Title:

Efficacy and Safety of Low Dose Desmopressin Orally Disintegrating Tablet in Men with Nocturia: Results of a Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study

Authors:

JP. Weiss et al.

Journal:

The Journal of Urology 2013

Efficacy and Safety of Low Dose Desmopressin Orally Disintegrating Tablet in Men with Nocturia: Results of a Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study

Jeffrey P. Weiss,*,†, Sender Herschorn,‡, Cerasela D. Albei§ and Egbert A. van der Meulen§

From the Department of Urology, SUNY Downstate College of Medicine, Brooklyn, New York (JPW), Division of Urology, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Canada (SH), Clinical Research, Ferring International PharmaScience Center U.S., Parsippany, New Jersey (CDA), and Global Biometrics, Ferring International PharmaScience Center, Copenhagen, Denmark (EAvdM)

Purpose: We investigated the efficacy and safety of 50 and 75 μg desmopressin orally disintegrating tablets in men with nocturia (2 or more nocturnal voids).

Materials and Methods: In this 3-month, randomized, double-blind, parallel study 50 and 75 μg desmopressin were compared with placebo. The co-primary efficacy end points were changes from baseline in mean number of nocturnal voids and proportions of patients achieving at least a 33% reduction from baseline in nocturnal voids (33% responders) during a 3-month treatment period.

Results: The full analysis set comprised 385 men (age range 20 to 87 years). The 50 and 75 μg doses significantly reduced the number of nocturnal voids (−0.37, $p < 0.0001$ and −0.41, $p = 0.0003$, respectively) and increased the odds of a 33% or greater response (OR 1.98, $p = 0.0009$ and OR 2.04, $p = 0.0004$, respectively) compared with placebo during 3 months. Desmopressin 50 and 75 μg increased the time to first void from baseline by approximately 40 minutes compared to placebo ($p = 0.006$ and $p = 0.003$, respectively). The response to desmopressin was seen by 1 week of treatment and was sustained. Significant increases in health related quality of life and sleep quality were observed compared to placebo. Desmopressin was well tolerated as only 2 subjects (age 74 and 79 years) on 50 μg had a serum sodium level of less than 130 mmol/L (vs 9 subjects on 75 μg).

Conclusions: Desmopressin (orally disintegrating tablet) is an effective and well tolerated treatment for men with nocturia. Treatment with 50 μg desmopressin, the minimum effective dose, provided sustained improvement of nocturia throughout the study and meaningful benefits to patients with an improved safety profile.

Key Words: nocturia, deamino arginine vasopressin, quality of life, sleep

Abbreviations and Acronyms

ADR = adverse drug reaction
AE = adverse event
BOO = bladder outlet obstruction
BPH = benign prostatic hyperplasia
FAS = full analysis set
N-QoL = nocturia quality of life
ODT = orally disintegrating tablet
QoL = quality of life
WPAI = work productivity and activity impairment

Accepted for publication December 19, 2012.
Study received institutional review board approval.
Supported by Ferring Pharmaceuticals.

* Correspondence: Department of Urology, SUNY Downstate College of Medicine, 445 Lenox Rd., Brooklyn, New York 11203 (telephone: 718-630-3786; FAX: 212-838-3213; e-mail: urojock@aol.com).

† Financial interest and/or other relationship with Ferring, Pfizer, Allergan, Astellas and Lilly.

‡ Financial interest and/or other relationship with Ferring, Astellas, Pfizer, Allergan, Watson, American Medical Systems, Eli Lilly, Cook and Gynecare.

§ Financial interest and/or other relationship with Ferring.

See Editorial on page 838.

Editor's Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1144 and 1145.

NOCTURIA is defined by the International Continence Society as the need to wake to void once or more per night.[1] It is a prevalent condition[2] associated with negative consequences for health, quality of life and productivity,[3–6] considered mainly due to the resultant sleep fragmentation[7] when 2 or more nocturnal voids are frequently experienced.[4,6,8]

The etiology of nocturia is multifactorial.[1] However, nocturnal polyuria, ie the overproduction of urine at night (defined as a nocturnal urine output greater than 33% of 24-hour output[1]) is seen in the majority (79% to 90%) of

0022-5347/13/1903-0965/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2012.12.112
Vol. 190, 965-972, September 2013
Printed in U.S.A.

