 (2)	3 (2)	1 (<1)	1 (<1)	1 (<1)	0	0	1 (1)	3 (3)
General Disorders and Administration Site Conditions												
Fatigue	1 (<1)	2 (<1)	2 (2)	7 (8)	1 (<1)	1 (<1)	0	6 (4)	1 (2)	1 (2)	1 (1)	3 (3)
Oedema peripheral	0	4 (2)	1 (<1)	2 (2)	0	2 (1)	3 (2)	1 (<1)	1 (2)	4 (7)	3 (3)	2 (2)
Infections and Infestations												
Nasopharyngitis	8 (4)	4 (2)	5 (5)	1 (1)	3 (2)	7 (4)	3 (2)	2 (1)	2 (3)	2 (3)	4 (4)	3 (3)
Upper respiratory tract infection	7 (3)	4 (2)	1 (<1)	3 (3)	8 (5)	2 (1)	6 (4)	2 (1)	1 (2)	1 (2)	5 (5)	2 (2)
Urinary tract infection	7 (3)	4 (2)	1 (<1)	2 (2)	2 (1)	4 (2)	1 (<1)	6 (4)	0	0	1 (1)	3 (3)
Investigations												
Blood sodium decreased	0	1 (<1)	0	2 (2)	1 (<1)	1 (<1)	0	5 (3)	0	2 (3)	1 (1)	7 (7)
Metabolism and Nutrition Disorders												
Hyponatraemia	1 (<1)	2 (<1)	1 (<1)	1 (1)	1 (<1)	4 (2)	5 (3)	4 (3)	2 (3)	3 (5)	3 (3)	8 (8)
Musculoskeletal and Connective Tissue Disorders												
Arthralgia	1 (<1)	4 (2)	1 (<1)	1 (1)	1 (<1)	6 (4)	1 (<1)	1 (<1)	0	0	0	2 (2)
Muscle spasms	2 (<1)	3 (1)	1 (<1)	3 (3)	3 (2)	3 (2)	2 (1)	3 (2)	0	0	0	5 (5)
Nervous System Disorders												
Headache	11 (5)	7 (3)	9 (9)	5 (5)	6 (4)	12 (7)	10 (6)	12 (8)	5 (8)	2 (3)	7 (8)	8 (8)
Dizziness	1 (<1)	1 (<1)	2 (2)	5 (5)	2 (1)	3 (2)	5 (3)	6 (4)	1 (2)	0	1 (1)	6 (6)
Psychiatric Disorders												
Insomnia	1 (<1)	1 (<1)	3 (3)	4 (4)	1 (<1)	1 (<1)	6 (4)	3 (2)	0	0	2 (2)	3 (3)
Respiratory, Thoracic and Mediastinal Disorders												
Cough	0	2 (<1)	0	1 (1)	2 (1)	4 (2)	4 (2)	1 (<1)	0	0	2 (2)	5 (5)

Note: Some subjects received different doses and are in more than 1 dose group.

MedDRA=Medical Dictionary for Regulatory Activities

Cross-reference: [Table 7.1.1.8]

Source Table 40 ISS

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/s/

WILLIAM A LUBAS
01/23/2013

DRAGOS G ROMAN
01/23/2013

Clinical Pharmacology Memorandum

Memo Date: December 26, 2012

Subject: Complete Response Resubmission (SN-0017)

NDA: 22517 (SN-0017) NOCDURNA™
[(desmopressin) Oral Disintegrating
Sublingual Tablets]

Sponsor Ferring Pharmaceuticals Inc.

Formulation Oral Disintegrating Sublingual Tablets

Indication NOCDURNA is indicated for treatment of
nocturia in adults

Proposed Dosing Women: 25 mcg daily, one hour before
bedtime, administered sublingually without
water
Men: 50 mcg daily, one hour before bedtime,
administered sublingually without water

**Clinical Pharmacology
Reviewer** Ritesh Jain, Ph.D.

Pharmacometrics Reviewer Anshu Marathe, Ph.D.

**Pharmacometrics Team
Leader (Acting)** Nitin Mehrotra, Ph.D.

**Clinical Pharmacology Team
Leader** Immo Zadezensky, Ph.D.

1. Recommendation: Studies submitted under this complete response resubmission of NDA 22517 are intended to support the use of 25 µg Nocdurna™ dose in women and 50 µg Nocdurna™ dose in men. The Office of Clinical Pharmacology finds this resubmission NDA 22517/SN-0017 acceptable from a Clinical Pharmacology standpoint.

2. Background: Ferring Pharmaceuticals Inc. is developing orally disintegrating sublingual tablets of desmopressin (Nocdurna™) for the treatment of nocturia in adults. The NDA for Nocdurna™ was originally submitted on 06/19/2009 as a 505(b)(2) application. The Agency on 04/22/2010 informed the Sponsor in the Complete Response (CR) letter that the application is not approvable in its present form because of the several clinical, clinical pharmacology and nonclinical issues.

The Office of Clinical Pharmacology did not agree with the sponsor's proposed dose of 100 µg in men during the original submission and proposed alternative starting dose of 50 µg with an option of dose titration up to 100 µg only for men <65 years of age. No dose escalation was allowed for men ≥ 65 years of age. This recommendation was based on the efficacy and safety data from trials CS 29 and CS 31. The sponsor in this current submission conducted separate placebo-controlled confirmatory trials, CS40 and CS41 in women and men at lower doses. The 25 µg dose was studied in women and dose levels of 50 and 75 µg were studied in men. Summary of clinical pharmacology findings are discussed in section 4.

In the CR letter, the following comments were sent to the sponsor concerning Clinical Pharmacology:

The pharmacokinetic information of the to-be-marketed formulation including the bioequivalence study (CS019) was derived using an analytical method that was not properly validated. In order to address this deficiency, you should:

- ***Reanalyze the bioequivalence study (CS019) pharmacokinetic samples with a validated analytical method and submit the data to the Agency for review, or***
- ***Collect the pharmacokinetic samples in future clinical trials and make every effort to improve and properly validate the bioanalytical method to analyze study samples at the proposed dose strength(s).***

However, during the end of review meeting the Sponsor brought into attention that pharmacokinetic (PK) samples from the relative bioavailability study, CS019, were no longer available and Office of New Drug Quality Assessment (ONDQA) biopharmaceutics reviewer granted a biowaiver for the PK evaluation of lower dose strengths during the IND stages. At the end of review meeting, we agreed with the Sponsor that biowaiver is still valid and they do not need assess PK at the proposed dose strengths. We also reminded that since the assay used for the PK samples in CS019 was not valid, it does not have a clinical bridge to satisfy requirements for the 505(b)(2) regulatory pathway for NDA approval. To satisfy the clinical bridge of the new product to any listed desmopressin products, in the current submission, the Sponsor provided a 1-month bridging toxicity and toxicokinetics study in dogs. In addition, the sponsor in this current submission conducted two placebo-controlled

confirmatory trials, CS40 and CS41 in women and men at lower doses. The 25 µg dose was studied in women and dose levels of 50 and 75 µg were studied in men.

Reviewers Comments: *Although there is no PK information with the current formulation at the proposed clinical doses, sponsor did provide the PK at higher dose strengths of a formulation very similar to the proposed to be marketed formulation. Please see Clinical Pharmacology review of the original submission DARRTS date 03/30/2010 for detailed discussion on the difference in two formulations. In addition, in this NDA Sponsor used to be marketed formulation in their pivotal Phase 3 trials and demonstrated a clear dose response relationship suggesting that the drug is bioavailable at the proposed dose strengths. Thus, the efficacy and clear dose response in the Phase 3 trials with the to be marketed formulation can be used as surrogate for the bioavailability of the drug.*

3. Summary of Clinical Pharmacology Findings of the Original Submission:

In the original submission, the clinical development program for this NDA is supported by one Phase 3 safety and efficacy trial (FE992026 CS29) and 17 clinical pharmacology trials. The Phase 3 trial was conducted in 2 parts. Part I was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study investigating the efficacy and safety of 4 doses (10 µg, 25 µg, 50 µg, or 100 µg) of desmopressin melt administered for 28 days for the treatment of adult nocturia. There were two co-primary endpoints. The first co-primary endpoint was change from baseline in the mean number of nocturnal voids, and the second was proportion of subjects with > 33% reduction in the mean number of nocturnal voids (referred as 33% responder rate), on Day 28 of the trial. In the original submission the sponsor planned to market Nocdurna™ in two dosage strengths 25 µg and 100 µg. The sponsor proposed the following gender-based Nocdurna™ doses:

- Women: 25 µg sublingual tablet, once daily at bedtime
- Men < 65: 100 µg sublingual tablet, once daily at bedtime.
- Men ≥ 65: 100 µg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment.

During our original review in the first cycle of this NDA, upon reanalysis of both efficacy and safety data, we recommend the following dosing regimen for Nocdurna™:

- 1) 25 µg QD for women.
- 2) 50 µg as the starting dose in men. The dose may be titrated up to 100 µg dose by weekly dose escalations in 25 µg increments only for men less than 65 years to optimize efficacy.
- 3) Dose escalation above the 50 µg starting dose for elderly men (age ≥ 65 years) is not recommended.

A reduced dose of 50 µg in men was recommended as the starting dose because the drug was shown to be effective by dose-response analysis. For men, the 50 µg dose showed a larger decline in the change from baseline in the mean number of nocturnal voids compared to placebo at all time points. For the 33% responder rate, the 50 µg dose shows treatment effect at all time points except on day 28 which was the pre-specified endpoint.

Based on the mechanism of action of desmopressin and the short half-life (2.8 hours) of the drug with minimal accumulation, the drug is expected to have an early onset of response which was observed in the trial. The choice of day 28 as the pre-specified endpoint was arbitrary and did not have any clinical significance.

The dose could be increased to 100 µg to meet treatment goals in men of age < 65 years as there was no incidence of hyponatremia across all doses in this age group. However, for elderly men (age ≥ 65 years), a dose-response analysis showed that the risk of hyponatremia increases with increasing desmopressin dose. At the sponsor's proposed dose of 100 µg, 20% of elderly men experienced hyponatremia. This was 4-fold higher than the proportion of elderly women who developed hyponatremia at the sponsor's proposed dose of 25 µg. Therefore, we propose 50 µg dose without titration because at this dose only 5% of the elderly men experienced hyponatremia which was comparable to elderly women at the 25 µg dose and the placebo hyponatremia rate (for details see Clinical Pharmacology review 03/30/2010).

4. Summary of Clinical Pharmacology Findings of the Current Submission:

To address the deficiencies cited in the complete response letter, in this resubmission to the complete response, Ferring conducted two placebo-controlled confirmatory trials, CS40 and CS41 in women and men for treatment of adult nocturia, at lower doses. Sponsor used proposed to be marketed formulation in these Phase 3 trials. In this resubmission no new information was submitted that requires Clinical Pharmacology assessment. Two Phase 3 trials submitted with this re-submission studied the 25 µg dose in women and dose levels of 50 and 75 µg in men. Unlike the previous submission where the co-primary endpoints were assessed on day 28, the co-primary endpoints in CS40 and CS41, change from baseline in the mean number of nocturnal voids and the proportion of subjects with >33% reduction in the mean number of nocturnal voids were assessed longitudinally over 3 months of treatment. Figure 1 shows the adjusted change from baseline in mean number of nocturnal voids during the 3 month of treatment in women and men. There is a separation between the placebo and the 25 µg dose group in women. There is a separation between the placebo and the treatment arms (50 and 75 µg dose groups) in men. The onset of drug action is seen in both women and men as early as week 1. There is no difference in the adjusted change from baseline in mean number of nocturnal voids between the 50 and 75 µg dose groups in men. Similarly there is no difference in the responder rate for the 50 and 75 µg dose groups in men (Figure 2).

There is dose-dependent increase in incidence of hyponatremia in women and men. The incidence of serum sodium values <130 mmol/L in women increased from <1%, 1%, and 3% in the placebo, 10 µg, and 25 µg groups, respectively, to 9% and 11% in the 50 µg and 100 µg groups. The only desmopressin dose group with a serum sodium value ≤125 mmol/L in females was 50 µg (4 subjects; 5%). The incidence of serum sodium values <130 mmol/L in men increased from 0%, 1%, <1%, and 2% in the placebo, 10 µg, 25 µg, and 50 µg groups, respectively, to 7% and 9% in the 75 µg and 100 µg groups. Three (1%) subjects in the 50 µg group, 4 (3%) subjects in the 75 µg group, and 2 (2%) subjects in the 100 µg group had a serum sodium value ≤125 mmol/L.

Since there is a dose dependent increase in hyponatremia and 25 and 50 µg doses are shown to be the minimum effective doses in women and men respectively in phase 3 trials, the sponsor's proposed dose of 25 µg in women and 50 µg in men is reasonable from a dose-response perspective. However, the benefit to risk ratio of desmopressin for the treatment of nocturia at these dose levels is deferred to the Clinical Division.

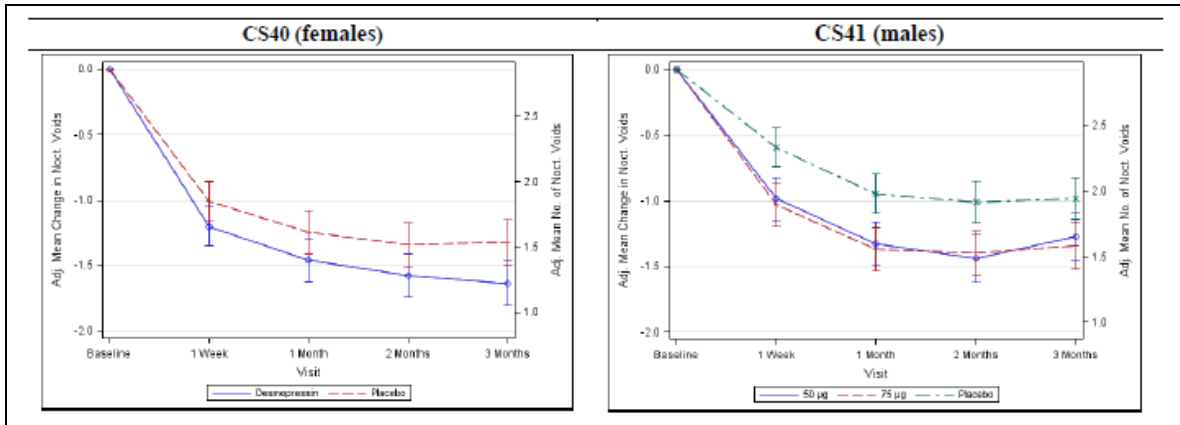


Figure 1: Adjusted change from baseline during 3 months of treatment in mean number of nocturnal voids in women (study CS40) and men (study CS41). *Source: Figure 4 from sponsor's summary of clinical efficacy report.*

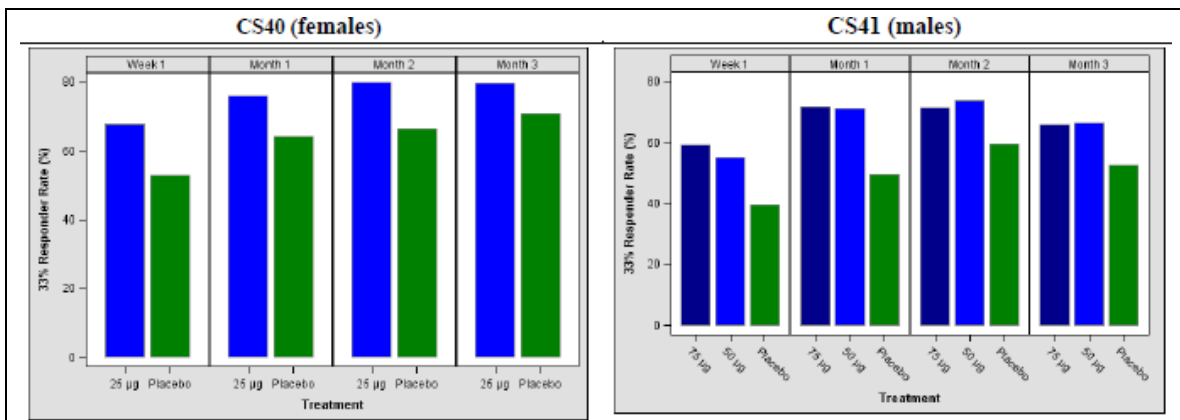


Figure 2: Adjusted 33% responder rate by treatment group and visit in women (study CS40) and men (study CS41). *Source: Figure 5 from sponsor's summary of clinical efficacy report.*

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/s/

RITESH JAIN
01/15/2013

ANSHU MARATHE
01/15/2013

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01/15/2013

IMMO ZADEZENSKY
01/16/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 22-517
Supporting document/s: 0017/ Resubmission
Applicant's letter date: July 30, 2012
CDER stamp date: July 30, 2012
Product: NOCDURNA™ (Desmopressin Sublingual Melt)
Indication: Treatment of nocturia in adults
Applicant: Ferring Pharmaceuticals Inc.
Review Division: DMEP
Reviewer: Parvaneh Espandiari, Ph.D
Supervisor/Team Leader: Karen Davis Bruno, Ph.D
Division Director: Mary Parks, MD
Project Manager: Jennifer Johnson

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22,517 are owned by Ferring Pharmaceuticals Inc. or are data for which Ferring Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22,517 that Ferring Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Ferring Pharmaceuticals Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22,517.

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1 Executive Summary

1.1 Introduction

NOCDURNA is being developed by Ferring Pharmaceuticals INC for the treatment of nocturia in adults as a new formulation (oral disintegrating tablets) for sublingual use. The NDA was originally submitted on 06/19/2009 as a 505(b)(2) application. The Sponsor referred to DDAVP® (Desmopressin acetate Tablets (NDA19-955), Desmopressin Acetate Nasal Spray (NDA 21-333), Desmopressin Acetate Tablets (NDA 21-795) and DMF 8396.

The Agency informed the Sponsor in the Complete Response letter dated on 04/22/2010 that the application cannot be approved in its present form because of the absence of adequate data to bridge the new product to any listed desmopressin products. Therefore, in the current submission, the Sponsor provided a 1-month bridging toxicity study in dogs with toxicokinetics to fulfill the nonclinical deficiency noted in the Complete Response letter issued.

1.2 Brief Discussion of Nonclinical Findings

Findings from a 1-month bridging toxicity study in dogs suggested the toxicological findings and the TK data with NOCDURNA were similar to DDAVP (RLD) and also were consistent with the pharmacological effects of the desmopressin. Study results showed no sex differences with the TK data and similarity in level of desmopressin levels in two compounds ($2 \times 200\mu\text{g}$ DDAVP tablets vs. $1 \times 240\mu\text{g}$ desmopressin orally disintegrating tablets).

In addition, results of previous non-clinical studies suggested the safe use of desmopressin via the sublingual route based on no evidence of any local reactions or any histopathological changes related to the test article in the cheek pouch of Syrian hamsters for 28 days. Findings of impurity qualification studies (a 13-week repeat-dose study in rats and two genotoxicity studies) suggested no new toxicities or potential of any genotoxicity with impurities. The NOAEL was established at HD ($10\mu\text{g}/\text{kg}/\text{day}=1\text{xMRHD}$) in the 13-week repeat-dose study in rats.

1.3 Recommendations

1.3.1 Approvability

P/T recommends approval of this application.

1.3.2 Additional Non Clinical Recommendations

No further studies are required.

1.3.3 Labeling

Section 8.1 Pregnancy

Category B:

Fertility studies have not been done. Teratology studies in rats and rabbits at doses 0.05-10 mcg/kg/day (approximately the human exposure in rats and 200-times higher exposure in rabbits, based on body surface area mg/m^2) revealed no harm to the fetus due to desmopressin. There are, however, no adequate and well controlled studies in

pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential or effects on fertility. Desmopressin was not mutagenic or clastogenic with or without metabolic activation in the Ames test for bacterial mutagenicity or the in vitro mouse lymphoma assay.

2 Drug Information

2.1 Drug

CAS Registry Number

16679-58-6

Generic Name

Desmopressin, arginine vasopressin

Proposed Trade Name

NOCDURNA (Desmopressin Sublingual Melt)

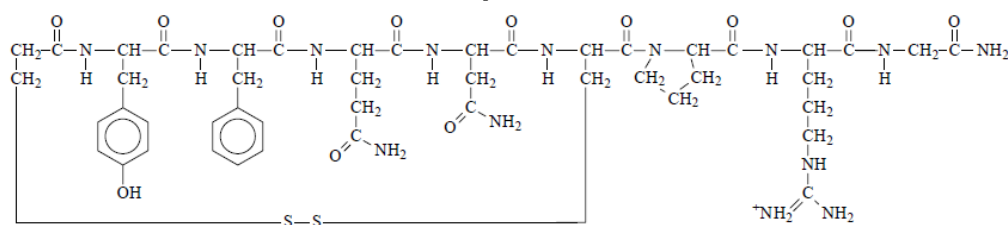
Chemical Name

1-deamino-8-D-arginine vasopressin

Molecular Formula/Molecular Weight

C₄₆H₆₄N₁₄O₁₂S₂•C₂H₄O₂•3H₂O/1183.34

Structure or Biochemical Description



Pharmacologic Class

Arginine vasopressin (synthetic anti-diuretic hormone analogue)

Planned Clinical Route of Administration

Sublingual administration

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDAs: 19955; 21333; 21795

IND 65890

DMF 8396

2.3 Drug Formulation

Each orally disintegrating tablet contains desmopressin acetate equivalent to 25 mcg and 50 mcg of desmopressin as free base. The inactive ingredients are gelatin, mannitol, and anhydrous citric acid. The proposed dosing regimens are for women 25µg daily and for men 50µg daily (in the 1st submission the proposed dose for men was up to 100µg daily).

Desmopressin Melt 25µg:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.025 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 25 µg desmopressin free base.

Desmopressin Melt 50µg:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.050 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 50 µg desmopressin free base.

2.7 Regulatory Background

Desmopressin has been marketed since 1972 in different formulations such as intranasal, intravenous, and oral formulations for the treatment of diabetes insipidus and primary nocturnal enuresis.

Regulatory background is summarized below:

- Originally, NDA was submitted as a 505(b)2 application on Jun 19, 2009 for Orally Disintegrating Tablets(25 mcg and 100 mcg).
- FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements in bioanalytical studies conducted by Cetero Research in Houston (April 1, 2005 until June 15, 2010). Therefore, the FDA informed the Sponsor that the applications can not be approved for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

- On April 22, 2012, in the Complete Response letter from the FDA, a bridging Tox study of one month duration comparing the new product to the RLD was suggested to the Sponsor: See nonclinical section of the CR letter:

NONCLINICAL

3. The nonclinical data you have provided qualify impurities new to this formulation and assess local toxicity. There are no nonclinical data provided to bridge to any listed desmopressin product. This bridge was supposed to be provided by the clinical bioequivalence study which utilized an analytic method that was not properly validated. In the absence of adequate clinical bridging information a comparative toxicology study of one month duration comparing your product to the listed drug product is needed.
- Currently, the NDA was resubmitted (July 30, 2012) for Orally Disintegrating Tablets (25 mcg and 50 mcg) with a 1-month bridging tox study in dogs.

3 Studies Submitted

3.1 Studies Reviewed

A 1-month bridging toxicity study in dogs

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

In DARRTS: P/T review # 1 and 1st submission NDA review

4 Pharmacology

Desmopressin is a synthetic analogue of antidiuretic hormone (Vasopressin). Its antidiuretic effects are mediated by stimulation of vasopressin 2 (V2) receptors; therefore, increasing water re-absorption in the kidney, and consequently reducing urine production.

The demonstration of pharmacological activity of desmopressin SML is based on referenced data; therefore, no additional pharmacology studies were conducted with desmopressin SLM.

4.1 Primary Pharmacology

No new information

4.2 Secondary Pharmacology

No new information

4.3 Safety Pharmacology

No new information

5 Pharmacokinetics/ADME/Toxicokinetics

The sponsor previously submitted PK studies in rats and domestic pigs to evaluate the bioavailability of desmopressin when administered via sublingual route. These studies were reviewed (P/T review#1 in DARRTS); and results suggested that desmopressin SLM (via sublingual route) had greater bioavailability (C_{max} , T_{max} , AUC and AUC/dose), about two-fold, compared to the referenced product (via oral).

6 General Toxicology

A 1-month bridging toxicity study in dogs was conducted to evaluate TK in animals that were exposed to the new product, Desmopressin Melt oral disintegrating tablets (ODT), or the RLD (desmopressin tablets).

DDAVP Tablets & Desmopressin Orally Disintegrating Tablets 1-Month Bridging Toxicity Study in Dogs	
Study #	72837
Study report location	(b) (4)
CRO/Laboratory name	(b) (4)
Date of study initiation	January 24, 2011
GLP compliance statement	Yes
GLP issues identified	No
QA statement	Yes
Drug, lot #, and % purity	DDAVP tablets (batch number: BE1891A); orally disintegrating desmopressin tablets (batch number 952458, 95.5%); placebo (batch number 1033643)

Key Study Findings

- The values of serum bilirubin were increased in two ODT desmopressin treated females (2/4) with no other-related changes. One of these females had a high bilirubin at baseline.
- TK data suggested no sex differences and similarity in level of desmopressin levels for both compounds (2 × 200 µg DDAVP tablets vs. 1 × 240 µg desmopressin orally disintegrating tablets).

Methods	
Doses	0 µg/animal (placebo orally disintegrating tablets); 400 µg/animal DDAVP (2 tablets of 200 µg); 240 µg/animal desmopressin (orally disintegrating tablet)
Frequency of dosing	daily for at least 28 days
Route of administration	DDAVP tablets: orally Desmopressin and placebo (orally disintegrating tablets): sublingually
Dose volume	N/A
Formulation/Vehicle	orally disintegrating placebo tablet
Species/Strain	Beagle dogs
Number/Sex/Group	4/sex/group
Age	6 to 7 months old
Weight	Males: 6.5 and 9.7 kg; Females: 6.1 and 7.9 kg
Satellite groups	None
Unique study design	None
Deviation from study protocol	None

Group	Test item	Dose concentration* (µg/tablet)	Dose * (µg/animal)	Animal Nos		Colour code
				Male	Female	
1	Placebo orally disintegrating tablet	0	0	1, 102, 3-4	5-8	White
2	DDAVP tablet	200	400	9-12	13-16	Blue
3	Desmopressin orally disintegrating tablet	240	240	17-20	21-24	Green

*Material as supplied

Reviewer: Females were exposed to the higher level of compounds due the lower mean body weights (400 µg of DDAVP in males was ~47-51 µg/kg/day and in females ~53-56 µg/kg/day; and 240 µg of desmopressin was ~28-29 µg/kg/day in males and ~32-34 µg/kg/day in females). According to the sponsor, the human bioavailabilities of desmopressin were used for adjusting the anticipated exposure, which were for the tablets was ~0.15%, and in the orally disintegrating tablet was ~0.25%. In dogs, the bioavailability of desmopressin for DDAVP tablets was ~0.85% and for the desmopressin orally disintegrating tablet was not known.

Observations and Results

Mortality

Animals were observed for any visible signs of ill health daily.
All animals survived to the end of the study.

Clinical Signs

Animals were observed daily for any visible signs of ill health or behavioral changes.
Results were not remarkable.

Body Weights

Animals were weighed once weekly, including first and last days of the study.

The groups mean body weight gain during the study was comparable across treatment groups.

Feed Consumption

From Day -7 to the end of the study, the consumption of food was estimated daily for each animal by weighing unconsumed diet ~2 hours after feeding.

Results were not remarkable.

Hematology

Blood samples were taken from all fasted overnight animals through jugular vein. See Table below from the Sponsor for parameters that were measured.

Table 2 Haematology and coagulation parameters

Parameter	Method/Equipment	Unit
Haemoglobin (Hb)	Direct measurement/ABX Pentra DX120SPS	mmol/l
Red blood cell count (RBC)	Direct measurement/ABX Pentra DX120SPS	10 ¹² /l
Reticulocyte count (RETIC)	Direct measurement/ABX Pentra DX120SPS	% and 10 ¹² /l
Haematocrit (HT)	Direct measurement/ABX Pentra DX120SPS	ml/100 ml
Mean cell volume (MCV)	Calculated/ABX Pentra DX120SPS	fl
Mean cell haemoglobin (MCH)	Calculated/ABX Pentra DX120SPS	fmol
Mean cell haemoglobin concentration (MCHC)	Calculated/ABX Pentra DX120SPS	mmol/l
White blood cell count (WBC)	Direct measurement/ABX Pentra DX120SPS	10 ⁹ /l
Differential leucocyte count (NEUTRO, LYMPHO, EOS, BASO, MONO)	Direct measurement/ABX Pentra DX120SPS	% and 10 ⁹ /l
Platelet count (Plt)	Direct measurement/ABX Pentra DX120SPS	10 ⁹ /l
Activated partial thromboplastin time (APTT)	IL Test™/ACL™(*)	sec.
Prothrombin time modified (Pt-m)	Modified IL Test™/ACL™(*)	sec.
Fibrinogen (Fib)	IL Test™/ACL™(*)	g/l

(* Instrumentation Laboratories, Automated Coagulation Laboratory)

Results were not remarkable.

Clinical Chemistry

Blood samples (~3 ml) were taken from all animals for clinical chemistry before start of treatment and before termination of treatment. See Table below for parameters that were measured.

Table 3 Clinical chemistry

Parameter	Method/Equipment	Unit
Alanine aminotransferase (ALAT)	Hitachi 917	µkat/l
Aspartate aminotransferase (ASAT)	Hitachi 917	µkat/l
Alkaline phosphatase (ALKPH)	Hitachi 917	µkat/l
Bilirubin (total) (TBILI)	Hitachi 917	µmol/l
Gamma-glutamyl transferase (GGT)	Hitachi 917	µkat/l
Cholesterol (CHOL)	Hitachi 917	mmol/l
Triglycerides (TRIG)	Hitachi 917	mmol/l
Carbamide (UREA)	Hitachi 917	mmol/l
Creatinine (CREAT)	Hitachi 917	µmol/l
Glucose (GLUC)	Hitachi 917	mmol/l
Sodium (Na)	Ion selective electrode/Hitachi 917	mmol/l
Potassium (K)	Ion selective electrode/Hitachi 917	mmol/l
Calcium (Ca)	Hitachi 917	mmol/l
Magnesium (Mg)	Hitachi 917	mmol/l
Inorganic phosphorus (P)	Hitachi 917	mmol/l
Chloride (Cl)	Ion selective electrode/Hitachi 917	mmol/l
Protein (total) (PROTEIN)	Hitachi 917	g/l
Albumin (ALB)	Hitachi 917	g/l
Globulin	Calculated	g/l
Albumin/Globulin (ALB/G) ratio	Calculated	No unit

In females treated with desmopressin, total bilirubin levels increased (ss) in 2 females with no other related changes in injury markers for liver or renal.

See Tables below from the Sponsor for mean and individual values:

GROUP (Dose)	TBILI			p
	Mean	S.D.	N	
1 (Placebo, 0 µg)	<0.95	>0.39	4	
2 (DDAVP, 400 µg)	1.08	0.35	4	
3 (Desmopressin, 240 µg)	1.85	0.47	4	*

Individual values	Females		
	GROUP (Dose)	Before start	At termination
		TBILI	TBILI
	ANIMAL NO	(b) (4)	
1 (Placebo, 0 µg)		[Redacted]	
2 (DDAVP, 400 µg)			
3 (Desmopressin, 240 µg)			

Reviewer: In desmopressin treated females, serum levels of bilirubin were normal in 2/4 and high in 2/4. One of the two females with elevated bilirubin had a baseline elevation prior to drug exposure. Table below showed that the higher serum levels of bilirubin in these two animals were not related to the higher level of exposure of compound. In this study, females had a higher level of exposure because they had lower mean body weights compared to males. However, drug exposure was variable in this study. The elevated serum bilirubin in high dose female dogs given desmopressin ODT appears to be incidental because:

- 1. It occurred in 1/4 female dogs given desmopressin ODT at 240ug but not with DDAVP tablets at 400ug of either gender despite similar AUC values across dosage forms. One of the 2 female dogs with the bilirubin elevation has a high background total bilirubin at baseline. This observation occurs at 240ug after 28 days in a female dogs which has systemic exposure >20X higher than anticipated at the MRHD=50ug*
- 2. The parameters that were evaluated in the bridging dog toxicology study, including TK were quite variable (limited animal numbers n=4)*

3. In the 13 week rat study, the qualitative increase in conjugated bilirubin in urine was observed in some males (4) and one female rat given SC desmopressin; however, there were no elevations in unconjugated bilirubin (plasma) in this study
4. Neither the dog or rat toxicity study showed any correlative histopathology (bile duct/liver), transaminase elevations or hematology parameters (hemolysis/anemia)

		Males TBILI													
GROUP (Dose)	ANIMAL NO	Before termination		Day 1					Day 28						
		<LOD	<LOD	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹
1 (Placebo, 0 µg)	1	<LOD	<LOD												
	102	<LOD	0.7												
	3	0.7	1.0												
	4	0.5	0.8												
2 (DDAVP, 400 µg)	9	0.9	1.4	9	675	0.5	1.20	1,041	990	9	324	0.5	1.33 ²	648	672
	10	<LOD	1.1	10	54.8	0.5	1.19 ²	107	118	10	344	1.0	1.01 ³	544	618
	11	0.8	0.9	11	251	1.0	1.16	387	353	11	122	1.0	1.28 ³	255	258
	12	<LOD	0.6	12	121	1.0	0.89 ²	218	205	12	281	0.5	1.31 ³	418	434
3 (Desmopressin, 240 µg)	17	1.4	1.0	17	242	0.5	1.25 ²	386	723	17	300	0.5	1.15 ³	489	966
	18	1.0	0.5	18	257	0.5	1.14 ³	450	694	18	252	0.5	1.18 ³	407	695
	19	0.5	1.0	19	392	0.5	1.46 ³	875	1,222	19	313	1.0	1.34 ³	701	1,007
	20	0.5	0.5	20	118	0.5	1.57 ³	393	777	20	103	2.0	1.18 ³	247	504

		Females TBILI													
GROUP (Dose)	ANIMAL NO	Before termination		Day 1					Day 28						
		<LOD	<LOD	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹
1 (Placebo, 0 µg)	5	0.8	1.1												
	6	1.2	0.8												
	7	0.8	<LOD												
	8	0.6	1.4												
2 (DDAVP, 400 µg)	13	0.7	1.2	13	160	0.5	1.42	241	190	13	150	0.5	0.89 ⁴	231	179
	14	1.4	1.5	14	110	1.0	0.84 ²	218	221	14	656	0.5	1.23 ³	892	959
	15	0.8	0.7	15	533	0.5	0.94	798	789	15	246	0.5	0.93 ²	262	262
	16	0.6	0.9	16	376	0.5	1.16	540	446	16	283	0.5	1.46 ³	384	336
3 (Desmopressin, 240 µg)	21	1.6	2.2	21	176	0.5	0.84 ²	288	414	21	661	0.5	1.19 ²	944	1,457
	22	0.9	2.3	22	96.5	0.5	0.98 ²	144	207	22	180	0.5	1.11 ³	422	634
	23	0.9	1.5	23	143	0.5	1.15 ²	180	278	23	226	1.0	1.09 ³	389	640
	24	1.4	1.4	24	371	1.0	0.98 ³	593	901	24	241	0.5	1.31 ³	403	654

Urinalysis

Urine samples were collected from all animals (housed individually in metal cages) for a period of 18 hours (±30 minutes) from early afternoon to the following morning. See Table below from the Sponsor for parameters that were measured:

Table 4 Urinalysis

Parameter	Method/Equipment	Unit/Range
Volume		ml
Specific gravity (SG)	Ames Multistix 10SG/Clinitek 500	No unit
pH	Ames Multistix 10SG/Clinitek 500	No unit
Colour (COLOUR)	Visual examination	No unit
Protein (PROTEIN)	Ames Multistix 10SG/Clinitek 500	g/l
Leucocytes (LEUC)	Ames Multistix 10SG/Clinitek 500	Cells/ μ l
Nitrite (NITRITE)	Ames Multistix 10SG/Clinitek 500	No unit
Blood (BLOOD)	Ames Multistix 10SG/Clinitek 500	Erythrocytes/ μ l
Glucose (GLUCOSE)	Ames Multistix 10SG/Clinitek 500	mmol/l
Ketones (KETONES)	Ames Multistix 10SG/Clinitek 500	mmol/l
Bilirubin (BILL)	Ames Multistix 10SG/Clinitek 500	No unit
Urobilinogen (UROBIL)	Ames Multistix 10SG/Clinitek 500	μ mol/l

Decreased urinary volume was noted in treated animals compared to control animals (more pronounced in Desmopressin treated animals compared to DDAVP treated animals). The sponsor reported that no statistical analysis was performed for the urine volume due to small number of animals in the control group (n=2). No significant differences were noted for other urinary parameters. See Tables below from the Sponsor:

Males

Before start of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	78.7	85.2	3	
2 (DDAVP, 400 μ g)	83.5	65.9	4	
3 (Desmopressin, 240 μ g)	63.8	68.1	4	

At termination of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	128.5	14.8	2	
2 (DDAVP, 400 μ g)	120.5	80.9	4	
3 (Desmopressin, 240 μ g)	104.8	59.0	4	

Group mean values Statistical group test not valid for groups with N<3

Females

Before start of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	59.5	39.6	4	
2 (DDAVP, 400 μ g)	59.5	35.4	4	
3 (Desmopressin, 240 μ g)	29.3	26.8	4	

At termination of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	115.0	7.1	2	
2 (DDAVP, 400 μ g)	103.8	30.5	4	
3 (Desmopressin, 240 μ g)	47.5	41.2	4	

Group mean values Statistical group test not valid for groups with N<3

No significant changes were reported with levels of the urinary bilirubin in females. See Tables below from the Sponsor:

Before start of treatment

At termination of treatment

GROUP (Dose)	BILIRUBIN		p
	No trace	Total	
1 (Placebo, 0 µg)	4	4	
2 (DDAVP, 400 µg)	4	4	
3 (Desmopressin, 240 µg)	4	4	
Total	12	12	

GROUP (Dose)	BILIRUBIN			p
	No trace	Small amounts	Total	
1 (Placebo, 0 µg)	4	0	4	
2 (DDAVP, 400 µg)	4	0	4	
3 (Desmopressin, 240 µg)	3	1	4	
Total	11	1	12	

Gross Pathology

Necropsy was performed on all animals and all macroscopic evaluation was reported. No remarkable differences were reported

Organ Weights

On the day of necropsy, all animals total body weights as well as weights of organs tissues were recorded. In addition, paired organs were weighed together.

The only significant changes were reported in desmopressin treated males for spleens. In this group, the spleen relative weight (% of body weight) were lower (ss) compared to control animals (with no other related changes). See Table below from the Sponsor:

Absolute (g) and relative (% of body wt and brain wt) organ weight

Males

GROUP (Dose)	SPLEEN				SPLEEN				SPLEEN			
	ABSOLUTE			p	% of BODY WT			p	% OF BRAIN WT			p
	MEAN	S.D.	N		MEAN	S.D.	N		MEAN	S.D.	N	
1 (Placebo, 0 µg)	50.65	13.83	4		0.572	0.124	4		64.2	13.0	4	
2 (DDAVP, 400 µg)	43.31	10.45	4		0.501	0.115	4		56.8	15.7	4	
3 (Desmopressin, 240 µg)	30.89	7.30	4		0.355	0.058	4	*	41.1	9.5	4	

* means $p < 0.05$, versus control group

Histopathology

Battery Considered Adequate? Yes

Peer Review Performed? Yes

All tissues were fixed in phosphate buffered neutral 4% formaldehyde with the exception of the eyes and testes (Modified Davidson's fixative). The lungs were infused with fixative at necropsy. Histological alterations were graded on a 5-grade system as follows: Grade 1-Minimal/Very few/Very small; Grade 2-Slight/Few/Small; Grade 3-

Moderate/ Moderate number/Moderate size; Grade 4-Marked/Many/Large; Grade 5-Massive/Extensive number/Extensive size. See Table below for organs/tissues that were evaluated from the Sponsor:

Organs and tissues	W e i g h	F i x	M i c r o	Organs and tissues	W e i g h	F i x	M i c r o
Abnormalities (gross lesions)		x	x	Pancreas		x	x
Adrenals	x	x	x	Pituitary	x	x	x
Aorta (thoracic)		x	x	Prostate	x	x	x
Brain	x	x	x	Salivary gland (right parotid, sublingual and submandibular)		x	x
Bone marrow smear		x		Sciatic nerve		x	x
Bones (medial condyl of right femur)		x	x	Skeletal muscle		x	x
Epididymides		x	x	Skin		x	x
Eyes with lens/optic nerve		x	x	Spinal cord (thoracic, lumbar)		x	x
Gall bladder		x	x	Spleen	x	x	x
Heart with aortic arch	x	x	x	Sternum (for bone marrow)		x	x
Intestine small (duodenum, jejunum, ileum)		x	x	Stomach		x	x
Intestine large (caecum, colon, rectum)		x	x	Testes	x	x	x
Joint (knee)		x	x	Thymus	x	x	x
Kidneys	x	x	x	Thyroid (incl. parathyroids)	x	x	x
Larynx		x	x	Tongue		x	x
Liver (all main lobes)	x	x	x	Trachea		x	x
Lungs (cranial and caudal lobes, both sides)		x	x	Ureters		x	x
Lymph nodes (right mandibular and mesenteric)		x	x	Urinary bladder		x	x
Mammary gland		x	x	Uterus (horn, cervix and oviducts)	x	x	x
Oesophagus		x	x	Vagina		x	x
Ovaries	x	x	x				

Treatment-related findings were reported in all dose groups (more incidences in the RLD treated groups). According to the Sponsor, these changes were well known as incidental background changes in laboratory Beagle dogs of this age (historical control data was not submitted).

See Tables below from the Sponsor:

ORGAN/FINDING	DOSE GROUP:	01		02		03	
		SEX: M	F	M	F	M	F
	ANIM.EXAM.:	4	4	4	4	4	4

LARGE INTESTINE	:						
- nodule.	:	-	-	-	1	-	-

HEART	:	4	4	4	4	4	4
- Mononucl cells focal:	:	1	-	-	-	-	-
Grade 1:	:	1	-	-	-	-	-

AORTA	:	4	4	4	4	4	4
- Mineralisation focal:	:	-	-	-	-	1	-
Grade 2:	:	-	-	-	-	1	-

LUNG	:	4	4	4	4	4	4
- Subpl fibr/alv metap:	:	-	1	-	1	-	-
Grade 1:	:	-	-	-	1	-	-
Grade 2:	:	-	1	-	-	-	-
- Inflamm cells focal:	:	2	4	1	2	2	2
Grade 1:	:	2	4	-	1	2	2
Grade 2:	:	-	-	1	1	-	-
- Macrophages alveolar:	:	2	1	3	2	1	1
Grade 1:	:	2	1	3	2	1	1

ORGAN/FINDING	DOSE GROUP:	01		02		03	
		SEX: M	F	M	F	M	F
	ANIM.EXAM.:	4	4	4	4	4	4

TONGUE	:	4	4	4	4	4	4
- Ulceration focal:	:	-	-	-	-	-	1
Grade 1:	:	-	-	-	-	-	1
- Mononucl cells focal:	:	-	-	1	-	-	-
Grade 1:	:	-	-	1	-	-	-

CECUM	:	4	4	4	4	4	4
- Inflammation multifo:	:	-	-	-	1	-	-
Grade 3:	:	-	-	-	1	-	-

LIVER	:	4	4	4	4	4	4
- EMH/mononucl cells:	:	1	1	2	1	2	-
Grade 1:	:	1	1	2	1	2	-

PANCREAS	:	4	4	4	4	4	4
- Atrophy exocrine:	:	1	-	2	-	-	-
Grade 1:	:	-	-	1	-	-	-
Grade 2:	:	1	-	-	-	-	-
Grade 3:	:	-	-	1	-	-	-

KIDNEYS	:	4	4	4	4	4	4
- Basophilia tubular:	:	-	-	2	-	1	-
Grade 1:	:	-	-	2	-	1	-
- Hyaline casts focal:	:	-	-	-	1	-	-
Grade 1:	:	-	-	-	1	-	-

CODES AND SYMBOLS USED AT FINDING LEVEL:

 GRADE 1 = Minimal / very few / very small
 GRADE 2 = Slight / few / small
 GRADE 3 = Moderate / moderate number / moderate size
 (= Finding unilateral in paired organs
 * = Comment in text of individual animal data

Toxicokinetics

Blood samples were taken on Day 1 and Day 28, from all animals at different time points: Pre-treatment, and 30 min, 1, 2, 4, 6, and 8 hours.

TK data are summarized below:

- The toxicokinetic evaluation verified that the treated animals were all exposed to desmopressin and no exposure was observed in the controls.
- There was no accumulation; both C_{max} and AUC values were constant between Day 1 and Day 28.
- Exposure based on AUC_{INF} values was similar in Groups 2 and 3.
- The relative bioavailability was 0.64 when comparing DDAVP tablets with desmopressin orally disintegrating tablets.
- No difference was seen between Group 2 (DDAVP tablets) and Group 3 (desmopressin orally disintegrating tablets) on the parameters of C_{max} , T_{max} and $T_{1/2}$ on either Day 1 or Day 28.
- No gender related difference was seen based on the evaluated toxicokinetic parameters.

See Tables below from the sponsor:

Summary of average toxicokinetic parameters after dosing of male and female dogs for 1 and 28 days with desmopressin

Group	Day		Dose (ug/animal)	Rsq	C_{max} (pg/ml)	T_{max} (hr)	$T_{1/2}$ ¹ (hr)	AUC_{INF} (hr*pg/ml)	Dose correlated AUC_{INF}	$AUC_{%Extrap}$ (%)	AUC_{0-8hr} (hr*pg/ml)	Dose correlated AUC_{0-8hr}	Cl_F (ml/hr/kg)	Vz_F (ml/kg)	λ_{z} (1/hr)	R_{acc}	R_A
2	1	N	400	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		0.99	285	0.7	1.10	444	414	1.24	440	410	191,309	307,461	0.65		
		Sd		0.00	223	0.3	0.19	328	315	0.89	326	313	125,225	224,278	0.12		
		CV%		0.47	78.34	37.64	17.69	73.82	76.21	72.14	73.94	76.35	65.46	72.95	18.18		
2	28	N	400	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		1.00	301	0.6	1.18	454	465	1.04	450	461	141,981	232,339	0.61	1.00	1.80
		Sd		0.00	163	0.2	0.21	230	266	0.29	227	263	76,696	106,890	0.11	0.00	1.80
		CV%		0.46	54.34	37.03	17.71	50.61	57.15	27.67	50.49	57.06	54.02	46.01	18.70	0.00	100.45
3	1	N	240	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		0.99	224	0.6	1.17	414	652	1.50	409	644	105,570	167,796	0.61		
		Sd		0.01	112	0.2	0.25	236	339	0.92	232	332	70,930	98,160	0.13		
		CV%		0.71	49.84	31.43	21.23	57.11	51.99	61.23	56.71	51.55	67.19	58.50	20.87		
3	28	N	240	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		1.00	285	0.8	1.19	500	820	0.99	495	811	67,581	115,629	0.58	1.00	1.58
		Sd		0.00	166	0.5	0.09	220	310	0.38	218	307	20,798	34,561	0.04	0.00	1.06
		CV%		0.46	58.37	65.27	7.42	43.93	37.81	38.05	43.94	37.90	30.77	29.89	7.03	0.00	67.27

¹ Average $T_{1/2}$ is based on both $T_{1/2}$ calculation intervals

Dosing Formulation Analysis

The LC-MS/MS method was used to analyze desmopressin in dog plasma (K3EDTA). Results were reproducible (28 or 82.4% out of 34 repeat analyses) and met acceptance criteria.

7 Genetic Toxicology

No new information

8 Carcinogenicity

No new information

9 Reproductive and Developmental Toxicology

No new information

10 Special Toxicology Studies

No new information

11 Integrated Summary and Safety Evaluation

NOCDURNA, a new formulation of desmopressin (desmopressin sublingual melt or desmopressin SLM), was submitted as a 505(b)(2) application. The new product

contains the active ingredient desmopressin, which is a structural analog of the natural human antidiuretic hormone (8-arginine vasopressin). There is extensive clinical experience with desmopressin because various formulations of this drug (oral-Minirin; IV injection, intranasal spray) have been on the market for a long time in many countries.

In the current submission, a 1-month bridge toxicology study in dogs was submitted based on the Agency recommendation. In this study, the toxicological findings and the TK data with NOCDURNA was very similar to DDAVP (RLD) and were consistent with the pharmacological effects of the desmopressin. In general there were no signs of systemic toxicity in any treated animals. Decreased in urinary volumes in treated animals were noted that were related to pharmacological effect of the compounds. The values of serum bilirubin were increased in two desmopressin treated females with no other-related changes. Findings from the TK data suggested no sex differences and similarity in level of desmopressin levels in two compounds (2 × 200µg DDAVP tablets vs. 1 × 240µg desmopressin orally disintegrating tablets).

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/s/

PARVANEH ESPANDIARI
11/28/2012

KAREN L DAVIS BRUNO
11/29/2012

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 22-517
Supporting document/s: 0017/ Resubmission
Applicant's letter date: July 30, 2012
CDER stamp date: July 30, 2012
Product: NOCDURNA™ (Desmopressin Sublingual Melt)
Indication: Treatment of nocturia in adults
Applicant: Ferring Pharmaceuticals Inc.
Review Division: DMEP
Reviewer: Parvaneh Espandiari, Ph.D
Supervisor/Team Leader: Karen Davis Bruno, Ph.D
Division Director: Mary Parks, MD
Project Manager: Jennifer Johnson

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1 Executive Summary

1.1 Introduction

NOCDURNA is being developed by Ferring Pharmaceuticals INC for the treatment of nocturia in adults as a new formulation (oral disintegrating tablets) for sublingual use. The NDA was originally submitted on 06/19/2009 as a 505(b)(2) application. The Sponsor referred to DDAVP® (Desmopressin acetate Tablets (NDA19-955), Desmopressin Acetate Nasal Spray (NDA 21-333), Desmopressin Acetate Tablets (NDA 21-795) and DMF 8396.

The Agency informed the Sponsor in the Complete Response letter dated on 04/22/2010 that the application cannot be approved in its present form because of the absence of adequate data to bridge the new product to any listed desmopressin products. Therefore, in the current submission, the Sponsor provided a 1-month bridging toxicity study in dogs with toxicokinetics to fulfill the nonclinical deficiency noted in the Complete Response letter issued.

1.2 Brief Discussion of Nonclinical Findings

Findings from a 1-month bridging toxicity study in dogs suggested the toxicological findings and the TK data with NOCDURNA were similar to DDAVP (RLD) and also were consistent with the pharmacological effects of the desmopressin. Study results showed no sex differences with the TK data and similarity in level of desmopressin levels in two compounds ($2 \times 200\mu\text{g}$ DDAVP tablets vs. $1 \times 240\mu\text{g}$ desmopressin orally disintegrating tablets).

In addition, results of previous non-clinical studies suggested the safe use of desmopressin via the sublingual route based on no evidence of any local reactions or any histopathological changes related to the test article in the cheek pouch of Syrian hamsters for 28 days. Findings of impurity qualification studies (a 13-week repeat-dose study in rats and two genotoxicity studies) suggested no new toxicities or potential of any genotoxicity with impurities. The NOAEL was established at HD ($10\mu\text{g}/\text{kg}/\text{day}=1\text{xMRHD}$) in the 13-week repeat-dose study in rats.

1.3 Recommendations

1.3.1 Approvability

P/T recommends approval of this application.

1.3.2 Additional Non Clinical Recommendations

No further studies are required.

1.3.3 Labeling

Section 8.1 Pregnancy

Category B:

Fertility studies have not been done. Teratology studies in rats and rabbits at doses 0.05-10 mcg/kg/day (approximately the human exposure in rats and 200-times higher exposure in rabbits, based on body surface area mg/m^2) revealed no harm to the fetus due to desmopressin. There are, however, no adequate and well controlled studies in

pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential or effects on fertility. Desmopressin was not mutagenic or clastogenic with or without metabolic activation in the Ames test for bacterial mutagenicity or the in vitro mouse lymphoma assay.

2 Drug Information

2.1 Drug

CAS Registry Number

16679-58-6

Generic Name

Desmopressin, arginine vasopressin

Proposed Trade Name

NOCDURNA (Desmopressin Sublingual Melt)

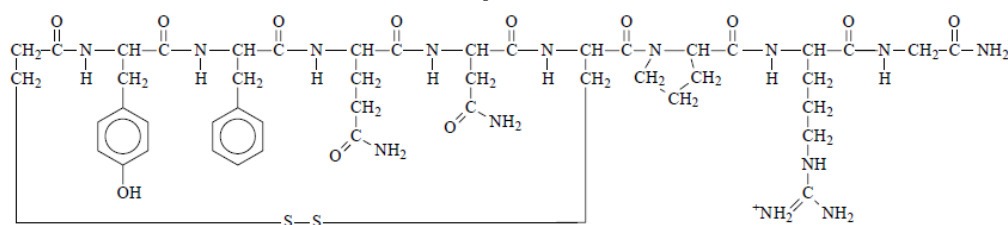
Chemical Name

1-deamino-8-D-arginine vasopressin

Molecular Formula/Molecular Weight

C₄₆H₆₄N₁₄O₁₂S₂•C₂H₄O₂•3H₂O/1183.34

Structure or Biochemical Description



Pharmacologic Class

Arginine vasopressin (synthetic anti-diuretic hormone analogue)

Planned Clinical Route of Administration

Sublingual administration

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDAs: 19955; 21333; 21795

IND 65890

DMF 8396

2.3 Drug Formulation

Each orally disintegrating tablet contains desmopressin acetate equivalent to 25 mcg and 50 mcg of desmopressin as free base. The inactive ingredients are gelatin, mannitol, and anhydrous citric acid. The proposed dosing regimens are for women 25µg daily and for men 50µg daily (in the 1st submission the proposed dose for men was up to 100µg daily).

Desmopressin Melt 25µg:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.025 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 25 µg desmopressin free base.

Desmopressin Melt 50µg:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.050 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 50 µg desmopressin free base.

2.7 Regulatory Background

Desmopressin has been marketed since 1972 in different formulations such as intranasal, intravenous, and oral formulations for the treatment of diabetes insipidus and primary nocturnal enuresis.

Regulatory background is summarized below:

- Originally, NDA was submitted as a 505(b)2 application on Jun 19, 2009 for Orally Disintegrating Tablets(25 mcg and 100 mcg).
- FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements in bioanalytical studies conducted by Cetero Research in Houston (April 1, 2005 until June 15, 2010). Therefore, the FDA informed the Sponsor that the applications can not be approved for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

- On April 22, 2012, in the Complete Response letter from the FDA, a bridging Tox study of one month duration comparing the new product to the RLD was suggested to the Sponsor: See nonclinical section of the CR letter:

NONCLINICAL

3. The nonclinical data you have provided qualify impurities new to this formulation and assess local toxicity. There are no nonclinical data provided to bridge to any listed desmopressin product. This bridge was supposed to be provided by the clinical bioequivalence study which utilized an analytic method that was not properly validated. In the absence of adequate clinical bridging information a comparative toxicology study of one month duration comparing your product to the listed drug product is needed.
- Currently, the NDA was resubmitted (July 30, 2012) for Orally Disintegrating Tablets (25 mcg and 50 mcg) with a 1-month bridging tox study in dogs.

3 Studies Submitted

3.1 Studies Reviewed

A 1-month bridging toxicity study in dogs

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

In DARRTS: P/T review # 1 and 1st submission NDA review

4 Pharmacology

Desmopressin is a synthetic analogue of antidiuretic hormone (Vasopressin). Its antidiuretic effects are mediated by stimulation of vasopressin 2 (V2) receptors; therefore, increasing water re-absorption in the kidney, and consequently reducing urine production.

The demonstration of pharmacological activity of desmopressin SML is based on referenced data; therefore, no additional pharmacology studies were conducted with desmopressin SLM.

4.1 Primary Pharmacology

No new information

4.2 Secondary Pharmacology

No new information

4.3 Safety Pharmacology

No new information

5 Pharmacokinetics/ADME/Toxicokinetics

The sponsor previously submitted PK studies in rats and domestic pigs to evaluate the bioavailability of desmopressin when administered via sublingual route. These studies were reviewed (P/T review#1 in DARRTS); and results suggested that desmopressin SLM (via sublingual route) had greater bioavailability (C_{max} , T_{max} , AUC and AUC/dose), about two-fold, compared to the referenced product (via oral).

6 General Toxicology

A 1-month bridging toxicity study in dogs was conducted to evaluate TK in animals that were exposed to the new product, Desmopressin Melt oral disintegrating tablets (ODT), or the RLD (desmopressin tablets).

DDAVP Tablets & Desmopressin Orally Disintegrating Tablets 1-Month Bridging Toxicity Study in Dogs	
Study #	72837
Study report location	(b) (4)
CRO/Laboratory name	(b) (4)
Date of study initiation	January 24, 2011
GLP compliance statement	Yes
GLP issues identified	No
QA statement	Yes
Drug, lot #, and % purity	DDAVP tablets (batch number: BE1891A); orally disintegrating desmopressin tablets (batch number 952458, 95.5%); placebo (batch number 1033643)

Key Study Findings

- The values of serum bilirubin were increased in two ODT desmopressin treated females (2/4) with no other-related changes. One of these females had a high bilirubin at baseline.
- TK data suggested no sex differences and similarity in level of desmopressin levels for both compounds (2 × 200 µg DDAVP tablets vs. 1 × 240 µg desmopressin orally disintegrating tablets).

Methods	
Doses	0 µg/animal (placebo orally disintegrating tablets); 400 µg/animal DDAVP (2 tablets of 200 µg); 240 µg/animal desmopressin (orally disintegrating tablet)
Frequency of dosing	daily for at least 28 days
Route of administration	DDAVP tablets: orally Desmopressin and placebo (orally disintegrating tablets): sublingually
Dose volume	N/A
Formulation/Vehicle	orally disintegrating placebo tablet
Species/Strain	Beagle dogs
Number/Sex/Group	4/sex/group
Age	6 to 7 months old
Weight	Males: 6.5 and 9.7 kg; Females: 6.1 and 7.9 kg
Satellite groups	None
Unique study design	None
Deviation from study protocol	None

Group	Test item	Dose concentration* (µg/tablet)	Dose * (µg/animal)	Animal Nos		Colour code
				Male	Female	
1	Placebo orally disintegrating tablet	0	0	1, 102, 3-4	5-8	White
2	DDAVP tablet	200	400	9-12	13-16	Blue
3	Desmopressin orally disintegrating tablet	240	240	17-20	21-24	Green

*Material as supplied

Reviewer: Females were exposed to the higher level of compounds due the lower mean body weights (400 µg of DDAVP in males was ~47-51 µg/kg/day and in females ~53-56 µg/kg/day; and 240 µg of desmopressin was ~28-29 µg/kg/day in males and ~32-34 µg/kg/day in females). According to the sponsor, the human bioavailabilities of desmopressin were used for adjusting the anticipated exposure, which were for the tablets was ~0.15%, and in the orally disintegrating tablet was ~0.25%. In dogs, the bioavailability of desmopressin for DDAVP tablets was ~0.85% and for the desmopressin orally disintegrating tablet was not known.

Observations and Results

Mortality

Animals were observed for any visible signs of ill health daily.
All animals survived to the end of the study.

Clinical Signs

Animals were observed daily for any visible signs of ill health or behavioral changes.
Results were not remarkable.

Body Weights

Animals were weighed once weekly, including first and last days of the study.

The groups mean body weight gain during the study was comparable across treatment groups.

Feed Consumption

From Day -7 to the end of the study, the consumption of food was estimated daily for each animal by weighing unconsumed diet ~2 hours after feeding.

Results were not remarkable.

Hematology

Blood samples were taken from all fasted overnight animals through jugular vein. See Table below from the Sponsor for parameters that were measured.

Table 2 Haematology and coagulation parameters

Parameter	Method/Equipment	Unit
Haemoglobin (Hb)	Direct measurement/ABX Pentra DX120SPS	mmol/l
Red blood cell count (RBC)	Direct measurement/ABX Pentra DX120SPS	10 ¹² /l
Reticulocyte count (RETIC)	Direct measurement/ABX Pentra DX120SPS	% and 10 ¹² /l
Haematocrit (HT)	Direct measurement/ABX Pentra DX120SPS	ml/100 ml
Mean cell volume (MCV)	Calculated/ABX Pentra DX120SPS	fl
Mean cell haemoglobin (MCH)	Calculated/ABX Pentra DX120SPS	fmol
Mean cell haemoglobin concentration (MCHC)	Calculated/ABX Pentra DX120SPS	mmol/l
White blood cell count (WBC)	Direct measurement/ABX Pentra DX120SPS	10 ⁹ /l
Differential leucocyte count (NEUTRO, LYMPHO, EOS, BASO, MONO)	Direct measurement/ABX Pentra DX120SPS	% and 10 ⁹ /l
Platelet count (Plt)	Direct measurement/ABX Pentra DX120SPS	10 ⁹ /l
Activated partial thromboplastin time (APTT)	IL Test™/ACL™(*)	sec.
Prothrombin time modified (Pt-m)	Modified IL Test™/ACL™(*)	sec.
Fibrinogen (Fib)	IL Test™/ACL™(*)	g/l

(* Instrumentation Laboratories, Automated Coagulation Laboratory)

Results were not remarkable.

Clinical Chemistry

Blood samples (~3 ml) were taken from all animals for clinical chemistry before start of treatment and before termination of treatment. See Table below for parameters that were measured.

Table 3 Clinical chemistry

Parameter	Method/Equipment	Unit
Alanine aminotransferase (ALAT)	Hitachi 917	µkat/l
Aspartate aminotransferase (ASAT)	Hitachi 917	µkat/l
Alkaline phosphatase (ALKPH)	Hitachi 917	µkat/l
Bilirubin (total) (TBILI)	Hitachi 917	µmol/l
Gamma-glutamyl transferase (GGT)	Hitachi 917	µkat/l
Cholesterol (CHOL)	Hitachi 917	mmol/l
Triglycerides (TRIG)	Hitachi 917	mmol/l
Carbamide (UREA)	Hitachi 917	mmol/l
Creatinine (CREAT)	Hitachi 917	µmol/l
Glucose (GLUC)	Hitachi 917	mmol/l
Sodium (Na)	Ion selective electrode/Hitachi 917	mmol/l
Potassium (K)	Ion selective electrode/Hitachi 917	mmol/l
Calcium (Ca)	Hitachi 917	mmol/l
Magnesium (Mg)	Hitachi 917	mmol/l
Inorganic phosphorus (P)	Hitachi 917	mmol/l
Chloride (Cl)	Ion selective electrode/Hitachi 917	mmol/l
Protein (total) (PROTEIN)	Hitachi 917	g/l
Albumin (ALB)	Hitachi 917	g/l
Globulin	Calculated	g/l
Albumin/Globulin (ALB/G) ratio	Calculated	No unit

In females treated with desmopressin, total bilirubin levels increased (ss) in 2 females with no other related changes in injury markers for liver or renal.

See Tables below from the Sponsor for mean and individual values:

GROUP (Dose)	TBILI			p
	Mean	S.D.	N	
1 (Placebo, 0 µg)	<0.95	>0.39	4	
2 (DDAVP, 400 µg)	1.08	0.35	4	
3 (Desmopressin, 240 µg)	1.85	0.47	4	*

Individual values	Females		
	GROUP (Dose)	Before start	At termination
		ANIMAL NO	TBILI
1 (Placebo, 0 µg)	(b) (4)		
2 (DDAVP, 400 µg)			
3 (Desmopressin, 240 µg)			

Reviewer: In desmopressin treated females, serum levels of bilirubin were normal in 2/4 and high in 2/4. One of the two females with elevated bilirubin had a baseline elevation prior to drug exposure. Table below showed that the higher serum levels of bilirubin in these two animals were not related to the higher level of exposure of compound. In this study, females had a higher level of exposure because they had lower mean body weights compared to males. However, drug exposure was variable in this study. The elevated serum bilirubin in high dose female dogs given desmopressin ODT appears to be incidental because:

- 1. It occurred in 1/4 female dogs given desmopressin ODT at 240ug but not with DDAVP tablets at 400ug of either gender despite similar AUC values across dosage forms. One of the 2 female dogs with the bilirubin elevation has a high background total bilirubin at baseline. This observation occurs at 240ug after 28 days in a female dogs which has systemic exposure >20X higher than anticipated at the MRHD=50ug*
- 2. The parameters that were evaluated in the bridging dog toxicology study, including TK were quite variable (limited animal numbers n=4)*

3. In the 13 week rat study, the qualitative increase in conjugated bilirubin in urine was observed in some males (4) and one female rat given SC desmopressin; however, there were no elevations in unconjugated bilirubin (plasma) in this study
4. Neither the dog or rat toxicity study showed any correlative histopathology (bile duct/liver), transaminase elevations or hematology parameters (hemolysis/anemia)

		Males TBILI													
GROUP (Dose)	ANIMAL NO	Before termination		Day 1					Day 28						
		<LOD	<LOD	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹
1 (Placebo, 0 µg)	1	<LOD	<LOD												
	102	<LOD	0.7												
	3	0.7	1.0												
	4	0.5	0.8												
2 (DDAVP, 400 µg)	9	0.9	1.4	9	675	0.5	1.20	1,041	990	9	324	0.5	1.33 ²	648	672
	10	<LOD	1.1	10	54.8	0.5	1.19 ²	107	118	10	344	1.0	1.01 ³	544	618
	11	0.8	0.9	11	251	1.0	1.16	387	353	11	122	1.0	1.28 ³	255	258
	12	<LOD	0.6	12	121	1.0	0.89 ²	218	205	12	281	0.5	1.31 ³	418	434
3 (Desmopressin, 240 µg)	17	1.4	1.0	17	242	0.5	1.25 ²	386	723	17	300	0.5	1.15 ³	489	966
	18	1.0	0.5	18	257	0.5	1.14 ³	450	694	18	252	0.5	1.18 ³	407	695
	19	0.5	1.0	19	392	0.5	1.46 ³	875	1,222	19	313	1.0	1.34 ³	701	1,007
	20	0.5	0.5	20	118	0.5	1.57 ³	393	777	20	103	2.0	1.18 ³	247	504

		Females TBILI													
GROUP (Dose)	ANIMAL NO	Before termination		Day 1					Day 28						
		<LOD	<LOD	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹	Animal No	C _{max} (pg/ml)	T _{max} (hr)	T _{1/2} (hr)	AUC _{INF} (hr*pg/ml)	Dose correlated AUC _{INF} ¹
1 (Placebo, 0 µg)	5	0.8	1.1												
	6	1.2	0.8												
	7	0.8	<LOD												
	8	0.6	1.4												
2 (DDAVP, 400 µg)	13	0.7	1.2	13	160	0.5	1.42	241	190	13	150	0.5	0.89 ⁴	231	179
	14	1.4	1.5	14	110	1.0	0.84 ²	218	221	14	656	0.5	1.23 ³	892	959
	15	0.8	0.7	15	533	0.5	0.94	798	789	15	246	0.5	0.93 ²	262	262
	16	0.6	0.9	16	376	0.5	1.16	540	446	16	283	0.5	1.46 ³	384	336
3 (Desmopressin, 240 µg)	21	1.6	2.2	21	176	0.5	0.84 ²	288	414	21	661	0.5	1.19 ²	944	1,457
	22	0.9	2.3	22	96.5	0.5	0.98 ²	144	207	22	180	0.5	1.11 ³	422	634
	23	0.9	1.5	23	143	0.5	1.15 ²	180	278	23	226	1.0	1.09 ³	389	640
	24	1.4	1.4	24	371	1.0	0.98 ³	593	901	24	241	0.5	1.31 ³	403	654

Urinalysis

Urine samples were collected from all animals (housed individually in metal cages) for a period of 18 hours (±30 minutes) from early afternoon to the following morning. See Table below from the Sponsor for parameters that were measured:

Table 4 Urinalysis

Parameter	Method/Equipment	Unit/Range
Volume		ml
Specific gravity (SG)	Ames Multistix 10SG/Clinitek 500	No unit
pH	Ames Multistix 10SG/Clinitek 500	No unit
Colour (COLOUR)	Visual examination	No unit
Protein (PROTEIN)	Ames Multistix 10SG/Clinitek 500	g/l
Leucocytes (LEUC)	Ames Multistix 10SG/Clinitek 500	Cells/ μ l
Nitrite (NITRITE)	Ames Multistix 10SG/Clinitek 500	No unit
Blood (BLOOD)	Ames Multistix 10SG/Clinitek 500	Erythrocytes/ μ l
Glucose (GLUCOSE)	Ames Multistix 10SG/Clinitek 500	mmol/l
Ketones (KETONES)	Ames Multistix 10SG/Clinitek 500	mmol/l
Bilirubin (BILL)	Ames Multistix 10SG/Clinitek 500	No unit
Urobilinogen (UROBIL)	Ames Multistix 10SG/Clinitek 500	μ mol/l

Decreased urinary volume was noted in treated animals compared to control animals (more pronounced in Desmopressin treated animals compared to DDAVP treated animals). The sponsor reported that no statistical analysis was performed for the urine volume due to small number of animals in the control group (n=2). No significant differences were noted for other urinary parameters. See Tables below from the Sponsor:

Males

Before start of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	78.7	85.2	3	
2 (DDAVP, 400 μ g)	83.5	65.9	4	
3 (Desmopressin, 240 μ g)	63.8	68.1	4	

At termination of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	128.5	14.8	2	
2 (DDAVP, 400 μ g)	120.5	80.9	4	
3 (Desmopressin, 240 μ g)	104.8	59.0	4	

Group mean values Statistical group test not valid for groups with N<3

Females

Before start of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	59.5	39.6	4	
2 (DDAVP, 400 μ g)	59.5	35.4	4	
3 (Desmopressin, 240 μ g)	29.3	26.8	4	

At termination of treatment

GROUP (Dose)	VOLUME			
	MEAN	S.D.	N	p
1 (Placebo, 0 μ g)	115.0	7.1	2	
2 (DDAVP, 400 μ g)	103.8	30.5	4	
3 (Desmopressin, 240 μ g)	47.5	41.2	4	

Group mean values Statistical group test not valid for groups with N<3

No significant changes were reported with levels of the urinary bilirubin in females. See Tables below from the Sponsor:

Before start of treatment

At termination of treatment

GROUP (Dose)	BILIRUBIN		p
	No trace	Total	
1 (Placebo, 0 µg)	4	4	
2 (DDAVP, 400 µg)	4	4	
3 (Desmopressin, 240 µg)	4	4	
Total	12	12	

GROUP (Dose)	BILIRUBIN			p
	No trace	Small amounts	Total	
1 (Placebo, 0 µg)	4	0	4	
2 (DDAVP, 400 µg)	4	0	4	
3 (Desmopressin, 240 µg)	3	1	4	
Total	11	1	12	

Gross Pathology

Necropsy was performed on all animals and all macroscopic evaluation was reported. No remarkable differences were reported

Organ Weights

On the day of necropsy, all animals total body weights as well as weights of organs tissues were recorded. In addition, paired organs were weighed together.

The only significant changes were reported in desmopressin treated males for spleens. In this group, the spleen relative weight (% of body weight) were lower (ss) compared to control animals (with no other related changes). See Table below from the Sponsor:

Absolute (g) and relative (% of body wt and brain wt) organ weight

Males

GROUP (Dose)	SPLEEN				p	SPLEEN				p				
	ABSOLUTE			N		% of BODY WT			N		% OF BRAIN WT			N
	MEAN	S.D.	N			MEAN	S.D.	N			MEAN	S.D.	N	
1 (Placebo, 0 µg)	50.65	13.83	4		0.572	0.124	4		64.2	13.0	4			
2 (DDAVP, 400 µg)	43.31	10.45	4		0.501	0.115	4		56.8	15.7	4			
3 (Desmopressin, 240 µg)	30.89	7.30	4		0.355	0.058	4	*	41.1	9.5	4			

* means $p < 0.05$, versus control group

Histopathology

Battery Considered Adequate? Yes

Peer Review Performed? Yes

All tissues were fixed in phosphate buffered neutral 4% formaldehyde with the exception of the eyes and testes (Modified Davidson's fixative). The lungs were infused with fixative at necropsy. Histological alterations were graded on a 5-grade system as follows: Grade 1-Minimal/Very few/Very small; Grade 2-Slight/Few/Small; Grade 3-

Moderate/ Moderate number/Moderate size; Grade 4-Marked/Many/Large; Grade 5-Massive/Extensive number/Extensive size. See Table below for organs/tissues that were evaluated from the Sponsor:

Organs and tissues	W e i g h	F i x	M i c r o	Organs and tissues	W e i g h	F i x	M i c r o
Abnormalities (gross lesions)		x	x	Pancreas		x	x
Adrenals	x	x	x	Pituitary	x	x	x
Aorta (thoracic)		x	x	Prostate	x	x	x
Brain	x	x	x	Salivary gland (right parotid, sublingual and submandibular)		x	x
Bone marrow smear		x		Sciatic nerve		x	x
Bones (medial condyl of right femur)		x	x	Skeletal muscle		x	x
Epididymides		x	x	Skin		x	x
Eyes with lens/optic nerve		x	x	Spinal cord (thoracic, lumbar)		x	x
Gall bladder		x	x	Spleen	x	x	x
Heart with aortic arch	x	x	x	Sternum (for bone marrow)		x	x
Intestine small (duodenum, jejunum, ileum)		x	x	Stomach		x	x
Intestine large (caecum, colon, rectum)		x	x	Testes	x	x	x
Joint (knee)		x	x	Thymus	x	x	x
Kidneys	x	x	x	Thyroid (incl. parathyroids)	x	x	x
Larynx		x	x	Tongue		x	x
Liver (all main lobes)	x	x	x	Trachea		x	x
Lungs (cranial and caudal lobes, both sides)		x	x	Ureters		x	x
Lymph nodes (right mandibular and mesenteric)		x	x	Urinary bladder		x	x
Mammary gland		x	x	Uterus (horn, cervix and oviducts)	x	x	x
Oesophagus		x	x	Vagina		x	x
Ovaries	x	x	x				

Treatment-related findings were reported in all dose groups (more incidences in the RLD treated groups). According to the Sponsor, these changes were well known as incidental background changes in laboratory Beagle dogs of this age (historical control data was not submitted).

See Tables below from the Sponsor:

ORGAN/FINDING	DOSE GROUP:	01		02		03	
		SEX: M	F	M	F	M	F
	ANIM.EXAM.:	4	4	4	4	4	4

LARGE INTESTINE	:						
- nodule.	:	-	-	-	1	-	-

HEART	:	4	4	4	4	4	4
- Mononucle cells focal:	:	1	-	-	-	-	-
Grade 1:	:	1	-	-	-	-	-

AORTA	:	4	4	4	4	4	4
- Mineralisation focal:	:	-	-	-	-	1	-
Grade 2:	:	-	-	-	-	1	-

LUNG	:	4	4	4	4	4	4
- Subpl fibr/alv metap:	:	-	1	-	1	-	-
Grade 1:	:	-	-	-	1	-	-
Grade 2:	:	-	1	-	-	-	-
- Inflamm cells focal:	:	2	4	1	2	2	2
Grade 1:	:	2	4	-	1	2	2
Grade 2:	:	-	-	1	1	-	-
- Macrophages alveolar:	:	2	1	3	2	1	1
Grade 1:	:	2	1	3	2	1	1

ORGAN/FINDING	DOSE GROUP:	01		02		03	
		SEX: M	F	M	F	M	F
	ANIM.EXAM.:	4	4	4	4	4	4

TONGUE	:	4	4	4	4	4	4
- Ulceration focal:	:	-	-	-	-	-	1
Grade 1:	:	-	-	-	-	-	1
- Mononucle cells focal:	:	-	-	1	-	-	-
Grade 1:	:	-	-	1	-	-	-

CECUM	:	4	4	4	4	4	4
- Inflammation multifo:	:	-	-	-	1	-	-
Grade 3:	:	-	-	-	1	-	-

LIVER	:	4	4	4	4	4	4
- EMH/mononucle cells:	:	1	1	2	1	2	-
Grade 1:	:	1	1	2	1	2	-

PANCREAS	:	4	4	4	4	4	4
- Atrophy exocrine:	:	1	-	2	-	-	-
Grade 1:	:	-	-	1	-	-	-
Grade 2:	:	1	-	-	-	-	-
Grade 3:	:	-	-	1	-	-	-

KIDNEYS	:	4	4	4	4	4	4
- Basophilia tubular:	:	-	-	2	-	1	-
Grade 1:	:	-	-	2	-	1	-
- Hyaline casts focal:	:	-	-	-	1	-	-
Grade 1:	:	-	-	-	1	-	-

CODES AND SYMBOLS USED AT FINDING LEVEL:

 GRADE 1 = Minimal / very few / very small
 GRADE 2 = Slight / few / small
 GRADE 3 = Moderate / moderate number / moderate size
 (= Finding unilateral in paired organs
 * = Comment in text of individual animal data

Toxicokinetics

Blood samples were taken on Day 1 and Day 28, from all animals at different time points: Pre-treatment, and 30 min, 1, 2, 4, 6, and 8 hours.

TK data are summarized below:

- The toxicokinetic evaluation verified that the treated animals were all exposed to desmopressin and no exposure was observed in the controls.
- There was no accumulation; both C_{max} and AUC values were constant between Day 1 and Day 28.
- Exposure based on AUC_{INF} values was similar in Groups 2 and 3.
- The relative bioavailability was 0.64 when comparing DDAVP tablets with desmopressin orally disintegrating tablets.
- No difference was seen between Group 2 (DDAVP tablets) and Group 3 (desmopressin orally disintegrating tablets) on the parameters of C_{max} , T_{max} and $T_{1/2}$ on either Day 1 or Day 28.
- No gender related difference was seen based on the evaluated toxicokinetic parameters.

See Tables below from the sponsor:

Summary of average toxicokinetic parameters after dosing of male and female dogs for 1 and 28 days with desmopressin

Group	Day		Dose (ug/animal)	Rsq	C_{max} (pg/ml)	T_{max} (hr)	$T_{1/2}$ ¹ (hr)	AUC_{INF} (hr*pg/ml)	Dose correlated AUC_{INF}	$AUC_{%Extrap}$ (%)	AUC_{0-8hr} (hr*pg/ml)	Dose correlated AUC_{0-8hr}	Cl_F (ml/hr/kg)	Vz_F (ml/kg)	λ_{z} (1/hr)	R_{acc}	R_A
2	1	N	400	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		0.99	285	0.7	1.10	444	414	1.24	440	410	191,309	307,461	0.65		
		Sd		0.00	223	0.3	0.19	328	315	0.89	326	313	125,225	224,278	0.12		
		CV%		0.47	78.34	37.64	17.69	73.82	76.21	72.14	73.94	76.35	65.46	72.95	18.18		
2	28	N	400	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		1.00	301	0.6	1.18	454	465	1.04	450	461	141,981	232,339	0.61	1.00	1.80
		Sd		0.00	163	0.2	0.21	230	266	0.29	227	263	76,696	106,890	0.11	0.00	1.80
		CV%		0.46	54.34	37.03	17.71	50.61	57.15	27.67	50.49	57.06	54.02	46.01	18.70	0.00	100.45
3	1	N	240	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		0.99	224	0.6	1.17	414	652	1.50	409	644	105,570	167,796	0.61		
		Sd		0.01	112	0.2	0.25	236	339	0.92	232	332	70,930	98,160	0.13		
		CV%		0.71	49.84	31.43	21.23	57.11	51.99	61.23	56.71	51.55	67.19	58.50	20.87		
3	28	N	240	8	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean		1.00	285	0.8	1.19	500	820	0.99	495	811	67,581	115,629	0.58	1.00	1.58
		Sd		0.00	166	0.5	0.09	220	310	0.38	218	307	20,798	34,561	0.04	0.00	1.06
		CV%		0.46	58.37	65.27	7.42	43.93	37.81	38.05	43.94	37.90	30.77	29.89	7.03	0.00	67.27

¹ Average $T_{1/2}$ is based on both $T_{1/2}$ calculation intervals

Dosing Formulation Analysis

The LC-MS/MS method was used to analyze desmopressin in dog plasma (K3EDTA). Results were reproducible (28 or 82.4% out of 34 repeat analyses) and met acceptance criteria.

7 Genetic Toxicology

No new information

8 Carcinogenicity

No new information

9 Reproductive and Developmental Toxicology

No new information

10 Special Toxicology Studies

No new information

11 Integrated Summary and Safety Evaluation

NOCDURNA, a new formulation of desmopressin (desmopressin sublingual melt or desmopressin SLM), was submitted as a 505(b)(2) application. The new product

contains the active ingredient desmopressin, which is a structural analog of the natural human antidiuretic hormone (8-arginine vasopressin). There is extensive clinical experience with desmopressin because various formulations of this drug (oral-Minirin; IV injection, intranasal spray) have been on the market for a long time in many countries.

In the current submission, a 1-month bridge toxicology study in dogs was submitted based on the Agency recommendation. In this study, the toxicological findings and the TK data with NOCDURNA was very similar to DDAVP (RLD) and were consistent with the pharmacological effects of the desmopressin. In general there were no signs of systemic toxicity in any treated animals. Decreased in urinary volumes in treated animals were noted that were related to pharmacological effect of the compounds. The values of serum bilirubin were increased in two desmopressin treated females with no other-related changes. Findings from the TK data suggested no sex differences and similarity in level of desmopressin levels in two compounds (2 × 200µg DDAVP tablets vs. 1 × 240µg desmopressin orally disintegrating tablets).

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/s/

PARVANEH ESPANDIARI
11/28/2012

KAREN L DAVIS BRUNO
11/29/2012

Summary Review for Regulatory Action

Date	April 22, 2010
From	Mary H. Parks
Subject	Division Director Summary Review
NDA/BLA #	22-517
Supplement #	
Applicant Name	Ferring Pharmaceuticals
Date of Submission	June 19, 2009
PDUFA Goal Date	April 22, 2010
Proprietary Name / Established (USAN) Name	Nocdurna
Dosage Forms / Strength	25 and 100 mcg tablets
Proposed Indication(s)	Adult nocturia
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	William Lubas, M.D., Ph.D.
Statistical Review	Wei Liu, Ph.D. J. Todd Sahlroot, Ph.D.
Pharmacology Toxicology Review	Parvaneh Espandiari, Ph.D. Karen Davis-Bruno, Ph.D.
CMC Review/OBP Review	John Hill, Ph.D. Suong Tran, Ph.D. Prasad Peri, Ph.D.
Microbiology Review	John Metcalfe, Ph.D. Stephen Langille, Ph.D.
Clinical Pharmacology Review	Ritesh Jain, Ph.D. Christine Garnett, Pharm.D. Sally Choe, Ph.D. Anshu Marathe, Ph.D.
DDMAC	NA
DSI	Roy Blay, Ph.D. Tejashri Purohit-Sheth, M.D.
CDTL Review	Dragos Roman, M.D.
OSE/DMEPA	LaToya Shenee' Toombs, Pharm.D. Judy Park, Pharm.D. Carlos Mena-Grillasca, R.Ph. Denise Toyer, Pharm.D.
SEALD	Ann Marie Trentacosti

Division Director Review

	Laurie Burke, Pharm.D.
Regulatory Affairs Team (Immediate Office)	Ann Marie Trentacosti Laurie Burke, Pharm.D.
Regulatory Project Management	Jennifer Johnson Enid Galliers

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

Division Director's Memo

1. Introduction

Vasopressin is a hypothalamic neuropeptide that is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and stored in the posterior pituitary where it is released in response to osmotic and non-osmotic stimuli. Vasopressin functions as an antidiuretic hormone (ADH) at physiologic plasma concentrations; vasoconstrictive activity occurs only at higher plasma levels. These different functions of vasopressin are mediated via three different vasopressin receptors: V1a (vascular and hepatic); V1b (anterior pituitary); and V2 (kidney). Of these, the most significant function of vasopressin is at the V2 receptor located on the renal collecting tubules. Stimulation of these receptors results in the renal water conservation to maintain plasma osmolality within a narrow range of 280 to 285 mEq/L. This is accomplished through vasopressin-mediated insertion of water channels (aquaporins) along the luminal surface of the collecting tubules with subsequent passive reabsorption of solute-free water down the inner medullary concentration gradient. In the absence of vasopressin, the distal collecting tubules remain impermeable to water and larger volumes of solute-free water are excreted. Derangements of AVP regulation, synthesis/release, or action result in hypernatremia (deficiency or non-response to hormone activity) or hyponatremia (excessive or inappropriate release for plasma osmolality).

The pharmacologic use of vasopressin has been accomplished through the development of desmopressin or synthetic vasopressin analogues which have a longer half-life than the naturally occurring hormone. Other attributes include greater V2 receptor selectivity enabling a more potent anti-diuretic effect than vasopressin. Desmopressin is available as a subcutaneous injection, nasal spray, and oral tablets and has been approved by the FDA for the following indications:

- as a treatment of central diabetes insipidus
- as a diagnostic in performing renal concentration capacity testing
- as a treatment of primary nocturnal enuresis in children
- as a treatment for type 1 von Willebrand's disease and hemophilia A

In this application, Ferring Pharmaceuticals is seeking an indication for Nocdurna, an orally disintegrating tablet formulation of desmopressin, for the treatment of adults with nocturia. The company is proposing different dosing regimen and monitoring based on gender and patient age as follows:

- Women – Nocdurna 25 mcg daily at bedtime
- Men < 65 years of age – Nocdurna 100 mcg daily at bedtime
- Men ≥ 65 years of age – Nocdurna 100 mcg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment

This product has been approved in Europe for the treatment of nocturia at doses of 60 mcg, 120 mcg, and 240 mcg but is limited to patients under the age of 65 years due to the risk of hyponatremia.

2. Background

Nocturia is defined by the International Continence Society as the complaint by an individual who is awoken at night on one or more occasions for the need to void. There are many variables affecting the frequency of nocturnal voids including fluid intake, prostatic conditions, pelvic floor dysfunction, and certain medications. In this clinical development program, the applicant identified adult patients with nocturia as an individual with an average of ≥ 2 nocturnal voids per night as determined by a 3-day frequency-volume diary taken during the screening period and specifically excluded patients with known renal/prostatic/pelvic disorders. Recommendations were made to limit fluid intake several hours prior to bedtime but no strict record of fluid intake was kept during this study. There are currently no FDA-approved drugs for this condition. As per the applicant, nocturia has a negative impact on sleep quality and subsequent daytime function. In addition, the applicant cites a greater risk of falls during the nighttime hours as individuals are awoken to void, and that this is a particular concern in the elderly population. However, the clinical development program for Nocdurna did not seek to demonstrate an effect of treatment on these clinical endpoints as a primary objective of the clinical trials. Instead, the primary efficacy endpoint was number of nocturnal voids. Reliance on this surrogate measure and whether it is a reliable predictor of clinical benefit is a consideration in the overall risk-benefit assessment of this application.

Based on the known physiologic effect of vasopressin, it is expected that a synthetic analogue of this hormone that binds to V2 receptors will reduce renal free water excretion. And if administered prior to bedtime, such a product will reduce the frequency of nocturnal voids. However, it is also expected that this reduction in free water excretion may result in a decrease in serum sodium and if severe, hyponatremia may ensue which may have serious clinical adverse effect. This serious side effect of desmopressin has been clearly documented with currently approved formulations with the indication for primary nocturnal enuresis recently removed for the nasal spray preparations due to an unacceptably high rate of hyponatremia reported in the postmarketing setting. The risk of hyponatremia is increased with age, with use of certain medications (e.g., anti-depressants), and with excessive fluid intake. Prolongation of desmopressin half-life may also increase the risk of hyponatremia. All these factors will also be considered in the overall risk-benefit assessment of this application. It should be noted that the use of this product in Europe for the treatment of nocturia has been associated with a few reports of severe hyponatremia, particularly in the elderly.

In his team leader memo, Dr. Dragos Roman has summarized these concerns in assessing risk-benefit of Nocdurna for the treatment of nocturia, as relayed to the company in meetings prior to this NDA submission.

3. CMC/Device

The CMC reviewer has recommended approval of this application. No additional studies are requested. Please see Dr. John Hill's review for details of the chemistry and manufacturing of this product.

4. Nonclinical Pharmacology/Toxicology

Additional nonclinical studies were conducted to characterize impurities in this product as well as the safety of this route of administration. Please see Dr. Parvaneh Espandiari's review for details of these studies.

The applicant did not conduct any nonclinical data to bridge between this product and any listed desmopressin product. Instead, it was relying on a clinical BE study which used an unacceptable analytical method. In the absence of adequate clinical bridging information, a comparative toxicology study of one month duration comparing Nocdurna to an approved desmopressin product will be needed.

5. Clinical Pharmacology

Please see Dr. Jain's review with secondary sign-off dated March 30, 2010 for complete discussion of the clinical pharmacology evaluation. The Office of Clinical Pharmacology/Division of Clinical Pharmacology finds the application acceptable but with the following recommendations for dosing:

- Women all ages – Nocdurna 25 mcg qd
- Men age < 65 years – Nocdurna 50 mcg qd as a starting dose with weekly dose escalations in 25 mcg increments up to a maximum dose of 100 mcg qd
- Men ≥ 65 years – Nocdurna 50 mcg qd with dose escalation not recommended

Their recommendation is based primarily on a re-analysis of data from the controlled portion of the pivotal clinical trial with a focus on subgroup analyses and assessment of efficacy at earlier time points than the pre-specified time point for efficacy determination. Uncontrolled extension portion of the pivotal trial was also relied upon as supportive of these recommendations. Please see Section 7 of this memo for further discussion of OCP's recommendation alongside the recommendations made by the clinical and statistical reviewers.

Under this section, I would emphasize the following findings from the Clinical Pharmacology studies which are relevant to the overall risk-benefit consideration of this application.

- Total systemic clearance of desmopressin decreases with increasing renal impairment. Exposure is increased by 2.4-fold and 3.6-fold in moderate and severe renal impairment, respectively. Mild renal impairment modestly increases exposure by 1.5-fold.
- Females appear to show a greater response to the pharmacologic effect of Nocdurna

- There is a low likelihood of drug-drug interaction through cytochrome P450 pathway. However, effect of Nocdurna co-administered with other drugs associated with hyponatremia was not investigated in any dedicated study.
- The half-life of Nocdurna is approximately 3 hrs

In an addendum dated April 2, 2010, Drs. Jain and Choe noted the absence of acceptable PK information for the to-be-marketed formulation due to the use of an unvalidated analytical method employed in its BE study, CS019. As a result, the applicant will need to reanalyze the BE PK samples using a validated analytical method or collect PK samples from additional clinical trials.

6. Clinical Microbiology

No outstanding deficiencies. Please see Dr. John Metcalfe's review for further details.

7. Clinical/Statistical-Efficacy

The primary sources of clinical efficacy are derived from a single trial and its uncontrolled extensions. The uncontrolled extensions were not designed with any prespecified analysis for efficacy and the stated objective was primarily to evaluate durability of effect observed in the controlled portion of the clinical trial. As a result of the limitation of this study design (i.e., absence of control group) and the decreasing number of patients exposed to drug for an extended period of time, this memo will rely primarily on the controlled portion of the clinical trial for a discussion of efficacy.

Study FE992026 CS029 – Part 1

CS029 was comprised of two parts. Part 1 was considered pivotal to the determination of efficacy and consisted of a 28-day randomized, double-blind, placebo-controlled, parallel treatment period. Study participants were randomized to placebo or 4 doses of Nocdurna (10 mcg, 25 mcg, 50 mcg, or 100 mcg). Randomization was also stratified by age < 65 or ≥ 65 years and by the absence/presence of nocturnal polyuria. Dr. Lubas has described the patient selection criteria. I would highlight that this trial specifically excluded patients with certain medical conditions which may increase the risk of hyponatremia including renal insufficiency (defined as an estimated GFR < 60 mL/min), use of a loop diuretic, and heart failure. In addition, serum sodium was to be within normal limits at study entry. Other diuretics and certain medications known to cause hyponatremia (e.g., SSRIs) were not prohibited.

There were two co-primary efficacy endpoints in the pivotal trial: the change in the mean number of nocturnal voids from baseline to Day 28 and the proportion of subjects with > 33% reduction in the mean number of nocturnal voids from baseline to Day 28. The rationale for the co-primary endpoints was to ensure that a small number of patients with outlier responses to therapy would not lead to a conclusion of effectiveness. The primary objective of this trial was to demonstrate superiority of one or more doses of Nocdurna compared to placebo on both of these endpoints. Drs. Lubas and Roman have discussed other secondary endpoints in their reviews. Of relevance are the sleep diaries and quality of life questionnaires.

A total of 799 individuals were randomized into Part 1 and 710 (89%) completed this 28-day study. Completion rate in the placebo group was 91% versus 84-94% across the different Nocturna dose groups which would suggest that a placebo-controlled study of longer duration is not limited by a high placebo discontinuation rate. A higher percentage of patients in the Nocturna treatment groups withdrew due to an adverse event and serum sodium ≤ 125 compared to placebo. As per protocol, any patient with a serum sodium ≤ 125 was to be discontinued from the study. This happened in one placebo (1%) patient versus 5 (3%) and 4 (3%) in the 50 and 100 mcg dose groups, respectively. Consent withdrawal comprised 4-6% of discontinuations across all study groups. Upon further inquiry, some of these consent withdrawals also included reports of an adverse event; however, review of these AEs did not result in a different safety conclusion from the overall database.

Data from 757 study participants were included in the ITT efficacy analysis. With respect to the pre-specified efficacy analysis plan, only the 100 mcg dose group demonstrated superior efficacy over placebo at Day 28 on both co-primary endpoints. The following table summarizes both co-primary endpoints.

Table 1. Efficacy Results Based on Pre-specified Efficacy Analysis Plan (ITT population)

Efficacy Endpoint	Placebo N=156	10 mcg N=155	25 mcg N=152	50 mcg N=148	100 mcg N=146
Nocturnal Voids					
Baseline mean	3.27 (1.16)	1.21 (1.02)	3.35 (1.32)	3.39 (1.07)	3.22 (1.10)
Baseline median	3.0	3.0	3.0	3.3	3.0
Min-max	2.0-7.7	2.0-7.7	2.0-8.7	2.0-7.3	2.0-7.3
Mean chg (SD)	-0.86 (1.05)	-0.83 (1.07)	-1.00 (1.13)	-1.18 (1.19)	-1.43 (1.22)
Mean difference (adj)	---	0.01	-0.12	-0.28	-0.61
95% CI	---	-0.22, +0.24	-0.35, +0.11	-0.51, -0.04	-0.85, -0.38
p-value vs pbo	---	p=0.93	p=0.31	p=0.02	p<0.0001
>33% reduction					
n (%)	73 (47%)	73 (47%)	77 (50%)	79 (53%)	103 (71%)
Odds ratio	--	1.017	1.15	1.29	2.89
95% CI	--	0.65, 1.6	0.73, 1.81	0.82, 2.05	1.79, 4.72
p-value vs pbo	--	p=0.94	p=0.55	p=0.27	p<0.0001

The above findings were consistent by the stratified subgroup of age < 65 and ≥ 65 years.

As will be discussed further under Section 8.0 the effective dose identified in Part 1 of Study CS029 was also associated with the highest risk of hyponatremia including 11% of individuals experiencing severe hyponatremia (< 125 mEq/L) compared to 1% observed in placebo, 10 mcg, and 25 mcg dose groups. In an effort to identify a safe and effective dose, the applicant and FDA reviewers evaluated efficacy and safety by certain subgroups and over multiple time points in this 28-day study. These analyses contributed to different dosing recommendations by the applicant, medical and clinical pharmacology reviewers.

Efficacy at Earlier Time Points

In addition to Day 28, the two co-primary endpoints were also collected on Days 8, 15, and 22. The following graphs from the applicant summarize these efficacy parameters over the course of the 28-day study.

Figure 1. Change from Baseline in Mean Number of Nocturnal Voids by Study Week

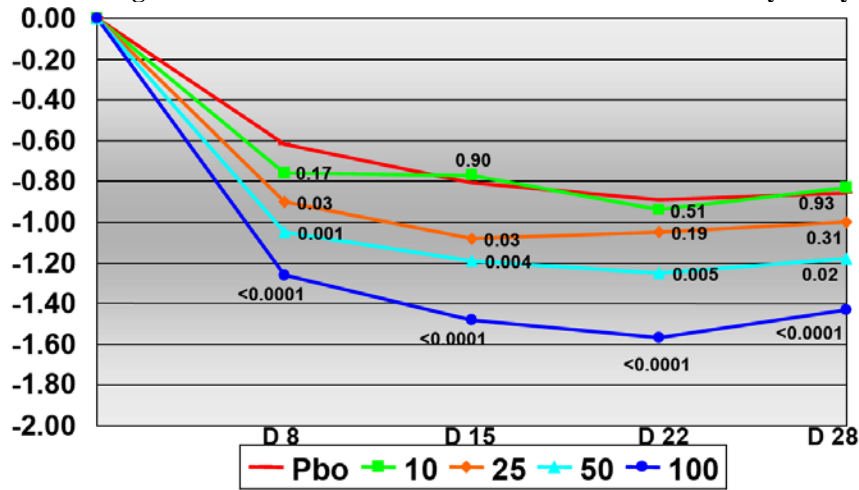
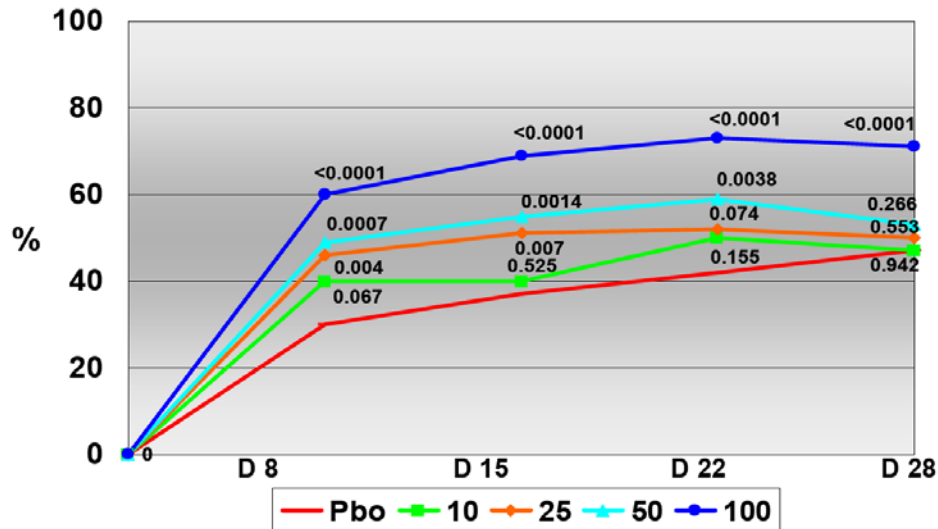


Figure 2. Percentage of Participants with > 33% Reduction in Nocturnal Voids by Study Week



Based on earlier time points, the 50 mcg dose was superior over placebo on both co-primary endpoints. The 25 mcg dose shows a significant difference to placebo on Days 8 and 15 only and the 10 mcg dose is clearly not significantly different from placebo at any time point.