men screened for inclusion in nocturia trials.[9] This underlying factor may explain why treating nocturia with therapies for BOO or overactive bladder, such as α-antagonists and antimuscarinics, have resulted in little therapeutic benefit.[10,11] Nocturnal polyuria is associated with decreased secretion of the antidiuretic hormone arginine vasopressin.[12,13]

Desmopressin is a synthetic analogue of arginine vasopressin with similar antidiuretic action but without its pressor effects,[13] and is a proven, well tolerated and effective treatment for nocturia and other polyuric conditions, eg central diabetes insipidus and bedwetting.[13] Desmopressin has a level 1, grade A recommendation from the International Consultation on Incontinence and European Association of Urology for the treatment of nocturia associated with polyuria,[14–16] and is currently approved for this indication in more than 80 countries outside the United States. Hyponatremia remains the only clinically relevant AE reported with desmopressin, with the highest incidence in elderly patients and at higher dose levels.[17]

Desmopressin has recently been formulated as an orally disintegrating tablet that overcomes issues related to swallowing difficulty, avoids ingestion of extra fluids and has improved bioavailability compared to the standard tablet.[8] Published data support not only the potential safety benefit of a lower dose range but also gender specific dosing since increased sensitivity to desmopressin has been documented in women.[8,18] This study (NCT01262456) was designed to establish dose recommendations in men with nocturia.

MATERIALS AND METHODS

Patients

Eligible patients were males 18 years old or older with nocturia (2 or more voids nightly determined via a 3-day frequency-volume chart completed immediately before randomization to treatment). Inclusion and exclusion criteria are listed in the supplementary table (http://jurology.com/). Key exclusion criteria were evidence of severe daytime voiding dysfunction (more than 1 urge incontinence or urgency episode daily or more than 8 daytime voids per day in the 3-day diary), suspicion of BOO or a urine flow less than 5 ml per second, surgery for BOO or BPH within 6 months of screening, urinary retention and/or post-void residual volume greater than 250 ml (confirmed by ultrasound if investigator suspected retention), history of urological malignancies, neurogenic detrusor activity or current genitourinary tract pathology that could interfere with voiding, polydipsia and hyponatremia (serum sodium less than 135 mmol/L). Patients on stable doses of α-antagonists and/or antimuscarinic agents for 3 months were allowed to participate. The trial was performed in accordance with the Declaration of Helsinki and approved by the institutional review board/ethics committee for each site. All patients provided written informed consent.

Study Design and Procedures

This was a multicenter, randomized, double-blind, placebo controlled, parallel group study. The primary objective was to test the safety and efficacy of 50 and 75 μg desmopressin ODT vs placebo in men with nocturia during 3 months of treatment.

Patients were randomized 1:1:1 to placebo, 50 μg desmopressin or 75 μg desmopressin once daily using a computer generated list prepared before study enrollment. Randomization was stratified by age (younger than 65 vs 65 years old or older). Patients were instructed to take the study drug every night 1 hour before bedtime, to drink only to satisfy thirst and to empty their bladder before bed. Evening intake of fluids with a diuretic effect such as coffee, tea, caffeinated soft drinks and alcoholic beverages was especially discouraged. Desmopressin and placebo ODT were supplied by Ferring Pharmaceuticals, and were indistinguishable with respect to appearance, smell, taste and packaging.

Diaries and Questionnaires

Patients completed 3-day voiding and sleep diaries immediately before randomization, after randomization, at week 1, month 1, month 2, month 3 and at the end of study part II to record the time and volume of voids and the time to the first nocturnal void. In the morning (before breakfast) patients also reported sleep quality using the sleep rating scale (1—poor/very tired to 10—excellent/wide awake). The Nocturia Quality of Life and Work Productivity and Activity Impairment questionnaires were also completed. Patients rated each of the 13 N-QoL statements from 0 (lowest) to 4 (highest), where 1 statement concerns global QoL and 12 cover the specific disease. Raw data were then transformed into a standardized score out of 100. The WPAI outcomes were expressed as impairment percentages of the 4 scores of absenteeism (work time