Efficacy By Gender

The efficacy over time is further evaluated by gender. With this analysis a significant effect on both co-primary endpoints is observed in females at the 25 and 50 mcg doses whereas a significant effect on both co-primary endpoints is only observed in males at the 100 mcg dose with variable significant effects at the 50 mcg dose.

Dr. Todd Sahlroot, deputy director for Office of Biometrics noted in his memo that this post-hoc analysis by gender generated modest p-values ranging between 0.01 to 0.04 in for females (see Table 2 from Dr. Sahlroot's review) that would likely be non-significant if adjustments were made for multiple comparisons.

Study FE992026 CS029 – Part 2

Part 2 was a 6-month, double-blind extension in which study participants randomized to Nocdurna in Part 1 continued on their assigned treatments and patients randomized to placebo in Part 1 were re-randomized (determined at start of Part 1) to one of the 4 Nocdurna doses. Of the 710 participants completing Part 1 of CS029, 665 elected to continue into Part 2. There were 136 individuals previously on placebo who re-randomized to Nocdurna 10, 25, 50, or 100 mcg daily dose groups.

Although this segment of CS029 is a 6-month extension, not all participants who entered Part 2 received double-blind treatment for this entire duration. The reason for this is because an individual would enter Part 2 at the completion of Part 1 after the final visit. However, Part 2 was declared completed after the last participant randomized completed Part 1. At this point, all participants entered the open-label, long-term extension study CS031, describe below. As a result the exposure during Part 2 ranged from 3 to 211 days.

Although one of the stated objectives of Part 2 was to demonstrate durability of effect achieved in Part 1 of one or more doses, the limited number of participants with long-term data decreased over time. This is illustrated in Tables 12 and 13 of Dr. Wei's review in which there were efficacy data at Day 169 in only 64 participants from both Part 1 and 2 with only 15 to 17 individuals in each of the 4 dose groups. From the descriptive data there appears to be a durable reduction in nocturia; however, the absence of a control group limits any conclusion on whether this effect is a result of drug therapy or the natural course of the condition with control of other factors.

Study FE992026 CS031

CS031 is a further extension to the pivotal trial but unlike Part 2 of CS029, this extension study is open-label. Participants completing at least Visit 3E of Part 2 were eligible for this study. All participants were initially continued on previously assigned treatment from Part 2. After the results of Study CS029 were available, this study was unblinded. Participants assigned to the ineffective dose of 10 mcg were then randomly assigned to one of the 3 higher doses at the next regularly scheduled visit. Limitations noted in Part 2 apply here and are even more amplified due to the limited number of patients.

8. Safety

Please see Dr. Lubas's review for a detailed discussion of safety.

Due to the short duration of controlled study period (28 days), the safety assessment in this NDA is limited. Despite this, the safety concern of hyponatremia associated with Nocurna use was evident and clearly dose-related (see Table 2).

Table 2. Incidence of Hyponatremia in CS029 Part 1

Serum Sodium	Placebo (N=160)	10 µg (N=163)	25 µg (N=158)	50 µg (N=158)	100 µg (N=160)
<130 mmol/L	2 (1%)	1 (1%)	2 (1%)	11 (7.0%)	18 (11%)
<130 but ≥125 mmol/L	1 (1%)	1 (1%)	2 (1%)	7 (4%)	14 (9%)
<125 mmol/L	1 (1%)	0	0	4 (3%)	4 (3%)

Across the different treatment periods (CS029 Parts 1 and 2 and CS031), there were a total of 17 participants who were withdrawn from the study for hyponatremia. Seven of these occurred in the 100 mcg dose group, 8 in the 50 mcg dose group, one in the 10 mcg dose group, and one in placebo.¹ Since this information is derived from controlled and uncontrolled extension periods, incidence rates and comparative analyses are of limited use. However, it is notable that all but 3 patients were older than 65 years, emphasizing the greater risk of hyponatremia in the elderly population. There were numerically greater cases in females than males but the overall small number of events would not support a conclusion that the risk is limited to or greater in one gender. The applicant contends that hyponatremia occurs early in treatment and proposes a monitoring scheme on Day 4 and 28 to mitigate risk of hyponatremia. However, there were also cases of hyponatremia occurring beyond this time point. Three patients had hyponatremia on days 331 (Na=122; dose 10 mcg), 337 (Na=122; dose 50 mcg), and 346 (Na 128; dose 50 mcg). An additional 4 patients had hyponatremia (124-128) beyond Day 28. This finding calls into question the ability of the proposed and untested monitoring scheme for risk mitigation.

As stated under Section 6.0, moderate and severe renal impairment increases exposure to Nocurna. In this clinical development program, patients were excluded if the eGFR was < 60 ml/min. Despite screening, several patients with renal impairment were still enrolled. Of concern was the development of renal impairment over time in this trial. It should be expected that availability of this product will result in use in at-risk or contraindicated patient population. Risk mitigation strategies will need to be proposed as assessed periodically to determine its effectiveness should Nocurna be approved.

¹ The hyponatremia in the placebo patient was unusual in that the patient presented on November 7 (screening) with a normal serum sodium of 137 mmol/L. Nine days later, a centrally analyzed lab result reported a serum sodium of 121 mmol/L but this was not associated with any symptoms. The patient was discontinued from the trial and a repeat lab value 3 days later without any intervention was normal at 138 mmol/L. It is unusual for an acute decrease in serum sodium to not have accompanying symptoms and the rapid correction without intervention might also suggest laboratory error.

9. Advisory Committee Meeting

An advisory committee panel was not convened on this review cycle.

10. Pediatrics

A waiver was requested and granted since the indication sought in this application is an adult condition.

11. Other Relevant Regulatory Issues

Please see reviews by Drs. Lubas and Roman regarding consults to DSI, OSE, DDMAC, and review of financial disclosure information. There are no deficiencies in these areas.

12. Labeling

Labeling negotiations will be deferred on this review cycle as the application will not be approved.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete response

- Risk Benefit Assessment

The pharmacologic action of desmopressin is well established and it should be expected that its use can reduce the frequency of nocturnal voids. After all, the product is approved to replace this hormone deficiency in diabetes insipidus with effective control of polyuria. However, for the indication to treat nocturia, several factors need to be considered beyond the expected pharmacologic action of an anti-diuretic drug. In this program the applicant selected a lower dose than currently approved in Europe. This may be, in part, to reduce the risk of hyponatremia. The FDA has also conveyed concerns that the risk of hyponatremia may outweigh the perceived benefit of reducing the number of times an individual gets up to void in the middle of the night, particularly if nocturia in an otherwise healthy population (i.e., no evidence of anatomical defect or other co-morbidity) may be controlled by modification of fluid intake.

The choice of two co-primary endpoints was proposed by the applicant to ensure a robust assessment of treatment effectiveness after 4 weeks in a controlled clinical trial. The applicant was only able to demonstrate effectiveness based on the pre-defined statistical plan at the highest dose studied. However, this dose still carried a risk of hyponatremia, some severe (< 125 mmol/L). The primary medical reviewer and the clinical pharmacology reviewer have argued that the choice of Day 28 as the pre-specified endpoint is arbitrary and does not have any clinical significance, thereby lending some support to the reliance on earlier time points for the selection of an efficacious and safer dosing regimen. Notwithstanding the post-hoc nature of this conclusion for efficacy, it should also be noted that the efficacy endpoint upon which a new dosing regimen is being identified is also of unknown clinical significance. The applicant was not able to identify an appropriate quality of life (QOL) questionnaire to link improvements in nocturia with patient reported outcomes. And even with the questionnaires utilized in this program, no significant difference in response between treatment and placebo was observed. Although there was prolongation of duration of sleep from onset of sleep to first void in the Nocdurna group over placebo, the overall duration of sleep was not different across the treatment groups.

Attempts were made by several parties to identify a safe and effective dosing regimen through subgroup analyses after re-analysis of data. Not surprisingly, this post-hoc approach to identifying a safe and effective dose has resulted in four different dosing regimen recommendations and one recommendation that no clinical benefit has been established to merit approval.

Applicant recommendations:

1. Women – Nocdurna 25 mcg daily at bedtime
2. Men < 65 years of age – Nocdurna 100 mcg daily at bedtime
3. Men ≥ 65 years of age – Nocdurna 100 mcg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment

Dr. Lubas's recommendations:

1. Nocdurna 25 mcg QD for women
2. Nocdurna 50 mcg QD for men

Office of Clinical Pharmacology recommendations:

1. Nocdurna 25 mcg QD for women
2. Nocdurna 50 mcg QD as a starting dose in men < 65 years of age. Titration weekly in 25 mcg increments up to 100 mcg QD.
3. Nocdurna 50 mcg QD in men ≥ 65 years of age.

Office of Biometrics recommendations:

1. No gender-based dosing. Include 25, 50, and 100 mcg QD as approved doses; titrate to effect as needed.

Dr. Roman's recommendations:

1. Complete response. Demonstrate clear clinical benefit that goes beyond a statistically successful reduction in the number of nocturnal voids. Such a clinical benefit should

include as a minimum a demonstration of improvement in a validated quality of life questionnaire that is found acceptable by the Agency.

If anything, the 5 different recommendations across three different review disciplines within the FDA highlight the lack of confidence in the evidence provided to demonstrate safety and effectiveness.

The 1962 amendment to the Federal Food, Drug and Cosmetic Act included a requirement that, in order to gain market approval, applicants need to demonstrate effectiveness of their product through the conduct of adequate and well-controlled studies which would provide substantial evidence that the drug will have the effect it purports. Under 21 CFR 314.126, adequate and well-controlled studies are further described as investigations which allow one to “distinguish the effect of a drug from other influences” (e.g., natural course of the disease/medical condition, placebo effect or biased observation). The legal definition of substantial evidence has been debated as to whether more than one adequate and well-controlled study is needed to gain market approval. This debate is appropriate to this application since it contains only one adequate and well-controlled study whose final results based on the proposed method of analysis are not being relied upon for approval. Instead, alternative analyses and data from uncontrolled studies are relied upon to find a safe and effective dose.

I concur with the applicant and reviewers that Nocurna 100 mcg is an effective dose based on this single adequate and well-controlled study. I also agree that the post-hoc analyses provide evidence *suggesting* other dosing regimens that are safer and *may* be effective for treating nocturia; however, I believe these additional lines of evidence are circumstantial more than substantial and require formal prospective evaluation before approval.

Study CS029 provided evidence that one can not make a significant distinction between Nocurna 10 mcg QD and placebo for the treatment of adult nocturia. However, CS029 provided useful information that there are different gender and age responses to the drug’s effects which merit further testing of the 25 and 50 mcg QD doses. It was also apparent that a longer duration of a controlled clinical study is feasible (placebo discontinuation rate in CS029 was only 91%) which will provide better information on durability of effect and safety.

Dr. Roman’s recommendation that the company provide evidence of improvements in quality of life measures is worthy of consideration. However, in discussing the requirements for approval of drugs to treat insomnia with the Division of Neuropharmacology Products, I was informed that QOL questionnaires are not relied upon or allowed in labeling for such drugs. If a nocturia-specific QOL questionnaire can be developed that is acceptable to the agency’s Study Endpoints and Labeling Development (SEALD) team, this will provide additional support for reliance on the surrogate endpoints of reduced frequency of nocturnal voids. However, this would not be relied upon to support an indication to improve sleep quality.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Should this application be approved, a REMS will likely be necessary to ensure its safe and effective use. At this juncture it can not be determined if this will be limited to a Medication Guide or a broader REMS. This can be determined upon review of the response to the CR action letter.

- Recommendation for other Postmarketing Requirements and Commitments

None identified at this point. Application will not be approved on this review cycle.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22517

ORIG-1

FERRING
PHARMACEUTICA
LS INC

NOCDURNA

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/s/

MARY H PARKS

04/22/2010

Clinical Team Leader Review

From: Dragos Roman, MD, Acting Team Leader

To: Mary Parks, M.D., Division Director, Division of Metabolism and Endocrinology Products

Date: April 9, 2010

NDA: 22-517; submitted on June 19, 2009; PDUFA goal date: April 22, 2010.

Applicant: Ferring Pharmaceuticals Inc.

Established Name: desmopressin acetate

Proposed Proprietary Name: Nocdurna

Formulation: Orally Disintegrating Tablets (25 µg and 100 µg)

Proposed indication: treatment of adult nocturia

Recommended regulatory action: Desmopressin Melt should not be approved for the treatment of adult nocturia without demonstrating a clear clinical benefit that goes beyond a statistically successful reduction in the number of nocturnal voids. Such clinical benefit should include as a minimum a demonstration of improvement in a validated quality of life questionnaire that is found acceptable by the Agency.

1. Background and regulatory history

1.1 General drug information

Desmopressin is a nonapeptide synthetic analogue of the pituitary hormone arginine vasopressin. Similar to its natural counterpart, desmopressin binds to V2 receptors in the distal and collecting tubules of the kidney and increases the permeability of these tissues to water which, in turn, decreases urine production while concomitantly enhancing water reabsorption¹. Desmopressin is different functionally from arginine vasopressin in several aspects. The chemical modifications added to the endogenous vasopressin molecule (desamination of a cysteine residue at position 1 and the substitution of L-arginine by D-arginine at position 8) increase and prolong the antidiuretic effect of vasopressin. Not only does desmopressin have a longer duration of action relative to vasopressin, but it also exhibits less vasopressive effect (the antidiuretic-to-vasopressor ratio is 3000-fold greater than vasopressin).

Desmopressin was approved in the USA initially as a nasal spray (1978) followed by an intravenous formulation (1984) and an oral formulation (1995). It is currently approved for the following indications: treatment of diabetes insipidus, primary nocturnal enuresis, type I von Willebrand's disease and hemophilia A, and as a diagnostic test that measures

¹ At high plasma concentrations, desmopressin also increases circulating levels of coagulation factor VIII and von Willebrand Factor, but this effect has no relevance to the current submission.

renal concentration capacity for patients with suspected renal disease. Orally administered desmopressin is largely destroyed in the gastrointestinal tract, but a sufficient amount is absorbed to produce therapeutic effects.

On June 19, 2009 Ferring Pharmaceuticals Inc. has submitted an NDA in support of a new indication (adult nocturia) and a new formulation (an orally disintegrating tablet for sublingual administration named desmopressin Melt). Of note, desmopressin Melt is approved for the nocturia indication in Europe and in other countries at daily doses ranging between 60 µg and 240 µg (the drug is administered once a day at bedtime; it is titrated starting with the lowest dose followed by weekly dose escalations, as needed). Importantly, desmopressin Melt it is not approved in Europe in adults >65 years of age for the nocturia indication due to the risk of developing hyponatremia.

1.2 Regulatory History

The Division met with representatives of Ferring Pharmaceuticals Inc. in an End-of-Phase-2 meeting (March 26, 2007) and a pre-NDA meeting (October 20, 2008).

During the End-of-Phase-2 meeting the Agency discussed and gave regulatory advice regarding the following: what is expected in a 505(b)(2) application that relies in part on the pharmacology and toxicology findings of desmopressin submitted under a previous NDA; Phase 3 trial design and choice of endpoints; choice of drug doses for the Phase 3 program; size of expected safety dataset at the time of registration; standards to be met for quality of life (QOL) instruments; and need for long-term efficacy data given that nocturia treatment is anticipated to be long-term.

Several additional comments made by the Division are worth highlighting. The Division indicated that it views nocturia as a convenience indication for a symptom that is associated with many disease states and even confounding treatments and that, in last analysis, approval of such an indication will require demonstration of efficacy with minimal safety risks. The division also expressed concern about the risk of hyponatremia and recommended a robust assessment of serum sodium measurements during therapy, particularly when associated with use of medications that may, by themselves, increase the risk of hyponatremia.

In the pre-NDA meeting the Division expressed again concern regarding the risk of hyponatremia associated with the use of desmopressin Melt in patients with nocturia, and indicated that the NDA to be filed in support of this new indication needs to establish that “the reduction in nocturnal voids represents a clinical benefit that would outweigh the risk of hyponatremia”. Extensive discussion focused on issues related to dose selection (given an unexpected gender-specific treatment effect, as well as the observed frequency of hyponatremia), and a proposal for post-approval sodium monitoring (to this proposal the Division expressed skepticism regarding the efficacy of an outpatient serum sodium monitoring program which has not been tested prospectively). In addition, the Division

asked for evidence to support the validity of the QOL questionnaires as well as the full results of QOL testing.

2. Application Review

2.1 Chemistry, Manufacturing and Control (CMC)

The drug substance in desmopressin Melt is desmopressin acetate, which is identical to the drug substance used in desmopressin tablets. The drug product contains, in addition to desmopressin, the following excipients: gelatin, mannitol, citric acid anhydrous and (b) (4). Gelatin and mannitol are matrix formers and citric acid is used as pH adjuster. The tablets are intended to be placed under the tongue where they disintegrate in < 10 seconds. Both drug product and drug substance were viewed as “satisfactory” by the CMC reviewer. Although the applicant developed a 25 µg, a 50 µg and a 100 µg desmopressin Melt, Ferring plans to market only the 25 µg and 100 µg orally disintegrating tablets (see efficacy and safety sections for dose selection). The composition of all the desmopressin Melt orally disintegrating tablets is reproduced below.

Table 1 Composition of desmopressin Melt 25, 50 and 100 µg

	Desmopressin Melt 25 µg	Desmopressin Melt 50 µg	Desmopressin Melt 100 µg
Desmopressin (µg)	25	50	100
Gelatin (mg)	(b) (4)		
Mannitol (mg)	(b) (4)		
Citric acid, anhydrous	(b) (4)		

The CMC review (Dr. John Hill, primary reviewer) is archived in DARRTS (March 9, 2010) and recommends approval from a CMC perspective pending an acceptable recommendation from the Office of Compliance regarding the manufacturing and testing facilities. The CMC reviewer does not recommend any Phase 4 studies.

2.2 Clinical Microbiology

The microbiology review (Dr. John W. Metcalfe primary reviewer) is archived in DARRTS as of February 12, 2010. It does not identify any deficiencies and recommends approval; it does not request any Phase 4 commitments and/or agreements.

2.3 Nonclinical pharmacology/toxicology

The active ingredient in Nocdurna is the same as that present in several approved desmopressin products and has been characterized from a pharmacology/toxicology perspective in previous desmopressin NDA submissions. According to the pharmacology/toxicology reviewer the application relies on the Agency’s findings of safety and efficacy of desmopressin from NDA19-955 (DDAVP® Desmopressin acetate Tablets held by Sanofi Aventis US), NDA 21-333 (Desmopressin Acetate Nasal Spray), and NDA 21-795 (Desmopressin Acetate Tablets; and DMF 8396). Several new non-clinical studies were conducted and submitted for desmopressin Melt with the goal to bridge this new formulation to the previously approved desmopressin products and to characterize three product-related impurities that were at (b) (4) concentration

levels than in the referenced listed drug: (Glu4) desmopressin, (Gly9-OH) desmopressin and (β Asp5) desmopressin. The new studies submitted for review are: 1) a local tolerability study to assess desmopressin's effect on the oral mucosa; 2) a 13-week repeat-dose study in rats aimed at characterizing the above-listed product-related impurities; 3) two genotoxicity studies; and 4) a study that compared the absorption of the sublingual desmopressin product to that of the oral product.

In the local tolerability study desmopressin was administered once daily in the cheek pouch of Syrian hamsters for 28 days without any evidence of local reactions or any histopathological changes related to the test article, thus supporting the use of desmopressin via the sublingual route.

In the 13-week toxicity study conducted in rats there were no new toxicities identified for the three above-mentioned impurities. The findings observed in this study were in general consistent with the pharmacological changes expected from a vasopressin analogue (decreased urinary volume, increased specific gravity and electrolyte concentration in urine).

The Ames test and the mouse lymphoma assay found no evidence of genotoxicity for the 3 impurities, when present at concentrations of up to (b) (4) %.

Pharmacokinetic evaluation of sublingual desmopressin was conducted in two species (rat and domestic pig) and indicated that sublingual desmopressin had a two-fold greater bioavailability for C_{max}, T_{max}, AUC and AUC/dose when compared to oral desmopressin, implying that, all other facts equal, less desmopressin will be needed with the sublingual product.

Dr. Parvaneh Espandiari, the primary pharmacology/toxicology reviewer, recommends approval of the application without any new studies. Her review is archived in DARRTS (March 26, 2010). She also recommends giving desmopressin a Category B status for labeling for the nocturia indication on the basis that: 1) no fertility studies have been done and 2) teratology studies conducted in rats and rabbits at doses that approximate human exposure in rats and 200-times higher exposure in rabbits do not show any harm to the fetus.

2.4 Clinical Pharmacology/Biopharmaceutics

The pharmacology and toxicology review (Dr. Jain Ritesh, primary reviewer) is archived in DARRTS (March 30, 2010). The reviewer finds the submission "acceptable" provided that a labeling agreement can be reached with the applicant. The reviewer recommends, based on the reanalysis of efficacy and safety data, the following dosing regimens: 25 μ g once a day for women; a 50 μ g daily starting dose for men < 65 years, to be titrated in weekly 25 μ g increments up to a 100 μ g dose; 3) of 50 μ g daily dose (without further escalation) for men > 65 years.

The clinical pharmacology reviewer also indicates that the drug elimination of desmopressin is dependent on renal function and that it is reduced with increasing renal

impairment. Patients whose renal function is moderately and severely impaired have a 2.4-fold and 3.6-fold increase in desmopressin exposure relative to healthy subjects, respectively. In patients with mild renal impairment the relative increase in desmopressin exposure is only 1.5-fold. Since serum sodium levels were the same in healthy individuals and in patients with mild renal impairment, and since there were no differences in the incidence of hyponatremia between the two groups, the clinical pharmacology reviewer does not recommend any restrictions of use for patients with mild renal impairment.

The absolute bioavailability of desmopressin Melt was 0.25%. The desmopressin maximum plasma concentrations (C_{max}) were observed at 0.5-2.0 hours after dosing. The elimination half-life was within the range of 2.8 -3.0 hours. The bioavailability of orally disintegrating desmopressin was greater by a factor of 1.52 when compared to a desmopressin tablet of an identical dose.

2.5 Statistics

The statistical reviewer (Dr. Wei Liu) concludes in his review that 1) based on the pre-specified multiple comparison scheme of Study CS29 Part I, 100 µg was the only dose that showed superiority against placebo, and 2) that there is sufficient statistical evidence to support a positive dose-response despite the fact that the results from pair-wise comparisons between doses below 100 µg and placebo failed to firmly establish the efficacy. Dr. Liu also indicates that, despite failing statistically, doses below 100 µg may have utility for some patients in the targeted population.

In his secondary review, Dr. Todd Sahlroot warns that dosing recommendations based on subgroup analyses are not convincing and that in an attempt to exclude risk they could also exclude much of the benefit. He also indicates that, although there is insufficient statistical evidence to support the efficacy of *specific* doses below 100 µg, there is visual and statistical evidence that 25 µg or 50 µg doses could be effective in a small percentage of patients. Therefore he recommends adding to the 100 µg dose approval the 25 µg and 50 µg doses but only as starting doses for the titration regimen.

2.6. Efficacy

2.6.1 Pivotal trials

The Phase 3 clinical program consisted of a randomized, double-blind, placebo-controlled, parallel-group, multi-center, 28-day efficacy trial (Study CS029, Part 1) in which adult patients with nocturia were randomized to one of 4 doses of desmopressin Melt (10, 25, 50, or 100 µg) or placebo. This initial phase of the trial was followed by what was supposed to be a 6 month double-blind extension (Study CS029, Part 2) in which patients on desmopressin continued on the same dose they had received during Part 1 of the trial, while patients on placebo were re-randomized to one of the 4 active treatment groups. After the study database was locked and the data analyzed, the 10 µg

dose-group was re-randomized to the higher desmopressin doses of 25, 50, and 100 µg. Once the data analysis was completed patients were unblinded and Study CS029, Part 2 became an open-label extension study (Study CS031).

In order to be enrolled in Study CS029, Part 1 patients had to be adults (age > 18 years) and had to have an average of ≥ 2 voids per night as determined from a 3-day voiding diary. Excluded were patients with renal insufficiency, hyponatremia, diabetes insipidus, bladder outlet obstruction or surgical treatment for bladder outlet obstruction/benign prostatic hyperplasia performed within the past 6 months, and several urological conditions (clinical suspicion of urinary retention and/or post void residual volume >150 mL, current or past urologic malignancy, clinical evidence of current genitourinary tract pathology, or neurogenic detrusor activity).

The 750 patients enrolled were stratified by age (<65, ≥ 65 years) and by absence or presence of nocturnal polyuria (defined as ratio of nighttime urine volume/24-hour urine volume $\geq 33\%$). Subjects were instructed to limit their fluid intake prior to drug self-administration, which took place approximately 1 hour prior to bedtime. The mean age at enrollment was a little over 60 years with patients ranging from 20 to 86 years; most patients were between 50-75 years (approximately 60%) and fewer than 20% of patients were less than 50 or over 75 years each. Men and women were enrolled in almost even numbers. The primary endpoint was a composite of (1) the mean reduction in the number of nocturnal voids and (2) the proportion of subjects with a > 33% reduction from baseline in the mean number of nocturnal voids. The protocol specified that the sponsor had to show statistical significance (p-value ≤ 0.05) for each of the components of the primary endpoint at the 28 day timepoint in order to be considered a statistical win. The primary efficacy endpoint (number of nocturnal voids) was evaluated on the basis of information collected in diaries over 3 consecutive 24-hour periods at baseline, days 8, 15, 22 and 28. Secondary endpoints were: the change in the initial period of undisturbed sleep, total sleep time, Patient Reported Outcomes (PROs) measured through several Quality Of Life questionnaires, and durability of effect in the open label extension study CS031.

Compliance was high during Part 1 (between 86% and 92% of patients per arm were >80% compliant with treatment). It was lower and more variable during Phase II (the percentage of patients with >80% compliance was mostly in the low 70s). The percentage of completers was in the high 80s or low 90s within Phase 1 and slightly lower during Phase 2 of the trial.

2.6.2 Primary efficacy analysis and related efficacy results

In his detailed clinical review, Dr. Lubas indicates that the 100 µg Nocturna dose was statistically superior to placebo for both components of the coprimary endpoint at the predefined time point of Day 28 (the statistical review concurred with this observation). The number of mean (SD) nocturnal voids decreased from 3.44 (1.1) at baseline to 1.79 (1.3) at Day 28, indicating a mean change of -1.43 (1.2) (p<0.0001); the same level of statistical significance (p<0.0001) was observed at all the timepoints at which this measurement was completed from Day 8 through Day 28 (i.e. days 8, 15, and 22). The

percentage of patients with > 33% reduction from baseline in mean number of nocturnal voids was 71% at Day 28 ($p < 0.0001$); all previous timepoints indicated the same level of statistical significance ($p < 0.0001$). When the same analysis was split by gender, both males and females reached statistical significance for all timepoints analyzed and for both components of the primary endpoint. Some discrete gender differences were present, however: while statistical analyses in the female subgroup had nominal p values < 0.0001 at all timepoints for both components of the primary endpoint, the same analyses in the male subgroup had p values that ranged from < 0.0001 to < 0.049 (the latter applies to the responder analysis for the day 28 timepoint).

In contrast to the 100 μ g dose, the 50 μ g dose was not statistically significant at all timepoints and in all gender subgroup analyses. Specifically, for the prespecified time point of Day 28 only the first part of the coprimary endpoint (reduction in number of voids) was statistically significant ($p = 0.021$) whereas the second part of the coprimary endpoint (responder analysis) it was not significant ($p = 0.27$). Interestingly, the 50 μ g dose was statistically significant with respect to both parts of the coprimary endpoint for the first three weeks of the efficacy trial (p -values ranging from 0.0007 to 0.0045). In the female subgroup, statistical significance was observed for each component of the coprimary endpoint at all the timepoints analyzed (i.e. Day 8 through Day 28). For males, however, the dose failed to reach statistical significance for the Day 28, although it was statistically significant for several but not all of the previous timepoints. (refer to Tables 4, 5, 11 and 12 of Dr. Lubas's review).

For the 25 μ g dose statistical significance was seen inconsistently (and not at Day 28). In the gender subgroup analyses females fared better than males, and had a statistical win for Day 28, but they still failed in 1/2 of the previous timepoints. The 10 μ g desmopressin dose did not show efficacy statistically.

The fact that statistically different results were seen at the same dose for different timepoints evaluated during the trial is somewhat puzzling since the drug's effect is not supposed to depend on repeated administrations (i.e. reaching a steady state) but is rather expected to be seen with the first dose and, with a half-life of < 3 hours, the drug should be practically eliminated before the next dose.

The gender-specific observations previously described, along with pharmacodynamic observations, suggest that women are more sensitive than men to the activity of desmopressin. This observation is amply discussed by Dr. Lubas in Section 7.5.3 of his review (drug-demographics interactions) and is further agreed by the clinical pharmacology reviewer. It is viewed, however, with skepticism in the statistical review because it did not find statistical confirmation; specifically, Dr. Liu states that for CS29 Part I, the overall treatment-by-gender interactions for the two co-primary endpoints were not significant at the 10% level (p -values were 0.1760 and 0.1049 for the mean change in nocturnal void number and the 33% responder proportion, respectively).

2.6.3 Secondary efficacy analyses

Desmopressin treatment resulted in statistically significant increases in the duration of the initial period of undisturbed sleep (sleep prior to the first void) when on-treatment changes at Day 28 were compared to placebo. Subjects treated with the 25 µg and 50 µg dose had a mean increase in their initial period of sleep of approximately 45 minutes while those treated with the 100 µg dose had a mean increase in initial sleep duration of a little over 1 hour relative to placebo. The improvement was statistically significant relative to placebo for all doses ≥ 25 µg. When analyzed by age subgroups, the dose effect was confirmed only in the younger patients (<65 age) and not in the older group. In contrast to the observations made for the initial period of undisturbed sleep, total sleep duration changes were not statistically significant relative to placebo for any of the doses investigated and there was no dose-effect.

Several patient reported outcome (PRO) analyses were secondary efficacy analyses for this submission. Applicant's PRO endpoints were analyzed for reliability and validity by the Study Endpoints and Label Development (SEALD) team (the SEALED consult is archived in DARRTS as of 10/1/2009, Ann M Trentacosti reviewer). The consult provides a review of three PRO instruments: Nocturia Quality of Life (N-QOL) questionnaire; Pittsburgh Sleep Quality Index (PSQI); and International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N). The consult was critical of the three instruments utilized by Ferring to assess the impact that the reduction of nighttime voids during desmopressin treatment may have on patients' quality of life. Specifically, the SEALED reviewer concludes that ICIQ-N and PSQI are not measures of the impact of nocturia and, since they were developed to assess other concepts (pelvic floor symptoms for ICIQ-N and different sleep disturbances for the PSQI), they "include domains and items that are not pertinent to nocturia patients." Regarding N-QOL, which was developed to measure the impact of nocturia and its treatment on patients' quality of life, the reviewer states that: 1) there is insufficient information submitted to date "to adequately assess whether the instrument represents a comprehensive, interpretable, and appropriate measure of its intended concept"; 2) the information submitted suggests that the instrument omits a key domain (psychological/emotional impacts of nocturia); and 3) the instrument includes items that are not measures of treatment effect. The consult concludes that "N-QOL does not appear to represent an adequate measure of the impact of nocturia or HRQL in nocturia patients in order to effectively support clinical efficacy or labeling claims". Regardless of these methodological comments and conclusions, there were no statistically significant differences between any of the desmopressin Melt treatment groups and placebo in any of the quality of life instrument scores during the pivotal study CS29, although mean responses were in general more favorable for the subjects in the Nocturna treatment groups.

Finally, with respect to the durability of desmopressin's effect, Dr. Lubas indicates that continued dose response up to 7 months supports persistence of efficacy and that this conclusion has to be placed in the context of the large patient drop out (>50%) during this part of the study.

2.7 Safety

The safety concerns of desmopressin Melt in adults with nocturia are centered around the issue of hyponatremia risk.

There were no deaths in the pivotal trials (one death due to acute respiratory failure occurred in a 43-year-old HIV patient more than one month after the completion of the trial). The infrequent SAEs recorded were consistent with background events and were of low frequency (there were no SAEs of hyponatremia). Adverse events that resulted in patient discontinuation during the placebo-controlled phase of the trial were hyponatremia, decreased blood sodium, nausea, headache, dry mouth, dizziness, fatigue, vomiting, and insomnia. With the exception of hyponatremia which was seen in as many as 4% of patients (and potentially even higher if the hyponatremia and decreased blood sodium categories were to be joined) all other adverse events occurred with a frequency of <1% or <2%.

Drug-to-placebo comparisons of treatment-emergent adverse event incidence described in the ISS were less informative because of the discordant drug-to-placebo exposure (placebo exposure in these analyses lasted for only 4 weeks while exposure to desmopressin Melt lasted for > 1 year in some subjects, thus giving the desmopressin group a >10-fold excess in exposure; consequently virtually all adverse events presented in the ISS were more frequent in the desmopressin group than placebo). These analyses will not be mentioned in this review.

Comparisons between the individual desmopressin arms and placebo for the first month (Part 1 of Study CS29) showed only small differences in treatment – emergent adverse event incidence: 59% placebo; 61% for 10µg; 62% for 25µg, 65% for 50 µg and 69% for 100 µg desmopressin. The only adverse events with an incidence that was two-fold higher in at least once of the desmopressin arms relative to placebo were nausea, diarrhea, dizziness, hyponatremia, and blood sodium decreased. Of these, nausea, hyponatremia, and decreased blood sodium were the only ones that exhibited a clear dose-response, particularly with higher desmopressin doses. The incidence of hyponatremia was 2% for placebo, 1% for the 10 and 25µg doses, 5% for the 50µg dose and 7% for the 100µg desmopressin dose. It should be mentioned that these differences are observed in a cohort of patients who were enrolled in the trial on the basis of having normal serum sodium levels at baseline.

Hyponatremia has emerged as the major adverse event associated with desmopressin Melt in adults with nocturia. This should not be surprising given the known mechanism of action of desmopressin and the previous safety experience accumulated so far with this drug (a nasal desmopressin product has been associated with hyponatremic seizures in children and as a consequence it is no longer in use for the enuresis indication). In Section 7.5.3 of his review (Drug-demographic interactions, Table 25), Dr. Lubas presents information that clearly identifies age as a risk factor for hyponatremia (the >65 age group being at higher risk than the < 65 age group). Severe hyponatremia (defined as serum sodium < 125 mmol/L) is of particular concern because it places patients at risk

for cerebral edema and seizures. Due to the decrease in renal function seen with advancing age, the elderly are less capable of limiting sodium excretion. When this physiological decline in renal function is coupled with the water reabsorption promoted by desmopressin (which is greater at higher doses) the risk of developing hyponatremia, including severe hyponatremia, is amplified and may shift considerably the benefit-to-risk balance in this age group.

2.8 Dose Selection

Different dosing recommendations were made by reviewers from different disciplines. The clinical reviewer recommended approval of a Nocturna daily dose of 25 µg in women and 50µg in men (without age restriction) because of the risk of severe hyponatremia at doses $\geq 50\mu\text{g}$ in women and 100 µg in men. In his extensive discussion regarding dose selection Dr. Lubas also entertains the possibility of approving the following dose regimens (without sodium monitoring):

- 25 µg dose for all women and 100 µg dose only for men under 65 years of age.
- 25 µg dose for all women, 100 µg dose for men under 65 and 50 µg dose for men 65 years of age and older.

The clinical pharmacology reviewer recommends:

- 25 µg dose for all women
- 100 µg dose for men under 65
- 100 µg dose for men under 65 with additional serum sodium monitoring on Day 4 and at one month of treatment.

The statistical reviewer recommends a dose of 100 µg for both males and females, regardless of age, with doses of 25 and 50 µg only as intermediary doses during the titration process.

The sponsor proposed the following gender- and age-based doses:

- Women: 25 µg sublingual tablet, once daily at bedtime
- Men < 65: 100 µg sublingual tablet, once daily at bedtime.
- Men ≥ 65 : 100 µg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment.

This diversity of recommendations (including the possible acceptance of more than one regimen by the same reviewer) is a clear reflection of the difficult task of selecting a dose regimen that provides a high degree of confidence in reducing the frequency of nighttime voids without increasing the risk of severe hyponatremia at the same time. This difficulty comes out, at least in part, from the fact that this clinical trial has generated unexpected observations such as 1) women being potentially more sensitive to the efficacy of the drug and possibly at higher risk for severe hyponatremia, 2) older men being at increased risk of severe hyponatremia, 3) a surprising risk of severe hyponatremia at lower doses than those currently prescribed in Europe where, despite higher approved desmopressin Melt doses, severe hyponatremia was not observed frequently in patients < 65 years. Furthermore, selection of a safe and effective dose is even more challenging when, due to

the limitation of the data generated in this trial, one has to integrate multiple criteria such as age, gender, sodium monitoring, that have not been tested independently and prospectively in a clinical trial. For instance, the applicant has proposed a monitoring scheme aimed at identifying patients at risk for severe hyponatremia early during desmopressin treatment, but this proposal fails short of providing reassurance because, as Dr. Lubas points out in his review, it has not been proved and validated prospectively.

2.9 Other regulatory issues

3.9.1 DSI

A DSI inspection was conducted at two sites that were selected on the basis of having the largest number of patients enrolled and the highest numbers of patients with protocol deviations. Minor deficiencies were noted but in final analysis the data for both sites were found to be acceptable and no significant regulatory violations were found (the DSI review has been archived in DARRTS on March 5, 2010, Dr. Roy Blay primary reviewer).

2.9.2 Pediatrics

A waiver for pediatric studies was recommended under PREA on the basis of the fact that adult nocturia, as we understand it today, is a condition without a relevant counterpart in children.

2.9.3 OSE consult

The Division of Medication Error Prevention and Analysis (DMEPA) has provided early during this review cycle a proprietary name consult that concluded that Nocturna is an acceptable proprietary name, not vulnerable to name confusion (the DSI review has been archived in DARRTS on November 10, 2009).

2.10 Labeling

Any labeling discussion will be deferred to the next review cycle since this reviewer does not recommend approval of the application based on the clinical information submitted to date.

3. Discussion of the adult nocturia indication and risk/benefit assessment of desmopressin Melt for this new indication

In this NDA submission the applicant proposes a new indication for desmopressin: treatment of nocturia. Adult nocturia is defined as follows in a 2002 consensus meeting of the Standardization Sub-committee of the International Continence Society:

Nocturia is waking up at night to void. This applies to any number of voids at any time during the night, as long as the person is awake before voiding. When voiding occurs during sleep, this is

nocturnal enuresis. Both conditions can be referred to as night-time voiding, although the distinction between the two is clearly determined by the state of wakefulness. The first morning void is not included as a night-time void since this is a natural expulsion of urine produced during the night. In addition, although many people may consider one nighttime void to be normal, they are still considered to have nocturia. For some individuals, the trigger for waking may not be a desire to void, yet voiding is perceived to be necessary once awake; however, these individuals are still considered to have nocturia. Those 9e.g., the infirm or frail elderly) who wake with the need to void, but are unable to reach the bathroom before voiding, have a mixture of nocturia and incontinence, not nocturnal enuresis. Patients experiencing nocturia may or may not be bothered by this condition and it is the level of bothersomeness that will determine their help-seeking behaviour.”²

In addition to providing a consensus definition of nocturia, the Standardization Subcommittee of the International Continence Society proposed also an algorithm for the diagnosis and management of nocturia. First of all, it should be recognized that not all patients with nocturia request an intervention. The subgroup of patients who seek treatment are first offered lifestyle advice (reduction of caffeine/alcohol intake, limiting excessive liquid and food volume intake prior to bedtime) which may result in a satisfactory response and clinical improvement. In addition, further investigations are required for a correct diagnosis and to separate patients with adult nocturia from 1) patients with polyuria (urine output exceeding 40 ml/ body weight over a 24 hour period – once identified, polyuria needs further investigation to establish its cause), 2) patients with nocturnal polyuria (defined as the production of an abnormally large volume during sleep – defined as > 20% in the young adults, > 33% in the elderly, and “somewhere between these two extremes” for middle age patients) and 3) bladder storage problems (reduced functional bladder capacity, reduced nocturnal bladder capacity, detrusor overactivity, bladder hypersensitivity, bladder outlet obstruction with post void residual volume, urogenital ageing, or sleep disturbances such as insomnia, obstructive central apnea syndrome, periodic legs syndrome, restless legs syndrome, parasomnias, sleep disorders related to medical diseases).

As illustrated by this extended summary of the consensus diagnostic criteria and their applicability to clinical practice, it is to be expected that the diagnosis of nocturia is very complex and quite challenging at times as even some of the criteria for competing diagnoses lack definition clarity (see the age-specific definition of nocturnal polyuria as an example). It is conceivable though that most of these issues can be resolved with adequate labeling that takes into consideration the complexities described above.

The applicant states that the aim of initiating desmopressin treatment in adults with nocturia is to decrease nocturnal urinary volume and number of nocturnal voids which in turn, in applicant’s words, will benefit patients as follows:

The resulting decrease in the number of night-time awakenings to void has the potential to reduce morbidity, either by reducing the risk of falls and fractures in the elderly population or by eliminating disrupted sleep and its consequences on daytime functioning in the younger population. The evidence accumulating on the impact of nocturia would suggest that effective

2 Van Kerrebroeck P et al: The Standardisation of Terminology in Nocturia: Report from the Standardisation Subcommittee of the International Continence Society. *Neurology and Urodynamics* 00: 179-193 (2002).

treatment would improve health-related quality of life for a significant proportion of adults over the age of 40 years.

In this application Ferring Pharmaceuticals Inc. has shown that administration of desmopressin Melt at a daily dose of 100 µg in the context of a randomized, placebo-controlled clinical trial enrolling patients with adult nocturia was statistically successful and resulted in a reduction of the number of nocturnal voids at the predefined timepoint (day 28). Leaving aside for a moment the complexity of the diagnosis of nocturia, the relative difficulty in identifying correctly this target population, as well as the dose selection issues, the question that needs to be answered before approving this application is whether the reduction in the number of nocturnal voids demonstrated in trial CS029 is enough evidence that desmopressin Melt provides a clinical benefit to patients with nocturia. Or, more specifically: does a mean reduction in nocturnal voids of 1.4 translate into a true clinical benefit for the potential patient who may undergo this treatment and, in the process, may also face the risk of hyponatremia and related complications. The evidence provided by the secondary endpoint analyses of the study argues in fact the contrary. None of the quality of life questionnaires and PROs has resulted in a statistically significant benefit over placebo. At this point it is not entirely clear whether this failure is entirely methodological related to questionnaire design, or simply reflects a lack of efficacy of the treatment on these particular endpoints, or is a consequence of a lack of statistical power of the study (or a combination of some or all), but it certainly does not provide evidentiary support for the rationale of the treatment, that a reduction in the number of nocturnal voids will bring along a clear clinical benefit. In addition to the PRO analyses, the failure to demonstrate a statistical difference in total sleep duration between drug and placebo, along with only a small but statistically significant prolongation of the duration of uninterrupted sleep prior to the first void (about one hour at the highest Desmopressin dose of 100 µg) adds further doubt that what one might intuitively suspect (that improvement of QOL will follow the reduction of nocturnal voids) is truly supported by the data generated in this clinical trial. It could also be that the mean reduction of 1.4 voids is not enough to translate into a true clinical benefit, but further investigations will need to clarify this question. Thus, in the opinion of this reviewer, the applicant has failed to demonstrate a clear benefit for desmopressin treatment in patients with nocturia despite a statistical win for the maximal dose of 100 µg/day. While reaching this conclusion and raising this concern, it should be stated that demonstrating quality of life improvements in nocturia patients is not an excessive approval standard. First of all, it is in accordance with the expected clinical benefits proposed by the applicant and, secondly, it is only a substitute for the ultimate targeted benefit and stated reason for initiating desmopressin treatment in patients with nocturia in the first place: a reduction in the number of fractures and falls associated with nighttime awakenings due to nocturia. It also acknowledges that conducting a clinical trial to demonstrate a reduction in the number of falls/fractures is not currently feasible since there are no robust quantitative data describing such treatment effect to even conceive a statistical analysis plan.

4. Recommendation

Desmopressin Melt should not be approved for the treatment of adult nocturia without demonstrating a clear clinical benefit that goes beyond a statistically successful reduction in the number of nocturnal voids. Such clinical benefit should include as a minimum a demonstration of improvement in a validated quality of life questionnaire that is found acceptable by the Agency.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

DRAGOS G ROMAN
04/09/2010

MARY H PARKS
04/09/2010

Addendum to the Clinical Pharmacology Review Dated March 30, 2010

NDA: 22-517	Submission Date(s): 06/19/2009
Brand Name	NOCDURNA
Generic Name	Orally Disintegrating Desmopressin Tablet
Clinical Pharmacology Reviewer	Ritesh Jain, Ph.D.
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
Clinical Pharmacology Team Leader	Sally Choe, Ph.D.
Pharmacometrics Team Leader (Acting)	Christine Garnett, Pharm.D.
OCP Division	Clinical Pharmacology–II
OND division	Metabolism and Endocrinology Products
Sponsor	Ferring Pharmaceuticals
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Orally Disintegrating Tablet: 25 µg and 100 µg
Proposed Indication	NOCDURNA is indicated for treatment of nocturia in adults
Proposed Dosing	Women 25 µg daily at bedtime Men < 65 100 µg daily at bedtime Men ≥ 65 100 µg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment

Recommendation and Comments:

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 22-517, dated 06/19/2009, and finds it acceptable. However, the following comments should be sent to the sponsor as appropriate:

NDA 22-517 lacks acceptable pharmacokinetic information from the proposed to-be marketed formulation. Therefore, the Office of Clinical Pharmacology recommends the following:

- 1) The bioequivalence study (CS019) pharmacokinetic samples were analyzed using an analytical method that was not properly validated. Thus, Sponsor should reanalyze the study samples with a validated analytical method and submit the data to the Agency for review.
- 2) Sponsor should collect the pharmacokinetic samples in future clinical trials and make every effort to improve and properly validate the bioanalytical method to analyze study samples at proposed dose strength.

Background:

This addendum to NDA 22-517 Clinical Pharmacology review dated March 30, 2010 addresses the lack of pharmacokinetic (PK) information with the proposed to-be marketed formulation in current submission.

In NDA 22-517 application, the pharmacokinetics of the proposed to-be-marketed orally disintegrating tablet formulation has been submitted in bioequivalence (BE) study (CS019) and dose linearity study (CS021). However, due to the invalid bioanalytical methods, the study results were not accepted by this reviewer. The sponsor used a bioanalytical method that is neither robust nor reproducible and had high QC failure rates during validation and study sample analysis. While this proposed to-be-marketed formulation has been evaluated in the pivotal efficacy/safety trial (CS29), there were no PK samples that were collected in this trial.

The absolute bioavailability study (CS004) is the only study that utilized a validated bioanalytical method for the analysis of PK samples with an orally disintegrating formulation. However, the formulation that was used in this absolute bioavailability is not identical to the proposed to-be marketed formulation. Table 1 below shows the tablet composition of the proposed to-be-marketed formulation and Table 2 shows the composition of the formulation used in the absolute bioavailability study (CS004).

Table 1: Composition of desmopressin to-be marketed orally disintegrating tablets at a) 25 µg strength and b) 100 µg strength.

a)

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.025 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)	(b) (4)	Ph.Eur./USP/JP, Curr. Ed.
Mannitol	(b) (4)	(b) (4)	Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous	(b) (4)	(b) (4)	Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 25 µg desmopressin free base.

b)

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.100 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)	(b) (4)	Ph.Eur./USP/JP, Curr. Ed.
Mannitol	(b) (4)	(b) (4)	Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous	(b) (4)	(b) (4)	Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 100 µg desmopressin free base.

Table 2: Composition of desmopressin orally disintegrating tablet used in absolute bioavailability study (CS004).

Component	200 µg	400 µg	800 µg
Desmopressin (µg)	200	400	800
Gelatin (mg)	(b) (4)	(b) (4)	(b) (4)
Mannitol (mg)	(b) (4)	(b) (4)	(b) (4)
Citric acid, anhydrous	(b) (4)	(b) (4)	(b) (4)

Reviewer's Comments:

- 1) The two formulations utilized in BE study (CS019) and the absolute bioavailability study (CS004) have different amounts of excipients and the impact of these changes are not clear even though they are not expected to impact the dissolution profile of the product, an orally disintegrating tablet. Thus, we recommend the sponsor to reanalyze the PK study samples from BE study, CS019 which evaluated the to-be marketed formulation and submit the results to the Agency for review.
- 2) This reviewer became aware of the Office of New Drug's decision on Complete Response for this application. Please see Dr. Mary Park's Division Director Memo for detail. Even though the sponsor previously communicated the difficulty in quantifying the exposure data at their currently proposed doses, 25 µg and 100 µg, the sponsor should collect the pharmacokinetic samples in future clinical trials and make every effort to improve the bioanalytical method to analyze study samples at proposed dose strength.
- 3) This reviewer also like to recommend the addition of "to be administered sublingually" in the HIGHLIGHTS section of the label under **DOSAGE AND ADMINISTRATION** section when the label of the product is ready to be reviewed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

RITESH JAIN
04/09/2010

SALLY Y CHOE
04/09/2010

CLINICAL REVIEW

Application Type NDA Type 5
Application Number(s) 22-517
Priority or Standard Standard

Submit Date(s) June 19, 2009
Received Date(s) June 22, 2009
PDUFA Goal Date April 22, 2010
Division / Office DMEP/ODEII

Reviewer Name(s) William Lubas M.D.,Ph.D.
Review Completion Date March 17, 2010

Established Name desmopressin acetate
(Proposed) Trade Name Nocdurna
Therapeutic Class vasopressin analogue
Applicant Ferring Pharmaceuticals Inc.

Formulation(s) Oral disintegrating tablet
Dosing Regimen Single dose at bedtime
Indication(s) Adult nocturia
Intended Population(s) Adults with nocturia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that Nocdurna be approved for the treatment of adult nocturia at the following doses: women 25 µg and men 50 µg.

1.2 Risk Benefit Assessment

Nocdurna demonstrated efficacy at doses of 25, 50 and 100 µg in women and at doses of 50 and 100 µg in men. However, because of concern over the risk of hyponatremia at doses of 50 and 100 µg in women and 100 µg in men the maximal recommended doses are 25 µg in women and 50 µg in men.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no need for Postmarket Risk Evaluation and Mitigation Strategies with the currently proposed dosing scheme.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for PostMarket Requirements. Should the sponsor consider seeking approval of higher doses such as 50 and 100 µg in women and 100 µg in men, which have been shown to be efficacious in pivotal study CS029, the sponsor will need to provide evidence that the monitoring scheme they have proposed will safely identify patients at risk of hyponatremia.

2 Introduction and Regulatory Background

2.1 Product Information

Vasopressin, the naturally occurring antidiuretic hormone, binds to receptors in the collecting duct and distal tubules of the kidney promoting water reabsorption and binds to receptors on smooth muscle cells in arterioles leading to vasoconstriction and an increase in systemic blood pressure. Desmopressin, a synthetic analogue of vasopressin, is modified to increase and prolong the antidiuretic effect while minimizing the effect on smooth muscle vasoconstriction.

Desmopressin is available as a subcutaneous injection, nasal spray, and oral tablets. It has been approved for the following indications:

- treatment of patients with diabetes insipidus who have a deficiency of endogenous vasopressin
- measurement of the kidney's ability to concentrate urine [i.e. renal concentration capacity testing (RCCT)] for patients with suspected renal disease
- treatment of children with primary nocturnal enuresis (PNE)
- treatment of patients with type I von Willebrand's disease and hemophilia A

The nasal spray is no longer marketed for the PNE indication because of a higher risk of hyponatremic seizures compared to the tablet formulation. The therapeutic dose for the treatment of bleeding disorders is about 15-fold higher than the dose used for the voiding indications, so treatment requires use of a high-dose nasal spray or injection.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently approved medications for the treatment of adult nocturia in the US. According to the sponsor, desmopressin has been approved for the treatment of adult nocturia, in subjects up to 65 years of age, in 68 countries worldwide.

Drugs used to treat over active spastic bladder or underactive flaccid bladder (e.g. oxybutynin, tolterodine, or bladder obstruction due to benign prostatic hypertrophy (e.g. tamsulosin,)) have been studied for the treatment of adult nocturia but have not been shown to be effective. Currently none of these products are indicated for the treatment of nocturia in the US.

2.3 Availability of Proposed Active Ingredient in the United States

Desmopressin is available in 0.1 and 0.2mg scored tablets for the treatment of PNE, central DI (diabetes insipidus) and Renal Concentration Capacity Testing.

Desmopressin is available as a 4 µg/mL IV injection for the treatment of central DI and to prevent bleeding in patients with hemophilia A or type I von Willebrand's Disease.

Desmopressin is available as a 10 µg/spray nasal spray, and as a 100 µg/mL rhinal tube capable of dispensing doses of 5 µg and above, intranasally, for the treatment of central DI.

Desmopressin is available as a 150 µg/spray nasal spray to prevent bleeding in patients with hemophilia A or type I von Willebrand's Disease.

2.4 Important Safety Issues With Consideration to Related Drugs

There are currently no other V2 receptor agonists approved in the US.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Desmopressin tablets NDA 21-795, originally referred to as Minirin tablets, were approved May 5, 2008 for the treatment of central diabetes insipidus, primary nocturnal enuresis and renal concentration capacity testing. The sponsor has now developed a rapid melting oral lyophilisate, desmopressin Melt, for the treatment of adult nocturia. Pharmacokinetic data indicate a linear relationship between the Tablet and Melt formulations as follows:

60 µg Melt corresponds to 0.1 mg Tablet formulation
120 µg Melt corresponds to 0.2 mg Tablet formulation
240 µg Melt corresponds to 0.4 mg Tablet formulation
360 µg Melt corresponds to 0.6 mg Tablet formulation

Desmopressin Melt (60 µg, 120 µg, and 240 µg) was first approved in February 2005 and is currently approved in 43 countries. In countries where desmopressin Melt is currently approved, use is limited to patients <65 years of age and no serum sodium monitoring is required. The two doses evaluated in the current submission, 25 and 100 µg of desmopressin Melt, would correspond to 0.042mg and 0.167mg of the tablet formulation.

A preNDA meeting was held with the sponsor on Oct. 20, 2008. At the meeting the sponsor had requested consideration for the approval of a 25 µg dose as a starting dose with dose titration to 50 and 100 µg as needed for improved efficacy. The Agency had mentioned that they would need to review all of the data but that the preliminary data in the ITT population, including both male and females patients, suggested that the 25 µg dose did not show efficacy. The sponsor proposed a potential monitoring scheme for the prevention of hyponatremia and was informed that such a scheme must be demonstrated to be effective and reliable. The sponsor was asked to submit a REMS in support of the proposed monitoring scheme. The sponsor agreed to submit Quality of Life questionnaire results to support the indication, and was informed that they would need to be reviewed by the SEALD group to determine if the methodology was acceptable to permit labeling claims.

2.6 Other Relevant Background Information

Nocturia vs. PNE

The currently approved indication of primary nocturnal enuresis, PNE, describes a condition in which individuals are not awoken at night by the urge to urinate and as such have leakage of urine while they sleep. The term “primary” refers to individuals who

have never had nighttime bladder control to be distinguished from “secondary” enuresis seen in individuals who have documented nighttime bladder control for at least 6 months and then lose it, usually temporarily, as a result of medical (e.g. UTI, diabetes etc.), or psychological conditions (e.g. difficulty in school, parental conflicts etc.). As children mature the incidence of PNE decreases with age so that by age five, 15% or less of children still have PNE. By age eight half of these will improve on their own without any specific therapy so the age at which treatment begins depends on parental concern and the treating physician’s judgment. About 1% of individuals above age 18 will continue to have enuresis, typically due to a physical disability or developmental delay and will require long term treatment.

Adult Nocturia refers to a condition, which becomes more prevalent and severe with age, in which individuals regularly need to wake up from sleep to void multiple times at night. The prevalence of adult nocturia in a large 5,503 patient population-based epidemiology study, the Boston Area Community Health Survey (BACH), was estimated at 28% in individuals age 30 to 79¹. These individuals do not typically have bedwetting accidents but are affected primarily by a decrease in the quality of their sleep. Sleep disruption, fragmentation and deprivation, during initial slow wave sleep that occurs in first third of the night, result in increased daytime fatigue and sleepiness, with diminished mental acuteness.

Adult nocturia can also lead to an increased risk of falls with resultant fractures in elderly subjects due to the need to navigate to the bathroom in the dark while in a sleepy state. The sponsor references research which shows a 2 fold increase in falls in individuals with adult nocturia of ≥ 2 voids per night². While falls are a problem, severe injuries such as hip fractures can have a drastic affect on the patient’s health. A study of public hospitals in Austria identified nocturia of ≥ 2 voids per night as an age-independent risk factor for hip-fractures in men age 40 to 80 years (0.9% vs. 2.7%, $p=0.03$)³. Also a study of elderly patients ≥ 70 years of age in Japan identified an increased mortality rate associated with the nocturia of ≥ 2 voids per night even after adjusting for several different factors that may have contributed to mortality⁴. While such

1 [The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey](#). Fitzgerald MP, Litman HJ, Link CL, McKinlay JB; BACH Survey Investigators. J Urol. 2007 Apr;177(4):1385-9.

2 [Nocturia: a risk factor for falls in the elderly](#). Stewart RB, Moore MT, May FE, Marks RG, Hale WE. J Am Geriatr Soc. 1992 Dec;40(12):1217-20.

3 [Nocturia is an age-independent risk factor for hip-fractures in men](#). Temml C, Ponholzer A, Gutjahr G, Berger I, Marszalek M, Madersbacher S. Neurourol Urodyn. 2009;28(8):949-52.

4 [ASSOCIATION BETWEEN NOCTURIA AND MORTALITY IN A COMMUNITY-DWELLING ELDERLY POPULATION AGED 70 YEARS AND OVER: RESULTS OF A 3-YEAR PROSPECTIVE COHORT STUDY IN JAPAN](#) Haruo Nakagawa*, Kaijun Niu, Atsushi Hozawa, Yoshihiro Ikeda, Yasuhiro Kaiho, Kaori Masuda-Ohmori, Ryoichi Nagatomi, Ichiro Tsuji, Yoichi Arai, Journal of Urol. Vol. 181, No. 4, Supplement, Saturday, April 25, 2009.

a study presents an interesting association, the authors did not include a reporting rate for fractures in the subgroups which would have been helpful in attributing any of the increased mortality to an increase in falls and fall related fractures.

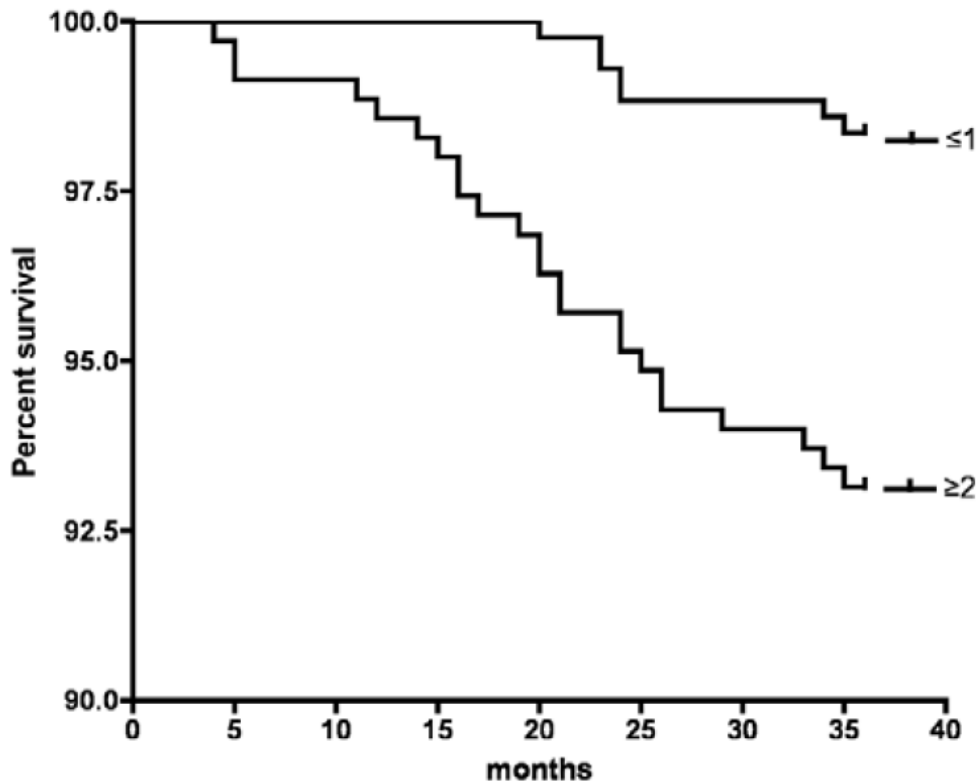


Fig. 1 Survival with/without nocturia

A similar finding was seen in a study of two Swedish counties, but again there was no definite data to show the increase in mortality was due to an increase in the rate of falls and fall related fractures⁵. Therefore, while it still needs to be shown that an improvement in nocturia could have a beneficial effect on mortality it seems reasonable to assume that a decrease in nighttime awakenings to go to the bathroom should be associated with better sleep quality and fewer falls in the elderly.

Etiology of Adult Nocturia

Vasopressin secretion from the hypothalamus is under a circadian rhythm with normally higher levels of release at night. Subjects with normal bladder function can have nocturnal polyuria due to a decrease in vasopressin secretion caused by a shift in the circadian rhythm with age, a reduced sensitivity to vasopressin, a nocturnal solute diuresis or varying combinations of all three mechanisms. Subjects with reduced bladder capacity due to detrusor instability can also present with nocturia but they are

5 [Mortality in the elderly in relation to nocturnal micturition](#) R. ASPLUND BJU International (1999), 84, 297–301

likely to have daytime symptoms as well. The ability of desmopressin to decrease nocturnal polyuria is dependent on the exact mechanism responsible for the symptoms. For example, desmopressin would be expected to be more effective in subjects with low night time vasopressin levels or decreased receptor sensitivity than it would be for subjects with a substantial nighttime solute diuresis.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Data quality and completeness were adequate to permit review.

3.2 Compliance with Good Clinical Practices

The Division requested the inspection of the following two sites: 020 and 024.

Investigator	Mitchell Efros	Site #	020	AccuMed Research Associates
CRA	Henry Blokpoel	(b) (6)		
Principal Investigator	Mitchell Efros	(b) (6)		
Sub Investigator	Anthony Bruno			
Sub Investigator	Louis Faiella, III			
Sub Investigator	Toby Handler			
Sub Investigator	John Mordente			
Regulatory Contact	Kerri Weingard			
Study Supplies contact	(b) (6)			
Site Coordinator	(b) (6)			
Site Coordinator	(b) (6)			
Budget/Contract contact	(b) (6)			
Main Site Coordinator	(b) (6)			
Institution main address				
AccuMed Research Associates				
1305 Franklin Ave, Suites 100 & 150, Garden				
City, NY, 11530, US				
Fax: 516-746-2191				

Clinical Review
William Lubas M.D., Ph.D.
NDA 22-517
Nocurna (desmopressin acetate)

Investigator	Stephen Fehnel	Site #	024	Advanced Clinical Concepts
CRA	Gloria Phillips	(b) (6)		
Principal Investigator	Stephen Fehnel	(b) (6)		
Sub Investigator	Radhika Allawadi			
Regulatory Contact	Jan Petrie			
Study Supplies contact	(b) (6)			
Site Coordinator				
Site Coordinator				
Site Coordinator				
Site Coordinator				
Budget/Contract contact				
Main Site Coordinator				
Institution main address Advanced Clinical Concepts 301 S. Seventh Ave, Suite 155, West Reading, PA, 19611, US Fax: 610-929-3699				

Efficacy seemed fairly similar across the sites, and so was not used to determine which study sites to audit. Site 020 was chosen because it enrolled the largest number of patients (e.g. 99 patients screened, 68 in ITT population), had the largest number of protocol deviations (e.g. 104) and had the second highest number of cases of hyponatremia (e.g. 3 patients with 11 events, Na < 130 mmol/L, ISS ADNA dataset). Site 024 was chosen because it had the largest number of cases of hyponatremia (e.g. 5 patients 9 events, Na < 130 mmol/L, ISS ADNA dataset).

The DSI clinical inspection summary dated March 5, 2010 determined that studies at both sites appeared to have been conducted adequately, and that the data generated by the clinical sites was acceptable in support of the current indication.

3.3 Financial Disclosures

Ferring is a privately owned company with no stock options and with complete private ownership of the relevant drug patents so they argue that the individual investigators who carried out these clinical studies on which the application relies had no financial interest in the company or the tested product. Formal requests for financial disclosure from the study investigators were not included as part of the original study evaluation and were not submitted with this application. A completed FDA 3454 form was submitted with the names of all investigators in these trials, stating that none of them had entered into any financial arrangements with these clinical investigators, none had any proprietary interest in this product and none had received any significant payments of any sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug substance of desmopressin Melt 25, 50 and 100 µg is desmopressin acetate, a synthetic analogue of the human arginine-vasopressin. This is identical to the drug substance used in desmopressin Tablet 0.1 and 0.2 mg (approved in US) and in desmopressin Melt 60, 120 and 240 µg (approved in Europe).

Table 1 Composition of desmopressin melt

Component	Quantity
Desmopressin (µg)	25, 50 and 100
Gelatin (mg)	(b) (4)
Mannitol (mg)	
Citric acid, anhydrous	

The gelatin used in the drug product was prepared from fish (b) (4). Therefore, it is possible that subjects allergic to fish may be allergic to the current formulation.

Due to the sensitivity of desmopressin acetate to humidity it is important to (b) (4). The final packaging in blister packages is designed to protect the drug product from humidity and light.

All units were shown to have a disintegration time of less than 10 seconds in water at 37°C.

4.2 Clinical Microbiology

None.

4.3 Preclinical Pharmacology/Toxicology

Study FE992026 DS TOX 0301, "Oral Irritation Test in the Syrian Hamster", tested the toxicity of the melt formulation compared to placebo on the cheek pouches in 20 Syrian hamsters. Oral lyophilisates containing up to 360 µg of desmopressin and placebo were devoid of any effect after daily dosing for 28 days in this local irritation test.

Study FE992026 DS PHA 0501 investigated the absorption of desmopressin across the oral mucosa following sublingual administration of the melt formulation in pigs. Absorption of the melt formulation through oral mucosa in anesthetized pigs with an

occluded esophagus was ~2-fold greater and T max was delayed ~2-fold compared to administration to conscious pigs with a non occluded esophagus (AUC/ μg 1.49 vs. 0.67 hrXpg/mL and Tmax 1.93 hours vs. 0.82 hours). As a comparison, absorption, AUC/ μg , was even lower and Tmax, was even sooner for desmopressin tablets given to conscious pigs with a non occluded esophagus (e.g. 0.20 hrXpg/mL and 0.67 hours, respectively).

Reference for additional Preclinical data is made to NDA 19-955, DDAVP tablets 0.1mg and 0.2mg (Aventis).

4.4 Clinical Pharmacology

Study FE992026 CS004 was an open-label, randomized, balanced, four-way cross over study of three doses of sublingual melt (200, 400 and 800 μg) and IV desmopressin (2 μg). Following sublingual administration desmopressin maximum plasma concentrations were observed at 0.5 - 2.0 hours post dose. The maximum plasma concentration was 14, 30 and 65 pg/mL after a sublingual dose of 200, 400 and 800 pg, respectively. After reaching maximum plasma concentration desmopressin was eliminated with a half-life in the range of 2.8 - 3.0 hours.

Study FE992026 CS020 was an open-label, randomized, two-period cross over bioequivalence study comparing 240 μg of the desmopressin melt to 0.4mg of the desmopressin tablet. AUC and AUCt were within the pre-specified bioequivalence range of 80-125%. However, Cmax was slightly low [95% CI: 73%, 103%]. The relative bioavailability of the melt formulation was 1.52 [95% CI: 1.25, 1.85] greater than the tablet. According to Dr. Jain, the data from this trial cannot be used for labeling as the bioassay used to measure lower serum levels of the drug product was different from the previously validated assay and gave irreproducible results.

Study FE992026 CS021 was an open-label, randomized, three-period, cross over study of three doses of sublingual melt (60, 120 and 240 μg). After sublingual administration desmopressin maximum plasma concentrations were observed at 1.0 – 1.5 hours after dosing. Inter-subject variability was high with CV% of 34-84% for Cmax and 41-122% for the different AUCs. After reaching maximum plasma concentration desmopressin was eliminated with a half-life in the range of 2.6 – 2.9 hours.

Study FE992026 CS001 was a controlled, stratified, single-dose PK study in subjects with no, mild, moderate and severe renal impairment. In healthy individuals 52% of an intravenous dose of desmopressin is eliminated unchanged via the kidneys. The observed mean terminal half life was 2.8, 4.0, 6.6 and 8.7 hours for patients with no, mild, moderate and severe renal impairment defined as creatinine clearances of > 80, 50-80, 30-49 and 5-29mL/min, respectively.

Reference for additional Clinical Pharmacology data is made to NDA 19-955, DDAVP tablets 0.1mg and 0.2mg (Aventis).

5 Sources of Clinical Data

The pivotal trial FE992026 CS029 and its open label extension CS031 were submitted electronically at <\\Cdsub1\EVSPROD\NDA022517\0000>. Additional submissions included the following:

- 0001 Request for proprietary name review for NOCDURNA™
 - 0002 Patent information
 - 0003 Index describing each SAS program submitted in the NDA
 - 0004 PK Dataset Responses
 - 0005 Responses to CMC and Nonclinical Information Requests and Updated Stability Information
 - 0006 4 month Safety Update Report
 - 0007 Responses to Clinical, Biostatistical, and CMC (Microbiology) Information Requests Includes Sodium ADNA Dataset from Noct 2A, 2B, 3A, 3B and 4 trials.
 - 0008 Response to Clinical Pharmacology and CMC Requests for additional information
 - 0009 Revised Draft Labeling – PI and Med Guide
 - 0010 Draft Labeling
- Pending: Response to Clinical questions about post marketing cases of hyponatremia (info received by email, still waiting for the DARRTS submission)

5.1 Tables of Studies/Clinical Trials

Table 2 Table of Clinical Trials

Study ID	No. of Centers	Study Dates (Start–Completion)	No. of Subjects Randomized / Completed / Dropouts	Design / Control	Route and Regimen	Sex (M/F) Mean Age (Range) Race (W/B/O)	Primary Efficacy Endpoints
FE992026 CS29 (Part I)	78 enrolled subjects	Part I Start: 04 Jun 2007	799 randomized/ 710 completed/ 89 discontinued	Randomized, double-blind, placebo- controlled, parallel-group	Oral placebo or Oral desmopressin Melt: 10 µg, 25 µg, 50 µg, or 100 µg	416M/341F 62.0 years (20–89) 80%W/15% B/5%O	Change from baseline to final visit (Day 28) in mean number of nocturnal voids; proportion of subjects with >33% reduction in the mean number of nocturnal voids.
		Part II End: 22 Feb 2008	665 enrolled/ 566 completed/ 99 discontinued	Placebo subjects re-randomized (at initial randomization) to active drug	Oral desmopressin Melt: 10 µg, 25 µg, 50 µg, or 100 µg	369M/296F 61.9 years (22-89) 82%W/14%B/4%O	Change from baseline to Months 2, 3, 5, and 7 in mean number of nocturnal voids; proportion of subjects with >33% reduction in the mean number of nocturnal voids
FE992026 CS31	70 enrolled subjects	6 Dec 2007 Ongoing	508 enrolled/ 379 ongoing as of 31 Dec 2008/ 129 discontinued	Open-label ^a	Oral desmopressin Melt: 10 µg, 25 µg, 50 µg, or 100 µg	291M/217F 62.2 years (23-88) 82%W/14%B/4%O	Change from baseline of CS29 in mean number of nocturnal voids, proportion of subjects with >33% reduction in the mean number of nocturnal voids, duration of first sleep period, total sleep time, and quality of life

B = Black; F = female; M = male; O = other; W = White
 a. Study CS31 was an open-label extension of Study CS29.

Source Table 1 sponsor's 2.7.3 Summary of Clinical Efficacy

FE992026CS029 (CS029) A Randomized, Double Blind, Placebo Controlled, Parallel Group, Multi-Center Study with a Double Blind Extension Investigating the Efficacy and Safety of a Fast-Dissolving (“Melt”) Formulation of Desmopressin for the Treatment of Nocturia in Adults

FE992026CS031 (CS031) A Multi-Center Extension Study Investigating the Long Term Efficacy and Safety of a Fast Dissolving (“Melt”) Formulation of Desmopressin for the Treatment of Nocturia in Adults

Note: CS031 is the open label extension of CS029.

5.2 Review Strategy

The efficacy review focused on the pivotal trial CS029 and its open label extension CS031. Independent reviews were performed by biostatistics, Dr. Wei Liu, and biometrics, Dr. Anshu Marathe, and discussions from these reviews were used in this medical officer’s final assessment. The safety review included information from the pivotal trials CS029 and CS031 using the melt formulation, as well as information from earlier nocturia trials using the tablet formulation (Noct 2, 3 and 4).

5.3 Discussion of Individual Studies/Clinical Trials

Study Design

Study CS029, Parts 1 & 2, and its open-label extension, study CS031, are the pivotal trials submitted for the approval of the treatment of adult nocturia. Study CS029 consisted of two parts. Part 1, was a randomized, double-blind, placebo-controlled, parallel-group, multi-center 28 day efficacy trial with subjects randomized to one of 4 doses of desmopressin Melt (10, 25, 50, or 100 µg) or placebo. Part 2 was a 6 month double-blind extension in which patients on active therapy during Part 1 continued on the same therapy while subjects initially assigned to the placebo group were re-randomized to one of the 4 active treatment groups. Study CS31, was initially a blinded continuation of CS029 Part 2, until the original study database was locked and data analyzed. Once the original data was analyzed patients who had originally been assigned to sub therapeutic doses of desmopressin Melt (e.g. 10 µg) during CS029 were randomly assigned to one of the doses with proven efficacy (e.g. 25, 50, or 100 µg).

Patient Population

Men and women over 18 years of age with adult onset nocturia

Inclusion Criteria

Adults with an average of ≥ 2 nocturnal voids per night as determined by a 3-day voiding diary.

Exclusion Criteria

Adults with the following medical conditions were excluded: renal insufficiency, hyponatraemia, diabetes insipidus, clinical suspicion of urinary retention and/or post void residual volume >150 mL, current or past urologic malignancy, clinical evidence of current genitourinary tract pathology, or neurogenic detrusor activity. Males with a clinical suspicion of bladder outlet obstruction and/or urine flow <5 mL/s or surgical treatment for bladder outlet obstruction/benign prostatic hyperplasia performed within the past 6 months.

Study FE992026CS029 Part 1

Subjects were randomized in equal proportions to one of the 4 active treatment groups (10, 25, 50, or 100 μg) or placebo. Since elderly patients are at higher risk of hyponatremia, subjects were stratified by age (<65 , ≥ 65 years). Since efficacy may be a function of the absence/presence of nocturnal polyuria, (ratio of nighttime urine volume/24-hour urine volume $\geq 33\%$) subjects were stratified by this condition as well. Approximately 750 subjects were to be enrolled, with approximately 150 subjects per treatment group. All treatments were taken orally at night approximately 1 hour prior to bedtime, and subjects were instructed to limit their fluid intake prior to drug self-administration. Subject were evaluated at a screening visit within 21 days of initial dosing, and returned for follow-up visits on Days 4, 8, 15, 22, and 28. The primary objectives of Part I were to demonstrate the superiority of one or more doses of the desmopressin Melt formulation compared to placebo in reducing the mean number of nocturnal voids and increasing the proportion of subjects with $>33\%$ reduction from baseline in mean number of nocturnal voids during the last week of therapy.

Patients were asked to record nocturnal voids in a diary on 3 consecutive 24-hour periods at baseline and on a weekly basis for four weeks (i.e. Days 8, 15, 22 and 28). Visit 7 on Day 28 was selected as the End-of-Study Visit and the predefined efficacy endpoint of Part I. The first morning void was not counted as a nocturnal void even though its volume was included as part of the nocturnal urine volume. Subjects recorded in a paper diary the time study drug was taken and the time of each nocturnal and daytime void. Urine volumes were recorded only prior to the Day 28 End-of-Study Visit.

Study FE992026CS029 Part 2

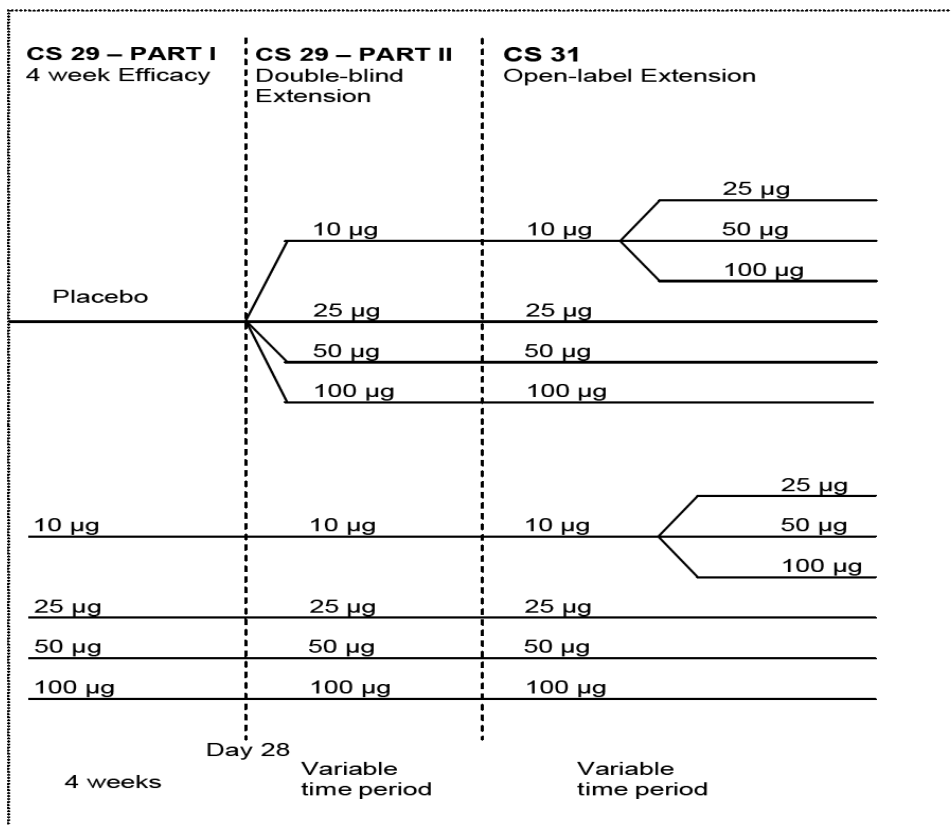
Upon completion of Part I all subjects on active treatment continued into Part II on the same treatment for up to an additional 6 months. Subjects assigned to placebo in Part I

were randomly assigned to 1 of the 4 active treatments. To ensure that the trial remained fully blinded during the full extent of both Parts I and II, re-randomization of subjects assigned to placebo after 4 weeks of treatment was predetermined at the time of initial randomization. Subjects were evaluated at follow-up visits on Days 4, 8, 15, 29, and every 4 weeks thereafter. The primary objective of Part II was to demonstrate the durability of effect achieved in Part I.

Study FE992026CS031

Study FE992026CS031, was initially a blinded continuation of FE992026CS029 Part 2, until the original study database was locked and data analyzed after approximately 10 months of treatment. Based on the results of FE992026CS029, which indicated the 10 µg dose was sub-therapeutic, subjects originally assigned to the 10 µg dose were randomly reassigned to one of the other doses of desmopressin Melt (i.e., 25 µg, 50 µg, or 100 µg). The study was ongoing until approximately February 2010 but data through 31 December 2008 are included in this submission.

Figure 1 Dosing during FE992026CS029 (CS029) Parts 1 & 2 and FE992026CS031 (CS031)



Source Figure 1 sponsor's 2.7.3 Summary of Clinical Efficacy

6 Review of Efficacy

Efficacy Summary

The pivotal trial CS029 was a randomized, double-blind, placebo-controlled, trial of 4 active treatment groups of Nocdurna (i.e. 10, 25, 50 and 100 µg). It enrolled adults 18 years of age and older with an average of ≥ 2 nocturnal voids demonstrated using a 3-day voiding diary. Subjects with urinary retention and/or a post void residual of $>150\text{mL}$ were excluded, although subjects could be enrolled if they had been on stable doses of alpha blockers or 5-alpha-reductase inhibitors for prostatic hypertrophy or antispasmodics for overactive bladder. The primary endpoint was a composite of (1) the mean reduction in the number of nocturnal voids and (2) the proportion of subjects with a $> 33\%$ reduction from baseline in the mean number of nocturnal voids. Nocturnal voids were recorded in a diary on 3 consecutive 24 hour periods at baseline and during the first four weeks of the study (e.g. Days 8, 15, 22 and 28). Day 28 was the designated prespecified endpoint, even though desmopressin should be capable of maximal effect at each of the earlier time points. Secondary endpoints were changes in the initial period of undisturbed sleep, total sleep time, a number of Quality Of Life questionnaires measuring Patient Reported Outcomes (PROs), and durability of effect in the open label extension CS031. Nocturnal urinary volume was also measured at baseline and Day 28.

There are currently no approved drug products in the US for the proposed indication i.e. treatment of adult nocturia. The Agency requested a coprimary endpoint that would show both a statistical decrease in nocturnal voids in the study population and a decrease of at least 33% from baseline in the number of nocturnal voids as this was taken to estimate a clinically relevant benefit in the majority of patients. The original protocol specified that the sponsor had to show statistical significance ($p\text{-value} \leq 0.05$) independently for both components of the primary endpoint to win approval for the indication. For all patients (men and women) Nocdurna was statistically significant at the 100µg dose with respect to both parts of the coprimary endpoint for all four weeks of the efficacy trial including the predefined time point of Day 28. The 50µg dose was highly statistically significant with respect to both parts of the coprimary endpoint for the first three weeks of the efficacy trial ($p\text{-values}$ ranging from 0.0007 to 0.0045), but for the prespecified time point of Day 28 only the first part of the coprimary endpoint was statistically significant ($p=0.021$) whereas the second part of the coprimary endpoint was not significant ($p=0.27$). In addition, the $p\text{-values}$ for stricter responder rates of 50% and 75% for the second part of the coprimary endpoint on Day 28 were 0.08 and 0.07, almost statistically significant. If the predefined endpoint had been either Day 8, 15 or 22 the efficacy of the 50 µg dose would have been confirmed. However, as the sponsor did not win on both parts of the coprimary at the prespecified time point of Day 28 the 50 µg dose was not a technical win from a statistical point of view. Similarly, since the 25 µg dose was only statistically significant on both parts of the coprimary endpoint on

study Days 8 and 15 but not on Days 22 and 28 (the prespecified time point) this dose too would not technically be supported by these study data.

A post hoc analysis of these data showed that there had been a much larger than expected difference in efficacy with respect to gender in this study. Women showed statistically significant efficacy for both parts of the coprimary endpoint on the prespecified time point of Day 28 for doses of 25 ($p=0.02$), 50 ($p=0.009$) and 100 μg ($p=0.0001$). From a pure statistical point of view it is not recommended to look at subgroup analyses such as these unless the sponsor can first show a statistically significant effect for “all patients” at a specific dose. As such the data in “all patients” does not support the validity of the efficacy findings seen in women at the lower doses of 50 and 25 μg . However, it is this medical officer’s assessment that there were a sufficient number of women enrolled in this study to perform an analysis on women only and this need not be looked at as simply a subgroup analysis. In addition, there is support for the observed gender differences seen here from other nonclinical and clinical studies to argue that it is scientifically justifiable to analyze the data separately by gender. Therefore, this medical officer concludes it is reasonable to accept the findings of efficacy in women at doses of 25 and 50 μg .

In the post hoc analysis men did show some limited efficacy at the 50 μg dose. The first part of the co-primary endpoint was statistically significant on Days 8 and 22 and almost statistically significant on Day 15 ($p=0.08$). The second part of the coprimary endpoint was statistically significant on Days 8, 15 and 22. However, neither parts of the coprimary endpoints were statistically significant on Day 28, the predefined endpoint. It is unlikely that the Day 28 observation represents a loss of efficacy as the ITT population showed persistent efficacy with 50 μg at Weeks 52 and 72 in the open label extension CS031. A closer look at the dose response data by gender shows an unexpected increase in the efficacy of the placebo in males on Day 28 (see arrows in Fig. 4). While it is possible to argue that this represents normal variability in the placebo group, a similar increase in efficacy is not seen with the 10 μg low dose group, which should also represent a dose which is expected to have minimal efficacy. It is this medical officer’s impression that this relative increase in efficacy in the male placebo group on Day 28 is responsible for the inability to demonstrate efficacy with the 50 μg dose. In contrast, the 50 μg dose on Day 28 does show a “statistically significant” increase relative to the 10 μg dose, which showed a more stable level of activity over the four week course of the study. However, as the null hypothesis was developed with respect to the placebo group a comparison with respect to the low dose, 10 μg group, which was not a predefined analysis would not be statistically justified. Except for the placebo group, efficacy across the 4 week trial shows a clear dose response in males with the point estimate of the 50 μg group in males similar to the response seen in women for the 25 μg dose (i.e. about 1 nocturnal void decrease (first coprimary) and a 50% increase in the 33% responder rate (second coprimary, see Fig. 4). These same doses also resulted in a maximal decrease (~300mL) in mean nocturnal urine volume on Day 28 (see Fig. 3) also supporting the efficacy of these doses. Therefore, it is this medical

officer's assessment that there is enough alternative evidence to support the finding that the 50 µg dose represents an effective starting dose in men and it would be reasonable to recommend dose titration up to 100 µg for men who don't achieve optimal efficacy at the lower dose, assuming titration to higher doses is not precluded by safety concerns.

The secondary endpoint of duration of sleep prior to first nighttime void also supports the efficacy at the lower doses. There were statistically significant mean increases from baseline to Day 28 in the initial sleep duration of 83, 85, and 107 minutes in the 25 µg, 50 µg, and 100 µg groups, respectively compared to an increase of only 38 minutes in the placebo group. Total sleep time increased slightly from 8 to 25% in all treatment groups but this effect was independent of the treatment dose.

A review of the PRO endpoints submitted by the sponsor was performed by the SEALD team. They determined that these endpoints did not adequately address the issues of nocturia and as such should not be used to assess the clinical impact of Nocdurna for the treatment of adult nocturia. In either case, none of the tests was statistically significant for the patients in the Nocdurna group although mean responses were in general more favorable for the subjects in the Nocdurna treatment groups.

In conclusion, it is this medical officer's assessment that there is enough clinical evidence to support the efficacy of Nocdurna in the treatment of adult nocturia in women at doses 25, 50 and 100 µg and in men at doses 50 µg and 100 µg.

6.1 Indication

The proposed indication is to treat patients with adult nocturia by decreasing the number of nocturnal voids and increasing the length of time prior to the first nocturnal void.

6.1.1 Methods

There is one pivotal double-blind trial, CS029, with an open-label extension, CS031, using the to-be-marketed sublingual melt formulation and 3 double-blind, short-term trials (NOCT 2A, 3A and 4A) and two open-label, long-term extensions (NOCT-2B and 3B) using the tablet formulation in this submission. Only the pivotal trial will be reviewed in this submission for efficacy. The tablet trials will be discussed in the Safety Review with respect to the risk of hyponatremia.

Demographics (CS029 Part 1)

The mean age of the ITT population was 62 years (median 64 years). Age ranged from 20 to 89 years, with 33% age 65 to < 75 and 16% ≥75 years of age. 45% of the subjects were female. The mean weight was 85.8kg and the mean BMI was 29.6 kg/m². Most subjects were Caucasian 80%, with 15% African American and 7% Hispanic. 80% of

ITT population met the serum sodium monitoring criteria (baseline serum sodium ≥ 135 mmol/L in all subjects; Day 4 and Day 28 serum sodium level ≥ 135 mmol/L in subjects ≥ 50 years of age).

Medical Officer's comments

In general the ITT population was overweight with the mean BMI just under the obesity cut off of 30 kg/m^2 . In section 6.1.4 it will be demonstrated that efficacy is significantly greater in women than men. So the fact the only 45% of the ITT population were women will limit the observed efficacy of the total population. While 80% of the population met the serum sodium criteria for safe use, 20% did not which means a substantial portion of the treated population would be at risk of hyponatremia if monitoring is not properly adhered to in a real use setting.

Table 3 Demographics

Demographic Characteristic	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Age (years)					
Mean (SD)	62.1 (13.39)	61.7 (14.41)	62.4 (13.22)	61.6 (11.80)	62.1 (12.34)
Median	64.0	64.0	64.5	63.5	65.5
Minimum, maximum	20, 86	23, 84	22, 89	28, 88	24, 85
Age Categories , N (%)					
<50 years	27 (17%)	29 (19%)	26 (17%)	22 (15%)	24 (16%)
50 to <65 years	54 (35%)	51 (33%)	50 (33%)	55 (37%)	44 (30%)
65 to <75 years	45 (28%)	42 (27%)	54 (36%)	52 (35%)	58 (40%)
≥75 years	30 (19%)	33 (21%)	22 (14%)	19 (13%)	20 (14%)
Sex, N (%)					
Female	66 (42%)	73 (47%)	65 (43%)	71 (48%)	66 (45%)
Male	90 (58%)	82 (53%)	87 (57%)	77 (52%)	80 (55%)
Race, N (%)					
Caucasian	136 (87%)	123 (79%)	120 (79%)	119 (80%)	111 (76%)
Black/African American	16 (10%)	21 (14%)	28 (18%)	24 (16%)	27 (18%)
Asian	3 (2%)	2 (1%)	2 (1%)	3 (2%)	6 (4%)
American Indian/ Alaskan Native	0	2 (1%)	0	0	0
Native Hawaiian/ other Pacific Islander	0	1 (1%)	1 (1%)	0	0
Other	1 (1%)	6 (4%)	1 (1%)	2 (1%)	2 (1%)
Ethnic Origin, N (%)					
Hispanic	13 (8%)	10 (6%)	10 (7%)	13 (9%)	6 (4%)
Not Hispanic	143 (92%)	145 (94%)	142 (93%)	135 (91%)	140 (96%)
Height (m)					
Mean (SD)	1.71 (0.111)	1.70 (0.110)	1.71 (0.106)	1.70 (0.096)	1.71 (0.111)
Median	1.7	1.7	1.7	1.7	1.7
Minimum, maximum	1.5, 1.9	1.2, 1.9	1.5, 2.0	1.4, 1.9	1.4, 2.0
Weight (kg)					
Mean (SD)	86.23 (19.423)	85.05 (18.103)	85.40 (19.460)	86.15 (20.064)	85.99 (19.682)
Median	84.0	84.0	83.9	83.8	84.0
Minimum, maximum	47.9, 140.70	42.3, 148.7	45.0, 178.0	46.7, 170.4	42.9, 151.7
BMI (kg/m ²)					
Mean (SD)	29.72 (6.719)	29.47 (6.259)	29.26 (6.452)	29.96 (7.487)	29.34 (6.439)
Median	27.84	28.65	28.29	28.64	27.90
Minimum, maximum	16.55, 53.09	16.52, 52.92	17.45, 59.66	16.61, 67.15	17.51, 58.09
Sodium Monitoring Criteria					
Met criteria	131 (84%)	131 (85%)	132 (87%)	112 (76%)	107 (73%)
Did not meet criteria	25 (16%)	24 (15%)	20 (13%)	36 (24%)	39 (27%)

Source Table 12 section 5.3.5.3.1 ISE

6.1.3 Subject Disposition

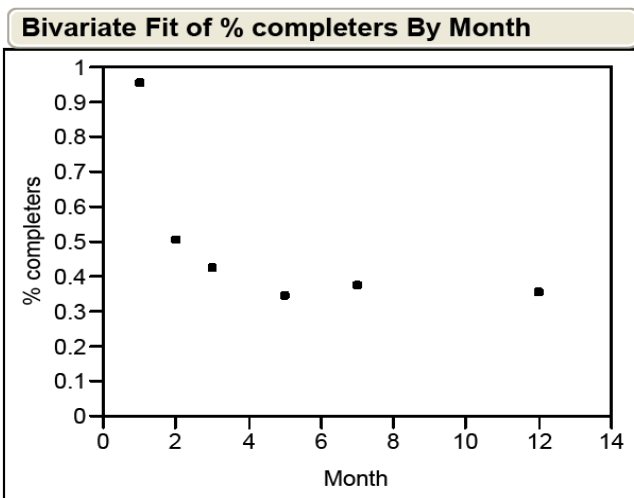
Most of the patients randomized to treatment completed Part I of the study (713/799=89%). Of the 11% that discontinued prematurely the most common reasons

for discontinuation were “withdrawal of consent” (4%), adverse event (2%), and “lost to follow-up” (2%). In contrast, there was a high drop out rate during the beginning of the long term extension, with 50% withdrawing between the end of Part 1 and the first month of the long-term extension (see [Fig. 2](#)). An additional 15% withdrew between the second month and the one year time point.

Medical Officer’s comment

The large attrition during the first month of the long term extension suggests that a large proportion of patients did not feel the drug effect was of a substantial enough benefit to warrant the inconvenience of continuing in the study protocol. The largest reasons for premature withdraw were “withdraw of consent” (20%), adverse events (5%) and “lost to follow up” (5%). Of those that survived the first two months most must have felt some benefit as they continued in the study for the rest of the year. It seems reasonable to assume that responders would be concentrated in the group that continued out to a year so it is not surprising that Figs. 5 and 6 in section 6.1.9 below show greater efficacy at month 7 compared to month 1.

Figure 2 Disposition of Patients during 4wk Efficacy Trial (month 1) and Long Term Extension (months 2-12)



Source ISE-ISE2-Table 14.2.5.1 CS29 Part 1, Table 14.3.2.1 Totals for weeks 8, 12, 20, 28, and 52-56

Analysis of Primary Endpoint(s)

There are currently no approved drug products in the US for the proposed indication i.e. treatment of adult nocturia. The Agency requested a coprimary endpoint that would show both a statistical decrease in nocturnal voids in the study population and a

decrease of at least 33% from baseline in the number of nocturnal voids as this was taken to estimate a clinically relevant benefit in the majority of patients. In deciding on the second part of the coprimary endpoint the Agency considered requiring higher percentages of efficacy for approval such as 50 or 75%, but there was a concern that if the endpoint was too stringent the results may reflect the effect on only a small subpopulation which while clearly representing a clinical benefit might not represent a benefit for the study population at large. For example it could be theoretically possible for 10% of the population to have a pronounced effect > 75% reduction with the rest of the population having no effect, thereby an estimate of the population with at least a 33% reduction might not be statistically significant. While such a treatment affect could still be used to approve a drug it would be necessary to develop a method to identify those sensitive patients that would benefit from the drug as part of the clinical development plan, as the risk benefit assessment would be against treatment of the majority of patients most of whom are not likely to respond to treatment but could still be at risk of adverse effects from the study drug. In the final analysis, Nocdurna showed statistically significant efficacy using >33%, >50% or > 75% reduction from baseline as the second part of the coprimary (see Appendix-Figure 10), and this turned out to be a moot issue, at least for the highest dose studied i.e. 100 µg.

CS029 Part 1

Co-primary efficacy endpoint

A total of 799 subjects were randomized during Part 1 of which 757 (95%) received at least one dose of study drug and provided post-baseline efficacy data included in the ITT analysis. The co-primary endpoints, measured from baseline to the final visit (Day 28), were change in the mean number of nocturnal voids [Table 2](#) and the proportion of subjects with >33% reduction in the mean number of nocturnal voids [Table 3](#).

Table 4 Change from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids (ITT, First part of co-primary endpoint)

Nocturnal Voids	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Overall					
Baseline Mean (SD)	3.27 (1.164)	3.21 (1.025)	3.35 (1.318)	3.39 (1.066)	3.22 (1.102)
Day 8					
Mean (SD)	2.65 (1.237)	2.45 (1.173)	2.45 (1.548)	2.33 (1.188)	1.96 (1.286)
Mean Δ (SD)	-0.62 (1.089)	-0.76 (1.055)	-0.90 (1.076)	-1.05 (1.130)	-1.26 (1.213)
p-value vs. placebo		p=0.1748	p=0.0317*	p=0.0011*	p<0.0001*
Day 15					
Mean (SD)	2.46 (1.175)	2.44 (1.304)	2.26 (1.373)	2.19 (1.146)	1.75 (1.219)
Mean Δ (SD)	-0.81 (1.018)	-0.77 (1.145)	-1.08 (1.157)	-1.19 (1.111)	-1.48 (1.129)
p-value vs. placebo		p=0.9003	p=0.0314*	p=0.0042*	p<0.0001*
Day 22					
Mean (SD)	2.39 (1.234)	2.27 (1.305)	2.29 (1.467)	2.13 (1.172)	1.66 (1.158)
Mean Δ (SD)	-0.89 (1.021)	-0.94 (1.162)	-1.05 (1.114)	-1.25 (1.064)	-1.57 (1.096)
p-value vs. placebo		p=0.5110	p=0.1864	p=0.0045*	p<0.0001*
Day 28					
Mean (SD)	2.41 (1.201)	2.38 (1.251)	2.35 (1.430)	2.21 (1.198)	1.79 (1.351)
Mean Δ (SD)	-0.86 (1.054)	-0.83 (1.069)	-1.00 (1.125)	-1.18 (1.187)	-1.43 (1.219)
p-value vs. placebo		p=0.9303	p=0.3104	p=0.0207*	p<0.0001*

Source Table 5 Sponsor's 2.7.3 Summary of Clinical Efficacy

The mean number of nocturnal voids for all patients was statistically significant for the two highest doses 50 and 100 µg. Statistically significant efficacy was also observed at the higher dose 100 µg in patients < 65 or ≥65 years of age or in patients with and without nocturnal polyuria.