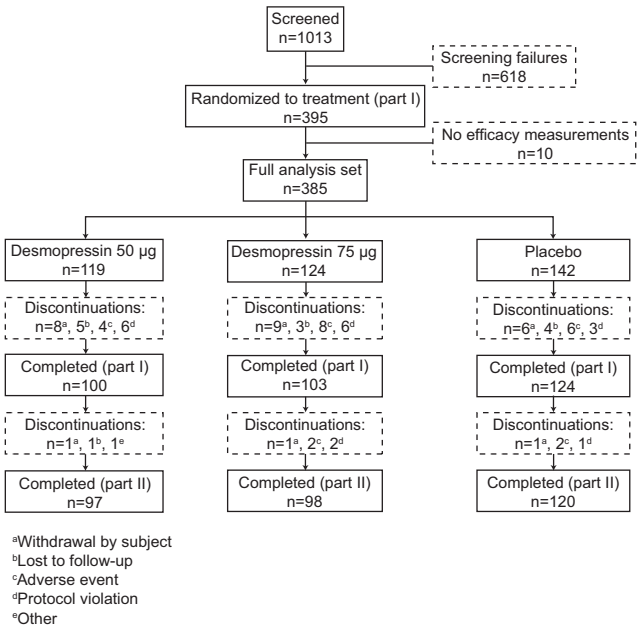

Figure 1. Patient disposition

missed), presenteeism (impairment at work/reduced on the job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism) and activity impairment.

End Points

The co-primary efficacy end points were the change from baseline in mean number of nocturnal voids and proportion of 33% responders during 3 months of treatment analyzed using a longitudinal analysis. A 33% responder was defined as a patient with a decrease of at least 33% in the mean number of nocturnal voids at each visit compared to baseline.

Secondary end points included change from baseline at 3 months in mean number of nocturnal voids, proportion of 33% responders, mean time to first void and mean nocturnal urine volume. The exploratory end points included mean self-rated sleep quality, N-QoL scores and WPAI percentages.

Safety and Tolerability

Safety and tolerability were monitored via observation and assessment of AEs. These were coded by the system organ class and preferred terms using MedDRA, and categorized by severity, seriousness and likelihood of causal relationship to study medication as rated by the investigator.

AEs and serum sodium were measured during screening and on all study visits (day 4, week 1, month 1, month 2 and month 3) after treatment. If serum sodium was 130

Table 1. *Baseline characteristics*

	Desmopressin 50 μg	Desmopressin 75 μg	Placebo
No. pts	119	124	142
Age:			
Mean (SD)	60.8 (13.2)	60.1 (11.6)	60.8 (14.2)
Median (min, max)	64 (20, 81)	64 (29, 80)	64 (21, 87)
No. age category (%):			
Younger than 65	62 (52)	64 (52)	74 (52)
65 or Older	57 (48)	60 (48)	68 (48)
Body mass index (kg/m^2):			
Mean (SD)	29.3 (4.77)	29.2 (4.79)	29.2 (5.25)
Median (min, max)	28.9 (19.9, 50.1)	28.6 (16.1, 47.0)	28.7 (18, 48.5)
No. race (%):			
White	99 (83)	99 (80)	112 (79)
Black/African-American	18 (15)	22 (18)	27 (19)
Other	2 (2)	3 (2)	3 (2)
No. nocturnal voids category (%):			
Less than 2	0 (0)	1 (less than 1)	1 (less than 1)
2–Less than 3	71 (60)	60 (48)	73 (51)
3–Less than 4	32 (27)	42 (34)	46 (32)
4–Less than 5	11 (9)	17 (14)	19 (13)
5–Less than 6	3 (3)	2 (2)	3 (2)
6–7	2 (2)	2 (2)	0
Nocturnal voids:			
Mean (SD)	2.88 (0.86)	2.99 (0.90)	2.90 (0.81)
Median (min, max)	2.67 (2.0, 6.0)	3 (1.67, 6.33)	2.67 (1.0, 5.67)
Mins to first nocturnal void:			
Mean (SD)	146 (53)	143 (56)	147 (58)
Median (min, max)	148 (16, 309)	140 (49, 262)	137 (19, 325)
No. mean daytime voids category (%):			
2–Less than 4	12 (10)	5 (4)	11 (8)
4–Less than 6	55 (46)	55 (44)	61 (43)
6–Less than 8	50 (42)	59 (48)	68 (48)
8 or More	2 (2)	5 (4)	2 (1)
Daytime voids:			
Mean (SD)	5.66 (1.27)	5.77 (1.17)	5.63 (1.17)
Median (min, max)	5.67 (3.33, 8.67)	6.0 (3.0, 9.0)	5.67 (3.0, 8.0)
Nocturnal vol (ml):			
Mean (SD)	607 (325)	647 (345)	620 (313)
Median (min, max)	508 (60; 1,792)	586 (75; 1,833)	548 (81.7; 1,877)
24-Hr vol (ml):			
Mean (SD)	1,373 (636)	1,447 (624)	1,360 (621)
Median (min, max)	1,249 (125; 3,045)	1,305 (333; 3,533)	1,246 (209; 3,542)
No. nocturnal polyuria (%)*	100 (84)	107 (86)	127 (89)
Fluid intake (ml/kg/24 hrs):			
Mean (SD)	13.4 (7.46)	13.9 (7.14)	13.4 (6.96)
Median (min, max)	12.5 (1.37, 37.2)	13.1 (2.83, 37.8)	11.8 (2.26, 38.7)

* Based on a nocturnal polyuria index (nocturnal volume/24-hour volume) 33% or greater.