Table 5 Proportion of Subjects with >33% Reduction from Baseline in Mean Number of Nocturnal Voids (ITT, Second part of co-primary endpoint)

>33% Responder	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Overall					
Day 8					
p-value vs. placebo ^a	47 (30%)	62 (40%)	70 (46%)	73 (49%)	88 (60%)
		p=0.0668	p=0.0036*	p=0.0007*	p<0.0001*
Day 15					
p-value vs. placebo ^a	57 (37%)	62 (40%)	78 (51%)	81 (55%)	100 (68%)
		p=0.5248	p=0.0072*	p=0.0014*	p<0.0001*
Day 22					
p-value vs. placebo ^a	66 (42%)	78 (50%)	79 (52%)	87 (59%)	106 (73%)
		p=0.1549	p=0.0743	p=0.0038*	p<0.0001*
Day 28					
p-value vs. placebo ^a	73 (47%)	73 (47%)	76 (50%)	79 (53%)	103 (71%)
		p=0.9420	p=0.5527	p=0.2662	p<0.0001*

The proportion of all patients with > 33% reduction in nocturnal voids was statistically significant for the highest dose, 100 µg, in patients < 65 or ≥65 years of age or in patients with or without nocturnal polyuria. Statistical significance was also observed if the proportion of subjects with > 50% or >75% reductions in mean nocturnal voids was measured (see Figure 10 in the Appendix).

Medical Officer's comment-

Desmopressin has a half-life of about 3 hours. Serum levels of desmopressin between 1 and 6 pg/mL result in a graded renal response. At doses up to 100µg, maximal urine concentration occurs within 3 hours of dosing with complete loss of affect on renal function by 7 to 8 hours post dosing. Efficacy should be apparent after the first dose, even though the predefined endpoint in the pivotal trial was chosen at 4 weeks. There is no reason to suspect a difference in efficacy between weeks 1 and 4. For example desmopressin (DDAVP) was initially approved to treat PNE in children using a predefined time point of 2 weeks.

For all patients (men and women) the efficacy of Nocdurna was statistically significant at the 100µg dose with respect to both parts of the coprimary endpoint for all four weeks of the efficacy trial including the predefined time point of Day 28. The 50µg dose was highly statistically significant with respect to both parts of the coprimary endpoint for the first three weeks of the efficacy trial (p-values ranging from 0.0007 to 0.0045), but was only statistically significant with respect to the first part of the coprimary endpoint for the predefined time point of Day 28 (p=0.021 and p= 0.27). In addition, the p-values for stricter responder rates of 50% and 75% for the second part of the coprimary endpoint on Day 28 were 0.08 and 0.07, almost statistically significant. If the predefined endpoint had been either Day 8, 15 or 22 the efficacy of the 50 µg dose would have been confirmed. As it stands it is this medical officer's assessment that there is enough data to support the efficacy of the 50 µg dose, even though the study did not technically achieve the predefined endpoint. First of all, there is no reason to suspect that the Day 28 data should be more accurate than data collected on Days 8, 15 and 22, and second of all there appears to be an unusual increase in the placebo efficacy in males on Day 28 which may be contributing to the lack of efficacy at this time point which will be discussed in more detail later in this review (see Section 6.1.7, Fig. 4).

6.1.5 Analysis of Secondary Endpoints(s)

Secondary Endpoints

Duration of Sleep Period Prior to First Night-time Void

There was a dose response for the duration of the initial period of undisturbed sleep from baseline to Day 28. Mean increases in initial sleep duration were 83, 85, and 107 minutes in the 25 µg, 50 µg, and 100 µg groups, respectively, see [Table 6](#). When a similar analysis was performed for subjects ≥65 and < 65 years of age, only the younger patients showed an increase in the duration of the initial sleep period with respect to dose. No similar analysis was reported with respect to gender.

Table 6 Change in Sleep Duration for the Initial Period of Undisturbed Sleep from Baseline to Final Visit (Day 28)

	Placebo	10 µg	25 µg	50 µg	100 µg
Initial Period of Undisturbed Sleep					
Baseline Mean (SD)	(N=148) 116.52 (58.728)	(N=149) 116.99 (71.364)	(N=142) 114.06 (64.465)	(N=140) 111.13 (68.569)	(N=136) 114.40 (55.829)
Day 28 Mean (SD)	(N=133) 155.75 (90.192)	(N=129) 169.95 (101.929)	(N=126) 194.30 (111.556)	(N=128) 195.67 (102.955)	(N=128) 219.11 (116.357)
Change from baseline Mean Δ (SD) p-value vs. placebo ^a	(N=126) 38.74 (88.794)	(N=126) 50.87 (111.471) p=0.3556	(N=121) 82.73 (105.572) p=0.0012*	(N=123) 85.05 (109.333) p=0.0008*	(N=121) 106.66 (116.180) p<0.0001*
Reported Total Sleep Time					
Baseline Mean (SD)	(N=156) 403.10 (83.684)	(N=155) 410.53 (72.756)	(N=152) 400.82 (77.812)	(N=148) 402.55 (83.665)	(N=146) 412.95 (81.318)
Day 28 Mean (SD)	(N=139) 427.46 (67.158)	(N=137) 420.19 (71.684)	(N=141) 416.46 (65.684)	(N=138) 426.56 (76.681)	(N=133) 431.52 (71.698)
Change from baseline Mean Δ (SD) p-value vs. placebo ^a	(N=139) 24.55 (80.658)	(N=137) 7.80 (58.550) p=0.0665	(N=141) 15.94 (53.923) p=0.1523	(N=138) 24.91 (72.206) p=0.9736	(N=133) 19.00 (68.937) p=0.8635

Δ = change; SD = standard deviation

* Statistically significant difference versus placebo, p≤0.05.

Note: Treatment difference based on linear model adjusted for age, absence/presence of nocturnal polyuria, and baseline number of nocturnal voids.

a. The p-values correspond to F-tests of effects in the model including all effects.

Cross-reference: [\[ISE Table 14.2.3\]](#), [\[ISE Table 14.4.1.1\]](#), [\[ISE Table 14.4.2.1\]](#), and [\[ISE Table 14.4.2.4\]](#)

Total sleep time increased slightly from 8 to 25% in all treatment groups but this effect was independent of the treatment dose.

Patient-Reported Outcome (PRO) scores

PRO scores for the following tests: Nocturia Quality of Life (N-QOL) questionnaire; Pittsburgh Sleep Quality Index (PSQI); and International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N) were also included as secondary outcomes.

N-QOL

The N-QOL is the only publically available self-administered PRO for the assessment of the impact of nocturia on quality of life, with evidence for validity in the literature⁶. It was initially developed from study questionnaires given to men at urology clinics in the United Kingdom, and more recently has been shown to be applicable to women as well⁷. The N-QOL was developed to measure the impact of nocturia on quality of life. It is divided into two sections: a Sleep/Energy Domain and a Bother/Concern domain each consisting of 6 questions, and a global quality of life question which is scored separately. The recall period for the test was two weeks. Higher scores for the 13 items in the test represented improved quality of life.

Table 7 Day 28 NQOL Data

Change from Baseline to Day 28 in the NQOL Questionnaire Per Protocol (PP) Population				
Stratum	Dose of Nocurna[†]			
	10 µg	25 µg	50 µg	100 mcg
Sleep Energy Domain				X
Difficult to concentrate the next day		X	X	
Feel low in energy the next day			X*	X
Require me to nap during the day	X*	X	X*	X
Less productive the next day		X	X	X
Participates less in activities I enjoy				
Difficult to get enough sleep at night			X	X
Bother/Concern Domain	X	X	X	X
Careful about when or how much I drink	X	X*	X	X
Disturbing others by getting up at night	X*	X	X	X
Preoccupied by about getting up at night	X*	X	X	X
Worried it will get worse	X	X	X	X
Worried there is no effective treatment	X	X	X*	X
How bothersome is it getting up at night	X	X	X	X
Overall Score	X*	X	X	X

6 [Abraham L, Hareendran A, Mills IW, Martin ML, Abrams P, Drake MJ, MacDonagh RP, Noble JG.](#) Development and validation of a quality-of-life measure for men with nocturia. [Urology](#). 2004 Mar;63(3):481-6.

7 [Mock LL, Parmelee PA, Kutner N, Scott J, Johnson TM 2nd.](#) Content validation of symptom-specific nocturia quality-of-life instrument developed in men: issues expressed by women, as well as men. [Urology](#). 2008 Oct;72(4):736-42. Epub 2008 Aug 5.

Global Quality Life Term	X*	X	X	X
†X-designates that the mean response was numerically more favorable than observed with the placebo, but not necessarily statistically significant. Source Table 14.4.5.6 Study CS029 report. * represents conditions that would <u>not</u> have been numerically more favorable than placebo in the ITT population. Source Table 14.4.5.1 Study CS029 report.				

Higher scores indicating better quality of life in the Per Protocol Population were seen for the Overall Score and Global Quality of Life Term with doses of 10, 25, 50 and 100µg compared to placebo. These results were primarily due to improvements in the Bother/Concern domain which were seen at all doses, and smaller improvements in the Sleep/Energy domain which was seen primarily at the higher doses of 50 and 100 µg. Somewhat less favorable results were seen using the ITT population. However, because of the large individual variability in the responses the standard deviations for these observations in both the PP and ITT populations were fairly large and no statistically significant differences were observed in any of the individual terms or group terms compared to placebo.

Medical Officer's comment-

Whereas the N-QOL is probably the most useful of the three proposed scales as it was developed specifically to measure the impact of nocturia on quality of life, the SEALD team reviewer, Ann Trentacosti, determined that this PRO did not adequately address psychological/emotional impacts of nocturia and thereby cannot be used to support a health related claim. Most of the items in the Bother/Concern domain were considered not useful as they did not measure the effectiveness of treatment, and the general quality of life question was considered too general as it could include "nonhealth-related aspects of life". Finally, since the overall score did not show statistical significance it is against the PRO guidance to focus on individual questions in an attempt to try to salvage a claim. When pressed the SEALD team would have preferred a PRO with the following questions.

- 1) *Are you feeling low in energy during the day?*
- 2) *Is it difficult to concentrate during the day?*
- 3) *Are you less productive during the day?*
- 4) *Do you participate less in activities that you enjoy?*
- 5) *Are you feeling more irritable or moody during the day?*
- 6) *Are you feeling preoccupied about getting up at night?*

PSQI

The PSQI was initially developed to measure effects on sleep in patients with depression and specific sleep disorders and as such cannot be expected to be directly applicable to the adult nocturia population. There are currently no published studies to support validation of this questionnaire in this study population. The sponsor chose only

5 out of the 19 items for testing in this population as these were considered more specific to the nocturia population. The self-rated items are grouped into 7 component scores: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. An overall score is calculated by summarizing the 7 components, with higher scores indicating worse sleep quality.

Table 8 Day 28 PSQI Data

Change from Baseline to Day 28 in the PSQI Questionnaire Per Protocol Population				
Stratum	Dose of Nocdurna[†]			
	10 µg	25 µg	50 µg	100 mcg
Subjective Sleep Quality		X	X	X
Sleep Latency	X		X	X
Sleep Duration				
Habitual Sleep Efficiency				
Sleep Disturbances				
Sleeping Medication				
Daytime Dysfunction	X	X	X*	X*
Global PSQI Score		X	X	X

†X-designates that the mean response was numerically more favorable than observed with the placebo, but not necessarily statistically significant. Source Table 14.4.7.6 Study CS029 stats report
 * represents conditions that would not have been numerically more favorable than placebo in the ITT population. Source Table 14.4.7.1 Study CS029 report.

There was a partial dose response in the Global score with more favorable treatment effects for doses of 100 µg > 50 µg > 25, 10 and 0 µg (PP population, Sponsor's Table 14.4.7.6, ITT population Table 14.4.7.1) but the results were not statistically significant. The favorable effects on sleep were seen primarily in adults less than 65 years of age and in adults with documented nocturnal polyuria.

ICIQ-N

The ICIQ-N is a self-administered questionnaire used to assess the frequency and bother of daytime and nighttime urination. There is a 4 item survey with out a global score so that each item is analyzed separately. Higher numbers indicate lower quality of life.

Table 9 Day 28 ICIQ-N Items 1 and 2

Change from Baseline to Day 28 in the ICIQ-Nocturia Questionnaire ITT Population (Question 1 and 2)				
Stratum	Dose of Nocdurna[†]			
	10 µg	25 µg	50 µg	100 mcg
How much does daytime urination bother you?		X		X
How much does night time urination bother you?	X	X	X	X

†X-designates that the mean response was numerically more favorable than observed with the placebo, but not necessarily statistically significant. Source Table 14.4.4.1 Study CS029 stats report

The mean responses for the question “How much does night time urination bother you?” showed a dose response for Nocdurna i.e. 100 µg (-2.5), < 50 µg (-2.2), < 25 µg (-2.1), < 10 µg (-1.8) and < placebo (-1.4).

The most common response for the question “How often do you urinate at night?” was 3 times on placebo and 2 times on any dose of Nocdurna, suggesting a response with any dose of Nocdurna. This questionnaire was not sensitive enough to identify a dose response.

Table 10 Day 28 ICIQ-N Items 3 and 4

Change from Baseline to Day 28 in the ICIQ-Nocturia Questionnaire ITT Population (Question 3 and 4)					
Stratum	Dose of Nocdurna				
	0 µg	10 µg	25 µg	50 µg	100 mcg
	Most frequent response[†]				
How often do you urinate during the day?	1-6	1-6	1-6	1-6	1-6
How often do you get up to urinate at night?	3	2	2	2	2

†X-The choices for day time voids were 1 to 6, 7 to 8, 9 to 10, 11 to 12 and 13 or more. The choices for night time voids were 1, 2, 3 and 4 or more Source Table 14.4.4.11 Study CS029 stats report

Medical Officer's comment-

Since the PSQI and ICI-Q were not developed specifically to measure the impact of nocturia on quality of life, the SEALD team would not have considered them useful in assessing clinical significance, even if they had shown evidence of statistical significance, which they did not.

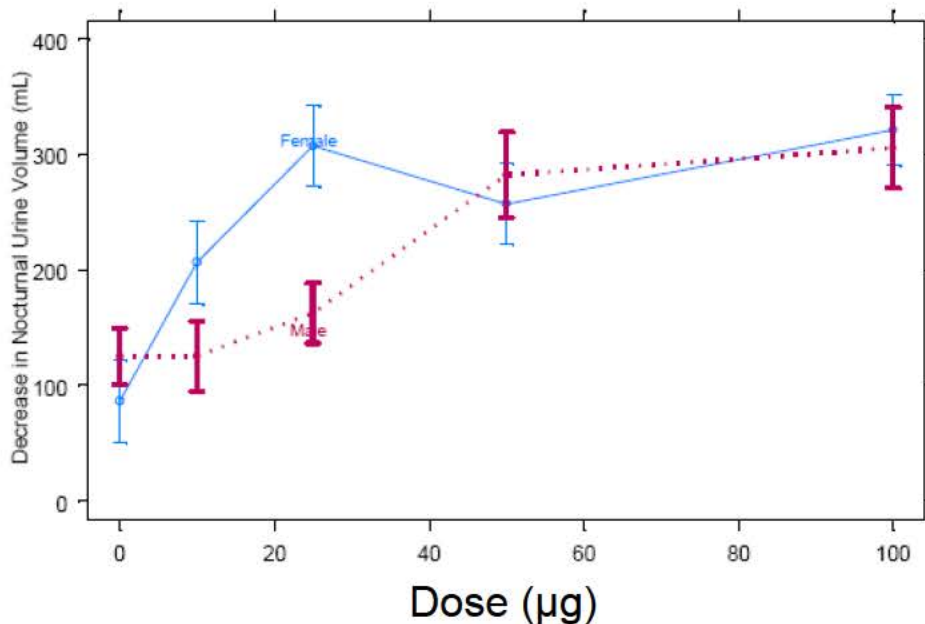
6.1.6 Other Endpoints

Change in Urine Volume

Nocturnal urine volume decreased from baseline to the final visit on Day 28 by 14% (placebo), 20% (10 μg), 28% (25 μg), 32% (50 μg) and 38% (100 μg). The mean decrease in urine volume ranged from 109mL with placebo to 312mL with 100 μg of NocduRNA. It has been estimated that adult bladder capacity can range between 600 and 800mL but the urge to urinate typically occurs at much lower levels between 150 and 300mL⁸. Therefore, the decrease in nocturnal urine volume seen with NocduRNA would be large enough to produce a decrease in the number of nighttime voids as observed in the co-primary endpoint.

There was a clear gender difference in urine volume, with women showing a near maximal response at 25 μg and men showing a near maximal response at 50 μg .

Figure 3 Mean Decrease in Nocturnal Urine Volume by Dose and by Gender



Source Sponsor's Figure 3. Modelling Report/Desmopressin Sensitivity in Females vs. Males.

⁸ <http://hypertextbook.com/facts/2001/DanielShaw.shtml>

24-Hour Urine volume also decreased but by a lower percentage: 9% (placebo), 13% (10 µg), 15% (25 µg), 15% (50 µg) and 19% (100 µg) from baseline to the final visit on Day 28. Whereas this decrease may seem small it could eventually lead to hyponatremia over time if certain patients do not adjust to the decreased urine output with an appropriate decrease in fluid intake during the day. Therefore the drug should not be used in patients who do not have normal thirst control.

At baseline, 90% of subjects had nocturnal polyuria (night time urine volume/total urine volume $\geq$ 33%). With increasing Nocdurna dose the percentage of subjects with nocturnal polyuria decreased to 84% (10 µg), 79% (25 µg), 73% (50 µg), and 71% (100 µg).

6.1.7 Subpopulations

As a post-hoc analysis the sponsor analyzed the co-primary endpoints with respect to gender, see Tables 11 and 12. In males the co-primary endpoints were statistically significant only at the highest dose of 100 µg ($p=0.005$). However, in females the co-primary endpoint was significant for doses of 25 mcg ($p=0.02$), 50 µg ($p=0.009$) and 100 µg ($p=0.0001$). Therefore, the sponsor is proposing different dosing schemes based on gender (e.g. 100 µg for men and 25 µg for women.)

Table 11 Change from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids with respect to gender (ITT, First part of co-primary endpoint)

Nocturnal Voids	Placebo	10 µg	25 µg	50 µg	100 µg
Males					
	(N=90)	(N=82)	(N=87)	(N=77)	(N=80)
Day 8					
Mean (SD)	2.60 (1.234)	2.57 (1.187)	2.60 (1.374)	2.55 (1.205)	2.20 (1.422)
Mean Δ (SD)	-0.60 (1.123)	-0.54 (0.938)	-0.80 (1.011)	-1.05 (1.221)	-1.23 (1.193)
p-value vs. placebo		p=0.9360	p=0.3606	p=0.0496*	p=0.0004*
Day 15					
Mean (SD)	2.48 (1.155)	2.58 (1.336)	2.42 (1.271)	2.48 (1.204)	1.96 (1.363)
Mean Δ (SD)	-0.71 (1.014)	-0.53 (1.017)	-0.98 (1.025)	-1.12 (1.221)	-1.46 (1.140)
p-value vs. placebo		p=0.3442	p=0.1892	p=0.0836	p<0.0001*
Day 22					
Mean (SD)	2.39 (1.217)	2.51 (1.438)	2.46 (1.442)	2.34 (1.240)	1.90 (1.245)
Mean Δ (SD)	-0.80 (1.041)	-0.60 (1.116)	-0.94 (1.106)	-1.26 (1.121)	-1.53 (1.085)
p-value vs. placebo		p=0.2779	p=0.6123	p=0.0339*	p<0.0001*
Day 28					
Mean (SD)	2.35 (1.175)	2.57 (1.319)	2.57 (1.351)	2.47 (1.224)	2.05 (1.554)
Mean Δ (SD)	-0.84 (1.092)	-0.54 (0.987)	-0.83 (1.149)	-1.13 (1.297)	-1.38 (1.281)
p-value vs. placebo		p=0.0944	p=0.5894	p=0.3778	p=0.0049*
Females					
	(N=66)	(N=73)	(N=65)	(N=71)	(N=66)
Day 8					
Mean (SD)	2.72 (1.248)	2.32 (1.151)	2.25 (1.745)	2.10 (1.130)	1.67 (1.038)
Mean Δ (SD)	-0.66 (1.047)	-1.00 (1.132)	-1.02 (1.153)	-1.05 (1.031)	-1.31 (1.244)
p-value vs. placebo		p=0.0424*	p=0.0271*	p=0.0094*	p<0.0001*
Day 15					
Mean (SD)	2.43 (1.209)	2.28 (1.258)	2.05 (1.482)	1.88 (0.997)	1.48 (0.965)
Mean Δ (SD)	-0.95 (1.014)	-1.05 (1.225)	-1.22 (1.309)	-1.27 (0.980)	-1.49 (1.124)
p-value vs. placebo		p=0.4737	p=0.0637	p=0.0176*	p<0.0001*
Day 22					
Mean (SD)	2.38 (1.266)	2.00 (1.087)	2.06 (1.479)	1.90 (1.055)	1.36 (0.974)
Mean Δ (SD)	-1.01 (0.989)	-1.32 (1.101)	-1.21 (1.113)	-1.25 (1.006)	-1.62 (1.114)
p-value vs. placebo		p=0.0371*	p=0.1247	p=0.0445*	p<0.0001*
Day 28					
Mean (SD)	2.50 (1.238)	2.17 (1.143)	2.05 (1.488)	1.92 (1.108)	1.47 (0.977)
Mean Δ (SD)	-0.88 (1.008)	-1.15 (1.072)	-1.22 (1.060)	-1.23 (1.062)	-1.51 (1.145)
p-value vs. placebo		p=0.0721	p=0.0200*	p=0.0091*	p<0.0001*

Δ = change; SD = standard deviation; BL = baseline

* Statistically significant difference versus placebo, p≤0.05.

Note: Treatment difference based on linear model adjusted for age, absence/presence of nocturnal polyuria, and baseline number of nocturnal voids.

Cross-reference: [ISE Table 14.3.1.12], [ISE Table 14.3.1.13], [ISE Table 14.3.3.12], and [ISE Table 14.3.3.13]

Table 12 Proportion of Subjects with >33% Reduction from Baseline in Mean Number of Nocturnal Voids with respect to gender (ITT, Second part of co-primary endpoint)

>33% Responder	Placebo	10 µg	25 µg	50 µg	100 µg
Males					
	(N=90)	(N=82)	(N=87)	(N=77)	(N=80)
Day 8 p-value vs. placebo ^a	30 (33%)	28 (34%) p=0.8677	37 (43%) p=0.2069	38 (49%) p=0.0408*	43 (54%) p=0.0072*
Day 15 p-value vs. placebo ^a	31 (34%)	25 (30%) p=0.5819	43 (49%) p=0.0380*	40 (52%) p=0.0179*	51 (64%) p=0.0001*
Day 22 p-value vs. placebo ^a	39 (43%)	34 (41%) p=0.7683	45 (52%) p=0.2543	46 (60%) p=0.0261*	55 (69%) p=0.0005*
Day 28 p-value vs. placebo ^a	45 (50%)	32 (39%) p=0.1502	36 (41%) p=0.2225	37 (48%) p=0.7375	52 (65%) p=0.0477*
Females					
	(N=66)	(N=73)	(N=65)	(N=71)	(N=66)
Day 8 p-value vs. placebo ^a	17 (26%)	34 (47%) p=0.0102*	33 (51%) p=0.0025*	35 (49%) p=0.0049*	45 (68%) p<0.0001*
Day 15 p-value vs. placebo ^a	26 (39%)	37 (51%) p=0.1564	35 (54%) p=0.0705	41 (58%) p=0.0269*	49 (74%) p<0.0001*
Day 22 p-value vs. placebo ^a	27 (41%)	44 (60%) p=0.0189*	34 (52%) p=0.1496	41 (58%) p=0.0444*	51 (77%) p<0.0001*
Day 28 p-value vs. placebo ^a	28 (42%)	41 (56%) p=0.0880	40 (62%) p=0.0197*	42 (59%) p=0.0405*	51 (77%) p<0.0001*

* Statistically significant difference versus placebo, p≤0.05.

a. p-values from logistic regression analysis

Cross-reference: [ISE Table 14.3.4.12], [ISE Table 14.3.4.13], [ISE Table 14.3.6.12], and [ISE Table 14.3.6.13]

Medical Officer's comment-

It is reasonable to ask why a difference in dose response by gender had not been seen in the original studies for the PNE indication. PNE studies used higher doses (typically 200 to 600mg) and patients were titrated to a maximal response for the length of the entire night (8 to 12 hours) compared to the 3 to 6 hours of efficacy needed to treat adult nocturia. It was possible to use higher doses in PNE studies with pediatric patients because children had a much lower risk of hyponatremia and there was less concern about baseline renal function.

Animal studies suggest one potential mechanism for the gender difference in sensitivity. Female rats have 2 to 3 fold higher levels of expression of V2-receptors which is attributed to the fact that this vasopressin receptor is located on the X chromosome in a region associated with a high probability of escaping X-inactivation. There is also some evidence from human studies that estrogens may lower the plasma osmotic threshold for vasopressin while androgens may

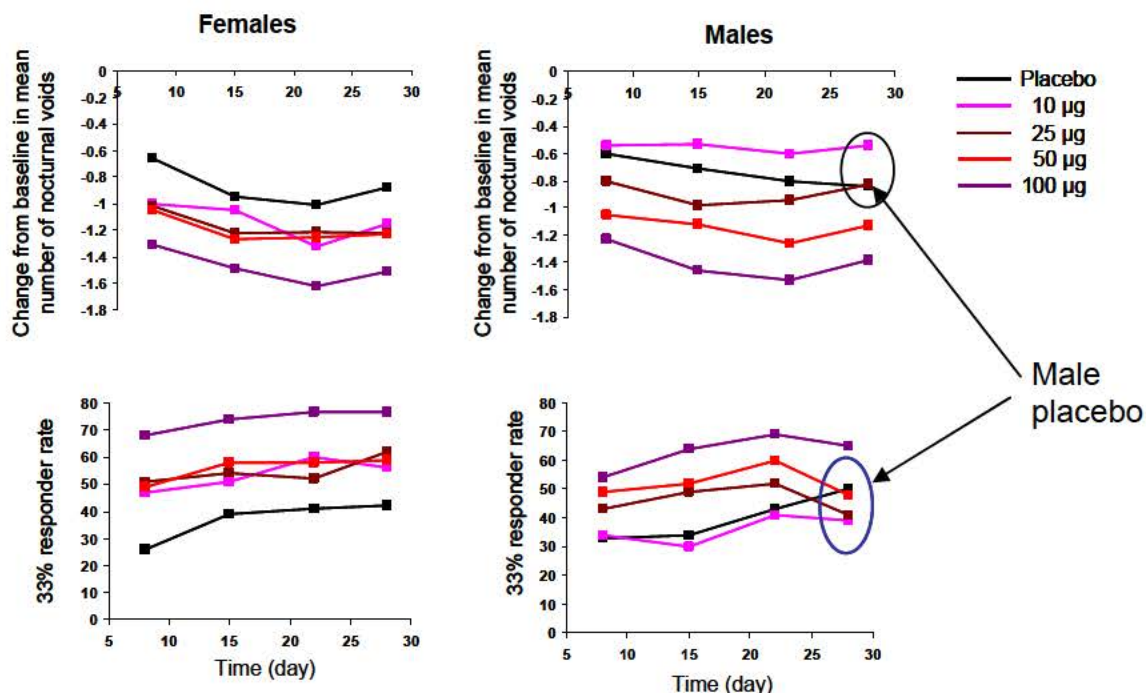
influence vasopressin sensitivity, supporting a role for hormonal influences on the activity of vasopressin.

It needs to be mentioned that the sponsor was not expecting the large difference in efficacy related to gender nor the increased risk of hyponatremia as these had not been seen in the earlier phase 2 trials. If the sponsor had had the foresight they could have elected to perform separate trials in men and women as opposed to one large combined study. From a statistical point of view the sponsor needed to win on all patients in this pivotal trial before efficacy could be looked at in subgroups. As such the biostatistics team is not willing to support the validity of the efficacy findings seen in women at the lower doses of 50 and 25µg. It is this medical officer's assessment that there were a sufficient number of women enrolled in this study to perform an analysis on women only and this need not be looked at as simply a subgroup analysis. In addition, there is support for the observed gender differences seen here from other nonclinical and clinical studies to argue that it is scientifically justifiable to analyze the data separately by gender. Therefore, this medical officer concludes it is reasonable to accept the findings of efficacy at doses of 25 and 50µg in women. Although, it is probably also reasonable, as recommended by the statistical team to request the sponsor to demonstrate they can reproduce these findings in a follow up study.

While statistically significant efficacy was seen in women at the 25 µg dose, there appeared to be slightly greater efficacy at the higher doses up to 100 µg. Therefore, it is this medical reviewer's assessment that it would be reasonable to recommend dose titration up to 100 µg for women who don't achieve optimal efficacy at the lower doses, assuming there is no significant difference in safety outcome at the higher doses. This issue will be addressed later in the safety review as the risk for hyponatremia does increase with dose.

Men did show some limited efficacy at the 50 µg dose. The first part of the co-primary endpoint was statistically significant on Days 8 and 22 and almost statistically significant on Day 15 ($p=0.08$). The second part of the coprimary endpoint was statistically significant on Days 8, 15 and 22. However, neither parts of the co-primary endpoint were statistically significant on Day 28, the predefined endpoint. It is unlikely that the Day 28 observation represents a loss of efficacy as the ITT population showed persistent efficacy with 50 µg at Weeks 52 and 72 in the open label extension CS31 (see Section 6.1.9).

Figure 4 Dose Response by Gender



Source- Figure generated by Dr. Anshu Marathe from Clinical Pharmacology.

A closer look at the dose response data by gender shows an unexpected increase in the efficacy of the placebo in males on Day 28 (See arrows in Fig. 4). While it is possible to argue that this represents normal variability in the placebo group a similar increase in efficacy is not seen with the 10 µg low dose group which should also represent a dose which is expected to have minimal efficacy. It is this medical officer's impression that this relative increase in efficacy in the male placebo group on Day 28 is responsible for the inability to demonstrate efficacy with the 50 µg dose. In contrast, the 50 µg dose on Day 28 does show a "statistically significant" increase relative to the 10 µg dose, which showed a more stable level of activity over the four week course of the study. However, as the null hypothesis was developed with respect to the placebo group a comparison with respect to the low dose, 10 µg group, which was not a predefined analysis would not be statistically justified.

Except for the placebo group, efficacy across the 4 week trial shows a clear dose response in males with the point estimate of the 50 µg group in males similar to the response seen in women for the 25 µg dose (i.e. about 1 nocturnal void decrease (first coprimary) and a 50% increase in the 33% responder rate (second coprimary)). These same doses had been previously shown to result in maximal urine volume on Day 28 (see Fig. 3). It is this medical officer's assessment that despite the inability to demonstrate statistical significance with respect to the placebo on Day 28, that there is enough alternative evidence to support the finding that the 50 µg dose does represent

an effective starting dose in males and it would be reasonable to recommend dose titration up to 100 µg for men who don't achieve optimal efficacy at the lower dose, assuming there is no significant difference in safety outcome at the higher doses. This issue will be addressed later in the safety review as the risk for hyponatremia does increase with dose.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Utilizing the strict predefined 28 Day co-primary endpoint, statistical significance was only observed for the 100 µg dose in the ITT population. Subgroup analysis by gender confirmed statistical significance in both male and female subjects at this dose. However, this dose was associated with a higher than acceptable risk of hyponatremia in women and in men above 65 years of age which is to be described in greater detail in the Section 7.3.4. As such the sponsor did several post hoc analyses to look for differences in efficacy by gender subgroup and to see if a monitoring scheme could be developed to safely identify those patients at risk of developing hyponatremia before the hyponatremia became "severe" (e.g. serum sodium < 125mmol/L). As a result of these analyses the sponsor is recommending different doses based on gender i.e. 25 µg in women and 100 µg in men and has proposed a monitoring scheme for men over 65 years of age (see the Section 7.3.4 for a description of the proposed monitoring scheme).

It is this medical officer's assessment that despite the fact that the ITT population did not show efficacy at the 25 and 50 µg doses to support subgroup analyses, as detailed in the ICH E9 guidance, that there is enough data to support such an analysis in this case. First of all there were a sufficient number of women enrolled in this study that it could have been a stand alone study in women had the sponsor decided not to include men. And second, there is support for the observed gender differences seen here from other nonclinical and clinical studies to argue that it is scientifically justifiable to analyze the data separately by gender. Therefore, this medical officer believes it is reasonable to accept the findings of efficacy at doses of 25 and 50µg in women, and would accept the sponsor's proposed dose of 25 µg. However, as there is evidence for improved efficacy at doses of 50 and 100 µg, this medical officer would recommend dose titration for those women who do not get adequate efficacy with 25 µg up to a maximum dose of 100 µg assuming a monitoring scheme can be validated that can limit the risk of hyponatremia at the higher doses.

Despite the fact that the 100 µg dose was statistically significant in the ITT population and in the male subgroup, this medical officer would recommend against approval of the 100 µg dose in men over 65 years of age until the sponsor's proposed monitoring scheme can be validated in a prospective trial. Instead, this medical officer would recommend a lower starting dose with a more acceptable risk of hyponatremia in men, such as the 50 µg dose, that would not rely on as yet to be validated monitoring scheme to guarantee adequate safety. As described above, this medical officer believes that the

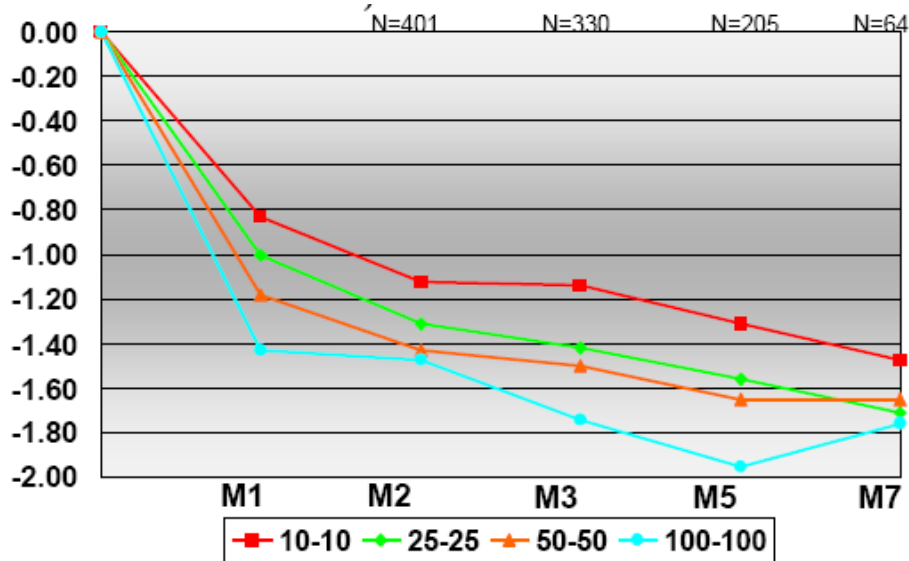
study design and efficacy differences with respect to gender would support a subgroup analysis in men as well. However, neither of the components of the co-primary endpoint were statistically significant at the 50 µg dose in men using the predefined endpoint of Day 28. As described previously there should be no difference in efficacy during the four weeks of the trial and both components of the co-primary endpoint were statistically significant on Days 8 and 22, supporting the efficacy of this dose. However, a statistician could argue that after adjusting for the multiplicity of these additional looks that the p-values at these earlier time points which range from 0.0261 to 0.0496 are not low enough to support efficacy. A closer look at the dose response data by gender, performed by this medical officer, identified an unexpected increase in efficacy in the male placebo group on Day 28 which is probably responsible for the inability to show efficacy for the 50 µg dose at this time point. In contrast, the 50 µg dose in males on Day 28 does show a “statistically significant” increase relative to the 10 µg dose, which showed a more stable level of activity over the four week course of the study. However, as the null hypothesis was developed with respect to the placebo group a comparison with respect to the low dose, 10 µg group, which was not a predefined analysis would still not be statistically justified.

Yet there is additional data to support the efficacy of the 50 µg dose in men. Except for the placebo group, efficacy across the 4 week trial shows a clear dose response in males with the point estimate of the co-primary endpoints for the 50 µg group in males giving results similar to the response seen in women for the 25 µg dose. In addition both the 50 µg dose in males and the 25 µg dose in females produced near maximal urine volume decreases of 300mL on Day 28, the predefined time point. Therefore, it is this medical officer’s assessment that despite the inability to demonstrate statistical significance with respect to the placebo on Day 28, that there is enough alternative evidence to support the use of the 50 µg dose as a starting dose in males. It seems reasonable to recommend dose titration up to 100 µg for men who don’t achieve optimal efficacy at the lower dose, assuming the safety of the sponsor’s proposed monitoring scheme can be validated for the higher dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No formal testing was performed by the sponsor on the data from the long term extension Study CS31 as there was no placebo group for comparison after the first month of therapy. The continued dose response out to month 7 (see Figs. 5 and 6) supports continued efficacy but the trend for increasing efficacy in both coprimary endpoints from month 1 to month 7 has to be taken in the context of the large patient drop out (>50%) during this part of the study which likely led to a selection bias for patients with greater efficacy.

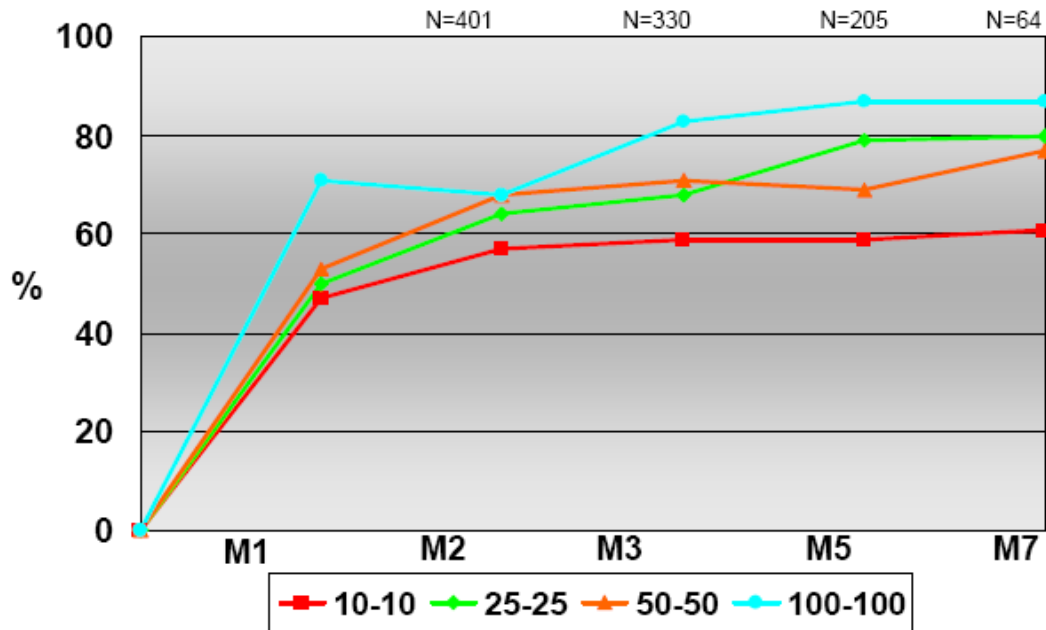
Figure 5 Monthly Change from Baseline in Mean Number of Nocturnal Voids (ITT, First part of co-primary endpoint)



Note: M1 = Month 1 (Day 28, Part I); M2 = Month 2 (Day 29, Part II); M3 = Month 3 (Day 57); M5 = Month 5 (Day 113); M7 = Month 7 (Day 169)

Data source Figure 8 CS029 study report

Figure 6 Monthly Proportion of Subjects with >33% Reduction from Baseline in Mean Number of Nocturnal Voids (ITT, Second part of co-primary endpoint)



Note: M1 = Month 1 (Day 28, Part I); M2 = Month 2 (Day 29, Part II); M3 = Month 3 (Day 57); M5 = Month 5 (Day 113); M7 = Month 7 (Day 169)

Data source Figure 9 CS029 study report

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

Pivotal trials CS029 and CS031 studied the safety and efficacy of 0 to 100 µg/day of desmopressin melt in the treatment of adult nocturia. Data from these trials was pooled in the ISS. Placebo exposure in these trials lasted for only 4 weeks while exposure to desmopressin melt lasted for > 1 year in some subjects. Total exposure was only 12 patient-years for patients in the placebo group compared to between 125 and 185 patient-years for the desmopressin melt treatment groups. Therefore it is not possible to directly compare events rates between the placebo and desmopressin groups outside of the double-blind, placebo-controlled, “Part I” period in CS029. The most common adverse events reported in any treatment group were hyponatremia, blood sodium increased, and headache which occurred primarily in the Nocdurna treatment groups. All the rest of the events occurred in less than 2% of patients per treatment group. No cases of hyponatremia or blood sodium decrease were considered serious. Nine pts (1.0%) were discontinued from the study due to “blood sodium decreased” in the Nocdurna treatment group compared to one patient in the placebo group (0.6%). Sixteen pts (1.9%) were discontinued from the study due to “hyponatremia” in the Nocdurna treatment group compared to no such patients in the placebo group (0%). There was a clear dose response for hyponatremia across the dose range 10 to 100 µg/day in study CS029 and across the dose range of 100 to 400 µg/day in studies Noct 2A, 3A and 4 see Section 7.5.1

Hyponatremia (serum sodium < 130 mmol/L) is a well described adverse reaction associated with the use of all desmopressin formulations. Severe hyponatremia (serum sodium < 125 mmol/L) or a rapid drop in serum sodium from baseline are especially serious as they can lead to cerebral edema and seizures. Elderly patients are more susceptible to the development of hyponatremia because of a decrease in renal function which makes it harder for them to limit sodium excretion and because of the increased frequency of comorbid conditions in the elderly population. Under normal circumstance the elderly can maintain fluid homeostasis, but their ability to respond to external stresses is limited. Conditions that can predispose to the development of hyponatremia include volume depletion (due to vomiting, diarrhea, severe burns, blood loss), medications (e.g. diuretics, SSRIs, NSAIDs, TCAs, antiepileptic drugs, chemotherapy agents), CHF, cirrhosis, renal failure, malignancies, pulmonary disorders (e.g. pneumonia, TB, acute respiratory failure), endocrine disorders (e.g. hypothyroidism, glucocorticoid deficiency) and SIADH (due to head trauma, neurosurgery, CNS

infections)⁹. In fact, hyponatremia is the most common electrolyte abnormality seen in the general hospital population with an incidence of about 1% in the US¹⁰.

Because of the concern for the risk of the development of hyponatremia, all patients were required to have baseline serum sodium levels ≥ 135 mmol/L in order to be included in the study. Despite this, a total of 57 (6.6%) subjects developed serum sodium < 130 mmol/L on various doses of Nocdurna compared to only one such patient (0.6%) in the placebo group. The rate of hyponatremia increased with increasing dose of drug with severe hyponatremia, defined as serum sodium < 125 mmol/L, seen primarily at doses of 50 μg and 100 μg .

In their analyses of these data, the sponsor determined that hyponatremia tended to occur early during treatment, primarily on Day 4 or Day 8 of treatment (see Section 7.5.2 Time Dependency for AEs). In female subjects, it was only seen in patients receiving doses of 50 μg or greater, and it was not observed in any subject, male or female ≤ 50 years of age (see Section 7.5.3 Drug-Demographic Interactions). As a result of these findings the sponsor developed criteria that should prevent the occurrence of severe hyponatremia based on gender (male dose-100 μg and female dose-25 μg) and based on gender & age (monitoring serum sodium levels on treatment Days 4 and 28 in men ≥ 65 years). If these monitoring criteria had been used to exclude patients at risk of hyponatremia during the study, there would have been no patients with severe hyponatremia (< 125 mmol/L) in the current study. In addition, of the 7 patients (0.9%) who met the monitoring criteria and yet developed sodium values between 125 and 130 mmol/L during the study, sodium levels returned to normal, > 130 mmol/L, by the next evaluation in all patients, even though only one of these patients had their Nocdurna dose discontinued. So the risk of progression to severe hyponatremia in these borderline patients appeared to be low. In contrast, without monitoring 11 patients (1.3%) had serum sodium levels < 125 mmol/L and 46 patients (5.3%) had serum sodium levels values between 125 and 130 mmol/L. While this ad hoc analysis is reassuring, this medical officer believes that it needs to be confirmed in a prospective study before it can be used to recommend dosing. In addition, the sponsor needs to provide evidence that the proposed monitoring scheme will be implemented appropriately in a real use situation. Therefore, this medical officer would not recommend approval of any dosing scheme that did would require monitoring based on only the currently available data.

While doses of 100 μg and above would need monitoring to minimize the risk of hyponatremia, it is possible that a lower dose such as 50 μg could be used safely in men without the need for monitoring. There were only two men in this pivotal study on

⁹ [Causes and management of hyponatremia](#). Palmer BF, Gates JR, Lader M. Ann Pharmacother. 2003 Nov;37(11):1694-702. Review

¹⁰ [Hyponatremia](#). Al-Salman J, Kemp D, Randall D. West J Med. 2002 May;176(3):173-6.

doses lower than 100 µg who developed severe hyponatremia. An 81 year old male, who had calculated creatinine clearances at baseline of 53 and 42, well below the exclusion criteria of < 60 mL/min, so he should never have been enrolled in the study, and a 78 year old male, who developed hyponatremia on day 327 of therapy as part of an intercurrent illness. The sponsor argues that this patient should have had the the Nocdurna dose transiently discontinued during the illness and that this would have prevented this episode. As the 10 µg has limited efficacy in males it is this medical officer's impression that this event was probably not drug related. Therefore, it seems reasonable not to require monitoring for the 50 µg dose in men with normal renal function or only mild renal impairment (creatinine clearance > 60 mL/min).

Possible dosing schemes that would not require monitoring include:

- approving the 25 µg dose for all women and approving the 100 µg dose only for men under 65 years of age.
- approving the 25 µg dose for all women and approving the 50 µg dose for all men, assuming the efficacy of the 50 mcg dose in men can be established
- approving the 25 µg dose for all women, approving the 50 µg dose for men 65 years of age and older, and approving the 100 µg dose for men under 65.

The last two scenarios would require acceptance of the efficacy of the 50 µg dose in men which is discussed in greater detail in the Efficacy Review under Section 6.1.8- Analysis of Clinical Information Relevant to Dosing Recommendations.

As the starting doses of 50 µg in men and 25 µg in women, being proposed in this medical review are likely to result in sub maximal efficacy in certain patients, this medical officer recommends that the sponsor consider performing a follow-up study to verify that the sponsor's proposed monitoring scheme can adequately identify patients at risk of severe hyponatremia who may benefit from being titrated to higher doses for better efficacy. From the current data it seems reasonable to permit dosing up to a maximum of 100 µg per day in such a study.

Desmopressin Melt (60 µg, 120 µg, and 240 µg) was first approved in February 2005. It is currently approved in Europe for the treatment of adult nocturia at doses of 120 and 240 µg in subjects under 65 years of age with no requirement for serum sodium monitoring. Since its launch in August 2005, the cumulative patient exposure to desmopressin melt is estimated to be (b) (4) patient-years through December 2008, based on average daily dose of 120 µg. The reported adverse reactions to desmopressin melt are consistent with the known safety profile of desmopressin tablets. Through December 2008 there have been 9 cases of hyponatremia. A total of 5 cases were in adult patients, 4 treated for nocturia (69 and 82 year old males, 63 and 85 year old females), and one treated for urinary incontinence (76 year old female). Given the currently approved dose in Europe ranges from 120 to 240 µg well above the dose of 25 µg in women and 50 µg in men recommended by this reviewer and there is no current recommendation to monitor baseline serum sodium in Europe, it is reassuring that there have been only 5 cases of hyponatremia reported with the melt formulation since

August 2005. There have been more cases of hyponatremia seen in adults with the desmopressin tablet formulation, 31 in patients treated for adult nocturia and 12 in patients treated for adult enuresis through December 2008. However, all but one of these cases were in patients treated with doses equivalent to 60 to 480 µg of the melt, well above the dosage recommended in this review.

In conclusion, the safety profile of desmopressin melt is similar to the tablets. The major safety concern in the adult nocturia population is hyponatremia which has an increased incidence with age, was seen primarily in elderly pts > 65 years of age and was seen in women at lower doses than in men. The sponsor's proposed dose of 25 µg in women has an adequate safety profile, however there were too many cases of severe hyponatremia in the pivotal trial in men over 65 years of age treated with the proposed 100 µg dose to recommend its approval. While the sponsor's proposed monitoring scheme seems to adequately identify patients at risk of severe hyponatremia it needs to be validated in a prospective real use study before it can be recommended for dosing. Therefore, the maximum recommended dose for men over 65 years of age is 50 µg. One possible alternative dosing scheme would be to recommend an additional titration up to 100 µg in men under 65 years of age who do not get adequate efficacy from the starting dose of 50 µg. While this medical reviewer agrees that the data support the safety of the use of the 100 µg dose in men under 65 years of age, this medical reviewer is concerned that such a dosing recommendation would result in an increased incidence of off-label use of the higher 100 µg dose in men over 65 years of age. Similar to what was seen in Europe where the nocturia indication is supposed to be limited to individuals under 65 years of age (see Postmarket Experience Section 8). Off-label use in men over 65 years of age, without any monitoring scheme to support safe use in the label, is likely to result in an increased number of cases of severe hyponatremia. Therefore, this medical officer recommends approval of only the single 50 µg dose in men, independent of age, until the sponsor can validate the safety of higher doses in men over 65 years of age with an appropriate monitoring scheme in a prospective trial.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review focused on the pivotal trials CS029 and CS031 using the melt formulation to treat adult nocturia. The earlier nocturia trials using the tablet formulation (Noct 2, 3 and 4) were also reviewed with respect to the risk of hyponatremia.

7.1.2 Categorization of Adverse Events

Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. In the ISS, common adverse

events were defined as adverse events that occurred with a crude incidence rate (percentage of treated subjects reporting the event) >2.0% in any treatment group. More common adverse events were defined as adverse events that occurred with a crude incidence rate >5.0% in any treatment group. Hyponatremia was coded “hyponatraemia” under Metabolism and Nutritional Disorders. Decreases in serum sodium or low serum sodium were coded as “blood sodium decreased” under Investigations.

For the purpose of this review, this medical officer defined “hyponatremia” as serum sodium < 130 mmol/L and “severe hyponatremia” as serum sodium < 125 mmol/L.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pivotal trials CS029 and CS031 studied the efficacy of 0 to 100 µg/day of desmopressin melt in the treatment of adult nocturia. Data from these trials was pooled in the ISS. Placebo exposure in these trials lasted for only 4 weeks while exposure to desmopressin melt lasted for > 1 year in some subjects. Therefore it is not possible to directly compare events rates between the placebo and desmopressin groups outside of the double-blind, placebo-controlled, “Part I” of CS029.

Clinical Trials Noct 2A (males), Noct 3A (females) and Noct 4A (adults) were designed with an initial open-label dose titration phase in which adult nocturia patients were titrated from 100 µg to 400 µg/day of Minirin tablets at weekly intervals until an optimal dose was determined. Patients who did not show a response of >20% (non responders), or showed a prolonged duration of action of the drug (hyper-responders) were not continued into the double-blind phase of the study. Because of the different study designs, there was no benefit in pooling these safety data with that from pivotal trials CS029 and CS031.

Clinical Trial CLN10.3.26 (children and adolescents) was designed with a placebo-controlled, dose titration period during the first 12 days of the study followed by a 6-week observation period at the highest effective dose for the prevention of enuresis. Again because of the different study design, there was no advantage to pooling these safety data with that from pivotal trials CS029 and CS031.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Total exposure was only 12 patient-years for patients in the placebo group compared to between 125 and 185 patient-years for the desmopressin melt treatment groups.

Table 13 Exposure Safety Dataset

Duration (weeks)	Placebo (N=160)	10 µg (N=195)	25 µg (N=227)	50 µg (N=217)	100 µg (N=224)	Total (N=1023)
0 - 1	7 (4.4)	8 (4.1)	5 (2.2)	9 (4.1)	16 (7.1)	45 (4.4)
>1 - 2	3 (1.9)	5 (2.6)	2 (0.9)	4 (1.8)	7 (3.1)	21 (2.1)
>2 - 3	2 (1.3)	6 (3.1)	3 (1.3)	4 (1.8)	6 (2.7)	21 (2.1)
>3 - 4	11 (6.9)	9 (4.6)	7 (3.1)	5 (2.3)	6 (2.7)	38 (3.7)
>4 - 12	136 (85.0)	23 (11.8)	26 (11.5)	24 (11.1)	24 (10.7)	233 (22.8)
>12 - 24	1 (0.6)	30 (15.4)	47 (20.7)	44 (20.3)	43 (19.2)	165 (16.1)
>24 -48	0	46 (23.6)	18 (7.9)	23 (10.6)	23 (10.3)	110 (10.8)
>48 - 72	0	67 (34.4)	78 (34.4)	59 (27.2)	62 (27.7)	266 (26.0)
>72	0	1 (0.5)	41 (18.1)	45 (20.7)	37 (16.5)	124 (12.1)
At least 1 year of exposure	0	54 (27.7)	114 (50.2)	102 (47.0)	97 (43.3)	367 (35.9)
Total patient-years	12.44	124.93	184.54	168.74	161.11	651.75

Cross Reference: [Table 14.5.4.1]

Source ISS Table 12

Demographic characteristics were similar across treatment groups. There were slightly more men than women (52 to 58%). The overwhelming majority of subjects were Caucasian (82 to 88%), so there is insufficient information to perform subgroup analyses to identify efficacy in subpopulations with respect to race. The mean age of the subjects was 62 years (median age: 64 years), so there was a good representation of the elderly population in this clinical study. It is important that the elderly are adequately represented in this study population as they are more likely to develop hyponatremia as a result of treatment with desmopressin. Mean height, weight and body mass index were similar between treatment groups.

Table 14 Demographics of Safety Dataset

Demographic Characteristic	Placebo (N=160)	10 µg (N=195)	25 µg (N=227)	50 µg (N=217)	100 µg (N=224)
Age (years)					
Mean (SD)	61.8 (13.66)	61.4 (14.08)	62.6 (13.07)	61.6 (12.14)	61.3 (12.97)
Median	64.0	64.0	65.0	63.0	64.0
Minimum, maximum	20, 86	23, 85	22, 89	28, 88	24, 85
Age category, n (%)					
<50 years	29 (18.1)	38 (19.5)	36 (15.9)	38 (17.5)	40 (17.9)
50 - <65 years	55 (34.4)	66 (33.8)	72 (31.7)	76 (35.0)	73 (32.6)
65 - <75 years	45 (28.1)	53 (27.2)	84 (37.0)	70 (32.3)	77 (34.4)
≥75 years	31 (19.4)	38 (19.5)	35 (15.4)	33 (15.2)	34 (15.2)
Sex, n (%)					
Female	67 (41.9)	94 (48.2)	96 (42.3)	99 (45.6)	105 (46.9)
Male	93 (58.1)	101 (51.8)	131 (57.7)	118 (54.4)	119 (53.1)
Race, n (%)					
Caucasian	140 (87.5)	159 (81.5)	183 (80.6)	179 (82.5)	177 (79.0)
Black/African American	16 (10.0)	24 (12.3)	36 (15.9)	32 (14.7)	35 (15.6)
Asian	3 (1.9)	3 (1.5)	3 (1.3)	3 (1.4)	9 (4.0)
American Indian/ Alaskan Native	0	2 (1.0)	0	0	0
Native Hawaiian/ other Pacific Islander	0	1 (0.5)	2 (0.9)	0	0
Other	1 (0.6)	6 (3.1)	3 (1.3)	3 (1.4)	3 (1.3)
Ethnic origin, n (%)					
Hispanic	13 (8.1)	18 (9.2)	13 (5.7)	18 (8.3)	13 (5.8)
Not Hispanic	147 (91.9)	177 (90.8)	214 (94.3)	199 (91.7)	211 (94.2)
Height (m)					
Mean (SD)	1.72 (0.110)	1.70 (0.108)	1.72 (0.108)	1.70 (0.102)	1.71 (0.110)
Median	1.7	1.7	1.7	1.7	1.7
Minimum, maximum	1.5, 1.9	1.2, 1.9	1.4, 2.0	1.4, 1.9	1.4, 2.0
Weight (kg)					
Mean (SD)	86.34 (19.661)	84.69 (17.971)	86.48 (18.892)	84.07 (19.598)	85.62 (19.854)
Median	84.0	83.1	86.2	82.6	82.9
Minimum, maximum	47.9, 140.7	42.3, 148.7	45.0, 178.0	46.3, 170.4	42.3, 151.7
Body mass index (kg/m ²)					
Mean (SD)	29.70 (6.763)	29.45 (6.278)	29.55 (6.444)	29.10 (6.985)	29.40 (6.525)
Median	27.69	28.45	28.41	27.34	28.05
Minimum, maximum	16.55, 53.09	16.52, 53.09	16.80, 59.66	16.61, 67.15	16.52, 58.09

Cross Reference: [Table 14.5.2]

Source ISS Table 13

7.2.2 Explorations for Dose Response

There was a clear dose response for the major adverse reaction, hyponatremia, across the dose range 10 to 100 µg/day in study CS029 and across the dose range of 100 to 400 µg/day in studies Noct 2A, 3A and 4 see Section 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

Study FE992026 DS TOX 0301, "Oral Irritation Test in the Syrian Hamster", tested the toxicity of the melt formulation compared to placebo on the cheek pouches in 20 Syrian hamsters. Oral lyophilisates containing up to 360 µg of desmopressin and placebo were devoid of any effect after daily dosing for 28 days in this local irritation test.

Study FE992026 DS PHA 0501 investigated the absorption of desmopressin across the oral mucosa following sublingual administration of the melt formulation in pigs. Absorption of the melt formulation through oral mucosa in anesthetized pigs with an occluded esophagus was ~2-fold greater and T max was delayed ~2-fold compared to administration to conscious pigs with a non occluded esophagus (AUC/µg 1.49 vs. 0.67 hrXpg/mL and Tmax 1.93 hours vs. 0.82 hours). As a comparison, absorption, AUC/µg, was lower and Tmax, was sooner for desmopressin tablets given to conscious pigs with a non occluded esophagus (e.g. 0.20 hrXpg/mL and 0.67 hours, respectively).

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolic, clearance and interaction workup data was submitted. Reference for preclinical studies is made to data from NDA 19-955 (DDAVP tablets).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Desmopressin is the only currently approved vasopressin 2 (V2) receptor agonist.

(b) (4)
[REDACTED]
[REDACTED]. However, this finding has not been reported with desmopressin.

7.3 Major Safety Results

Total, serious, and severe adverse events, as well as adverse events leading to discontinuation or assessed by the study investigator to be possibly/probably related to the study drug were all more common in the NocduRNA treatment groups compared to the placebo group (see Table 12). However, none of these categories including those possibly/probably related to the study drug showed a clear dose response as is typically expected from a drug-related effect. Therefore, it is more likely that the difference in reporting rates shown here are due to the larger > 10-fold difference in exposure (total-pt years) for patients treated with NocduRNA compared to placebo.

Table 15 Summary of Adverse Events by Study Dose

Adverse Events Category	Placebo		10 ug		25 ug		50 ug		100 ug		Total	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Safety Dataset	160 (100.0%)		195 (100.0%)		227 (100.0%)		217 (100.0%)		224 (100.0%)		1023 (100.0%)	
Total Patient-Years	12.44		124.93		184.54		168.74		161.11		651.75	
All Adverse Events	76 (47.5%)	102	150 (76.9%)	478	169 (74.4%)	549	176 (81.1%)	639	179 (79.9%)	610	750 (73.3%)	2378
Deaths	0	0	0	0	0	0	0	0	0	0	0	0
Serious Adverse Events	1 (0.6%)	1	10 (5.1%)	12	7 (3.1%)	7	18 (8.3%)	21	16 (7.1%)	20	52 (5.1%)	61
AEs Leading to Discontinuation	7 (4.4%)	7	15 (7.7%)	20	13 (5.7%)	23	28 (12.9%)	43	27 (12.1%)	47	90 (8.8%)	140
Severe Adverse Events	2 (1.3%)	2	21 (10.8%)	29	22 (9.7%)	27	33 (15.2%)	41	21 (9.4%)	32	99 (9.7%)	131
ADRs	47 (29.4%)	58	90 (46.2%)	132	83 (36.6%)	121	102 (47.0%)	170	110 (49.1%)	177	432 (42.2%)	658

Source ISS Table 14.6.1.1; ADR = adverse drug reaction (adverse event assessed by the Investigator as possibly/probably related to study drug)

7.3.1 Deaths

There were no deaths in the pivotal trial or up to 30 days after the last dose of study drug. One death, 43 days after the end of treatment, due to acute respiratory failure in a patient with HIV was considered unrelated to drug by the clinical investigator.

7.3.2 Nonfatal Serious Adverse Events

There were 51 (5.9%) subjects with nonfatal serious AEs in the NocduRNA treatment groups during the pivotal trial. No serious AE occurred in more than 1% of study patients treated with desmopressin. No cases of hyponatremia or blood sodium decrease were considered serious.

Table 16 Nonfatal Serious Adverse Events

System Organ Class MedDRA Preferred Term	Placebo (N=160) n (%)	10 µg (N=195) n (%)	25 µg (N=227) n (%)	50 µg (N=217) n (%)	100 µg (N=224) n (%)
Any serious adverse event	1 (0.6)	10 (5.1)	7 ^a (3.1)	18 (8.3)	16 ^b (7.1)
Cardiac Disorders					
Atrial fibrillation	0	1 (0.5)	0	2 (0.9)	1 (0.4)
Myocardial infarction	0	1 (0.5)	1 (0.4)	0	1 (0.4)
General Disorders and Administration Site Conditions					
Chest pain	0	1 (0.5)	0	0	1 (0.4)
Infections and Infestations					
Cellulitis	0	0	0	1 (0.5)	1 (0.4)
Pneumonia	0	1 (0.5)	0	1 (0.5)	0
Musculoskeletal and Connective Tissue Disorders					
Osteoarthritis	0	0	1 (0.4)	1 (0.5)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)					
Prostate cancer ^c	1 (1.1)	0	0	0	1 (0.8)

Note: Preferred terms are sorted within system organ classes in decreasing order of frequency in the 100 µg group.

- An event of diarrhoea in Subject (b) (6) was captured as a serious adverse event, but was changed to non-serious by the Investigator after interim database lock [CS31, Section 10.3.2]. The event was not reported to Ferring Pharmacovigilance or to the Institutional Review Board.
- Relationship to study drug and whether or not the event was serious were missing for Subject (b) (6) therefore, the 3 laboratory adverse events reported for this subject (platelet count decreased, neutrophil count decreased, and white blood cell count decreased) were categorized as serious and as related to study drug [CS31, Section 10.3.2].
- Male-specific event; denominator is based on the male population.

Source ISS Table 17

7.3.3 Dropouts and/or Discontinuations

There were 83 AEs leading to discontinuation in patients treated with Nocdurna during the pivotal trial. The most common events in any treatment group were hyponatremia, blood sodium decreased, and headache which occurred primarily in the Nocdurna treatment groups. All the rest of the events occurred in less than 2% of patients per treatment group.

Table 17 AEs Leading to Study Discontinuation in Two or More Subjects

System Organ Class	Placebo (N=160)	10 µg (N=195)	25 µg (N=227)	50 µg (N=217)	100 µg (N=224)
MedDRA Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Any adverse event leading to premature discontinuation	7 (4.4)	15 (7.7)	13 (5.7)	28 (12.9)	27 (12.1)
Eye Disorders					
Dry eye	0	2 (1.0)	0	0	0
Gastrointestinal Disorders					
Nausea	0	0	1 (0.4)	2 (0.9)	3 (1.3)
Vomiting	0	0	2 (0.9)	0	2 (0.9)
Dry mouth	1 (0.6)	2 (1.0)	0	3 (1.4)	1 (0.4)
Abdominal pain	0	1 (0.5)	0	1 (0.5)	0
Constipation	1 (0.6)	0	0	1 (0.5)	0
General Disorders and Administrative Site Conditions					
Fatigue	0	0	0	1 (0.5)	3 (1.3)
Infections and Infestations					
Urinary tract infection	0	0	0	0	2 (0.9)
Investigations					
Blood sodium decreased	1 (0.6)	0	0	3 (1.4)	6 (2.7)
Glomerular filtration rate decreased	0	0	0	2 (0.9)	1 (0.4)
Metabolism and Nutrition Disorders					
Hyponatraemia	0	0	2 (0.9)	9 (4.1)	5 (2.2)
Musculoskeletal and Connective Tissue Disorders					
Muscle spasms	0	0	0	1 (0.5)	1 (0.4)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)					
Prostate cancer ^a	1 (1.1)	0	0	0	1 (0.8)
Nervous System Disorders					
Headache	1 (0.6)	0	2 (0.9)	1 (0.5)	5 (2.2)
Dizziness	0	2 (1.0)	1 (0.4)	2 (0.9)	2 (0.9)
Psychiatric Disorders					
Insomnia	1 (0.6)	0	0	1 (0.5)	0
Renal and Urinary Disorders					
Nephrolithiasis	0	0	1 (0.4)	1 (0.5)	0
Vascular Disorders					
Hypertension	1 (0.6)	0	0	0	1 (0.4)

Note: Preferred terms are sorted within system organ classes in decreasing order of frequency in the 100 µg group.

a. Male-specific event; denominator is based on the male population.

Source ISS Table 18

7.3.4 Significant Adverse Events (Hyponatremia)

Hyponatremia

Hyponatremia (serum sodium < 130 mmol/L) is a well described adverse reaction associated with the use of all desmopressin formulations. Severe hyponatremia (serum sodium < 125 mmol/L) or a rapid drop in serum sodium from baseline are especially serious as they can lead to cerebral edema and seizures. Elderly patients are especially susceptible to the development of hyponatremia because of a decrease in renal function which makes it harder for them to limit sodium excretion. Under normal circumstance they can maintain fluid homeostasis, but their ability to respond to external stresses is limited. Conditions that can predispose to the development of hyponatremia include volume depletion (due to vomiting, diarrhea, severe burns, blood loss), medications (e.g. diuretics, SSRIs, NSAIDs, TCAs, antiepileptic drugs, chemotherapy agents), CHF, cirrhosis, renal failure, malignancies, pulmonary disorders (e.g. pneumonia, TB, acute respiratory failure), endocrine disorders (e.g. hypothyroidism, glucocorticoid deficiency) and SIADH (due to head trauma, neurosurgery, CNS infections)¹¹. In fact, hyponatremia is the most common electrolyte abnormality seen in the general hospital population with an incidence of about 1% in the US¹².

Because of the concern for the risk of the development of hyponatremia, all patients were required to have baseline serum sodium levels ≥ 135 mmol/L in order to be included in the study. Despite this, a total of 57 (6.6%) subjects developed serum sodium <130 mmol/L on various doses of Nocdurna compared to only one such patient (0.6%) in the placebo group. The rate of hyponatremia increased with increasing dose of drug with severe hyponatremia, defined as serum sodium < 125 mmol/L, seen primarily at doses of 50 μ g and above, see Table 18.

11 [Causes and management of hyponatremia](#). Palmer BF, Gates JR, Lader M. Ann Pharmacother. 2003 Nov;37(11):1694-702. Review

12 [Hyponatremia](#). Al-Salman J, Kemp D, Randall D. West J Med. 2002 May;176(3):173-6.

Table 18 The Number of Patients with the Lowest Serum Sodium in each Serum Sodium Category

	Placebo N (%)	10 ug N (%)	25 ug N (%)	50 ug N (%)	100 ug N (%)	Total N (%)
Safety Dataset	160 (100.0%)	195 (100.0%)	227 (100.0%)	217 (100.0%)	224 (100.0%)	1023 (100.0%)
Serum Sodium						
Observed N	158 (98.8%)	192 (98.5%)	226 (99.6%)	215 (99.1%)	219 (97.8%)	1010 (98.7%)
>= 135 mmol/l	147 (91.9%)	163 (83.6%)	176 (77.5%)	141 (65.0%)	137 (61.2%)	764 (74.7%)
< 135 mmol/l	11 (6.9%)	29 (14.9%)	50 (22.0%)	74 (34.1%)	82 (36.6%)	246 (24.0%)
130-134 mmol/l	10 (6.3%)	25 (12.8%)	45 (19.8%)	52 (24.0%)	56 (25.0%)	188 (18.4%)
125-129 mmol/l	0	3 (1.5%)	5 (2.2%)	16 (7.4%)	22 (9.8%)	46 (4.5%)
< 125 mmol/l	1 (0.6%)	1 (0.5%)	0	6 (2.8%)	4 (1.8%)	12 (1.2%)

Source Sponsor's ISS Table 14.6.7.1.1 ISS CS029 and CS031

Medical Officer's comment-

This difference in the rates of hyponatremia is partially overestimated as placebo patients had a much shorter duration of exposure, usually one month, compared to the Nocurna treated patients, who were treated for up to 1 to 2 years. However, as hyponatremia tends to occur primarily in the first month of treatment adjusting for the difference in exposure does not change the general results substantially. Looking at sodium values measured during the double-blind portion of CS029 (see Table 19) shows a slightly lower overall rate of hyponatremia in the Nocurna treatment groups but a similar pattern with severe hyponatremia seen primarily at doses above 50 µg.

Table 19 Number of Pts with Hyponatremia in the Double-Blind Phase of CS029

Serum Sodium	placebo	10 µg	25 µg	50 µg	100 µg	Total Nocurna pts
125-129 mmol/L	0 (0.0%)	1 (0.5%)	2 (0.9%)	8 (3.7%)	15 (6.7%)	26 (3.0%)
< 125 mmol/L	1 (0.6%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	4 (1.8%)	7 (0.8%)
Data Source ADNA lab dataset CS029: Visit 3, 4, 5, 6 and 7.						

In their analyses of these data, the sponsor determined that hyponatremia tended to occur early during treatment, primarily on Day 4 or Day 8 of treatment (see Section 7.5.2 Time Dependency for AEs). In female subjects, it was only seen in patients receiving doses of 50 µg or greater, and it was not observed in any subject, male or female ≤50 years of age (see Section 7.5.3 Drug-Demographic Interactions). As a result of these findings the sponsor developed criteria that should prevent the occurrence of severe hyponatremia based on gender (male dose-100 µg and female dose-25 µg) and

based on gender & age (monitoring serum sodium levels on treatment Days 4 and 28 in men $\geq$ 65 years). If these monitoring criteria had been used to exclude patients at risk of hyponatremia during the study, there would have been no patients with severe hyponatremia ($<$ 125 mmol/L) in the current study. In addition, of the 7 patients (0.9%) who met the monitoring criteria and yet developed sodium values between 125 and 130 mmol/L during the study, sodium levels returned to normal, $>$ 130mmol/L, by the next evaluation in all patients, even though only one of these patients had their Nocdurna dose discontinued. So the risk of progression to severe hyponatremia in these borderline patients appeared to be low. In contrast, without monitoring 11 patients (1.3%) had serum sodium levels $<$ 125mmol/L and 46 patients (5.3%) had serum sodium levels values between 125 and 130 mmol/L.

Table 20 The Number of Patients with the Lowest Serum Sodium in each Serum Sodium Category if Sponsor's Serum Monitoring Criteria are Applied

	Placebo N (%)	10 ug N (%)	25 ug N (%)	50 ug N (%)	100 ug N (%)	Total N (%)
Safety Dataset	160 (100.0%)	195 (100.0%)	227 (100.0%)	217 (100.0%)	224 (100.0%)	1023 (100.0%)
Serum Sodium						
Observed N	131 (81.9%)	156 (80.0%)	182 (80.2%)	157 (72.4%)	145 (64.7%)	771 (75.4%)
$\geq$ 135 mmol/l	127 (79.4%)	138 (70.8%)	148 (65.2%)	125 (57.6%)	114 (50.9%)	652 (63.7%)
$<$ 135 mmol/l	4 (2.5%)	18 (9.2%)	34 (15.0%)	32 (14.7%)	31 (13.8%)	119 (11.6%)
130-134 mmol/l	4 (2.5%)	18 (9.2%)	33 (14.5%)	29 (13.4%)	28 (12.5%)	112 (10.9%)
125-129 mmol/l	0	0	1 (0.4%)	3 (1.4%)	3 (1.3%)	7 (0.7%)
$<$ 125 mmol/l	0	0	0	0	0	0

Source Sponsor's ISS Table 14.6.7.1.2

Medical Officer's comment-

This medical officer agrees with the findings of the post hoc analysis: that limiting Nocdurna use only to subjects with baseline sodium levels of 135 or greater, monitoring serum sodium levels on Days 4 or 28 of therapy for men over 65 years of age and limiting women to the 25 μ g dose would have prevented severe hyponatremia. However, this medical officer believes that this ad-hoc analysis needs to be confirmed in a prospective study before it can be used to recommend dosing. In addition, the sponsor needs to provide evidence that the proposed monitoring scheme will be implemented appropriately in a real use situation. Therefore, this medical officer would recommend an initial approval with a dosing scheme that did not require monitoring for men over 65 years of age until the proposed monitoring scheme could be validated.

While doses of 100 µg and above would need monitoring to minimize the risk of hyponatremia, the question arises whether a lower dose such as 50 µg can be used safely in men without the need for monitoring. There were only two men in this pivotal study on doses lower than 100 µg who developed severe hyponatremia.

- An 81 year old male, who had a sodium level of 124mmol/L on the 50 µg dose: Patient (b) (6) had hyponatremia on Day 8 of dosing and was discontinued from the study. However, this patient had calculated creatinine clearances at baseline of 53 and 42 well below the exclusion criteria of < 60 mL/min and should never have been enrolled in the study.*
- A 78 year old male, who had a sodium level of 123mmol/L on the 10 µg dose: Patient (b) (6) had an episode of hyponatremia on day 327 of therapy shortly after being started on moxifloxacin for a pulmonary infection. The sponsor argues that this patient should have had the Nocurna dose transiently discontinued during the intercurrent illness and that this would have prevented this episode. As the 10 µg has limited efficacy in males it is this medical officer's impression that this event was probably not drug related.*

Therefore, it seems reasonable not to require monitoring for the 50 µg dose in men with normal renal function or only mild renal impairment (Creatinine clearance > 60 mL/min).

Possible dosing schemes that would not require monitoring include:

- approving the 25 µg dose for all women and approving the 100 µg dose only for men under 65 years of age.*
- approving the 25 µg dose for all women and approving the 50 µg dose for all men, assuming the efficacy of the 50 mcg dose in men can be established*
- approving the 25 µg dose for all women, approving the 50 µg dose for men 65 years of age and older, and approving the 100 µg dose for men under 65.*

The last two scenarios would require acceptance of the efficacy of the 50 µg dose in men which is discussed in greater detail in the Efficacy Review under Section 6.1.8- Analysis of Clinical Information Relevant to Dosing Recommendations.

As the starting doses of 50 µg in men and 25 µg in women, being proposed in this medical review are likely to result in sub maximal efficacy in certain patients, this medical officer recommends that the sponsor consider performing a follow up study to verify that the sponsor's proposed monitoring scheme can adequately identify patients at risk of severe hyponatremia who may benefit from being

titrated to higher doses for better efficacy. From the current data it seems reasonable to permit dosing up to a maximum of 100 µg per day in such a study.

Hyponatremia in Clinical Trials Noct 2A/B, 3A/B and 4A with Minirin Tablets.

Clinical Trials Noct 2A (males), Noct 3A (females) and Noct 4A (adults) were designed with an initial open-label dose titration phase in which patients were titrated from 100 µg to 400 µg per day of Minirin tablets at weekly intervals until an optimal dose was determined. The optimal dose was defined as the lowest dose giving the maximum response. Patients who did not show a response of >20% (non responders), or showed a prolonged duration of action of the drug (hyper-responders) were not continued into the double-blind phase of the study. Following a one week washout period, a three week randomized, double-blind, parallel group, placebo controlled study was performed with patients receiving either their optimal dose (100 to 400 µg of Minirin tablets) or placebo. Patients in studies 2A and 3A were given the option to continue into 10-month open-label extensions, trials 2B and 3B, respectively.

Noct 2A (males)

9 pts (4%) had serum Na levels < 130 mmol/L; 6 of them were symptomatic.

All episodes occurred during the dose titration phase.

1 (100 µg), 2 (200 µg) and 6 (400 µg)

Three pts were enrolled in the double-blind part of the study, and received drug without repeat hyponatremia, two pts with hyponatremia were withdrawn after the washout period for lack of efficacy.

Noct 2B (males)

One pt (1%) with a serum Na of 128 mmol/L on 400 µg, who was asymptomatic during the dose titration phase, was enrolled in the extension trial and had a serum Na of 128 mmol/L on Day 12 associated with a headache.

Noct 3A (females)

14 pts (6%) had serum Na levels < 130 mmol/L; 9 of them were symptomatic.

All episodes occurred during the dose titration phase.

3 (100 µg), 2 (200 µg) and 9 (400 µg)

Two pts were enrolled in the double-blind part of the study, and received drug without repeat hyponatremia, one pt with hyponatremia was withdrawn after the washout period for lack of efficacy.

Noct 3B (females)

One pt (1%) had a serum Na of 125 mmol/L and symptoms on 400 µg during a four-month visit. Her dose of Minirin was lowered to 100 µg and she was started on diuretic therapy. A few days later she returned with a serum Na of 124 mmol/L and was hospitalized for hyponatremia.

Noct 4

9 pts (5%) had serum Na levels < 130 mmol/L; 2 of them were symptomatic.

All episodes occurred during the dose titration phase.

6 at <130: 1 (100 µg), 0 (200 µg) and 5 (400 µg)

3 at <125: 1 (100 µg), 1 (200 µg) and 1 (400 µg)

Two pts were enrolled in the double-blind part of the study, and received drug without repeat hyponatremia, one pt received a lower dose and was asymptomatic.

Medical Officer's comments

Since patients were prescreened for efficacy and risk for being hyper-responders these safety data cannot be extrapolated to the nocturia population in general.

Be that as it may, there is useful information that can be taken from these studies. Almost half of the patients (49%) needed to be titrated up to 400 µg of tablets (equivalent to 240 µg of melt) to get a maximal response, so most patients in the pivotal trial, CS029, who were treated with the lower doses of 10 to 100 µg of the melt formulation, were probably receiving sub maximal therapy. However this does not preclude the fact that individual patients may consider a partial response beneficial enough to pursue therapy.

In general, the rate of hyponatremia was dose related, and not all patients were symptomatic. From a positive point of view this could mean that these were patients who had a transient decrease in sodium that would have resolved on its own. From a negative point of view this could mean that these were patients who were unlikely to be identified until the sodium levels were so low that patients were at risk of cerebral edema or seizure.

Only two men developed hyponatremia with the 0.1mg tablet (equivalent to 60 µg of melt) dose compared to 9 women. These two men had serum sodium levels of 126 and 129mmol/L, not in the severe hyponatremia range, and they received higher doses than the maximum dose of 50 µg recommended in this review. All of the other cases of hyponatremia which were seen with 0.2 and 0.4 mg of tablets (equivalent to 120 and 240 µg of melt) were dosed well above the maximal doses of the melt formulation recommended in this review (i.e. 25 µg for women and 50 µg for men).

Most of the cases of hyponatremia occurred during the initial dose titration/screening phase except for 2 cases (1%): (b) (6), a 77.3 y/o male who developed a serum sodium of 128mmol/L on a dose of 400 µg on study day 63, and (b) (6) a 60.7 y/o female who developed a serum sodium of 125mmol/L on a dose of 200 µg on study day 166 (source NOCT ADNA dataset). Therefore, these data do not preclude monitoring as a possible method to identify patients at risk of hyponatremia at lower doses of the melt formulation.

Hyponatremia in the ISS

A review of the treatment related adverse events shows a dose related increase in both “blood sodium decreased” and “hyponatremia” terms consistent with a drug-related event. The event rates at the highest proposed dose of 100 µg approach 5 to 6% (see Table 21).

Table 21 Subset of Treatment Emergent Adverse Events (Safety Dataset)

System Organ Class MedDRA Preferred Term	Placebo (N=160) n (%)	10 µg (N=195) n (%)	25 µg (N=227) n (%)	50 µg (N=217) n (%)	100 µg (N=224) n (%)
Investigations					
Blood sodium decreased	1 (0.6)	2 (1.0)	2 (0.9)	6 (2.8)	11 (4.9)
Glomerular filtration rate decreased	0	1 (0.5)	2 (0.9)	4 (1.8)	5 (2.2)
Blood glucose increased	1 (0.6)	0	7 (3.1)	3 (1.4)	3 (1.3)
Blood pressure increased	2 (1.3)	5 (2.6)	1 (0.4)	3 (1.4)	2 (0.9)
Metabolism and Nutrition Disorders					
Hyponatraemia	1 (0.6)	4 (2.1)	4 (1.8)	15 (6.9)	14 (6.3)

Note: Preferred terms are sorted within system organ classes in decreasing order of frequency in the 100 µg group.

a. Female-specific event; denominator is based on the female population.

Cross Reference: [ISS Tables 14.6.2.1 and 14.6.9.1]

Source ISS Table 15

7.3.5 Submission Specific Primary Safety Concerns

See Hyponatremia Section 7.3.4

7.4 Supportive Safety Results

See Post Marketing Experience Section 8

7.4.1 Common Adverse Events

Adverse events that occurred the most commonly with NocduRNA included dry mouth, headache, hyponatremia/blood sodium decreased, URI, UTI, nausea, nasopharyngitis and dizziness. Because of the large difference in exposure it is not possible to directly compare AE rates seen with NocduRNA to the placebo group. The high rate of reporting of dry mouth probably reflects that fact that it was specifically asked about at each study visit. The fact that “GFR decreased” shows a dose response may be drug related, but the event rate is quite low. Four of the twelve patients with an AE of “GFR decreased” had sodium levels less than 135 mmol/L. The lowest sodium levels for these patients were 133, 133, 127 and 124 mmol/L. Three subjects were receiving 100 µg and one subject was receiving 50 µg of NocduRNA during the sodium troughs. It seems prudent to

recommend following sodium measurements in patients treated with Nocdurna in whom the physician is concerned about potential worsening in renal function.

Preferred Term†	Placebo N=160 %	10 µg N=195 %	25 µg N=227 %	50 µg N=217 %	100 µg N=224 %
Dry Mouth	25	39	31	33	32
Headache	5	8.7	7	9.7	11
Upper Respiratory Tract Infection	1.9	5.6	7.5	7.8	9.8
Urinary Tract Infection	0	5.1	2.6	4.6	6.7
Hyponatraemia	0.6	2.1	1.8	6.9	6.3
Nausea	0.6	5.1	4.4	6	5.8
Nasopharyngitis	2.5	6.7	6.2	5.5	5.8
Dizziness	0	4.6	4	4.6	4.9
Blood Sodium Decreased	0.6	1	0.9	2.8	4.9
Cough	0	0.5	3.5	5.1	4.5
Hypertension	0.6	3.6	4	4.6	4.5
Insomnia	0.6	4.1	2.2	4.6	4
Oedema Peripheral	0.6	3.1	0.4	4.6	4
Bronchitis	0	2.6	3.5	2.8	4
Gastroesophageal Reflux Disease	0	2.6	2.2	0.9	4
Diarrhoea	1.3	6.2	5.7	6.9	3.6
Muscle Spasms	0.6	3.1	4	3.2	3.6
Pharyngolaryngeal Pain	0.6	3.1	2.6	3.2	3.6
Sinusitis	0.6	4.6	3.5	2.8	3.1
Constipation	1.9	2.6	4	2.3	3.1
Anxiety	0	0.5	0.4	0.5	3.1
Back Pain	0	4.1	4.4	5.5	2.7
Fatigue	1.3	6.7	0.9	3.2	2.7
Pollakiuria	0.6	3.1	1.3	2.8	2.7
Influenza	0	1.5	2.2	4.1	2.2
Vomiting	0	2.1	3.1	3.7	2.2
Arthralgia	0.6	2.6	2.2	2.8	2.2
Abdominal Pain Upper	1.3	2.1	1.8	1.8	2.2
Glomerular Filtration Rate Decreased	0	0.5	0.9	1.8	2.2
Pain In Extremity	0.6	2.1	2.6	0.9	2.2
Blood Glucose Increased	0.6	0	3.1	1.4	1.8
Rash	0.6	1.5	1.3	2.8	1.3
Gastroenteritis Viral	0	1.5	0.4	2.8	1.3
Pain	0	0.5	2.6	2.3	1.3
Blood Pressure Increased	1.3	3.1	0.4	1.4	1.3
Contusion	0	2.1	3.1	0.5	1.3
Stomach Discomfort	0	2.6	0.4	0	0.9

Table 22 AEs from Safety Dataset ADAE Occurring at $\geq 2\%$ in any Treatment Group					
Preferred Term†	Placebo N=160 %	10 µg N=195 %	25 µg N=227 %	50 µg N=217 %	100 µg N=224 %
Anaemia	0	2.1	1.3	1.4	0.4
Joint Sprain	0	2.1	2.6	0.9	0.4
Nasal Congestion	0	1.5	2.6	0.9	0.4
Dermatitis Contact	0	0	2.2	0.9	0.4
Muscle Strain	0	0	2.2	0.9	0.4
Dry Eye	0	2.1	0.9	0	0.4

† Subjects could have been on more than one dose. N refers to all subjects exposed to a given dose. Source- ADAE dataset excluding data with missing values for AEDOSE (dose at time of AE)

Laboratory Findings

A comparison of a partial list of clinical and hematology labs observed during the first month of double blind treatment is given in Table 20. No dose response was seen for any of the tests except for low sodium values, which was observed using 135, 130 or 125 mmol/L as the lower limit.

Table 23 Number of Patients with Lab Abnormalities during the 28 Day Double-blind Study Period

Lab test	Placebo N=159	10 µg N=161	25 µg N=158	50 µg N=157	100 µg N=157
Alt (>ULN)	3	4	4	6	3
Ast (>ULN)	7	4	4	4	6
GGT (>ULN)	8	9	8	9	5
Alk Phos (>ULN)	1	2	2	0	0
Direct Bili High (>ULN)	0	1	1	0	0
Creatinine High (>ULN)	1	0	1	4	1
BUN High (>ULN)	7	4	4	8	3
Potassium Low (< ULN)	3	3	3	1	6
Glc High (> ULN)	64	60	60	59	56

Lab test	Placebo N=159	10 µg N=161	25 µg N=158	50 µg N=157	100 µg N=157
Uric Acid High (>ULN)	9	6	7	6	2
Hemoglobin Low (< ULN)	12	11	13	6	13
Hemoglobin High (> ULN)	3	6	7	1	2
Serum Sodium (<135mEq/L)	11	18	15	39	47
Serum Sodium (<130mEq/L)	1	1	2	11	18
Serum Sodium (<125mEq/L)	1	0	0	3	4
Data source ADLB ISS-dataset Visits 3 to 7 e.g. Days 4, 8, 15, 22 and 28 (+/-3)					

Tables listing the incidence of shifts of $\geq 5\%$ overall from normal to < LLN or > ULN in hematology and clinical lab variables for all lab values are given in the appendix for reference ([see Sponsor's ISS Tables 33 through 36](#)). While all of these tests showed higher rates in all NocduRNA treatment groups compared to the placebo group this reflects the much larger time of exposure to NocduRNA (e.g. up to 1 to 2 years) compared to placebo (e.g. 1 month). None of these lab values, except for low sodium values, showed a dose response which would suggest a drug-related event.

The one placebo patient and three patients receiving 50 µg of NocduRNA who had sodium levels under 125mEq/L during the first month of therapy were all female. Of the four patients receiving 100 µg of NocduRNA who had sodium levels under 125mEq/L during the first month of therapy half were male (n=2) and half were female (n=2).

7.4.3 Vital Signs

There were no dose response changes with respect to mean or % change from the mean in blood pressure or heart rate. There were no dose response changes with respect to markedly abnormal increases or decreases in blood pressure or heart rate. Overall no clinically significant findings in vital signs or physical exams were identified in these studies.

7.4.4 Electrocardiograms (ECGs)

No information about ECG measurements between treatment groups was included in this submission.

7.4.5 Special Safety Studies/Clinical Trials

No information regarding special safety studies was included in this submission.

7.4.6 Immunogenicity

No information regarding immunogenicity was included in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Hyponatremia is a well described AE associated with the use of desmopressin. In the pivotal trial CS029 the rate of hyponatremia increased from 2 to 11.6% across the dose range of 10 to 100 µg, with severe hyponatremia, defined as serum sodium < 125 mmol/L, seen primarily at doses of 50 and 100 µg, see Table 18. In the other phase III trials Noct 2A, 3A and 4, there was also a dose related increase in hyponatremia over the dose range of 100 to 400 µg of Nocdurna.

In the pivotal trial CS029 the AE “GFR decreased” showed a dose response of 0.5 to 2.2% over the dose range of 10 to 100 µg of Nocdurna which may be drug-related (see Section 7.4.1 Common Adverse Events and Section 7.5.4 Drug-Disease Interactions.)

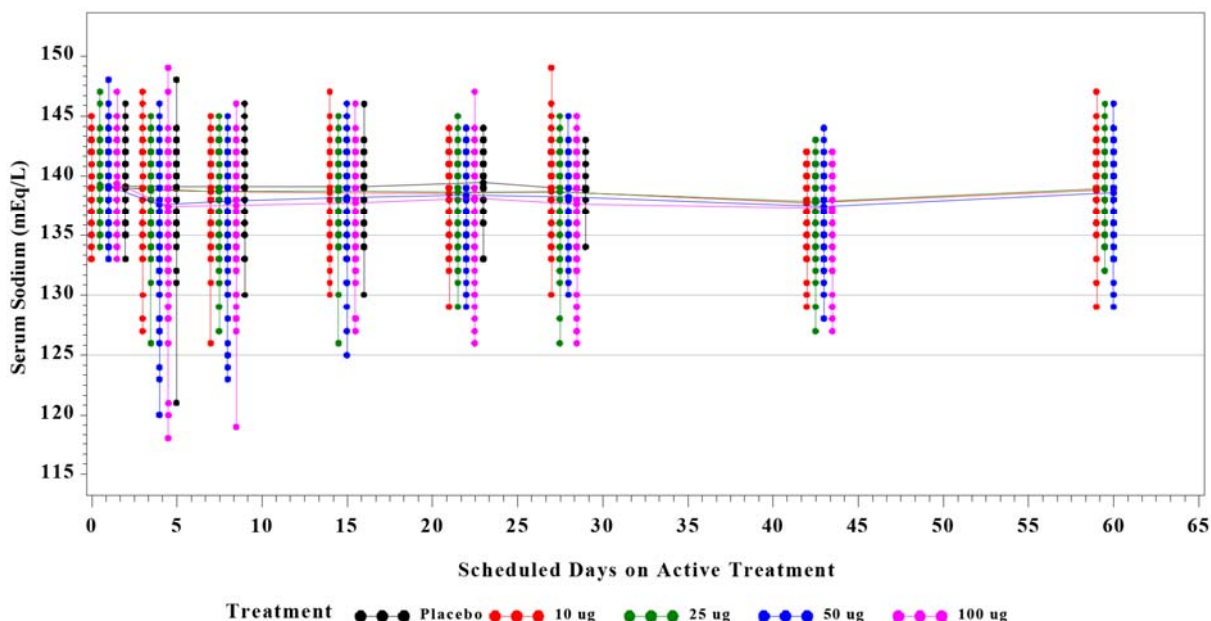
In the pivotal trial CS029 the AE “Upper Respiratory Tract Infection” showed a dose response of 1.9 to 9.8% over the dose range of 10 to 100 µg of Nocdurna. It is this medical officer’s impression that this is probably a chance occurrence as there is no clear dose response with respect to the rate of other similar AEs such as “nasopharyngitis, cough, bronchitis or sinusitis”.

Other more common AEs observed in the pivotal trial CS029 that may be drug-related include dry mouth, headache, UTI, nausea, dizziness, peripheral edema and diarrhea, but they did not show a dose dependency.

7.5.2 Time Dependency for Adverse Events

In their analyses of these data, the sponsor determined that hyponatremia tended to occur early during treatment, primarily on Days 4 or 8 of treatment. Whereas this may be true of severe hyponatremia (< 125mmol/L), hyponatremia in the range of 125 to 130mmol/L is seen through out the length of the trial.

Figure 7 Minimum Serum Sodium Levels



Source Fig. 3 from ISS.

7.5.3 Drug-Demographic Interactions

Gender

Efficacy was shown to be significantly greater at lower doses in women compared to men (see Section 6.1.7 Subpopulations); therefore it is not surprising that hyponatremia was also seen at lower doses in women compared to men. The single episodes of hyponatremia in men on doses of 10 and 50 μ g were described previously (see Section 7.3.4 Hyponatremia) and are probably related to an intercurrent illness after almost a year on therapy and to moderate renal impairment at baseline, respectively. In contrast, there was no clear explanation for the five cases of severe hyponatremia seen in women taking the 50 μ g dose, and the 50 μ g dose should not be approved in women unless a monitoring scheme can be validated for this dose similar to what the sponsor recommends to do with the 100 μ g dose in men. A monitoring scheme in women would probably need to be enacted for women age 50 and above as severe hyponatremia was seen in women at age 51 and 56 on the 50 μ g dose (see Age below).

Table 24 Minimum Serum Sodium by Gender

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		100 µg n (%)	
	Males (N=93)	Females (N=67)	Males (N=101)	Females (N=94)	Males (N=131)	Females (N=96)	Males (N=118)	Females (N=99)	Males (N=119)	Females (N=105)
Observed N	92 (98.9)	66 (98.5)	99 (98.0)	93 (98.9)	130 (99.2)	96 (100.0)	117 (99.2)	98 (99.0)	116 (97.5)	103 (98.1)
≥135	87 (93.5)	60 (89.6)	83 (82.2)	80 (85.1)	100 (76.3)	76 (79.2)	72 (61.0)	69 (69.7)	72 (60.5)	65 (61.9)
<135	5 (5.4)	6 (9.0)	16 (15.8)	13 (13.8)	30 (22.9)	20 (20.8)	45 (38.1)	29 (29.3)	44 (37.0)	38 (36.2)
130-134	5 (5.4)	5 (7.5)	15 (14.9)	10 (10.6)	29 (22.1)	16 (16.7)	36 (30.5)	16 (16.2)	32 (26.9)	24 (22.9)
125-129	0	0	0	3 (3.2)	1 (0.8)	4 (4.2)	8 (6.8)	8 (8.1)	10 (8.4)	12 (11.4)
<125	0	1 (1.5)	1 (1.0)	0	0	0	1 (0.8)	5 (5.1)	2 (1.7)	2 (1.9)

Cross Reference: [Table 14.6.7.2]

Source ISS Table 24

Age

The incidence of hyponatremia increases with age. This is at least partially related to the normal decrease in renal function with age which makes it more difficult for elderly patients to limit sodium excretion. There were only two patients with severe hyponatremia under age 65 and both were women, age 51 and 56, receiving the 50 µg dose. Therefore, any monitoring scheme for doses of 50 µg and above in women would probably need to be enacted for women age 50 and above. The single episode of hyponatremia on the 10 µg dose was a 78 year old male with an intercurrent illness which was described previously (see Section 7.3.4 Hyponatremia). In summary, there were no women at any age (i.e. < or ≥65) with severe hyponatremia on doses of 25 µg or less, and there were no men <65 years of age with severe hyponatremia on doses of 100 µg or less.

Table 25 Minimum Serum Sodium Values by Age (< 65, ≥ 65 years)

Serum Sodium (mmol/L)	Placebo n (%)		10 µg n (%)		25 µg n (%)		50 µg n (%)		100 µg n (%)	
	<65 years (N=84)	≥65 years (n=76)	<65 years (N=104)	≥65 years (n=91)	<65 years (N=108)	≥65 years (n=119)	<65 years (N=114)	≥65 years (n=103)	<65 years (N=113)	≥65 years (n=111)
Observed N	82 (97.6)	76 (100.0)	102 (98.1)	90 (98.9)	107 (99.1)	119 (100.0)	112 (98.2)	103 (100.0)	110 (97.3)	109 (98.2)
≥135	76 (90.5)	71 (93.4)	92 (88.5)	71 (78.0)	91 (84.3)	85 (71.4)	85 (74.6)	56 (54.4)	83 (73.5)	54 (48.6)
<135	6 (7.1)	5 (6.6)	10 (9.6)	19 (20.9)	16 (14.8)	34 (28.6)	27 (23.7)	47 (45.6)	27 (23.9)	55 (49.5)
130-134	6 (7.1)	4 (5.3)	10 (9.6)	15 (16.5)	15 (13.9)	30 (25.2)	22 (19.3)	30 (29.1)	24 (21.2)	32 (28.8)
125-129	0	0	0	3 (3.3)	1 (0.9)	4 (3.4)	3 (2.6)	13 (12.6)	3 (2.7)	19 (17.1)
<125	0	1 (1.3)	0	1 (1.1)	0	0	2 (1.8)	4 (3.9)	0	4 (3.6)

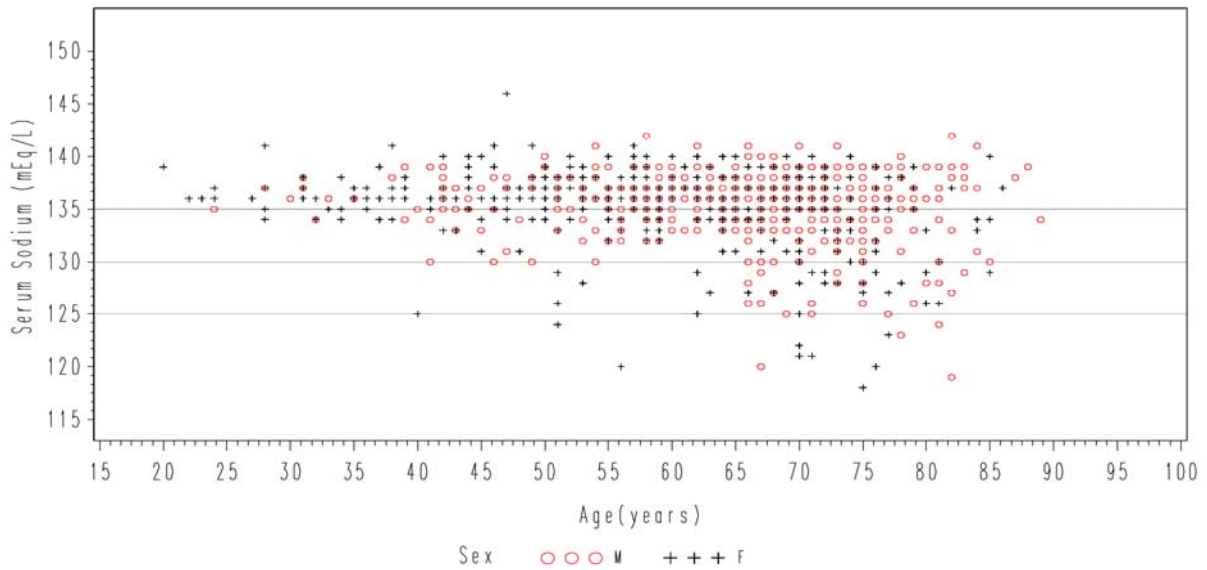
Cross Reference: [Table 14.6.7.3]

Source ISS Table 26

Fig. 8 show there were 8 women and 4 men with minimum serum sodium levels under 125 mmol/L and the two patients under 65 years of age were women who were on the 50 µg dose (see Table 25). Fig. 9 shows there are no subjects with serum sodium levels under 125 mmol/L after the Day 4 and Day 28 monitoring is employed but there

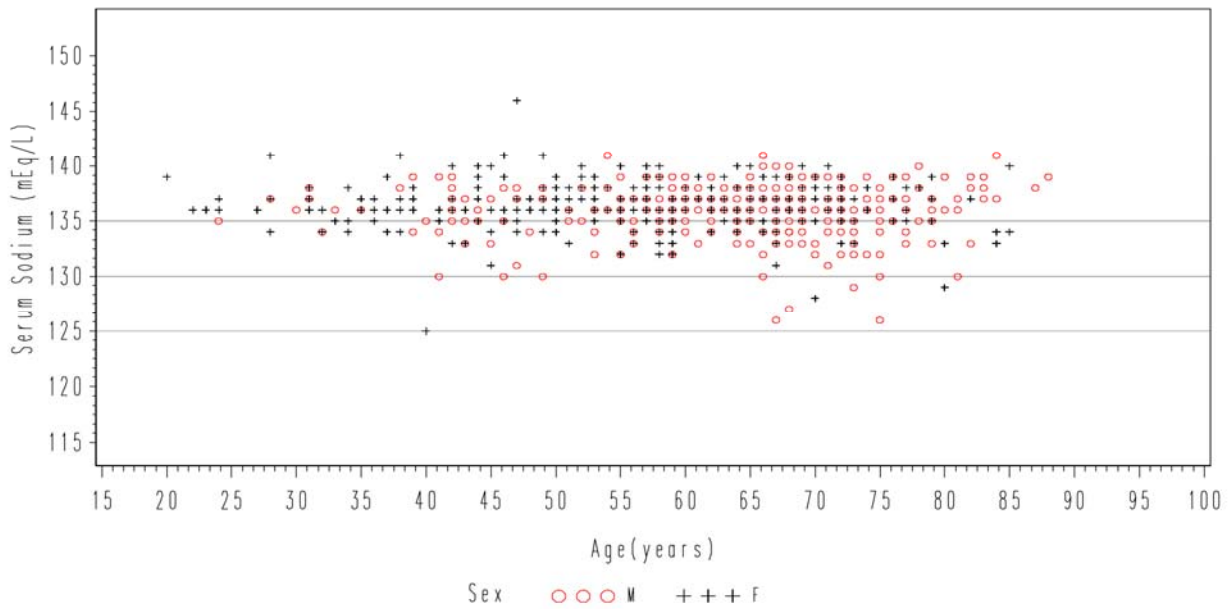
were 4 men and 3 women with serum sodium levels between 125 and 129mmol/L. Sodium levels returned to normal > 130mmol/L by the next evaluation in all of these seven patients, even though only one of these patients had the Nocurna dose discontinued due the event (pt (b) (6) Na=129 mmol/L).

Figure 8 Minimum Serum Sodium by Age without Monitoring



Source ISS Figure 8.1.1

Figure 9 Minimum Serum Sodium by Age with Day 4 and Day 28 Monitoring



Source ISS Fig. 8.1.2

Race

No non-Caucasian subjects had hyponatremia but there were too few subjects (20 to 47 per treatment group) to draw any definite conclusions with regards to relative risk of hyponatremia with respect to race.

7.5.4 Drug-Disease Interactions

Renal Function

In the PK Renal Study CS001 it was shown that the terminal half life of IV desmopressin is greatly increased in subjects with moderate to severe renal impairment. This is to be expected as most of an intravenous dose of desmopressin in healthy individuals is excreted unchanged via the kidneys. The observed mean terminal half life was 2.8, 4.0, 6.6 and 8.7 hours for patients with no, mild, moderate and severe renal impairment defined as creatinine clearances of > 80, 50-80, 30-49 and 5-29mL/min, respectively. Dose adjustments would be necessary to treat patients with moderate to severe renal function. The sponsor is currently, proposing to contraindicate use in such patients.

When analyzing the effect of GFR on the risk of hyponatremia this medical officer found that an unusually high percentage of patients were enrolled into the study despite having a low calculated creatinine clearance, < 60mL/min at the baseline visit (i.e. CS029: Visit 1, Up to 21 days prior to Day 1) that should have excluded them from the study. In the ITT population for example of the 751 pts for which a lab value was available in the ADLB dataset 99 (13%) had baseline values <60 mL/min. The sponsor is proposing to contraindicate use in patients with “moderate to severe renal impairment” defined by the sponsor in the proposed labeling as creatinine clearance < 50 mL/min. However, according to the KDOQI guidelines moderate renal impairment corresponds to a GFR of 30 to 59 mL/min. In addition, the current protocol was designed to exclude patients with baseline levels below 60 mL/min. So this medical officer recommends that the sponsor revise the proposed labeling to exclude patients with GFR < 60 mL/min.

As expected the data shows that patients with GFR < 60 mL/min are more likely to develop hyponatremia than the rest of the population. Of the 46 pts in the ITT population with hyponatremia (sodium <130mmoL/L) at some point during the study, 14/46=30% had low baseline creatinine clearance compared to 32/46=70% with creatinine clearance of 60 mL/min and above for a relative increased risk of 30/13=2.3 fold. Of the 5 pts in the ITT population with severe hyponatremia (sodium < 125mmoL/L) 2/5=40% had low baseline creatinine clearance levels compared to 3/5=60% with creatinine clearance levels of 60 and above for a relative increased risk of 40/13=3.1 fold. Baseline creatinine levels for these 5 pts were 0.5, 0.7, and 1.1 for calculated creatinine clearance ≥60 mL/min, and 1.2 and 1.3mg/dL for <60 mL/min.

Liver Function

Desmopressin has not been shown to undergo significant liver metabolism in *in vitro* studies with human microsomes. Formal *in vivo* studies have not been performed. No dose adjustments are being recommended for patients with liver disease.

Hypertension

Two patients on hydrochlorothiazide for hypertension developed severe hyponatremia during the study (002-100451, Na= 122mmol/L; and 031-101058, Na= 120mmol/L). However there was no clear difference in the rate of hyponatremia seen with respect to the history of hypertension (e.g. 5/338=1.5%, with hypertension vs. 6/525=1.1%, without hypertension). Theoretically patients with hypertension should be at greater risk of renal disease and as such might be expected to have a higher risk of hyponatremia (see Renal Function). Also, patients whose hypertension is treated with diuretics may also be at greater risk of hyponatremia (see Drug-Drug Interactions.)

7.5.5 Drug-Drug Interactions

No direct drug interaction studies were submitted. However, drugs which have an effect on renal function or fluid/electrolyte balance could increase the risk of water retention and hyponatremia seen with the use of desmopressin containing products. Drugs that can induce SIADH (e.g. TCAs), SSRIs, chlorpromazine, and carbamazepine, opiate analgesics, NSAIDs, lamotrigine and diuretics should be used with caution in patients taking desmopressin. No consistent pattern was observed with respect to the incidence of hyponatremia and concomitant medications of interest in the pivotal trial. However, three patients with hyponatremia were treated with diuretics. One patient, (b) (6), received furosemide for swollen ankles that day before the sodium measurement of 120 mmol/L, whereas two other patients were on hydrochlorothiazide for the treatment of hypertension during the episodes.

7.6 Additional Safety Evaluations

None

7.6.1 Human Carcinogenicity

No information regarding carcinogenicity was included in this submission. The current desmopressin PI states that studies have not been performed with desmopressin acetate to evaluate carcinogenic potential, or mutagenic potential or effects on fertility.

7.6.2 Human Reproduction and Pregnancy Data

No information regarding human reproduction or use in pregnancy was obtained from the pivotal trial as females of reproductive age were required to use a reliable method of contraception. Literature data on a limited number (n=53) of exposed pregnancies in

women with diabetes insipidus do not indicate any adverse effects of desmopressin on pregnancy or on the health of the fetus/newborn child¹³. Animal studies do not indicate any direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. Nevertheless, the sponsor recommends caution when prescribing desmopressin to pregnant women.

Results from analyses of milk from nursing mothers receiving a high dose of desmopressin (300 µg intranasally) indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

7.6.3 Pediatrics and Assessment of Effects on Growth

The submission includes a Pediatric PK/PD study (CS006), an open-label oral tolerability study in children and adolescents (CS022), and a double-blind, randomized placebo-controlled dose titration study in children and adolescents (CLN 10.3.26, the DRY study).

Study CS006 was a double-blind, randomized, placebo-controlled, parallel group study with six different doses of the melt formulation: 30, 60, 120, 240, 360 and 480 µg. A total of 87 subjects age 6 to 12 years with an average of ≥ 3 wet nights per week over a two week period were randomized. Subjects were overhydrated prior to dosing and maintained in an overhydrated state during the study by replacing urinary losses with oral intake of an equivalent amount of tap water. Maximum urinary osmolality was observed at the three highest doses, e.g. 240, 360 and 480 µg. The mean duration of action, using a cut-off level of 125 mOsm/kg was 3.0, 5.8, 8.1, 9.7, 10.2 and 10.5 hours for doses, 30, 60, 120, 240, 360 and 480 µg, respectively. This likely represents an underestimation of the duration of the real effect for the highest doses as samples were only measured for the initial 12 hours post dosing as per the study protocol. In summary, the data showed that it was possible to control urinary output for 8 to 10 hours with a dose in the range of 120 to 360 µg of the melt formulation.

Study CS022 was a 6 wk open-label, cross-over study comparing 120 µg and 240 µg of the melt formulation to 0.2mg and 0.4mg of the tablet. 200 subjects age 5 to 15 years, who had been stabilized on doses of 0.2 or 0.4mg of desmopressin tablets, were randomized to receive either 120 µg of melt followed by 0.2 mg of the tablet, 0.2 mg of the tablet followed by 120 µg of melt, 240 µg of the melt followed by 0.4mg of the tablet or 0.4mg of the tablet followed by 240 µg of the melt. Each study dose was administered for 3 weeks so subjects were treated for a total of 6 weeks. There was no statistically significant difference between formulations in the mean incidence of

13 [DDAVP use during pregnancy: an analysis of its safety for mother and child](#). Ray JG. *Obstet Gynecol Surv* 1998;53:450-5.

bedwetting per week (1.85 ± 1.89 for the melt and 1.86 ± 1.83 for the tablet). The safety profile was similar for the two formulations.

Study 10.3.26 was a double-blind, randomized, placebo-controlled, dose-titration study with up to three doses of the melt or an equivalent placebo in children and adolescents. On study Day 1, 132 subjects age 5 to 16 years were randomized to one tablet of placebo or melt (120 μg). After Day 3 they were titrated up to 2 tablets of placebo or melt (240 μg) if they still experienced one or more wet nights in the previous three days. After Day 6 they could be titrated up to 3 tablets of placebo or melt (360 μg) if they still experienced one or more wet nights in the previous three days. Similar assessments were performed on Day 9 and Day 12. The dose was maintained if patients were completely dry or increased to a maximum of 3 tablets of desmopressin melt or placebo if the subjects had one or more wet nights in the previous 3 days. After the titration period subjects were maintained on the highest effective dose for a period of 6 weeks. Efficacy was estimated by the reduction in the number of wet nights between the last two weeks of treatment compared to the initial two weeks prior to treatment. The mean reduction in the number of wet nights from baseline was greater in the melt group (3.2 ± 4.7 vs. 2.7 ± 4.6) but the difference was not statistically significant ($p=0.65$). The efficacy of the melt was similar to the level of reduction seen with other desmopressin trials, but the placebo patients exhibited a higher than expected response which accounted for the lack of a statistically significant effect. An extensive investigation by the sponsor could not identify a single cause to explain the unexpected high placebo response in this study. The safety profile was similar for the two formulations. Even though the melt formulation is currently approved in Europe for the treatment of PNE at doses of 120 and 240 μg , the sponsor is not seeking to market the melt formulation for this indication in the US at this time. It is this medical officer's recommendation that should the sponsor reconsider marketing the melt formulation for PNE at a future time that they would need to repeat another double-blind study to show statistical significance compared to placebo.

Effects on Growth

The pediatric studies included in this submission were off too short a duration to (e.g. 6 to 8 weeks) to evaluate effects on growth. Desmopressin has been used clinically for enuresis in children since 1975. A PubMed search of "desmopressin AND growth" by this medical reviewer found no references describing a negative effect on growth rate in children on desmopressin therapy. Long term studies of desmopressin from the literature have not shown a significant effect of treatment on growth in the pediatric population¹⁴.

14 1-deamino-8-D-arginine vasopressin in the treatment of central diabetes insipidus in childhood. [Becker DJ, Foley TP Jr. J Pediatr.](#) 1978 Jun;92(6):1011-5.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdosage

Overdosing with desmopressin leads to prolongation of the duration of action with an increased risk of water retention and hyponatremia. Hyponatremia was seen in pivotal trial CS029 in women on doses of 50 µg and 100 µg and in men over age 65 on the dose of 100 µg. Decreased renal function is likely to increase the risk for overdose as the drug is primarily excreted unmetabolized in the urine. There is no specific antidote for desmopressin. Patients will need to have fluid intake restricted and have their fluid and electrolyte status followed and treated symptomatically.

Drug Abuse Potential

The sponsor states that no assessment of physiological or psychological dependency has been performed to date, and based upon the lack of effect of desmopressin on the central nervous system, physiological or psychological dependency is not expected to occur with this drug. This medical reviewer agrees with this assessment.

Withdrawal and Rebound

No studies were performed to evaluate rebound or withdrawal effects due to desmopressin. These findings had not been previously reported with the currently approved indications and there is no reason to suspect such findings in adults treated for nocturia.

7.7 Additional Submissions / Safety Issues

The 4-month safety update was integrated into the rest of the safety review as per the new clinical review template guidance.

The sponsor submitted a Risk Evaluations and Mitigations Strategy (REMS) to communicate the risks of hyponatremia and recommend serum sodium monitoring based on age and gender. The sponsor proposed a Medication Guide as the only REMS element and proposed to limit initial promotion of Nocdurna to urologists.

Medical Officer's comment-

This medical officer does not recommend approval of Nocdurna at doses that would require a yet-to-be-validated monitoring scheme and as such there is no need for a REMS as part of the current approval. This medical officer agrees with the sponsor that it would be prudent to limit initial promotion to urologists, but does not see the need to make this a post marketing commitment as the doses which are recommended for approval do not necessitate that physicians follow a strict monitoring scheme once the patient's eligibility for treatment has been established.

8 Postmarket Experience

Desmopressin Tablets

Desmopressin Tablets have been approved in Europe for the treatment of adult nocturia in subjects under 65 years of age since 2001, and are currently approved for this indication in 68 countries worldwide. As of December 2008, there have been a total of 76 spontaneously reported cases containing 161 events in patients treated for nocturia. The most frequent reported events were hyponatremia (31), confusional state (9), and convulsions (including epilepsy and grand mal convulsion) (7). There is one fatal case of hyponatremia reported in the literature¹⁵. It involved an 80 year old women with a history of breast cancer who was started on a 0.2mg dose of DDAVP tablets by her urologist. She typically drank eight glasses of water a day and the family reported that she developed fatigue, confusion and inability to concentrate after the first dose of DDAVP. Three days after starting the medication she was admitted to the ER with a serum sodium of 108 mmol/L. She developed a fever, a right-sided infiltrate and despite being intubated rapidly decompensated. An autopsy attributed the death to a retroperitoneal hemorrhage from an unidentified area adjacent to the head of the pancreas. The same article described another case of hyponatremia in an 89 year old female who had been safely treated with DDAVP for 3 years until she was admitted to the hospital with a stroke. During the admission she was encouraged to increase her fluid intake by the staff. On hospital Day 2 she developed confusion and unresponsiveness, with a serum sodium of 120 mmol/L. She recovered with fluid restriction and DDAVP was not resumed after discharge. The reference mentions that it is possible that a stroke can impair normal thirst mechanisms which protect against electrolyte imbalances.

Through December 2008 there have been 73 cases of hyponatremia reported with the tablet formulation. 31 cases were in patients treated for adult nocturia and 12 were in patients treated for adult enuresis. The one patient on the 0.05 mg dose of the tablet (equivalent to 30 µg melt) was an 88 year old male who had asymptomatic hyponatremia (sodium =125 mmol/L) on day 3 of dosing. All of the other patients, in whom the dosage was known, were on doses which are greater than the dose recommended by this medical reviewer. Of the 10 patients on the 0.1 mg tablet dose (equivalent to 60 µg melt) 8 (80%) were women for whom the maximal dose recommended by reviewer would be 25 µg. Only 8 of the 43 cases (19%) were in patients under 65 year of age. This suggests there was a substantial degree of inappropriate off-label use of desmopressin in elderly pts > 65 years of age in countries where it is approved for adult nocturia. There was one hyponatremic seizure in an 80 year old female treated for nocturia with 0.2mg of the tablet formulation three days after

15 [Hyponatremia associated with desmopressin for the treatment of nocturnal polyuria](#). Shindel A, Tobin G, Klutke C. Urology. 2002 Aug;60(2):344.

starting the medication. There was one other possible case of a seizure in a man of unknown age and treated for an unknown condition, given a doubtful dose of two “500mg” tablets, from a consumer report with limited information. There was also one report of a hypochloremic seizure in a 53 year old female treated with 0.4mg of the tablet for nocturia. All other electrolytes were supposedly normal in this patient, which would be an unusual presentation for a desmopressin induced seizure.

Table 26 Post Marketing Cases of Hyponatremia in Adults Treated with Desmopressin Tablets

Tablet dose	Melt equivalent dose	Number of patients
0.05	30	1
0.1	60	10
0.2	120	18 [†]
0.4	240	4
0.8	480	1
2	1200	1 [‡]
unknown		7
[†] Includes one pt prescribed a dose range of 0.2 to 0.4 mg [‡] Accidental overdose of 6 mg over 3 days Source Submission 0010 Jan. 14 th 2010		

Desmopressin Melt

Desmopressin Melt (60 µg, 120 µg, and 240 µg) was first approved in February 2005. It is currently approved in Europe for the treatment of adult nocturia at doses of 120 and 240 µg in subjects under 65 years of age with no requirement for serum sodium monitoring. Since its launch in August 2005, the cumulative patient exposure to desmopressin melt is estimated to be (b) (4) patient-years through December 2008, based on average daily dose of 120 µg. The reported adverse reactions to desmopressin melt are consistent with the known safety profile of desmopressin tablets. A total of 189 post-marketing adverse drug reaction cases in connection with treatment with desmopressin melt have been received through December 2008. The majority of the cases (116/189=61%) were non-serious, 24 (13%) were serious and 59 (31%) were reported as other (e.g. lack of effect, no adverse event reported, overdose, or exposure during pregnancy). For the majority of cases for which time to onset of event is known, time to onset was within 7 days of starting the medication. The majority of the cases concern children and adolescents treated for nocturnal enuresis. A total of 21 cases (11%) were in adults and of these 13 (7%) were in the elderly population (≥65 years). Overall, among all post-marketing cases reported for desmopressin Melt through December 2008, the most frequently reported adverse events were lack of effect (58), headache (22), abdominal pain (16), rash/urticaria/skin reaction (16), nausea (10),

hyponatremia (9), weight increase (8), vomiting (8) and diarrhea (6). The most frequent reported events in the nocturia population treated with desmopressin melt were hyponatremia (4), lack of effect (4), headache (3) and nausea (2).

Through December 2008 there have been 19 cases describing potentially allergic complaints with desmopressin melt. These included 12 cases of rash (of which one was serious due to generalization of the rash), 4 cases of non-serious urticaria, and 1 case each of hypersensitivity, blisters on lips, and eczema.

Medical Officer's comment-

Since gelatin used in the drug product was prepared from fish ^{(b) (4)}, it is possible that some of these allergic reactions may due to fish allergies.

Through December 2008 there have been 9 cases of hyponatremia. Four cases were in patients treated for nocturia (69 and 82 year old males, 63 and 85 year old females). One case concerned a 76-year-old female treated for urinary incontinence and the remaining four cases concerned children. There were 4 hyponatremic seizures in these cases. All were in children from age 17 months to 8 years. Two treated for diabetes insipidus and two treated for PNE. There was one adult, the 63 year old female, who developed a hyponatremic coma on the 120 µg dose 4 days after starting therapy. All five patients with the hyponatremic seizures or coma recovered without sequelae.

Medical Officer's comment-

A review of the 5 cases of hyponatremia seen in adults with the Melt formulation identified only one case, ^{(b) (6)}, an 82 year old male with a history of recurrent seizures, for whom the treatment dose was unknown, who could have developed hyponatremia at the proposed doses recommended by this reviewer. The three women were receiving doses of 60 to 120 µg above the maximal recommended melt dose of 25 µg for women, and the other man was prescribed 60 µg melt tablets but was instructed to take up to two 60 µg tablets as needed; both dosages are above the maximal melt dose recommended by this reviewer of 50 µg for men.

In conclusion, the post marketing data clearly identified only one patient who developed hyponatremia on a dose at or below the maximal dose recommendations in this review. That was an 88 year old man who had asymptomatic hyponatremia (sodium =125 mmol/L) on day 3 of dosing with 0.05mg of the tablet (equivalent to 30 µg of melt).

9 Appendices

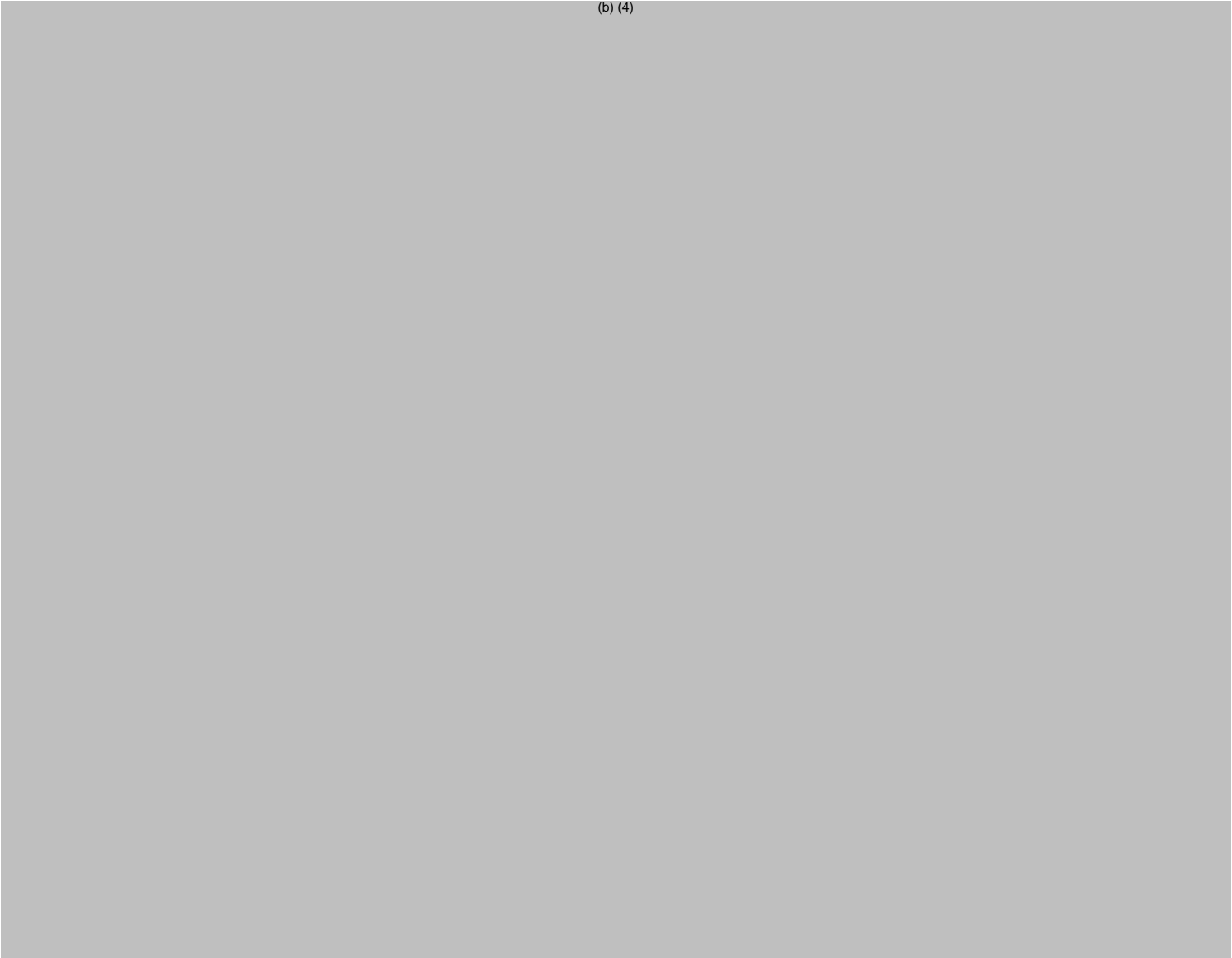
9.1 Literature Review/References

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2. Nocturia: a risk factor for falls in the elderly. Stewart RB, Moore MT, May FE, Marks RG, Hale WE. *J Am Geriatr Soc.* 1992 Dec; 40(12):1217-20.
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4. Association between nocturia and mortality in a community-dwelling elderly population aged 70 years and over: Results of a 3-year prospective cohort study in Japan. Haruo Nakagawa*, Kaijun Niu, Atsushi Hozawa, Yoshihiro Ikeda, Yasuhiro Kaiho, Kaori Masuda-Ohmori, Ryoichi Nagatomi, Ichiro Tsuji, Yoichi Arai, *Journal of Urol.* Vol. 181, No. 4, Supplement, Saturday, April 25, 2009.
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10. Hyponatremia. Al-Salman J, Kemp D, Randall D. *West J Med.* 2002 May; 176(3):173-6.
11. Causes and management of hyponatremia. Palmer BF, Gates JR, Lader M. *Ann Pharmacother.* 2003 Nov; 37(11):1694-702. Review

12. Hyponatremia. Al-Salman J, Kemp D, Randall D. West J Med. 2002 May; 176(3):173-6.
13. DDAVP use during pregnancy: an analysis of its safety for mother and child. Ray JG. Obstet Gynecol Surv 1998;53:450-5.
14. 1-deamino-8-D-arginine vasopressin in the treatment of central diabetes insipidus in childhood. Becker DJ, Foley TP Jr. J Pediatr. 1978 Jun; 92(6):1011-5.
15. Hyponatremia associated with desmopressin for the treatment of nocturnal polyuria. Shindel A, Tobin G, Klutke C. Urology. 2002 Aug; 60(2):344.

9.2 Labeling Recommendations

(b) (4)



(b) (4)

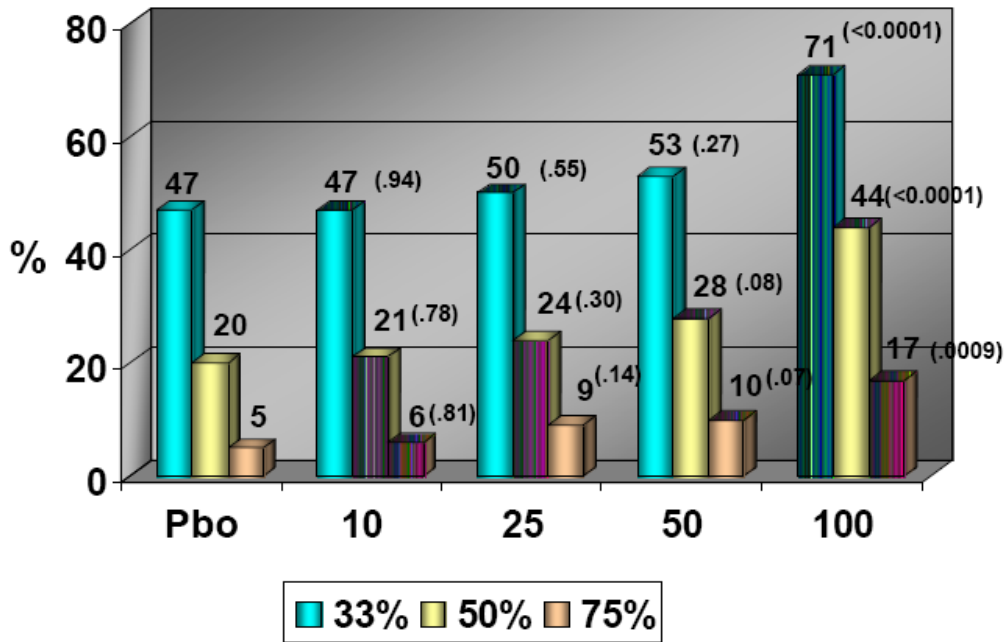


9.3 Advisory Committee Meeting

There was no advisory committee meeting held for this application.

9.4 Additional Tables and Figure

Figure 10 33%, 50% and 75% Responders on Day 28



Note: p-values versus placebo are presented.

Cross-reference: [Table 14.3.5.7], [Table 14.3.5.10], and [Table 14.3.5.11] (Part I), and [Appendix A13, ISE Table 14.3.8.1] and [Appendix A13, ISE Table 14.3.8.4]

Source- Study CS029 Study Report Fig. 7

Reference Table from sponsor's ISS

Table 33. Incidence of Shifts (≥5.0% Overall) to Low or High in Hematology Laboratory Variables

	Placebo (N=160) n/N (%)	10 µg (N=195) n/N (%)	25 µg (N=227) n/N (%)	50 µg (N=217) n/N (%)	100 µg (N=224) n/N (%)
Hemoglobin shift from high/normal to low	4/135 (3.0)	24/177 (13.6)	24/204 (11.8)	25/198 (12.6)	19/196 (9.7)
Hematocrit shift from high/normal to low	0/136 (0.0)	17/180 (9.4)	24/210 (11.4)	24/201 (11.9)	19/199 (9.5)
Red blood cells shift from high/normal to low	5/128 (3.9)	25/169 (14.8)	22/204 (10.8)	28/188 (14.9)	21/187 (11.2)
White blood cells shift from high/normal to low shift from low/normal to high	4/142 (2.8) 2/142 (1.4)	13/181 (7.2) 20/181 (11.0)	17/208 (8.2) 19/212 (9.0)	18/201 (9.0) 11/196 (5.6)	18/201 (9.0) 17/200 (8.5)
Neutrophils shift from high/normal to low shift from low/normal to high	2/143 (1.4) 1/145 (0.7)	14/182 (7.7) 38/182 (20.9)	14/211 (6.6) 36/213 (16.9)	14/202 (6.9) 37/194 (19.1)	22/208 (10.6) 41/204 (20.1)
Monocytes shift from high/normal to low shift from low/normal to high	0/146 (0.0) 0/146 (0.0)	29/185 (15.7) 14/185 (7.6)	40/216 (18.5) 14/215 (6.5)	40/204 (19.6) 12/204 (5.9)	31/207 (15.0) 14/207 (6.8)
Eosinophils shift from low/normal to high	2/140 (1.4)	19/180 (10.6)	22/210 (10.5)	22/193 (11.4)	23/203 (11.3)

Note: Only rows for which at least 1 subject had a shift from low/normal to high (or high/normal to low) are presented.
 Cross Reference: [Table 14.7.1.2]

Reference Tables from sponsor's ISS

Table 34. Incidence of Shifts ($\geq 5.0\%$ Overall) to Low or High in Clinical Chemistry Laboratory Variables

	Placebo (N=160) n/N (%)	10 µg (N=195) n/N (%)	25 µg (N=227) n/N (%)	50 µg (N=217) n/N (%)	100 µg (N=224) n/N (%)
Glucose					
shift from high/normal to low	2/147 (1.4)	16/184 (8.7)	21/218 (9.6)	22/201 (10.9)	13/207 (6.3)
shift from low/normal to high	32/96 (33.3)	93/135 (68.9)	100/152 (65.8)	84/132 (63.6)	84/133 (63.2)
Uric acid					
shift from high/normal to low	0/149 (0.0)	0/185 (0.0)	0/219 (0.0)	1/204 (0.5)	1/209 (0.5)
shift from low/normal to high	4/143 (2.8)	13/177 (7.3)	18/211 (8.5)	21/197 (10.7)	8/203 (3.9)
BUN					
shift from low/normal to high	3/143 (2.1)	10/178 (5.6)	18/213 (8.5)	22/198 (11.1)	14/205 (6.8)
Sodium					
shift from high/normal to low	4/147 (2.7)	14/181 (7.7)	37/218 (17.0)	52/201 (25.9)	54/205 (26.3)
Potassium					
shift from high/normal to low	2/148 (1.4)	8/185 (4.3)	12/218 (5.5)	11/200 (5.5)	16/206 (7.8)
Chloride					
shift from high/normal to low	0/148 (0.0)	10/184 (5.4)	12/219 (5.5)	24/202 (11.9)	24/208 (11.5)
Phosphorus					
shift from high/normal to low	4/148 (2.7)	15/184 (8.2)	27/214 (12.6)	22/196 (11.2)	26/206 (12.6)
shift from low/normal to high	2/148 (1.4)	18/183 (9.8)	18/214 (8.4)	20/196 (10.2)	27/206 (13.1)
AST					
shift from low/normal to high	5/146 (3.4)	20/180 (11.1)	16/213 (7.5)	22/199 (11.1)	16/201 (8.0)
ALT					
shift from low/normal to high	3/149 (2.0)	12/182 (6.6)	13/214 (6.1)	15/196 (7.7)	16/205 (7.8)
GGT					
shift from high/normal to low	0/136 (0.0)	14/172 (8.1)	15/209 (7.2)	13/187 (7.0)	7/197 (3.6)
shift from low/normal to high	10/144 (6.9)	33/171 (19.3)	41/212 (19.3)	47/191 (24.6)	38/200 (19.0)

Note: Only rows for which at least 1 subject had a shift from low/normal to high (or high/normal to low) are presented.
 Cross Reference: [Table 14.7.2.2]

Table 35. Incidence of Urinalysis Changes

Absent to Present	Placebo (N=160) n/N (%)	10 µg (N=195) n/N (%)	25 µg (N=227) n/N (%)	50 µg (N=217) n/N (%)	100 µg (N=224) n/N (%)
Urine protein	15 (9.4)	66 (33.8)	96 (42.3)	90 (41.5)	73 (32.6)
Urine glucose	1 (0.6)	12 (6.2)	15 (6.6)	9 (4.1)	13 (5.8)
Urine ketone	4 (2.5)	32 (16.4)	46 (20.3)	42 (19.4)	46 (20.5)
Urine occult blood	5 (3.1)	29 (14.9)	34 (15.0)	29 (13.4)	29 (12.9)
Urine leukocyte esterase	12 (7.5)	46 (23.6)	64 (28.2)	46 (21.2)	47 (21.0)
Urine nitrite	0	3 (1.5)	9 (4.0)	7 (3.2)	9 (4.0)
Urine bilirubin	3 (1.9)	19 (9.7)	38 (16.7)	35 (16.1)	29 (12.9)

Cross Reference: [Table 14.7.3.11]

Reference Table from sponsor's ISS

Table 36. Incidence of Markedly Abnormal Changes in Laboratory Variables

Parameter (markedly abnormal criterion)	Placebo (N=160) n/N (%)	10 µg (N=195) n/N (%)	25 µg (N=227) n/N (%)	50 µg (N=217) n/N (%)	100 µg (N=224) n/N (%)
Hematology					
Hemoglobin (≤ 115 g/L for males, ≤ 95 g/L for females)	0	6/172 (3.5)	5/199 (2.5)	6/190 (3.2)	4/193 (2.1)
Hematocrit (≤ 0.37 for males, ≤ 0.32 for females)	4/127 (3.1)	17/168 (10.1)	24/200 (12.0)	26/189 (13.8)	16/191 (8.4)
Red blood cells ($\leq 3,500 \times 10^9/L$)	0	1/165 (0.6)	1/197 (0.5)	3/186 (1.6)	1/187 (0.5)
White blood cells					
$\geq 16.0 \times 10^9/L$	0	0	0	0	1/193 (0.5)
$\leq 2.8 \times 10^9/L$	0	1/177 (0.6)	1/203 (0.5)	0	3/193 (1.6)
Neutrophils (≥ 0.90)	0	0	1/207 (0.5)	0	0
Monocytes (≥ 0.20)	0	0	0	1/204 (0.5)	2/206 (1.0)
Eosinophils (≥ 0.10)	0	4/180 (2.2)	4/209 (1.9)	6/191 (3.1)	4/202 (2.0)
Platelets ($\geq 700 \times 10^9/L$)	0	1/175 (0.6)	0	1/196 (0.5)	2/197 (1.0)
Lymphocytes ^a (≤ 10)	0	7/110 (6.4)	3/162 (6.9)	7/147 (4.8)	2/140 (1.4)
Clinical Chemistry					
Glucose					
≥ 10 mmol/L	1/94 (1.1)	2/134 (1.5)	5/151 (3.3)	5/129 (3.9)	2/131 (1.5)
≤ 2.8 mmol/L	0	0	3/151 (2.0)	5/129 (3.9)	2/131 (1.5)
Uric acid (≥ 0.62 mmol/L for males, ≥ 0.51 mmol/L for females)	0	2/177 (1.1)	2/211 (0.9)	3/197 (1.5)	2/203 (1.0)
BUN (≥ 10.7 mmol/L)	1/143 (0.7)	3/178 (1.7)	8/213 (3.8)	9/198 (4.5)	6/205 (2.9)
Creatinine (≥ 177 µmol/L)	0	1/185 (0.5)	2/219 (0.9)	3/203 (1.5)	1/209 (0.5)
Sodium (≤ 130 mmol/L)	0	7/181 (3.9)	3/218 (1.4)	16/201 (8.0)	20/205 (9.8)
Potassium					
≥ 5.8 mmol/L	0	5/184 (2.7)	8/212 (3.8)	7/196 (3.6)	9/203 (4.4)
≤ 3.0 mmol/L	0	0	2/212 (0.9)	1/196 (0.5)	0
Chloride (≤ 90 mmol/L)	0	2/184 (1.1)	0	4/202 (2.0)	5/207 (2.4)
Calcium (≤ 1.8 mmol/L)	0	0	0	1/200 (0.5)	1/205 (0.5)
Phosphorus					
≥ 1.9 mmol/L	0	0	0	1/188 (0.5)	0
≤ 0.5 mmol/L	0	1/182 (0.5)	0	0	0
Total protein (≥ 90 g/L)	0	0	0	0	1/205 (0.5)
Albumin (≤ 25 g/L)	0	0	0	0	1/207 (0.5)
AST ($> 3 \times$ ULN)	0	0	0	2/199 (1.0)	0
ALT ($> 3 \times$ ULN)	0	0	0	2/196 (1.0)	1/205 (0.5)
GGT ($> 3 \times$ ULN)	0	1/172 (0.6)	1/209 (0.5)	1/187 (0.5)	0

ULN=upper limit of normal

Note: Markedly abnormal criteria are specified in [CS29, Appendix A9].

Note: Only rows for which at least 1 subject had a markedly abnormal value are presented. Only subjects with a normal baseline value and at least 1 markedly abnormal post-baseline value are included.

a. Only subjects with normal baseline and at least 1 post-baseline value are included for all tests other than lymphocytes.

Cross Reference: [Tables 14.7.1.3 and 14.7.2.3]

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

WILLIAM A LUBAS
04/07/2010

DRAGOS G ROMAN
04/07/2010

Secondary Statistical Review

NDA: 22-517
Sponsor: Ferring
Drug: Nocdurna (desmopressin melt) doses 10, 25, 50 and 100 mcg
Indication: Nocturia in adults
Documents reviewed: NDA submission dated 6/22/09
Primary statistical reviewer: Wei Liu, Ph.D.
Medical Reviewer: Bill Lubas, M.D. (HFD-510)
Secondary statistical reviewer: J Todd Sahlroot, Ph.D.

Introduction

The purpose of this secondary review is to discuss the statistical evidence from Trial CS29 (Part 1) supporting the efficacy of Nocdurna (desmopressin melt) to treat nocturia. Nocturia is the condition of waking up at night one or more times to urinate, negatively affecting sleep quality and daytime function. Desmopressin is approved in the U.S. for other indications. Desmopressin melt is approved in 43 countries (not the U.S.) for the treatment of adult nocturia at doses of 60, 120 and 240 mcg. There are currently no FDA-approved medications for the treatment of adult nocturia.

Dr. Liu concluded in his primary statistical review that only the highest dose of Nocdurna (100 mcg) was superior to placebo on both co-primary efficacy endpoints. The sponsor and other FDA reviewers are recommending lower, gender-based doses due to the risk of hyponatremia which increases at higher doses. Dr. Liu suggested doses below 100 mcg, although not statistically superior to placebo, could be efficacious in some patients, based on his finding of a linear dose-response. I feel several key statistical issues deserve additional discussion beyond their coverage in the primary statistical review: (1) primary analysis results; (2) subgroup (gender) results; and (3) dosing. These issues overlap, and will be discussed in the given order.

Design

Trial S29 (Part 1) was a randomized, placebo-controlled, multiple-dose double-blind 4-week trial of Nocdurna in 799 adults with nocturia. Roughly equal numbers of patients were randomized to 0, 10, 25, 50 or 100 mcg of Nocdurna. Randomization was stratified by age (<65, >65) and nocturnal polyuria status. There were two co-primary endpoints:

- Change in the daily (over 3 days) mean number of nocturnal voids from baseline to Day 28

- Proportion of subjects with >33% reduction from baseline in the mean number of nocturnal voids at Day 28

Endpoints were assessed weekly. Statistical significance at Day 28 was required on both co-primary endpoints for a given dose to be considered efficacious.

Type 1 error was controlled across the 4 doses using a pre-defined multiple comparison procedure. The procedure started by comparing the highest dose (100 mcg) to placebo on the co-primary endpoints at Day 28. If both p-values were significant at the 5% level, then testing proceeded to the 50 mcg dose and so on. Testing stopped at a given dose if either co-primary endpoint was not statistically significant.

Results

Table 1 shows results for the co-primary endpoints at Day 28.

Table 1. Co-primary endpoint results

	Placebo (n=156)	10 mcg (n=157)	25 mcg (n=152)	50 mcg (n=148)	100 mcg (n=146)
Mean baseline # voids/night	3.27	3.21	3.35	3.39	3.22
Mean change from baseline	-0.86	-0.83	-1.00	-1.18	-1.43
Adj mean difference with placebo and 95% CI		0.01 (-.22, .24) p=.93	-0.12 (-.35, .11) p=.31	-0.28 (-.51, -.04) p=.02	-0.61 (-.85, -.38) p<.001
33% responders (%)	73 (47%)	73 (47%)	77 (50%)	79 (53%)	103 (71%)
Odds ratio with placebo		1.02 p=.94	1.15 p=.55	1.30 p=.27	2.89 p<.001

Only 100 mcg met the pre-specified criterion for efficacy. 10 mcg was clearly a no-effect dose. 25 and 50 mcg were shown to be not different statistically from placebo *according to the pre-defined sequential testing procedure*. The sponsor declared the trial to be positive based on these results, and I agree. There was also a clear dose-response, linear with a positive slope. There were, therefore, a few patients who benefited from 25 or 50 mcg who would not have without the medication (a numerical difference, not statistical). It has been argued that 50 mcg failed statistical significance on the response endpoint due to the high placebo response rate, especially in males (Tables 1 and 2). This explanation --- "odd" behavior in a control group -- may seem reasonable on its face but is not a satisfactory reason for discounting the negative result.

Another issue was the occurrence of significant results for lower doses at time points prior to Week 4 (Fig. 1 and 2). For example, 50 mcg was superior to placebo (p<.05 on both co-primary endpoints) at Weeks 1, 2 and 3. 25 mcg was superior to placebo at Weeks 1 and 2. Other FDA reviewers think these results

show that 50 mcg is an effective dose. They argue that the effect seen at early time points is consistent with desmopressin's rapid onset of action. Therefore, the Week 4 endpoint is no more clinically relevant than earlier time points. I consider the results at early time points to be suggestive but not confirmatory.

Gender

Table 2 shows (post-hoc) results by gender.

Table 2. Primary co-endpoint results by gender

Females	Placebo (n=66)	10 mcg (n=73)	25 mcg (n=65)	50 mcg (n=71)	100 mcg (n=66)
Change from baseline	-0.88	-1.15	-1.22	-1.23	-1.51
p-value vs placebo		P=.93	p=.02	p=.01	p<.001
33% responders (%)	28 (42%)	41 (56%)	40 (62%)	42 (59%)	51 (77%)
p-value vs placebo		P=.07	p=.02	p=.04	p<.001
Males	(n=90)	(n=82)	(n=87)	(n=77)	(n=80)
Change from baseline	-0.84	-0.54	-0.83	-1.13	-1.38
p-value vs placebo		P=.09	p=.59	p=.38	p=.005
33% responders (%)	45 (50%)	32 (39%)	36 (41%)	37 (48%)	52 (65%)
p-value vs placebo		P=.15	p=.22	p=.74	p=.048

The sponsor has recommended Nocturna doses of 25 mcg in females and 100 mcg in males (with hyponatremia monitoring if age >65). The recommendation relies not on the primary results but on the subgroup results in Table 2. The proposed dosing is meant to avoid the risk of hyponatremia which increases at higher doses and also with age (Table 3). Note the p-values for females. The four darkly shaded p-values in Table 2 (females; 25 and 50 mcg) all lie between .01 and .04. These p-values are not impressive and would be adjusted to non-significance with, for example, a Bonferroni correction.

FDA clinical pharmacology and medical reviewers have recommended 50 mcg in males, with or without titration (see Appendix). This recommendation is not supported in any way by the subgroup data ($p \geq .38$ on the co-primary endpoints). The response rate in males at 50 mcg (48%) was actually lower than the placebo rate (50%).

I looked at treatment-by-gender interactions to see whether differential dosing could be justified by statistical differences in treatment effects between men and women. Generally, different p-values for subgroups (in this example, significant p-values in females and non-significant p-values in males) may, or may not, indicate a significant treatment-by-subgroup interaction. In this case, the treatment-by-gender interaction (4 d.f.) was not significant ($p=.14$)

The medical officer stated (draft review, p. 38) “*there is support for the observed gender differences seen here from other nonclinical and clinical studies to argue that it is scientifically justifiable to analyze the data separately by gender.*” On page 40, “*...there were a sufficient number of women enrolled in this study that it could have been a stand alone study in women had the sponsor decided not to include men.*” I think the issue is not so much one of subgroups as it is the weakness of the results.

Conclusions (including dosing recommendations based on current data)

The sponsor has proposed dosing by gender, 25 mcg in females and 100 mcg in males. The 25 mcg dose (females) is also supported by FDA clinical pharmacology and medical reviewers. The reviewers recommend 50 mcg in males, with or without titration in younger patients. These lower doses may avoid the risk of hyponatremia which increases with dose. The FDA dosing recommendations appear to use the sponsor’s dosing recommendation as a starting point or anchor. This starting point is based on subgroup analyses which are not convincing. These dosing recommendations are intended to exclude risk but also exclude much of the benefit.

While there is insufficient statistical evidence supporting the efficacy of *specific* doses less than 100 mcg, there is clear visual and statistical evidence that 25 or 50 mcg could be effective in a small percentage of patients. This is supported by the strictly monotonic increase in response *across* doses (Table 1, Fig. 1 and 2). The lower doses were not statistically different from placebo but nevertheless could serve as starting or titration doses. A lower, ineffective dose in a given patient could be increased with the knowledge that sufficient titration will eventually lead to an effective dose in that patient, assuming that 100 mcg is included in the titration path. My recommendation therefore is to include 25, 50 and 100 mcg as approved doses for both males and females. Lower doses should be fairly represented in the label as starting/titration doses with limited efficacy.

If these data are considered insufficient to inform patients and physicians on dosing, then additional data should be generated. This could be accomplished with two adequately powered trials, one each in males and females. Each trial would include 0, 25, 50 and 100 mcg of Nocdurna and therefore would require approximately 80% of the sample size of the original trial.

Appendix: Dosing recommendations

Sponsor

- women 25 mcg
- men 100 mcg with hyponatremia monitoring on Days 4 and 28 for men >65 years of age

FDA medical

- women maximum 25 mcg
- men maximum 50 mcg (no hyponatremia monitoring)

FDA clinical pharmacology

- women 25 mcg
- men 50 mcg as a starting dose with titration as needed for <65 years of age

FDA statistics

- no gender based dosing. Include 25, 50 and 100 mcg as approved doses. Titrate to effect as needed.

Figure 1

Mean change from baseline over time (Sponsor's Study Report Figure 3)

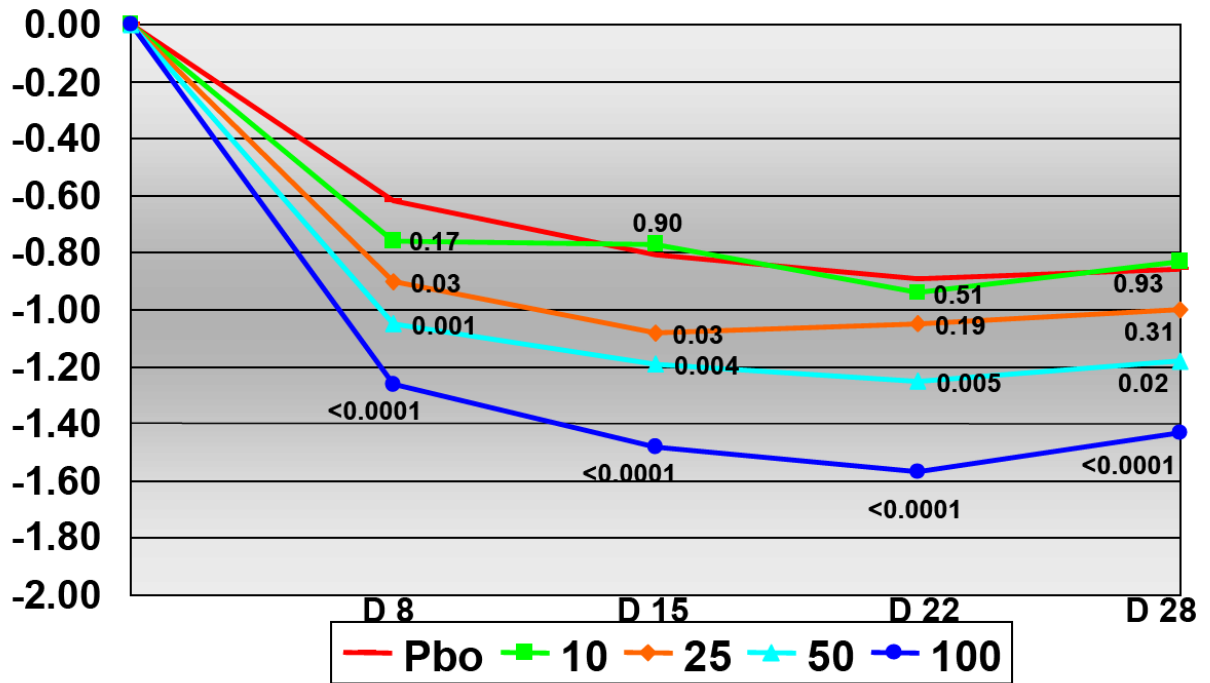


Figure 2

Response rate over time (sponsor's Study Report Fig 6)

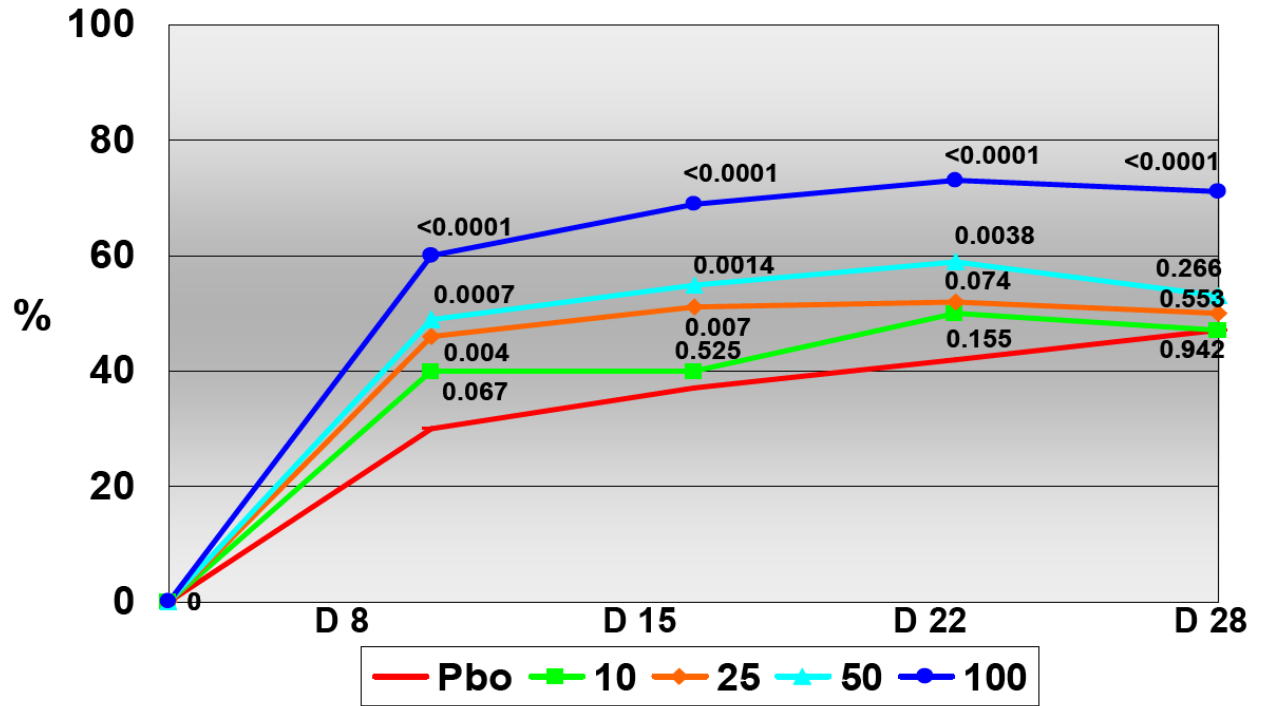


Table 3. Number of Pts with Hyponatremia in the Double-Blind Phase of CS29 Part 1 (Draft Medical Review, page 55).

Serum Sodium	placebo	10 µg	25 µg	50 µg	100 µg	Total Nocturna pts
125-129 mmol/L	0 (0.0%)	1 (0.5%)	2 (0.9%)	8 (3.7%)	15 (6.7%)	26 (3.0%)
< 125 mmol/L	1 (0.6%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	4 (1.8%)	7 (0.8%)
Data Source ADNA lab dataset CS029: Visit 3, 4, 5, 6 and 7.						

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

JON T SAHLROOT
04/01/2010

THOMAS J PERMUTT
04/02/2010
I concur with Dr. Sahlroot.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 022517/0000
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Applicant: Ferring Pharmaceutical Ltd.
Date(s): Received 6/22/2009
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1. EXECUTIVE SUMMARY

The safety and efficacy of NOCDURNA were evaluated in patients with nocturia in two Phase 3 studies, CS29 and CS31. CS29 was conducted in 2 parts. Part I was a double-blind, placebo-controlled, multi-center, randomized, parallel-group study investigating the efficacy and safety of 4 doses (10, 25, 50, and 100 µg) of NOCDURNA administered at bedtime for 28 days for the treatment of nocturia in adults to demonstrate the superiority to placebo in reducing the mean number of nocturnal voids. The CS29 Part II was a 6 month double-blind extension in which patients on active therapy during Part I continued on the same therapy while subjects initially assigned to the placebo group were re-randomized to one of the 4 active treatment groups to demonstrate the durability of effect achieved in Part I. Study CS31 is a long-term open-label efficacy and safety extension of the CS29, where subjects who had originally been assigned to sub therapeutic doses of NOCDURNA (e.g. 10 µg) during CS29 were randomly assigned to the other doses of NOCDURNA (i.e., 25 µg, 50 µg, or 100 µg). Subjects in CS31 were unblinded after approximately 10 months of treatment with expected total treatment duration (double blind extension plus open-label study) of at least 12 months. The number of patients treated in CS29 Parts 1 and 2, and in CS31 was, respectively, 799, 665, and 508. The CS29 Part I is the primary efficacy study for the nocturia indication.

A list of abbreviation and definition of terms has been provided in the NDA and is attached in this document as Appendix I.

1.1 Conclusions and Recommendations

1.1.1 Efficacy Conclusions:

Based on the pre-specified multiple comparison scheme in Study CS29 Part I, we conclude that only the highest dose of nocdurna (100 µg) showed superiority versus placebo on both co-primary efficacy endpoints (mean number of nocturnal voids from baseline to Day 28 and proportion of subjects with >33% reduction in the mean number of nocturnal voids at Day 28) at the two-sided 0.05 significance level for the overall ITT population in CS29 Part I. The FDA medical officer has identified safety concerns, primarily hyponatremia, for this dose. Although the results from pair-wise comparisons between doses below 100 µg and placebo failed to firmly establish the efficacy of these doses, there is sufficient statistical evidence to support a positive dose-response; the dose response slope across all the doses (10, 25, 50, and 100 µg) was statistically significantly different from zero for both co-primary efficacy endpoints. Treatment differences across doses were approximately linearly proportional. This suggests that doses below 100 µg may have utility for some patients in this population.

For dose response durability to Month 7 using CS29 Part II data, it is hard to draw any conclusions based on sponsor's Tables 12 and 13, and Figures 4 and 5, due to not using the completers' data. For example, the sponsor used only 39% and 12% of the 529 subjects (N=205, and N=64) to represent the durability from Month 0 to Month 5 and Month 7, respectively.

Treatment-by-gender interaction p-values were not significant at the 10% level for both co-primary endpoints. However, the sponsor's subgroup analyses by gender suggested different

treatment responses for males and females. In females nocturna was nominally superior to placebo on both co-primary endpoints at doses of 25, 50 and 100 µg, but in males only at the highest drug dose 100 µg.

1.1.2 Safety Conclusions:

FDA medical officer indicated that the main safety endpoint of concern is hyponatremia, specifically Na < 125 and between 125 and 130. There are significantly more hyponatremia (<130 mM) in patients treated with 50 µg or higher dose of nocturna as compared to that in placebo group. For the age groups, significant incidence rates by treatment vs. placebo were observed only at 100 µg for patients ≥65 years.

Recommendations for Labeling:

ref. Sponsor's Proposed Labeling section 14 (submitted on 06/24/2009)

(b) (4)



No additional comments on the sponsor's labeling.

1.2 Brief Overview of Clinical Studies

Ferring Pharmaceuticals Inc. submitted a New Drug Application, NDA 22-5173, for Desmopressin Melt with the proposed trade name, **NOCDURNA™** for the approval of the treatment of adult nocturia. Desmopressin is a synthetic analogue of the naturally occurring antidiuretic hormone vasopressin which is the primary physiologic determinant of free water excretion by promoting free water reabsorption and reducing urine production. Desmopressin is modified with increase and prolong the antidiuretic effect while minimizing the effect on smooth muscle vasoconstriction. The vast majority (>90%) of desmopressin is used worldwide to treat primary nocturnal enuresis (PNE). It is also approved in the US for renal concentration testing (RCCT), and to treat central diabetes insipidus (CDI) and Hemophilia A/von Woudebrand's disease. The nocturia indication is approved for desmopressin tablets in 56 countries worldwide. The melt approved in 43 countries.

The objective of the submitted study is to investigate the efficacy and safety of several doses of the melt formulation of desmopressin in a broad population of patients with nocturia.

The trial was conducted in two Phase 3 studies, CS29 and CS31. CS29 was conducted in 2 parts. Part I was a double-blind, placebo-controlled, multi-center, randomized, parallel-group study investigating the efficacy and safety of 4 doses (10, 25, 50, and 100 µg) of NOCDURNA administered at bedtime for 28 days for the treatment of nocturia in adults to demonstrate the superiority to placebo in reducing the mean number of nocturnal voids. Randomization was stratified by age (<65, ≥65 years). Elderly subjects have the highest prevalence of nocturia and are also at greatest risk for hyponatraemia. Randomization was also stratified by the absence/presence of nocturnal polyuria, defined as a ratio of nighttime urine volume/24-hour urine volume ≥33%. A total of 799 subjects were randomized to Part I and 757 included in the ITT population. Of the 710 subjects who completed Part I of the study, 665 subjects continued into Part II. The CS29 Part II was a 6 month double-blind extension in which patients on active therapy during Part I continued on the same therapy while subjects initially assigned to the placebo group were re-randomized to one of the 4 active treatment groups to demonstrate the durability of effect achieved in Part I. A total of 508 subjects entered into CS31 from CS29 Part II. Study CS31 is a long-term open-label efficacy and safety extension of the CS29, where subjects who had originally been assigned to sub therapeutic doses of NOCDURNA (e.g. 10 µg) during CS29 were randomly assigned to the other doses of NOCDURNA (i.e., 25 µg, 50 µg, or 100 µg). Subjects in CS31 were unblinded after approximately 10 months of treatment with expected total treatment duration (double blind extension plus open-label study) of at least 12 months. The CS29 Part I is the primary efficacy study for the nocturia indication.

Men and women had to be over 18 years of age with an average of ≥2 nocturnal voids per night as determined by a 3-day voiding diary. Subjects with the following medical conditions were excluded: renal insufficiency, hyponatraemia, diabetes insipidus, clinical suspicion of urinary retention and/or post void residual volume >150 mL, current or past urologic malignancy, clinical evidence of current genitourinary tract pathology, or neurogenic detrusor activity, males with a clinical suspicion of bladder outlet obstruction and/or urine flow <5 mL/s or surgical treatment for bladder outlet obstruction/benign prostatic hyperplasia performed within the past 6 months. The clinical trial population (n=757) across all treatment arms had an overall median age of approximately 64 years (range 20 to 89 years). The majority of subjects participating were Caucasian. The ethnic/racial distribution was 80.4% Caucasian, 15.3% black, 2.1% Asian, and 1.8% others.

The primary endpoints are the change in the mean number of nocturnal voids from baseline to final visit in CS29 Part I (Day 28), and the proportion of subjects with >33% reduction in the mean number of nocturnal voids from baseline to final visit in CS29 Part I (Day 28).

The study was conducted at 78 sites in the United States and Canada. The study CS31 started on December 6, 2007 and is ongoing until approximately February 2010.

1.3 Statistical Issues and Findings

- (1) The subjects in the placebo group had very high treatment response as compared to subjects treated with nocturna:
- reduction in mean number of nocturnal voids from baseline evaluation to Day 28
-0.86 (placebo) compared to -0.83 (10 µg), -1.00 (25 µg), -1.18 (50 µg) and -1.43 (100 µg)
 - proportion of subjects with >33% reduction in the mean number of nocturnal voids from baseline to Day 28
47% (placebo) compared to 47% (10 µg), 50% (25 µg), 53% (50 µg) and 71% (100 µg)

2. INTRODUCTION

2.1 Overview

Nocturia is defined by the International Continence Society (ICS) as the complaint that the individual has to wake up at night one or more times to void, with a negative impact on sleep quality and daytime function. It is a common and bothersome condition in males and females that increases in both prevalence and severity with age. Nocturia is the clinical consequence of excess nocturnal urine production relative to bladder capacity. Vasopressin, an antidiuretic hormone, increases the water permeability of the luminal membrane of the renal cortical and medullary collecting ducts, thereby promoting free water reabsorption and reducing urine production. Desmopressin is a synthetic analogue of vasopressin and modified to increase and prolong the antidiuretic effect while minimizing the effect on smooth muscle vasoconstriction.

The vast majority (>90%) of desmopressin is used worldwide to treat primary nocturnal enuresis (PNE). It is also approved in the US for renal concentration testing (RCCT), and to treat central diabetes insipidus (CDI) and Hemophilia A/von Willebrand's disease. The nocturia indication is approved for desmopressin tablets in 56 countries worldwide. The melt approved in 43 countries.

The objective of the submitted study is to investigate the efficacy and safety of several doses of the melt formulation of desmopressin in a broad population of patients with nocturia. The pivotal trial consists of Study CS29 Parts 1 and 2, and its open-label extension, study CS31, for the approval of the treatment of adult nocturia. Study CS29 is the primary study establishing desmopressin Melt efficacy for the nocturia indication.

Men and women had to be over 18 years of age with an average of ≥ 2 nocturnal voids per night. The medical conditions for excluding patients were: renal insufficiency, hyponatraemia, diabetes insipidus, clinical suspicion of urinary retention and/or post void residual volume >150 mL, current or past urologic malignancy, clinical evidence of current genitourinary tract pathology, or neurogenic detrusor activity, males with a clinical suspicion of bladder outlet obstruction and/or urine flow <5 mL/s or surgical treatment for bladder outlet obstruction/benign prostatic hyperplasia performed within the past 6 months.

The study was conducted in 78 centers in the US and Canada. The study CS29 started on June 2007. CS31 started on December 6, 2007 and is ongoing until approximately February 2010; data through 31 December 2008 are included in their submission of the Integrated Summary of Effectiveness (ISE).

The studies were performed and the data were submitted to FDA in compliance with Good Clinical Practice.

2.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. Individual study reports were submitted for each study. In addition, integrated summaries of efficacy and safety were also submitted. The data were submitted in SAS Xport transport format.

Application:	NDA022517/0000
Company	Ferring Pharmaceutical Inc.
Drug	Nocturna (desmopressin acetate)
CDER EDR link	\\CDSESUB1\EVSPROD\NDA022517\0000 \m5\53-clin-stud-rep\535-rep-effic-safety-stud\nocturia
Letter date	June 19, 2009

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The submitted trials consisted of 3 parts:

- 4-week efficacy (CS29 Part I),
- double-blind extension (CS29 Part II), and
- open-label extension (CS31).

CS29 Part I was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study investigating the efficacy and safety of 4 doses (10 µg, 25 µg, 50 µg, or 100 µg taken once per night approximately 1 hour prior to bedtime) of desmopressin Melt administered for 28 days for the treatment of nocturia in adults.

Randomization was stratified by age (<65, ≥65 years). Elderly subjects have the highest prevalence of nocturia and are also at greatest risk for hyponatraemia. Randomization was also stratified by the absence/presence of nocturnal polyuria, defined as a ratio of nighttime urine volume/24-hour urine volume ≥33%.

A total of 799 subjects were randomized to treatment in Part I of the study: 160 subjects each were assigned to placebo and 100 µg, 163 subjects were assigned to 10 µg, and 158 subjects each were assigned to 25 µg and 50 µg.

The primary objectives of Part I were to demonstrate, after 28 days of treatment, the superiority of one or more doses of the Melt formulation of desmopressin to placebo in reducing the mean number of nocturnal voids and increasing the proportion of subjects with >33% reduction from baseline in mean number of nocturnal voids.

Upon completion of Part I of the study, all subjects on active treatment continued into Part II on the same treatment for approximately 1 to 6 months. Subjects assigned to placebo in Part I were randomly assigned to 1 of the 4 active treatments in Part II. Subjects began Part II at the Final Visit for Part I (Day 28) and returned for follow-up visits on Days 4, 8, 15, 29, and every 4 weeks thereafter. The total treatment duration for each subject depended on when that subject was randomized in Part I and was estimated to be a minimum of 4 weeks and a maximum of 6 months. Of the 710 subjects who completed Part I of the study, 665 subjects continued into Part II. Of the 145 placebo subjects who completed Part I, 136 continued into Part II and were re-randomized (in blinded fashion) to one of the active treatment groups. Parts I and II of CS29 also assessed treatment safety. The primary objective of Part II was to demonstrate the persistence of effect achieved in Part I of one or more doses of desmopressin Melt.

Subjects enrolled in Study CS29 who had completed at least the visit at Day 15 of Part II or at Day 43 of CS29 were eligible to roll over into CS31. A total of 508 subjects entered into CS31 from CS29 Part II. Subjects were initially assigned in a blinded manner to the same treatment group until the database for CS29 was locked, then subjects in CS31 were unblinded after approximately 10 months of treatment. Subjects assigned to the 10 µg dose were randomly assigned to the other doses of desmopressin Melt (i.e., 25 µg, 50 µg, or 100 µg). The overall design for dosing is presented in Figure 1.

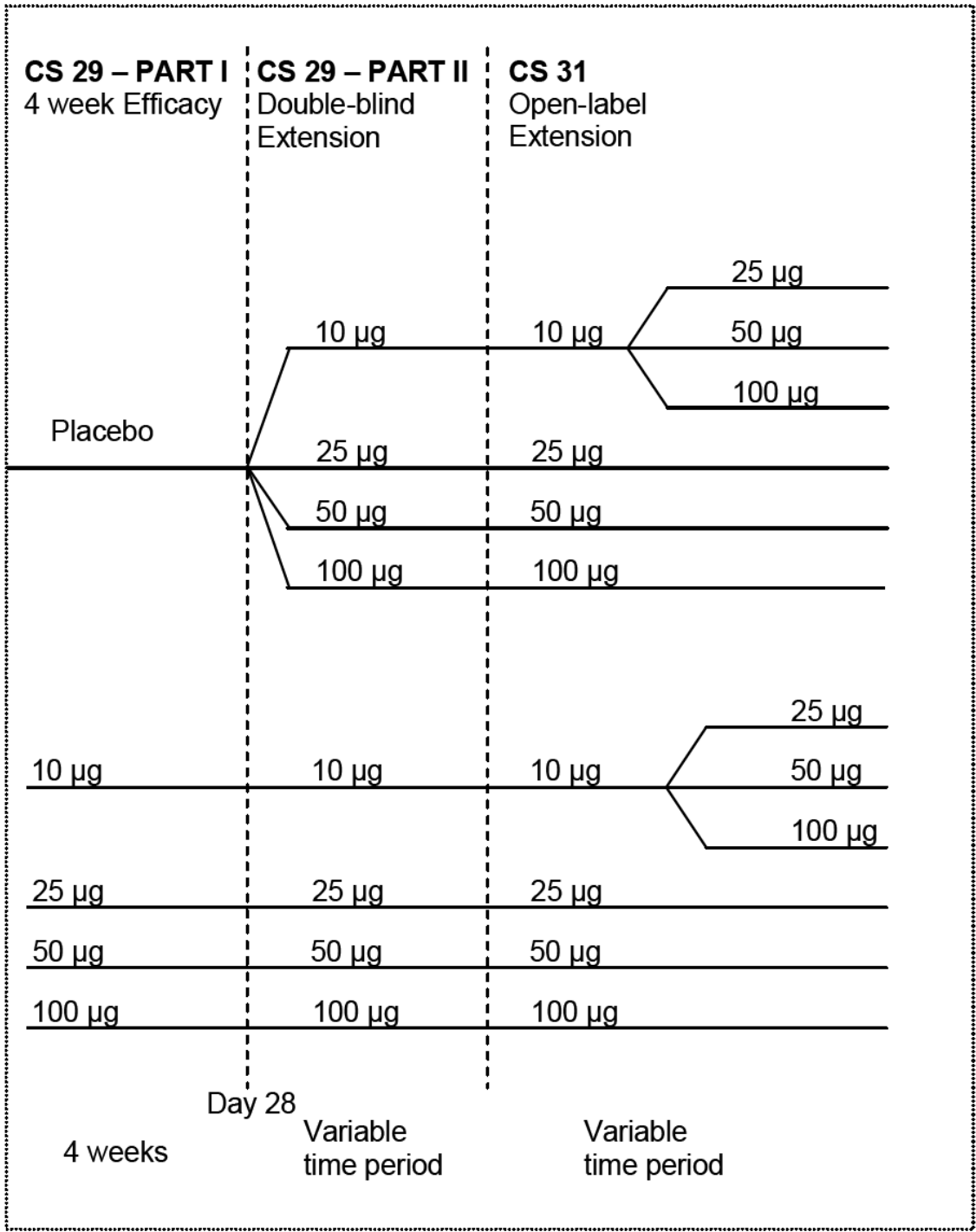
Primary endpoints

- (1) change in mean number of nocturnal voids from baseline evaluation to final visit (Day 28)
- (2) proportion of subjects with >33% reduction in the mean number of nocturnal voids from baseline to final visit (Day 28)

Secondary endpoints:

- Durability of effect achieved in Part I
- Change in initial period of undisturbed sleep, defined as the elapsed time in minutes from going to bed with the intention of sleeping to the time of awakening for the first nocturnal void
- Change in duration of total sleep time
- Change in nocturia-specific quality of life as assessed by scores on the International Consultation on Incontinence Modular Questionnaire - Nocturia (ICIQ-N) and the Nocturia Quality of Life Questionnaire (NQoL)
- Change in quality of sleep as assessed by the global score of the Pittsburgh Sleep Quality Index (PSQI)
- Change in overall Quality of Life as assessed by the SF-12

Figure 1 Dosing During CS 29 Part I & 2 and CS 31



Description of the conducted CS29 and CS31 is summarized in Table 1.

Table 1 Description of Clinical Efficacy Studies

Study ID	No. of Centers	Study Dates (Start–Completion)	No. of Subjects Randomized / Completed / Dropouts	Design / Control	Route and Regimen	Sex (M/F) Mean Age (Range) Race (W/B/O)	Primary Efficacy Endpoints
FE992026 CS29 (Part I)	78 enrolled subjects	Part I Start: 04 Jun 2007	799 randomized/ 710 completed/ 89 discontinued	Randomized, double-blind, placebo- controlled, parallel-group	Oral placebo or Oral desmopressin Melt: 10 µg, 25 µg, 50 µg, or 100 µg	416M/341F 62.0 years (20–89) 80%W/15% B/5%O	Change from baseline to final visit (Day 28) in mean number of nocturnal voids; proportion of subjects with >33% reduction in the mean number of nocturnal voids.
(Part II)		Part II End: 22 Feb 2008	665 enrolled/ 566 completed/ 99 discontinued	Placebo subjects re-randomized (at initial randomization) to active drug	Oral desmopressin Melt: 10 µg, 25 µg, 50 µg, or 100 µg	369M/296F 61.9 years (22-89) 82%W/14%B/4%O	Change from baseline to Months 2, 3, 5, and 7 in mean number of nocturnal voids; proportion of subjects with >33% reduction in the mean number of nocturnal voids
FE992026 CS31	70 enrolled subjects	6 Dec 2007 Ongoing	508 enrolled/ 379 ongoing as of 31 Dec 2008/ 129 discontinued	Open-label ^a	Oral desmopressin Melt: 10 µg, 25 µg, 50 µg, or 100 µg	291M/217F 62.2 years (23-88) 82%W/14%B/4%O	Change from baseline of CS29 in mean number of nocturnal voids, proportion of subjects with >33% reduction in the mean number of nocturnal voids, duration of first sleep period, total sleep time, and quality of life

Ref. Table 1 in ISE.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

All randomized subjects who received any study drug were included in one or more the following analysis datasets:

Intent-to-Treat (ITT) Dataset (Full Analysis Dataset). All randomized subjects who received at least one dose of study drug and provided at least one primary efficacy measure (i.e., number of nocturnal voids) during Part I were included in the ITT analysis dataset.

Per-Protocol (PP) Dataset. Subjects in the ITT analysis dataset were excluded from the Per Protocol analysis dataset if they violated any inclusion criteria, met any exclusion criteria, were treated with a regimen other than the one to which they were randomized, took less than 80% of their assigned treatment, or failed to sufficiently complete their diaries (sufficient diary completion was defined in the statistical analysis plan prior to database lock). These major protocol deviations were tabulated by treatment group and all protocol deviations were listed.

Observed Cases (OC) Dataset. Subjects from the PP dataset who had information on mean number of nocturnal voids for both the screening visit and the final visit in Part I (Day 28) were included in the OC dataset. The mean number of nocturnal voids was defined to be missing if no information was available on the number of nocturnal voids for any of the 3 consecutive nights prior to the respective visit. The OC Dataset was used for sensitivity analysis of the 2 co-primary endpoints.

Safety Dataset. All subjects who received at least one dose of study drug or placebo and had at least one safety assessment were included in the safety analysis dataset. If a subject was

ineligible or received the incorrect dose of investigational treatment, and had at least one administration of the investigational product, data were included in the safety dataset.

A total of 1412 subjects were screened for Part I of the study; 613 subjects were screening failures and 799 subjects were randomized to treatment. The most common recorded reasons for screening failure were renal insufficiency (15%) and not averaging ≥ 2 nocturnal voids over the 3-day screening period (10%). The most common reasons for discontinuation overall were withdrawal of consent (4%), adverse event (2%), and lost to follow-up (2%). Subject disposition in Part I was summarized in [Table 2](#).

Table 2 Subject Disposition (CS 29 Part I)

	Placebo	10 µg	25 µg	50 µg	100 µg	Total
Randomized	160	163	158	158	160	799
Completed, N (%)	145 (91%)	144 (88%)	148 (94%)	138 (87%)	135 (84%)	710 (89%)
Prematurely withdrawn	15 (9%)	19 (12%)	10 (6%)	20 (13%)	25 (16%)	89 (11%)
Adverse event	1 (1%)	4 (2%)	0	5 (3%)	6 (4%)	16 (2%)
Serum sodium ≤ 125 mmol/L	1 (1%)	0	0	5 (3%)	4 (3%)	10 (1%)
Protocol violation	2 (1%)	0	0	0	1 (1%)	3 (<1%)
Patient withdrew consent	6 (4%)	5 (3%)	6 (4%)	4 (3%)	9 (6%)	30 (4%)
Lost to follow-up	2 (1%)	4 (2%)	1 (1%)	5 (3%)	3 (2%)	15 (2%)
Other	2 (1%)	4 (2%)	0	1 (1%)	1 (1%)	8 (1%)
Not reported	1 (1%)	2 (1%)	3 (2%)	0	1 (1%)	7 (1%)

N = Number of subjects.

% = Percentage of subjects.

Notes:

- (1) Completed denotes the subjects completing Part I. In general completers are the subjects who complete the last visit (day 28) in Part I.
- (2) Withdrawals include all withdrawals from the time of randomization up to and including the last visit (day 28) in Part I.
- (3) All percentages are computed relative to number of randomized subjects.
- (4) A subject is included in Per Protocol dataset if the subject contributes with any data to the Per Protocol analysis.
- (5) A subject is included in Observed Cases dataset if the subject is in the Per Protocol dataset and contributes with diary data at baseline and at Day 28.

Ref. Table 8 in fe992026cs29-report-body-1

Of the 710 subjects who completed Part I of the study, 665 subjects continued into Part II. Of the 145 placebo subjects who completed Part I, 136 continued into Part II and were re-randomized (in blinded fashion) to one of the active treatment groups. The most common reasons for discontinuation overall in Part II were withdrawal of consent (8%), adverse event (2%), and lost to follow-up (2%). A summary of subject disposition in Part II is presented in [Table 3](#).

Table 3 Subject Disposition (CS 29 Part II)

	10 µg	25 µg	50 µg	100 µg	Placebo to:				Total
					10 µg	25 µg	50 µg	100 µg	
Randomized	135	135	132	127	31	37	34	34	665
Completed, N (%)	107 (79%)	120 (89%)	120 (91%)	107 (84%)	25 (81%)	32 (86%)	29 (85%)	26 (76%)	566 (85%)
Prematurely withdrawn	28 (21%)	15 (11%)	12 (9%)	20 (16%)	6 (19%)	5 (14%)	5 (15%)	8 (24%)	99 (15%)
Withdraw consent	15 (11%)	7 (5%)	7 (5%)	10 (8%)	4 (13%)	2 (5%)	3 (9%)	2 (6%)	50 (8%)
Adverse event	2 (1%)	3 (2%)	1 (1%)	1 (1%)	1 (3%)	1 (3%)	1 (3%)	4 (12%)	14 (2%)
Lost to follow-up	3 (2%)	2 (1%)	0	5 (4%)	0	1 (3%)	0	0	11 (2%)
Decreased sodium	0	0	0	1 (1%)	0	0	1 (3%)	1 (3%)	3 (1%)
Excluded medication	1 (1%)	0	0	0	0	0	0	0	1 (<1%)
Other	4 (3%)	2 (1%)	4 (3%)	2 (2%)	1 (3%)	1 (3%)	0	1 (3%)	15 (2%)
Not reported	3 (2%)	1 (1%)	0	1 (1%)	0	0	0	0	5 (1%)

N = Number of subjects.

% = Percentage of subjects.

Notes:

- (1) Completed denotes the subjects completing Part II. Completers are those subjects that were still active in the study when the CS31 study began.
- (2) Withdrawals include all withdrawals from Visit 1E up to and including the last visit (day 169) in Part II.
- (3) All percentages are computed relative to number of subjects moved into Part II of the study.
- (4) A subject is included in Observed Cases dataset if the subject contributes with any diary data at any visit in Part II.

Ref. Table 9 in fe992026cs29-report-body-1

Of the 799 randomized subjects in Part I, 757 subjects who received at least 1 dose of study drug and had follow-up data were included in the ITT analysis dataset. Overall, 10% of ITT subjects had a major protocol violation and were excluded from the PP analysis dataset. Of the 682 PP subjects, 10% did not have both screening and final visit data on number of nocturnal voids and were excluded from the OC analysis dataset. All 799 randomized subjects received at least 1 dose of study drug (desmopressin or placebo) and had at least 1 safety assessment and, therefore, were included in the safety analysis dataset. A summary of subjects included in each analysis dataset in Part I is presented in [Table 4](#).

Table 4 Study Subjects by Analysis Dataset (CS 29 Part I)

	Placebo	10 µg	25 µg	50 µg	100 µg	Total
ITT	156	155	152	148	146	757
PP	137	139	141	135	130	682
OC	122	122	131	123	116	614
Safety	160	163	158	158	160	799

Ref. Table 10 in fe992026cs29-report-body-1

No formal testing was performed in Part II, with only descriptive statistics of the OC dataset provided. Subjects included in each analysis dataset in Part II are presented in [Table 5](#).

Table 5 Study Subjects by Analysis Dataset (CS 29 Part II)

Analysis Dataset	10 µg	25 µg	50 µg	100 µg	Placebo to:				Total
					10 µg	25 µg	50 µg	100 µg	
ITT	135	135	132	127	31	37	34	34	665
OC	106	100	94	104	22	29	27	22	504
Safety	135	135	132	127	31	37	34	34	665

Ref. Table 11 in fe992026cs29-report-body-1

Of the 799 randomized subjects in Part I, 406 were <65 years of age and 393 were ≥65 years of age. Of the 665 randomized subjects in Part II, 333 were <65 years of age and 332 were ≥65 years of age. The majority (≥90%) of randomized subjects had nocturnal polyuria; subjects with nocturnal polyuria comprised 86% (Part I) or 87% (Part II) of subjects younger than 65 and 94% of subjects at least 65 years old. A summary of study subjects by stratification is presented in [Table 6](#).

Table 6 Study Subjects by Stratification (CS29)

Parameter	Part I			Part II		
	Nocturnal Polyuria		Total	Nocturnal Polyuria		Total
	Absent	Present		Absent	Present	
Age <65 years						
Randomized	55	351	406	43	290	333
Safety	55	351	406	43	290	333
ITT	51	331	382	43	290	333
PP	41	308	349	35	274	309
OC	34	277	311	31	219	250
Age ≥65 years						
Randomized	24	369	393	20	312	332
Safety	24	369	393	20	312	332
ITT	23	352	375	20	312	332
PP	21	312	333	19	278	297
OC	19	284	303	17	237	254
Total						
Randomized	79	720	799	63	602	665
Safety	79	720	799	63	602	665
ITT	74	683	757	63	602	665
PP	62	620	682	54	552	606
OC	53	561	614	48	456	504

Ref. Table 12 in fe992026cs29-report-body-1

Demographic Characteristics

A summary of demographic characteristics of subjects in the ITT analysis dataset in Part I is presented in [Table 7](#).

Demographic characteristics of subjects who enrolled in Part II were similar to those of subjects in Part I. Of the 665 ITT subjects in Part II, 296 (45%) were female and 369 (55%) were male; 82% of all subjects were White, 14% were Black/African American, 2% were Asian, and 2% were either native Hawaiian/other Pacific Islander or of “Other” races (Part II). Hispanics comprised 6% of the study population. The mean age of the ITT subjects was 61.9 years (median age: 64 years), and age ranged from 22 to 89 years. Mean height was 1.7 m, mean weight was 85.9 kg, and mean BMI was 29.6 kg/m².

Table 7 Subject Demographics (CS 29 Part I)

Demographic Characteristic	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Age (years)					
Mean (SD)	62.1 (13.39)	61.7 (14.41)	62.4 (13.22)	61.6 (11.80)	62.1 (12.34)
Median	64.0	64.0	64.5	63.5	65.5
Minimum, maximum	20, 86	23, 84	22, 89	28, 88	24, 85
Sex, N (%)					
Female	66 (42%)	73 (47%)	65 (43%)	71 (48%)	66 (45%)
Male	90 (58%)	82 (53%)	87 (57%)	77 (52%)	80 (55%)
Race, N (%)					
Caucasian	136 (87%)	123 (79%)	120 (79%)	119 (80%)	111 (76%)
Black/African American	16 (10%)	21 (14%)	28 (18%)	24 (16%)	27 (18%)
Asian	3 (2%)	2 (1%)	2 (1%)	3 (2%)	6 (4%)
American Indian/ Alaskan Native	0	2 (1%)	0	0	0
Native Hawaiian/ other Pacific Islander	0	1 (1%)	1 (1%)	0	0
Other	1 (1%)	6 (4%)	1 (1%)	2 (1%)	2 (1%)
Ethnic Origin, N (%)					
Hispanic	13 (8%)	10 (6%)	10 (7%)	13 (9%)	6 (4%)
Not Hispanic	143 (92%)	145 (94%)	142 (93%)	135 (91%)	140 (96%)
Height (m)					
Mean (SD)	1.71 (0.111)	1.70 (0.110)	1.71 (0.106)	1.70 (0.096)	1.71 (0.111)
Median	1.70	1.70	1.70	1.70	1.70
Minimum, maximum	1.50, 1.90	1.20, 1.90	1.50, 2.00	1.40, 1.90	1.40, 2.00
Weight (kg)					
Mean (SD)	86.23 (19.423)	85.05 (18.103)	85.40 (19.460)	86.15 (20.064)	85.99 (19.682)
Median	84.00	84.00	83.90	83.75	84.00
Minimum, maximum	47.90, 140.70	42.30, 148.70	45.00, 178.00	46.70, 170.40	42.90, 151.70
BMI (kg/m ²)					
Mean (SD)	29.72 (6.719)	29.47 (6.259)	29.26 (6.452)	29.96 (7.487)	29.34 (6.439)
Median	27.84	28.65	28.29	28.64	27.90
Minimum, maximum	16.60, 53.10	16.50, 52.90	17.40, 59.70	16.60, 67.10	17.50, 58.10

Ref. Table 13 in fe992026cs29-report-body-1

At baseline, the median number of nocturnal voids overall was 3.0, and ranged from 2.0 to 8.7. The majority (54%) of subjects averaged ≤ 3 nocturnal voids, with 28% averaging >3 to 4 nocturnal voids and 11% averaging >4 to 5 nocturnal voids. A summary of the number of subjects by the baseline number of nocturnal voids is presented in [Table 8](#).

Table 8 Number of Subjects by Baseline Number of Voids (CS 29 Part I)

Number of Nocturnal Voids	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Mean (SD)	3.274 (1.1637)	3.211 (1.0250)	3.346 (1.3183)	3.385 (1.0660)	3.224 (1.1025)
Median	3.000	3.000	3.000	3.333	3.000
Minimum, Maximum	2.00, 7.67	2.00, 7.67	2.00, 8.67	2.00, 7.33	2.00, 7.33
≤ 3	85 (54%)	80 (52%)	86 (57%)	71 (48%)	86 (59%)
$>3 - 4$	42 (27%)	50 (32%)	36 (24%)	48 (32%)	37 (25%)
$>4 - 5$	16 (10%)	20 (13%)	14 (9%)	20 (14%)	15 (10%)
$>5 - 6$	8 (5%)	3 (2%)	8 (5%)	5 (3%)	5 (3%)
$>6 - 7$	4 (3%)	1 (1%)	5 (3%)	3 (2%)	2 (1%)
>7	1 (1%)	1 (1%)	3 (2%)	1 (1%)	1 (1%)

Ref. Table 15 in fe992026cs29-report-body-1

3.1.3 Sponsor's Statistical Methodologies

Efficacy Analysis

Superiority to placebo will be demonstrated in a step-down approach simultaneously on the two co-primaries. By virtue of the step-down approach in the pre-specified order (from highest to lowest dose), the family wise error (FWE) rate is controlled at the 5% nominal significance level. The trial will be declared positive only if in the 100µg group a statistically significant positive effect as compared to placebo on both co-primaries has been demonstrated in the ITT group. And only then, the next higher dose group, i.e. the 50µg group, can be claimed superior to placebo, if it shows a statistically significant improvement over placebo on both co-primaries, etc.

First co-primary endpoint

The first co-primary were analyzed by an analysis of covariance (ANCOVA) with the change from baseline in the average number of nocturnal voids as the outcome (dependent) variable, main effects for each of two factors used to stratify the randomization (age (<65 , ≥ 65), and presence/absence of nocturnal polyuria), the five study treatments, and a covariate for the baseline average number of nocturnal voids as independent variables. Resulting two-sided 95% confidence limits of adjusted contrasts and associated p-values of each of the dose-group versus placebo were provided.

Interactions of dose-group versus age (<65 , ≥ 65) and dose-group versus presence/absence of nocturnal polyuria were tested at the 10% level. Testing were performed by including both interactions in the model and then removing the least significant one until either none, one, or both the interactions are significant at the 10% level.

The adequacy of the model was assessed by Cook's D by leverage points plot based on the ITT dataset. If the plot reveal a substantial number of influential points, alternative non-parametric Wilcoxon rank sum on change from baseline adjusting for the four sub-strata generated by the age (<65, >=65) and absence/presence of nocturnal polyuria factors were applied for each dose-group vs. placebo comparison.

The change in number of nocturnal voids from the baseline visit to Day 28 was presented for the ITT, the PP, and the Observed Cases datasets by treatment and number of nocturnal voids at baseline and by treatment and strata and number of nocturnal voids at baseline. In addition changes from baseline to Day 8, Day 15, and Day 22 were presented in a similar manner for both the ITT and the PP datasets.

Second co-primary endpoint

Test for treatment difference were based on the likelihood ratio test in a logistic regression analysis using the 33% responder status as dependent variable, and having main effects for each of two factors used to stratify the randomization (age (<65, >=65), and presence/absence of nocturnal polyuria), the five study treatments, and a covariate for the baseline number of nocturnal voids as independent variables.

The difference between treatment and placebo were expressed as an odds ratio with two-sided 95% confidence limits accompanied by the associated p-values of each of the dose-group versus placebo comparisons.

Interactions of dose-group versus age (<65, >=65) and dose-group versus presence/absence of nocturnal polyuria were tested at the 10% level. Testing were performed by including both interactions and then removing the least significant one until either none, one or both the interactions are significant at the 10% level.

The adequacy of the logistic regression model was assessed by means of a Hosmer-Lemeshow goodness-of-fit test. If a lack of fit of the logistic model is apparent, then exact methods for pooling odds ratios as estimated by exact methods in each of the four sub-strata (age (<65, >=65) times absence/presence of nocturnal polyuria) were obtained, and homogeneity of odds ratios (of each dose group vs. placebo) would, in that case, be tested using Zelen's test.

All secondary endpoints will be tested in a manner identical to the first co-primary endpoints.

Missing values

Missing values for the co-primary endpoint of the mean number of nocturnal voids in CS29 Part I were imputed using last-observation-carried-forward (LOCF). Missing values for secondary endpoints and for data in CS29 Part II and CS31 were not imputed.

Study Groups

The studies for evaluation of clinical efficacy were grouped as indicated:

- Study Group 1: CS29 (Part I) – used to demonstrate primary efficacy and onset of effect
- Study Group 2: CS29, including Part I and Part II, and CS31 – used to indicate persistence of effect

Subjects in the placebo group of CS29 Part I were not included in Study Group 2. Subjects on the 10 µg dose were included up to the time point of dose escalation.

Subgroup Analysis

Subgroups included:

- <65 years and ≥65 years of age
- Gender
- Gender and age (male <50 years, male ≥50 years, female <50 years, female ≥50 years)
- Race (Caucasian, not Caucasian)

No interim analysis was planned.

3.1.4 Sponsor’s Efficacy Results

Mean Number of Nocturnal Voids

A summary of baseline values and mean change from baseline to Day 28 or the final visit in mean number of nocturnal voids is presented by treatment group for the ITT analysis dataset in [Table 9](#). The reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 µg (p<0.0001) and 50 µg (p=0.0207) groups.

Table 9 Change from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids (ITT, CS Part I)

Nocturnal Voids	Placebo	10 µg	25 µg	50 µg	100 µg
Baseline	(N=156)	(N=155)	(N=152)	(N=148)	(N=146)
Mean (SD)	3.274 (1.1637)	3.211 (1.0250)	3.346 (1.3183)	3.385 (1.0660)	3.224 (1.1025)
Median	3.000	3.000	3.000	3.333	3.000
Minimum, maximum	2.00, 7.67	2.00, 7.67	2.00, 8.67	2.00, 7.33	2.00, 7.33
Overall	(N=156)	(N=155)	(N=152)	(N=148)	(N=146)
Mean Δ (SD)	-0.86 (1.054)	-0.83 (1.069)	-1.00 (1.125)	-1.18 (1.187)	-1.43 (1.219)
Median	-0.83	-0.67	-1.00	-1.00	-1.33
Minimum, maximum	(-4.0, 1.7)	(-4.3, 2.3)	(-3.7, 2.3)	(-5.0, 2.0)	(-5.0, 4.3)
Mean difference (adj)		0.010	-0.120	-0.277	-0.613
[95% CI, uncorrected]		[-0.221, 0.242]	[-0.353, 0.112]	[-0.511, -0.042]	[-0.848, -0.378]
p-value vs. placebo		p=0.9303	p=0.3104	p=0.0207*	p<0.0001*

Δ = change; SD = standard deviation; adj = adjusted; CI = confidence interval

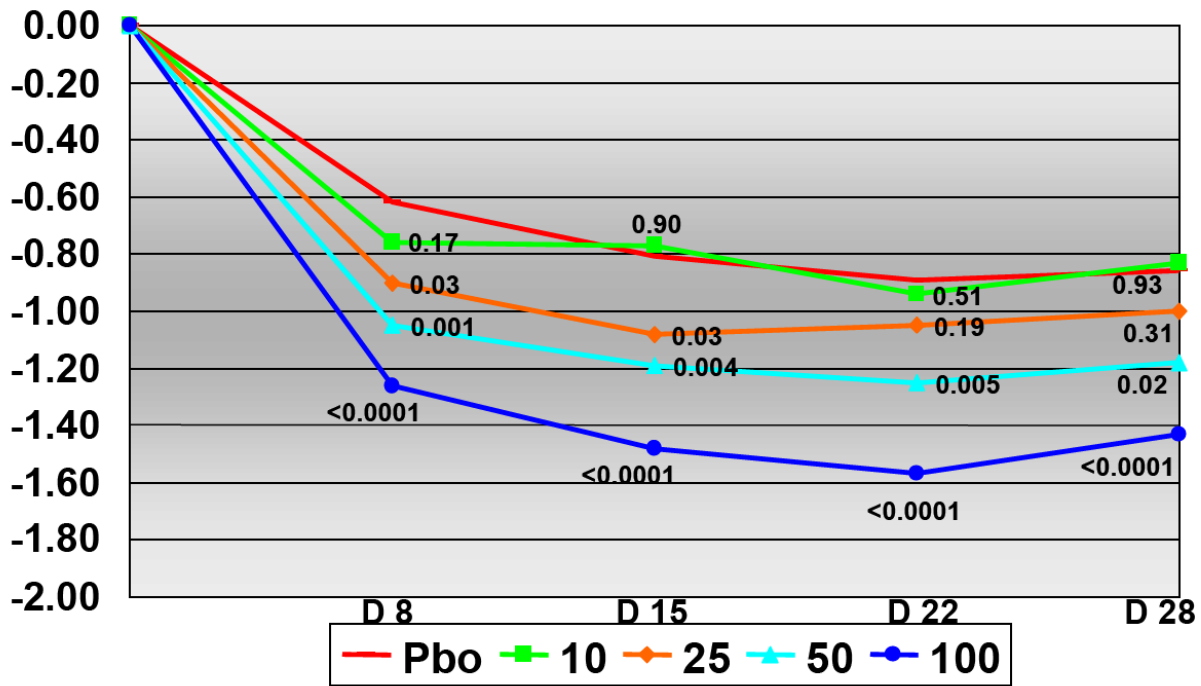
* Statistically significant difference versus placebo, p≤0.05.

Note: Treatment difference and 95% CI were based on linear model adjusted for age, absence/presence of nocturnal polyuria, and baseline number of nocturnal voids.

Ref. Table 21 in fe992026cs29-report-body-1 and Table 18 ISE.