Table 2. *Summary of co-primary end point changes from baseline*

	Desmopressin 50 μg	Desmopressin 75 μg	Placebo
No. nocturnal voids:*			
No. pts	119	124	142
Adjusted mean	−1.25	−1.29	−0.88
Treatment difference vs placebo	−0.37	−0.41	
95% CI	−0.57, −0.17	−0.61, −0.22	
p Value†	0.0003	<0.0001	
Proportion of 33% responders:‡			
Adjusted probability	0.67	0.67	0.50
Adjusted odds	2.01	2.08	1.02
Odds ratio	1.98	2.04	
95% CI	1.32, 2.96	0.38, 3.03	
p Value†	0.0009	0.0004	

* Repeated measures ANCOVA of change from baseline at week 1, month 1, month 2 and month 3, adjusted for age stratification factor (younger than 65 years, 65 years old or older), visit and baseline nocturnal voids.
† Statistically significant difference vs placebo, $p \leq 0.05$.
‡ Generalized estimating equation logistic regression of 33% responder status at week 1, month 1, month 2 and month 3, adjusted for age stratification factor (younger than 65 years, 65 years old or older), visit and baseline nocturnal voids.

mmol/L or less, the patient was asked to visit the trial site as soon as possible for further evaluation. Patients with a serum sodium of 125 mmol/L or less were withdrawn from the study immediately.

Additional safety measurements included a standard battery of blood and urine analyses, vital signs and physical examinations. All patients who received 1 or more doses of desmopressin or placebo were included in the safety analyses.

Statistical Analysis

The trial was powered to demonstrate superiority to placebo simultaneously on the 2 co-primary end points. Using assumptions on means, variances and correlations of the number of voids at the various points based on data from men in a previous trial,[8] simulations estimated that a sample size of 130 patients per group yielded at least 95% power to detect a treatment effect of 0.3 voids, as well as finding a subsequent statistically significant time averaged odds ratio of 33% responder status.

Testing was performed using a hierarchical step-down approach. The 75 μg dose had to be significant at the 2-sided 5% nominal significance level on both co-primary end points vs placebo before testing the 50 μg, thereby protecting the overall Type 1 error to be 5% or less.

All primary, secondary and exploratory end points were analyzed based on the full analysis set which included all randomized and exposed patients with at least 1 efficacy assessment after dosing initiation. Two-sided tests were used for all efficacy end points.

Change from baseline in mean number of nocturnal voids was analyzed longitudinally using a repeated measures ANCOVA with change in mean number of nocturnal voids as the dependent variable. The second co-primary end point, proportion of 33% responders, was analyzed using a generalized estimating equation method with the 33% responder status as the dependent variable. For both analyses observed values were used, baseline mean nocturnal voids was a covariate, and treatment, visit (including a treatment by visit interaction term) and age stratification (younger than 65, 65 years old or older) were factors. If the treatment by visit interaction was not significant at the 5% level, it was removed from the model.

All secondary end points were tested using cross-sectional analyses at month 3, using respective baseline as covariate, and age stratification and treatment as factors. Missing values were imputed using last observation carried forward. The exploratory end points were analyzed in a manner similar to the secondary end points. SAS® version 9.2 was used.