The trend of changes from baseline in mean number of nocturnal voids versus treatment time in week, along with p-values for each desmopressin Melt dose compared to placebo, is displayed in [Figure 2](#).

Figure 2 Change from Baseline in Mean Number of Nocturnal Voids by Study Week



Note: p-values versus placebo are presented for each week of treatment.
 Ref. Figure 3 in fe992026cs29-report-body-1.

Proportion of Subjects with >33% Reduction in Mean Number of Nocturnal Voids

The proportions of subjects with >33% reduction in the mean number of nocturnal voids from baseline to Day 28 or the final visit increased with increasing dose (47% to 71%). The proportion of subjects with >33% reduction in mean number of nocturnal voids, compared to placebo, was summarized for the ITT analysis dataset in Table 10. Statistical significant was observed for only the highest dose 100 µg (p<0.0001) group.

Table 10 Proportion of Subjects with >33% Reduction from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids (ITT, CS29 Part I).

	Placebo	10 µg	25 µg	50 µg	100 µg
Overall	(N=156)	(N=155)	(N=152)	(N=148)	(N=146)
33% responder	73 (47%)	73 (47%)	77 (50%)	79 (53%)	103 (71%)
Odds ratio		1.017	1.147	1.296	2.893
[95% CI, uncorrected]		[0.647, 1.598]	[0.729, 1.807]	[0.821, 2.050]	[1.795, 4.715]
p-value vs. placebo		p=0.9420	p=0.5527	p=0.2662	p<0.0001*

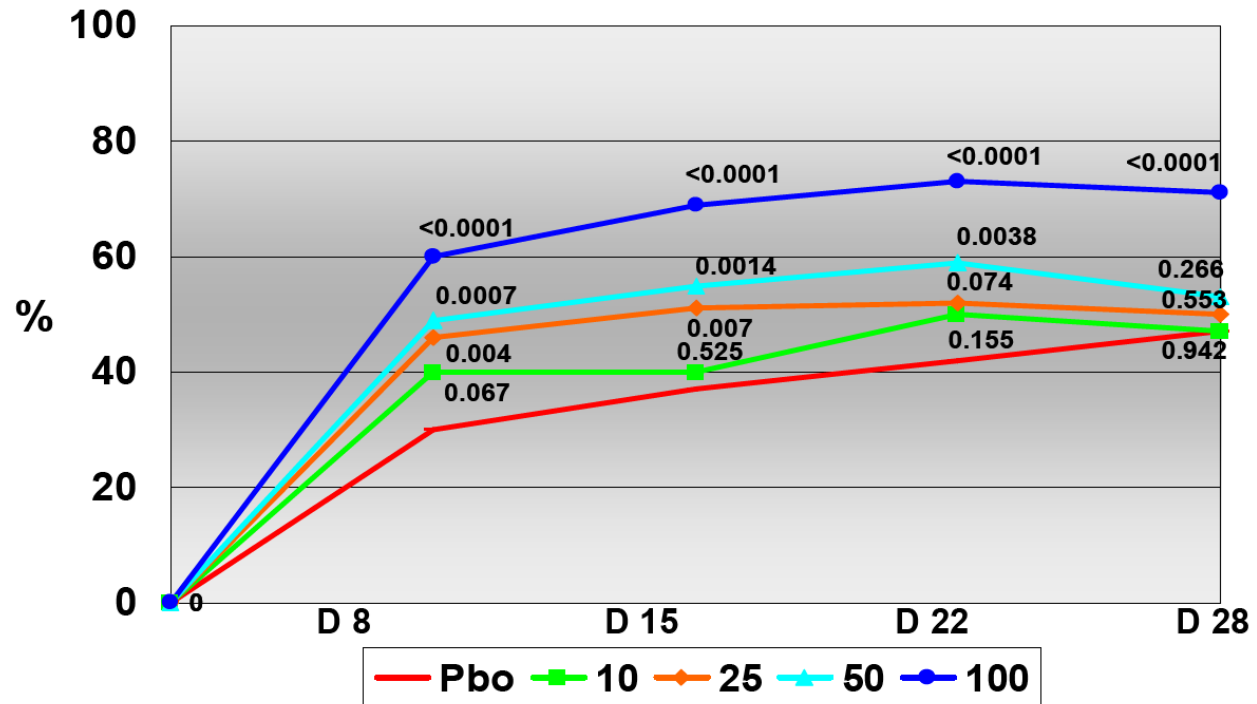
* Statistically significant difference versus placebo, p≤0.05.

Note: p-values correspond to LR-tests of effects in the model including all effects. Odds ratio and 95% CI were based on logistic regression adjusting for age, absence/presence of nocturnal polyuria, and baseline number of nocturnal voids.

Ref. Table 22 in fe992026cs29-report-body-1 and Table 19 ISE.

Weekly change from baseline in the proportion of subjects with >33% reduction in the mean number of nocturnal voids, along with p-values for each desmopressin Melt dose compared to placebo, is displayed in Figure 3.

Figure 3 33% Responders by Study Week



Note: p-values versus placebo are presented for each week of treatment.
 Ref. Figure 6 in fe992026cs29-report-body-1.

In summary, the primary efficacy results suggest superiority of nocturna against placebo only at 100 µg dose according to the pre-specified procedure.

Secondary Efficacy Endpoints

Change in Sleep Time

The duration of the initial period of undisturbed sleep increased from baseline to Day 28 in all treatment groups, with greater increases observed with increasing dose of desmopressin. Mean total sleep time increased in all treatment groups in CS29 Part I; no pattern was observed by dose of desmopressin. Based on F-tests of effects, baseline reported overall sleep duration ($p < 0.0001$) was the only statistically significant predictor for change from baseline to Day 28 in reported total sleep time. A summary of change from baseline to Day 28 in sleep endpoints is presented by treatment group in Table 11.

Table 11 Change from Baseline to Final Visit (Day 28) in Sleep Endpoints (ITT, CS29 Part I).

	Placebo	10 µg	25 µg	50 µg	100 µg
Initial Period of Undisturbed Sleep					
Baseline Mean (SD)	(N=148) 116.52 (58.728)	(N=149) 116.99 (71.364)	(N=142) 114.06 (64.465)	(N=140) 111.13 (68.569)	(N=136) 114.40 (55.829)
Day 28 Mean (SD)	(N=133) 155.75 (90.192)	(N=129) 169.95 (101.929)	(N=126) 194.30 (111.556)	(N=128) 195.67 (102.955)	(N=128) 219.11 (116.357)
Median	140.00	149.00	164.50	188.50	206.25
Minimum, maximum	0.0, 476.7	2.5, 565.0	4.0, 474.3	0.0, 458.3	0.0, 495.0
Change from baseline Mean Δ (SD)	(N=126) 38.74 (88.794)	(N=126) 50.87 (111.471)	(N=121) 82.73 (105.572)	(N=123) 85.05 (109.333)	(N=121) 106.66 (116.180)
Median Δ	41.67	50.83	62.33	62.67	95.50
Minimum, maximum Δ	-273.0, 385.7	-316.5, 456.7	-103.5, 412.5	-233.3, 452.7	-166.0, 398.7
Mean difference (adj) [95% CI, uncorrected] p-value vs. placebo ^a		11.668 [-13.118, 36.454] p=0.3556	41.458 [16.415, 66.501] p=0.0012*	42.579 [17.661, 67.498] p=0.0008*	63.975 [38.950, 88.999] p<0.0001*
Reported Total Sleep Time					
Baseline Mean (SD)	(N=156) 403.10 (83.684)	(N=155) 410.53 (72.756)	(N=152) 400.82 (77.812)	(N=148) 402.55 (83.665)	(N=146) 412.95 (81.318)
Day 28 Mean (SD)	(N=139) 427.46 (67.158)	(N=137) 420.19 (71.684)	(N=141) 416.46 (65.684)	(N=138) 426.56 (76.681)	(N=133) 431.52 (71.698)
Median	438.33	420.00	415.00	429.67	440.00
Minimum, maximum	231.7, 660.0	220.0, 623.3	260.0, 553.3	105.0, 600.0	240.0, 620.0
Change from baseline Mean Δ (SD)	(N=139) 24.55 (80.658)	(N=137) 7.80 (58.550)	(N=141) 15.94 (53.923)	(N=138) 24.91 (72.206)	(N=133) 19.00 (68.937)
Median Δ	20.33	10.00	10.00	20.00	20.00
Minimum, maximum Δ	-135.0, 525.0	-130.0, 163.3	-113.3, 228.3	-168.3, 293.3	-160.0, 196.7
Mean difference (adj) [95% CI, uncorrected] p-value vs. placebo ^a		-12.519 [-25.894, 0.856] p=0.0665	-9.677 [-22.936, 3.582] p=0.1523	-0.225 [-13.553, 13.104] p=0.9736	-1.180 [-14.649, 12.290] p=0.8635

SD = standard deviation; Δ = change; adj = adjusted

* Statistically significant difference versus placebo, $p \leq 0.05$.

Note: Treatment difference and 95% CI were based on linear model adjusted for age, absence/presence of nocturnal polyuria, and baseline number of nocturnal voids.

a. The p-values correspond to F-tests of effects in the model including all effects.

Ref. Table 21 in ISE.

Persistence of Effect for Study Group 2

Descriptive statistics were used to document durability of effect during Part II of the study. Changes from baseline to Day 29 of Part II (Month 2 of study), Day 57 (Month 3), Day 113 (Month 5), and Day 169 (Month 7) in the mean number of nocturnal voids were assessed. A total of 529 subjects received desmopressin during both Part I and Part II of the study. It should be noted that few subjects had data on Day 169 because few subjects had reached Month 7 (Day 169 of Part II) when the rollover into Study CS31 was initiated. A summary of change from baseline in mean number of nocturnal voids during Part II of the study is presented in [Table 12](#) and [Figure 4](#), respectively.

Table 12 Change from Baseline in Mean Number of Nocturnal Voids (OC Analysis Dataset in Part II)

	10 µg	25 µg	50 µg	100 µg	Placebo to:			
					10 µg	25 µg	50 µg	100 µg
Baseline Mean ^a	(N=134) ^b 3.214	(N=135) 3.454	(N=132) 3.402	(N=127) 3.184	(N=31) 3.204	(N=37) 3.459	(N=34) 3.049	(N=34) 3.578
Mean Δ to Day 29	(N=104) -1.12	(N=100) -1.31	(N=93) -1.43	(N=104) -1.47	(N=22) -1.20	(N=28) -1.19	(N=27) -1.00	(N=22) -1.5
Mean Δ to Day 57	(N=86) -1.14	(N=85) -1.42	(N=78) -1.50	(N=81) -1.74	(N=17) -1.08	(N=24) -1.53	(N=21) -1.03	(N=16) -1.35
Mean Δ to Day 113	(N=53) -1.31	(N=56) -1.56	(N=49) -1.65	(N=47) -1.95	(N=11) -0.76	(N=15) -1.67	(N=13) -1.21	(N=11) -1.76
Mean Δ to Day 169	(N=17) -1.47	(N=15) -1.71	(N=17) -1.65	(N=15) -1.76	(N=3) -1.78	(N=3) -2.00	(N=4) -2.33	(N=2) -2.50

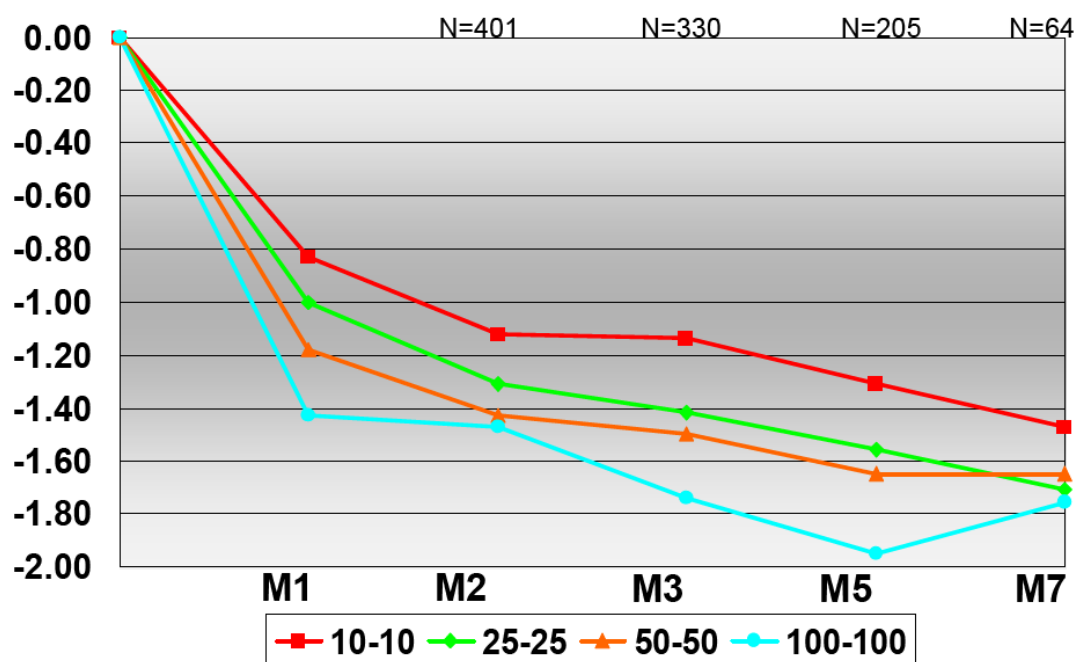
a. Baseline data are from the ITT analysis dataset in Part II.

b. Baseline value was missing for 1 subject.

Ref. Table 26 in fe992026cs29-report-body-1.

In Figure 4, the change at M1 (Month 1) represents the results obtained at Day 28 of Part I. The active treatment groups are shown by the dose received in Part I and Part II (e.g., 10-10 indicates 10 µg in Part I and 10 µg in Part II).

Figure 4 Monthly Change from Baseline in Mean Number of Voids (Subjects Maintained on Active Treatment)



Note: M1 = Month 1 (Day 28, Part I); M2 = Month 2 (Day 29, Part II); M3 = Month 3 (Day 57); M5 = Month 5 (Day 113); M7 = Month 7 (Day 169)

Ref. Figure 8 in fe992026cs29-report-body-1.

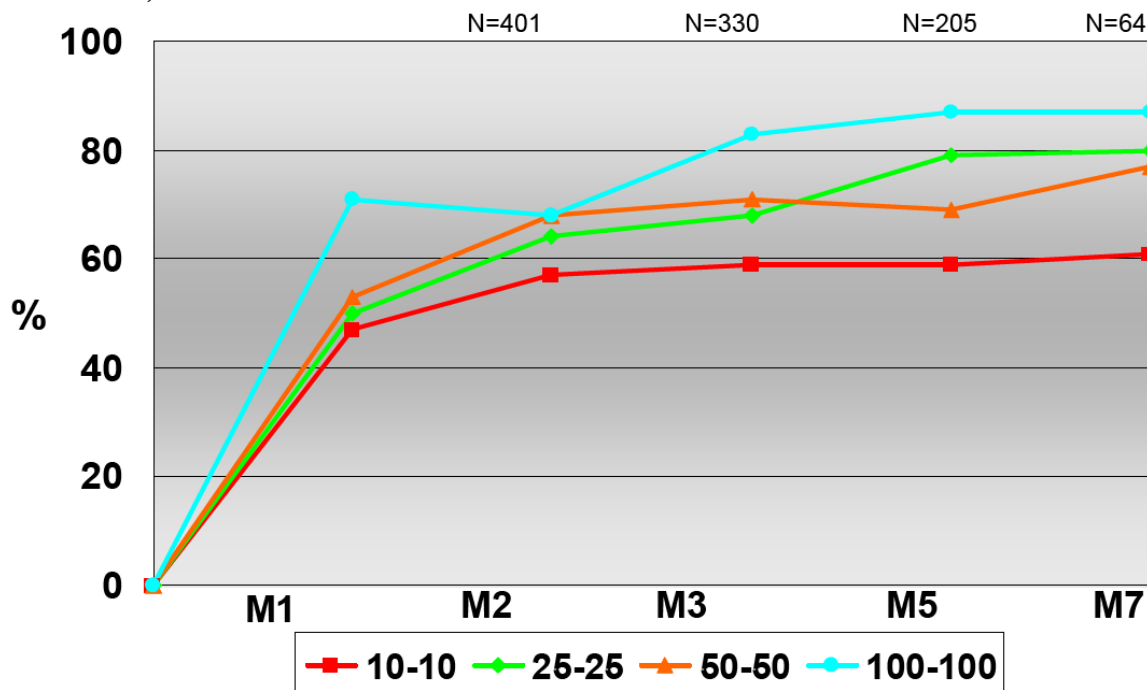
A summary of 33% responder status during Part II of the study is presented in [Table 13](#) and [Figure 5](#), respectively.

Table 13 Proportion of Subjects with >33% Reduction from Baseline in Mean Number of Nocturnal Voids (OC Analysis Dataset in Part II)

33% Responder Rate	10 µg	25 µg	50 µg	100 µg	Placebo to:			
					10 µg	25 µg	50 µg	100 µg
Day 29, n (%)	(N=104) 59 (57%)	(N=100) 64 (64%)	(N=93) 63 (68%)	(N=104) 71 (68%)	(N=22) 16 (73%)	(N=28) 12 (43%)	(N=27) 13 (48%)	(N=22) 16 (73%)
Day 57, n (%)	(N=86) 51 (59%)	(N=85) 58 (68%)	(N=78) 55 (71%)	(N=81) 67 (83%)	(N=17) 7 (41%)	(N=24) 17 (71%)	(N=21) 9 (43%)	(N=16) 11 (69%)
Day 113, n (%)	(N=53) 31 (58%)	(N=56) 44 (79%)	(N=49) 34 (69%)	(N=47) 41 (87%)	(N=11) 6 (55%)	(N=15) 11 (73%)	(N=13) 7 (54%)	(N=11) 8 (73%)
Day 169, n (%)	(N=17) 11 (61%)	(N=15) 12 (80%)	(N=17) 13 (76%)	(N=15) 13 (87%)	(N=3) 3 (100%)	(N=3) 2 (67%)	(N=4) 4 (100%)	(N=2) 2 (100%)

Ref. Table 27 in fe992026cs29-report-body-1.

Figure 5 33% Responders by Study Month (Subjects Maintained on Active Treatment)



Note: M1 = Month 1 (Day 28, Part I); M2 = Month 2 (Day 29, Part II); M3 = Month 3 (Day 57); M5 = Month 5 (Day 113); M7 = Month 7 (Day 169)

Ref. Figure 9 in fe992026cs29-report-body-1.

Change in Initial Period of Undisturbed Sleep

A summary of change from baseline to Day 28 in initial period of undisturbed sleep is presented by treatment group in [Table 14](#), suggesting the duration of the initial period of undisturbed sleep increased from baseline to Day 28 in all treatment groups, with greater increases observed with increasing dose of desmopressin.

Table 14 Change from Baseline to Final Visit (Day 28) in Duration of Initial Period of Undisturbed Sleep (Part I)

Initial Period of Undisturbed Sleep (min)	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Baseline	(N=148)	(N=149)	(N=142)	(N=140)	(N=136)
Mean (SD)	117 (58.7)	117 (71.4)	114 (64.5)	111 (68.6)	114 (55.8)
Median	110	103	102	109	107
Minimum, maximum	(0, 324)	(0, 470)	(0, 308)	(0, 440)	(0, 300)
Change from Baseline	(N=126)	(N=126)	(N=121)	(N=123)	(N=121)
Mean (SD)	38.7 (88.79)	50.9 (111.47)	82.7 (105.57)	85.1 (109.33)	106.7 (116.18)
Median	41.7	50.8	62.3	62.7	95.5
Minimum, maximum	(-273, 386)	(-317, 457)	(-104, 413)	(-233, 453)	(-166, 399)
Estimate [95% CI]		11.668 [-13.118, 36.454]	41.458 [16.415, 66.501]*	42.579 [17.611, 67.498]*	63.975 [38.950, 88.999]*

* Statistically significant difference, based on 95% confidence intervals.

Ref. Table 28 in fe992026cs29-report-body-1.

Mean increases in the initial period of undisturbed sleep observed in CS29 Part I appeared continuous beyond 8 weeks, with a trend for greater increases with increasing desmopressin dose. A summary of change from baseline to 8 weeks, 12 weeks, 20 weeks, 28 weeks, 52-56 weeks, and 72-76 weeks in the initial period of undisturbed sleep is presented by treatment group for the ITT analysis dataset for CS29 and CS31 in [Table 15](#).

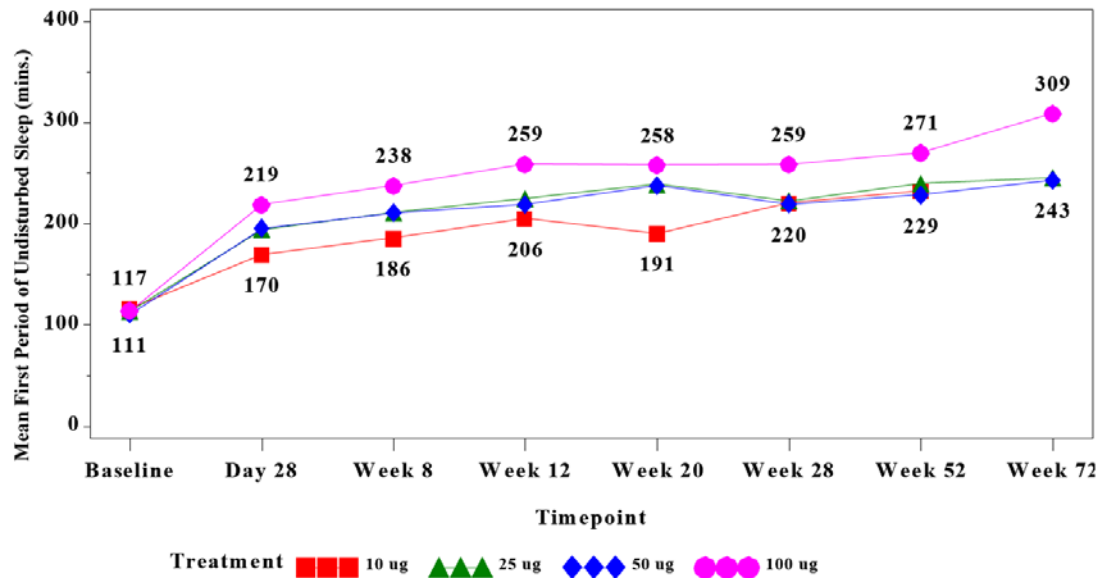
Table 15 Change from Baseline in Initial Period of Undisturbed Sleep (ITT, CS29 and CS31)

Nocturnal Voids	10 µg	25 µg	50 µg	100 µg
8 Weeks	(N=97)	(N=87)	(N=85)	(N=94)
Mean (SD)	185.98 (124.512)	211.23 (116.696)	211.04 (111.790)	238.09 (112.305)
Mean Δ (SD)	77.64 (118.822)	96.58 (112.750)	104.72 (120.236)	126.63 (114.501)
12 Weeks	(N=79)	(N=73)	(N=67)	(N=76)
Mean (SD)	205.50 (128.944)	225.41 (121.025)	219.29 (107.802)	259.09 (115.311)
Mean Δ (SD)	97.57 (116.855)	116.70 (110.738)	118.71 (112.450)	144.77 (116.376)
20 Weeks	(N=57)	(N=52)	(N=60)	(N=64)
Mean (SD)	190.76 (121.621)	239.35 (112.929)	238.08 (146.356)	258.35 (120.404)
Mean Δ (SD)	94.58 (113.909)	115.60 (105.136)	134.67 (152.191)	153.27 (122.179)
28 Weeks	(N=63)	(N=81)	(N=60)	(N=61)
Mean (SD)	220.78 (126.395)	222.97 (115.418)	219.66 (113.327)	258.97 (108.106)
Mean Δ (SD)	113.90 (122.505)	115.41 (114.950)	105.54 (136.046)	145.82 (117.099)
52-56 Weeks	(N=45)	(N=85)	(N=76)	(N=72)
Mean (SD)	232.50 (116.297)	240.04 (146.746)	228.69 (115.753)	270.83 (115.374)
Mean Δ (SD)	120.91 (134.943)	118.87 (145.285)	125.56 (125.714)	160.63 (118.287)
72-76 Weeks	(N=0)	(N=27)	(N=31)	(N=21)
Mean (SD)		245.64 (125.835)	243.22 (142.492)	309.06 (117.810)
Mean Δ (SD)		131.90 (121.039)	144.10 (142.618)	191.95 (107.123)

SD = standard deviation; □ = change
 Ref. Table 29 in ISE.

The initial period of undisturbed sleep is shown by treatment across CS29 and CS31 in Figure 6.

Figure 6 Initial Period of Undisturbed Sleep by Treatment (ITT, CS29 & CS31)



Ref. Figure 10 in ISE.

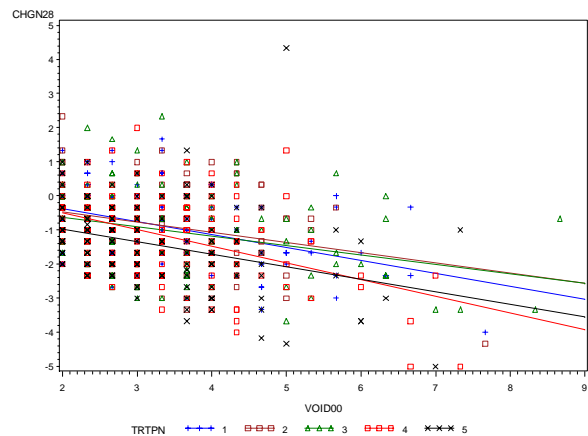
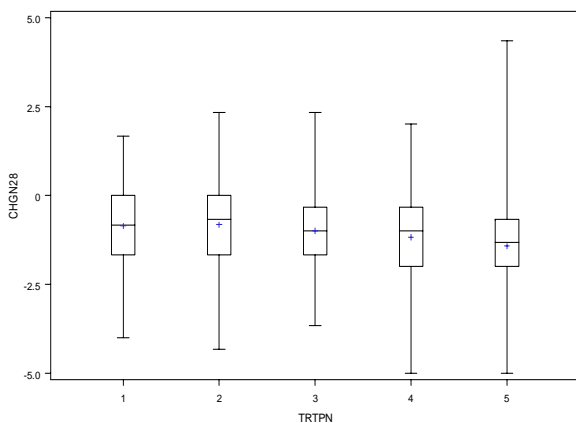
3.1.5 This reviewer's findings

This reviewer checked the distributions of the mean number of voids from baseline to Day 28 and the trends of the mean nocturnal number of voids against the baseline values by treatment on ITT population as shown in Figures 7 (A, B).

Figure 7 Plots of Changes from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids (CS29 Part I, ITT population). A: boxplots by treatment. B: plot of change from Baseline to Day 28 versus baseline values.

A

B



There appears no abnormal pattern in Figure 7.

Efficacy Conclusions

For CS29 Part I, there is enough evidence to support dose-response that the dose response slope across all the doses (10, 25, 50, and 100 µg) is statistically significant for not being zero for both co-primary efficacy endpoints. However, based on the pre-specified multiple comparison scheme, the superiority of nocturna to placebo in reducing the number of nocturnal voids is only observed at dose 100 µg for both co-primary endpoints at Day 28.

To reconcile the sample sizes in Table 3 (also in Table 1, a total of 566 subjects completed Part II of the study) and Table 13 (there were total 76 subjects at Day 169), recall that completers were defined as those subjects who were still active in the study when the CS31 study began. According to the study design “Subjects enrolled in Study CS29 who had completed at least the visit at Day 15 of Part II or at Day 43 of CS29 were eligible to roll over into CS31”, the date for recording patients completed was likely to be 3E visit (Day 15 of CS29 Part II). This is also supported by comparing Tables 3 and 13, where we can see that at each dose, the number of completers (Table 3) is larger than the number of subjects existed at any visit Day (Days 29, 57, 113, and 169 in Table 13). It is clear that the number of “completers” in Table 3 was counted before 4E visit (Day 29 of Part II) instead of the final day for Part II study.

For dose response durability to Month 7 using CS29 Part II data, it is hard to draw any conclusions based on Tables 12 and 13, and Figures 4 and 5, due to not using the completers’ data. For example, the sponsor used only 39% and 12% of the 529 subjects (N=205, and N=64) to represent the durability from Month 0 to Month 5 and Month 7, respectively.

3.2 Evaluation of Safety

All safety analyses were performed using the safety dataset.

3.2.1 Sponsor’s Brief Summary of Adverse Events

The overall incidence of subjects with adverse events was generally similar across the placebo and desmopressin dose groups. The number of adverse events was similar across the desmopressin dose groups and higher than in the placebo group.

Across treatment groups, 59% (placebo) to 69% (100 µg) of subjects reported one or more treatment-emergent adverse events, with an overall incidence of 63% during Part I of the study. An overall summary of treatment-emergent adverse events during Part I is presented by treatment group in [Table 16](#).

Table 16 Summary of Treatment-Emergent Adverse Events (Part I).

	Placebo (N=160)	10 µg (N=163)	25 µg (N=158)	50 µg (N=158)	100 µg (N=160)
All AEs	94 (59%)	100 (61%)	98 (62%)	103 (65%)	110 (69%)
Deaths	0	0	0	0	0
SAEs	1 (1%)	2 (1%)	1 (1%)	2 (1%)	0
AEs leading to discontinuation	8 (5%) ^a	6 (4%)	2 (1%) ^b	13 (8%) ^b	13 (8%) ^b
Severe AEs	4 (3%)	8 (5%)	5 (3%)	13 (8%)	7 (4%)
Adverse drug reactions (ADRs)	62 (39%)	62 (38%)	61 (39%)	73 (46%)	80 (50%)

AE = adverse event;

SAE = serious adverse event;

ADR = AE assessed by the Investigator as possibly/probably related to study drug

a. Three placebo subjects discontinued soon after beginning Part II and initiation of active study drug: Subject (b) (6) in placebo-to-50 µg (constipation), Subject (b) (6) in placebo-to-50 µg (hyponatraemia), and Subject (b) (6) in placebo-to-100 µg (fatigue and headache). These subjects are not counted in this table as discontinuing during Part I.

b. One subject in the group was counted as discontinuing during both Part I and Part II and was removed from the Part I discontinuations.

Ref. Table 36 in fe992026cs29-report-body-1.

3.2.2 Hyponatraemia

FDA medical officer indicated that the main safety endpoint of concern is hyponatremia, specifically Na < 125 and between 125 and 130. Hyponatremia (e.g. serum sodium < 130mmol/L) is a well described adverse reaction associated with the use of all desmopressin formulations. Severe hyponatremia (e.g. serum sodium < 125mmol/L) or a rapid drop in serum sodium from baseline are especially serious as they can lead to seizures and cerebral edema. Hyponatremia with seizures has been seen in children especially with the nasal spray formulation which results in higher serum levels of desmopressin.

Sponsor's analysis on hyponatraemia

A total of 34 (4%) subjects developed hyponatraemia, with serum sodium levels below 130 mM, during Part I. The descriptive summary of serum sodium levels in Part I is presented by treatment group in Table 17.

Table 17 Incidence of Hyponatraemia (CS29 Part I)

Serum Sodium	Placebo (N=160)	10 µg (N=163)	25 µg (N=158)	50 µg (N=158)	100 µg (N=160)
<130 mmol/L	2 (1%)	1 (1%)	2 (1%)	11 (7.0%)	18 (11%)
<130 but ≥125 mmol/L	1 (1%)	1 (1%)	2 (1%)	7 (4%)	14 (9%)
<125 mmol/L	1 (1%)	0	0	4 (3%)	4 (3%)

Ref. Table 49 in fe992026cs29-report-body-1 ISE.

For hyponatraemia in CS29 and CS31, a summary of serum sodium levels is presented by treatment group in Table 18.

Table 18 Incidence Within Categories of Minimum Serum Sodium Values. Ref ISSE

Serum Sodium (mmol/L)	Placebo (N=160) n (%)		10 µg (N=195) n (%)		25 µg (N=227) n (%)		50 µg (N=217) n (%)		100 µg (N=224) n (%)	
	Serum Sodium Monitoring Criteria Applied									
	No	Yes ^a	No	Yes ^a	No	Yes ^a	No	Yes ^a	No	Yes ^a
Observed N	158 (98.8)	131 (81.9)	192 (98.5)	156 (80.0)	226 (99.6)	182 (80.2)	215 (99.1)	157 (72.4)	219 (97.8)	145 (64.7)
≥135	147 (91.9)	127 (79.4)	163 (83.6)	138 (70.8)	176 (77.5)	148 (65.2)	141 (65.0)	125 (57.6)	137 (61.2)	114 (50.9)
<135	11 (6.9)	4 (2.5)	29 (14.9)	18 (9.2)	50 (22.0)	34 (15.0)	74 (34.1)	32 (14.7)	82 (36.6)	31 (13.8)
130-134	10 (6.3)	4 (2.5)	25 (12.8)	18 (9.2)	45 (19.8)	33 (14.5)	52 (24.0)	29 (13.4)	56 (25.0)	28 (12.5)
125-129	0	0	3 (1.5)	0	5 (2.2)	1 (0.4)	16 (7.4)	3 (1.4)	22 (9.8)	3 (1.3)
<125	1 (0.6)	0	1 (0.5)	0	0	0	6 (2.8)	0	4 (1.8)	0

a. Excludes subjects <50 years of age whose Day 0 serum sodium was <135 mmol/L and subjects 50 years of age whose serum sodium was <135 mmol/L on Days 0, 4, and 28. Subjects 50 years of age with missing sodium measurements on Days 4 and 28 were also excluded.

Ref. Table 19 in ISS.

3.2.3 Reviewer’s finding

This reviewer performed statistical test for hyponatremia using the safety population as shown in Table 19 below.

Table 19 Incidence of Hyponatraemia, CS29 Part I (Safety population)

Serum Sodium	Placebo (n=160)	10 µg (n=163)	25 µg (n=158)	50 µg (n=158)	100 µg (n=160)
< 130 mmol/L	2 (1%)	1 (1%)	2 (1%)	12 (8%)	18 (11%)
OR (95% CI)		0.49 (0.01, 9.47)	1.01 (0.07, 14.13)	6.46 (1.40, 60.42)	9.96 (2.32, 90.01)
p-value (2-sided)		0.6204	1	0.0060	0.0003
< 130 but ≥ 125 mmol/L	1 (1%)	1 (1%)	2 (1%)	9 (6%)	14 (9%)
OR (95% CI)		0.98 (0.01, 77.52)	2.03 (0.11, 121)	9.55 (1.30, 423.6)	15.16 (2.25, 648.6)
p-value (2-sided)		1	0.6215	0.01018	0.0008
< 125 mmol/L	1 (1%)	0	0	3 (2%)	4 (3%)
OR (95% CI)		NA	NA	3.07 (0.24, 162.6)	4.06 (0.40, 202)
p-value (2-sided)				0.3695	0.3711

Table 19 shows that patients treated with 25 µg or less drug had similar hyponatraemia incidence as to those with placebo. However, patients in 50 µg and 100 µg dose groups had statistically significant more hyponatraemia incidence (< 130 mM) than in the placebo group.

3.2.4 Safety Conclusions

FDA medical officer indicated that the main safety endpoint of concern is hyponatremia, specifically Na < 125 and between 125 and 130. There are significantly more hyponatremia

(<130 mM) in patients treated with 50 µg or higher dose of nocdurna as compared to that in placebo group.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Too few subjects (13 to 18 subjects per treatment group) did not have nocturnal polyuria to make meaningful comparisons.

4.1 Gender, Race and Age

Too few subjects were non-Caucasian to make meaningful comparisons between Caucasians and non-Caucasians.

4.1.1 Sponsor's Efficacy Subgroup Analysis

Analysis of Primary Efficacy Endpoints by Age Stratification

The sponsor did the analysis on the primary efficacy endpoints by age stratification. For both co-primary endpoints, superiority to placebo was observed at significant level 0.05 only for the 100 µg group for both age stratification factors (see Tables 20 and 21, respectively).

Table 20 Change from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids (ITT Analysis Dataset in Part I)

Nocturnal Voids	Placebo	10 µg	25 µg	50 µg	100 µg
Age <65 years	(N=81)	(N=80)	(N=76)	(N=77)	(N=68)
Mean Δ (SD)	-0.94 (1.067)	-1.05 (1.049)	-1.09 (1.162)	-1.29 (1.038)	-1.69 (1.115)
p-value vs. placebo		p=0.3703	p=0.4254	p=0.1230	p<0.0001*
Age ≥65 years	(N=75)	(N=75)	(N=76)	(N=71)	(N=78)
Mean Δ (SD)	-0.77 (1.040)	-0.58 (1.043)	-0.91 (1.088)	-1.06 (1.328)	-1.22 (1.269)
p-value vs. placebo		p=0.3362	p=0.5163	p=0.0880	p=0.0085*

Ref. Table 21 in fe992026cs29-report-body-1.

Table 21 Proportion of Subjects with >33% Reduction from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids (ITT, CS29 Part I).

	Placebo	10 µg	25 µg	50 µg	100 µg
Age <65 years	(N=81)	(N=80)	(N=76)	(N=77)	(N=68)
33% responder	43 (53%)	46 (58%)	40 (53%)	45 (58%)	56 (82%)
p-value vs. placebo		p=0.5748	p=0.9762	p=0.5330	p=0.0003*
Age ≥65 years	(N=75)	(N=75)	(N=76)	(N=71)	(N=78)
33% responder	30 (40%)	27 (36%)	36 (47%)	34 (48%)	47 (60%)
p-value vs. placebo		p=0.6455	p=0.3428	p=0.3043	p=0.0124*

* Statistically significant difference versus placebo, p≤0.05.

Note: Odds ratio and 95% CI were based on logistic regression adjusting for age, absence/presence of nocturnal polyuria, and baseline number of nocturnal voids.

Ref. Table 22 in fe992026cs29-report-body-1.

Analysis of Primary Efficacy Endpoints by Gender

The sponsor did a post-hoc analysis of the co-primary endpoint with respect to gender.

Among females, efficacy was demonstrated for both co-primary endpoints for all but the lowest dose of desmopressin. Among males, statistically significant differences from placebo were observed for the 100 µg group in the reduction in mean number of nocturnal voids (p=0.0049) and the proportion of male subjects with >33% reduction in mean number of nocturnal voids

(p=0.0477). Based on these gender differences, the MED (minimum effective dose) for females is 25 µg and the MED for males is 100 µg.

A summary of the mean change from baseline to the final visit in mean number of nocturnal voids and the proportion of subjects with >33% reduction in the mean number of nocturnal voids from baseline to the final visit is presented by gender in [Table 22](#).

Table 22 Change from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids and Proportion of Subjects with >33% Reduction from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids by Gender (ITT, CS29 Part I)

Co-Primary Endpoints	Placebo	10 µg	25 µg	50 µg	100 µg
Females	(N=66)	(N=73)	(N=65)	(N=71)	(N=66)
Nocturnal Voids					
Mean Δ (SD)	-0.88 (1.01)	-1.15 (1.07)	-1.22 (1.06)	-1.23 (1.06)	-1.51 (1.14)
Median	-0.67	-1.00	-1.33	-1.00	-1.33
Minimum, maximum	(-3.3, 1.0)	(-4.3, 1.0)	(-3.3, 1.0)	(-4.0, 2.0)	(-5.0, 1.0)
p-value vs. placebo ^a		p=0.0721	p=0.0200*	p=0.0091*	p<0.0001*
33% Responder Rate	28 (42%)	41 (56%)	40 (62%)	42 (59%)	51 (77%)
p-value vs. placebo ^b		p=0.0880	p=0.0197*	p=0.0405*	p<0.0001*
Males					
Females	(N=90)	(N=82)	(N=87)	(N=77)	(N=80)
Nocturnal Voids					
Mean Δ (SD)	-0.84 (1.09)	-0.54 (0.987)	-0.83 (1.15)	-1.13 (1.30)	-1.38 (1.28)
Median	-1.00	-0.67	-0.67	-1.00	-1.33
Minimum, maximum	(-4.0, 1.7)	(-3.0, 2.3)	(-3.7, 2.3)	(-5.0, 1.3)	(-4.3, 4.3)
p-value vs. placebo ^a		p=0.0944	p=0.5894	p=0.3778	p=0.0049*
33% Responder Rate	45 (50%)	32 (39%)	36 (41%)	37 (48%)	52 (65%)
p-value vs. placebo ^b		p=0.1502	p=0.2225	p=0.7375	p=0.0477*

Δ = change; SD = standard deviation

* Statistically significant difference versus placebo, p≤0.05.

a. p-value comparisons with placebo were based on an ANCOVA model adjusting for nocturnal polyuria (Y/N), age (<65 years, ≥65 years), and baseline number of voids; no adjustment for multiplicity applied.

b. p-value comparisons with placebo were based on a Wald test in a logistic regression model adjusting for nocturnal polyuria (Y/N), age (<65 years, ≥65 years), and baseline number of voids; no adjustment for multiplicity applied.

Ref. Table 25 in fe992026cs29-report-body-1.

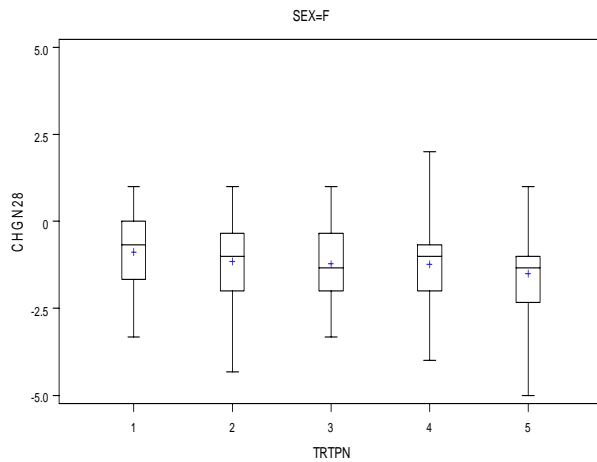
4.1.2 This reviewer's subgroup analyses

The sponsor showed different treatment effects by gender (see Table 24) and different efficacious dosages from overall analyses. In order to explain the difference between the overall analysis and the analyses by sex this reviewer checked the distributions of the mean number of voids from baseline to Day 28 on ITT population for each gender group (CS29 Part I). Comparison of the distributions revealed that there are some deviations in the distribution of mean number of voids of females from that of males as well as from the distribution of the

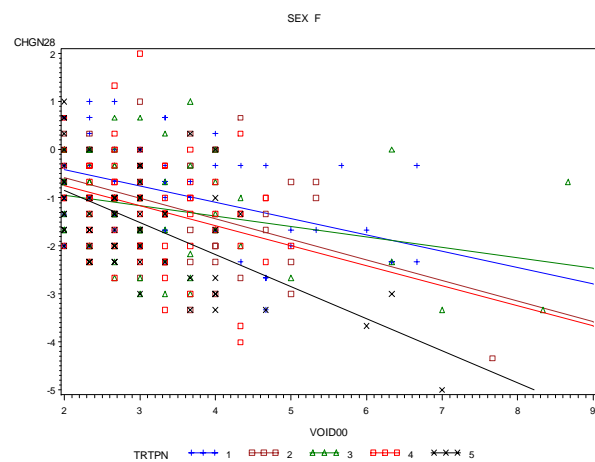
overall ITT population as shown in Figure 8 A and C. These differences are also shown from the dependence of treatment effect on baseline values by gender (Figure 8 B and D).

Figure 8 Plots of Changes from Baseline to Final Visit (Day 28) in Mean Number of Nocturnal Voids by Sex (CS29 Part I, ITT population). A and C: boxplots by treatment. B and D: plots of changes from Baseline to Day 28 versus baseline values.

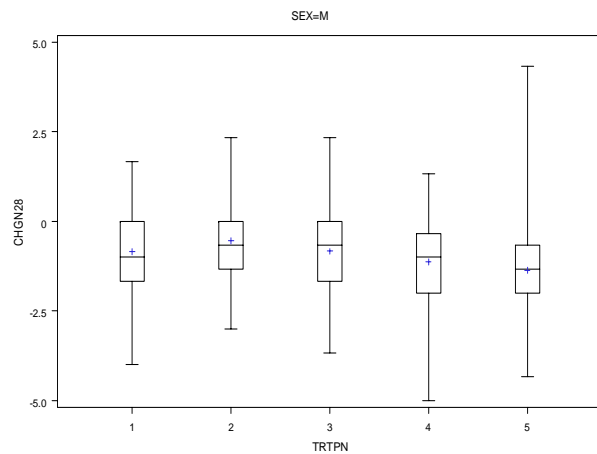
A (females)



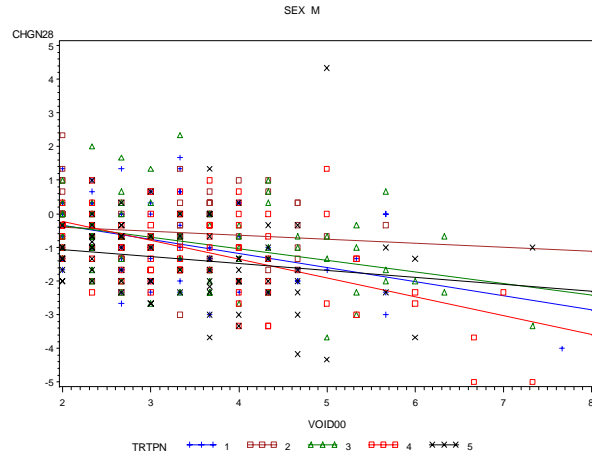
B (females)



C (males)



D (males)



For CS29 Part I, the overall treatment-by-gender interactions for the two co-primary endpoints were not significant at the 10% level (p-values are 0.1760 and 0.1049 for the Mean change in nocturnal void number and the 33% responder proportion, respectively), as shown in Figures Tables 9 and 10, respectively. However, the high response rate of patients in the placebo group leads to various results in significance for testing the treatment-by-gender interaction when

comparing each dose against placebo. It is observed in the pair-wise comparison that at the 10% level for the mean change in number of nocturnal voids the treatment-by-gender interaction was not significant at dose 100 µg (p-value > 0.16) and 50 µg (p-value > 0.15), respectively, but significant at the dose 25 µg (p-value < 0.06). For the 33% responder proportion endpoint, the treatment-by-gender interaction was significant at the 10% level for every dose of nocturna versus placebo. The female subjects have higher treatment response than males for both co-primary endpoints.

Figure 9 Mean Change in Number of Nocturnal Voids from Baseline to Final Visit (Day 28) by Treatment for Gender (ITT, CS29 Part I).

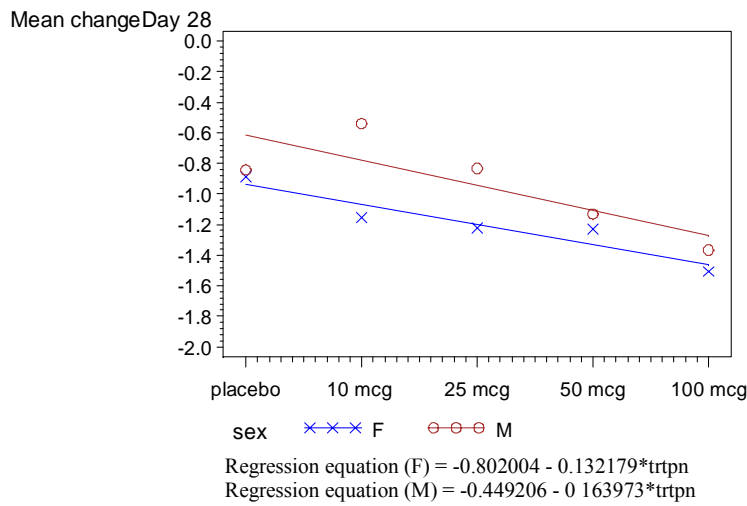
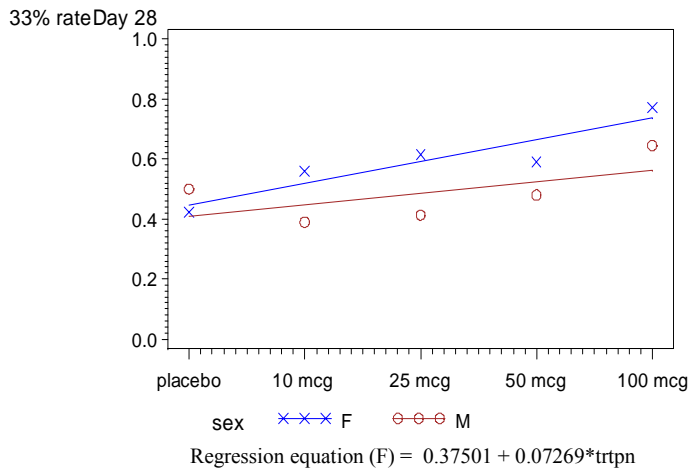


Figure 10 Proportion of subjects with >33% Reduction in Mean Number of Nocturnal Voids from Baseline to Final Visit (Day 28) by Treatment for Gender (ITT, CS29 Part I)



Regression equation (M) = $0.37157 + 0.03815 \cdot \text{trtpn}$

APPEARS THIS WAY ON ORIGINAL

For the subgroup analysis on the two age groups (<65 years, ≥65 years), the distributions of the mean number of voids from baseline to Day 28 and the trends of the mean nocturnal number of voids against the baseline values by treatment on ITT population were similar to each other (data not shown) and to the overall distribution as shown in Figure 7. The overall treatment-by-age interaction for the two co-primary endpoints were not significant at 10% level (p-values are 0.3010 and 0.3395 for the Mean change in nocturnal void number and the 33% responder proportion, respectively), as shown in Figures 11 and 12, respectively. The young subjects (<65 years) have higher treatment response than older patients (≥65 years) in both co-primary efficacy endpoints.

Figure 11 Mean Change in Number of Nocturnal Voids from Baseline to Final Visit (Day 28) by Treatment for Age Stratification (ITT, CS29 Part I).

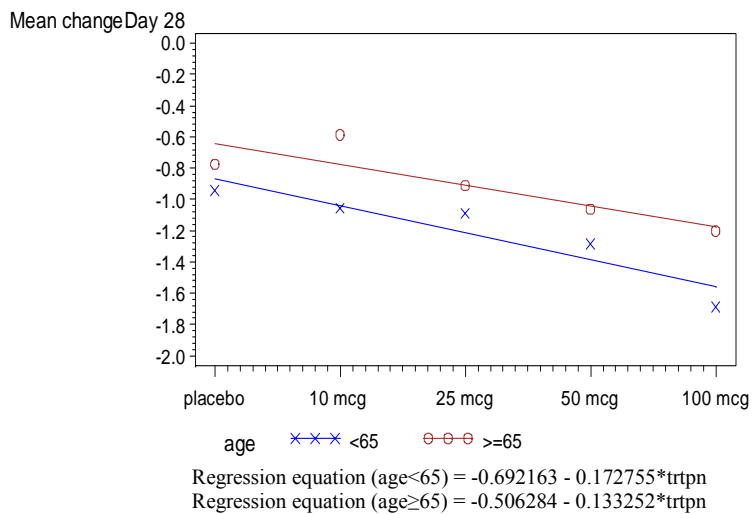
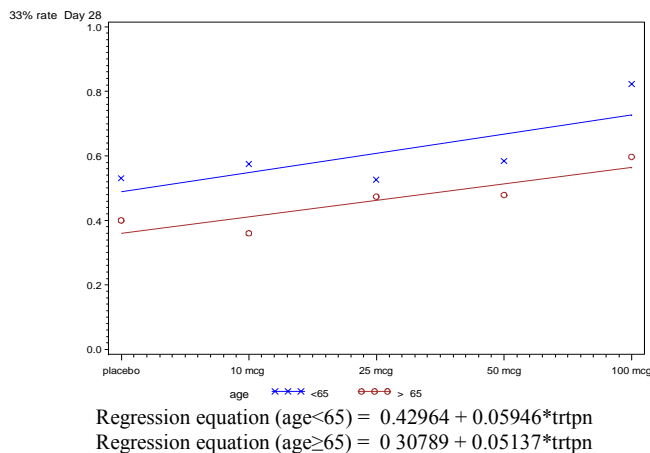


Figure 12 Proportion of subjects with >33% Reduction in Mean Number of Nocturnal Voids from Baseline to Final Visit (Day 28) by Treatment for Age Stratification (ITT, CS29 Part I)



4.1.3 Safety Subgroup Analysis

The sponsor listed the incidence of hyponatraemia in the placebo and the 4 doses treatment groups by gender and age using the safety data either CS29 Parts 1 and 2 or CS29 and CS31. However, such comparisons are not reasonable because there were neither a placebo group in CS29 Part II nor in CS31. Therefore, this reviewer summarized the incidence of hyponatraemia in the placebo and the 4 doses treatment groups by gender and age using the safety data of CS29 Parts 1 as shown in Table 23 and Table 24, respectively.

Table 23 Incidence of Hyponatraemia by Gender, CS29 Part I (Safety population)

Female (21)					
Serum Sodium	Placebo (n=67)	10 µg (n=76)	25 µg (n=67)	50 µg (n=80)	100 µg (n=73)
< 130 mmol/L	2 (3%)	1 (1%)	1 (1%)	9 (11%)	8 (11%)
OR (95% CI) p-value (2-sided)		0.44 (0.01, 8.55) 0.5998	0.49 (0.01, 9.72) 1	4.09 (0.80, 40.24) 0.06678	3.97 (0.75, 39.73) 0.10
< 130 but ≥ 125 mmol/L	1 (1%)	1 (1%)	1 (1%)	6 (7%)	6 (8%)
OR (95% CI) p-value (2-sided)		0.88 (0.01, 70.11) 1	1 (0.01, 79.67) 1	5.30 (0.62, 249.8) 0.1263	5.85 (0.68, 275.9) 0.118
< 125 mmol/L	1 (1%)	0 (0%)	0 (0%)	3 (4%)	2 (3%)
OR (95% CI) p-value (2-sided)		NA	NA	2.56 (0.20, 137) 0.6258	1.85 (0.09, 111.3) 1
Male (14)					
Serum Sodium	Placebo (n=93)	10 µg (n=87)	25 µg (n=91)	50 µg (n=78)	100 µg (n=87)
< 130 mmol/L	0 (0%)	0 (0%)	1 (1%)	3 (4%)	10 (11%)
OR (95% CI) p-value (2-sided)		NA	NA	NA	NA
< 130 but ≥ 125 mmol/L	0 (0%)	0 (0%)	1 (1%)	3 (4%)	8 (9%)
OR (95% CI) p-value (2-sided)		NA	NA	NA	NA
< 125 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)
OR (95% CI) p-value (2-sided)		NA	NA	NA	NA

Table 24 Incidence of Hyponatraemia by Age, CS29 Part I (Safety population)

Age, <65					
Serum Sodium	Placebo (n=84)	10 µg (n=85)	25 µg (n=80)	50 µg (n=82)	100 µg (n=75)
< 130 mmol/L	0 (0%)	0 (0%)	0 (0%)	4 (5%)	2 (3%)
OR (95% CI) p-value (2-sided)		NA	NA	NA	NA
< 130 but ≥ 125 mmol/L	0 (0%)	0 (0%)	0 (0%)	3 (4%)	2 (3%)
OR (95% CI) p-value (2-sided)		NA	NA	NA	NA
< 125 mmol/L	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
OR (95% CI) p-value (2-sided)		NA	NA	NA	NA
Age, ≥65					
Serum Sodium	Placebo (n=76)	10 µg (n=78)	25 µg (n=78)	50 µg (n=76)	100 µg (n=85)
< 130 mmol/L	2 (3%)	1 (1%)	2 (3%)	8 (11%)	16 (19%)
OR (95% CI) p-value (2-sided)		0.48 (0.01, 9.45) 0.6176	0.97 (0.07, 13.76) 1	4.32 (0.82, 43.11) 0.09774	8.49 (1.89, 78.8) 0.0009
< 130 but ≥ 125 mmol/L	1 (1%)	1 (1%)	2 (3%)	6 (8%)	12 (14%)
OR (95% CI) p-value (2-sided)		0.97 (0.01, 77.46) 1	1.97 (0.10, 118) 1	6.36 (0.74, 299.6) 0.1163	12.19 (1.72, 533.9) 0.0028
< 125 mmol/L	1 (1%)	0 (0%)	0 (0%)	2 (3%)	4 (5%)
OR (95% CI) p-value (2-sided)		NA	NA	2.02 (0.10, 121.2) 1	3.68 (0.35, 184.8) 0.3711

In CS29 Part I safety data, no statistical significance is observed in pyhonatremia by nocturna treatment vs. placebo in neither sex. For the age groups, significant difference of treatment vs. placebo were observed only at 100 µg for patients ≥65 years.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Efficacy

Based on the pre-specified multiple comparison scheme in Study CS29 Part I, we conclude that only the highest dose of nocdurna (100 µg) showed superiority versus placebo on both co-primary efficacy endpoints (mean number of nocturnal voids from baseline to Day 28 and proportion of subjects with >33% reduction in the mean number of nocturnal voids at Day 28) at the two-sided 0.05 significance level. The FDA medical officer has identified safety concerns, primarily hyponatremia, for this dose. Although the results from pair-wise comparisons between doses below 100 µg and placebo failed to firmly establish the efficacy of these doses, there is sufficient statistical evidence to support a positive dose-response; the dose response slope across all the doses (10, 25, 50, and 100 µg) was statistically significantly different from zero for both co-primary efficacy endpoints. Treatment differences across doses were approximately linearly proportional. This suggests that doses below 100 µg may have utility for some patients in this population.

For dose response durability to Month 7 using CS29 Part II data, it is hard to draw any conclusions based on sponsor's Tables 12 and 13, and Figures 4 and 5, due to not using the completers' data. For example, the sponsor used only 39% and 12% of the 529 subjects (N=205, and N=64) to represent the durability from Month 0 to Month 5 and Month 7, respectively.

Treatment-by-gender interaction p-values were not significant at the 10% level for both co-primary endpoints. However, the sponsor's subgroup analyses by gender suggested different treatment responses for males and females. In females nocdurna was nominally superior to placebo on both co-primary endpoints at doses of 25, 50 and 100 µg, but in males only at the highest drug dose 100 µg.

It is noted that the subjects in the placebo group had very high treatment response as compared to subjects treated with nocdurna:

- reduction in mean number of nocturnal voids from baseline evaluation to Day 28
-0.86 (placebo) compared to -0.83 (10 µg), -1.00 (25 µg), -1.18 (50 µg) and -1.43 (100 µg)
- proportion of subjects with >33% reduction in the mean number of nocturnal voids from baseline to Day 28
47% (placebo) compared to 47% (10 µg), 50% (25 µg), 53% (50 µg) and 71% (100 µg).

Safety

FDA medical officer indicated that the main safety endpoint of concern is hyponatremia, specifically Na < 125 and between 125 and 130. There are significantly more hyponatremia (<130 mM) in patients treated with 50 µg or higher dose of nocdurna as compared to that in placebo group. For the age groups, significant incidence rates by treatment vs. placebo were observed only at 100 µg for patients ≥65 years.

5.2 Conclusions and Recommendations

Efficacy

Based on the pre-specified multiple comparison scheme in Study CS29 Part I, we conclude that only the highest dose of nocdurna (100 µg) showed superiority versus placebo on both co-primary efficacy endpoints (mean number of nocturnal voids from baseline to Day 28 and proportion of subjects with >33% reduction in the mean number of nocturnal voids at Day 28) at the two-sided 0.05 significance level for the overall ITT population in CS29 Part I. The FDA medical officer has identified safety concerns, primarily hyponatremia, for this dose. Although the results from pair-wise comparisons between doses below 100 µg and placebo failed to firmly establish the efficacy of these doses, there is sufficient statistical evidence to support a positive dose-response; the dose response slope across all the doses (10, 25, 50, and 100 µg) was statistically significantly different from zero for both co-primary efficacy endpoints. Treatment differences across doses were approximately linearly proportional. This suggests that doses below 100 µg may have utility for some patients in this population.

For dose response durability to Month 7 using CS29 Part II data, it is hard to draw any conclusions based on sponsor's Tables 12 and 13, and Figures 4 and 5, due to not using the completers' data. For example, the sponsor used only 39% and 12% of the 529 subjects (N=205, and N=64) to represent the durability from Month 0 to Month 5 and Month 7, respectively.

Treatment-by-gender interaction p-values were not significant at the 10% level for both co-primary endpoints. However, the sponsor's subgroup analyses by gender suggested different treatment responses for males and females. In females nocdurna was nominally superior to placebo on both co-primary endpoints at doses of 25, 50 and 100 µg, but in males only at the highest drug dose 100 µg.

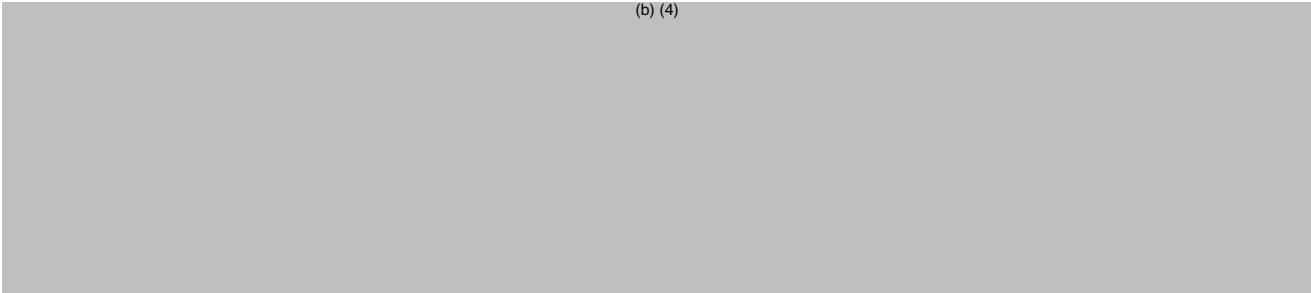
Safety Conclusion:

FDA medical officer indicated that the main safety endpoint of concern is hyponatremia, specifically Na < 125 and between 125 and 130. There are significantly more hyponatremia (<130 mM) in patients treated with 50 µg or higher dose of nocdurna as compared to that in placebo group. For the age groups, significant incidence rates by treatment vs. placebo were observed only at 100 µg for patients ≥65 years.

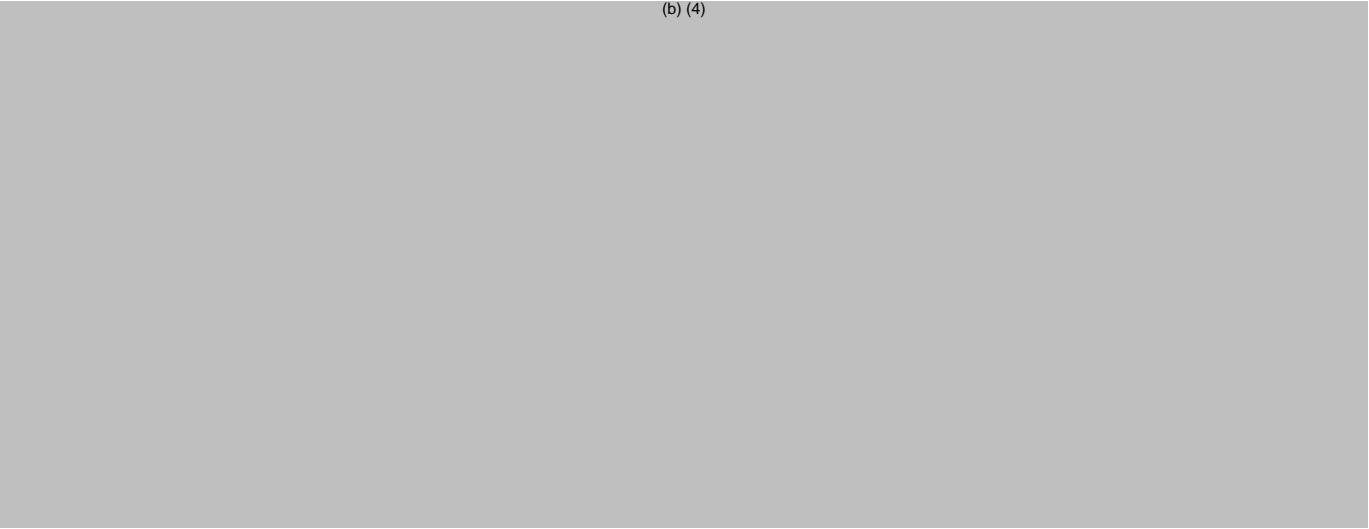
Recommendations for Labeling.

ref. Sponsor's Proposed Labeling section 14 (submitted on 06/24/2009)

(b) (4)



(b) (4)



No additional comments for the sponsor's labeling.

APPENDIX

Appendix I: List of Abbreviations and Definitions of Terms

AE	adverse event
ADR	adverse drug reaction
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the plasma concentration-time curve
AVP	arginine vasopressin
BP	blood pressure
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
CI	confidence interval
C _{max}	maximal observed plasma concentration
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EoS	End-of-Study
FWE	family wise error
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
Hgb	hemoglobin
ICF	informed consent form
ICH	International Conference on Harmonisation
ICIQ-N	The International Consultation on Incontinence Modular Questionnaire - Nocturia
ICS	International Continence Society
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
LOCF	last observation carried forward
MED	minimum effective dose
MedDRA	Medical Dictionary for Regulatory Activities
NQoL	Nocturia Quality of Life Questionnaire
NSAID	non-steroidal anti-inflammatory drug
OAB	overactive bladder
OC	observed cases
PD	pharmacodynamics
PK	pharmacokinetics
PP	Per-Protocol

PSQI	Pittsburgh Sleep Quality Index
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SF-12v2	Short Form-12 version 2
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SSRI	selective serotonin reuptake inhibitor
$t_{1/2}$	terminal half-life
T_{max}	time of maximal observed plasma concentration
ULN	upper limit of normal
UII	urinary urge incontinence
WBC	white blood cell
WebEZ	web-based centralized patient randomization system
First sleep period	Time elapsed from bedtime to either first void or morning arising
Hyponatraemia	Serum sodium value below the lower limit of the normal reference range; for this study, hyponatraemia referred to a serum sodium <130 mmol/L, with an emphasis on values <125 mmol/L
Nocturnal enuresis	A condition in which a person who has bladder control while awake urinates while asleep
Nocturnal polyuria	Increased nocturnal output of urine. In this protocol, it was defined as a ratio of nighttime urine volume over the 24-hour urine volume to be equal to or greater than 33%
Nocturnal urine	The total urine volume from 5 minutes after bedtime until rising in the morning, including the first void within 30 minutes of rising
Nocturnal void	A void occurring from 5 minutes after bedtime until rising in the morning with the intention of getting up
Nocturia	The complaint that an individual has to wake up at night one or more times to void
Overactive bladder	Urgency, with or without urge incontinence, usually accompanied by frequency and nocturia
Polydipsia	Excessive fluid consumption, defined as fluid intake leading to urine production exceeding 40mL/kg body weight/24 hours
Urine osmolality	Concentration of electrolytes in urine
Uroflometry	A measurement of the rate of urine expelled from the bladder during bladder emptying. Flow rate is measured as mL/sec voided

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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

/s/

WEI LIU
04/01/2010

THOMAS J PERMUTT
04/02/2010
See Dr. Sahlroot's secondary review, with which I concur.

NDA: 22-517	Submission Date(s): 06/19/2009
Brand Name	NOCDURNA
Generic Name	Orally Disintegrating Desmopressin Tablet
Clinical Pharmacology Reviewer	Ritesh Jain, Ph.D.
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
Clinical Pharmacology Team Leader	Sally Choe, Ph.D.
Pharmacometrics Team Leader (Acting)	Christine Garnett, Pharm.D.
OCP Division	Clinical Pharmacology–II
OND division	Metabolism and Endocrinology Products
Sponsor	Ferring Pharmaceuticals
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Orally Disintegrating Tablet: 25 µg and 100 µg
Proposed Indication	NOCDURNA is indicated for treatment of nocturia in adults
Proposed Dosing	Women 25 µg daily at bedtime Men < 65 100 µg daily at bedtime Men ≥ 65 100 µg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 22-517, dated 06/19/2009, and finds it acceptable provided that a mutual agreement regarding the label language can be reached between the sponsor and the Agency. In addition, based on the reanalysis of efficacy and safety data Office of Clinical Pharmacology recommends following dosing regiment:

- 1) 25 µg QD for women
- 2) 50 µg as the starting dose in men. The dose may be titrated up to 100 µg dose by weekly dose escalations in 25 µg increments only for men less than 65 years to optimize efficacy.
- 3) Dose escalation above the 50 µg starting dose for elderly men (age ≥ 65 years) is not recommended.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The purpose of this application (NDA 22-517) is to provide data to support sublingually disintegrating oral tablet of desmopressin (NOCDURNA or Minirin Melt or Desmopressin Melt) for the treatment of adult nocturia. Desmopressin (dDAVP, 1-deamino-8-D-arginine vasopressin) is a synthetic analogue of the naturally occurring antidiuretic hormone, 8-arginine vasopressin. Desmopressin acts by increasing reabsorption of water in the distal and collecting tubules of the kidney, thereby concentrating the urine and decreasing nocturnal urine output. Desmopressin has been marketed in the United States and around the world for more than 30 years for different indications and in different formulations such as nasal spray, intravenous formulation, and as an oral tablet formulation. Currently approved indications for desmopressin includes: central diabetes insipidus (CDI), primary nocturnal enuresis (PNE), type I von Willebrand's disease, and hemophilia A.

The proposed indication for this NDA is adult nocturia, with the aim of decreasing nocturnal urinary frequency and volume, thereby prolonging the time to first nocturnal void in patients with this condition. NOCDURNA is a freeze-dried orally disintegrating tablet which is designed to dissolve rapidly in the mouth when placed under the tongue. The sponsor is planning to market NOCDURNA in two dosage strengths 25 µg and 100 µg. The sponsor proposed the following gender-based NOCDURNA doses:

- Women: 25 µg sublingual tablet, once daily at bedtime
- Men < 65: 100 µg sublingual tablet, once daily at bedtime.
- Men ≥ 65: 100 µg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment.

The clinical development program for this NDA is supported by one Phase 3 safety and efficacy trial (FE992026 CS29) and 17 clinical pharmacology trials. The Phase 3 trial

was conducted in 2 parts. Part I was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study investigating the efficacy and safety of 4 doses (10 µg, 25 µg, 50 µg, or 100 µg) of desmopressin melt administered for 28 days for the treatment of adult nocturia. There were two co-primary endpoints. The first co-primary endpoint was change from baseline in the mean number of nocturnal voids, and the second was proportion of subjects with > 33% reduction in the mean number of nocturnal voids (referred as 33% responder rate), on Day 28 of the trial. Upon completion of Part I, all subjects on active treatment were allowed to continue into Part II on the same treatment for approximately 1 to 6 months. Subjects assigned to placebo in Part I were randomly assigned to 1 of the 4 active treatments in Part II. Study CS29 was followed by a long-term open-label safety efficacy study CS31. In Phase 3 trial lowering of serum sodium levels (sodium level < 130 mM) or Hyponatremia is identified as one of the treatment related safety issue. Hyponatremia may have serious consequences such as seizures and coma that can lead to death.

Dosing Recommendation

The sponsor has proposed a gender-based NOCDURNA doses. Based on the analysis of safety and efficacy data from the Phase 3 trial, the sponsor is proposing 25 µg dose for women and 100 µg for men. Sponsor's rationale for dose selection was based on statistically significant difference between placebo and treatment arm for both the co-primary endpoints at day 28. However, upon reanalysis of both efficacy and safety data, we recommend the following dosing regimen for NOCDURNA:

- 1) 25 µg QD for women.
- 2) 50 µg as the starting dose in men. The dose may be titrated up to 100 µg dose by weekly dose escalations in 25 µg increments only for men less than 65 years to optimize efficacy.
- 3) Dose escalation above the 50 µg starting dose for elderly men (age ≥ 65 years) is not recommended.

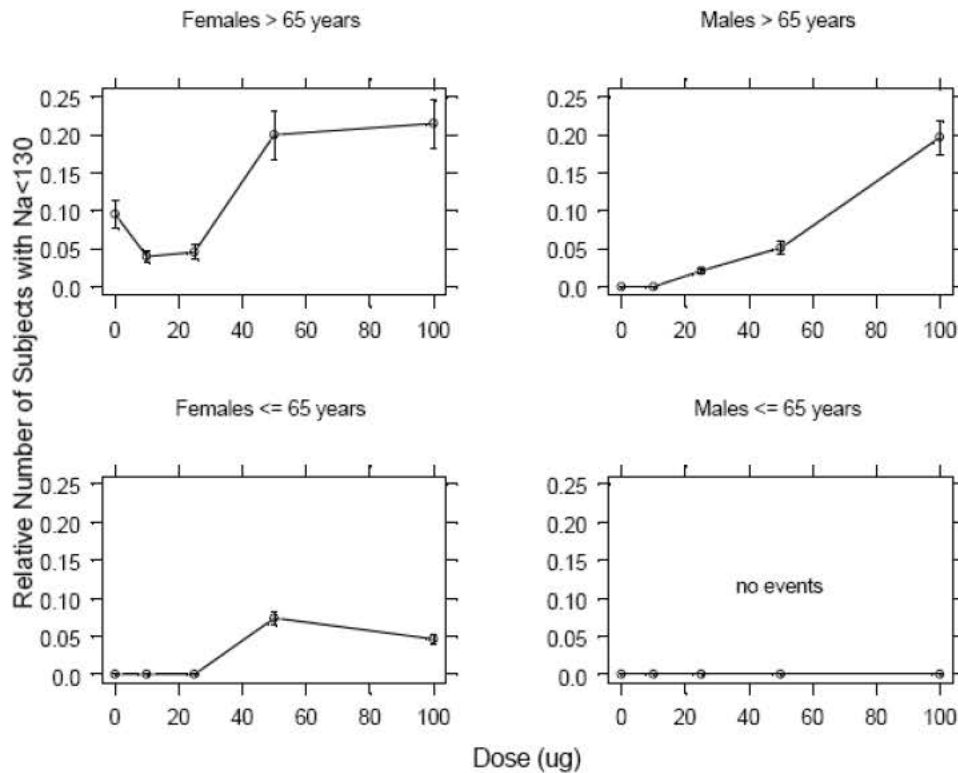
The proposed dosing regimen for women is acceptable because 25 µg was shown to be effective to that of placebo. The incidence of hyponatremia at this dose was comparable to placebo.

We recommend a reduced dose of 50 µg in men as the starting dose because the drug was shown to be effective by dose-response analysis as described below. The dose could be increased to 100 µg to meet treatment goals in men of age ≤ 65 years. There was no incidence of hyponatremia across all doses in this age group (**Figure 1**). However, for elderly men (age > 65 years), a dose-response analysis showed that the risk of hyponatremia increases with increasing desmopressin dose (**Figure 1**). At the sponsor's proposed dose of 100 µg, 20% of elderly men experienced hyponatremia. This was 4-fold higher than the proportion of elderly women who developed hyponatremia at the sponsor's proposed dose of 25 µg. Therefore, we propose 50 µg dose without titration because at this dose only 5% of the elderly men experienced hyponatremia which is comparable to elderly women at the 25 µg dose and the placebo hyponatremia rate.

The sponsor has proposed a 100 µg dose with sodium monitoring on day 4 and at one month of treatment in elderly men. We are concerned, that sodium monitoring may not

reduce the risk of hyponatremia. Therefore, we recommend a lower dose of 50 µg without sodium monitoring.

Figure 1: Proportion of subjects experiencing hyponatremia at 0-100 µg desmopressin doses stratified by gender and age.



Dose- Response for Efficacy

There was a clear evidence of dose-response for effectiveness in both men and women in the short term pivotal efficacy trial (Part 1 of CS 29) and the long term trial (Part 2 of CS 29). Sponsor’s rationale for dose selection was based on subgroup analysis for efficacy, where females at 25 µg and males at 100 µg showed statistically significant difference for both the co-primary endpoints at day 28 (**Table 1**).

Table 1: Sponsor’s analysis of primary efficacy endpoints by gender

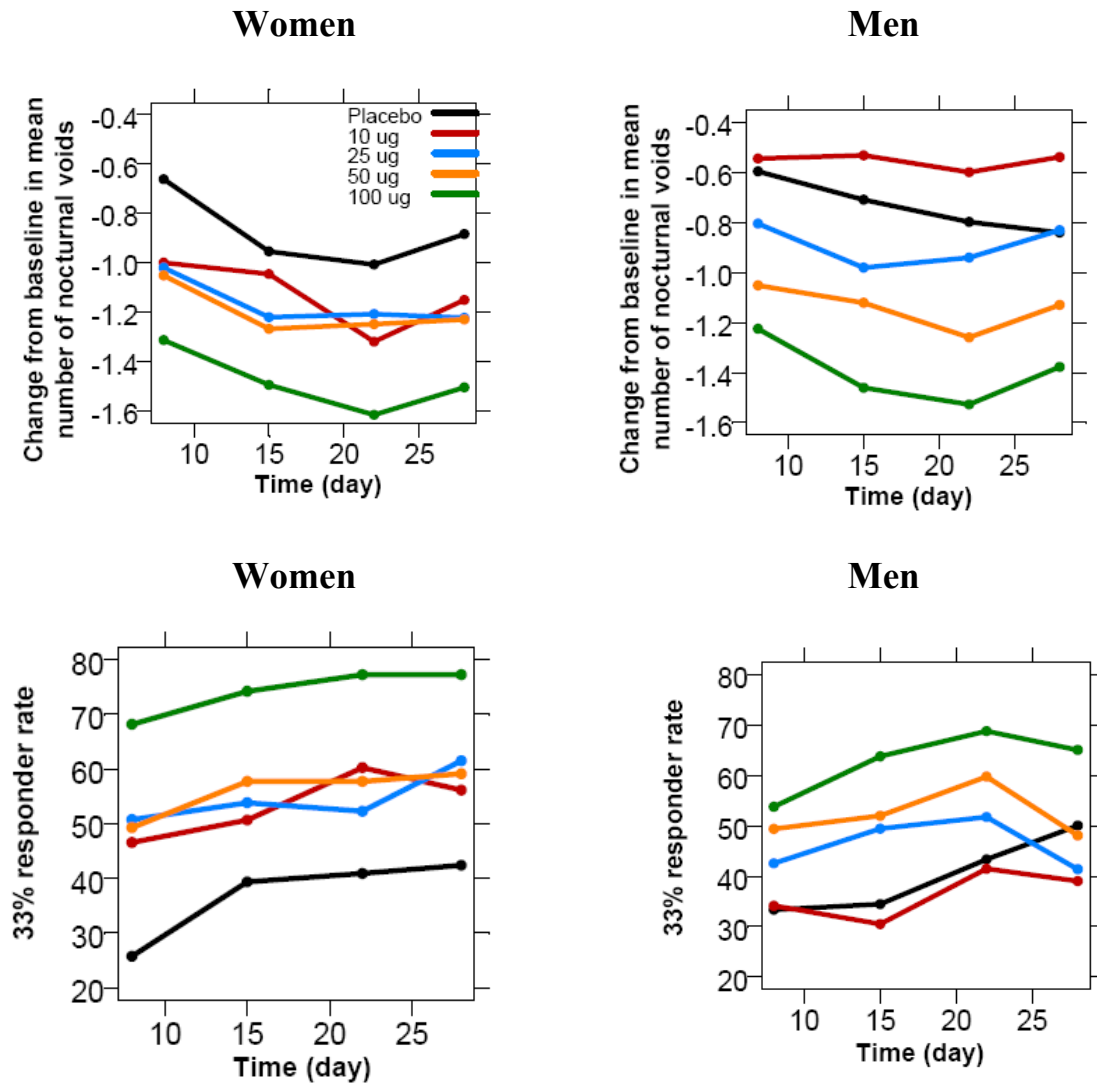
Co-Primary Endpoints	10 µg	25 µg	50 µg	100 µg
Nocturnal Voids				
Females	p=0.0721	p=0.0200*	p=0.0091*	p<0.0001*
Males	p=0.0944	p=0.5894	p=0.3778	p=0.0049*
33% Responder Rate				
Females	p=0.0880	p=0.0197*	p=0.0405*	p<0.0001*
Males	p=0.1502	p=0.2225	p=0.7375	p=0.0477*

Reanalysis of the short term trial showed a clear separation between the treatment arms and placebo for both co-primary endpoints at all time points in women as shown in **Figure 2**. For men, both 50- and 100-µg doses showed a larger decline in the change

from baseline in the mean number of nocturnal voids compared to placebo at all time points.

For the 33% responder rate, the 100 µg dose shows clear separation from placebo at all time points in men, whereas the 50 µg dose shows treatment effect at all time points except on day 28 which was the pre-specified endpoint.

Figure 2: Time-profiles for change from baseline in mean number of nocturnal voids in (Top Left) women and (Top Right) men for various treatment arms in Part I of CS29. Corresponding time-profiles for 33% responder rate in (Bottom Left) women and (Bottom Right) men.

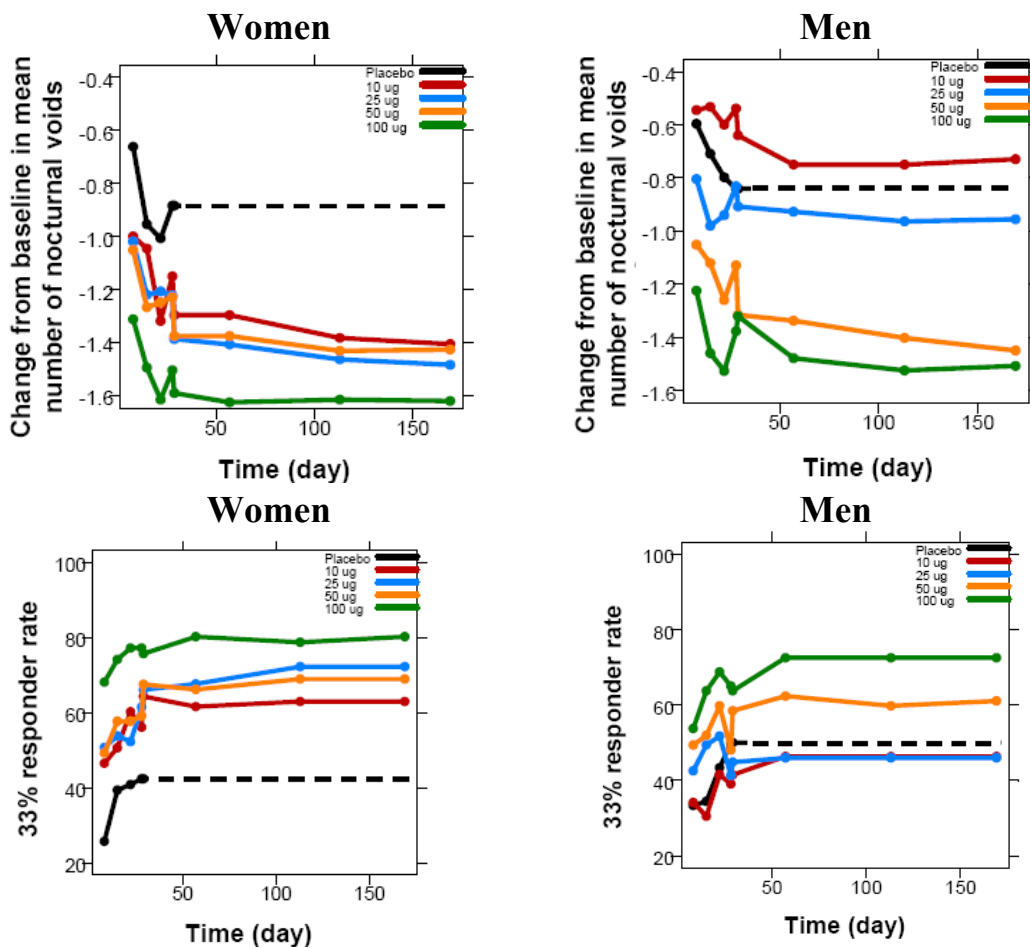


Statistically significant difference from placebo for both co-primary endpoints was achieved for the 100 µg dose group in men at all time points including day 28. While statistically significant difference from the placebo for both endpoints was achieved on day 22 for the 50 µg dose group in men—day 28 did not show statistical significance. Since 50 µg dose in men does not showed statistical significance on day 28, the sponsor proposed higher dose of 100 µg for men which was statistically significant on day 28.

The choice of day 28 as the pre-specified endpoint was arbitrary and does not have any clinical significance. Also, in men a decline in responder rate that is observed for the treatment arms only on day 28 and an increase in the placebo arm are due to inexplicable reasons. Also, variability in response can be attributed to the fact that the clinical trial was not powered to show statistical significance based on gender, as this is the first study to observe gender differences in response.

Our rationale for recommending 50 µg dose in men is also supported by long term extension study. In the long term trial, clear separation between the 10- and 100- µg dose groups is observed for both co-primary endpoints (**Figure 3**). Because the placebo was removed in Part II, the black dotted lines in **Figure 3** show the observation from day 28 carried forward. In the absence of a placebo-control in this open-label extension of the trial, a positive dose-response relationship is supportive of the long-term efficacy of the drug based on the E9 Guidance for Industry.

Figure 3: Time-profiles for change from baseline in mean number of nocturnal voids in (Top Left) women and (Top Right) men for various treatment arms in Part I and II of CS29. Corresponding time-profiles for 33% responder rate in (Bottom Left) women and (Bottom Right) men.



Thus, short and long term efficacy data suggest comparable effectiveness for both the co-primary endpoints for women at 25 µg and men at 50 µg dose levels except for day 28 (Figure 2 and 3). The onset of response for 25 and 50 µg in women and men is observed as early as 8 days after treatment. Thus, based on a reduced risk of hyponatremia and comparable effectiveness for men at the 50 µg dose with women at 25 µg dose, a reduced dose of 50 µg as the starting dose is recommended in men. In order to optimize the effectiveness in men less than 65 years, the dose may be titrated up to a maximum 100 µg daily dose by weekly dose escalations in 25 µg increments. Dose escalation for elderly men (age ≥ 65 years) is not recommended due to the increased risk of hyponatremia. For further details please refer to Pharmacometric Review in section 4.2.

Pharmacokinetics

Clinical pharmacology studies that focused on characterizing the pharmacokinetics of the melt formulation include: 1) relative bioavailability study CS019 comparing minirin melt (240 µg) formulation vs minirin tablet formulation (200 X 2 µg), and 2) dose linearity study CS021 (60 µg, 120 µg, and 240 µg). According to the sponsor's analysis, the bioavailability of minirin melt formulation relative to tablet formulation was estimated to be 1.57. In dose linearity study, the sponsor asserts the three desmopressin dose levels of 60, 120 and 240 µg show dose linearity in terms of desmopressin AUC_{inf}, AUC_τ, and C_{max}. However, the pharmacokinetic results obtained from these studies can not be relied upon due to the fact that sponsor used an invalid bioanalytical method to assess the plasma concentrations. The sponsor used a bioanalytical method that is neither robust nor reproducible and had high QC failure rates. Also, this same analytical method was previously found unacceptable by the FDA's Division of Scientific Inspection team (DSI) on similar reasons.

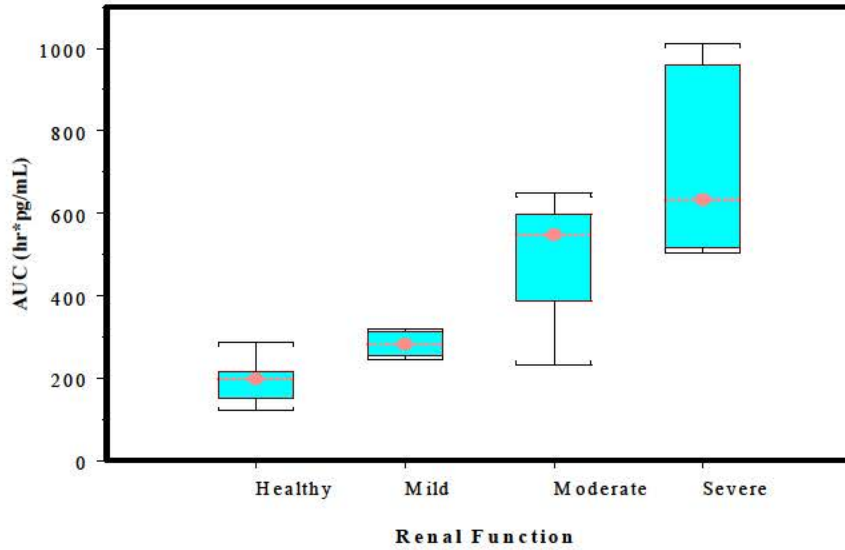
In vitro Metabolism

In-vitro metabolism studies using human and rat liver microsomes indicated that desmopressin is not metabolized in the microsomes to any significant extent. Also, *In-vitro* results showed that the desmopressin did not inhibit the baculovirus-expressed human cytochrome P450 activity (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4).

Renal Impairment

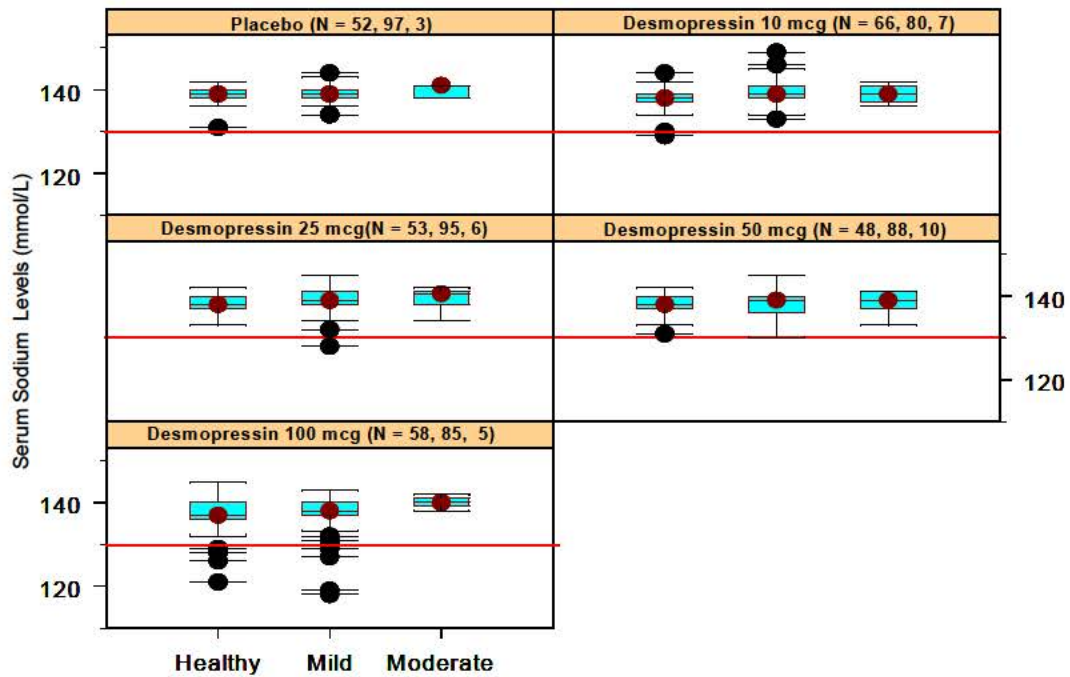
In healthy subjects, approximately 52% of an i.v. bolus dose of desmopressin is eliminated unchanged via the kidneys. Following intravenous administration (2 µg dose), the total systemic clearance (CL) of desmopressin decreased with increasing renal impairment. Subsequently, in moderate and severe renal impaired patients, 2.4 fold and 3.6 fold increase in desmopressin exposure were seen as compared to healthy subjects, respectively. In mild renal impairment patients, 1.5 fold increase in desmopressin exposure was seen as compared to healthy subjects (**Figure 4**). In this study, the sponsor used a bioanalytical method that is validated and acceptable.

Figure 4: Effect of Renal Impairment on Desmopressin Exposure



Sponsor proposes no dose adjustment for patients with mild renal impairment, and contraindicates desmopressin in patients with moderate and severe renal impairment. Sponsor’s rationale is adequate and supported by the analysis of Phase 3 safety data (trial CS29, Day 28) where renal function showed no influence on risk of hyponatremia (Figure 5). Serum sodium levels are similar in healthy and mild renal impaired patients at all the dose groups.

Figure 5: No Influence of Renal Function on Risk of Hyponatremia



Source: Data source study CS 29 at day 28

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

NOCDURNA (Minirin Melt or Desmopressin Melt) is a freeze-dried orally disintegrating tablet which is designed to dissolve rapidly in the mouth when placed under the tongue. NOCDURNA™ contains the active ingredient desmopressin (as the acetate), which is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The modifications comprises of desamination of the N-terminal and a replacement of L-arginine by D-arginine in position 8 in the peptide sequence. Desmopressin is more potent and has prolonged duration of action, and decreased pressor activity as compared to vasopressin. The ratio of antidiuretic activity to vasopressor activity for desmopressin is > 3000:1 compared to 1:1 for native vasopressin. Also desmopressin has longer half-life (~ 3 hrs) compared to the native vasopressin (< 15 minutes). Desmopressin binds to V2 receptors in renal collecting ducts, increasing water reabsorption, increasing urine concentration and decrease urine production, which in turns leads to decrease in voiding frequency.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?

The sponsor submitted this application for NOCDURNA under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The proposed indication for this NDA 22-517 of NOCDURNA (desmopressin melt or Minirin Melt) orally disintegrating tablets is adult nocturia, with the aim of decreasing nocturnal urinary frequency and volume and prolonging the time to first nocturnal void in patients with this condition. Desmopressin has been marketed in USA and around the world for more than 30 years as different formulations such as nasal spray, intravenous formulation, and as an oral tablet formulation. Approved indications include central diabetes insipidus (CDI), primary nocturnal enuresis (PNE), type I von Willebrand's disease, and hemophilia A.

In Europe, the Minirin melt formulation has been approved for treating patients with nocturia under the age of 65. The approved doses in Europe are 60 µg, 120 µg, and 240 µg, with a dosing regimen of starting with a lowest dose and weekly dose escalation as needed up to a maximum dose of 240 µg.

In this application, the sponsor has not conducted any pharmacokinetics studies for the proposed dose of 25 µg and 100 µg. During the EOP-2/pre-NDA meeting the sponsor asked/submitted a request for a waiver of PK studies at the proposed dose strengths of 25 µg and 100 µg, based on the PK data that the sponsor collected at doses of 60 µg, 120 µg, and 240 µg. The biowaiver request at the proposed dose strengths was made due to the fact that the analytical method was not sensitive to measure desmopressin in blood following administration of lower strengths.

Agency agreed to waive conducting pharmacokinetics studies for new proposed strengths of Minirin Melt provided:

- 1) Desmopressin pharmacokinetics is linear over the proposed dose range,

2) The different formulation strengths are proportionally similar in their active and inactive ingredients, and

3) The dissolution profiles of the different formulations strengths are comparable to those of the higher strengths used in previous pharmacokinetic studies

The sponsor submitted all the required information and biowaivers for lower strengths were granted by ONDQA (Reviewed by Dr. Houda Mahayni; DARRTS date, 01/14/2009). Although, the biowaiver was granted, the ONDQA reviewer in her review noted that “the study show a trend more than a conclusive evidence of dose linearity. The study had many deficiencies including, missing data, extrapolated PK parameters, high variability, and unacceptable analytical method”.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

	Desmopressin Acetate
Description	white, fluffy, amorphous powder
Chemical Name	1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monacetate (salt) trihydrate
Molecular Formula	C ₄₆ H ₆₄ N ₁₄ O ₁₂ S ₂ ·C ₂ H ₄ O ₂ ·3H ₂ O
Molecular Weight	1183.34

Formulation: In addition to the active ingredient (Desmopressin Acetate), the oral disintegrating tablet also contains the following inactive ingredients: gelatin, mannitol and citric acid. The composition of the formulations for the different tablets strengths are shown in the **Table 2** below:

Table 2 : Composition of desmopressin melt tablets a) 25 µg, b) 50 µg, c) 100 µg.

a)

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.025 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin		(b) (4)	Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 25 µg desmopressin free base.

b)

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.050 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin		(b) (4)	Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 50 µg desmopressin free base.

c)

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.100 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin		(b) (4)	Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 100 µg desmopressin free base.

2.1.3 What is the mechanism of action and therapeutic indication?

NOCDURNA™ contains the active ingredient desmopressin (as the acetate), which is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. It belongs to the pharmacologic class of posterior pituitary hormone. It works by acting on in the collecting duct of the kidneys by increasing urine concentration and decrease urine production, which in turns leads to decrease in voiding frequency. Desmopressin binds to V2 receptors in renal collecting ducts, increasing water reabsorption. It also in high dosages stimulates release of factor VIII from endothelial cells. The proposed indication is for treatment of nocturia in adults.

2.1.4 What are the proposed dosage and route of administration?

NOCDURNA is formulated as an orally disintegrating tablet that appears as a white, circular freeze-dried unit. The unit disintegrates instantly once applied under the tongue. Apart from desmopressin, the drug product contains gelatin, mannitol and citric acid. The sponsor is planning to market the NOCDURNA in two dosage strengths 25 µg and 100 µg. The sponsor proposed the following dosing recommendation for NOCDURNA:

- Women: 25 µg sublingual tablet, once daily at bedtime
- Men < 65: 100 µg sublingual tablet, once daily at bedtime.
- Men ≥ 65: 100 µg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment.

2.1.5 Is any DSI (Division of Scientific Investigation) inspection requested for any of the clinical studies?

No. DSI inspection was not requested from clinical pharmacology standpoint.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical development is supported by one Phase 3 efficacy and safety trial (FE992026 CS29). There were two co-primary efficacy endpoints in this trial. The Phase 3 study was conducted in 2 parts. Part I was a randomized, double-blind, placebo controlled, parallel-group, multicenter study investigating the efficacy and safety of 4 doses (10 µg, 25 µg, 50 µg, or 100 µg) of desmopressin Melt administered for 28 days for the treatment of nocturia in adults. The primary objectives of Part I were to demonstrate, after 28 days of treatment, the superiority of one or more doses of the Melt formulation of desmopressin to placebo in reducing the mean number of nocturnal voids and increasing the proportion of subjects with >33% reduction from baseline in mean number of nocturnal voids.

Upon completion of Part I of the study, all subjects on active treatment were allowed to continue into Part II on the same treatment for approximately 1 to 6 months. Subjects assigned to placebo in Part I were randomly assigned to 1 of the 4 active treatments in Part II. Study CS29 was followed by a long-term open-label safety efficacy study CS31.

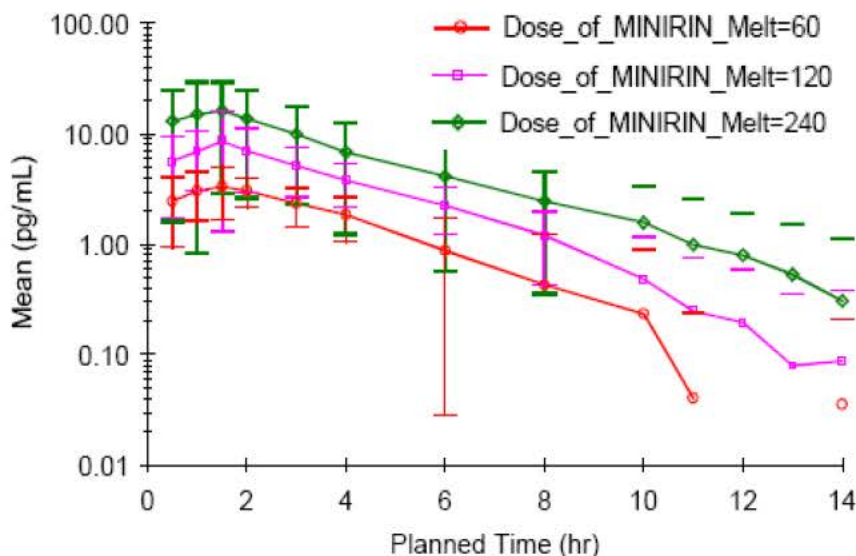
In this application, clinical pharmacology studies focused on the characterization of the pharmacokinetics of melt formulation includes a) relative bioavailability study (CS019) comparing minirin melt (240 µg) formulation vs minirin tablet formulation (200 X 2 µg), b) dose linearity study (CS021) (60 µg, 120 µg, and 240 µg) c) The absolute bioavailability (CS004) of minirin melt d) pharmacokinetics in renally impaired patients (CS001) e) pharmacokinetics in healthy lactating females (45A05-118), and f) in vitro metabolism studies.

2.2.2 What are the basic pharmacokinetic characteristics of Desmopressin?

Following the intravenous administration (2 µg dose), the mean of total systemic clearance (CL) of desmopressin ± SD value was 9.57 ± 3.35 L/hr. The distribution volume of desmopressin after intravenous administration is 33 L. Mean terminal $t_{1/2}$ was 2.8 hours in healthy subjects.

According to sponsor, the pharmacokinetic profile following oral administration of Minirin melt formulation at dose strengths of 60 µg, 120 µg, and 240 µg is shown in **Figure 6**.

Figure 6: Mean Desmopressin Plasma Concentration (Log scale) by treatment.



Summary of pharmacokinetic parameter at 60 µg, 120 µg, and 240 µg following oral administration of Minirin melt is presented in **Table 3**.

Table 3: Summary of Pharmacokinetics parameters following oral administration of 60 µg, 120 µg, and 240 µg Minirin melt.

PK parameter	Dose of desmopressin Melt		
	60 µg N=14	120 µg N=24	240 µg N=23
AUC [pg h/mL]			
Mean	21.589	39.283	79.555
SD	9.157	16.268	59.782
Geomean	20.032	36.443	67.697
CV%	40.7	40.8	57.9
AUC_t [pg-h/mL]			
Mean	13.731	34.060	70.030
SD	7.375	16.844	57.513
Geomean	12.213	29.883	52.093
CV%	50.9	62.0	121.8
C_{max} [pg/mL]			
Mean	4.033	9.577	19.044
SD	1.548	7.123	15.003
Geomean	3.809	8.031	14.998
CV%	34.1	62.4	83.6
t_{max} [h]			
Mean	1.479	1.240	1.060
SD	0.651	0.597	0.507
Median	1.500	1.500	1.000
Min – Max	0.50 – 3.00	0.50 – 3.00	0.50 – 2.00
t_{1/2} [h]			
Mean	3.256	2.738	2.813
SD	1.213	0.710	0.312
Harmonic mean	2.941	2.597	2.779
Quartile range	2.44 – 3.36	2.28 – 3.09	2.51 – 3.06

Reviewer's Comment: According to the sponsor, the three desmopressin dose levels of 60, 120, and 240 µg showed dose linearity in terms of desmopressin AUC_{inf}, AUC_τ and C_{max}. However, the pharmacokinetic results obtained from these studies can not be relied on due to the fact that they used an analytical method that was previously found unacceptable by the FDA DSI inspection team.

2.2.3 Do desmopressin transfer into human breast milk?

The transfer of desmopressin in human breast milk was conducted in six healthy nursing mother of age 27-40 years. A single nasal dose of desmopressin (~300 µg) was administered to these subjects. The ratios of the AUC in milk/plasma were below 0.4 in all 6 subjects, indicating that mean level of desmopressin over time was consistently lower in milk than in plasma. The ratios of desmopressin concentrations in milk/plasma for the first 3 ml milk portions ranged between 0.0 and 1.169. The median milk/plasma ratio was 0.0 at 30 minutes, 0.005 at 60 minutes, 0.015 at 2 hours, 0.043 at 4 hours, 0.066 at 6 hours, and 0.133 at 8 hours. The total amount of desmopressin excreted in the milk over the 8 hours ranged between 491 pg and 16 ng, which correspond to 0.0001 - 0.005 % of the administered dose.

Reviewer's Comment: The sponsor's bioanalytical method and analysis of results seem acceptable. In this study an increased trend of milk/plasma ratio for desmopressin was observed for the duration of study (8 hours), hence accumulation of desmopressin in breast milk cannot be ruled out. Also the oral bioavailability of desmopressin from ingested milk in babies is not known and further studies in lactating women on continuous treatment are desirable. Therefore, labeling language will reflect that a caution should be exercised when desmopressin is administered to nursing mother.

2.2.4 Are the active moieties in the plasma appropriately identified and measured?

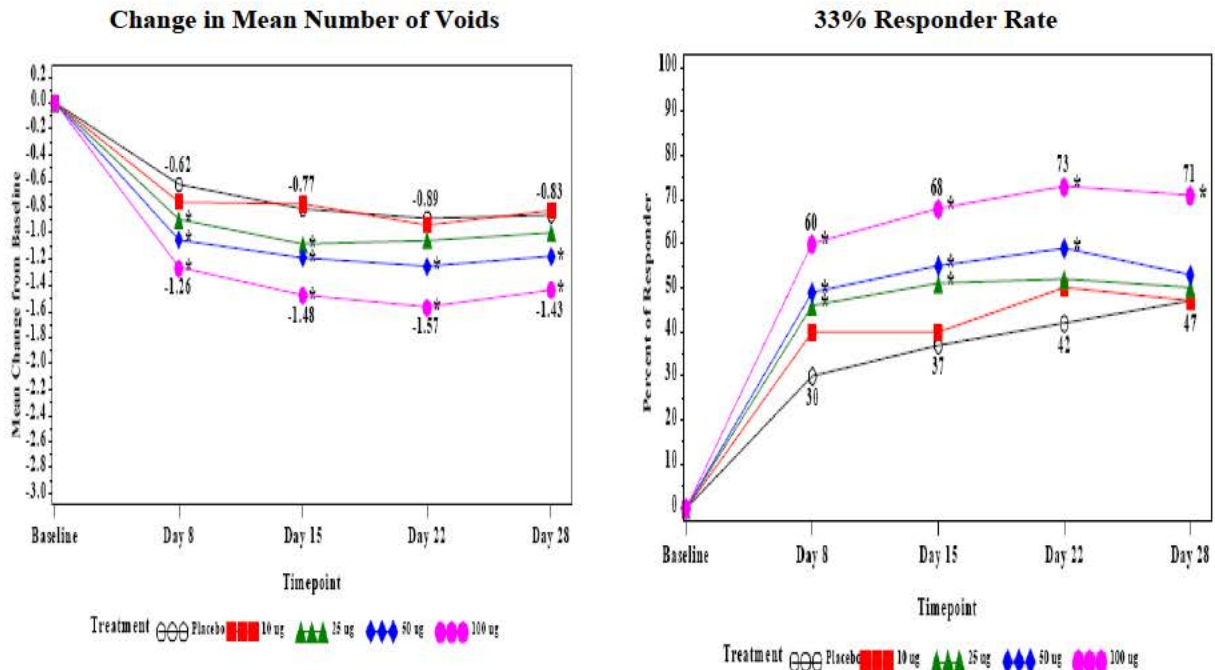
The sponsor used radioimmunoassay (RIA) for the determination of desmopressin in human plasma samples. The sponsor used two different methods for plasma sample preparation. The first method is based on liquid- liquid extraction technique and the second was based on solid phase extraction technique. The results of the study samples that utilized solid-phase extraction can not be relied on because of high QC failures and also the method was rejected by FDA DSI inspection team. For details see section 2.6.

2.2.5 Exposure Response Analysis

2.2.5.1 What are the characteristics of the dose-response relationships for efficacy?

Sponsor's analysis of time-profiles of both co-primary endpoints for various treatment groups in Part I of CS29 are shown in **Figure 7**. Overall, an increase in response is observed with increasing doses of desmopressin. For the change from baseline in mean number of nocturnal voids (first co-primary endpoint), both 50 and 100 µg doses were statistically significant at all time points. For the 33% responder rate (second co-primary endpoint), the 50 µg dose was statistically significant at all time points except for day 28. The 100 µg dose was statistically significant at all time points.

Figure 7: Time-profiles for (Left) change from baseline in mean number of nocturnal voids and (Right) 33% responder rate for various treatment arms in Part I of CS29. The various treatment arms placebo, 10, 25, 50 and 100 µg of desmopressin are denoted by black, red, green, blue and pink lines. Various time points include baseline and days 8,15, 22 and 28. * denotes statistical difference versus placebo, $p \leq 0.05$. The absolute values for the placebo and 100 µg treatment arms are denoted in the figure



Sponsor’s analysis of efficacy data stratified based on gender is shown in **Table 4**. For women, the 25 µg dose was determined to be the minimum effective dose as statistical significance was achieved for both the co-primary endpoints ($p=0.02$ and $p=0.0197$) on Day 28. For men, statistical significance for the both the co-primary endpoints was achieved only for the 100 µg dose ($p<0.0001$). Thus, sponsor’s proposed dose is 25 µg for women and 100 µg for men. For sponsor’s dose response analysis please refer to Section 4.2 Pharmacometric Review.

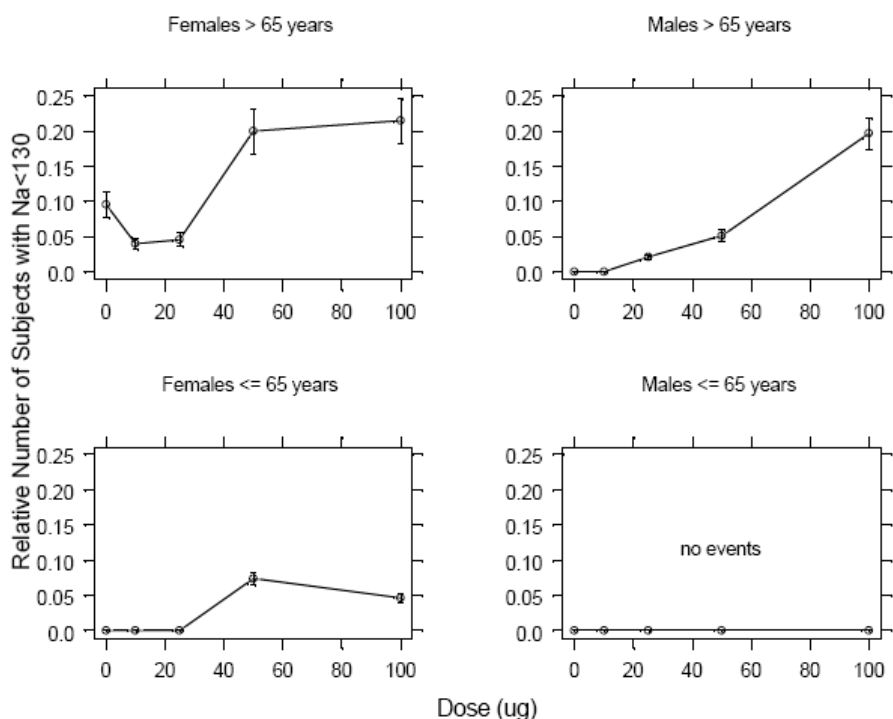
Table 4: Sponsor’s analysis of primary efficacy endpoints by gender

Co-Primary Endpoints	10 µg	25 µg	50 µg	100 µg
Nocturnal Voids				
Females	$p=0.0721$	$p=0.0200^*$	$p=0.0091^*$	$p<0.0001^*$
Males	$p=0.0944$	$p=0.5894$	$p=0.3778$	$p=0.0049^*$
33% Responder Rate				
Females	$p=0.0880$	$p=0.0197^*$	$p=0.0405^*$	$p<0.0001^*$
Males	$p=0.1502$	$p=0.2225$	$p=0.7375$	$p=0.0477^*$

2.2.5.2 What are the characteristics of the dose-response relationships for safety?

Sponsor's analysis showed that there is an evidence of dose-response for hyponatremia in elderly men and women (age greater than 65 years) as shown in **Figure 8**. At the sponsor's proposed dose of 100 µg for men, 20% of the elderly subjects experienced hyponatremia (Na < 130 mM). The proportion of subjects with hyponatremia increased with increasing dose (0–100 µg) in elderly men, suggesting that a lower dose would reduce the risk of hyponatremia. No cases of hyponatremia were observed in men less than 65 years for all doses. While dose-response is also observed for elderly women, at the sponsor's proposed dose of 25 µg for women, only 5% of the elderly subjects developed hyponatremia which is lower than the placebo rate of 10%. No cases of hyponatremia were observed in women less than 65 years at the 25 µg dose.

Figure 8: Proportion of subjects experiencing hyponatremia at 0-100 µg desmopressin doses stratified by gender and age



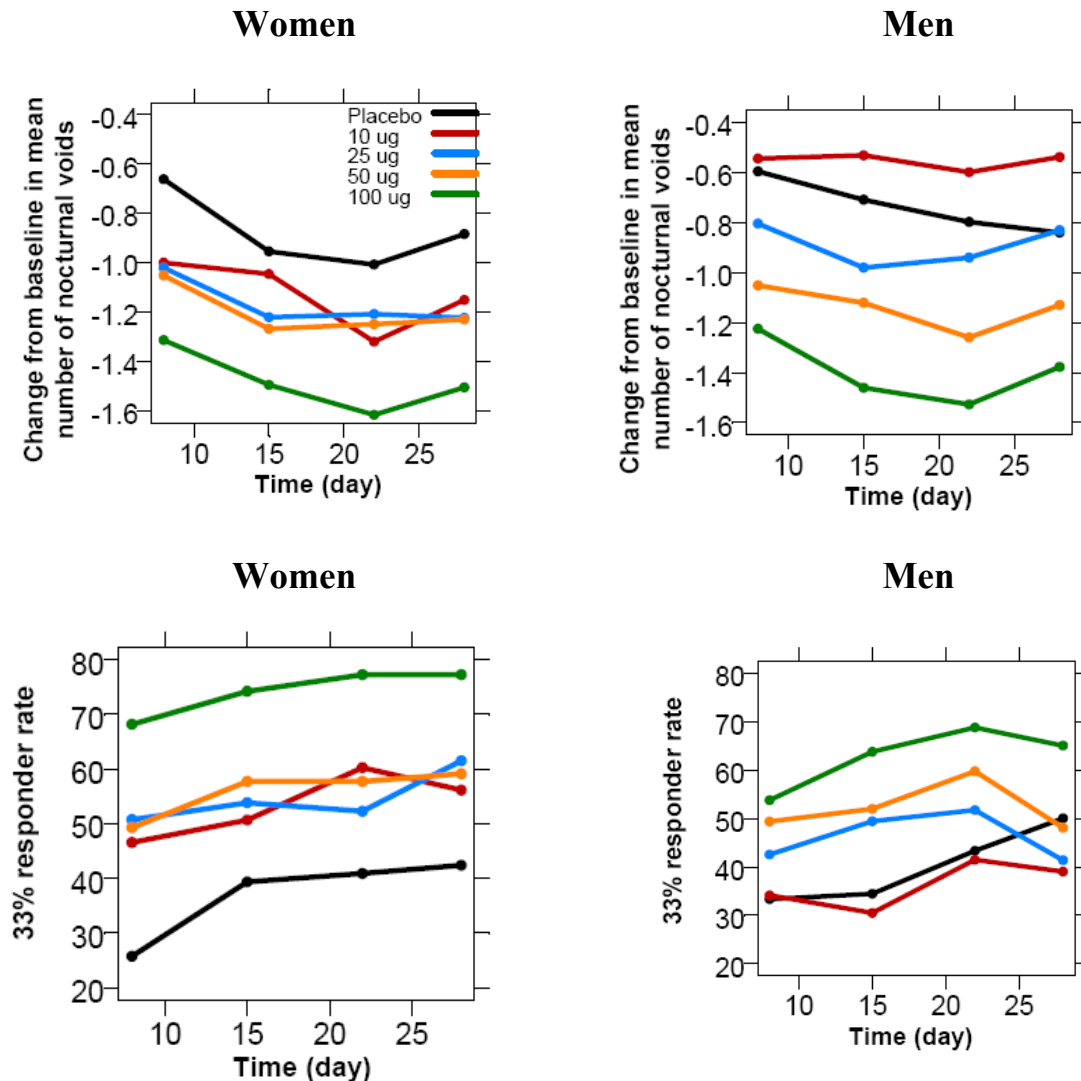
2.2.5.3 Based on the dose-response relationship for efficacy and safety, does the sponsor's dosing recommendation for men and women appropriate?

No, a reduced dose of 50 µg as the starting dose is recommended in men. In order to optimize the effectiveness in men less than 65 years, the dose may be titrated up to a maximum 100 µg daily dose by weekly dose escalations in 25 µg increments. Dose escalation for elderly men (age ≥ 65 years) is not recommended due to the increased risk of hyponatremia.

Reviewer's reanalysis of the short term trial showed a clear separation between the treatment arms and placebo for both co-primary endpoints at all time points in women as shown in **Figure 9**. For men, both 50- and 100- μg doses showed a larger decline in the change from baseline in the mean number of nocturnal voids compared to placebo at all time points. For the 33% responder rate, the 100 μg dose shows clear separation from placebo at all time points in men, whereas the 50 μg dose shows treatment effect at all time points except on day 28 which was the pre-specified endpoint.

Statistically significant difference from placebo for both co-primary endpoints was achieved for the 100 μg dose group in men at all time points including day 28. While statistically significant difference from the placebo for both endpoints was achieved on day 22 for the 50 μg dose group in men, day 28 did not show statistical significance. Since, 50 μg dose in men does not showed statistical significance on day 28 the sponsor proposed higher dose of 100 μg for men which was statistically significant on day 28.

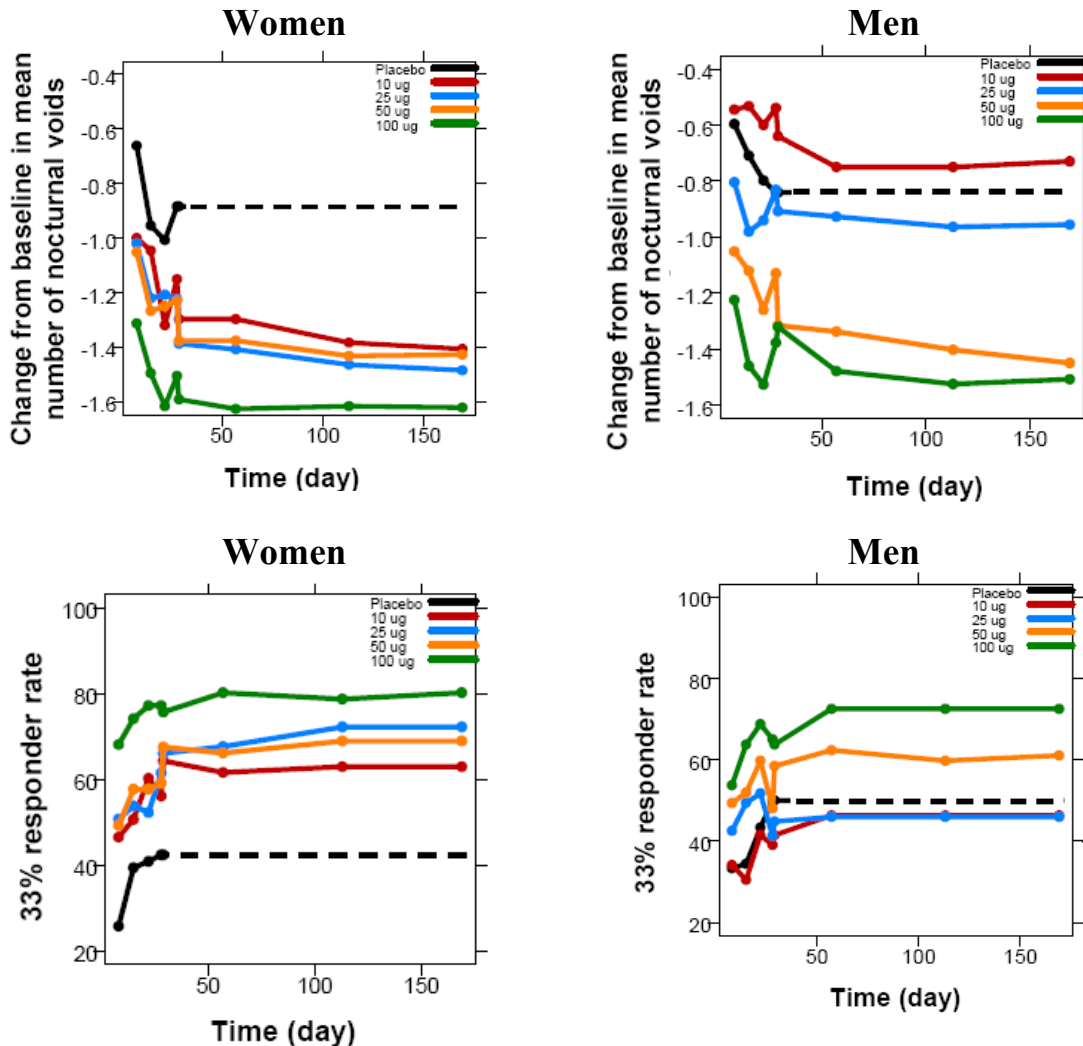
Figure 9: Time-profiles for change from baseline in mean number of nocturnal voids in (Top Left) women and (Top Right) men for various treatment arms in Part I of CS29. Corresponding time-profiles for 33% responder rate in (Bottom Left) women and (Bottom Right) men.



The choice of day 28 as the pre-specified endpoint was arbitrary and does not have any clinical significance. Also, in men a decline in responder rate that is observed for the treatment arms only on day 28 and an increase in the placebo arm are due to inexplicable reasons. Also, variability in response can be attributed to the fact that the clinical trial was not powered to show statistical significance based on gender, as this is the first study to observe gender differences in response.

The rationale for recommending 50 µg dose in men is also supported by long term extension study. In the long term trial, clear separation between the 10- and 100- µg dose groups is observed for both co-primary endpoints (**Figure 10**). Because the placebo was removed in Part II, the black dotted lines in **Figure 10** show the observation from day 28 carried forward. In the absence of a placebo-control in this open-label extension of the trial, a positive dose-response relationship is supportive of the long-term efficacy of the drug.

Figure 10: Time-profiles for change from baseline in mean number of nocturnal voids in (Top Left) women and (Top Right) men for various treatment arms in Part I and II of CS29. Corresponding time-profiles for 33% responder rate in (Bottom Left) women and (Bottom Right) men.



Short and long term efficacy data suggest comparable effectiveness for both the co-primary endpoints for women at 25 µg and men at 50 µg dose levels except for day 28 (**Figure 9 and 10**). The onset of response for 25 and 50 µg in women and men is observed as early as 8 days after treatment. Thus, based on a reduced risk of hyponatremia and comparable effectiveness for men at the 50 µg dose with women at 25 µg dose, a reduced dose of 50 µg as the starting dose is recommended in men. In order to optimize the effectiveness in men less than 65 years, the dose may be titrated up to a maximum 100 µg daily dose by weekly dose escalations in 25 µg increments. Dose escalation for elderly men (age ≥ 65 years) is not recommended due to the increased risk of hyponatremia.

Please refer to section 4.2 Pharmacometric Review for further information on reviewer's dose-response analysis for efficacy.

Reviewer's Comment: Thus, based on a reduced risk of hyponatremia and comparable effectiveness for men at the 50 µg dose with women at 25 µg dose, a reduced dose of 50 µg as the starting dose is recommended in men. In order to optimize the effectiveness in men less than 65 years, the dose may be titrated up to a maximum 100 µg daily dose by weekly dose escalations in 25 µg increments. Dose escalation for elderly men (age ≥ 65 years) is not recommended due to the increased risk of hyponatremia.

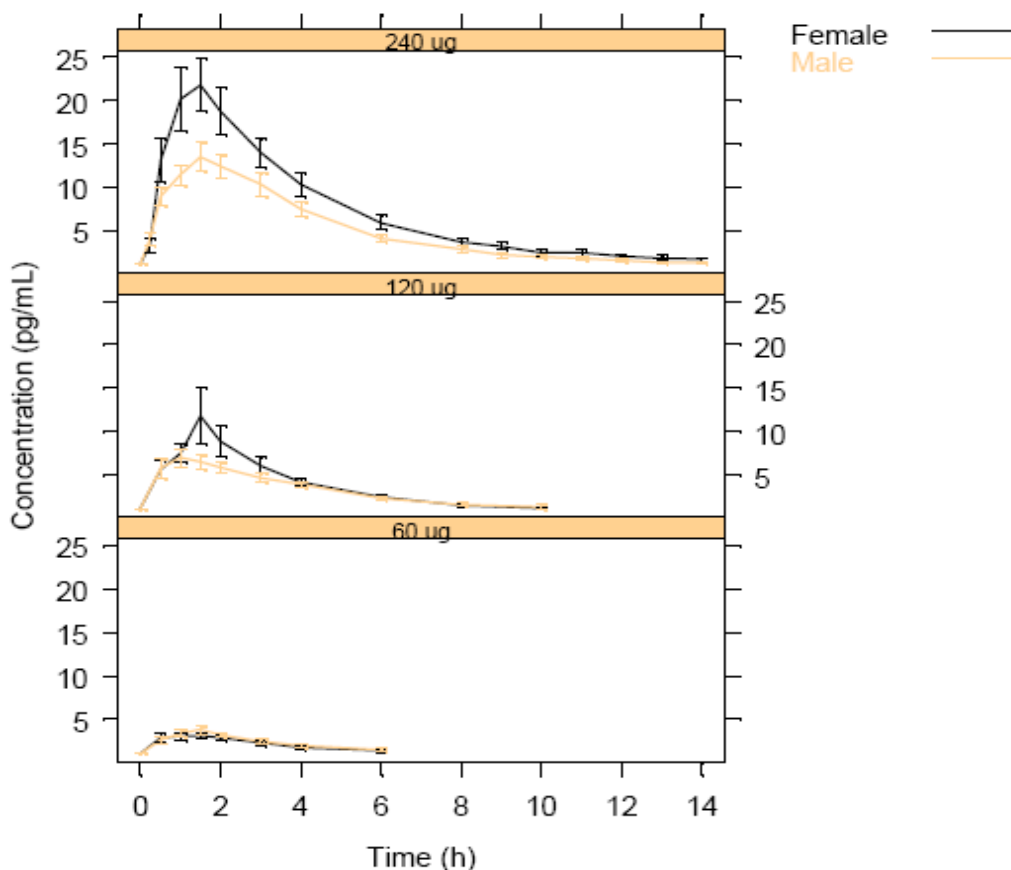
2.3 Intrinsic Factors

2.3.1 Is there age, gender, or weight effect on the desmopressin pharmacokinetics?

In the pivotal Phase 3 trial (CS029), a clear gender difference in the effect of desmopressin on reduction in number of nocturnal voids per night was observed. To investigate this effect and to link it to possible difference in pharmacokinetics between male and female, the sponsor conducted a further analysis pooling single dose pharmacokinetic data from healthy subjects from studies CS21 (dose linearity study) and CS020 (relative bioavailability study).

Mean desmopressin concentration profiles are shown by dose and gender in **Figure 11**. Sponsor's covariate analysis using non linear mixed effect modeling showed age and gender to be not statistically significant while weight was statistically significant on $\log(C_{\max})$ and borderline significant on $\log(\text{AUC})$. Also according to the sponsor, when adjusted for body weight, gender difference in drug exposure was not statistically significant.

Figure 11: Mean Concentration time profile of desmopressin following administration of oral dispersible tablet.



Reviewer's Comment: Although sponsor pooled the data from two studies CS21 and CS20 and conducted pharmacokinetic analysis between males and females, the pharmacokinetics information obtained in these PK studies can not be relied on because of the invalid bioanalytical method used to assess the plasma concentrations. The sponsor used a bioanalytical method that is neither robust nor reproducible and had high QC failure rates. More than 50% of the samples were reanalyzed in these data sets because of the reasons listed before. Also, this same method was previously rejected by FDA DSI inspection team for the same issues.

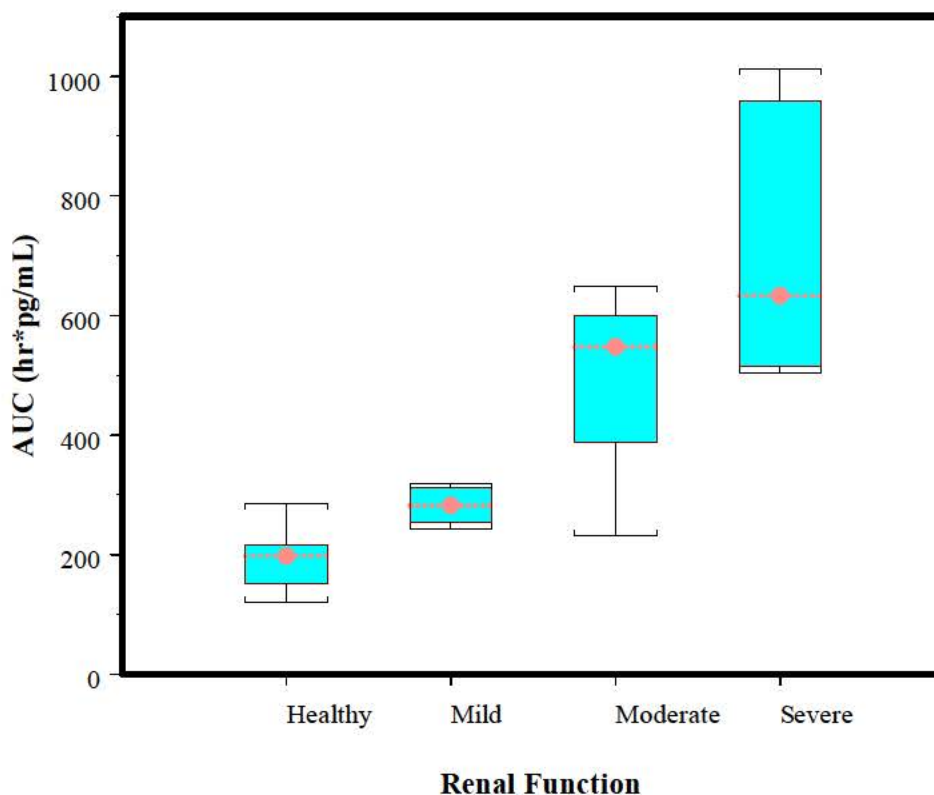
2.3.2 Does the renal function affect the pharmacokinetic of desmopressin? What is the impact of any differences in exposure on efficacy or safety responses?

The renal impairment study was conducted in healthy volunteers and patients with mild, moderate and severe renal impairment, following a single dose intravenous administration of desmopressin. This study investigated the effects of renal function on the pharmacokinetics of single i.v. doses of 2 µg desmopressin. Subjects were stratified on the basis of renal function (creatinine clearance) to one of four groups: normal renal

function (>80mL/min), mild (50-80 mL/min), moderate (30-49 mL/min), or severe (5-29 mL/min) renal impairment. The classification of renal impairment was based on creatinine clearance (glomerular filtration rate) estimated with the Cockcroft & Gault formula.

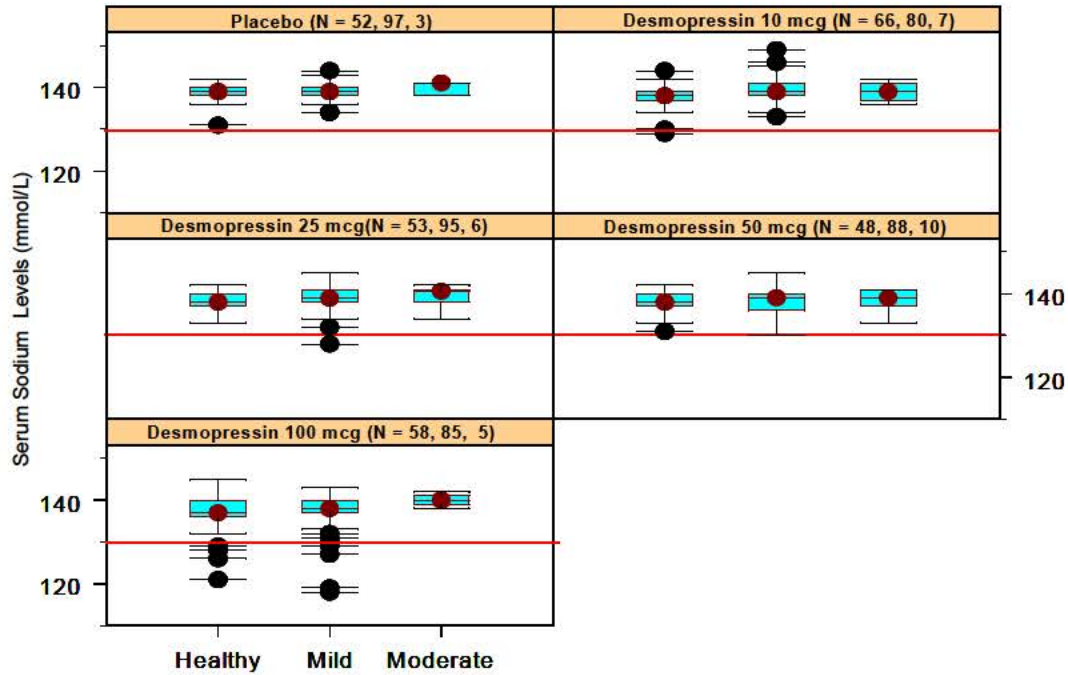
In healthy subjects, approximately 52% of an i.v. bolus dose of desmopressin is eliminated unchanged via the kidneys. Following intravenous administration (2 µg dose), the total systemic clearance of desmopressin decreased with increasing renal impairment. The geometric mean ± SD values of total systemic clearance (CL) were 9.57 ± 3.35 L/hr, 6.34 ± 0.72 L/hr, 3.92 ± 2.08 L/hr and 2.61 ± 0.78 L/hr for healthy subjects and subjects with mildly, moderately and severely impaired renal function, respectively. The distribution volume of desmopressin after intravenous administration is 33 L. Mean terminal $t_{1/2}$ increased significantly from 2.8 in normal subjects to 4.0, 6.6 and 8.7 hours for mild, moderate and severe renal impairment, respectively. Mean AUC increased from 186 in normal subjects to 281, 453 and 682 pg*h/mL for mild, moderate and severe renal impairment, respectively. These increases correspond to 3.6 fold, 2.4 fold, and 1.5 fold increase in severe, moderate, and mild renal impairment patients compared to healthy subjects (**Figure 12**), respectively.

Figure 12: Effect of Renal Impairment on Desmopressin Exposure



Sponsor proposes for no dose adjustment for patients with mild renal impairment, and contraindication for patients with moderate and severe renal impairment. Sponsor's rationale is adequate and supported by the analysis Phase 3 safety data where renal function have no influence on risk of hyponatremia (**Figure 13**). Serum sodium levels seem similar in healthy and mild renal impaired patients at all the dose groups.

Figure 13: No Influence of Renal Function on Risk of Hyponatremia



Source: Data source study CS 29 at day 28

Reviewer's Comment: In the renal impaired study sponsor used a bioanalytical method that is validated and acceptable. Sponsor utilized liquid-liquid extraction technique for the sample preparation, which is robust, reproducible and acceptable.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interaction

2.4.1.1 What is the CYP inhibition/induction potential of Desmopressin?

In-vitro metabolism studies using human and rat liver microsomes indicated that desmopressin is not metabolized in the microsomes to any significant extent. Also, *In-vitro* results showed that the desmopressin have no inhibition on the baculovirus-expressed human cytochrome P450 activity (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4).

Table 5: Effect of 10µM desmopressin and standard inhibitors on human cytochrome P450 enzyme subtype activity

Cytochrome P450 subtype	Percent inhibition		Standard inhibitor	IC ₅₀ (µM)	
	Exp 1	Exp 2		Exp 1	Exp 2
1A2	2.4	-6.8	Furafylline	2.7	3.9
2A6	-0.9	-4.0	Tranylcypromine	2.2	2.0
2B6	2.4	0.9	Tranylcypromine	4.3	2.5
2C8	3.7	-8.1	Quercetin	1.5	1.4
2C9	0.1	-1.1	Sulfaphenazole	4.3	6.0
2C19	-1.7	0.7	Tranylcypromine	18.3	17.3
2D6	-2.1	0.9	Quinidine	0.12	0.16
2E1	0.3	-4.5	Tranylcypromine	28.7	25.2
3A4	-0.4	0.3	Ketoconazole	0.03	0.04

2.5 General Biopharmaceutics

2.5.1 What is the absolute bioavailability of desmopressin oral disintegrating tablet?

Absolute bioavailability of three different doses of desmopressin oral disintegrating tablet was conducted in healthy non-smoking male volunteers (CS004). This formulation was one of the several oral disintegrating table formulations, which was not the proposed commercial formulation. The study was a four-way crossover study comparing the bioavailability of oro-dispersible tablets containing 200 µg, 400 µg and 800 µg desmopressin with the bioavailability of 2 µg desmopressin administered as solution for injection in 24 subjects. The composition of the formulation used in this study is shown in **Table 6**. Also, the composition of to be marked formulation is shown in **Table 7**.

Table 6 : Formulation of Desmopressin Melt used in Study CS004

Component	200 µg	400 µg	800 µg
Desmopressin (µg)	200	400	800
Gelatin (mg)	(b) (4)		
Mannitol (mg)			
Citric acid, anhydrous			
(b) (4)			

Table 7 : To-be Marketed Formulation of Desmopressin Melt

Component	60 µg	120 µg	240 µg
Desmopressin (µg)	60	120	240
Gelatin (mg)	(b) (4)		
Mannitol (mg)			
Citric acid, anhydrous			
(b) (4)			

After sublingual administration of this Melt, which is not the proposed commercial formulation, desmopressin maximum plasma concentrations (C_{max}) were observed at 0.5-2.0 hours after dosing. The geometric mean C_{max} were 14.25, 30.21, and 65.25 pg/mL after 200, 400, and 800 µg, respectively. The elimination half life $t_{1/2}$ was within the range of 2.8 -3.0 hours. The key pharmacokinetic parameters are summarized in **Table 8**.

Table 8: Summary of pharmacokinetic parameters after sublingual administration of desmopressin Melt tablet (CS004)

Parameter	Unit	Desmopressin Melt (200 µg)		Desmopressin Melt (400 µg)		Desmopressin Melt (800 µg)	
		Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI
AUC	hr*pg/mL	64	[52-78]	150	[122-184]	283	[205-389]
AUC _t	hr*pg/mL	47	[36-60]	119	[86-164]	259	[186-362]
C_{max}	pg/mL	14	[11-18]	30	[23-41]	65	[46-92]
t_{max}	hr	1.5 [†]	0.5-2.0 ^{**}	1.0 [†]	0.75-2.0 ^{**}	1.5 [†]	0.75-2.0 ^{**}
$t_{1/2}$	hr	2.8	27.9 ^{***}	3.0	24.7 ^{***}	2.9	16.3 ^{***}

[†]: median, ^{**}: range, ^{***} CV% geo. mean

Absolute bioavailability (%F) was determined to be 0.23%, 0.27%, and 0.26% after a sublingual dose of 200 µg, 400 µg and 800 µg, respectively. The overall pooled estimate of the absolute BA was 0.25% [0.21%-0.31%] for desmopressin administered as desmopressin Melt.

Table 9: Absolute Bioavailability (%F) of desmopressin Melt tablet after oral administration of 200 µg, 400 µg, and 800 µg dose.

Treatment	Point estimate	95% confidence interval	
		Lower	Upper
200 µg sublingual	0.23	0.18	0.29
400 µg sublingual	0.27	0.21	0.34
800 µg sublingual	0.26	0.20	0.33
Pooled	0.25	0.21	0.31

2.5.2 What is the relative bio-availability of oral dispersible tablet?

Sponsor conducted two relative bioavailability studies (CS020 and CS019) comparing desmopressin melt formulation (oral disintegrating tablet) to that of currently approved desmopressin tablets formulation.

The study CS020 used a desmopressin melt formulation that was not to-be marketed formulation. However, study CS019 was conducted with to-be marketed melt formulation. Composition of formulation that were used in study CS020 and CS019 is shown in **Table 10** and **Table 11**, respectively.

Table 10: Formulation of Desmopressin Melt used in Study CS020

Component	30 µg	60 µg	120 µg	240 µg	360 µg	480 µg	
Desmopressin (µg)	30	60	120	240	360	480	
Gelatin (mg)							(b) (4)
Mannitol (mg)							
Citric acid, anhydrous							
(b) (4)							

Table 11: Formulation of Desmopressin Melt used in Study CS019

Component	60 µg	120 µg	240 µg	
Desmopressin (µg)	60	120	240	
Gelatin (mg)				(b) (4)
Mannitol (mg)				
Citric acid, anhydrous				
(b) (4)				

Ferring Pharmaceuticals

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Study CS020 was a single-center, open-label, randomized, 2-period, cross-over study investigating the relative BA of two doses of desmopressin Tablet (2x0.2 mg) and a single dose of desmopressin Melt (240 µg). A summary of the PK parameters for both treatments is provided in **Table 12**.

Table 12: Summary of pharmacokinetic parameters for desmopressin Tablets and desmopressin Melt (CS020)

Parameter	Unit	Desmopressin oral tablets (2x200µg)		Desmopressin melt tablets (240µg)	
		Geom. mean	95% CI	Geom. mean	95% CI
AUC	hr*pg/mL	77	[63-94]	79	[64-98]
AUC _t	hr*pg/mL	72	[58-88]	73	[59-91]
C _{max}	pg/mL	21	[17-26]	18	[15-22]
t _{max}	hr	1.0 [*]	0.5-3.0 ⁺⁺	1.5 [*]	0.5-4.0 ⁺⁺

* median

++ Range

The analysis of F_{relative} of the Melt tablet versus the oral tablet showed that the relative BA was significantly greater than 1. The oral BA of desmopressin was greater when formulated as melt than as tablets (comparing identical dosages) (**Table 13**). The oral BA of desmopressin from the melt relative to the tablet was 1.52 (CV=54%).

Table 13: Statistical summary of relative bioavailability comparing melt and tablet formulation

Ratio	PK parameter	Degrees of freedom	Estimated mean	95% CI	p-value
Melt/Tablet	AUC	26	1.518	1.245-1.851	0.0002
Melt/Tablet	AUC _t	26	1.514	1.233-1.857	0.0003

NB: pharmacokinetic parameters are divided by dose strength before analysis (356 µg and 240 µg)

Study CS019 was designed as an open-label, replicated, randomized, cross-over study with four periods and two sequences investigating the bioequivalence of a single dose of desmopressin Tablets (2x0.2 mg) and a single desmopressin Melt (240 µg) dose of desmopressin administered sublingually. The sponsor claims this as a bioequivalence study acknowledging that the formulations are not of the same molar doses.

Sponsor’s analysis of study CS019 showed that for AUC_{inf} and AUC_{τ} the point estimate and 90% CIs for the ratio of “Melt / Tablet” were included within the BE limits of 80-125% . However, for C_{max} the lower limit of the 90% CI was slightly below the lower limit of the BE criteria.

Table 14: Statistical summary of pharmacokinetic parameters for desmopressin Melt (Test) and desmopressin Melt (Reference)

	Point estimate	90% CI
AUC: Ratio “Test / Reference”	1.0561	[0.9179, 1.2150]
AUC_{τ} : Ratio “Test / Reference”	1.0581	[0.9137, 1.2252]
C_{max} : Ratio “Test / Reference”	0.8296	[0.7385, 0.9320]

In this study, the relative bioavailability of desmopressin in the oral lyophilisate relative to desmopressin in the MINIRIN tablet was 1.57.

Reviewer’s Comment: The pharmacokinetics information obtained in these PK studies (CS19 and CS 20) can not be relied on because of the invalid bioanalytical method used to assess the plasma concentrations. The sponsor used a bioanalytical method that is neither robust nor reproducible and had high QC failure rates. More than 50% of the samples were reanalyzed in these data sets because of the reasons listed before. Also, this same method was previously rejected by FDA DSI inspection team for the same issues.

2.6 Analytical

2.6.1 How are the active moieties identified and measured in the plasma/serum? Does the analytical methods appropriately validated?

In this NDA, bioanalytical methods based on radioimmunoassay (RIA) have been used for the determination of desmopressin in human plasma samples. Sponsor used two different sample preparation methods for the analysis of plasma samples. One utilizes liquid-liquid extraction technique for sample preparation and other utilizes solid phase extraction technique.

In the radioimmunoassay, a known amount of antibody and tracer (Desmopressin labeled with ¹²⁵I) are added to the reconstituted extract and incubated. Desmopressin present in the sample and the tracer added will compete in forming a complex with the antibody. After separation, using charcoal suspension followed by centrifugation, only the complexes remain in the supernatant. The radioactivity is measured in a gamma counter. The higher the concentration of desmopressin in the sample extracted from plasma, the lower the radioactivity will be. The concentration of desmopressin in extracted plasma samples is read against a standard curve.

This RIA method that utilizes liquid-liquid extraction as sample preparation was initially validated at Ferring [MV-571-004-00] and validated by AAIPharma [AAIPharma LA381 validation report]. In validation at AAIPharma, the precision and accuracy at four concentrations were tested, 2.50, 5.00, 50.0 and 150 pg desmopressin/ml plasma, respectively. The inter-assay precision and accuracy results for the validation performed at AAIPharma are presented in **Table 15**, as the inter-assay imprecision (expressed at % CV) at the 2.50 pg desmopressin/ml plasma level was exceeding 30%, the lower limit of quantitation (LLOQ) was set to 5.00 pg desmopressin/ml plasma.

Table 15: Summary of accuracy and precision results utilizing liquid-liquid extraction technique.

Reference Code	Desmopressin concentration (pg/mL)			
	2.50	5.00	50.0	150
[AAI LA381 validation report]				
Mean inter-occasion accuracy (%)	107	101	99.0	92.7
Mean inter-occasion precision ^a (%)	30.8	15.0	6.53	8.75

^aexpressed as coefficient of variation

The RIA method that utilizes solid phase extraction technique was developed and validated under study code [MVR-PD-0023.01] at Ferring Pharmaceuticals A/S, Copenhagen, Denmark. The method was validated aiming at a LLOQ of 0.80 pg desmopressin/ml in plasma. The method used two calibration curve ranges, low calibration curve 0.382 – 45.8 pg desmopressin/ml plasma and high calibration curve 9.16 – 1099 pg/ml. The inter-assay precision and accuracy results for these validations are presented in **Table 16**.

Table 16: Summary of accuracy and precision results utilizing solid phase extraction technique

Reference code	Desmopressin concentration (pg/mL)						
	0.80 ^b	2.40 ^b	16.0 ^b	36.0 ^b	36.0 ^c	60.0 ^c	100 ^c
[MVR-PD-0023.01]							
Mean inter-occasion accuracy (%)	125	108	94	106	97	96	95
Mean inter-occasion precision ^a (%)	28	6	8	16	13	11	10

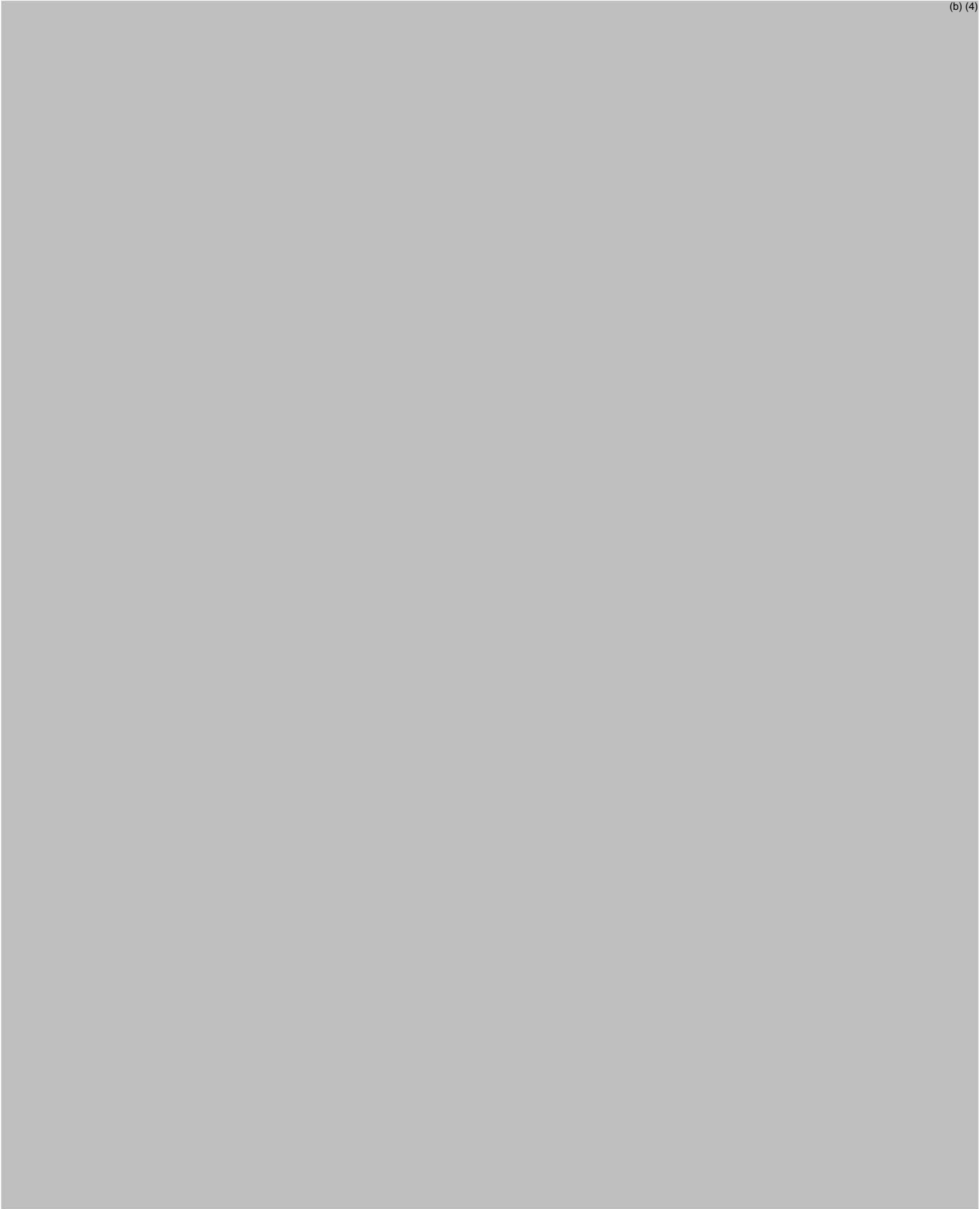
For the most of the clinical studies involving PK measurement [CS012], [CS019], [CS020] and [CS21], the determination of plasma concentrations of desmopressin was performed using solid phase extraction technique.

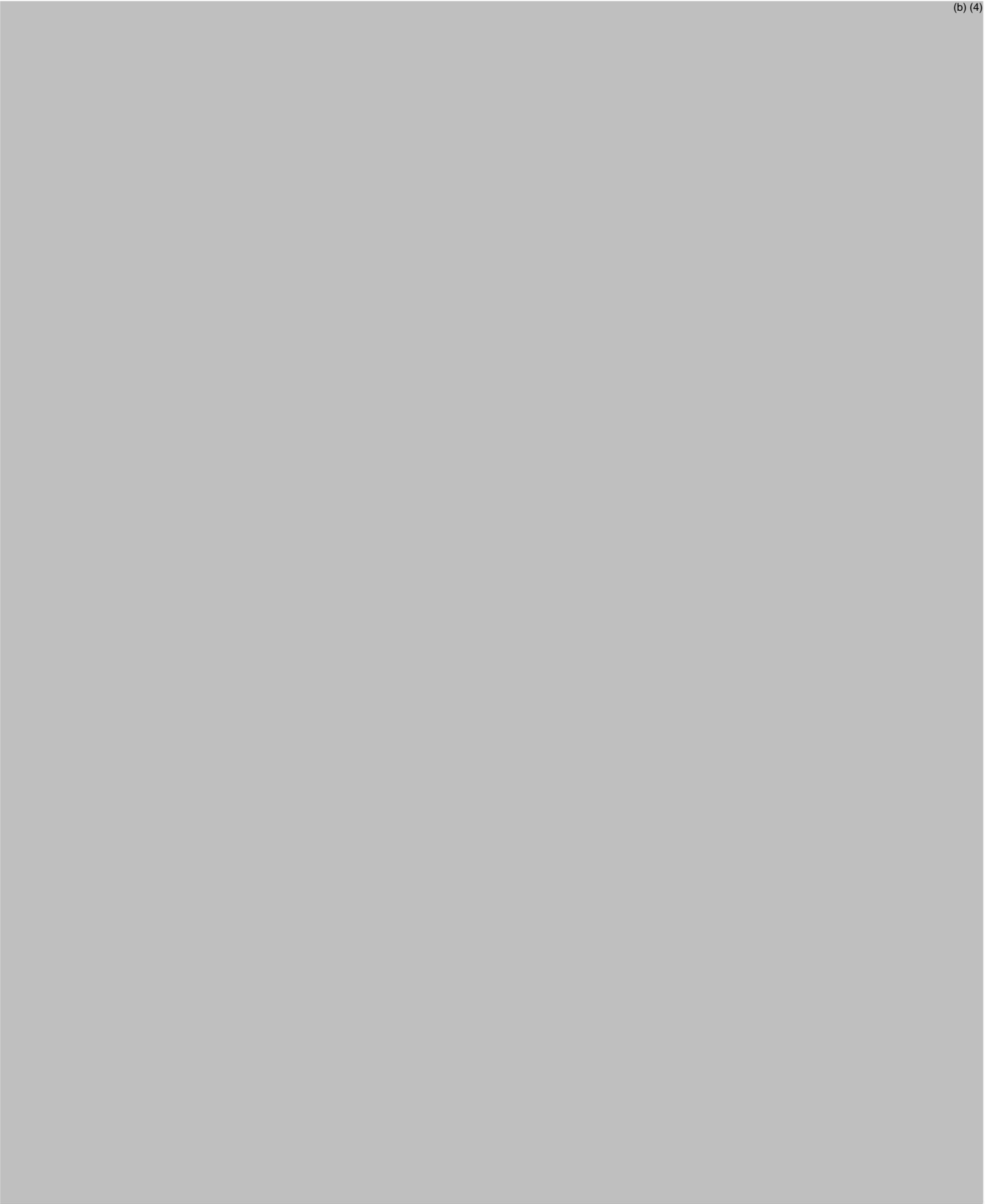
Reviewer' Comment: The method validation utilizing solid phase extraction is not acceptable, due to high rate of QC failures during validation. The method is not reliable to assure accuracy of the analytical runs. In most of the studies involving this method for sample analysis, there were very high rates of run failures and sample re-analysis (Please refer individual study reports, Section 4.2 of the review). Also, this method has been previously rejected by FDA DSI inspection team based on similar issues (Refer Review by Dr. Sriram Subramaniam DARRT dated Dec 7, 2005 for NDA 21795). However, the method that utilized liquid-liquid extraction technique for the sample preparation is robust, reproducible, and acceptable.

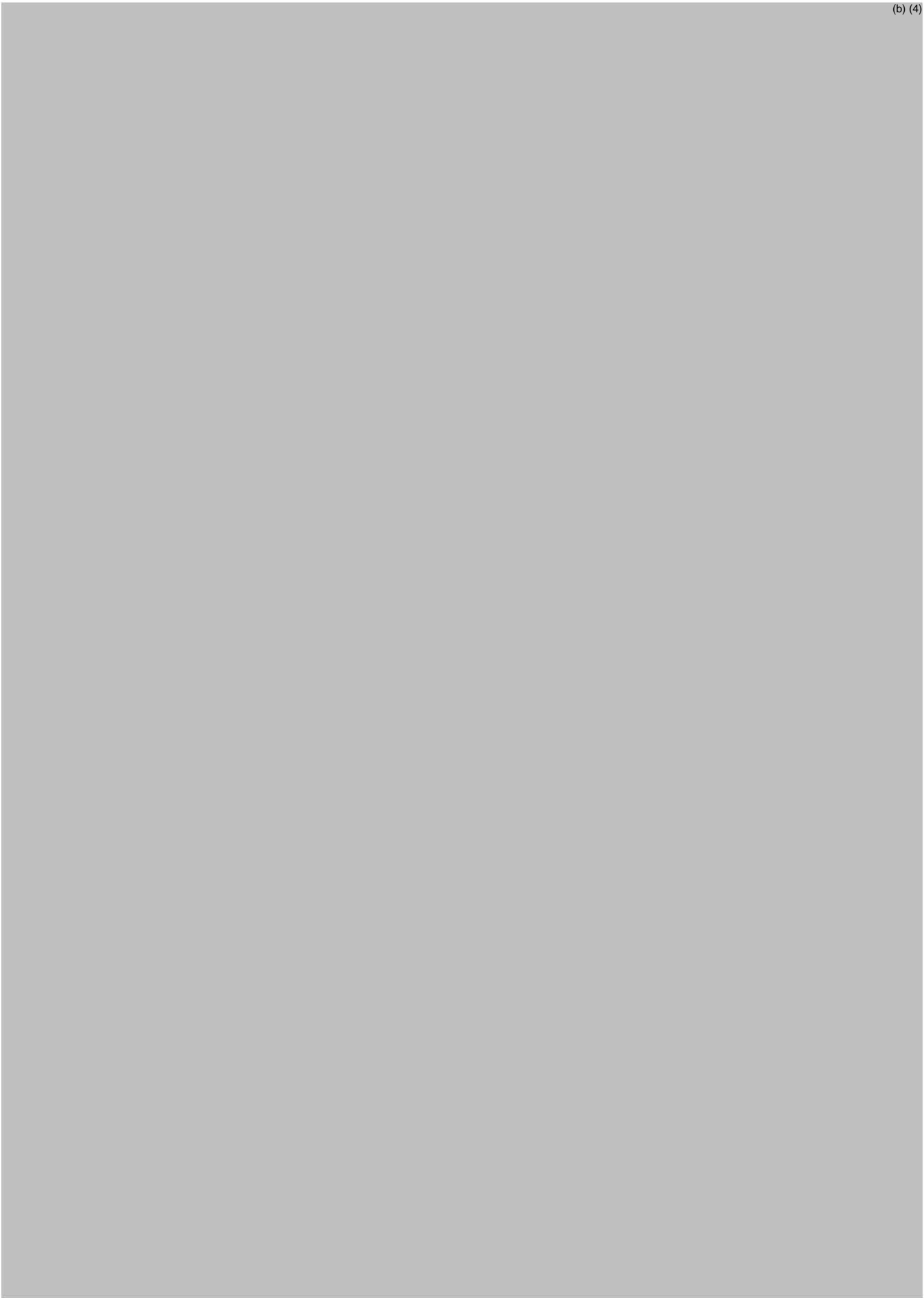
3 DETAILED LABELING RECOMMENDATION

The following are the labeling recommendations relevant to clinical pharmacology for NDA 22517. The ~~red-strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

(b) (4)







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4 APPENDIX

4.1 SPONSOR'S PROPOSED LABEL

4.2 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	22-517
Submission Number (Date)	N000, June 19, 2009
Compound	Nocdurna (Desmopressin Melt)
Clinical Division	DMEP / HFD 560
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Christoffer W. Tornoe, Ph.D.

4.2.1 Summary of Findings

4.2.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

4.2.1.1.1 Is there evidence of dose-response for effectiveness in men and women?

Yes, there is evidence of dose-response for effectiveness in both men and women in the short term pivotal efficacy trial (Part 1 of CS 29) and the long term trial (Part 2 of CS 29) as shown in Figure 14 and Figure 15, respectively. The figures show the time-profiles of both the co-primary endpoints (change from baseline in mean number of nocturnal voids and 33% responder rate) stratified by gender for various treatment groups. There is an increase in response with increasing doses of desmopressin for both women and men and a clear separation is observed between the 10- and 100- µg dose groups in both short term and long term trials.

In the short term trial, a clear separation between the treatment arms and placebo is observed for both co-primary endpoints at all time points in women as shown in Figure 14. For men, both 50- and 100- µg doses show a larger decline in the change from baseline in the mean number of nocturnal voids compared to placebo at all time points. For the 33% responder rate, whereas the 100 µg dose shows clear separation from placebo at all time points in men, the 50 µg dose shows treatment effect at all time points except on day 28 which was the pre-specified endpoint. In men, a decline in responder rate is observed for the treatment arms only on day 28 and an increase in the placebo arm due to inexplicable reasons. Statistically significant difference from placebo for both co-primary endpoints was achieved for the 100 µg dose group in men at all time points including day 28 (Table 17 and Table 18). While statistically significant difference from the placebo for both endpoints was achieved on day 22 for the 50 µg dose group in men, day 28 did not show statistical significance. The variability in response can be attributed to the fact that the clinical trial was not powered to show statistical significance based on gender, as this is the first study to observe gender differences in response. The choice of day 28 as the pre-specified endpoint was arbitrary and does not have any clinical significance because desmopressin has a short half-life (2.8 h) and it does not accumulate. Furthermore, its mechanism of action suggests an early onset of response. Desmopressin binds to the vasopressin receptors in the renal collecting ducts, thereby increasing water re-absorption and decreasing urine production.

In the long term trial, clear separation between the 10- and 100- μg dose groups is observed for both co-primary endpoints (Figure 15). Subjects from the placebo arm of Part I who were randomized to treatment arms were not included in the analysis. Because the placebo was removed in Part II, the black dotted lines in Figure 15 show the observation from day 28 carried forward. In the absence of a placebo-control in this open-label extension of the trial, a positive dose-response relationship is supportive of the long-term efficacy of the drug based on the E9 Guidance for Industry.

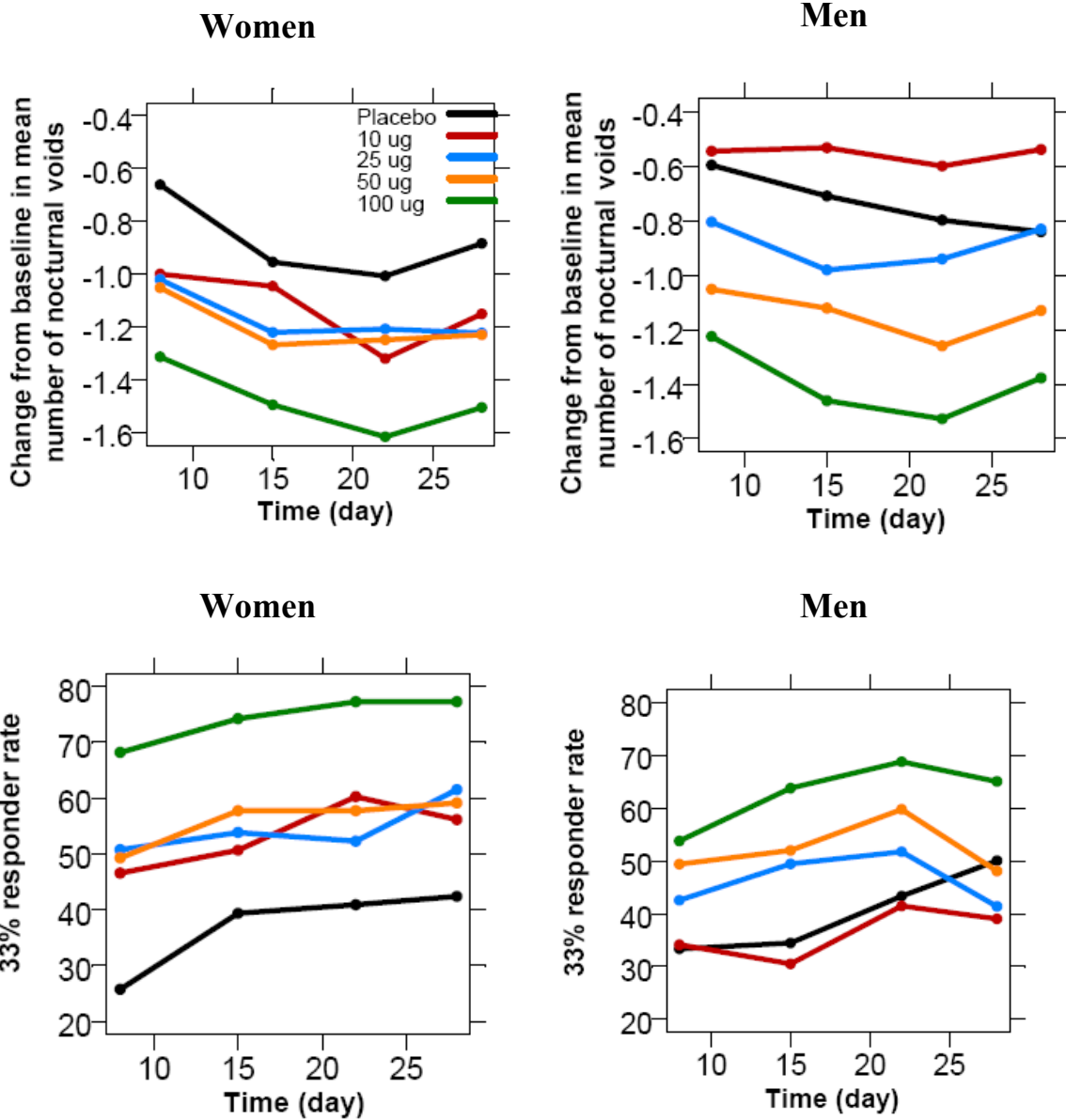


Figure 14: Time-profiles for change from baseline in mean number of nocturnal voids in (Top Left) women and (Top Right) men for various treatment arms in Part I of CS29. Corresponding time-profiles for 33% responder rate in (Bottom Left) women and (Bottom Right) men.

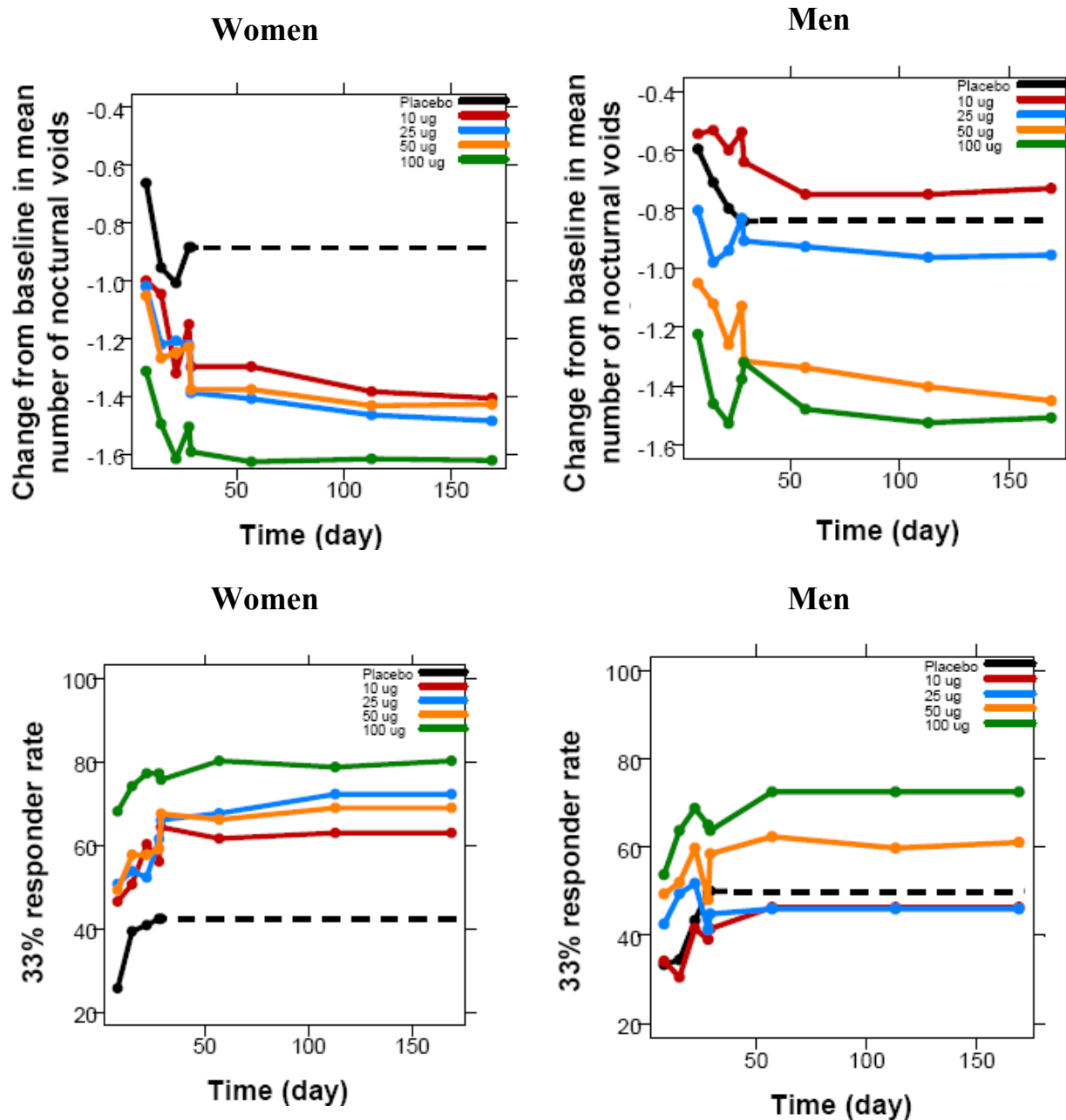


Figure 15: Time-profiles for change from baseline in mean number of nocturnal voids in (Top Left) women and (Top Right) men for various treatment arms in Part I and II of CS29. Corresponding time-profiles for 33% responder rate in (Bottom Left) women and (Bottom Right) men.

4.2.1.1.2 Is there evidence of dose-response for hyponatremia in men and women?

Yes, there is evidence of dose-response for hyponatremia in elderly men and women (age greater than 65 years) as shown in Figure 16. At the sponsor's proposed dose of 100 μg for men, 20% of the elderly subjects experienced hyponatremia ($\text{Na} < 130 \text{ mM}$). The proportion of subjects with hyponatremia increased with increasing dose (0–100 μg) in elderly men, suggesting that a lower dose would reduce the risk of hyponatremia. No cases of hyponatremia were observed in men less than 65 years for all doses.

While dose-response is also observed for elderly women, at the sponsor's proposed dose of 25 μg for women, only 5% of the elderly subjects developed hyponatremia which is lower than the placebo rate of 10%. No cases of hyponatremia were observed in women less than 65 years at the 25 μg dose.

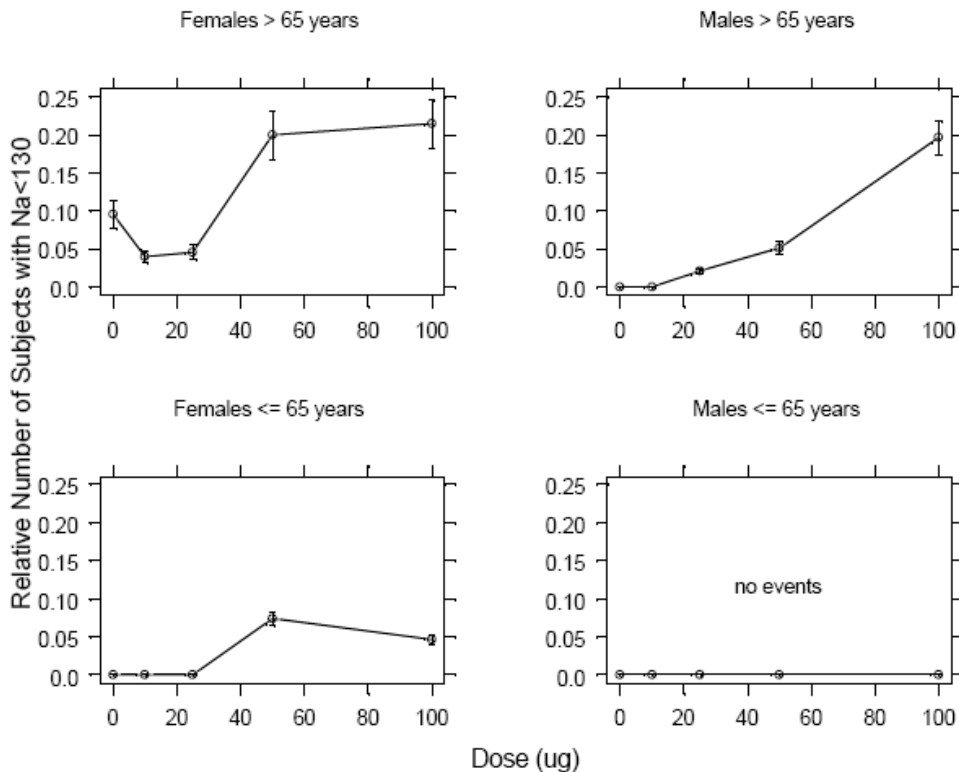


Figure 16: Proportion of subjects experiencing hyponatremia at 0-100 μg desmopressin doses stratified by gender and age.

Source: Sponsor's Figure 10 on page 20 in summary of modeling report

4.2.1.1.3 Is there evidence of gender-difference in effectiveness of desmopressin melt?

Yes, there is evidence of gender-difference in effectiveness based on data from the short term and long term trials (see Figure 14 and Figure 15) and women are more sensitive to the drug than men. This is particularly evident for the low dose groups (10 and 25 μg) where a large decrease in the mean number of voids is observed in women compared to men. For the 10 μg dose, a 2-fold (1.9-fold on day 8 and 2.1-fold on day 28) reduction in the mean number of nocturnal voids was observed in women compared to men. The difference was reduced in the highest dose group of 100 μg where only a 1.1-fold higher response was observed in women than men at all time point till day 28.

Gender-difference in effectiveness is further supported by the biomarker data from the trial, where women are 2-fold more sensitive to drug effect. The dose-response curves in women and men for decrease in urinary volume are shown in Figure 21. An increase in response is observed with increasing doses followed by a saturation phase where increasing dose does not further decrease nocturnal urine volume. The data show that

maximal response is achieved for doses of 25 µg in women and 50 µg in men. These findings also explain the reduced differences in response observed in women and men at the higher dose.

Gender differences in response are supported biologically. Vasopressin receptor (V₂R) is located on the X chromosome and has a high probability of escaping X inactivation in females, thereby increasing the expression of these receptors in females compared to men. Studies in Sprague-Dawley rats have shown a 1.7-fold higher expression of V₂R protein in females compared to males.

4.2.1.1.4 Is the proposed gender-based dose regimen (25 µg QD for women and 100 µg QD for men) appropriate?

No, 100 µg QD in men is not appropriate because of increased risk of hyponatremia in elderly men (age greater than 65 years), 20% of the subjects experienced hyponatremia at the 100 µg dose (Figure 16). The female dose of 25 µg QD is appropriate from a safety perspective with a relatively low proportion of elderly women (5%) experiencing hyponatremia and no cases of hyponatremia were observed for women less than 65 years at the 25 µg dose (Figure 16).

Since, there is evidence of dose-response for incidence of hyponatremia in elderly men (Figure 16), a lower male dose of 50 µg would result in a reduced risk of hyponatremia. At the 50 µg dose, only 5% of the elderly men experienced hyponatremia, which is comparable to elderly females at the 25 µg dose level and lower than the placebo hyponatremia rate of 10%. No cases of hyponatremia were observed in men less than 65 years for all doses (0–100 µg).

Short and long term efficacy data suggest comparable effectiveness for both the co-primary endpoints for women at 25 µg and men at 50 µg dose levels except for day 28 (Figure 14 and Figure 15). The onset of response for 25 and 50 µg in women and men is observed as early as 8 days after treatment. Dose-response plots for both co-primary endpoints on day 22 of the controlled trial (CS29 Part1) show comparable or slightly better effectiveness for men at 50 µg and women at 25 µg dose (Figure 17).

Thus, based on a reduced risk of hyponatremia and comparable effectiveness for men at the 50 µg dose with women at 25 µg dose, a reduced dose of 50 µg as the starting dose is recommended in men. In order to optimize the effectiveness in men less than 65 years, the dose may be titrated up to a maximum 100 µg daily dose by weekly dose escalations in 25 µg increments. Dose escalation for elderly men (age ≥ 65 years) is not recommended due to the increased risk of hyponatremia.

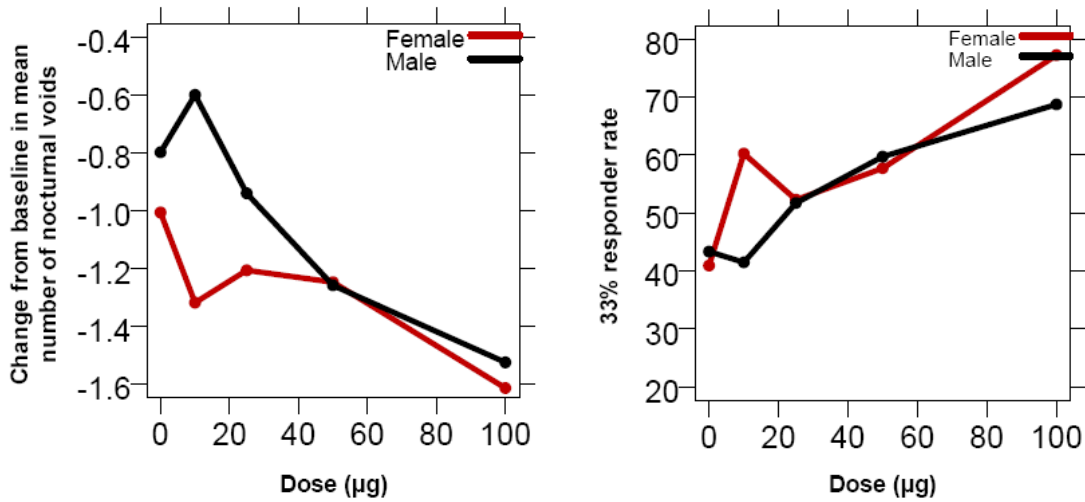


Figure 17: Dose-response plots for (Left) change from baseline in mean number of nocturnal voids and (Right) 33% responder rate for male and female subjects on day 22.

4.2.1.1.5 Is sodium monitoring in elderly men (age/gender based) needed?

No, sodium monitoring in elderly men is not needed at the reduced dose of 50 µg because the risk of hyponatremia is reduced to levels observed in elderly women at the 25 µg dose and placebo (Figure 16). However, at the sponsor’s proposed dose of 100 µg in men, sodium monitoring in elderly men would be needed.

4.2.1.2 Recommendations

The Division of Pharmacometrics recommends a reduced desmopressin dose of 50 µg as the starting dose in men. The dose may be titrated up to 100 µg dose by weekly dose escalations in 25 µg increments only for men less than 65 years to optimize efficacy. Dose escalation above the 50 µg starting dose for elderly men (age ≥ 65 years) is not recommended.

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4.2.1.3 Label Statements

The labeling recommendations relevant to clinical pharmacology for NDA 22517 are provided in Section 3. Please refer to the pharmacodynamics, dosage and administration sections of the detailed labeling recommendations

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4.2.2 Results of Sponsor's Analysis

4.2.2.1 Studies

Data from the pivotal Phase 3 trial (CS29) were used in this analysis. The trial was conducted in three parts and the study design is illustrated in Figure 18. The first part (Part I of CS 29) was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study investigating the efficacy and safety of 4 doses (10, 25, 50 or 100 µg) of desmopressin melt administered for 28 days for the treatment of nocturia in adults. The co-primary endpoints of the trial were change from baseline in the mean number of nocturnal voids and proportion of subjects with > 33% reduction in the mean number of nocturnal voids (referred as 33% responder rate) on Day 28 of the trial. Upon completion of Part I, all subjects on active treatment were allowed to continue into Part II on the same treatment for approximately 1 to 6 months. Subjects from the placebo arm in Part I, were re-randomized to the four treatment groups. CS31 is an ongoing long-term, open-label efficacy and safety study.

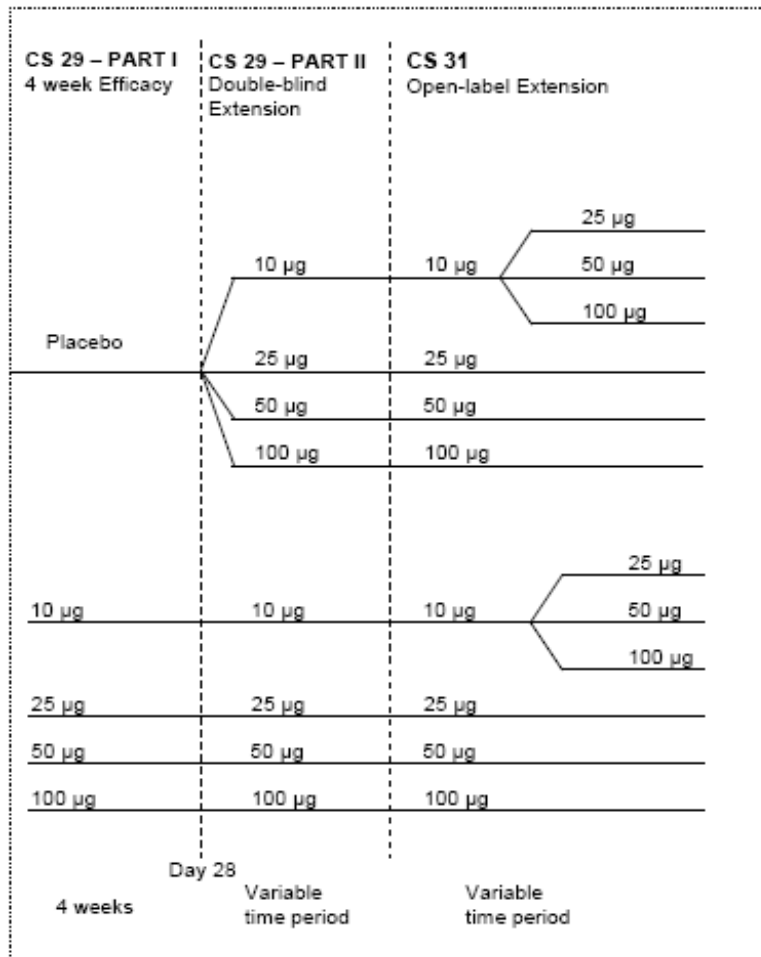


Figure 18: Study design of the pivotal trial CS29.

Source: Sponsor's Figure 1 on page 10 in Summary of Clinical Efficacy

4.2.2.2 Results

4.2.2.2.1 Dose-Response Analysis

The time-profiles of both co-primary endpoints for various treatment groups in Part I of CS29 are shown in Figure 19. Overall, an increase in response is observed with increasing doses of desmopressin. For the change from baseline in mean number of nocturnal voids (first co-primary endpoint), both 50 and 100 µg doses were statistically significant at all time points. For the 33% responder rate (second co-primary endpoint), the 50 µg dose was statistically significant at all time points except for day 28. The 100 µg dose was statistically significant at all time points.

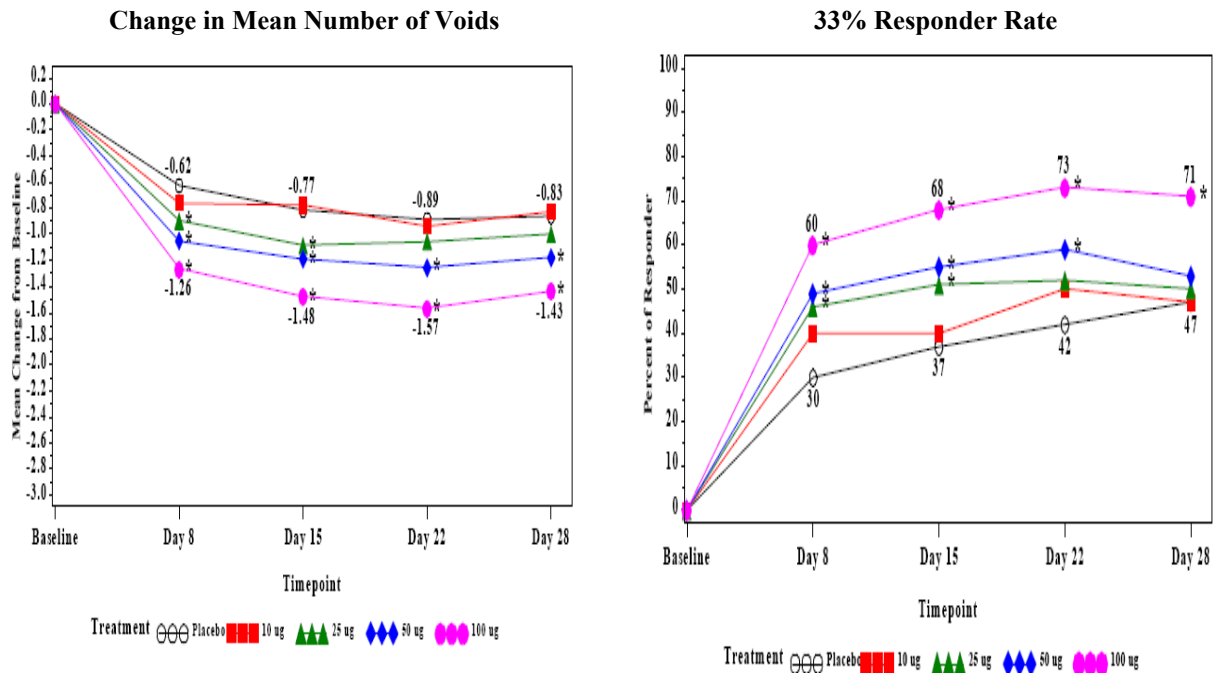


Figure 19: Time-profiles for (Left) change from baseline in mean number of nocturnal voids and (Right) 33% responder rate for various treatment arms in Part I of CS29. The various treatment arms placebo, 10, 25, 50 and 100 µg of desmopressin are denoted by black, red, green, blue and pink lines. Various time points include baseline and days 8,15, 22 and 28. * denotes statistical difference versus placebo, $p \leq 0.05$. The absolute values for the placebo and 100 µg treatment arms are denoted in the figure.

Source: Sponsor's Figures 2 and 3 on pages 31-32 in Summary of Clinical Efficacy

The efficacy data was further stratified based on gender and are shown in Table 17 and Table 18. The p-values denoting statistical significance for the co-primary endpoints for the four doses are also shown. For women, the 25 µg dose was determined to be the minimum effective dose as statistical significance was achieved for both the co-primary endpoints ($p=0.02$ and $p=0.0197$). For men, statistical significance for the both the co-primary endpoints was achieved only for the 100 µg dose ($p<0.0001$). Thus, sponsor's proposed dose is 25 µg for women and 100 µg for men.

Table 17: Statistical Analysis of Mean Number of Nocturnal Voids by Gender

Nocturnal Voids	Placebo	10 µg	25 µg	50 µg	100 µg
Males					
	(N=90)	(N=82)	(N=87)	(N=77)	(N=80)
Day 8					
Mean (SD)	2.60 (1.234)	2.57 (1.187)	2.60 (1.374)	2.55 (1.205)	2.20 (1.422)
Mean Δ (SD)	-0.60 (1.123)	-0.54 (0.938)	-0.80 (1.011)	-1.05 (1.221)	-1.23 (1.193)
p-value vs. placebo		p=0.9360	p=0.3606	p=0.0496*	p=0.0004*
Day 15					
Mean (SD)	2.48 (1.155)	2.58 (1.336)	2.42 (1.271)	2.48 (1.204)	1.96 (1.363)
Mean Δ (SD)	-0.71 (1.014)	-0.53 (1.017)	-0.98 (1.025)	-1.12 (1.221)	-1.46 (1.140)
p-value vs. placebo		p=0.3442	p=0.1892	p=0.0836	p<0.0001*
Day 22					
Mean (SD)	2.39 (1.217)	2.51 (1.438)	2.46 (1.442)	2.34 (1.240)	1.90 (1.245)
Mean Δ (SD)	-0.80 (1.041)	-0.60 (1.116)	-0.94 (1.106)	-1.26 (1.121)	-1.53 (1.085)
p-value vs. placebo		p=0.2779	p=0.6123	p=0.0339*	p<0.0001*
Day 28					
Mean (SD)	2.35 (1.175)	2.57 (1.319)	2.57 (1.351)	2.47 (1.224)	2.05 (1.554)
Mean Δ (SD)	-0.84 (1.092)	-0.54 (0.987)	-0.83 (1.149)	-1.13 (1.297)	-1.38 (1.281)
p-value vs. placebo		p=0.0944	p=0.5894	p=0.3778	p=0.0049*
Females					
	(N=66)	(N=73)	(N=65)	(N=71)	(N=66)
Day 8					
Mean (SD)	2.72 (1.248)	2.32 (1.151)	2.25 (1.745)	2.10 (1.130)	1.67 (1.038)
Mean Δ (SD)	-0.66 (1.047)	-1.00 (1.132)	-1.02 (1.153)	-1.05 (1.031)	-1.31 (1.244)
p-value vs. placebo		p=0.0424*	p=0.0271*	p=0.0094*	p<0.0001*
Day 15					
Mean (SD)	2.43 (1.209)	2.28 (1.258)	2.05 (1.482)	1.88 (0.997)	1.48 (0.965)
Mean Δ (SD)	-0.95 (1.014)	-1.05 (1.225)	-1.22 (1.309)	-1.27 (0.980)	-1.49 (1.124)
p-value vs. placebo		p=0.4737	p=0.0637	p=0.0176*	p<0.0001*
Day 22					
Mean (SD)	2.38 (1.266)	2.00 (1.087)	2.06 (1.479)	1.90 (1.055)	1.36 (0.974)
Mean Δ (SD)	-1.01 (0.989)	-1.32 (1.101)	-1.21 (1.113)	-1.25 (1.006)	-1.62 (1.114)
p-value vs. placebo		p=0.0371*	p=0.1247	p=0.0445*	p<0.0001*
Day 28					
Mean (SD)	2.50 (1.238)	2.17 (1.143)	2.05 (1.488)	1.92 (1.108)	1.47 (0.977)
Mean Δ (SD)	-0.88 (1.008)	-1.15 (1.072)	-1.22 (1.060)	-1.23 (1.062)	-1.51 (1.145)
p-value vs. placebo		p=0.0721	p=0.0200*	p=0.0091*	p<0.0001*

Δ = change; SD = standard deviation; BL = baseline

* Statistically significant difference versus placebo, $p \leq 0.05$.

Note: Treatment difference based on linear model adjusted for age, absence/presence of nocturnal polyuria, and baseline number of nocturnal voids.

Source: Sponsor's Table 17 on page 34 in Summary of Clinical Efficacy report. * denotes statistical significance ($p \leq 0.05$).

Table 18: Statistical Analysis of Responder Rate by Gender

>33% Responder	Placebo	10 µg	25 µg	50 µg	100 µg
Males					
	(N=90)	(N=82)	(N=87)	(N=77)	(N=80)
Day 8 p-value vs. placebo ^a	30 (33%)	28 (34%) p=0.8677	37 (43%) p=0.2069	38 (49%) p=0.0408*	43 (54%) p=0.0072*
Day 15 p-value vs. placebo ^a	31 (34%)	25 (30%) p=0.5819	43 (49%) p=0.0380*	40 (52%) p=0.0179*	51 (64%) p=0.0001*
Day 22 p-value vs. placebo ^a	39 (43%)	34 (41%) p=0.7683	45 (52%) p=0.2543	46 (60%) p=0.0261*	55 (69%) p=0.0005*
Day 28 p-value vs. placebo ^a	45 (50%)	32 (39%) p=0.1502	36 (41%) p=0.2225	37 (48%) p=0.7375	52 (65%) p=0.0477*
Females					
	(N=66)	(N=73)	(N=65)	(N=71)	(N=66)
Day 8 p-value vs. placebo ^a	17 (26%)	34 (47%) p=0.0102*	33 (51%) p=0.0025*	35 (49%) p=0.0049*	45 (68%) p<0.0001*
Day 15 p-value vs. placebo ^a	26 (39%)	37 (51%) p=0.1564	35 (54%) p=0.0705	41 (58%) p=0.0269*	49 (74%) p<0.0001*
Day 22 p-value vs. placebo ^a	27 (41%)	44 (60%) p=0.0189*	34 (52%) p=0.1496	41 (58%) p=0.0444*	51 (77%) p<0.0001*
Day 28 p-value vs. placebo ^a	28 (42%)	41 (56%) p=0.0880	40 (62%) p=0.0197*	42 (59%) p=0.0405*	51 (77%) p<0.0001*

* Statistically significant difference versus placebo, $p \leq 0.05$.

a. p-values from logistic regression analysis

Source: Sponsor's Table 18 on page 35 in Summary of Clinical Efficacy report. * denotes statistical significance ($p \leq 0.05$).

The safety data was also stratified by age and gender. Figure 16 shows the proportion of subjects with hyponatremia ($Na < 130mM$) versus dose. For men and women less than 65 years of age, at the sponsor's recommended dose of 100 and 25 µg, no incidence of hyponatremia was observed. For elderly women (age > 65 years), at the 25 µg dose, 5% of the subjects experienced hyponatremia. For elderly males, an increase in response was observed with increasing doses of desmopressin and a relatively high proportion of subjects (20%) experienced hyponatremia at the 100 µg dose. Thus, the sponsor's proposed sodium monitoring in elderly men (age ≥ 65 years) on day 4 and one month of treatment.

4.2.2.3 Population-Pharmacodynamic Model

An E_{max} dose-response model with weight adjusted dose (dose/weight) and with linear placebo effect was used to describe the dose effect on nocturnal urine volume data from Part I of study CS29. The day 28 nocturnal urine volume (V) was describes as:

$$V = (\alpha + \beta V_{base}) \left(1 - \frac{E_{max} d_n}{ED_{50} + d_n} \right)$$

$$d_n = \frac{dose}{body\ weight / 80}$$

where, V_{base} is the pre-dose urine volume and $(\alpha + \beta V_{base})$ represents the placebo effect. Categorized covariates gender, weight (grouped according to $<$, ≥ 80 kg) and age (grouped according to $<$, ≥ 60 years) on ED_{50} were tested. Tests of covariates showed that

gender difference on weight corrected ED₅₀ was a significant covariate. Final parameter estimates and the fitted profiles of nocturnal urine volume versus dose are shown in Table 22 and Figure 22 in Appendix A. Parameter estimates indicate that females have a lower ED₅₀ than males suggesting higher sensitivity of the drug in females. The relative sensitivity of (ED₅₀ for males/ ED₅₀ for females) was estimated as 2.7 with a 95% CI of 1.3-8.1.

4.2.2.4 Conclusions

- The 25 and 100 µg doses were recommended for women and men as these were determined to be the minimum effective doses where statistical significance was achieved for both co-primary endpoints.
- Sodium monitoring was recommended on day 4 and one month of treatment for elderly males (age ≥ 65 years) based on the high incidence of hyponatremia in this patient group.

Reviewer's comments on Sponsor's Analysis:

- *The sponsor's gender based dose selection was purely driven by p-value and did not consider the magnitude of both the co-primary endpoints. The clinical trial was not powered to show statistical significance by gender.*
- *The sponsor's recommended dose of 100 µg in men significantly increases the risk of hyponatremia in elderly men.*
- *The sponsor's proposed sodium monitoring scheme (day 4 and one month of treatment) is not guaranteed to decrease the incidence of hyponatremia. It might be better to reduce the dose to 50 µg in elderly men where there is lower incidence of hyponatremia.*
- *The sponsor's population pharmacodynamic model is generally adequate and acceptable. The sponsor's 2.7-fold higher sensitivity in females is consistent with a 2-fold higher sensitivity shown in the reviewer's analysis.*

4.2.3 Results of REVIEWER's Analysis

4.2.3.1 Objectives

The reviewer's analysis objectives are:

1. To determine whether sponsor's gender-based dose regimen (25 µg QD for women and 100 µg QD for men) is appropriate?
2. To determine whether sodium monitoring in elderly men (age/gender based) is needed?

4.2.3.2 Methods

4.2.3.2.1 Data Sets

Data sets used are summarized in Table 19.

Table 19: Analysis Data Sets.

Study Number	Name	Link to EDR
CS29 Part I	advd-1.xpt adsl-1.xpt	\\Cdsub1\evsprod\NDA022517\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nocturia\5351-stud-rep-contr\fe992026cs29\datasets\analyses
CS 29 Part II	advd-1.xpt adsl-2.xpt	\\Cdsub1\evsprod\NDA022517\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nocturia\5351-stud-rep-contr\fe992026cs29\datasets\analyses

4.2.3.2.2 Software

S-PLUS and SAS were used for the reviewer's analyses.

4.2.3.3 Results

4.2.3.3.1 *Dose-Response Analysis for Efficacy*

The time-profiles of both the co-primary endpoints stratified by gender for various treatment groups in Part I of CS29 are shown in Figure 14. There is an evidence of dose-response as increase in response is observed with increasing doses of desmopressin for both women and men. For women, clear separation between the treatment arms and placebo is observed for both co-primary endpoints at all time points. For men, both 50 and 100 µg doses show a larger decline in the change from baseline in the mean number of nocturnal voids compared to placebo at all time points. For the 33% responder rate, whereas the 100 µg dose shows clear separation from placebo at all time points in men, the 50 µg dose shows treatment effect at all time points except on day 28. In men, a decline in responder rate is observed for the treatment arms due to inexplicable reasons only at day 28 which was the pre-specified endpoint.

As explained earlier, the sponsor's rationale for selecting 25 in women and 100 µg in men was purely driven by p-values (Table 17) obtained on day 28 and the magnitude of anti-diuretic effect (absolute values of both the co-primary endpoints) was not considered. When the magnitude of response is compared between women and men, it is observed that up to day 22, men at 50 µg dose show similar or slightly better response as women at 25 µg dose. This can be visualized clearly on the dose-response curve for day 22 in Figure 17. Day 22 was considered in our analysis because as explained earlier day 28 did not have any clinical significance and based on the short half-life (2.5 hours) and the drug's mechanism of action, an early onset of response is expected.

Since, a decline in response was observed on day 28, it was worthwhile to explore whether the decline was indicative of loss of treatment effect. Thus long term data from Part II of the trial was pooled with data from Part I. Figure 15 shows the time-profiles of the primary endpoints stratified by gender utilizing data from Part I and Part II of CS29. For all the missing data, the last observation was carried forward (LOCF). Subjects from the placebo arm of Part I who were randomized to treatment arms were not included in the analysis. Since the placebo was removed in Part II, the black dotted lines show the observation from day 28 carried forward. Overall an increase in response is observed in the long-term study and the decline in response on day 28 was not sustained. At the end of Part II of the trial, comparable efficacies were observed for women at 25 µg and men at 50 µg dose levels. The change from baseline in the mean number of nocturnal voids was -1.48 for women at 25 µg and -1.45 for men at 50 µg doses on day 169 at the end of part 2 of the trial. The 33% response rate was 72.3% and 61% for women at 25 µg and men at 50 µg doses respectively.

In Part I, a total of 799 subjects were randomized to treatment. 11% of the subjects prematurely discontinued and among treatment groups, discontinuation varied from 6 to 16 % (Table 20). Among the 710 subjects who completed Part I, 665 subjects continued to Part II. 15% of the subjects in Part II discontinued prematurely and the discontinuation among various treatment groups varied from 9% to 24% (Table 21).

Table 20: Subject Disposition for CS29 (Part I)

	Placebo	10 µg	25 µg	50 µg	100 µg	Total
Randomized	160	163	158	158	160	799
Completed, N (%)	145 (91%)	144 (88%)	148 (94%)	138 (87%)	135 (84%)	710 (89%)
Prematurely withdrawn	15 (9%)	19 (12%)	10 (6%)	20 (13%)	25 (16%)	89 (11%)
Adverse event	1 (1%)	4 (2%)	0	5 (3%)	6 (4%)	16 (2%)
Serum sodium ≤125 mmol/L	1 (1%)	0	0	5 (3%)	4 (3%)	10 (1%)
Protocol violation	2 (1%)	0	0	0	1 (1%)	3 (<1%)
Patient withdrew consent	6 (4%)	5 (3%)	6 (4%)	4 (3%)	9 (6%)	30 (4%)
Lost to follow-up	2 (1%)	4 (2%)	1 (1%)	5 (3%)	3 (2%)	15 (2%)
Other	2 (1%)	4 (2%)	0	1 (1%)	1 (1%)	8 (1%)
Not reported	1 (1%)	2 (1%)	3 (2%)	0	1 (1%)	7 (1%)

Source: Sponsor's Table 8 on page 47 in Study Report of FE992026cs29 (Study 29).

Table 21: Subject Disposition for CS29 (Part II)

	10 µg	25 µg	50 µg	100 µg	Placebo to:				Total
					10 µg	25 µg	50 µg	100 µg	
Randomized	135	135	132	127	31	37	34	34	665
Completed, N (%)	107 (79%)	120 (89%)	120 (91%)	107 (84%)	25 (81%)	32 (86%)	29 (85%)	26 (76%)	566 (85%)
Prematurely withdrawn	28 (21%)	15 (11%)	12 (9%)	20 (16%)	6 (19%)	5 (14%)	5 (15%)	8 (24%)	99 (15%)
Withdrew consent	15 (11%)	7 (5%)	7 (5%)	10 (8%)	4 (13%)	2 (5%)	3 (9%)	2 (6%)	50 (8%)
Adverse event	2 (1%)	3 (2%)	1 (1%)	1 (1%)	1 (3%)	1 (3%)	1 (3%)	4 (12%)	14 (2%)
Lost to follow-up	3 (2%)	2 (1%)	0	5 (4%)	0	1 (3%)	0	0	11 (2%)
Decreased sodium	0	0	0	1 (1%)	0	0	1 (3%)	1 (3%)	3 (1%)
Excluded medication	1 (1%)	0	0	0	0	0	0	0	1 (<1%)
Other	4 (3%)	2 (1%)	4 (3%)	2 (2%)	1 (3%)	1 (3%)	0	1 (3%)	15 (2%)
Not reported	3 (2%)	1 (1%)	0	1 (1%)	0	0	0	0	5 (1%)

Source: Sponsor's Table 9 on page 47 in Study Report of FE992026cs29 (Study 29).

In the combined Part I and Part II of the study, 29% of the subjects withdrew prematurely. Since, the LOCF method to impute missing data is known to be sensitive to the drop-out rates in the trial, pooled data from Part I and Part II were analyzed using the mixed-effect model repeated measures (MMRM) approach which is a likelihood-based method and is known to be more robust to the drop-out rates in the trial. Figure 20 shows the predicted response-time profiles for the change and percent change from baseline in the mean number of nocturnal voids stratified by gender using the MMRM approach. The continuous variable, percentage change from baseline was calculated instead of the 33% responder rate (categorical) in order to perform the MMRM analysis using the model specified below:

$$\text{Mean or \% change in \# of voids} = \text{Dose} + \text{Time} + \text{Baseline} + \text{Dose*Time}$$

Consistent with the LOCF analysis, the decline in response on day 28 was not sustained and overall there is an increase in response with time. Again, comparable efficacies were observed for women at 25 µg and men at 50 µg dose levels at the end of Part II of the study. Thus, based on both short and long-term data, a 2-fold higher dose is needed in men to obtain similar response as in women.

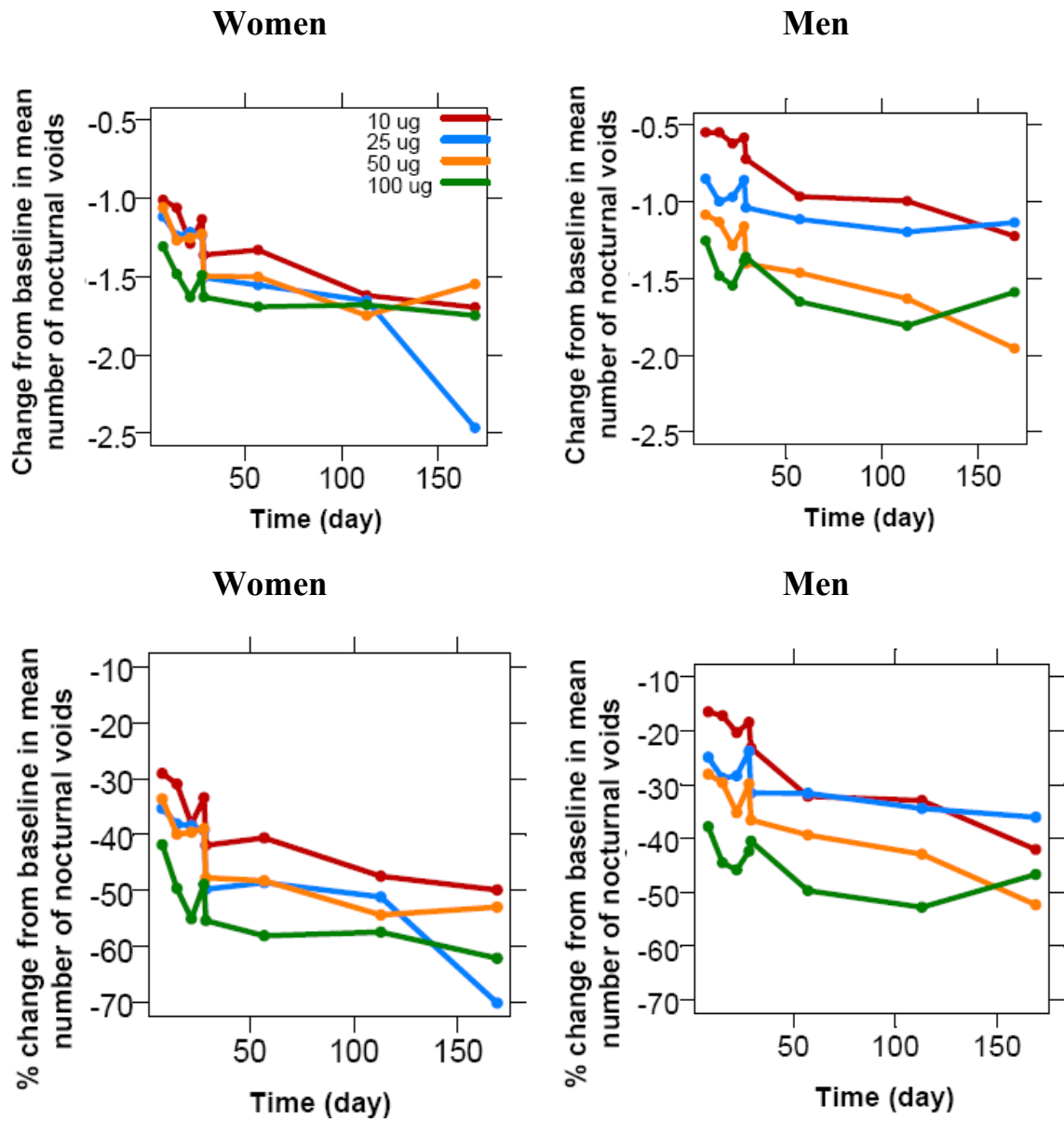


Figure 20: Time-profiles for change from baseline in mean number of nocturnal voids in A) women and B) men for various treatment arms in Part I and II of CS29. Corresponding time-profiles of percentage change from baseline in nocturnal voids in C) women and D) men.

A 2-fold higher dose in men is also supported by the biomarker data. The dose-response curves in women and men for decrease in urinary volume are shown in Figure 21. An increase in response is observed with increasing doses followed by a saturation phase where increasing dose does not decrease the nocturnal urine volume further. The data shows the desmopressin dose at which the maximal response is achieved is 25 μg in women and 50 μg in men. This suggests a 2-fold higher sensitivity to the drug in women compared to men. This is also consistent with a 2.7-fold higher sensitivity shown by sponsor’s population pharmacodynamic model. The maximum response (E_{max}) was similar in both women and men and was equal to 300 ml.

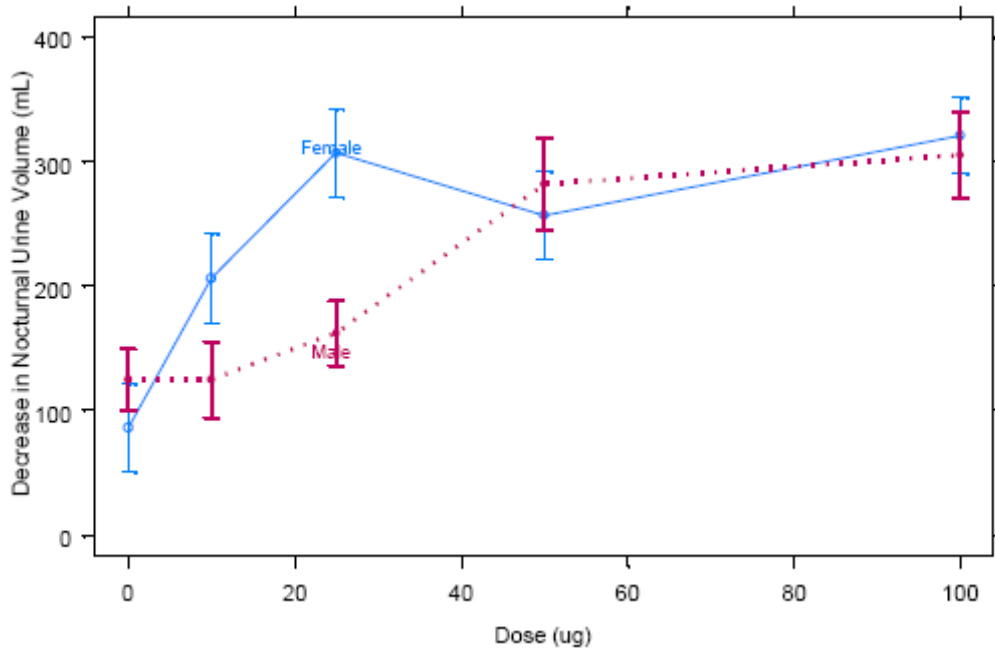


Figure 21: Dose-response curve for decrease in urinary volume in women and men.
 Source: Sponsor's Figure 3 on page 12 in Modeling Report and Sponsor's Figure 2 on page 17 in Clinical Overview Report

4.2.3.3.2 Dose-Response Analysis for Safety

A serious treatment related adverse event experienced by patients in the pivotal study CS29 was hyponatremia. Hyponatremia is known to potentially cause seizures and coma that can lead to death. A dose-response analysis for the proportion of hyponatremic subjects with $\text{Na} < 130 \text{ mM}$, shows an increase with increasing doses in elderly men (age > 65 years) (Figure 16). In elderly men, at the sponsor's proposed dose of $100 \mu\text{g}$, 20% of the subjects experienced hyponatremia. This was 4-fold higher than the proportion of elderly women who developed hyponatremia at the sponsor's proposed dose of $25 \mu\text{g}$. Thus, the sponsor has recommended sodium monitoring in elderly men. At the $50 \mu\text{g}$ dose, a significant reduction in the risk of hyponatremia is observed in men. At this dose only 5% of the elderly men experienced hyponatremia which is comparable to elderly women at the $25 \mu\text{g}$ dose and the placebo hyponatremia rate. Thus sodium monitoring will not be needed in elderly men at the $50 \mu\text{g}$ dose level. For men of age ≤ 65 years, no incidence of hyponatremia was observed across all doses. For women of age ≤ 65 years, no incidence of hyponatremia was observed at the $25 \mu\text{g}$ dose level.

4.2.3.4 Conclusions

- $100 \mu\text{g}$ QD dose in men is not appropriate due to safety concerns. $25 \mu\text{g}$ QD dose for women is appropriate. A reduced dose of $50 \mu\text{g}$ as the starting dose is recommended in men. The daily dose may be titrated up to a maximum $100 \mu\text{g}$ daily dose by weekly dose escalation in $25 \mu\text{g}$ increments only for men less than 65 years of age to optimize efficacy. Dose escalation for elderly men (age ≥ 65 years) is not recommended due to the increased risk of hyponatremia.

- Sodium monitoring in elderly men will not be needed at the reduced dose of 50 µg. However, at the sponsor's proposed dose of 100 µg in men, sodium monitoring in elderly men would be needed.

APPEARS THIS WAY ON ORIGINAL

4.2.4 APPENDIX A: Results of SPONSORS's POPULATION Analysis

Table 22: Parameter Estimates for the Nocturnal Urine Volume Model

Parameter	Estimate	SE
E_{max} (none)	0.364	0.084
ED ₅₀ (males) (μg)	43.2	21.7
ED ₅₀ (females) (μg)	16.1	15.9
Relative Sensitivity (Female/Male)	2.68	1.67
α (mL)	136	24.2
β (none)	0.696	0.033
Residual SD	229	8.3

Source: Sponsor's Table 4 on page 13 in Modeling Report.

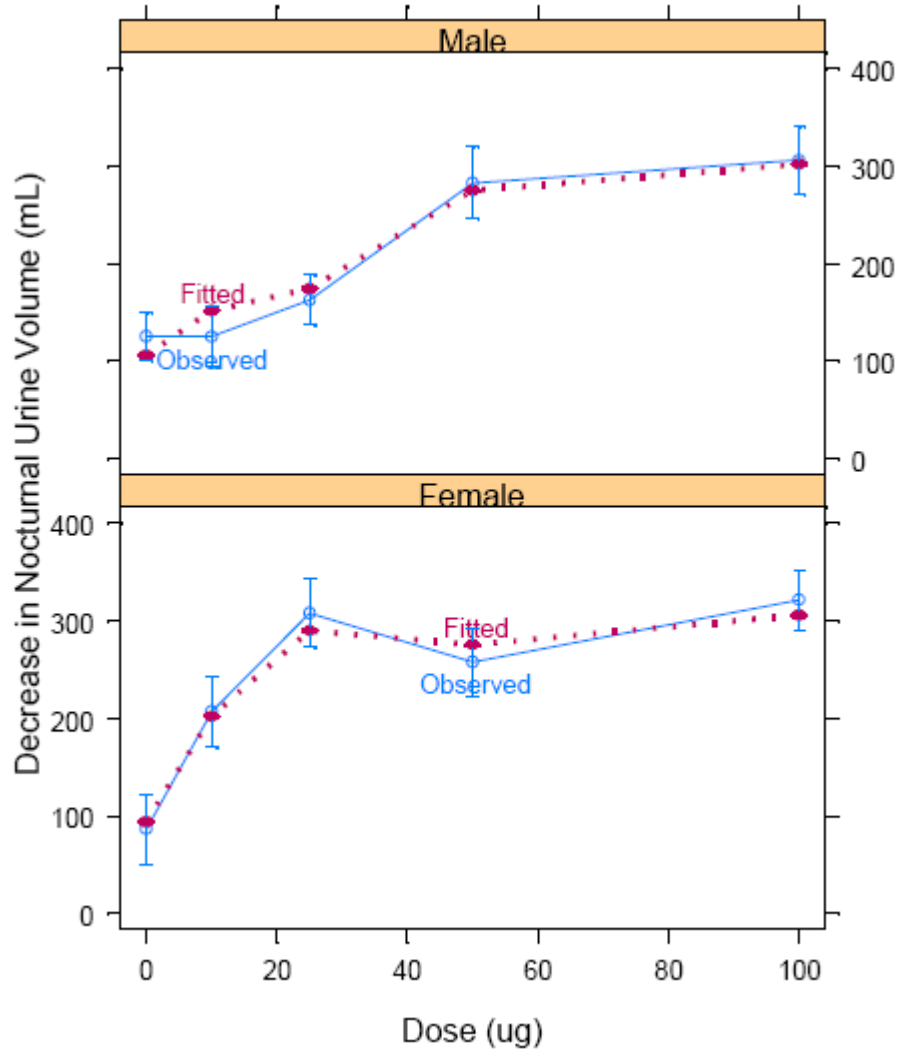


Figure 22: Mean observed and fitted decrease in urinary volume by gender and dose.
Source: Sponsor's Figure 4 on page 14 in Modeling Report.

4.3 INDIVIDUAL STUDY REVIEW

4.3.1 Study FE992026 CS001- Single dose pharmacokinetics after intravenous administration of desmopressin in healthy volunteers and patients with mild, moderate and severe renal impairment

NOC DURNA

1(3)

Clinical Study Report

FE992026 CS001
Desmopressin and renal impairment

Minirin®

SYNOPSIS (based on CSR dated 22 August 2002 and CSR Erratum dated 29 May 2009)

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Minirin®	Volume:	
Name of Active Ingredient: Desmopressin	Page:	
Title of Study: Single Dose Pharmacokinetics after Intravenous Administration of Desmopressin in Healthy Volunteers and Patients with Mild, Moderate and Severe Renal Impairment		
Investigator(s): Karl-Heinz Molz, MD		
Study centre(s): APEX Research GmbH, Landsbergerstrasse 476, D-81241 Munich, Germany		
Publication (reference): N.A.		
Studied period: Date of first enrolment: 19.10.2000 Date of last completion: 20.02.2001	Phase of development: I/II	
Objectives: <i>Primary objective:</i> To investigate the pharmacokinetics of intravenous administration of desmopressin in subjects with mild, moderate and severe renal impairment compared to subjects with normal renal function. <i>Secondary objectives:</i> To investigate safety and tolerability of intravenous desmopressin in this study population.		
Methodology: Prospective, controlled, single intravenous administration study.		
Number of patients (planned and analysed): A total of 24 subjects were enrolled in the study: 18 subjects with varying degrees of renal impairment and 6 normal, healthy volunteers. Subjects were stratified on the basis of their renal function to one of the four groups:		
<i>Group</i>	<i>Creatinine Clearance</i>	<i>Renal function</i>
1	> 80 mL/min	Normal
2	50-80 mL/min	Mildly impaired
3	30-49 mL/min	Moderately impaired
4	5-29 mL/min	Severely impaired
	<i>N</i>	
	6	6
	6	6
	6	6
	6	6
Diagnosis and main criteria for inclusion: Subjects were to be male or female Caucasian aged 18-70 years. Subjects with normal renal function were to be healthy. Subjects with mildly, moderately and severely impaired renal function were to have an estimated creatinine clearance as stated above and were to be stable in terms of any co-incident disease.		
Test product, dose and mode of administration, batch number: Minirin® 4 µg/mL solution for injection in 1mL ampoule. Dose: 2 µg (0.5 mL) desmopressin acetate corresponding to 1.78 µg desmopressin free base, by intravenous administration. Batch number: BB 6089.		
Duration of treatment: one single dose.		
Reference therapy, dose and mode of administration, batch number: Not applicable.		

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Minirin®	Volume:	
Name of Active Ingredient: Desmopressin	Page:	
CRITERIA FOR EVALUATION: PHARMACOKINETICS: The pharmacokinetic parameters included the maximum plasma concentration (C_{max}), time of maximum plasma concentration (t_{max}), area under the plasma concentration-time curve to infinity (AUC) and from time zero to time t (AUC_t), rate constant associated with the first (λ_1) and second (λ_2) exponential phase of the plasma concentration-time curve, half-lives associated with the first ($t_{1/2,1}$) and second ($t_{1/2,2}$) exponential phase of the desmopressin concentration-time curve, total systemic clearance (CL), initial volume of distribution (V_1) and the volumes of distribution at the terminal phase (V_2) and at steady state (V_{ss}), fraction of drug eliminated during the first (f_1) and second (f_2) exponential phase of the plasma concentration curve, cumulative amount of drug excreted unchanged in the urine (A_e), renal clearance (CL_R) and fraction of drug eliminated unchanged in the urine (f_e). SAFETY: The safety assessments included adverse events, biochemistry, haematology and vital signs (blood pressure, pulse rate and body weight). STATISTICAL METHODS: PHARMACOKINETICS: Pharmacokinetic analysis was to be performed on all subjects who received a single dose of desmopressin and who belonged to the intention-to-treat (ITT) and per protocol (PP) populations. The PP population was the primary population for analysis. The ITT population consisted of all subjects who received any trial medication and who contributed to any pharmacokinetic data. The PP population consisted of ITT evaluable subjects who were not major protocol violators. Subject Nos. 10 and 20 were excluded from the PP population as visual investigation of the plasma concentration profile showed odd plasma concentration profiles that could not possibly be the response of an i.v. administration. The pharmacokinetics of desmopressin in plasma were analysed for each subject with a two compartmental model using WinNonlin Pro (version 3.1.). All pharmacokinetic variables were presented by descriptive statistics by category of renal impairment. Furthermore, individual desmopressin concentration time profiles and mean desmopressin concentration time profiles per renal group were provided. One-way analysis of variance (ANOVA) of $t_{1/2,1}$, $t_{1/2,2}$ and log transferred AUC, CL and CL_R including the Dunnett multiple comparison procedure were used to assess the pairwise difference between the three renal impairment groups and the healthy subjects. Model assumptions were checked using a test for normality, normal quantile plot, homogeneity of variance test, as well as residual plots stratified by renal impairment group. An exploratory non-parametric analysis of variance using ranks of each variable was performed in case model assumptions were not met. SAFETY: All subjects who received the study drug were to be included in the safety population for the evaluation of safety and tolerability of intravenous desmopressin. Treatment emergent adverse events were summarised for clinical interpretation and expressed in terms of intensity and relation to study medication. Summary statistics were presented for changes in biochemistry, haematology and vital signs from baseline (Pre-dose) to 24 hours post-dose. The parameters were listed and flagged for out-of-normal range.		

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Minirin®	Volume:	
Name of Active Ingredient: Desmopressin	Page:	
SUMMARY - CONCLUSIONS:		
PHARMACOKINETIC RESULTS:		
The compartmental pharmacokinetic analysis showed that a 2-compartmental model with a weighting scheme of $1/(Y_{\text{predicted}})^2$ could adequately describe the data. In healthy subjects, about 52% of an i.v. bolus dose of desmopressin is eliminated unchanged via the kidneys. The geom. mean ($\pm$SD) renal clearance (CL_R) and the geom. mean ($\pm$SD) total systemic clearance (CL) is 4.98 ± 1.14 L/hr and 9.57 ± 3.35 L/hr, respectively, and the arit. mean ($\pm$SD) volume of distribution (V_z) is 40.25 ± 10.71 L in healthy subjects. In healthy subjects the harm. mean ($\pm$SD) elimination half-lives associated with the first ($t_{1/2\alpha 1}$) and second ($t_{1/2\beta 2}$) exponential phase is 0.32 hours and 2.8 hours, respectively. The arit. mean ($\pm$SD) fraction of drug eliminated during the first (f_1) and second (f_2) exponential phase is 0.23 ± 0.05 and 0.77 ± 0.05, respectively. Administration of desmopressin to patients with renal impairment resulted in a significant decrease of renal clearance, and hence total systemic clearance. As the volume of distribution did not change, this resulted in a significant increase in terminal half-life of desmopressin from 3 hours in healthy subjects to 9 hours in patients with severe renal impairment.		
SAFETY RESULTS:		
Desmopressin administered as a single bolus injection was safe and well tolerated in healthy volunteers, and in patients with mild, moderate and severe impairment of renal function. No deaths or serious adverse events occurred during this study.		
CONCLUSION:		
In healthy volunteers, 52% of an intravenous dose of desmopressin is eliminated unchanged via the kidneys. Renal clearance and systemic clearance decreased with progressing renal impairment, and hence terminal half-life increased, as the volume of distribution did not increase. Even if a change in pharmacokinetic parameters throughout progressing renal impairment was observed, the changes observed in patients with mild renal impairment are probably of no clinical relevance. In patients with moderately and severely renal impaired function, clearance and terminal half-life changed significantly resulting in a clinical relevant increase in terminal half-life from 3 hours in healthy subjects to 9 hours in patients with severely impaired renal function.		
Date of the clinical study report: 22 August 2002		
Date of erratum: 29 May 2009		

Reviewers Comments: Sponsor's analysis and conclusion seems reasonable. Also, the bioanalytical method that was used to assess the plasma concentration was validated. The sponsor used liquid-liquid extraction method for the sample preparation. The lower limit of quantification for desmopressin was 2.5 pg/mL. The precision of the assay, as determined from analysis of quality control (QC) samples ranged between 5.68 % to 7.91 %. The mean accuracy for QC samples ranged in between 101% to 107%.

4.3.2 Study FE992026 CS004- Absolute bioavailability of three different doses of desmopressin in an orodispersible tablet in healthy non-smoking male volunteers

Clinical Study Report

FE992026 CS004
BA Desmopressin Orodispersible

Desmopressin
Orodispersible Tablet

2. SYNOPSIS

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished product: N.A.	Volume:	
Name of Active Ingredient: Desmopressin	Page:	
Title of Study: Absolute bioavailability of three different doses of desmopressin in an orodispersible tablet in healthy non-smoking male volunteers		
Investigator(s): Dr. med. Horst Jürgen Heuer AAI Deutschland GmbH & Co. KG		
Study centre(s): Single-centre Study (see above)		
Publication (reference): N.A.		
Studied period : Date of first enrolment: 30.01.2002 Date of last completion: 08.03.2002		Phase of development: I
Objectives: <u>Primary Objective:</u> To investigate the absolute bioavailability of desmopressin administered as a fast orodispersible tablet of 200, 400 and 800 µg <u>Secondary Objectives:</u> To investigate the pharmacokinetics of desmopressin administered as a fast orodispersible tablet of 200, 400 and 800 µg To investigate the safety and tolerability of desmopressin administered as a fast orodispersible tablet		
Methodology: The study was performed in an open, randomised, balanced, four-way crossover design. Each subject was, in a randomised order, administered 200 µg, 400 µg and 800 µg of desmopressin in an orodispersible tablet and 2 µg as an i.v. bolus. Between doses there was a wash-out of 72 hours. <u>Blood samples</u> Blood samples were collected according to the following schedule: pre-dose and 15, 30 and 45 min and at 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dosing. After intravenous administration additional blood samples were collected at 5 and 10 minutes post-dosing. <u>Assay</u> Desmopressin plasma concentrations were determined by a validated RIA method at (b) (4)		

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished product: N.A.	Volume:	
Name of Active Ingredient: Desmopressin	Page:	
<u>Pharmacokinetic analysis</u> The pharmacokinetic parameters were assessed by use of non-compartmental methods.		
Number of subjects (planned and analysed): Number of subjects in total: 24 (planned and analysed) Number of subjects for each treatment group: 24 (planned and analysed)		
Diagnosis and main criteria for inclusion: Healthy , non smoking , male subjects , 18-55 years of age		
Test product, dose and mode of administration, batch number: 200 µg, 400 µg and 800 µg desmopressin as orodispersible tablet administered under the tongue (oromucosal use). Batch numbers: 27941L397 (200 µg desmopressin acetate tablets) 27921L398 (400 µg desmopressin acetate tablets) 27931L400 (800 µg desmopressin acetate tablets)		
Duration of treatment: All subjects were dosed four times in a four-way crossover experiment. Between each administration there was a washout period of 72 hours.		
Reference therapy, dose and mode of administration, batch number: I. v. bolus injection of 2 µg desmopressin Batch number : CE 6638: 4 µg/mL desmopressin acetate solution for injection		

SYNOPSIS

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished product: N.A.	Volume:	
Name of Active Ingredient: Desmopressin	Page:	
<u>Criteria for evaluation:</u>		
Pharmacokinetics:	F, AUC, C_{max} and t_{max} AUC _t , CL (i.v.), CL/F (orodispersible tablet), V_z (i.v.), V_z/F (orodispersible tablet), λ_z , $t_{1/2}$ The pharmacokinetic parameters were assessed by use of non-compartmental methods.	
Safety:	Number and type of adverse events, changes in laboratory parameters (hematology, biochemistry, urinalysis), changes in physical examinations, vital signs and ECG	
<u>Statistical methods:</u>		
The statistical analysis was descriptive and reflected the explorative nature of the study. All 24 randomised subjects were included in each of the three analysis sets: intention-to-treat (ITT), per protocol (PP) and safety. However, individual subject data was excluded from both the ITT analysis and the PP analysis.		
<u>Pharmacokinetics:</u> All pharmacokinetic parameters were analysed for the ITT analysis set and per protocol analysis set to investigate the influence of the outliers observed and described in the Statistical Analysis Plan. The average absolute bioavailability and 95% confidence interval were estimated for each dose of desmopressin as an orodispersible tablet. Linearity between dose of desmopressin as an orodispersible tablet and AUC was investigated using an ANOVA model. Furthermore, log-transformed data of AUC and C_{max} were compared between doses of desmopressin administered as an orodispersible tablet by pairwise one-sample t-tests. All other pharmacokinetic parameters were presented using descriptive statistics and no formal statistical testing was performed.		
<u>Safety:</u> All endpoints were presented using descriptive statistics and no formal statistical testing was performed.		

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished product: N.A.	Volume:	
Name of Active Ingredient: Desmopressin	Page:	

SUMMARY - CONCLUSIONS:

PHARMAKOKINETIC RESULTS:

After i.v. administration the volume of distribution at steady state (V_{ss}) was 29.7 L in the geometric mean. The clearance was calculated to be 8.5 L/hr and the elimination half-life was determined to be 2.8 hours in the geometric mean.

From the per protocol analysis the following was observed: The absolute bioavailability was estimated to 0.26%, 0.30% and 0.29% after 200 µg, 400 µg and 800 µg of desmopressin administered sublingual as a fast orodispersible tablet, respectively. The overall pooled estimate of the absolute bioavailability was 0.28% (0.23% - 0.34%) for desmopressin in an orodispersible tablet. AUC and C_{max} increased significantly with dose of desmopressin in an orodispersible tablet. A high variability was observed for AUC and C_{max} and it increased with dose (AUC: %CV of 46.9, 48.3 and 85.5 for 200 µg, 400 µg and 800 µg, respectively). Linearity between dose of desmopressin as a fast orodispersible tablet and AUC could not be demonstrated properly due to the high variability observed.

After sublingual administration desmopressin maximum plasma concentrations were observed at 0.5 – 2.0 hours after dosing. The maximum plasma concentration was 14.25, 30.21 and 65.25 pg/mL after a sublingual dose of 200, 400 and 800 µg, respectively. After reaching the maximum value desmopressin was eliminated with a half-life in the range of 2.8 – 3.0 hours.

SAFETY RESULTS:

The tolerability of desmopressin in sublingual doses of 200 µg, 400 µg and 800 µg and in an intravenous dose of 2 µg was good. Only few adverse drug reactions occurred all of which were mild or moderate in intensity. The most frequent adverse event was headache. The doses of desmopressin administered did not have an influence on the incidence of adverse events. No serious adverse events occurred. Mean values of vital signs and serum sodium concentrations determined as safety parameters during the study were not changed to a clinically relevant degree.

Name of Sponsor/Company: Ferring Pharmaceuticals A/S	Individual Study table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished product: N.A.	Volume:	
Name of Active Ingredient: Desmopressin	Page:	
CONCLUSION:		
All pharmacokinetic parameters were analysed for the ITT analysis set and PP analysis set. The per protocol analysis was considered as primary. From the per protocol analysis the following was observed: The overall pooled estimate of the absolute bioavailability was 0.28% (95% CI: 0.23% - 0.34%) for desmopressin administered as a fast orodispersible tablet. AUC and C_{max} increased significantly with dose of desmopressin as an orodispersible tablet. A high variability was observed for AUC and C_{max} and it increased with dose (AUC; %CV of 46.9, 48.3 and 85.5 for 200 µg, 400 µg and 800 µg, respectively). Linearity between dose of desmopressin as a fast orodispersible tablet and AUC could not be demonstrated properly due to the high variability observed. Thirteen subjects (54.2%) reported a total of 24 treatment emergent adverse events whereas five subjects (20.8%) reported a total of eleven treatment related adverse events judged as related to the study medication. The two most frequently reported adverse events were headache and clinically significant laboratory tests. No tendency towards any relationship between dose of desmopressin administered and incidence of adverse events or adverse drug reactions was seen. With respect to the number of events, headache was the most frequent adverse event reported by 25% of the subjects. In most of the subjects who had an adverse event a clinically significant finding for a laboratory parameter at the post-study examination constituted this adverse event. Date of the report: 25 June 2002		

Reviewer's Comment: Due to some errors in dose calculation the sponsor did reanalysis of the pharmacokinetic data and the report is attached below.

CONFIDENTIAL

Reason

The reason for this amendment is that the dose used for the intra venous administration in study FE99026 CS004 was specified according to desmopressin acetate and not to desmopressin free base as the sublingual administrated doses was¹. The molecular weight of desmopressin free base is 1068 g/mol. An exact molecular weight of desmopressin acetate can not be specified, as each batch contains varying levels of H₂O and contaminants. However, at the Pharmaceutical Analysis Department the following relationship between the dose of desmopressin and dose of desmopressin acetate is used²:

$\text{Dose of desmopressin} = \text{Dose of desmopressin acetate} \times 0.89$

This results in a change of the i.v. dose from 2 µg to 1.78 µg and has an impact on the calculated bioavailability (f) and of the following pharmacokinetic parameters for the i.v. administration AUC/D, CL, V_z and V_{ss}. The results and discussion and conclusion parts and following tables have been changed accordingly: table 1, table 2, table 3, table 4, table 6 and table 7.

Results and discussion

4.1 Pharmacokinetic Analysis

After i.v. administration the mean volume of distribution at steady state (V_{ss}) was 26.5 L (Table 1). The mean clearance was calculated to be 7.6 L/hr (Table/L) and the mean elimination half-life was determined to be 2.8 hours (Table 1).

For the per protocol analysis set the bioavailability was determined to be 0.24%, 0.28% and 0.25% after a sublingual dose of 200 µg, 400 µg and 800 µg, respectively (Table 6).

For the ITT analysis set the bioavailability was determined to be 0.29%, 0.32% and 0.25%, after a sublingual dose of 200 µg, 400 µg and 800 µg, respectively (Table 7).

When estimated with all three dose levels the bioavailability was 0.25% with a 95% confidence interval of 0.21-0.31% (Table 6) and 0.27% with a 95% confidence interval of 0.21-0.34% (Table 7) for the per protocol and ITT population, respectively.

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5 Conclusion

After sublingual administration desmopressin maximum plasma concentrations were observed at 0.5 – 2.0 hours after dosing. The maximum plasma concentration was 14.25, 30.21 and 65.25 pg/mL after a sublingual dose of 200, 400 and 800 µg, respectively. After reaching the maximum value desmopressin was eliminated with an elimination half-life in the range of 2.8 – 3.0 hours. The bioavailability was determined to be 0.25% with a 95% confidence interval of 0.21 – 0.31%.

Reviewer's Comment: In this study absolute bioavailability of three different doses of desmopressin oral disintegrating tablet was conducted in healthy non-smoking male volunteers. The bioanalytical method used for the analysis of pharmacokinetic samples is appropriate. However, the formulation that was used in this study was **not-to-be marketed formulation**. Both the formulations (to-be marketed vs formulation used in this study) were orally disintegrating tablets with minor changes in excipient. The impact of these changes is not known. Thus, the results from this study should be interpreted with caution and appropriate labeling changes will reflect the difference in formulation that was used.

4.3.3 Study FE992026 CS019- An Open-Label, Replicated, Randomised, Cross-over Study with Four Periods and Two Sequences Investigating the Bioequivalence of a Single Dose of MINIRIN Tablets (2 X 0.2m g) and a Single MINIRIN Melt (240 µg) Dose of Desmopressin Administered Sublingually.

Clinical Study Report
Desmopressin
FE992026 CS019

Final Version
11 February 2005
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SYNOPSIS

TITLE OF STUDY: An Open-Label, Replicated, Randomised, Cross-over Study with Four Periods and Two Sequences Investigating the Bioequivalence of a Single Dose of MINIRIN Tablets (2x0.2 mg) and a Single MINIRIN Melt (240 µg) Dose of Desmopressin Administered Sublingually	
INVESTIGATOR(S): Principal Investigator Dr. Med. Frank Richard	
STUDY CENTRE(S): PAREXEL International GmbH , Klinikum Westend, Haus 18, Spandauer Damm 130, D-14050 Berlin, Germany	
PUBLICATION (REFERENCE): Not Applicable	
STUDIED PERIOD (YEARS): First subject first visit: 23 April 2004 Last subject last visit: 30 August 2004	PHASE OF DEVELOPMENT: I
OBJECTIVES: <i>Primary Objective:</i> To investigate the bioequivalence of a single, 240 µg desmopressin dose administered sublingually as an oral lyophilisate versus a single oral 400 µg dose (two tablets) of the currently marketed 0.2 mg MINIRIN tablet. <i>Secondary Objectives:</i> To compare the pharmacokinetics of a single, 240 µg sublingually administered oral lyophilisate of desmopressin and a single 400 µg dose (two tablets) of the currently marketed 0.2 mg MINIRIN tablets. To investigate the safety and tolerability of the oral lyophilisate of desmopressin versus a single oral 400 µg dose (two tablets) of MINIRIN.	
METHODOLOGY: A single-centre, open-label, randomised, four-period, two-sequence cross-over study with replicate design in non-smoking healthy male and female subjects. Two sequences were used, TRTR and RTRT, where T (test) is the oral lyophilisate and R (reference) is the MINIRIN tablet. Thus, each subject was randomised to receive 240 µg of desmopressin in a sublingually administered oral lyophilisate on two treatment days and 2x0.2 mg of the marketed tablet on two treatment days. Between doses there was a washout period of at least 72 hours. A screening visit took place 21 to 2 days before the first administration of study drug, and included medical history, physical examination, vital signs (supine blood pressure and pulse rate), urine pregnancy test (females), 12-lead ECG, routine lab and urine samples, serology, drug screen, serum sodium (S-Na), in- and exclusion criteria, and informed consent. In each of the four periods, the subjects were admitted at the study centre in the afternoon on the day before dosing (Day -1) and remained at the site for at least 36 hours post-dose. On day -1, vital signs, drug screen, S-Na level and assessment of AE were performed. The following morning, after fasting for at least eight hours, the subjects were administered the study drug in one of the two randomly assigned fixed sequences (TRTR or RTRT). Blood sampling for pharmacokinetic determination was performed at pre-dose (i.e. 0-30 minutes pre-dosing), 30 min, and 1, 1.5, 2, 3, 4, 6, 8, 10, 11, 12, 13 and 14 hours after dosing. A volume of 9 mL was drawn at each time point. The pharmacokinetic parameters were evaluated by non-compartmental methods (WinNonlin® Pro ver. 4.1, Pharsight Corporation, USA).	

<i>Assay</i> Desmopressin plasma concentrations were determined by a validated RIA method at Ferring Pharmaceuticals A/S. The lower limit of quantification (LLQ) was 0.8 pg/mL.
<i>Miscellaneous</i> Adverse events were recorded. A post-study examination was performed on Day 2 of Study Period 4. The study was GCP-compliant.
NUMBER OF SUBJECTS: 65 subjects (33 females and 32 males) were randomised, and 64 subjects completed the study.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy non-smoking male or female subjects, 18–55 years of age.
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: 240 µg desmopressin in the oral lyophilisate administered sublingually without water. Batch number: 95198
DURATION OF TREATMENT: All subjects were dosed four times in a four-period cross-over study in two sequences. Subjects arrived at the study site in the afternoon (Day –1) prior to dosing and stayed in-house for 36 hours post-dose (Day 1). In total, subjects were admitted for approximately 52 hours for each dosing. Between each administration of study drug there was a washout period of at least 72 hours.
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Two 0.2 mg MINIRIN tablets taken almost simultaneously with 240 mL water. Batch number: EL 8050.
CRITERIA FOR EVALUATION: <i>Pharmacokinetics:</i> AUC, AUC_t and C_{max} <i>Safety:</i> Number and type of adverse events, clinical chemistry, haematology, urine analysis, vital signs and 12-lead ECG
STATISTICAL METHODS: The per protocol set was used for all statistical analyses and summaries of pharmacokinetic results. The primary endpoints AUC, AUC_t and C_{max} were analysed by an analysis of variance (ANOVA) in the natural logarithmic scale. The ANOVA model included the fixed effects “sequence”, “group”, “period (nested in group)” and “formulation” and the random effect “subject (sequence)”. In this model “group” related to groups of subjects who were included in the study one after another. Tabulations of derived PK parameters were made by sequence group, treatment and period, which in a descriptive way allowed reviewing the data for any potential carry-over. The point-estimate with corresponding confidence interval for the test-reference difference on the log-scale was estimated using the SAS-based linear mixed effect, restricted maximum likelihood procedure (PROC MIXED) with an unstructured variance-covariance structure (but securing non-negative definite covariance matrix). This is in agreement with the recommendations in the FDA Guideline for replicated crossover designs to address average bioequivalence. Point-estimate and corresponding confidence interval for the difference were retransformed to obtain point-estimate and confidence interval for the test/reference ratio. Any missing AUC was substituted by the corresponding AUC_{adj}. Bioequivalence between the two treatments is claimed if the 90% confidence interval for the ratio of treatment means of both AUC and AUC_t are within the bioequivalence limits of 80–125%, and if the 90% confidence interval for the ratio of treatment means of C_{max} is within the limits of 75–133%. An additional ANOVA, using the same model, was performed on dose-adjusted AUC, AUC_t and C_{max} in order to estimate the relative bioavailability of the oral lyophilisate versus MINIRIN. For this purpose dose-adjustment was achieved by multiplying the primary pharmacokinetic endpoints of the oral lyophilisate with 356/240 prior to submission of these data to the ANOVA. The same model as applied for AUC

and C_{max} (but without prior dose adjustment and log-transformation) was applied for the analysis of t_{max} . No statistical tests were made for the other secondary pharmacokinetic endpoints.

Adverse events, changes in laboratory safety parameters and changes in vital signs were presented by treatment using descriptive statistics. No formal statistical testing was performed.

PHARMAKOKINETIC RESULTS:

For AUC and AUC_t the 90% CIs for the ratio "test / reference" were included within the bioequivalence limits of 80-125% (AUC: [0.92; 1.22], AUC_t : [0.91; 1.22]), but for C_{max} the lower limit of the 90% CI was slightly below the lower limit of the bioequivalence interval of [75%; 133%] (C_{max} [0.74 ; 0.93]). C_{max} was found to be statistically significantly lower for the oral lyophilisate (240 μ g) with an estimate of 83% of C_{max} for MINIRIN Tablet (2 x 0.2 mg), and t_{max} was statistically significantly later for the oral lyophilisate by about 17 minutes.

The relative bioavailability of the oral lyophilisate versus MINIRIN Tablet, based on dose adjusted values, was estimated to be 1.57 for both AUC and AUC_t and 1.23 for C_{max} .

SAFETY RESULTS:

No death and no serious TEAE occurred. Also, no TEAE lead to withdrawal and no severe TEAE were reported.

In total, 65 treatment-emergent adverse events (TEAEs) were reported for 31 subjects (47.7%), with slightly more TEAEs reported and subjects affected after administration of MINIRIN as compared to the oral lyophilisate: during the periods with MINIRIN application, 37 TEAEs for 24 subjects (37.5%) were recorded, while during the periods with the oral lyophilisate application 28 TEAEs for 17 subjects (26.2%) were documented.

No death and no serious TEAE occurred. Also, no TEAE lead to withdrawal and no severe TEAE were reported.

No clinically significant abnormal values were found for haematology, biochemistry or urinalysis variables, and no obvious treatment effects were observed from measurements of S-Na, vital signs and ECG or during physical examinations.

No serious or severe AEs occurred in the study, and both treatments appeared to be safe. Single dose administration of 240 μ g oral lyophilisate and 2x0.2 mg MINIRIN Tablets was safe and well tolerated as assessed by AEs, vital signs, ECGs, clinical laboratory tests, and physical examinations.

CONCLUSIONS:

Bioequivalence between the oral lyophilisate 240 μ g and MINIRIN Tablet 2x0.2 mg could not be demonstrated. For AUC and AUC_t the 90% confidence intervals were fully contained within the pre-specified bioequivalence limits of 80-125% (AUC: [92%; 122%], AUC_t : [91%; 122%]). However, for C_{max} , the 90% confidence interval was just below the acceptance range of 75-133% (C_{max} : [74%; 93%]). C_{max} was found to be statistically significantly lower for the oral lyophilisate (240 μ g) with an estimate of 83% of C_{max} for MINIRIN Tablet (2 x 0.2 mg), and t_{max} was statistically significantly later by about 17 minutes for the oral lyophilisate (240 μ g).

A reliable estimate of the extent of absorption was achieved. The relative bioavailability of desmopressin in the oral lyophilisate relative to desmopressin in the MINIRIN tablet was 1.57. Thus, as expected an increased bioavailability from the oral lyophilisate compared to the MINIRIN tablet was observed.

No serious or severe AEs were observed. Single dose administration of 240 μ g oral lyophilisate and 2x0.2 mg MINIRIN Tablets was safe and well tolerated as assessed by AEs, vital signs, ECGs, clinical laboratory tests, and physical examinations.

Reviewer's Comment: The pharmacokinetics information obtained in this study can not be relied on because of the invalid bioanalytical method used to assess the plasma concentrations. The sponsor used a bioanalytical method that is not robust and reproducible and had high QC failure rates. More than 50% of the samples were reanalyzed in these data sets because of the QC failures or other reasons. Also, the method was previously rejected by FDA DSI inspection team for the same issues.

4.3.4 Study FE992026 CS020: An open-labelled, randomized, two period cross-over study investigating the relative bioavailability of two single doses of the current marketed desmopressin tablet (2x200 µg) and a single dose of desmopressin administered as a new orodispersible tablet (240 µg)

Clinical Study Report
Desmopressin orodispersible tablet
FE992026 CS020

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SYNOPSIS

TITLE OF STUDY: An Open-labelled, Randomised, Two Period Cross-over Study Investigating the Relative Bioavailability of Two Single Doses of the Current Marketed MINIRIN Tablet (2x200 µg) and a Single Dose of Desmopressin Administered as a New Orodispersible Tablet (240 µg)	
INVESTIGATOR(S): Dr. Josef Waitzinger, AAI Deutschland GmbH & Co KG	
STUDY CENTRE(S): Single-centre study	
PUBLICATION (REFERENCE): N.A.	
STUDIED PERIOD (YEARS): 26 May 2003 to 01 July 2003	PHASE OF DEVELOPMENT: I
OBJECTIVES: <i>Primary Objective:</i> To investigate the relative bioavailability of one single 240 µg dose of desmopressin administered as a new orodispersible tablet versus 2x200 µg MINIRIN tablets. <i>Secondary Objectives:</i> To investigate the pharmacokinetics of one single 240 µg orodispersible tablet and of 2x200 µg MINIRIN tablets. To investigate the safety and tolerability of the doses of desmopressin administered to healthy volunteers as either of the two formulations.	
METHODOLOGY: An open-labelled, randomised, two period cross-over study in non-smoking healthy male and female volunteers. Each subject was, in a randomised order, administered 240 µg of desmopressin in a orodispersible tablet and 2x200 µg MINIRIN tablets. Between the doses there was a washout period of seven days. The orodispersible tablet was allowed to dissolve under the tongue, without the administration of water. The MINIRIN tablets were swallowed with 240 ml of water. <u>Blood samples</u> Blood samples (14 mL) were collected according to the following schedule: pre-dose, 15 and 30 mins after dosing, and at 1, 1.5, 2, 3, 4, 6, 8, 9, 10, 11, 12, 13, and 14 hours after dosing. <u>Assay</u> Desmopressin plasma concentrations were determined by a validated RIA method at Ferring Pharmaceuticals A/S. The lower limit of quantification (LLOQ) was set to 0.80 pg/ml and the upper limit of quantification (ULOQ) was set to 100 pg/ml. <u>Pharmacokinetic analysis</u> The pharmacokinetic parameters were assessed by use of non-compartmental methods (WinNonlin ver. 4.0. Pharsight Corporation, USA).	
NUMBER OF SUBJECTS: Number of subjects in total: 28 (14 males and 14 females) Number of subjects for each treatment group: 28 (cross-over design) Number of subjects screened: 56 No formal sample size calculation was performed.	

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy, non-smoking male and female volunteers, 18-55 years of age.
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: 240 µg desmopressin in the orodispersible tablet administered sublingually without water. Batch Number: 23012FBM
DURATION OF TREATMENT: All subjects were dosed two times in a two-period cross-over experiment. Between each administration there was a washout period of seven days.
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: 2x200 µg MINIRIN tablets administered almost simultaneously with 240 mL water. Batch number: DK 7370 F
CRITERIA FOR EVALUATION: Primary endpoints: Pharmacokinetics: AUC, C _{max} . Secondary endpoints: Pharmacokinetics: AUC _t , t _{max} , λ _z , t _{1/2} . Safety: Number and type of adverse events, clinical chemistry, haematology, urine analysis, vital signs and ECG.
STATISTICAL METHODS: <u>Statistical methods:</u> The statistical analysis was descriptive. All 28 randomised subjects were included with all their data in the each of the 3 analyses sets: intention-to-treat (ITT), per protocol (PP), and safety. Descriptive statistics was used to summarise each pharmacokinetic parameter by formulation. t _{max} , λ _z and t _{1/2} were also described by harmonic mean. In addition, descriptive statistics for AUC, C _{max} and t _{max} were presented by period and formulation. The average relative bioavailability of the two tested products was investigated in agreement with the FDA guideline 'Statistical Approaches to Establishing Bioequivalence' (2001) and the EMEA/CPMP Guideline (2001). The nonparametric Wilcoxon test was used to compare t _{max} between formulations. No statistical tests were made for the other secondary endpoints. <u>Pharmacokinetics:</u> Descriptive statistics was used to summarise each pharmacokinetic parameter by formulation. Pharmacokinetics was evaluated by non-compartmental methods. <u>Safety:</u> Adverse events, changes in laboratory safety parameters and changes in vital signs are presented using descriptive statistics and no formal statistical testing was performed.
PHARMACOKINETIC RESULTS: Measurable levels of desmopressin were obtained in all healthy volunteers after administration of the MINIRIN tablets and the orodispersible tablet. The sampling schedule provided a reliable estimate of the extent of absorption, as the AUC _t derived from measurements were, for all subjects on both treatments, more than 80% of the AUC. The 90% confidence intervals for AUC ([87% , 121%]) and AUC _t ([86% , 121%]) were fully contained within the pre-specified bioequivalence range 80-125%, but not for C _{max} ([73% , 103%]). The supplementary bioequivalence analysis excluding subject 018 repeated the bioequivalence results within the Guidance criteria for AUC (90% CI: [89% , 124%]) and AUC _t (90% CI: [88% , 124%]). For C _{max} the 90%

CI was [76% , 106%]).

The two treatments, 240 µg desmopressin in an orodispersible tablet and 2x200 µg MINIRIN tablets, were not statistically significantly different comparing C_{max} . t_{max} is obtained slightly, but statistically significantly later after the administration of the orodispersible tablet than after the MINIRIN tablet.

A reliable estimate of the extent of absorption was achieved. The relative oral bioavailability was 1.52 (95% CI [1.25 , 1.85]), thus an increased oral bioavailability from the orodispersible tablet compared to the MINIRIN tablet is observed.

SAFETY RESULTS:

Desmopressin administered as the 240 µg orodispersible tablet and in 2x200 µg MINIRIN tablets was well tolerated. No SAEs occurred, there were no withdrawals due to AEs, and only one subject received concomitant medication due to AEs. Most of the 21 AEs that occurred were mild or moderate in intensity. The most frequent AE was headache, which accounted for approximately 50% of the AEs. Mean values of vital signs and S-Na concentrations remained unchanged during the study.

CONCLUSIONS:

Bioequivalence between MINIRIN 2x200 µg and the orodispersible tablet 240 µg was demonstrated. For AUC and AUC_t the 90% confidence intervals (AUC: [87% , 121%]), AUC_t ([86% , 121%]) were fully contained within the pre-specified bioequivalence range 80-125%. For C_{max} , the 90% [73% , 103%] confidence interval was not obtained within this acceptance range. When an additional analysis excluding a subject with a high absorption was performed, the C_{max} ratio of the orodispersible tablet versus MINIRIN was ([76 , 106%]).

t_{max} was obtained slightly, but statistically significantly later after the administration of the orodispersible tablet than after the MINIRIN tablet.

A reliable estimate of the extent of absorption was achieved. The relative oral bioavailability of desmopressin in the orodispersible tablet relative to desmopressin in the MINIRIN tablet was 1.52 (95% CI: [1.25 , 1.85]). Thus, an increased oral bioavailability from the orodispersible tablet compared to the MINIRIN tablet was observed as expected.

No safety concerns were observed.

Reviewer's Comment: The pharmacokinetics information obtained in this study can not be relied on because of the invalid bioanalytical method used to assess the plasma concentrations. The sponsor used a bioanalytical method that is not robust and reproducible and had high QC failure rates. More than 50% of the samples were reanalyzed in these data sets because of the QC failures or other reasons. Also, the method was previously rejected by FDA DSI inspection team for the same issues.

4.3.5 Study FE992026 CS021- A three-period crossover study comparing the exposure of oral lyophilisates containing 60, 120 and 240 µg desmopressin in 24 healthy non-smoking subjects

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Desmopressin
FE992026 CS021

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SYNOPSIS

TITLE OF STUDY: A three-period crossover study comparing the exposure of oral lyophilisates containing 60, 120 and 240 µg desmopressin in 24 healthy non-smoking subjects	
INVESTIGATOR: Dr. med. R. Fuhr, PAREXEL International GmbH	
STUDY CENTRE: Single-centre study at PAREXEL International GmbH, Clinical Pharmacology Research Unit, Berlin, Germany	
PUBLICATION (REFERENCE): N/A	
STUDIED PERIOD (YEARS): First patient, first visit 22 July 2004 Last patient, last visit 14 September 2004	PHASE OF DEVELOPMENT: Phase I
OBJECTIVES: <i>Primary Objective:</i> To determine whether dose-exposure linearity of desmopressin existed when administered as oral lyophilisates of 60, 120 and 240 µg. <i>Secondary Objectives:</i> To investigate the pharmacokinetics of desmopressin administered as oral lyophilisates of 60, 120 and 240 µg. To investigate the safety and tolerability of desmopressin administered as oral lyophilisates.	
METHODOLOGY: This was a single-centre, open-labelled, randomised, balanced, three-period crossover Phase-I study in non-smoking healthy subjects. Each subject, in a randomised order, received 60 µg, 120 µg and 240 µg of desmopressin as oral lyophilisates. Between doses there was a washout period of at least 72 h. The oral lyophilisates were administered sublingually without concomitant administration of water. In order to 'standardise' the buccal mucosa before the administration of the oral lyophilisate, the subject was asked to brush his/her teeth without toothpaste in the morning of the drug administration. A staff member placed the oral lyophilisate sublingually with a pair of tweezers. This was done in order to avoid contamination of the pharmacokinetic plasma samples with desmopressin from the formulation.	
NUMBER OF SUBJECTS: A total of 61 subjects were screened and 24 were initially enrolled in the study. There was one drop-out, which was replaced. A total of 24 subjects completed the study as planned. Twenty-five subjects received at least one dose of study medication and were therefore included in the safety and PK analysis.	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy non-smoking male or female subjects, 18-55 years of age.	

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Desmopressin in 60, 120 and 240 µg as oral lyophilisates. Batch numbers: 60 µg: 95194 120 µg: 100096 240 µg: 95198
DURATION OF TREATMENT: The 24 subjects, who completed the study as scheduled, were dosed at three different occasions in a three-period crossover experiment with at least 72 h washout between the treatment periods.
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: N/A
CRITERIA FOR EVALUATION: <u>Efficacy:</u> <u>Primary endpoint:</u> Pharmacokinetics: AUC, AUC_t and C_{max} <u>Secondary endpoint:</u> Pharmacokinetics: % Extrap. AUC, t_{max}, t_{1/2} and λ_z <u>Safety:</u> Number and type of adverse events, clinical chemistry, haematology, urinalysis, vital signs and 12-lead ECG.
STATISTICAL METHODS: <u>Pharmacokinetics:</u> The relationship between AUC (and C_{max}) and dose of desmopressin administered as an oral lyophilisate tablet was described using the power model, which fitted a linear relationship between log (Y), where Y was the PK variable of interest (AUC or C_{max}), and log (dose): $\log(Y_{ijk}) = s_i + p_j + \beta \cdot \log(\text{DOSE}_k) + \log(\varepsilon_{ijk})$ where s_i was a random subject effect, p_j was a fixed period effect, DOSE_k represented the effect of the kth dose and ε_{ijk} was a normally distributed random error with mean zero. This model is usually referred to as the power model because after exponentiation it translates into: $Y_{ijk} = \alpha \times (D_k)^\beta$ where α depended only on subject period and error. Beta and its 90% confidence interval were calculated from the model specified above. Perfect linearity between dose and AUC respectively C_{max} corresponded to an estimated slope of β=1. If the confidence interval did include the value 1, the data did not give clear evidence against the assumption of dose linearity. All the secondary pharmacokinetic parameters were presented using descriptive statistics and graphical displays. No formal statistical testing was performed. <u>Safety:</u> Safety assessment was based on descriptive statistics and frequency summaries. No formal statistical testing was performed. Adverse events, changes in laboratory safety parameters, vital signs and ECGs

were summarised.
PHARMACOKINETIC RESULTS: The three desmopressin dose levels of 60, 120 and 240 µg as oral lyophilisates showed dose linearity in the ANOVA (power) model with regard to the primary pharmacokinetic variables, desmopressin AUC, AUC _t and C _{max} , as the 90% confidence intervals included the value 1 for all parameters. An estimated slope of β=1 indicated perfect linearity between dose and desmopressin AUC as well as between dose and desmopressin C _{max} , respectively. Measurable levels of desmopressin were obtained in all subjects after administration of the different doses of the oral lyophilisate. The inter-subject variability of the desmopressin plasma concentration data was high, as expressed by a CV% of 34-84% for C _{max} and a CV% of 41-122% for the different AUCs. Doses of 60 to 240 µg were rapidly absorbed as evidenced by peak plasma levels occurring on average 1 to 1.5 hours after dosing. The study drug was eliminated from plasma with an average half-life of approximately 2.6–2.9 hours.
SAFETY RESULTS: Single sublingual doses of 60 µg, 120 µg and 240 µg desmopressin in oral lyophilisates were well tolerated. There were no deaths and no serious or other significant adverse events during this study, and none of the subjects withdrew due to an adverse event. None of the Treatment Emergent Adverse Events (TEAEs), that all had resolved until the end of the study, required medical treatment. There were a total of 11 TEAEs, all of mild or moderate intensity in 10 of the 25 subjects. Three TEAEs occurred in 3 subjects following 60 µg desmopressin, 2 TEAEs in 2 subjects after 120 µg desmopressin and 6 TEAEs in 6 subjects following 240 µg desmopressin. The most frequent TEAEs with altogether 5 events were renal and urinary disorders such as pollakiuria and polyuria. Seven TEAEs were considered to be possibly related to the intake of the oral lyophilisates among which were 3 events of pollakiuria (including two events of moderate intensity) and one event of polyuria. No apparent effect was observed on clinical safety data (laboratory assessments, vital signs, 12-lead ECG and physical examination) following sublingually administered doses of desmopressin. In particular, none of the subjects developed hyponatraemia, after sublingual dosing with desmopressin.
CONCLUSIONS: • Exposure as measured by AUC, AUC_t and C_{max} showed a dose-proportional increase with increasing dose following sublingual administration of 60 µg, 120 µg, and 240 µg. Dose linearity was confirmed for the pharmacokinetic parameters C_{max}, AUC and AUC_t in an ANOVA power model as the 90% CI included unity. • Single sublingual doses of 60 µg, 120 µg and 240 µg desmopressin administered as oral lyophilisates were well tolerated. • No apparent, clinically significant changes were observed in clinical chemistry including serum sodium, haematology and urinalysis parameters after the three sublingual desmopressin doses as well as there were no apparent effects on vital signs and 12-lead ECG parameters. • No serious or severe AEs occurred.

Reviewer's Comment: According to sponsor, the three desmopressin dose levels of 60, 120 and 240 µg showed dose linearity in terms of desmopressin AUC, AUC_t and C_{max}. However, the pharmacokinetic results obtained from these studies can not be relied because the sponsor used a bioanalytical method that is not robust and reproducible and had high QC failure rates. More than 50% of the samples were reanalyzed in these data sets because of the QC failures or other reasons. Also, the method was previously rejected by FDA DSI inspection team for the same issues.

4.3.6 Study 45A05-118 Transfer of Desmopressin into Human Breast Milk

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Desmopressin FE992026, FE999912; Trial Code: 45A05/118; 45A05-118
Octostim nasal spray, 1.5 mg/ml
Clinical Trial Report Synopsis

Date: 14 May 2009
DC-Synopsis-49; Ver. 1.0
Supersedes: None
Page 1 of 2

45A05-118

SYNOPSIS

TITLE OF STUDY: Transfer of Desmopressin into Human Breast Milk	
INVESTIGATOR: Dr. Ellen Vinge	
STUDY CENTRE: Department of Clinical Pharmacology, Lund University Hospital, S-221 85 Lund	
PUBLICATION: N/A	
FINAL STUDY REPORT DATE: 22 May 1994	PHASE OF DEVELOPMENT: I
OBJECTIVES: The aim of the present study was to estimate the amount of drug transferred into human milk after a high (about 300 µg) single intranasal dose of desmopressin (Octostim®) to healthy lactating women. The dose was equivalent to that used in coagulation disorders.	
METHODOLOGY: This was an open, single dose study. Desmopressin was administered as 2 puffs of nasal spray - one in each nostril. Samples of venous blood and milk were taken during 8 hours after drug administration (just before dosing and at 30, 60, 120, 240, 360, and 480 minutes post-dose).	
NUMBER OF SUBJECTS: The plan was to enrol 6 subjects. Due to a dosing error, 2 subjects who completed the study were excluded from analysis. Consequently 2 additional subjects were enrolled, making the total number of subjects completing 8 and the total number included in the analyses 6.	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Inclusion criteria were: • healthy nursing mother • age >18 years • >4 months after delivery • written informed consent to participation in the study Subjects using other medication during the study, subjects with known hypersensitivity to desmopressin or vasopressin, with hyponatraemia ($\text{Na}^+ < 133 \mu\text{mol/l}$), with a history of heart disease, allergy, hypertension or cardiac arrhythmia, with a history or sign of liver, renal or endocrine disease, or addictions to drugs or alcohol were excluded.	

Ferring Pharmaceuticals

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Desmopressin FE992026, FE999912; Trial Code: 45A05/118; 45A05-118
 Octostim nasal spray, 1.5 mg/ml
 Clinical Trial Report Synopsis

Date: 14 May 2009
 DC-Synopsis-49; Ver.1.0
 Supersedes: None
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TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Octostim® 1.5 mg/ml nasal spray, one puff in each nostril, aiming at a dose of 300 µg (the actual calculated doses ranged between 285 µg and 345 µg). Batch no.: N/A
DURATION OF TREATMENT: Single dose
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: N/A
CRITERIA FOR EVALUATION: <i>Desmopressin transfer:</i> Desmopressin concentrations in plasma and milk (using a desmopressin specific RIA), milk/plasma ratio, and excreted amount of desmopressin. <i>Safety:</i> Adverse events and standard haematology and biochemistry safety parameters.
STATISTICAL METHODS: Model independent pharmacokinetic parameters were presented (C_{max}, T_{max}, and AUC). For calculations of excreted amounts, plasma levels below the limit of determination were set at that level (2.5 pg/ml).
PHARMACOKINETIC RESULTS: <i>Plasma</i> C_{max} ranged between 233 and 1520 pg/ml. T_{max} was 30 minutes in 3 subjects and 60 minutes in 3 subjects. Eight hours after dosing, the plasma levels ranged between 40 and 242 pg/ml. <i>Milk</i> 1st portion (n=6): C_{max} ranged between 8.79 and 595 pg/ml. T_{max} ranged from 60 to 480 minutes. Eight hours after dosing, the levels in milk ranged between 4.16 and 101 pg/ml. 2nd portion (n=4): C_{max} ranged between 12 and 153 pg/ml. T_{max} was 60 minutes in 3 subjects and 420 minutes in 1 subject. Eight hours after dosing, the levels in milk ranged between 6.3 and 82.1 pg/ml. <i>Milk/plasma ratios:</i> Ranged between 0.0 and 1.2 in the 1st portion and 0.0 and 0.6 in the 2nd portion. <i>Excreted amounts:</i> Ranged between 491 pg and 16 ng (0.0001-0.005% of the dose administered).
SAFETY RESULTS: No adverse events were reported. The laboratory safety profile revealed no clinically relevant changes.
CONCLUSIONS: Although desmopressin is transferred to human breast milk, it does not seem likely that the transferred amounts would give any clinical effects in the infants.

Reviewer's Comment: The sponsor's bioanalytical method and analysis of results seem acceptable. In this study an increased trend of milk/plasma ratio for desmopressin was observed for the duration of study (8 hours), hence accumulation of desmopressin in breast milk cannot be ruled out. Also the oral bioavailability of desmopressin from

ingested milk in babies is not known and further studies in lactating women on continuous treatment are desirable. Therefore, labeling language will reflect that a caution should be exercised when desmopressin is administered to nursing mother.

4.3.7 Study FE992026-DS-PHA-0101: In vitro metabolism of desmopressin by human and rat liver microsomes

SUMMARY

Title

In vitro metabolism of dDAVP by human and rat liver microsomal enzymes

Purpose

To investigate metabolism of dDAVP by liver microsomes and its potential for pharmacokinetic drug-drug interactions.

Materials

Test Material: Human and rat liver microsomes

Recording equipment: Perkin Elmer HPLC UV and MicroMass LC/MS/MS

Test article: dDAVP, Sigma V-1005
lots 38H58011 & 79H59031

Other products: FE106850

Methods

The metabolism of dDAVP by liver microsomes of human and rat origin was investigated. Compound degradation was monitored by HPLC using either UV or mass spectrophotometric detection.

Results

	Percent remaining after 60 minutes		
	Human	Rat	w/o microsomes
dDAVP	87±3 (n=3)	91±12 (n=3)	104
FE106850	0	1	

The values are the mean ± SD.

Discussion/Conclusion

It is concluded that dDAVP is not extensively metabolised by human or rat liver microsomes *in vitro*. It is unlikely that the disappearance of compound detected in these experiments would have any physiological significance especially when considered in light of the extensive and rapid metabolism of the comparator non-peptide compound FE106850.

4.3.8 Study FE992026-DS-PHA-0102: Effect of desmopressin on human cytochrome P450 enzyme subtype activity in vitro

NUC/DURNA

7/16

FINAL REPORT # FE992026 DS PHA 0102
FINAL VERSION DATED 26/01/2001

7/16

SUMMARY

Title

Effect of ddavp on human cytochrome P450 enzyme subtype activity *in vitro*

Purpose

To investigate the effect of dDAVP on the *in vitro* activity of baculovirus-expressed human cytochrome P450 activity.

Materials

Test Material: Microsomes from baculovirus cells expressing human cytochrome P450 subtypes.

Recording equipment: Labsystems Fluoroscan Ascent FL fluorimeter

Test article: dDAVP, Sigma V-1005
lot 79H59031

Other products: Substrates:

Cambridge Bioscience, U.K.
3-cyano-7-ethoxycoumarin (CEC) C-684
7-ethoxy-4-trifluoromethylcoumarin (EFC) E-2882
(AMMC) B-700
7-methoxy-4-trifluoromethylcoumarin (7-MFC) B-740
Dibenzylfluorescein (DBF) B-750
3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin (AMMC) B700

Sigma, U.K.
Coumarin C4261

Inhibitors:

Sigma, U.K.
Ketoconazole K1003
Sulfaphenazole S0758
Quercetin Q0125
Tranlycypromine P8511
Quinidine Q0750

Ultrafine Chemicals, U.K.
Furafylline UC165

Methods

Cytochrome P450 activity was monitored using fluorescent endpoint measurement for each of the subtypes. The effect of 10µM dDAVP was investigated by addition of 10µM dDAVP into each subtype/ fluorescent substrate incubation. Inhibition was detected by changes in the endpoint fluorescent reading.

Results

Cytochrome P450 subtype	% inhibition
1A2	-2.2
2A6	-2.5
2B6	1.7
2C8	-2.2
2C9	-0.5
2C19	-0.5
2D6	-0.6
2E1	-2.1
3A4	-0.1

Values shown are the percentage inhibition by 10µM dDAVP and are the mean of two separate determinations.

Discussion/Conclusion

DDAVP displays no inhibition (or potentiation) of any of the expressed human cytochrome P450 subtypes tested. It is concluded therefore that it would display no drug-drug interactions through inhibition of the metabolism of co-administered drugs.

4.4 OCP FILING MEMO

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	22-517	Brand Name	NOCDURNA	
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	ORALLY DISINTEGRATING DESMOPRESSIN TABLET	
Medical Division	DMEP	Drug Class		
OCP Reviewer	Ritesh Jain, Ph.D.	Indication(s)	Treatment of Nocturia in Adults	
OCP Team Leader	Sally Choe, Ph.D.	Dosage Form	Orally Disintegrating Tablets: 25 mcg and 100 mcg	
Pharmacometrics Reviewer	Anshu Marathe, Ph.D Christoffer Tornoe, Ph.D	Dosing Regimen	Women: 25 mcg sublingual tablet, once daily at bedtime Men: 100 mcg sublingual tablet, once daily at bedtime.	
Date of Submission	06/19/2009	Route of Administration	Sublingual	
Estimated Due Date of OCP Review	03/25/2010	Sponsor	Ferring Pharmaceuticals	
Medical Division Due Date		Priority Classification	S	
PDUFA Due Date	04/22/2010			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	2		Studies: FE992026-DS-PHA0101 and FE992026-DS-PHA0102
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		Studies: FE992026 CS021 , FE992026 CS007 and FE992026 CS012
multiple dose:				
Patients-				

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single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		Study: FE992026 CS001
hepatic impairment:				
PD -				
Phase 2:	X	3		Studies: 45A07-37, 45A07-38
Phase 3:	X	2		Studies: FE992026 CS29, FE992026 CS31
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		Studies: FE992026 CS007A, 45A07-39
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1		Pooled PK analysis and Population PD analysis was done to investigate gender and age difference in Desmopressin sensitivity. Data from Studies CS29,CS31, CS20 and CS21 is included in the analysis
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	X	1		Study FE992026 CS004
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		Study FE992026 CS020
Bioequivalence studies -				
traditional design: single / multi dose:				
replicate design: single / multi dose:	X	1		Study FE992026 CS019
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
PK in Lactating Women	X	1		Study 45A05-118
PK and PD in Children with Primary Nocturnal Enuresis	X	1		Study FE992026 CS0006
Effect Circadian Variation on PK	X	1		Study 45A07-39
Pediatric development plan				
Genotype/phenotype studies				
Chronopharmacokinetics				
Literature References				
Total Number of Studies		20		

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NDA_BLA or Supplement 090808

APPEARS THIS WAY ON ORIGINAL

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	Exposure-Response guidance?				
14	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?	√			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?				The sponsor has requested a full waiver for pediatric studies. Sponsors justification for the waiver is that this application is for indication of nocturia in adults.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, this application is fileable from Clinical Pharmacology Perspective. DSI inspection is not requested for any studies in this application.

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

Comments that should be forwarded to the Applicant for the 74-day letter:

1) Please provide the electronic pharmacokinetics data set for a) bioequivalence study FE992026 CS019 b) dose linearity study FE992026 CS021. All the data sets should be submitted as SAS transport files. The data set should include the parameters containing (but not limited to) the following column headings: Subject ID, Study ID, Time, Concentration, Treatment, Sequence, Period, AUC_{INF}, C_{max}, T_{max}, Percentage AUC_{extrapolated}, T_{1/2}, BMI, Gender, Age, Body Weight, Comments (If any). You may include any other relevant columns in the datasets. A description of each data item should be provided in a Define.pdf file.

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2) Please submit the electronic pooled PK data set from the studies FE992026 CS020 and FE992026 CS021. The data sets should be submitted as SAS transport files. The data set should include the parameters containing (but not limited to) the following column headings: Subject ID, Study ID, Time, Concentration, AUC_{INF} , C_{max} , Dose, BMI, Gender, Age, Body Weight, Comments (If any). You may include any other relevant columns in the datasets. A description of each data item should be provided in a Define.pdf file.

Sponsor is requested to submit this information within 2 weeks.

<u>Ritesh Jain</u>	<u>08/21/2009</u>
Reviewing Clinical Pharmacologist	Date
<u>Sally Choe</u>	<u>08/21/2009</u>
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo (Internal Memo)

1. Background

Desmopressin (dDAVP, 1-deamino-8-D-arginine vasopressin) is a synthetic analogue of the naturally occurring antidiuretic hormone, 8-arginine vasopressin. It acts by increasing reabsorption of water in the distal and collecting tubules of the kidney, thereby concentrating the urine and decreasing nocturnal urine output to a volume which is more compatible with bladder capacity.

Desmopressin has been marketed in USA and around the world for more than 30 years as different formulations such as nasal spray, intravenous formulation, and as an oral tablet formulation. Approved indications include central diabetes insipidus (CDI), primary nocturnal enuresis (PNE), type I von Willebrand's disease, and hemophilia A.

The proposed indication for this NDA of desmopressin Melt (NOCDURNA or Minirin Melt) is adult nocturia, with the aim of decreasing nocturnal urinary frequency and volume and prolonging the time to first nocturnal void in patients with this condition.

Minirin Melt is a freeze-dried orally disintegrating tablet which is designed to dissolve rapidly in the mouth when placed under the tongue. The sponsor is planning to market the Minirin Melt in two dosage strengths 25 mcg and 100 mcg.

The daily recommended dose for Minirin Melt is:

- Women: 25 mcg sublingual tablet, once daily at bedtime
- Men <65: 100 mcg sublingual tablet, once daily at bedtime.
- Men $\geq$ 65: 100 mcg daily at bedtime with additional serum sodium monitoring on Day 4 and at one month of treatment.

The sponsor requested a biowaiver for Minirin Melt at dose strengths 10, 25, 50 and 100 mcg during an EOP-2 meeting which was held on March 26, 2007. Agency agreed to waive conducting pharmacokinetics studies for new lower strengths of Minirin Melt provided:

- 1) Desmopressin pharmacokinetics is linear over the proposed dose range
- 2) The different formulation strengths are proportionally similar in their active and inactive ingredients
- 3) The dissolution profiles of the different formulations strengths are comparable to those of the higher strengths used in previous pharmacokinetic studies.

The sponsor submitted all the required information and a biowaiver for lower strength was granted by ONDQA (Reviewed by Dr. Houda Mahayni; DARRTS date, 01/14/2009).

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2. Clinical Pharmacology Studies:

In the Clinical Pharmacology Program, the sponsor has submitted a total of 17 studies (Appendix 1). The Clinical Pharmacology studies, which the review will focus in this application, are listed below:

• **In-vitro-Metabolism Studies (2)**

– **Studies FE992026-DS-PHA0101 and FE992026-DS-PHA0102**

- To characterize the in vitro metabolism of Desmopressin by rat and human liver microsomes. Also to study the inhibition effect of Desmopressin on human cytochrome P450 enzyme subtype.

– **Conclusion:**

- No metabolism of Desmopressin in human liver and rat liver microsomes.
- Desmopressin does not show any inhibition to CYP isoenzyme in *in-vitro* studies.

• **Relative Bioavailability Study (1)**

– **Study FE992026 CS019:**

- An open-label, replicated, randomised, cross-over study with four periods and two sequences investigating the bioequivalence between a single dose of MINIRIN Tablets (2x0.2 mg) and a single to-be marketed formulation of MINIRIN oro-dispersable tablet (240 mcg) administered sublingually.

• **Conclusion:**

Parameter	Mean Ratio Oral Tablet/Final Oro- dispersible formulation	90% CI	Comment
AUC	1.056	(0.9179-1.2150)	Met the BE Criteria
AUCt	1.058	(0.9137-1.2252)	Met the BE Criteria
Cmax	0.829	(0.7385-0.9320)	Failed to meet BE criteria

• **Dose Linearity Study (1)**

– **Study FE992026 CS021:**

- A three-period crossover study to determine whether dose exposure linearity of Desmopressin when administered as an orally disintegrating tablet (to-be marketed) of 60, 120 and 240 mcg in 24 healthy non-smoking subjects.

- **Conclusion:** Sponsor claims dose linearity (60 mcg-240 mcg) for the doses studied.

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- **Absolute Bioavailability Study (1)**
 - **Study FE992026-CS004:**
 - A four-way crossover study comparing the bioavailability of orally dispersible tablet containing 200, 400 and 800 mcg Desmopressin with the bioavailability of 2 mcg Desmopressin administered as solution for injection (i.v.).
 - **Conclusion:** Based on Sponsor's analysis the absolute bioavailability of orally disintegrating tablets (not the to-be marketed) was found to be ~0.25%.

- **Specific Population: Renal Impairment Study (1)**
 - **Study FE992026 CS001:**
 - Single dose pharmacokinetics after intravenous administration of Desmopressin in healthy volunteers and patients with mild, moderate and severe renal impairment
 - **Conclusion:** As compared to healthy subjects, statistically significant increase in exposure was seen for moderate and severe renally impaired subjects, but not for mild renal impaired subjects.
 - Based on Sponsor's analysis mean AUC increased from 186 in normal subjects to 281, 453 and 682 pg*h/mL for mild, moderate and severe renal impaired patients respectively.

- **Transfer of Desmopressin into Human Breast Milk (1)**
 - **Study 45A05-118:**
 - The study was an open, single dose study in healthy nursing mothers. A single dose (300 mcg) of desmopressin (Octostim, 1 .5 mg/ml) was administered as 2 puffs of nasal spray - one in each nostril.
 - **Conclusion:** Desmopressin seems to be transferred in human breast milk following high intranasal dose.
 - The total amounts of Desmopressin excreted over the 8-hour observation period ranged from 491 pg to 16 ng, corresponding to 0.0001-0.005% of the dose administered.
 - Sponsor claim's that transformed amount will not result in any clinical effects to infants.
 -

- **Population PD analysis and Pooled PK analysis:**
 - Population PD and Pooled PK analysis was done to investigate the effect of gender and age difference in desmopressin sensitivity and pharmacokinetics. Data from Studies CS29,CS31 are included to conduct population PD analysis, and data from studies CS20 and CS21 were included in the pooled PK analysis
 - **Conclusion:** Based on the analysis, differences in pharmacodynamic response led to a dose recommendation stratified by gender and age.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

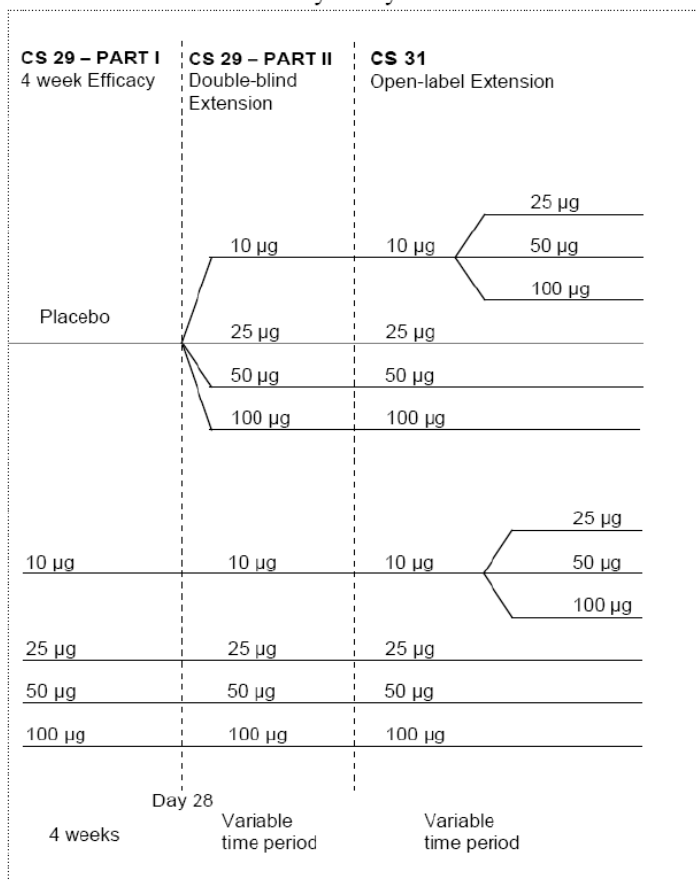
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3. Phase 3 Studies

Study FE992026 CS29 (hereafter referred to as CS29) [CS29] is the primary study establishing desmopressin Melt efficacy for the nocturia indication. The primary efficacy endpoint in the Phase III study was change in the mean number of nocturnal voids and the proportion of subject with > 33% reduction in the mean number of nocturnal voids. The study was conducted in 2 parts. Part I was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study investigating the efficacy and safety of 4 doses (10 µg, 25 µg, 50 µg, or 100 µg) of desmopressin Melt administered for 28 days for the treatment of nocturia in adults. Upon completion of Part I of the study, all subjects on active treatment continued into Part II on the same treatment for approximately 1 to 6 months.

Subjects enrolled in Study CS29 who had completed at least Visit 3E (Day 15 of Part II or Day 43 of CS29) were eligible to roll over into a long-term open-label efficacy and safety extension study FE992026 CS31 [CS31].

Figure 1: Summary of Phase III Clinical Efficacy Study



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Potential Key Review Questions

- ✓ What is the exposure-response relationship for NOCDURNA in terms of safety and efficacy?
- ✓ Is dosing recommendation based on gender and age appropriate?
- ✓ Is dosing recommendation appropriate in renal impaired patients?

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APPENDIX 1

Table 1. Overview of studies on the pharmacokinetics and pharmacodynamics of desmopressin

Study identifier	Desmopressin formulation and dose	Healthy subjects or diagnosis of patients	Duration of treatment	CTD section
[FE992026 CS004]	200, 400 and 800 µg as Melt, sublingually; 2 µg as i.v. bolus	Healthy non-smoking male subjects	4 single doses: 3 oral and one i.v. bolus	[5.3.1.1]
[FE992026 CS020]	240 µg as Melt, sublingually.	Healthy, non-smoking, male or female subjects	One dose of 240 µg orally disintegrating tablet, one dose of 2 x 200 µg Mimirin tablets	[5.3.1.1]
[FE992026 CS021]	60, 120 and 240 µg as Melt, sublingually	Healthy, non-smoking, male or female subjects	Three single doses	[5.3.1.1]
[FE992026 CS019]	240 µg as Melt, sublingually.	Healthy, non-smoking, male or female subjects	Two doses of 240 µg as an orally disintegrating tablet, two doses of 2 x 0.2 mg Mimirin	[5.3.1.2]
[FE992026 DS PHA 0101]	<i>In vitro</i> study	Human and rat liver microsomes	-	[5.3.2.2]
[FE992026 DS PHA 0102]	<i>In vitro</i> study	Human cytochrome P450	-	[5.3.2.2]
[FE992026 CS007]	10 µg, 20 µg and 40 µg, as Melt, sublingually	Healthy, non-smoking male and female subjects	Three single doses	[5.3.3.1]
[FE992026 CS012]	200 µg as Melt, sublingually	Healthy, non-smoking male or female subjects	Three single doses	[5.3.3.1]
[45A05-118]	Nasal spray (Octostim®) 300 µg	Healthy lactating females	Single dose	[5.3.3.1]
[FE992026 CS001]	Mimirin® 4 µg/mL 2 µg i.v. bolus injection	Healthy volunteers, creatinine clearance > 80 ml/min Renally-impaired subjects with creatinine clearance: 50-80 ml/min 30-49 ml/min 5-29 ml/min	Single dose	[5.3.3.2]
[FE992026 CS007A]	10 µg, 20 µg and 40 µg, as Melt, sublingually	Over-hydrated, healthy, non-smoking male and female subjects	3 single doses	[5.3.4.1]
[FE992026 CS006]	30, 60, 120, 240, 360 and 480 µg, as Melt sublingually 0.4 mg Mimirin® tablets, orally.	Children with monosymptomatic Primary Nocturnal Enuresis	One administration of Melt and 12 weeks treatment with Mimirin tablets	[5.3.5.4]
[45A07-37]	0.2, 0.4, 0.8 mg Mimirin® tablets, orally	Women with nocturia (≥2 voids/night)	4 weeks	[5.3.5.4]

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Study identifier	Desmopressin formulation and dose	Healthy subjects or diagnosis of patients	Duration of treatment	CTD section
[45A07-38]	0.1, 0.2, 0.4 mg Minirin [®] tablets orally Placebo	Elderly male or female subjects with ≥ 2 voids/night and nocturnal urinary output ≥ 0.9 ml/min	Dose-titration 1 week each dose, then 2 weeks chosen dose or 2 weeks placebo	[5.3.5.4]
[45A07-39]	0.2 mg Minirin [®] tablet orally day / night 2 μ g Minirin [®] solution for i.v. injection, 4 μ g/mL i.v. day / night	Healthy elderly male volunteers	4 single doses i.v. day / i.v. night oral day / oral night	[5.3.5.4]
MICP98-1	0.4 mg Minirin [®] tablet, orally	Male and female subjects with ≥ 2 nocturnal voids/night	Single dose 0.4 mg, 0.4 mg at bedtime for 3 consecutive nights	[5.3.5.4]
[PTF-DOCNOC]	0.2 mg Minirin [®] tablet, orally	Elderly male or female subjects with > 2 voids / night	0.2 mg on 3 consecutive nights	[5.3.5.4]

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for DA_BLA or Supplement 090808

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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

/s/

RITESH JAIN
03/26/2010

Anshu Marathe
03/29/2010

CHRISTINE E GARNETT
03/30/2010

SALLY Y CHOE
03/30/2010



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

APPLICATION NUMBER: 22-517
SUPPORTING NUMBER: 000
APPLICATION LETTER DATE: Jun/19/2009
PRODUCT: NOCDURNA™ (Desmopressin Sublingual Melt)
INTENDED CLINICAL POPULATION: Treatment of nocturia in adults
SPONSOR: Ferring Pharmaceuticals Inc.
DOCUMENTS REVIEWED: e-CTD submission.
REVIEW DIVISION: DMEP
PHARM/TOX REVIEWER: Parvaneh Espandiari. Ph.D
PHARM/TOX SUPERVISOR: Dr. Karen Davis Bruno
DIVISION DIRECTOR: Dr. Mary Parks
PROJECT MANAGER: Jennifer Johnson

Date of review submission to DARRTS: March/25/2010

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I. Recommendations

A. Recommendation on approvability:

P/T recommends approval of this application. No further studies are required.

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling:

Section 8.1 Pregnancy

Category B:

Fertility studies have not been done. Teratology studies in rats and rabbits at **doses 0.05-10 mcg/kg/day (approximately the human exposure in rats and 200-times higher exposure in rabbits, based on body surface area mg/m²)** revealed no harm to the fetus due to desmopressin. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential or effects on fertility. Desmopressin was not mutagenic or clastogenic with or without metabolic activation in the Ames test for bacterial mutagenicity **or the in vitro mouse lymphoma assay.**

II. Summary of nonclinical findings:

A. Brief overview of nonclinical findings

NOCDURNA is seeking market approval for the treatment of nocturia in adults as a new formulation for sublingual use. It is instantly disintegrated at the administration site. Submitted non-clinical studies for the safety and the efficacy of the new product were conducted to assess the test article's impurities as well as its potential for any local reactions. These non-clinical studies in conjunction with the Agency's previous findings of safety and efficacy for desmopressin when administered via other routes are sufficient to support the safety of sublingual administration of NOCDURNA for treatment of nocturia in adults, once daily at bedtime (up to 100 mcg for men and 25mcg for women).

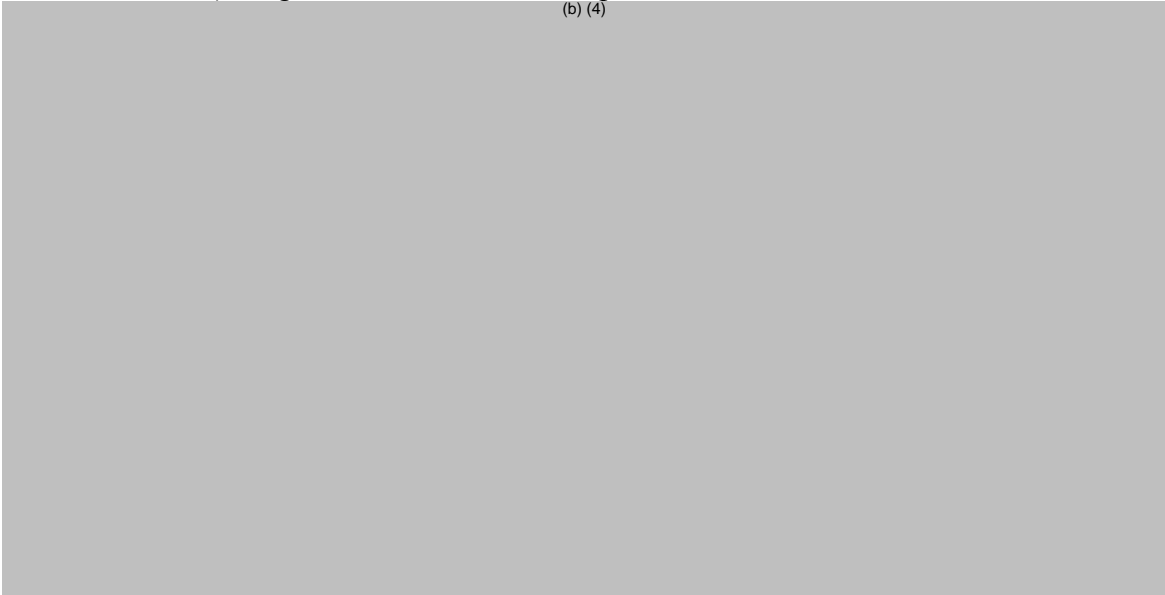
NOCDURNA, a new formulation of desmopressin (desmopressin sublingual melt or desmopressin SLM), was submitted as a 505(b)(2) application. The new product contains the active ingredient desmopressin, which is a structural analog of the natural human antidiuretic hormone (8-arginine vasopressin). There is extensive clinical experience with desmopressin because various formulations of this drug (oral-Minirin; IV injection, intranasal spray) have been on the market for a long time in many countries. NDA 22517 relies on

the Agency's previous findings of safety and efficacy of desmopressin for the proposed indication and product (NDA19-955, DDAVP® Desmopressin acetate Tablets held by Sanofi Aventis US; NDA 21-333 Desmopressin Acetate Nasal Spray; NDA 21-795 Desmopressin Acetate Tablets; and DMF 8396). However, a few non-clinical studies were submitted for desmopressin SLM to bridge to the previous approved desmopressin products. These studies include: local tolerability study (in the cheek pouch of Syrian hamsters for 28 days); impurity qualification studies (a 13-week repeat-dose study in rats as well as two genotoxicity studies); and a comparison absorption study (sublingual vs. oral).

In the local tolerability study, desmopressin was administered once daily in the cheek pouch of Syrian hamsters for 28 days. Results suggested no evidence of any local reactions or any histopathological changes related to the test article. Thus, the nonclinical data support the safe use of desmopressin via the sublingual route.

The sponsor's drug substance contains 3 impurities, ([Glu⁴]desmopressin, [Gly⁹-OH]desmopressin and [β Asp⁵]desmopressin, that are (b) (4) concentration levels than in the referenced listed drug (DDAVP Tablets, NDA#19-955) drug substance. See below Sponsor's Table Below:

(b) (4)



Therefore, the sponsor conducted a 13-week toxicity study in rats and two genotoxicity studies with drug substance containing these 3 impurities (at higher levels of concentration that mentioned in the above table, (b) (4) % for each impurity) to demonstrate the safety of the new product. Results of the repeat – dose study in rat showed only pharmacological changes consistent with desmopressin in urinary parameters (decreased urinary volume and pH; increased specific gravity and concentration of sodium, potassium, chloride and protein and increased relative kidney weights.) The NOAEL was the highest dose tested (10 μ g/kg/day=1xMRHD). No new toxicities were identified with the inclusion of the 3 impurities. Genotoxicity studies, an Ames test and a mouse lymphoma assay, were also conducted for qualification of these 3 impurities in the drug

substance. Results of these two genotoxicity studies presented no potential of any genotoxicity with these three impurities. Therefore, the three toxicology studies demonstrated the safety of the three impurities when present at concentration of up to ^(b)₍₄₎ %.

B. Pharmacologic activities:

Desmopressin, a synthetic analogue of antidiuretic hormone (ADH), vasopressin, has a more potent, prolonged duration of action as well as decreased pressor activity compared to ADH. The demonstration of pharmacological activity of desmopressin SML is based on referenced data; therefore, no additional pharmacology studies were conducted with desmopressin SLM.

C. Pharmacokinetics activity:

A PK study was conducted in two species (rat and domestic pig) to assess the bioavailability of desmopressin when administered via sublingual route. Findings of this study showed desmopressin SLM (via sublingual route) had greater bioavailability (C_{max} , T_{max} , AUC and AUC/dose), about two fold, compared to the referenced product (via oral). Thus, less quantity of the new product is needed for the treatment of the nocturia in adults.

D. Nonclinical safety issues relevant to clinical use:

None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22517

Review number: 1

Supporting document#/date/type of submission: 000; 06/19/2009; original application (e-CTD submission); 505(b)(2) application, referencing the listed drug desmopressin tablets and NDA 19-955 (Sanofi Aventis)

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Ferring, Pharmaceuticals Inc.

Manufacturer for drug substance: Ferring, Pharmaceuticals Inc.

Reviewer name: Parvaneh Espandiari

Division name: DMEP

HFD #: 510

Review completion date: 08/28/2009

Drug:

Trade name: NOCDURNA (Desmopressin Sublingual Melt)

Generic name: desmopressin, arginine vasopressin

Chemical name: 1-Desamino-8-D-arginine vasopressin acetate; 1-(3-Mercaptopropranoic acid)-8-D-arginine- vasopressin monoacetate (*1-desamino-8-D-arginine vasopressin*), DDAVP

CAS registry number: 16679-58-6

Molecular formula/molecular weight:
C₄₆H₆₄N₁₄O₁₂S₂•C₂H₄O₂•3H₂O/1183.34

Structure:

Nonapeptide, differs from endogenous antidiuretic hormone (ADH) at position 1 where it is deamidated and position 8 where L-arg is replaced by D-arg.

SCH₂CH₂CO-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH₂ • CH₃COOH • 3H₂O

3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate

Relevant INDs/NDAs/DMFs: NDAs: 19955; 21333; 21795; IND65890 and; DMF 8396

Drug class: Arginine vasopressin (synthetic anti-diuretic hormone analogue)

Intended clinical population: Treatment of nocturia in adults

Clinical formulation:

Each orally disintegrating tablet contains desmopressin acetate equivalent to 25 mcg, 50 mcg and 100 mcg of desmopressin as free base. The inactive ingredients are gelatin, mannitol, and anhydrous citric acid

Scanned from sponsor's submission:

Desmopressin Melt 25µg is an orally disintegrating tablet:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.025 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol	(b) (4)		Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous	(b) (4)		Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 25 µg desmopressin free base.

Desmopressin Melt 50µg is an orally disintegrating tablet:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.050 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol	(b) (4)		Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous	(b) (4)		Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 50 µg desmopressin free base.

Desmopressin Melt 100µg is an orally disintegrating tablet:

The components of the dosage form and their amount per unit are listed below:

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.100 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol	(b) (4)		Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous	(b) (4)		Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 100 µg desmopressin free base.

Route of administration: Orally Disintegrating Tablet: proposed up to 25 mcg in females and 100 mcg in males.

See scanned Table below from sponsor:

-----**DOSAGE AND ADMINISTRATION**-----

Dosing chart (2.1):

(b) (4)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA22517 are owned by Ferring, Pharmaceuticals Inc. or are data for which Ferring, Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22517 that Ferring, Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that Ferring, Pharmaceuticals Inc. does not own (or from FDA reviews or

summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22517.

Studies reviewed within this submission:

• **Single Dose Toxicity Studies**

- 1) Desmopressin: Pharmacokinetics and oral bioavailability in the rat and domestic pig
- 2) Pharmacokinetics in the domestic pig following administration of two different dosage forms and a pig PK study (Tablet vs. Melt sublingual administration).

• **Repeat Dose Toxicity Studies**

- 1) 13 -week Subcutaneous Toxicity Study in Rats

• **Genetic Toxicology Studies**

- 1) Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 100, TA 1537 and TA 98 and *Escherichia coli* WP2uvrA
- 2) EF992026 Mouse Lymphoma Cell Mutation Assay

• **Local tolerance Study:**

- 1) Oral Irritation in the Syrian Hamster

Studies not reviewed within this submission:

None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Desmopressin is a synthetic analogue of antidiuretic hormone (ADH), vasopressin, which has a more potent, prolonged duration of action as well as decreased pressor activity compared to ADH. In general, desmopressin increases urine concentration, decreases urine production through binding to V2 receptors, selective agonist for the vasopressin V2-receptor, in renal collecting ducts.

2.6.2.2 Primary pharmacodynamics

No new information.

2.6.2.3 Secondary pharmacodynamics

No new information.

2.6.2.4 Safety pharmacology

No new information.

Pharmacodynamic drug interactions

No new information.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

New studies were conducted to characterize the PK profile/bioavailability of desmopressin sublingual melt (SLM) in two species (rat and domestic pig). Results of studies showed that desmopressin SLM has several fold higher bioavailability (~2X) to oral treatment of desmopressin tablets.

2.6.4.2 Methods of Analysis

The plasma levels of desmopressin were detected in pigs by radioimmunoassay (RIA) (under the GLP with the Quality Assurance Statement).

2.6.4.3 Absorption

Study Title: Pharmacokinetics in the domestic pig following administration of two different dosage forms.

Study report #: FE992026 DS PHA 0501 - Final and CRO study code: (b) (4)
1475/090

Volume # and page#: Electronic submission

Conducting laboratory and location: (b) (4)

Date of initiation: Date: 22 May 2006

Background: This study was designed to investigate the absorption of desmopressin by sublingual administration of MINIRIN Melt to pigs.

Methods:

The absorption of the test article was investigated with a 3-way-cross-over study in six female pigs:

- Group A: 1st treatment, MINIRIN Melt (240 µg) was treated under the tongue of anaesthetized pigs (for 2 hours). To prevent swallowing, the esophagus of pigs in this group was occluded using an endotracheal tube.
- Group B: 2nd treatment, MINIRIN Melt (240 µg) was administered sublingually to conscious pigs.
- Group C: 3rd treatment, MINIRIN Tablets (2 x 200 µg) were administered orally.

Blood samples were collected pre dose and at 10, 20, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8 and 10 hours after treatment and analyzed by radioimmunoassay for desmopressin.

Results:

See Scanned Figure below from Sponsor:

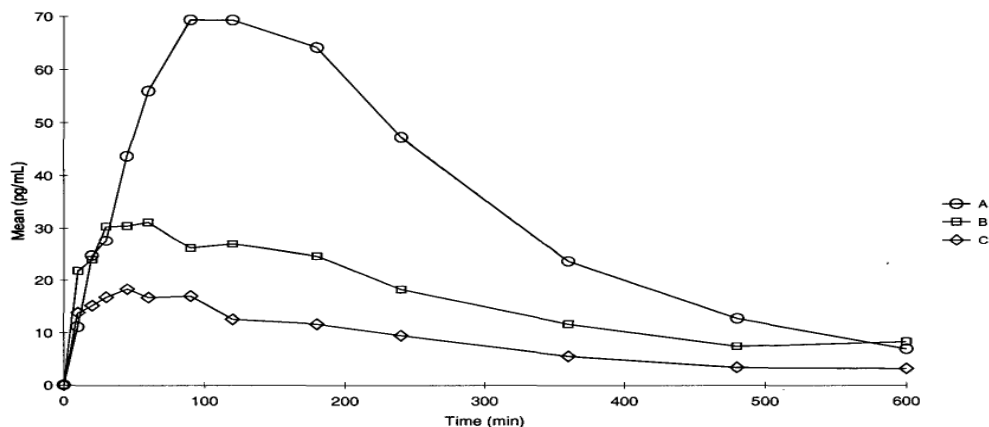


Figure 1: Mean plasma concentration vs. time curves of desmopressin after administration of MINIRIN Melt to anaesthetised pigs with occluded oesophagus (A) or conscious pigs with non-occluded oesophagus (B,) and administration of MINIRIN Tablets to conscious pigs (C).

In Group A (anaesthetized pigs), the plasma level of desmopressin was detected after 10 minutes of treatment indicating that desmopressin was absorbed sublingually. In this group, C_{max} occurred at 1.93 hrs. In Group B (conscious pigs, passage through the esophagus was not prevented), C_{max} was observed at 0.82 hrs. In Group C, (oral administration) C_{max} occurred at 0.67 hrs. The results showed that desmopressin SLM increased the absorption compared to desmopressin tablets. When corrected for administrated doses, the mean AUC value for Group A was greater than the other group's values. Mean AUC/ μ g administrated values were 1.49, 0.67 and 0.20 hr.pg/mL, for Groups A, B, and C, respectively. The prolonged absorption time of the test article in pigs with occluded esophagus is probably related to the longer time that test article remains in the sublingual cavity.

Conclusion: Results of this study showed that the bioavailability of desmopressin SLM was several-fold (~2fold) higher than desmopressin tablets.

2.6.4.4 Distribution

No new studies

2.6.4.5 Metabolism

No new studies

2.6.4.6 Excretion

No new studies

2.6.4.7 Pharmacokinetic drug interactions

No new studies

2.6.4.8 Other Pharmacokinetic Studies

Study Title: Desmopressin: Pharmacokinetics and oral bioavailability in the rat and domestic pig

Study report #: FE 992026 DS PHA 03 02; FE 992026 DS PHA 03 03

Volume # and page#: Electronic submission

Conducting laboratory and location:

(b) (4)

Date of initiation: 08 July 2004

Background: This study was designed to investigate the oral bioavailability of different doses of desmopressin in rats.

Methods: Desmopressin was administered (i.v. at 0.445 µg/kg or orally at 20, 50 and 100 µg/kg) to rats (n=40) and domestic pigs (i.v. at 0.1 µg/kg or orally at 200 and 500 µg (n=6). Desmopressin plasma levels were detected by radioimmunoassay up to 480 minutes.

See scanned sponsor's Tables:

Table 1: Doses of desmopressin in the rat study

Group	Route	Dose ¹⁾ (µg/kg)	Animal nos.
1	Intravenous	0.445	1-10
2	Oral	20	11-20
3	Oral	50	21-30
4	Oral	100	31-40

Table 2: Doses of desmopressin in the pig study

Route	Dose ¹⁾
Intravenous	0.1 µg/kg
Oral	200 µg
Oral	500 µg

Results:

See scanned sponsor Figures and Tables:

In Rats:

Plasma levels of Desmopressin after i.v. and p.o. administration:

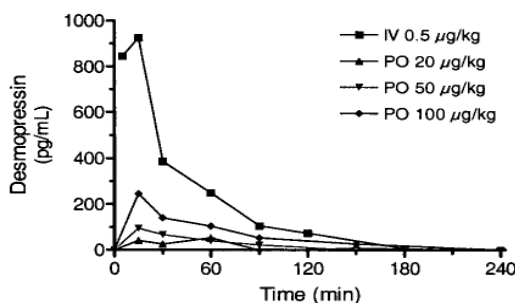


Figure 1. Mean plasma levels of desmopressin after iv. and po. administration to rats. For each time point n = 4 or 5.

PK values after oral administration:

Table 4. Mean pharmacokinetic parameters of desmopressin after oral administration to rats. Dose 20, 50 and 100 µg/kg (free base)

Dose (ug/kg)	T _{max} (min)	C _{max} (pg/mL)	AUC ₀₋₁₁ (min*pg/mL)	AUC _{inf} (min*pg/mL)	AUC _{ext} (%)	T _{1/2} (min)	F* (%)
20	60	52.9	3468.2	NA	NA	NA	0.19
50	15	95.1	5114.4	5663.8	21.9	37.3	0.12
100	15	246.8	14169.4	14836.7	12.6	48.5	0.16

• For 20 µg/kg AUC₀₋₁₁ was used for the calculation of F. For 50 and 100 µg/kg AUC_{inf} was used for the calculation of F.

PK values after i.v. administration:

Table 3. Mean pharmacokinetic parameters of desmopressin after intravenous administration to rats. Dose 0.445 µg/kg (free base)

AUC ₀₋₁₁ (min*pg/mL)	AUC _{inf} (min*pg/mL)	AUC _{ext} (%)	Cl (mL/min/kg)	λ _z (1/min)	T _{1/2} (min)	V _z (mL/kg)	V _{ss} (mL/kg)
41335.9	41379.8	0.6	10.8	0.0274	25.3	392.0	427.0

In pigs:

Plasma levels of Desmopressin after i.v. and p.o. administration:

See scanned sponsor Figure 2:

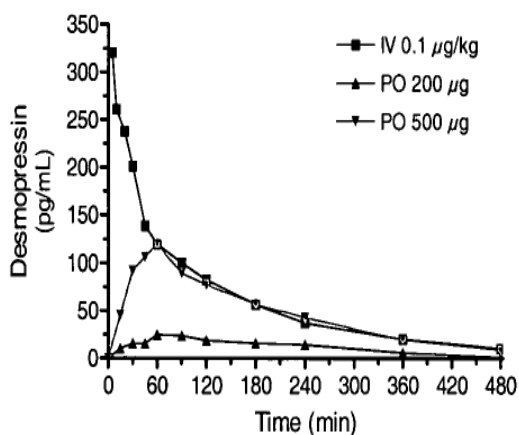


Figure 2. Mean plasma levels of desmopressin after iv. and po. administration to pigs. n = 5 (iv and 500 µg) or 6 (200 µg).

In Pigs:

PK values after oral administration:

Table 6. Pharmacokinetic parameters of desmopressin after oral administration to pigs. Doses 200 and 500 µg (desmopressin acetate)

Dose	Pig	T _{max} (min)	C _{max} (pg/mL)	AUC ₀₋₁₁ (min*pg/mL)	AUC _{inf} (min*pg/mL)	AUC _{ext} (%)	T _{1/2} (min)	F (%)	
200	1	15	18.5	3663	NA	NA	NA	0.21	
	2	60	24.2	4295	NA	NA	NA	NA	
	3	90	51.3	9515	NA	NA	NA	0.50	
	4	90	20.7	4386	5120	20.9	132.3	0.30	
	5	60	33.5	9116	11644	21.7	228.8	0.61	
	6	90	20.7	3364	4192	30.7	116.5	0.23	
	NObs	6	6	6	6	6	6	6	5
	Mean	67.5	28.2	5723.0	6985.5	24.4	159.2	0.37	
	SD	29.6	12.5	2811.4	4061.2	5.4	60.8	0.18	
	Min	15	18.5	3364	4192	20.9	116.5	0.21	
	Max	90	51.3	9515	11644	30.7	228.8	0.61	
CV%	43.9	44.5	49.1	58.1	22.3	38.2	47.4		
500	1	60	121.0	19679	20905	5.9	113.9	0.55	
	3	60	144.0	20420	22685	10.0	137.7	0.54	
	4	45	44.2	8537	9783	18.0	142.5	0.28	
	5	45	187.0	39760	41891	5.1	113.6	1.15	
	6	15	126.0	22084	23515	6.1	111.4	0.65	
	NObs	5	5	5	5	5	5	5	
	Mean	45.0	124.4	22096.1	23755.7	9.0	123.8	0.63	
	SD	18.4	51.8	11230.8	11548.5	5.4	15.0	0.32	
	Min	15	44.2	8537	9783	5.1	111.4	0.28	
	Max	60	187.0	39760	41891	18.0	142.5	1.15	
	CV%	40.8	41.7	50.8	48.6	59.7	12.1	50.9	

NA: Not applicable

PK values after i.v. administration:

Table 5. Pharmacokinetic parameters of desmopressin after intravenous administration to pigs. Dose 0.1 µg/kg (desmopressin acetate)

Pig	AUC ₀₋₁₁ (min*pg/mL)	AUC _{inf} (min*pg/mL)	AUC _{ext} (%)	Cl (mL/min/kg)	T _{1/2} (min)	λ _z (1/min)	V _z (mL/kg)	V _{ss} (mL/kg)
1	30728	33030	7.0	2.75	126.6	0.0055	502.2	474.7
3	33198	34907	4.9	2.50	109.7	0.0063	396.2	353.2
4	28886	30321	4.7	2.86	102.5	0.0068	423.2	399.2
5	29362	30909	5.0	2.84	113.5	0.0061	465.0	441.7
6	28224	29421	4.1	3.03	110.3	0.0063	481.4	415.8
NObs	5	5	5	5	5	5	5	5
Mean	30079.7	31717.7	5.1	2.80	112.5	0.0062	453.6	416.9
SD	1970.3	2223.4	1.1	0.19	8.9	0.0005	43.2	45.6
Min	28224	29421	4.1	2.50	102.5	0.0055	396.2	353.2
Max	33198	34907	7.0	3.03	126.6	0.0068	502.2	474.7
CV%	6.6	7.0	21.2	6.8	7.9	7.6	9.5	10.9

Results and Discussion:

The PK and bioavailability of the test article were investigated in two species (rat and pig) with different route of administration (i.v. and oral). The bioavailability of desmopressin in rats was close to human values and its elimination was faster than in human. In pigs: its bioavailability at 500 µg was higher than 200 µg which was higher than in human values; however, the PK of desmopressin after i.v. treatment was close to human values. Results suggested that both models are appropriate for testing oral peptide delivery system for desmopressin.

Table 7. Comparative pharmacokinetics of desmopressin in different species. Values for rat and pig are from the present study. References for dog and human studies are given in brackets.

	Rat	Dog*	Pig	Human**
T_½ (min)	25.3	61.1	112.5	55 min-3.62 h
Clearance (mL/min/kg)	10.8	7.4	2.8	1.7-2.6
V_{ss} (mL/kg)	427	499	417	206-373
T_{max} (min)	15	26	45-68	60-71
F (%)	0.12-0.19	0.83	0.37-0.63	0.1-0.24

* [13]

** [1, 2, 20-25]

2.6.4.9 Discussion and Conclusions

The PK characteristics of desmopressin are well understood because previous of extensive nonclinical and clinical experience with desmopressin. Accordingly, the sponsor has referred to NDA#19955. To bridge to the referenced information, the sponsor conducted the absorption study in the domestic pig. Results suggested the bioavailability of desmopressin SLM was ~ 2 fold higher than desmopressin tablets.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Desmopressin FE992026, FE999912;
2.6.5.1 Pharmacokinetics: Overview
DN-OVERVIEW-99;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
Page 1 of 1

2.6.5.1 Pharmacokinetics: Overview

Test Article: Desmopressin

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
Absorption Pharmacokinetics in the domestic pig following administration of two different dosage forms	Domestic female pigs	Sublingual and oral	In life phase: (b) (4)	[FE 992026 DS PHA 0501]	4.2.2.2
Distribution	No new studies				
Metabolism	No new studies				
Excretion	No new studies				
Pharmacokinetic Drug Interactions	No new studies				
Other	No new studies				

Desmopressin FE992026, FE999912;
2.6.5.3 Pharmacokinetics: Absorption after a Single Dose
DN-SUMMARY-279;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
Page 1 of 1

2.6.5.3 Pharmacokinetics: Absorption after a Single Dose

Test Article: Desmopressin
Location in CTD: 4.2.2.2
Study No.: [FE 992026 DS PHA 0501]

Species	Domestic pig			Domestic pig			Domestic pig		
Number of Animals/Gender (M/F)	6 F (Anaesthetised)			6 F (Conscious)			6 F (Conscious)		
Feeding Condition	Overnight fasting			Overnight fasting			Overnight fasting		
Vehicle/Formulation	Orally disintegrating tablet			Orally disintegrating tablet			Tablet		
Method of Administration	Sublingual, oesophagus occluded			Sublingual, oesophagus not occluded			Oral		
Dose (µg/animal)	240			240			2 × 200		
Sample (e.g., whole blood, plasma, serum etc)	Plasma			Plasma			Plasma		
Analyte	Desmopressin			Desmopressin			Desmopressin		
Assay	RIA			RIA			RIA		
PK Parameters:	Mean	SD	N	Mean	SD	N	Mean	SD	N
T _{max} (h)	1.93	1.18	5	0.82	0.56	6	0.67	0.47	6
C _{max} (pg/mL)	73.7	54.4	6	37.4	23.2	6	21.2	11.1	6
AUC ₀₋₄ (h×pg/mL)	342	242	6	162	96.3	6	80.7	27.5	6
AUC _{INF} (h×pg/mL)	442	196	5	276	69.8	2	131	27.8	2
AUC _{%EX} (%)	8.90	5.55	5	8.75	1.05	2	15.5	4.63	2
T _{1/2} (h)	2.32	0.380	5	2.24	0.412	2	2.17	0.454	2
AUC/dose	1.49	1.03	6	0.67	0.41	6	0.20	0.07	6

Additional information: RIA : Radioimmunoassay

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Summary:

The sponsor is relying on the previous findings of safety efficacy for desmopressin. However, *in vivo* (a 13-week study in rats) and *in vitro* (Ames test and mouse lymphoma

assay) non-clinical studies were conducted to characterize the local toxicity and to qualify the slightly different impurity profile of the test article (desmopressin SLM contains three impurities of [Glu4]desmopressin, [Gly9-OH]desmopressin and [βAsp5]desmopressin at a level of (b) (4) respectively). In the 13-week study in rats, sponsor noted that the SC administration was selected to compare to the current routes of human administration (oral and intranasal). Findings of this study were consistent with the pharmacological effects of the desmopressin. The absolute kidney weights were ↑ (ss) for MD and HD treated animals with no microscopic findings. The increased kidney weights might be due to the pharmacological effects of the test article in maximizing tubular reabsorption. Incidences of cystic/cleft-like spaces and granulomatous inflammation were noted at the sc injection site (not clinically relevant to the new product). The NOAEL was 10 µg/kg/day (HD), only pharmacological effects of the desmopressin were noted. In addition, results from two *in vitro* genotoxicity studies (Ames test and mouse lymphoma assay) showed no potential of any genotoxicity with these 3 impurities at higher concentration than that proposed for CMC specifications for each impurity. These studies showed that the toxicological profile of the new product, desmopressin SLM, was consistent with desmopressin tablets, suggesting that the present of these 3 impurities does not alter the toxicity profile of desmopressin. The local tolerability study was conducted once daily in the cheek pouch of Syrian hamsters for 28 day for the safety efficacy of the new route of desmopressin of the new product. Results suggested no evidence of any local reactions or any histopathological changes related to the test article.

Study title: 13 -week Subcutaneous Toxicity Study in Rats

Background:

The toxicity of desmopressin 3 impurities ([Glu4]desmopressin,[Gly9-OH]desmopressin and [βAsp5]desmopressin at a level of (b) (4) % for each impurity) was investigated by daily subcutaneous injection in 13 week rat study.

Key findings:

- Significant pharmacological changes in urine samples were noted in all treated animals at HD (females and males): ↓ volume, reduced pH and higher concentrations of electrolytes (sodium, potassium and chloride), specific gravity and protein concentration. In addition, the urinary color was darker in HD female rats.
- At all dose levels, absolute and relative kidney weights ↑ with no macroscopic findings (ss at MD and HD with relative kidney weights).
- Histopathology showed an increased incidence of cystic/cleft-like spaces and granulomatous inflammation at sc injection site in all treated males and at HD with females (not clinically relevant to clinical sublingual route).
- NOAEL= 10µg/kg/day (the high dose)

Reviewer: *The purpose of this study was to evaluate the toxicological profile of desmopressin with 3 impurities ([Glu4]desmopressin,[Gly9-OH]desmopressin and [βAsp5]desmopressin at a level of (b) (4) % for each impurity) by daily s.c. for 13 weeks in rats. In general the toxicological profile is similar to desmopressin, suggesting no significant effect of 3 impurities at tested concentration levels. The incidences of cystic/cleft-like spaces and granulomatous inflammation at sc injection site are not*

clinically relevant since the test article is proposed for sublingual formulation for marketing and there was no irritation sublingually in the local irritation in hamster study. Findings were attributed to the pharmacological effect of the test article and were not considered to be adverse. Based on the ICH Q3A Guidance for Industry for impurities, the sponsor performed this study as one of the requirements for qualification of impurities. Results of this study showed no safety concerns. However, the TK data of this study were not presented; therefore, there is not sufficient data with this study to bridge to the clinical exposure or to determine therapeutic dose safety margins.

Study no.: (b) (4) : 58881 and Ferring Ref No: FE992026DSTOX0501

Volume #, and page #: Vol. 1; 228 pages

Conducting laboratory and location: (b) (4)

Date of study initiation: 20 March 2006

GLP compliance: yes

QA report: yes (X) no ()

Drug, lot #, and % purity: Bach#: CRS-MIX-Desmopressin-2005:1; 102% of label claim (the test article was spiked with 3 impurities: ([Glu⁴]desmopressin, Gly⁹-OH]desmopressin, and [βAsp⁵]desmopressin, at concentration levels of (b) (4) % , respectively).

Methods

<u>Doses:</u>	Control vehicle or 0.1, 1.0, 10.0 µg desmopressin/kg/day
<u>Species/source</u>	SD rats / (b) (4)
<u>Age:</u>	5 weeks old
<u>Weight:</u>	Males: 103-135 g; females; 103-129 g
<u>Number/sex/group:</u> (main study)	10/sex/group
<u>Number/sex/group (TK)</u>	None
<u>Number/sex/group</u> (recovery)	None
<u>Route, formulation, dose</u> <u>volume</u>	once/day/for 92 days; SC administration; volume of injection was 1 ml/kg/day

Study Design Summary:

Observation and Times:

<u>Clinical Findings:</u>	recorded daily
<u>Body weights:</u>	recorded on the day of arrival, first day of study and weekly
<u>Food consumption:</u>	started on Day1 and recorded weekly
<u>Ophthalmoscopy:</u>	performed before treatment, and during Wk 13 on animals treated with control or HD.

<u>Urinalysis:</u>	urine samples were taken before termination (over night)																																																																																																																																																																																
<u>Hematology:</u>	blood samples were taken during the last week of treatment																																																																																																																																																																																
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<u>Gross pathology:</u>	for specified organs/tissues																																																																																																																																																																																
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<u>Toxicokinetics:</u>	Not done																																																																																																																																																																																
<u>Histopathology:</u>	specified organs/tissues were fixed (4%formaldehyde) and examined Adequate Battery: yes (X), no () See Table below from sponsor <table border="1"> <thead> <tr> <th>Organs and tissues</th> <th>W e i g h</th> <th>F i x</th> <th>M i c r o</th> <th>Organs and tissues</th> <th>W e i g h</th> <th>F i x</th> <th>M i c r o</th> </tr> </thead> <tbody> <tr> <td>Abnormalities (gross lesions)</td> <td></td> <td>x</td> <td>x</td> <td>Pancreas</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Adrenals</td> <td>x</td> <td>x</td> <td>x</td> <td>Pituitary</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Aorta (thoracic)</td> <td></td> <td>x</td> <td>x</td> <td>Prostate</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Brain</td> <td>x</td> <td>x</td> <td>x</td> <td>Salivary glands (right parotid, sublingual and submandibular)</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Bone marrow smear</td> <td></td> <td>x</td> <td></td> <td>Sciatic nerve</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Bones (right femur)</td> <td></td> <td>x</td> <td>x</td> <td>Seminal vesicles</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Epididymides</td> <td>x</td> <td>x</td> <td>x</td> <td>Skeletal muscle</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Eyes with lens/optic nerve</td> <td></td> <td>x</td> <td>x</td> <td>Skin</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Heart</td> <td>x</td> <td>x</td> <td>x</td> <td>Spinal cord (cervical, thoracic, lumbar)</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Injection site</td> <td></td> <td>x</td> <td>x</td> <td>Spleen</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Intestine small (duodenum, jejunum, ileum)</td> <td></td> <td>x</td> <td>x</td> <td>Sternum (for bone marrow)</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Intestine large (caecum, colon, rectum)</td> <td></td> <td>x</td> <td>x</td> <td>Stomach (glandular, non glandular)</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Joint (knee)</td> <td></td> <td>x</td> <td>x</td> <td>Testes</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Kidneys</td> <td>x</td> <td>x</td> <td>x</td> <td>Thymus</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Larynx</td> <td></td> <td>x</td> <td>x</td> <td>Thyroids (incl. parathyroid)</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Liver</td> <td>x</td> <td>x</td> <td>x</td> <td>Tongue</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Lungs</td> <td></td> <td>x</td> <td>x</td> <td>Trachea</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Lymph nodes (mesenteric and right mandibular)</td> <td></td> <td>x</td> <td>x</td> <td>Ureters</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Mammary gland</td> <td></td> <td>x</td> <td>x</td> <td>Urinary bladder</td> <td></td> <td>x</td> <td>x</td> </tr> <tr> <td>Oesophagus</td> <td></td> <td>x</td> <td>x</td> <td>Uterus (horn, cervix and oviducts)</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Ovaries</td> <td>x</td> <td>x</td> <td>x</td> <td>Vagina</td> <td></td> <td>x</td> <td>x</td> </tr> </tbody> </table> Peer review: yes (X), no () Incidences were described in the following way: - "no trace" = no trace in 2-3 visual fields (+) "trace" = a few in 2-3 visual fields + "slight" = a few in each visual field ++ "moderate" = several in each visual field +++ "marked" = numerous in each visual field	Organs and tissues	W e i g h	F i x	M i c r o	Organs and tissues	W e i g h	F i x	M i c r o	Abnormalities (gross lesions)		x	x	Pancreas		x	x	Adrenals	x	x	x	Pituitary	x	x	x	Aorta (thoracic)		x	x	Prostate	x	x	x	Brain	x	x	x	Salivary glands (right parotid, sublingual and submandibular)		x	x	Bone marrow smear		x		Sciatic nerve		x	x	Bones (right femur)		x	x	Seminal vesicles		x	x	Epididymides	x	x	x	Skeletal muscle		x	x	Eyes with lens/optic nerve		x	x	Skin		x	x	Heart	x	x	x	Spinal cord (cervical, thoracic, lumbar)		x	x	Injection site		x	x	Spleen	x	x	x	Intestine small (duodenum, jejunum, ileum)		x	x	Sternum (for bone marrow)		x	x	Intestine large (caecum, colon, rectum)		x	x	Stomach (glandular, non glandular)		x	x	Joint (knee)		x	x	Testes	x	x	x	Kidneys	x	x	x	Thymus	x	x	x	Larynx		x	x	Thyroids (incl. parathyroid)	x	x	x	Liver	x	x	x	Tongue		x	x	Lungs		x	x	Trachea		x	x	Lymph nodes (mesenteric and right mandibular)		x	x	Ureters		x	x	Mammary gland		x	x	Urinary bladder		x	x	Oesophagus		x	x	Uterus (horn, cervix and oviducts)	x	x	x	Ovaries	x	x	x	Vagina		x	x
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Hematology ^a		
Parameter	Examined	Not examined

Hemoglobin (HGB)	x	
Hematocrit (HCT)	x	
Red blood cell count (RBC)	x	
Reticulocyte count		x
Platelet count (PLT)	x	
Mean platelet volume (MPV)		x
Mean corpuscular volume (MCV)	x	
Mean corpuscular hemoglobin (MCH)	x	
Mean corpuscular hemoglobin concentration (MCHC)	x	
Red cell distribution width (RDW)		x
Hemoglobin distribution width (HDW)		x
White Blood cell count (WBC)	x	
Differential leukocyte count (% and absolute)	x	
Cytologic morphology		x
Platelet morphology		x
Leukocyte morphology	x	
Activated Partial Thromboplastin Time (APTT)	x	
Prothrombin Time (PT)	x	

^a Observations/Times:

Clinical Chemistry ^a		
Parameter	Examined	Not examined
Aspartate aminotransferase (AST)	x	
Alanine aminotransferase (ALT)	x	
Alkaline phosphatase (ALP)	x	
Blood urea nitrogen (BUN)	x	
Creatinine	x	
Glucose	x	
Cholesterol	x	
Triglycerides	x	
Total protein	x	
Albumin	x	
Globulin	x	
Albumin/globulin	x	
Total bilirubin	x	
Sodium	x	
Potassium	x	
Chloride	x	
Calcium	x	
Phosphorous (PO ₄)		x
Gamma-glutamyl transferase (GGT)	x	

^a Observations/Times:

Parameters that were tested in urine:
See scanned sponsor table below:

Urinalysis

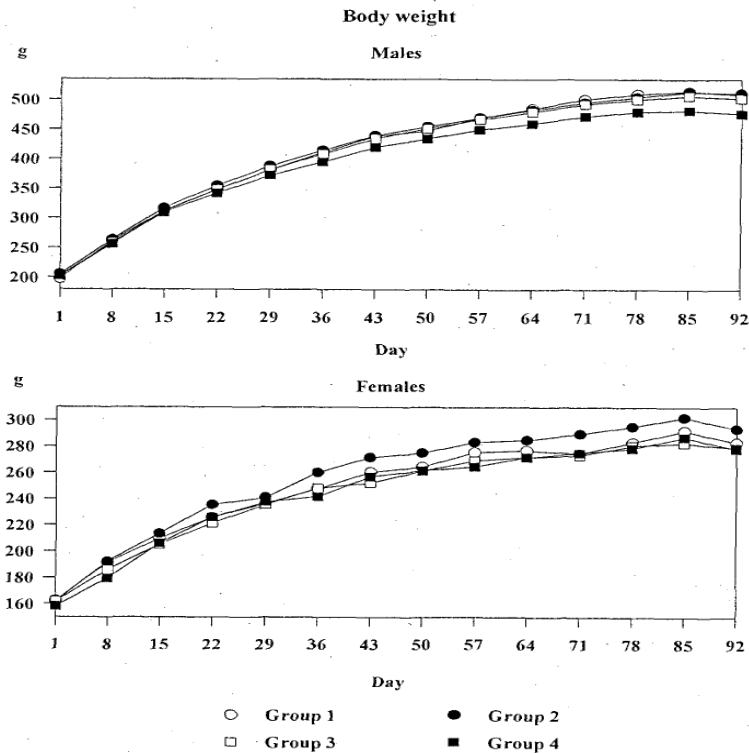
Parameter	Method/Equipment	Unit/Range
Volume		ml
Sodium (Na)	Ion selective electrode/ Cobas Mira S	mmol/l
Potassium (K)	Ion selective electrode/ Cobas Mira S	mmol/l
Chloride (Cl)	Ion selective electrode/ Cobas Mira S	mmol/l
Specific gravity (SG)	Ames Multistix 10SG/Clinitek 100/500	No unit
pH	Ames Multistix 10SG/Clinitek 100/500	No unit
Colour (COLOUR)	Visual examination	No unit
Protein (PROTEIN)	Ames Multistix 10SG/Clinitek 100/500	g/l
Leucocytes (LEUC)	Ames Multistix 10SG/Clinitek 100/500	Cells/ μ l
Blood (BLOOD)	Ames Multistix 10SG/Clinitek 100/500	Erythrocytes/ μ l
Glucose (GLUCOSE)	Ames Multistix 10SG/Clinitek 100/500	mmol/l
Ketones (KETONES)	Ames Multistix 10SG/Clinitek 100/500	mmol/l
Bilirubin (BILL)	Ames Multistix 10SG/Clinitek 100/500	No unit
Urobilinogen (UROBIL)	Ames Multistix 10SG/Clinitek 100/500	μ mol/l

Results (additional data to supplement summary above):

Body weights:

Body weight gain: No ss changes were detected in mean body weight or mean body weight gain in treated animals to control animals.

See scanned sponsor Figures below:



Hematology:

In males: The amount of platelets ↓ (ss) only in the LD treated males.

See scanned sponsor Tables below:

Males

GROUP	Hb				RBC				HT				MCV				MCH			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	9.60	0.28	10		9.14	0.33	10		47.4	1.7	10		52.0	1.2	10		1.06	0.05	10	
2	9.47	0.33	10		9.24	0.37	10		47.1	2.1	10		50.8	2.2	10		1.03	0.07	10	
3	9.48	0.37	10		9.11	0.33	10		46.9	1.7	10		51.4	1.2	10		1.04	0.05	10	
4	9.67	0.34	10		9.21	0.33	10		47.7	1.8	10		51.8	1.1	10		1.07	0.05	10	

GROUP	MCHC				WBC				% NEUTRO				NEUTRO				% LYMPHO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	20.2	0.2	10		14.80	2.27	10		5.3	2.9	10		0.81	0.47	10		93.6	3.0	10	
2	20.2	0.2	10		14.03	2.43	10		8.1	4.2	10		1.11	0.65	10		90.5	4.5	10	
3	20.3	0.2	10		13.57	2.55	10		6.2	3.0	10		0.80	0.29	10		91.4	4.0	10	
4	20.3	0.2	10		14.79	2.83	10		4.7	2.5	10		0.71	0.42	10		94.3	2.3	10	

Males

GROUP	LYMPHO				% EOS				EOS				% BASO				BASO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	13.83	2.09	10		0.5	0.7	10		0.06	0.10	10		0.0	0.0	10		0.00	0.00	10	
2	12.71	2.40	10		0.8	0.9	10		0.11	0.14	10		0.0	0.0	10		0.00	0.00	10	
3	12.48	2.76	10		1.4	1.3	10		0.17	0.16	10		0.0	0.0	10		0.00	0.00	10	
4	13.91	2.60	10		0.7	0.8	10		0.11	0.14	10		0.0	0.0	10		0.00	0.00	10	

GROUP	% MONO				MONO				Plt				APTT				Pt			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	0.6	0.7	10		0.09	0.11	10		579	43	10		17.6	3.8	10		15.4	0.6	10	
2	0.6	0.5	10		0.08	0.08	10		495	73	10	*	18.8	5.2	9		15.5	0.6	9	
3	1.0	0.9	10		0.12	0.12	10		515	79	10		20.1	5.9	10		15.3	0.8	10	
4	0.3	0.5	10		0.06	0.10	10		514	43	10		16.2	3.3	10		15.3	0.5	10	

Males

GROUP	FIB			
	Mean	S.D.	N	p
1	3.21	0.36	10	
2	3.26	0.37	9	
3	2.83	0.87	10	
4	3.34	0.31	10	

In Females: no changes were observed.
See scanned sponsor Tables below:

males

GROUP	Hb				RBC				HT				MCV				MCH			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	9.29	0.41	10		8.47	0.41	10		45.5	2.4	10		53.8	1.3	10		1.10	0.00	10	
2	9.11	0.20	10		8.51	0.30	10		44.6	1.2	10		52.7	1.4	10		1.08	0.04	10	
3	9.32	0.48	10		8.44	0.50	10		45.4	2.7	10		53.9	2.0	10		1.11	0.03	10	
4	9.18	0.32	10		8.47	0.23	10		45.1	1.5	10		53.2	0.9	10		1.10	0.00	10	

GROUP	MCHC				WBC				% NEUTRO				NEUTRO				% LYMPHO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	20.4	0.3	10		12.39	2.88	10		8.0	4.6	10		0.98	0.58	10		90.2	5.3	10	
2	20.4	0.2	10		11.84	1.57	10		8.1	3.7	10		0.95	0.41	10		90.2	4.5	10	
3	20.5	0.2	10		12.39	2.55	10		7.7	5.0	10		0.93	0.63	10		91.2	5.3	10	
4	20.5	0.2	10		11.97	1.79	10		6.6	3.2	10		0.78	0.41	10		92.1	3.4	10	

Females

GROUP	LYMPHO				% EOS				EOS				% BASO				BASO			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	11.20	2.74	10		1.5	1.6	10		0.18	0.21	10		0.0	0.0	10		0.00	0.00	10	
2	10.70	1.70	10		1.5	1.6	10		0.18	0.19	10		0.0	0.0	10		0.00	0.00	10	
3	11.32	2.61	10		1.0	0.9	10		0.12	0.12	10		0.0	0.0	10		0.00	0.00	10	
4	11.04	1.74	10		1.0	0.7	10		0.12	0.10	10		0.0	0.0	10		0.00	0.00	10	

GROUP	% MONO				MONO				Plt				APTT				Pt			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	0.3	0.7	10		0.04	0.08	10		532	97	10		14.5	2.2	10		14.5	0.6	10	
2	0.2	0.4	10		0.02	0.04	10		511	95	10		14.9	5.5	10		15.9	3.0	10	
3	0.1	0.3	10		0.01	0.03	10		535	78	10		14.6	3.1	10		14.7	0.3	10	
4	0.3	0.5	10		0.03	0.05	10		519	61	10		15.1	2.2	10		14.9	0.8	10	

Females

GROUP	FIB			
	Mean	S.D.	N	p
1	2.54	0.18	10	
2	2.49	0.38	10	
3	2.34	0.26	10	
4	2.30	0.35	10	

Clinical chemistry:

In males: the levels of magnesium ↓ (ss) only in the HD treated animals.
See scanned sponsor Tables below:

Males

GROUP	ALAT				ASAT				ALKPH				BILI				GGT			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	1.72	0.25	10		1.53	0.24	10		2.72	0.51	10		1.45	0.66	10		0.00	0.01	10	
2	1.72	0.25	10		1.59	0.25	10		2.55	0.25	10		1.11	0.66	10		0.01	0.01	10	
3	1.78	0.31	10		1.68	0.32	10		2.69	0.45	10		1.11	0.32	10		0.01	0.01	10	
4	1.73	0.36	10		1.54	0.27	10		2.74	0.47	10		1.16	0.52	10		0.01	0.00	10	

GROUP	CHOL				TRIG				UREA				CREAT				GLUC			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	2.95	0.46	10		1.91	0.54	10		7.19	0.94	10		30.1	3.7	10		9.15	2.34	10	
2	2.87	0.28	10		2.12	0.56	10		7.27	0.99	10		32.0	5.9	10		9.41	3.18	10	
3	2.82	0.38	10		2.24	0.82	10		7.08	0.60	10		32.9	9.5	10		10.27	3.20	10	
4	2.99	0.43	10		2.04	0.69	10		7.77	0.52	10		32.5	7.1	10		7.55	0.97	10	

GROUP	Na				K				Ca				Mg				P			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	154.6	3.6	10		6.58	0.87	10		3.16	0.15	10		1.20	0.09	10		3.08	0.24	10	
2	154.7	2.5	10		6.27	0.69	10		3.07	0.24	10		1.11	0.16	10		3.01	0.40	10	
3	155.2	3.6	10		6.27	0.63	10		3.11	0.18	10		1.20	0.16	10		3.07	0.45	10	
4	155.7	3.4	10		6.47	0.61	10		3.10	0.09	10		1.09	0.07	10	**	2.78	0.41	10	

GROUP	C1				PROTEIN				ALB				GLOBULIN				ALB/G Ratio			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	107.2	3.0	10		72.4	3.3	10		44.2	2.6	10		28.2	2.0	10		1.57	0.14	10	
2	107.4	1.2	10		71.2	4.7	10		43.1	2.1	10		28.1	3.4	10		1.55	0.15	10	
3	107.5	2.8	10		72.6	3.6	10		43.8	1.4	10		28.8	2.7	10		1.53	0.12	10	
4	107.6	2.9	10		71.3	2.1	10		43.4	2.7	10		27.9	2.5	10		1.57	0.23	10	

In Females: no changes were noted.
See scanned sponsor Tables below:

Females

GROUP	ALAT				ASAT				ALKPH				BILI				GGT			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	1.18	0.26	10		1.53	0.21	10		2.06	0.48	10		1.77	0.48	10		0.01	0.01	10	
2	1.45	0.33	10		1.72	0.29	10		2.16	0.42	10		1.23	0.63	10		0.01	0.01	10	
3	1.38	0.22	10		1.66	0.24	10		2.10	0.47	10		1.56	0.65	10		0.01	0.01	10	
4	1.27	0.25	10		1.62	0.21	10		1.78	0.14	10		1.40	0.37	10		0.01	0.01	10	

GROUP	CHOL				TRIG				UREA				CREAT				GLUC			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	3.31	0.63	10		0.95	0.31	10		6.92	0.68	10		33.9	4.1	10		8.63	2.64	10	
2	3.07	0.46	10		0.96	0.42	10		6.90	0.74	10		35.9	8.9	10		9.82	1.71	10	
3	2.78	0.72	10		1.03	0.39	10		6.32	0.99	10		30.7	5.4	10		8.30	1.33	10	
4	2.79	0.43	10		1.00	0.46	10		7.34	0.88	10		31.0	4.4	10		9.62	1.59	10	

Females

GROUP	Na				K				Ca				Mg				P			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	156.4	5.0	10		6.78	0.95	10		3.13	0.13	10		1.31	0.22	10		2.63	0.37	10	
2	154.7	4.6	10		6.24	0.95	10		3.10	0.20	10		1.32	0.18	10		2.79	0.58	10	
3	156.3	4.4	10		6.19	0.55	10		3.08	0.20	10		1.22	0.09	10		2.67	0.27	10	
4	155.1	4.8	10		5.89	0.64	10		3.12	0.18	10		1.32	0.07	10		2.78	0.17	10	

GROUP	Cl				PROTEIN				ALB				GLOBULIN				ALB/G Ratio			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	109.7	2.0	10		73.3	5.8	10		47.1	4.4	10		26.2	3.7	10		1.83	0.28	10	
2	108.9	4.1	10		72.3	2.8	10		47.5	2.6	10		24.8	1.9	10		1.93	0.21	10	
3	109.9	2.8	10		72.4	4.5	10		48.9	3.2	10		23.5	2.8	10		2.11	0.32	10	
4	108.5	4.2	10		72.1	2.3	10		47.9	2.0	10		24.2	3.2	10		2.02	0.34	10	

Urinalysis:

- At HD, in all treated animals, changes in urine samples were noted: lower volume (ss); reduced pH, higher concentrations of electrolytes (sodium, potassium, and chloride), and higher specific gravity/protein concentration (attributed to pharmacological effect of the desmopressin).
- The darker color of urine samples was noted at HD with females (not attributed to blood in urine).

- At HD, all animals had an increased concentration of sodium, K, Cl in urine.
- Microscopic findings of spun sediment showed a higher protein content at HD in males.

See scanned sponsor Tables below:

In Males:

males

GROUP	VOLUME				Na				K				Cl			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	15.0	4.4	10		28.1	10.3	10		140.1	32.4	10		39.6	24.5	10	
2	17.9	7.7	10		42.6	13.7	10		126.7	46.5	10		39.0	17.6	10	
3	19.7	5.3	10	*	34.6	12.9	10		106.7	24.2	10		26.4	12.3	10	
4	8.2	0.9	10	**	82.4	25.7	10	**	243.7	45.0	10	**	104.9	26.8	10	**

GROUP	SPECIFIC GRAVITY					Total	p
	1.010	1.015	1.020	1.025	≥1.030		
1	5	2	3	0	0	10	
2	3	6	1	0	0	10	
3	6	4	0	0	0	10	
4	0	0	2	7	1	10	**
Total	14	12	6	7	1	40	

GROUP	pH				Total	p
	7.0	7.5	8.0	8.5		
1	0	4	5	1	10	
2	2	5	3	0	10	
3	0	5	5	0	10	
4	8	2	0	0	10	**
Total	10	16	13	1	40	

GROUP	COLOUR			Total	p
	Light yellow	Yellow	Dark yellow		
1	2	8	0	10	
2	3	7	0	10	
3	5	5	0	10	
4	0	7	3	10	
Total	10	27	3	40	

GROUP	PROTEIN				Total	p
	Trace	0.3 g/l	1.0 g/l	>3.0 g/l		
1	1	6	2	1	10	
2	0	4	6	0	10	
3	0	7	3	0	10	
4	0	0	6	4	10	**
Total	1	17	17	5	40	

GROUP	LEUCOCYTES				Total	p
	No trace	15 cells/ μ l	70 cells/ μ l	125 cells/ μ l		
1	1	2	5	2	10	
2	0	0	8	2	10	
3	0	3	6	1	10	
4	0	3	5	2	10	
Total	1	8	24	7	40	

GROUP	BLOOD			Total	p
	No trace	25 cells/ μ l	200 cells/ μ l		
1	10	0	0	10	
2	9	1	0	10	
3	10	0	0	10	
4	9	0	1	10	
Total	38	1	1	40	

GROUP	GLUCOSE		Total	p
	No trace	Total		
1	10	10		
2	10	10		
3	10	10		
4	10	10		
Total	40	40		

GROUP	KETONES				Total	p
	No trace	Trace	1.5 mmol/l	3.9 mmol/l		
1	0	2	8	0	10	
2	1	4	5	0	10	
3	0	2	8	0	10	
4	0	0	9	1	10	
Total	1	8	30	1	40	

GROUP	BILIRUBIN		Total	p
	No trace	Small amounts		
1	10	0	10	
2	10	0	10	
3	10	0	10	
4	6	4	10	
Total	36	4	40	

GROUP	UROBILINOGEN	Total	p
	3.2 $\mu\text{mol/l}$		
1	10	10	
2	10	10	
3	10	10	
4	10	10	
Total	40	40	

GROUP	ERYTHROCYTES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	8	1	1	0	0	10	
2	5	3	2	0	0	10	
3	8	1	1	0	0	10	
4	7	2	0	1	0	10	
Total	28	7	4	1	0	40	

GROUP	LEUCOCYTES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	7	3	0	0	0	10	
2	6	4	0	0	0	10	
3	5	2	3	0	0	10	
4	1	5	3	0	1	10 **	
Total	19	14	6	0	1	40	

GROUP	EPITHELIAL CELLS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	4	3	3	0	0	10	
2	0	5	5	0	0	10	
3	4	1	5	0	0	10	
4	0	2	7	1	0	10	
Total	8	11	20	1	0	40	

GROUP	CRYSTALS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	0	0	7	3	10	
2	0	1	0	8	1	10	
3	0	0	2	7	1	10	
4	0	0	0	9	1	10	
Total	0	1	2	31	6	40	

GROUP	URATES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	0	9	1	0	10	
2	1	1	8	0	0	10	
3	2	1	6	1	0	10	
4	0	3	7	0	0	10	
Total	3	5	30	2	0	40	

GROUP	HYALINE CASTS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	10	0	0	0	0	10	
2	10	0	0	0	0	10	
3	10	0	0	0	0	10	
4	10	0	0	0	0	10	
Total	40	0	0	0	0	40	

GROUP	GRANULAR CASTS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	10	0	0	0	0	10	
2	10	0	0	0	0	10	
3	10	0	0	0	0	10	
4	10	0	0	0	0	10	
Total	40	0	0	0	0	40	

GROUP	BACTERIA					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	0	0	8	2	10	
2	0	0	0	10	0	10	
3	0	0	0	10	0	10	
4	0	0	0	10	0	10	
Total	0	0	0	38	2	40	

In Females:

GROUP	VOLUME				Na				K				Cl			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	14.6	4.2	10		31.1	8.8	10		97.7	43.4	10		34.6	24.4	10	
2	12.0	3.0	10		42.6	13.3	10	*	119.3	36.5	10		54.8	15.7	10	
3	15.0	7.7	10		41.3	18.9	10		92.2	43.2	10		35.3	22.3	10	
4	4.5	1.0	10	**	92.4	38.6	10	**	247.2	55.3	10	**	126.9	37.6	10	**

GROUP	SPECIFIC GRAVITY						Total	p
	≤1.005	1.010	1.015	1.020	1.025	≥1.030		
1	1	3	2	2	2	0	10	
2	0	0	7	0	2	1	10	
3	0	4	4	1	1	0	10	
4	0	0	0	0	0	10	10 **	
Total	1	7	13	3	5	11	40	

GROUP	pH				Total	p
	6.0	6.5	7.0	7.5		
1	0	1	8	1	10	
2	0	3	7	0	10	
3	0	3	4	3	10	
4	3	7	0	0	10	**
Total	3	14	19	4	40	

GROUP	COLOUR			Total	p
	Light yellow	Yellow	Dark yellow		
1	5	5	0	10	
2	2	8	0	10	
3	4	6	0	10	
4	0	0	10	10	**
Total	11	19	10	40	

GROUP	PROTEIN					Total	p
	No trace	Trace	0.3 g/l	1.0 g/l	>3.0 g/l		
1	6	2	1	1	0	10	
2	2	2	5	1	0	10	
3	4	3	2	1	0	10	
4	0	0	1	7	2	10**	
Total	12	7	9	10	2	40	

GROUP	LEUCOCYTES				Total	p
	No trace	15 cells/ μ l	70 cells/ μ l	125 cells/ μ l		
1	6	3	1	0	10	
2	4	5	0	1	10	
3	4	5	1	0	10	
4	9	1	0	0	10	
Total	23	14	2	1	40	

GROUP	BLOOD	Total	p
	No trace		
1	10	10	
2	10	10	
3	10	10	
4	10	10	
Total	40	40	

GROUP	GLUCOSE	Total	p
	No trace		
1	10	10	
2	10	10	
3	10	10	
4	10	10	
Total	40	40	

GROUP	KETONES		Total	p
	No trace	Trace		
1	10	0	10	
2	10	0	10	
3	10	0	10	
4	9	1	10	
Total	39	1	40	

GROUP	BILIRUBIN		Total	p
	No trace	Small amounts		
1	10	0	10	
2	10	0	10	
3	10	0	10	
4	9	1	10	
Total	39	1	40	

GROUP	UROBILINOGEN		Total	p
	3.2 $\mu\text{mol/l}$	16 $\mu\text{mol/l}$		
1	10	0	10	
2	10	0	10	
3	10	0	10	
4	9	1	10	
Total	39	1	40	

GROUP	ERYTHROCYTES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	8	2	0	0	0	10	
2	9	1	0	0	0	10	
3	9	1	0	0	0	10	
4	9	1	0	0	0	10	
Total	35	5	0	0	0	40	

GROUP	LEUCOCYTES					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	6	2	2	0	0	10	
2	7	3	0	0	0	10	
3	9	1	0	0	0	10	
4	7	3	0	0	0	10	
Total	29	9	2	0	0	40	

GROUP	EPITHELIAL CELLS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	2	4	4	0	0	10	
2	1	3	6	0	0	10	
3	1	3	6	0	0	10	
4	1	3	6	0	0	10	
Total	5	13	22	0	0	40	

GROUP	CRYSTALS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	3	2	5	0	10	
2	0	1	3	6	0	10	
3	0	1	3	5	1	10	
4	0	1	6	3	0	10	
Total	0	6	14	19	1	40	

GROUP	URATES						Total	p
	No trace	Traces	Slight	Moderate	Marked			
1	2	3	4	1	0	10		
2	3	4	3	0	0	10		
3	4	2	3	1	0	10		
4	1	5	4	0	0	10		
Total	10	14	14	2	0	40		

GROUP	HYALINE CASTS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	10	0	0	0	0	10	
2	10	0	0	0	0	10	
3	10	0	0	0	0	10	
4	10	0	0	0	0	10	
Total	40	0	0	0	0	40	

GROUP	GRANULAR CASTS					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	10	0	0	0	0	10	
2	10	0	0	0	0	10	
3	10	0	0	0	0	10	
4	10	0	0	0	0	10	
Total	40	0	0	0	0	40	

GROUP	BACTERIA					Total	p
	No trace	Traces	Slight	Moderate	Marked		
1	0	0	0	7	3	10	
2	0	0	0	8	2	10	
3	0	0	0	5	5	10	
4	0	0	0	10	0	10	
Total	0	0	0	30	10	40	

Gross pathology: not remarkable

Organ weights: Relative kidney wt increased with MD and HD in males and females. No other changes were notes with any other organs in treated animals.

See scanned sponsor Tables below:

In males:

males

GROUP	BODY WT, g				ADRENALS				ADRENALS				BRAIN				BRAIN			
					ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	508.7	53.8	10		46.9	7.8	10		0.0093	0.0015	10		2253	91	10		0.446	0.036	10	
2	510.4	25.4	10		51.5	5.8	10		0.0101	0.0014	10		2262	80	10		0.444	0.021	10	
3	503.8	42.1	10		50.8	10.9	10		0.0101	0.0022	10		2213	89	10		0.441	0.029	10	
4	477.5	31.9	10		48.4	11.0	10		0.0102	0.0023	10		2230	157	10		0.468	0.029	10	

GROUP	EPIDIDYMIDES				EPIDIDYMIDES				HEART				HEART				KIDNEYS			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	1500	141	10		0.298	0.039	10		1600	137	10		0.316	0.026	10		2916	300	10	
2	1413	67	10		0.278	0.019	10		1580	152	10		0.309	0.025	10		3158	275	10	
3	1439	140	10		0.287	0.029	10		1688	217	10		0.335	0.031	10		3240	336	10	
4	1401	100	10		0.295	0.035	10		1563	135	10		0.328	0.026	10		3146	265	10	

GROUP	KIDNEYS				LIVER				LIVER				PITUITARY				PITUITARY			
	RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	0.575	0.050	10		16557	1659	10		3.26	0.17	10		13.5	2.5	10		0.00266	0.00048	10	
2	0.618	0.027	10		17532	1971	10		3.43	0.24	10		13.6	2.9	10		0.00266	0.00051	10	
3	0.643	0.041	10	**	16578	1410	10		3.30	0.22	10		15.9	5.0	10		0.00317	0.00106	10	
4	0.660	0.044	10	**	16014	1555	10		3.35	0.22	10		14.0	5.1	10		0.00294	0.00109	10	

GROUP	PROSTATE				PROSTATE				SPLEEN				SPLEEN				TESTES			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	622	112	10		0.123	0.021	10		1075	134	10		0.212	0.024	10		3980	377	10	
2	666	92	10		0.131	0.019	10		1071	228	10		0.209	0.037	10		3793	176	10	
3	746	183	10		0.149	0.039	10		980	130	10		0.195	0.022	10		3954	298	10	
4	649	100	9		0.138	0.025	9		1021	180	10		0.213	0.029	10		3972	213	10	

GROUP	TESTES				THYMUS				THYMUS				THYROIDES				THYROIDES			
	RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE			
	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p	MEAN	S.D.	N	p
1	0.79	0.12	10		412	91	10		0.081	0.013	10		24.4	5.2	10		0.00485	0.00120	10	
2	0.74	0.05	10		428	104	10		0.084	0.018	10		28.1	7.2	10		0.00548	0.00126	10	
3	0.79	0.07	10		432	81	10		0.086	0.013	10		25.4	4.1	10		0.00507	0.00086	10	
4	0.84	0.08	10		403	85	10		0.085	0.020	10		26.5	6.6	10		0.00557	0.00142	10	

In Females:

GROUP	BODY WT, g				ADRENALS				ADRENALS				BRAIN				BRAIN			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE							
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	283.0	17.7	10		68.0	7.6	10		0.0241	0.0032	10		2019	66	10		0.717	0.058	10	
2	294.2	18.0	10		72.6	10.1	10		0.0247	0.0034	10		2070	105	10		0.705	0.038	10	
3	280.6	22.7	10		71.0	6.5	10		0.0254	0.0023	10		2049	67	10		0.735	0.066	10	
4	278.0	12.9	10		73.4	6.9	10		0.0264	0.0023	10		2046	75	10		0.737	0.040	10	

GROUP	HEART				HEART				KIDNEYS				KIDNEYS				LIVER			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p	Mean	S.D.	N	p
1	1029	80	10		0.365	0.035	10		1679	103	10		0.595	0.048	10		8937	1223	10	
2	1053	80	10		0.359	0.027	10		1849	110	10	*	0.629	0.029	10		9077	790	10	
3	1024	119	10		0.365	0.033	10		1882	177	10	**	0.672	0.048	10	**	8651	879	10	
4	990	119	10		0.356	0.037	10		1990	135	10	**	0.716	0.038	10	**	8825	1059	10	

GROUP	LIVER				PITUITARY				PITUITARY				OVARIES				OVARIES			
	RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE			
	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p
1	3.17	0.50	10		16.3	3.4	10		0.00577	0.00112	10		103.1	11.1	10		0.0364	0.0026	10	
2	3.09	0.26	10		17.1	3.8	10		0.00581	0.00119	10		107.2	13.9	10		0.0366	0.0057	10	
3	3.09	0.22	10		15.4	4.9	10		0.00544	0.00144	10		99.1	13.4	10		0.0353	0.0035	10	
4	3.17	0.31	10		16.8	4.3	10		0.00603	0.00146	10		105.6	15.2	10		0.0380	0.0048	10	

GROUP	SPLEEN				SPLEEN				THYMUS				THYMUS				THYROIDES			
	ABSOLUTE				RELATIVE				ABSOLUTE				RELATIVE				ABSOLUTE			
	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p
1	632	88	10		0.224	0.037	10		314	53	10		0.111	0.020	10		19.0	3.7	10	
2	705	100	10		0.240	0.033	10		321	72	10		0.109	0.024	10		19.1	5.5	10	
3	695	59	10		0.249	0.024	10		315	37	10		0.113	0.016	10		21.2	5.6	10	
4	685	118	10		0.246	0.037	10		301	71	10		0.108	0.023	10		19.4	4.2	10	

GROUP	THYROIDES				UTERUS				UTERUS			
	RELATIVE				ABSOLUTE				RELATIVE			
	Mean	S.D	N	p	Mean	S.D	N	p	Mean	S.D	N	p
1	0.00673	0.00130	10		644	134	10		0.227	0.038	10	
2	0.00646	0.00166	10		710	138	10		0.244	0.060	10	
3	0.00753	0.00175	10		728	167	10		0.260	0.063	10	
4	0.00697	0.00146	10		697	273	10		0.254	0.113	10	

Histopathology:

Adequate Battery: yes (x), no () — explain

Peer review: yes (x), no ()

At injection site, hemorrhage was reported in all treated animals (including controls). Incidences and severity of cystic/cleft-like spaces and granulomatous inflammation were dose-related. However, this effect is not clinically relevant to the new product (sublingual formulation is proposed for marketing).

See scanned sponsor Tables below:

Males

GROUP	Inflammation, granulomatous				Total	p
	No findings	Minimal	Slight	Moderate		
1	9	1	0	0	10	
2	5	3	2	0	10	
3	3	4	2	1	10	*
4	2	2	4	2	10	**
Total	19	10	8	3	40	

Females

GROUP	Inflammation, granulomatous				Total	p
	No findings	Minimal	Slight	Moderate		
1	3	1	5	1	10	
2	2	3	3	2	10	
3	2	3	4	1	10	
4	1	1	3	5	10	
Total	8	8	15	9	40	

* means $p < 0.05$ versus control group

** means $p < 0.01$ versus control group

Males

GROUP	Mononuclear cells, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	5	5	0	0	10	
2	5	5	0	0	10	
3	7	3	0	0	10	
4	9	1	0	0	10	
Total	26	14	0	0	40	

Females

GROUP	Mononuclear cells, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	7	3	0	0	10	
2	8	2	0	0	10	
3	8	2	0	0	10	
4	10	0	0	0	10	
Total	33	7	0	0	40	

Males

GROUP	Haemorrhage, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	6	4	0	0	10	
2	6	2	2	0	10	
3	5	3	2	0	10	
4	7	3	0	0	10	
Total	24	12	4	0	40	

Females

GROUP	Haemorrhage, focal				Total	p
	No findings	Minimal	Slight	Moderate		
1	7	1	2	0	10	
2	8	0	2	0	10	
3	6	3	1	0	10	
4	7	3	0	0	10	
Total	28	7	5	0	40	

Males

GROUP	Cystic/cleftlike space				Total	p
	No findings	Minimal	Slight	Moderate		
1	7	2	1	0	10	
2	2	7	1	0	10	
3	3	6	1	0	10	
4	2	4	4	0	10	
Total	14	19	7	0	40	

Females

GROUP	Cystic/cleftlike space				Total	p
	No findings	Minimal	Slight	Moderate		
1	2	7	1	0	10	
2	3	6	1	0	10	
3	2	7	1	0	10	
4	1	7	2	0	10	
Total	8	27	5	0	40	

Conclusion: The toxicology profile of desmopressin with 3 impurities ([Glu⁴]desmopressin, Gly⁹-OH]desmopressin, and [βAsp⁵]desmopressin, at concentration levels of (b) (4) respectively) was consistent with desmopressin suggesting no significant changes by these 3 impurities.

2.6.6.4 Genetic toxicology

Study title: Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 100, TA 1537 and TA 98 and *Escherichia coli* WP2uvrA

Key findings: The test article up to 5000 µg/plate didn't induce bacterial mutations in either the presence or absence of S9-mix with any of the tested bacterial strains

Study no.: 77539; Ferring Ref.#: FE992026DSMUT0501; (b) (4) Report #: 25446

Volume # and page #: Vol.1; p, 33

Conducting laboratory and location: (b) (4)

Date of study initiation: 25 February 2005

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: FE 992026 (Batch No. CRS_MIX_Desmopressin_2005:1), purity of 100% (test article was spiked with 3 impurities: ([Glu⁴]desmopressin, Gly⁹-OH]desmopressin, and [βAsp⁵]desmopressin, at concentration levels of (b) (4) %, respectively).

Methods:

Strains/species/cell line:

Salmonella typhimurium (TA98, TA100, TA1535, TA1537) and *Escherichia coli* WP 2uvrA (pKM101). S9 was prepared from Aroclor 1254 treated SD rats.

Doses used in definitive study:

17, 50, 167, 500, 1667 and 5000 µg/plate (5000 µg/plate = ~220 µg/mL).

Basis of dose selection:

Precipitation of test material at 5000 µg/plate

Negative controls:

Sterile, ultra-pure water was used as the vehicle control

Positive controls:

2-aminoanthracene (2-AAN) sodium azide (NaN₃), 9-aminoacridine (9-AA), 2-nitrofluorene (2-NF) and N-ethyl-N-nitro-N-nitrosoguanidine (ENNG). Only NaN₃ was dissolved in DMSO, other positive controls were dissolved in sterile, ultra-pure water.

Incubation and sampling times:

A mixture of test article (100µL of different doses) negative or positive controls, with S9 or buffer solution (containing trace histamine, biotin and tryptophan) and 100µL of bacterial

were rapidly mixed and poured onto agar plates and incubated at 37°C for 2 or 3 days. Following incubation, these colonies were counted by a Cardinal Colony Counter.

Results

Study validity:

All positive and negative controls gave appropriate responses.

See list of Criteria for a valid study from Sponsor:

A test was considered acceptable if, for each strain:

- i) the bacteria demonstrated their typical responses to crystal violet, ampicillin and u.v. light.
- ii) at least 2 of the vehicle control plates were within the following ranges: TA 1535, 4-30; TA 1537, 1-20; TA 98, 10-60; TA 100, 60-200 and *E. coli* WP2uvrA 1-60.
- iii) on at least 2 of the positive control plates there were at least x 2 the mean vehicle control mutant numbers per plate, or in the case of TA 100, at least x 1.5 the mean vehicle control mutant numbers per plate.
- iv) no toxicity or contamination was observed in at least 4 dose levels.
- v) in cases where a mutagenic response was observed, no more than one dose level was discarded before the dose that gave the highest significant mean colony number.

Where these criteria were met, a significant mutagenic response was recorded if there was:

- i) for *S. typhimurium* strains TA 1535, TA 1537, and TA 98 and for *E. coli* WP2uvrA, at least a doubling of the mean concurrent vehicle control values at some concentration of the test item. For *S. typhimurium* strain TA 100, a 1.5-fold increase over the control value was considered significant. If the mean colony count on the vehicle control plates was less than 10, then a value of 10 was assumed for assessment purposes. In such cases, a minimum count of 20 was required before a significant mutagenic response was registered.
- ii) a dose related response, although at high dose levels this relationship could be inverted because of, for example, (1) toxicity to the bacteria generally, (2) specific toxicity to the mutants and (3) inhibition of foreign compound metabolising enzymes where mutagens require metabolic activation by the liver.
- iii) a reproducible effect in independent tests.

Study outcome:

Under this test condition, FE 992026, didn't induce bacterial mutations.

See scanned Tables below:

7 Tables

Table 1 First Mutation Assay

Mean Number of Revertant Colonies Per Plate in the Presence of S9 Mix (FLI 103).

Test Item	Dose Level µg per plate	TA 1535	TA 1537	TA 98	TA 100	WP2uvrA
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
STERILE WATER	100	14 ± 4	8 ± 2	22 ± 4	107 ± 21	4 ± 4
FE 992026	17	15 ± 8	6 ± 1	19 ± 3	110 ± 17	4 ± 3
	50	12 ± 4	7 ± 2	22 ± 3	95 ± 12	4 ± 3
	167	13 ± 2	7 ± 1	23 ± 8	96 ± 7	3 ± 1
	500	10 ± 4	7 ± 1	25 ± 6	109 ± 22	6 ± 4
	1667	15 ± 5	6 ± 3	23 ± 7	110 ± 6	2 ± 1
	5000	17 ± 4	9 ± 3	21 ± 8	92 ± 17	3 ± 2
Positive controls	Compound	2AAN	2AAN	2AAN	2AAN	2AAN
	Dose Level µg per plate	2	2	0.5	0.5	20
	Mean ± SD	581 ± 69	279 ± 39	515 ± 23	861 ± 78	1000 ± 438

SD Standard Deviation
2AAN 2-Aminoanthracene

Table 1 (continued) First Mutation Assay

Mean Number of Revertant Colonies Per Plate in the Absence of S9 Mix.

Test Item	Dose Level µg per plate	TA 1535	TA 1537	TA 98	TA 100	WP2uvrA
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
STERILE WATER	100 µL	28 ± 1	4 ± 1	22 ± 12	168 ± 94	8 ± 2
FE 992026	17	31 ± 5	10 ± 5	24 ± 14	152 ± 131	10 ± 4
	50	37 ± 10	8 ± 1	16 ± 5	139 ± 89	9 ± 9
	167	40 ± 8	6 ± 1	19 ± 9	128 ± 95	6 ± 4
	500	41 ± 13	2 ± 2	28 ± 5	185 ± 164	1 ± 1
	1667	44 ± 5	5 ± 3	23 ± 4	161 ± 139	7 ± 1
	5000	35 ± 8	5 ± 2	26 ± 4	148 ± 104	4 ± 4
Positive controls	Compound	NaN ₃	9AA	2NF	NaN ₃	ENNG
	Dose Level µg per plate	1	80	1	1	2
	Mean ± SD	415 ± 46	2509 ± 1595	1107 ± 148	1231 ± 58	198 ± 86

SD Standard Deviation
NaN₃ Sodium azide
9AA 9-Aminoacridine
2NF 2-Nitrofluorene
ENNG N-Ethyl-N-nitro-N-nitrosoguanidine

Table 3 First Mutation Assay Repeat with TA 100
 Mean Number of Revertant Colonies Per Plate in the Absence of S9 Mix.

Test Item	Dose Level µg per plate	TA 100
		Mean ± SD
STERILE WATER	100 µL	109 ± 18
FE 992026	17	106 ± 5
	50	101 ± 13
	167	106 ± 11
	500	104 ± 9
	1667	101 ± 10
	5000	102 ± 15
Positive controls	Compound	NaN ₃
	Dose Level µg per plate	1
	Mean ± SD	993 ± 54

SD Standard Deviation
 NaN₃ Sodium azide

Table 2 Second Mutation Assay

Mean Number of Revertant Colonies Per Plate in the Presence of S9 Mix (FLI 103).

Test Item	Dose Level µg per plate	TA 1535	TA 1537	TA 98	TA 100	WP2uvrA
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
STERILE WATER	100 µL	15 ± 3	12 ± 2	51 ± 8	133 ± 5	4 ± 3
FE 992026	17	21 ± 5	13 ± 1	46 ± 7	140 ± 13	4 ± 1
	50	16 ± 4	12 ± 4	48 ± 9	136 ± 3	7 ± 5
	167	18 ± 5	14 ± 2	48 ± 8	125 ± 16	9 ± 3
	500	15 ± 1	12 ± 3	53 ± 11	112 ± 10	5 ± 3
	1667	16 ± 5 (P)	20 ± 6	53 ± 12 (P)	119 ± 13	3 ± 2
	5000	13 ± 4 (TL+P)	10 ± 3 (VTL+P)	39 ± 5 (TL+P)	98 ± 10 (TL+P)	4 ± 2 (VTL+P)
Positive controls	Compound	2AAN	2AAN	2AAN	2AAN	2AAN
	Dose Level µg per plate	2	2	0.5	0.5	20
	Mean ± SD	411 ± 30	429 ± 11	838 ± 62	753 ± 26	979 ± 98

SD Standard Deviation
 2AAN 2-Aminoanthracene
 TL Thin Lawn
 P Precipitation
 VTL Very Thin Lawn

**Table 2
(continued) Second Mutation Assay**

Mean Number of Revertant Colonies Per Plate in the Absence of S9 Mix.

Test Item	Dose Level µg per plate	TA 1535	TA 1537	TA 98	TA 100	WP2 _{uvrA}
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
STERILE WATER	100 µL	19 ± 1	9 ± 3	27 ± 9	143 ± 15	3 ± 4
FE 992026	17	23 ± 5	7 ± 6	30 ± 5	137 ± 16	6 ± 4
	50	22 ± 6	11 ± 2	35 ± 2	148 ± 8	6 ± 1
	167	21 ± 4	11 ± 7	31 ± 5	141 ± 9	6 ± 5
	500	19 ± 2	14 ± 5	36 ± 12	154 ± 15	9 ± 1
	1667	20 ± 6	13 ± 7	32 ± 9	159 ± 8	5 ± 4
	5000	21 ± 4 (STL)	3 ± 2 (VTL+P)	43 ± 12 (STL)	151 ± 8 (STL+P)	4 ± 2 (STL)
Positive controls	Compound	NaN ₃	9AA	2NF	NaN ₃	ENNG
	Dose Level µg per plate	1	80	1	1	2
	Mean ± SD	855 ± 46	4323 ± 412	979 ± 120	1824 ± 66	568 ± 53

SD Standard Deviation
 NaN₃ Sodium azide
 9AA 9-Aminoacridine
 2NF 2-Nitrofluorene
 ENNG N-Ethyl-N-nitro-N-nitrosoguanidine
 STL Slightly Thin Lawn
 P Precipitation
 VTL Very Thin Lawn

Conclusion: Results of this study qualified desmopressin containing with 3 impurities ([Glu⁴]desmopressin, Gly⁹-OH]desmopressin, and [βAsp⁵]desmopressin, at concentration levels of (b) (4) %, respectively).

Study Title: FE992026 Mouse Lymphoma Cell Mutation Assay

Study no.: (b) (4) study #: 776744; (b) (4) report #: 25517; Ferring Ref. #: FE992026DSMUT0502

Volume # and page #: Vol. 1, p 1-60

Conducting laboratory and location:

(b) (4)

Date of study initiation: 25 February 2005

GLP compliance: yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: U25017/125/16; 102% of label claim (the test article was spiked with 3 impurities: ([Glu⁴]desmopressin, Gly⁹-OH]desmopressin, and [βAsp⁵]desmopressin, at concentration levels of (b) (4) %, respectively).

Key study findings:

In the mouse lymphoma L5178Y/TK^{+/-} cell line FE992026 was not genotoxic in the absent or presence S9-mix.

Methods:Strains/species/cell line:

Mouse lymphoma L5178Y/TK^{+/-} cell line was used to detect gene mutation and chromosomal damage (clastogenicity and /or aneuploidy).

Doses used in definitive study:

Mutagenicity assays were performed (+/- S9 mix) with up to 5000 µg/mL.

The concentrations of FE 992026 tested were as follows (µg/mL):

See Scanned below from sponsor:

Assay 1 (in the absence of S9 mix ¹):	156, 313, 625, 1250, 2500 and 5000
Assay 2 (in the presence of S9 mix ¹):	156, 313, 625, 1250, 2500 and 5000
Assay 3 (in the absence of S9 mix ²):	125, 250, 500, 1000, 2000, 3000, 4000 and 5000
Assay 4 (in the presence of S9 mix ¹):	250, 500, 1000, 2000, 3000 and 4000

¹ Experiment using a 4 h exposure period

² Experiment using a 24 h exposure period

Each dose range selection was based on all available results at the time the selection was made.

Basis of dose selection:

The highest practical concentration limited by the solubility or pH of the test item

Negative controls:

The control cultures were treated with the basic culture medium (R0P).

Positive controls:

Ethyl methanesulphonate (EMS), methyl methanesulphonate (MMS) and 3-methylcholanthrene (3-MC)

Incubation and sampling times:

The assay was carried out with cultures of 3×10^5 (for 4 hrs) or 3×10^5 (for 24 hrs) cells, a dose range of test compound (156, 313, 626, 1250, 2500 and 5000 µg/mL for 3 hrs or 125, 250, 500, 1000, 2000, 3000, 4000 and 5000 µg/mL 24 hrs) as well as positive/negative controls and +/- S9. After incubation (at 37°C with different exposure time), followed with an expression period (2 days with daily adjusted cell population), the mutagenic potential of test compound (for TK^{-/-}) was evaluated.

Study validity:

All positive and negative controls were gave appropriate responses.

Results:

Maximum concentrations of test compound were limited to 5000 µg/mL (+/-S9, respectively) for 3hrs or 24hrs of treatment.

See scanned Table below:

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Absence of S9 Mix (4 h Exposure)
Summary of Means of Data (Assay 1)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁻⁶)	IMF (Induced Mutant Fraction x10 ⁻⁶)	Ratio of Small to Large Colonies	Statistical Comparison
R ₀ P	(4 ml added)	100	54	-	0.77	-
EMS	250	69	454	400	0.33	*
MMS	10	45	657	603	2.00	*
FE 992026	156	NPS	NPS	-	-	-
	313	NPS	NPS	-	-	-
	625	101	52	-	1.83	-
	1250	88	64	10	0.82	-
	2500	100	52	-	1.03	-
	5000	27	63	8	0.86	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P <0.05)
 Test for linear trend of mutant fraction with concentration of FE 992026 = not significant (P = 0.58)
 NPS = Not Plated – Surplus

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Presence of S9 Mix (4 h Exposure)
Summary of Means of Data (Assay 2)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁻⁶)	IMF (Induced Mutant Fraction x10 ⁻⁶)	Ratio of Small to Large Colonies	Statistical Comparison
R ₀ P	(4 ml added)	100	48	-	0.64	-
3-MC	2.5	23	1206	1158	1.71	*
FE 992026	156	NPS	NPS	-	-	-
	313	121	59	11	0.59	-
	625	139	65	17	0.29	-
	1250	121	36	-	0.50	-
	pptn 2500	62	43	-	1.08	-
	pptn 5000	NPT/P	NPT/P	-	-	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P <0.05)
 Test for linear trend of mutant fraction with concentration of FE 992026 = not reported – slope negative
 NPS = Not Plated - Surplus
 NPT/P = Not Plated – Toxic/Dense precipitation
 pptn = Precipitation

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Absence of S9 Mix (24 h Exposure)
Summary of Means of Data (Assay 3)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁻⁶)	IMF (Induced Mutant Fraction x10 ⁻⁶)	Ratio of Small to Large Colonies	Statistical Comparison
R ₀ P	(4 ml added)	100	55	-	0.66	-
EMS	150	29	1359	1304	0.27	*
MMS	5	36	1026	971	1.71	*
FE 992026	125	79	58	1	0.61	-
	250	90	43	-	0.71	-
	500	84	52	-	1.46	-
	1000	72	72	17	0.56	-
	pptn 2000	16	41	-	0.49	-
	pptn 3000	NPT/P	NPT/P	-	-	-
	pptn 4000	NPT/P	NPT/P	-	-	-
pptn 5000	NPT/P	NPT/P	-	-	-	

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P <0.05)
 Test for linear trend of mutant fraction with concentration of FE 992026 = not reported – slope negative
 NPT/P = Not Plated – Toxic/Dense precipitation
 pptn = Precipitation

FE 992026
Mouse Lymphoma Mutation Assay
Mutation Test in the Presence of S9 Mix (4 h Exposure)
Summary of Means of Data (Assay 4)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10 ⁻⁶)	IMF (Induced Mutant Fraction x10 ⁻⁶)	Ratio of Small to Large Colonies	Statistical Comparison
R ₀ P	(4 ml added)	100	65	-	0.77	-
3-MC	2.5	45	977	913	0.96	*
FE 992026	250	135	47	-	0.82	-
	500	110	54	-	1.03	-
	1000	85	67	2	0.73	-
	pptn 2000	46	43	-	0.35	-
	pptn 3000	17	58	-	0.92	-
	pptn 4000	NPT/P	NPT/P	-	-	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
 * = Significant difference in log mutant fraction compared with vehicle control (P <0.05)
 Test for linear trend of mutant fraction with concentration of FE 992026 = not reported – slope negative
 NPT/P = Not Plated – Toxic/Dense precipitation
 pptn = Precipitation

Summary: Results of this study showed that FE992026, which contains (b) (4) levels of 3 impurities ([Glu⁴]desmopressin, Gly⁹-OH]desmopressin, and [βAsp]desmopressin, at concentration levels of (b) (4) %, respectively) than the reference product, was devoid of mutagenic or clastogenic activity.

2.6.6.7 Local tolerance

Study title: ORAL IRRITATION IN THE SYRIAN HAMSTER

Background: The study was conducted for 28 days in Syrian Hamsters (10/sex, 1 application/day) to determine the local reaction of desmopressin SLM.

Key findings:

Oral lyophilisates containing 360 µg desmopressin or placebo (both packed in oil) showed similar effects when administered to the cheek pouches of Syrian hamsters daily for 28 days. Results showed no cheek pouch irritation after 28 days with the test article.

Study no.: 52338 (b) (4); Ferring Ref. No: FE992026DSTOX0301

Volume #, and page #: Electronic submission

Conducting laboratory and location: (b) (4)

Date of study initiation: 08 January 2004

Batch No and impurity: 23006FBG; sum of impurity 0.4%

GLP compliance: yes

QA report: yes (X) no ()

Methods:

The test article and placebo were treated in the cheek pouch of each animal in different groups: The animals were treated as follows:

See scanned Table below from sponsor:

Animal No	Sex	Group No	Treatment	Colour code
1 - 3	M	1	Untreated	White
4 - 6	F			
7 - 9	M	2	Placebo	Blue
10 - 12	F			
13 - 16	M	3	Test article	Green
17 - 20	F			

The pouches were examined macroscopically and microscopically were graded as:

See scanned below from sponsor:

Reaction	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4

The microscopic findings were graded according to the following grading system:

Reaction	Numerical grading
1. Epithelium	
Normal, intact	0
Cell degeneration or flattening	1
Metaplasia	2
Focal erosion	3
Generalised erosion	4
2. Leucocyte infiltration (per high power field)	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked	4
3. Vascular congestion	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked, with disruption of vessels	4
4. Oedema	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked	4

The test article was classified according to the five response categories given in the table below:

Irritation Index	
0	None
1 to 4	Minimal
5 to 8	Mild
9 to 11	Moderate
12 to 16	Severe

Results:

In general, there were no microscopic findings in 3 group (group average was for all animals 0).

Clinical Signs:

See scanned below from sponsor:

Clinical signs and body weight gain

Animal No 3 had a wound on the nose from Day 15 to Day 29. Animal No 11 had a wound on the neck from Day 4 to Day 15, probably due to the collar; from Day 15 until termination on Day 29 the skin was red, but intact. Animal No 12 had a wound on the neck from Day 2 to Day 11, probably due to the collar. Animal No 19 had oedema in both cheek pouches from Day -5 to -3. No other abnormalities were observed during the study period. All animals had normal and similar body weight gain during the study period.

FE992026

ORAL IRRITATION TEST IN
THE SYRIAN HAMSTER

Individual body weight (g)

All groups (untreated, placebo and test article group)

Animal No	Sex	Day -11	Day -6	Day -5	Day -4	Day -3	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Weight gain (Day -11 to 29)
1	M												(b) (4)
2	M												
3	M												
4	F												
5	F												
6	F												
7	M												
8	M												
9	M												
10	F												
11	F												
12	F												
13	M												
14	M												
15	M												
16	M												
17	F												
18	F												
19	F												
20	F												

Microscopic Findings:

The average of macroscopic scores were 0.1 for males and 0.0 for females for control groups (untreated and placebo groups). For the test article treated groups, the average macroscopic scores were 0.1 for males and 0.1 for females. For the recovery animals, on Day 36, only the female hamster showed very slight erythema.

See scanned Tables below from sponsor:

ORAL IRRITATION TEST IN
THE SYRIAN HAMSTER

Macroscopic findings. Scores for erythema – Untreated group (colour code: white)

Animal No	Sex	Treatment	Cheek Pouch	Mean Score	Left - right	Group Average
1	Male	Untreated	Left	0.1	0.1	0.1
			Right	0.0		
2			Left	0.2	0.2	
			Right	0.0		
3			Left	0.0	0.0	
			Right	0.0		
4	Female	Untreated	Left	0.0	0.0	0.0
			Right	0.0		
5			Left	0.0	0.0	
			Right	0.0		
6			Left	0.2	-0.1	
			Right	0.3		

Animal No	Sex	Treatment	Cheek Pouch	Mean Score	Left - right	Group Average
7	Male	Placebo	Left	0.0	0.0	0.1
			Right	0.0		
8			Left	0.1	0.1	
			Right	0.0		
9			Left	0.2	0.1	
			Right	0.1		
10	Female	Placebo	Left	0.1	-0.1	0.0
			Right	0.2		
11			Left	0.0	0.0	
			Right	0.0		
12			Left	0.3	0.1	
			Right	0.2		

Macroscopic findings. Scores for erythema – Test article group (colour code: green)

Animal No	Sex	Treatment	Check Pouch	Mean Score	Left - right	Group Average		
13	Male	Test article	Left	0.1	0.1	0.1		
			Right	0.0				
Left			0.1	0.1				
Right			0.0					
15			Left	0.2	0.1			
			Right	0.1				
16			Left	0.1	-0.1			
			Right	0.2				
17			Female	Test article	Left	0.1	0.1	0.1
					Right	0.0		
Left	0.2	0.1						
Right	0.1							
19	Left	0.4			0.2			
	Right	0.2						
20	Left	0.1			0.1			
	Right	0.0						

Recovery score Day 36		
Animal No	Check pouch	Day 36 Score before termination
13	Left	0
	Right	0
20	Left	1
	Right	0

FE992026

ORAL IRRITATION TEST IN
THE SYRIAN HAMSTER

Grading of Microscopic Findings for Oral Irritation Studies

Group No. 1 – Untreated

Reaction	Animal No		1		2		3		4		5		6	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Epithelium	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Leucocyte infiltration	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vascular congestion	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Individual Primary Irritation Index	0		0		0		0		0		0		0	

Group No. 2 - Placebo

Reaction	Animal No		7		8		9		10		11		12	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Epithelium	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Leucocyte infiltration	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vascular congestion	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Individual Primary Irritation Index	0		0		0		0		0		0		0	

Group No. 3 – Test article

Reaction	Animal No		14		15		16		17		18		19	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Epithelium	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Leucocyte infiltration	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vascular congestion	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Individual Primary Irritation Index	0		0		0		0		0		0		0	

Recovery animals

Reaction	Animal No		13		20	
	Left	Right	Left	Right	Left	Right
Epithelium	0	1	0	0	0	0
Leucocyte infiltration	0	2	0	0	0	0
Vascular congestion	0	0	0	0	0	0
Oedema	0	0	0	0	0	0
Individual Primary Irritation Index			-3		0	

ORAL IRRITATION TEST IN THE SYRIAN HAMSTER

Macroscopic findings. Scores for erythema – Test article group (colour code: green)

Animal No	Sex	Treatment	Check Pouch	Mean Score	Left - right	Group Average
13	Male	Test article	Left	0.1	0.1	0.1
			Right	0.0		
14			Left	0.1	0.1	
			Right	0.0		
15			Left	0.2	0.1	
			Right	0.1		
16			Left	0.1	-0.1	
			Right	0.2		
17	Female	Test article	Left	0.1	0.1	0.1
			Right	0.0		
18			Left	0.2	0.1	
			Right	0.1		
19			Left	0.4	0.2	
			Right	0.2		
20			Left	0.1	0.1	
			Right	0.0		

Conclusion:

There were no significant differences in the average macroscopic scores for treated animals compared to control animals (average of 1 for all treated animals and 0.1 for males and 0.0 for females in control animals). Results showed no local reactions with desmopressin after 28 days suggesting the test article is safe to use sublingually.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Desmopressin FE992026, FE999912;
2.6.7.1 Toxicology: Overview
DN-OVERVIEW-103; Ver. 1.0

Date: 24 Mar 2009
Supersedes: None
Page 1 of 1

2.6.7.1 Toxicology: Overview

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (µg/kg/day)*	GLP Compliance	Testing Facility	Study Number	Location in CTD
Single-Dose Toxicity	No new data							
Repeat-Dose Toxicity	No new data							
13-week toxicity study in rats	Sprague Dawley, NINC:SD rats	Subcutaneous injection	13 weeks	0, 0.1, 1, 10	Yes	(b) (4)	[58881]	4.2.3.2
Genotoxicity	No new data							
Ames test	<i>S. typhimurium</i> TA 1535, 100, 1537, 98 & <i>E. coli</i> WZ2007A	Direct plating & Pre-incubation	2 or 3 days	17-5000 µg/plate	Yes	(b) (4)	[775739]	4.2.3.3.1
Mouse lymphoma assay	L5178Y clone 3.7.2.C	Assay 1 – S9 Assay 2 + S9 Assay 3 – S9 Assay 4 + S9	4 hours 4 hours 24 hours 4 hours	156-5000 150-5000 125-5000 250-4000 µg/mL	Yes	(b) (4)	[775744]	4.2.3.3.1
Carcinogenicity	No new data							
Reproductive and Developmental Toxicity	No new data							
Local Tolerance	No new data							
Oral irritation in hamsters	Syrian hamster	Orally in the cheek pouch	28 days	0, 0, 360 µg/day	Yes	(b) (4)	[52338]	4.2.3.6
Other Toxicity Studies	No new data							

* Unless otherwise specified, for Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined

Desmopressin FE992026, FE999912;
2.6.7.7 Repeat-Dose Toxicity
DN-SUMMARY-276;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
Page 1 of 2

2.6.7.7 Repeat-Dose Toxicity

Report Title: Desmopressin: 13-week subcutaneous toxicity study in rats				Test Article: Desmopressin				
Species/Strain:	Rat/Sprague Dawley Ntac:SD	Duration of Dosing:	13 weeks	Study No.:	[58881]			
Initial Age:	5 weeks	Duration of Postdose:	None	Location in CTD:	4.2.3.2			
Date of First Dose:	W/b 28 Feb 2005	Method of Administration:	Subcutaneous injection	GLP Compliance:	Yes			
Special Features:	None	Vehicle/Formulation:	0.9 % NaCl	No Observed Adverse Effect Level:	10 µg/kg/day			
Daily Dose (µg/kg)	0 (Control)		0.1		1		10	
Number of Animals	10M	10F	10M	10F	10M	10F	10M	10F
Toxicokinetics: AUC	ND	ND	ND	ND	ND	ND	ND	ND
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight Gain (g, %^a)	311.9	120.8	98	109	96	97	88	99
Food Consumption (g, %^a)	2364.0	1549.6	100	106	101	101	97	101
Water Consumption (%^a)	ND	ND	ND	ND	ND	ND	ND	ND
Clinical Observations	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Chemistry	-	-	-	-	-	-	-	-
Urinalysis								
Volume (mL)	15.0	14.6	17.9	12.0	19.7*	15.0	8.2**	4.5**
Sodium (mmol/L)	28.1	31.1	42.6*	42.6*	34.6	41.3	82.4**	92.4**
Potassium (mmol/L)	140.1	97.7	126.7	119.3	106.7	92.2	243.7**	247.2**
Chloride (mmol/L)	39.6	34.6	39.0	54.8	26.4	35.3	104.9**	126.9**
Specific gravity (no unit)	1.014	1.016	1.014	1.019	1.012	1.015	1.025**	1.030**
pH (no unit)	7.9	7.0	7.6	6.9	7.8	7.0	7.1**	6.4**

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Desmopressin FE992026, FE999912;
2.6.7.7 Repeat-Dose Toxicity
DN-SUMMARY-276;Ver.1.0

Date: 24 Mar 2009
Supersedes: None
Page 2 of 2

Daily Dose (µg/kg)	0 (Control)		0.1		1		10	
Organ Weights^a								
Absolute Kidney Weight (mg, %)	2916	1679	108	110*	111	112**	108	119**
Relative Kidney Weight (%^a)	0.575	0.595	107	106	112**	113**	115**	120**
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology								
Injection site changes	+	+	+	+	+	+	++	++
Postdose Evaluation:	ND	ND	ND	ND	ND	ND	ND	ND

- No noteworthy findings. + Mild ++ Moderate +++ Marked

* - p<0.05 ** - p<0.01

^a At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

ND Not done

Desmopressin FE992026, FE999912;
2.6.7.8 Genotoxicity: *In Vitro*
DN-SUMMARY-277, Ver.1.0

Date: 24 Mar 2009
Supersedes: None
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2.6.7.8 Genotoxicity: *In Vitro*
2.6.7.8A Study No. 775739

Report Title: FE 992026: Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537 and TA 98 and <i>Escherichia coli</i> WP2 <i>uvrA</i>				Test Article: Desmopressin	
Test for Induction of:	Reverse mutation in bacterial cells	No. of Independent Assays:	2	Study No.:	[775739]
Strains:	<i>S. typhimurium</i> : TA 1535, TA 100, TA 1537, TA 98; <i>E. coli</i> : WP2 <i>uvrA</i>	No. of Replicate Cultures:	3	Location in CTD:	4.2.3.3.1
Metabolising System:	Aroclor 1254-induced rat liver S-9 mix	No. of Cells Analysed/Culture:	Not applicable	GLP Compliance:	Yes
Vehicles: For Test Article:	Sterile, ultrapure water	For Positive Controls:	DMSO	Date of Treatment:	15 Mar – 11Apr 2005
Cytotoxic Effects:	Thinning of back ground lawn with all strains at 5000 µg/plate both in the presence and absence of S9 mix	Genotoxic effects:	None		

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Desmopressin FE992026, FE999912;
2.6.7.16 Local Tolerance
DN-SUMMARY-278, Ver.1.0

Date: 24 Mar 2009
Supersedes: None
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2.6.7.16 Local Tolerance

Test Article: Desmopressin

Species/Strain	Method of Administration	Doses (µg/animal/day)	No. and Gender per Group	Noteworthy Findings	Study Number
Syrian hamster	Insertion of an orally disintegrating tablet into the left cheek pouch	0 (untreated) 0 (placebo) 360	3 M + 3 F 3 M + 3 F 4 M + 4 F	There were no noteworthy findings in any group	Scantox [52338] in 4.2.3.6

2.6.7.1 Toxicology: Overview

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (µg/kg/day) ^a	GLP Compliance	Testing Facility	Study Number	Location in CTD
Single-Dose Toxicity	No new data							
Repeat-Dose Toxicity	(b) (4)							
13-week toxicity study in rats	Sprague Dawley, Niac-SD rats	Subcutaneous injection	13 weeks	0, 0.1, 1, 10	Yes		[58881]	4.2.3.2
Genotoxicity								
Ames test	<i>S. typhimurium</i> TA 1535, 100, 1537, 98 & <i>E. coli</i> WP2 <i>uvrA</i>	Direct plating & Pre-incubation	2 or 3 days	17-5000 µg/plate	Yes		[775739]	4.2.3.3.1
Mouse lymphoma assay	L5178Y clone 3.7.2.C	Assay 1 – S9 Assay 2 + S9 Assay 3 – S9 Assay 4 + S9	4 hours 4 hours 24 hours 4 hours	156-5000 156-5000 125-5000 250-4000 µg/mL	Yes		[775744]	4.2.3.3.1
Carcinogenicity	No new data							
Reproductive and Developmental Toxicity	No new data							
Local Tolerance								
Oral Irritation in hamsters	Syrian hamster	Orally in the cheek pouch	28 days	0, 0, 360 µg/day	Yes		[52338]	4.2.3.6
Other Toxicity Studies	No new data							

^a Unless otherwise specified. For Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined.

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OVERALL CONCLUSIONS AND RECOMMENDATIONS

The proposed NDA 22517 by Ferring Pharmaceuticals Inc for NOCDURNA™, desmopressin sublingual melt (desmopressin SLM), was submitted as a 505(b)(2). NOCDURNA is designed for the treatment of nocturia in adults (daily dose of 25µg for women and 100µg for men). The new product has an active ingredient of desmopressin and several excipients including gelatin, mannitol and citric acid. These excipients are widely used in many approved products and are considered inactive “GRAS” ingredients. The active ingredient of desmopressin has a structural analog of the natural human antidiuretic hormone (8-arginine vasopressin); it also belongs to the pharmacologic class of posterior pituitary hormones. In general, desmopressin increases urine concentration, decreases urine production (through binding to V2 receptors, selective agonist for the vasopressin V2-receptor) in renal collecting ducts. There is extensive clinical experience with desmopressin since different formulations of this drug (oral-Minirin; IV injection, intranasal spray) have been on the market for a long time in many countries.

Most non-clinical data for desmopressin SLM referred to other NDAs including: NDA19955, DDAVP® Desmopressin acetate Tablets held by Sanofi Aventis US; NDA 21-333 Desmopressin Acetate Nasal Spray; NDA 21-795 Desmopressin Acetate Tablets; and DMF 8396. To bring to the previous findings of safety and efficacy for desmopressin, non-clinical studies were submitted with this NDA including: a study of the oral absorption in female domestic pigs (orally disintegrating tablets across the mucous membrane); a 28-day local tolerability study (mucous membrane of the cheek pouch) in Syrian hamsters to demonstrate safety for the proposed route of administration; and three studies to qualify the new impurity profile (a 13-week subcutaneous toxicity study in rats; an Ames test; a mouse lymphoma assay).

Pharmacokinetic Summary:

Pre-clinical data for PK studies referred to NDA#19955. New PK information was related to the absorption of the new product in the domestic pig. Results suggested the bioavailability of desmopressin SLM was about 2 fold higher than desmopressin tablets. In addition, C_{max} for 240µg/kg desmopressin SLM was 73.7±54.4pg/ml compared to C_{max} for 2x200µg/kg desmopressin tablet was 21.2±11.1pg/ml. The only human study in which the sponsor used validated analytical method is Study # CS004. In this study, the doses used were 200 mcg, 400 mcg and 800 mcg. Also the formulation used in this study was not-to be marketed formulation (orally disintegrating tablets with minor changes in composition to marketed formulation). However, the PK of this study can be used to calculate for lower doses.

See Table below from sponsor:

Parameter	Unit	Desmopressin Melt (200 µg)		Desmopressin Melt (400 µg)		Desmopressin Melt (800 µg)	
		Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI
AUC	hr*pg/mL	64	[52-78]	150	[122-184]	283	[205-389]
AUC _t	hr*pg/mL	47	[36-60]	119	[86-164]	259	[186-362]
C _{max}	pg/mL	14	[11-18]	30	[23-41]	65	[46-92]
t _{max}	hr	1.5 [†]	0.5-2.0 ^{††}	1.0 [†]	0.75-2.0 ^{††}	1.5 [†]	0.75-2.0 ^{††}
t _{1/2}	hr	2.8	27.9 ^{†††}	3.0	24.7 ^{†††}	2.9	16.3 ^{†††}

[†]: median, ^{††}: range, ^{†††} CV% geo. mean

Toxicology Summary:

The safety profile of desmopressin has been well established. Therefore, the sponsor is relying on the previous findings of safety and efficacy for desmopressin administered orally (NDA19-955). To bridge to this information, the sponsor conducted toxicity studies to characterize the local toxicity of desmopressin when administered sublingually and to qualify the slightly different impurity profile for NOCDURNA compared with the reference product. New studies related to the safety profile of the desmopressin SLM were: a local irritation study in Syrian hamsters; and 3 studies for the impurity qualification (a 13-week study in rats, an Ames test, and a mouse lymphoma assay). The local tolerability study in the cheek pouch of Syrian hamsters (360 µg/day desmopressin or with excipients of the test article for 28 days) resulted in no local reaction or any histopathological changes related to the test article. Findings of this study suggested that desmopressin SLM was devoid of any local irritations.

For impurity qualification for the drug substance, toxicity studies were performed including a subcutaneous 13-week toxicity study in rats and two genotoxicity studies (Ames test and a mouse lymphoma assay). In these studies the impurities contained in the batch of desmopressin were: [Glu⁴]desmopressin, [Gly⁹-OH]desmopressin and [βAsp⁵]desmopressin, at concentrations levels of (b) (4) %, respectively. Findings of the 13-week study in rats were due to the pharmacological effects of desmopressin. These effects were: at HD, decreased urinary volume and pH; increased specific gravity and concentration of sodium, potassium, chloride and protein; and at all doses, increased (ss) absolute kidney weights at MD and HD. The NOAEL was 10µg/kg/day with 1 fold MRHD (systemic exposure at the maximum clinical dose, 100µg/day based on body surface area comparisons). However, in this study, TK data were not presented. Two genotoxicity studies, an Ames test and a mouse lymphoma assay, also were performed for qualification of test article's impurities. Results of these studies showed no potential for any genotoxicity with impurities at (b) (4) concentration than current product specifications. Therefore, desmopressin SLM with 3 impurities of [Glu⁴]desmopressin, [Gly⁹-OH]desmopressin and [βAsp⁵]desmopressin, at concentrations levels of (b) (4) %, respectively were qualified with these *in vivo* (a 13-week rat study) and *in vitro* (Ames test and mouse lymphoma assay) studies.

Although these studies showed no safety concerns with the desmopressin SLM, there are not sufficient preclinical studies to bridge to the prior approved products from nonclinical studies. Given that, still, no further studies are required due to available clinical data. For example, in the repeat dose study in rat, the TK data was not present to bridge to the clinical exposure or to determine the therapeutic dose safety margins based on AUC. However, this study is not necessary since the TK of desmopressin SLM and desmopressin tablets have been studied in clinical trials, which have indicated similar efficacy and bioequivalence. Therefore, no further studies are required. Desmopressin SLM is a new equivalent formulation.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA
NDA-19955	ANRPT-14	SANOFI AVENTIS US LLC	DDAVP TABLETS

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/s/

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03/26/2010

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03/29/2010