RESULTS

This study was conducted at 50 primary and secondary care centers across the United States and Canada from February 2011 to January 2012. Of 1,013 screened subjects 395 were randomized to treatment

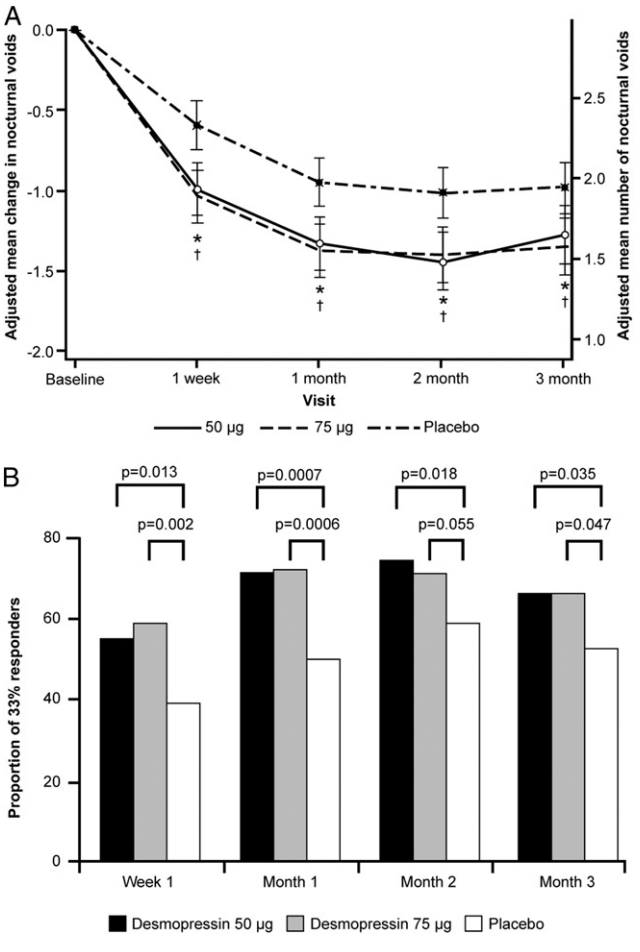

Figure 2. Adjusted mean and change from baseline in mean number of nocturnal voids (*A*) and adjusted 33% responder rates (*B*). Asterisk indicates 50 μg, dagger indicates 75 μg; $p < 0.01$, statistically different from placebo at given point; repeated measures ANCOVA adjusted for age stratification factor (younger than 65 years, 65 years old or older), visit and baseline nocturnal voids.

(fig. 1). The most common reason for screening failure was nonfulfillment of the inclusion/exclusion criteria (53%) such as evidence of severe daytime voiding dysfunction (16%), renal impairment (16%) and averaging less than 2 nocturnal voids during screening (11%).

Of the 395 randomized patients 385 had at least 1 efficacy assessment after dosing initiation and were included in the FAS and 327 (83%) completed part I. Similar numbers of patients discontinued prematurely in each treatment group (fig. 1). Two patients were randomized to 50 μg desmopressin but received 75 μg desmopressin and placebo, and they were included in the 50 μg desmopressin group in the FAS. Baseline characteristics are summarized in table 1. The majority of patients had 2 to less than 3 nocturnal voids. A daytime frequency of more than 6 voids was reported by 50% to 68% of patients. The most common concomitant medications, as evaluated by ATC (anatomical therapeutic chemical) group, were lipid modifying agents, vitamins, agents acting on the renin-angiotensin system, antithrombotic agents, urological agents (includes eg antispasmodics, drugs used in erectile dysfunction, and drugs used in BPH), and anti-inflammatory and antirheumatic products. Drugs for the treatment of BPH were used by 16% of patients. Overall, demographic characteristics were similar among the 3 treatment groups. Compliance was high and 98% of the FAS took more than 80% of the planned doses (based on returned medication quantities).

Compared with placebo, 50 and 75 μg desmopressin significantly decreased the mean number of nocturnal voids from baseline (−0.37, $p < 0.0001$ and −0.41, $p = 0.0003$, respectively) and increased the odds of achieving greater than 33% responder status (OR 1.98, $p = 0.0009$ and OR 2.04, $p = 0.0004$, respectively) to similar extents during 3 months as assessed by longitudinal analysis (table 2). The treatment difference was similar for patients younger than 65 years and those 65 years old or older (test for interaction $p = 0.57$ and 0.87, respectively). Desmopressin reduced the number of nocturnal voids from baseline by week 1 and maintained the reduction over time (fig. 2, *A*). Similarly, desmopressin increased the proportion of 33% responders by week 1 and maintained the response throughout the trial (fig. 2, *B*).

The secondary efficacy end points change from baseline in mean number of nocturnal voids, 33% responder status, time to first nocturnal void and nocturnal urine volume all demonstrated significant changes from baseline for both desmopressin dose groups compared to placebo at 3 months (table 3).

Analyses of N-QoL scores reported by patients receiving 50 μg desmopressin compared to those receiving placebo at 3 months showed statistical significance in the total score as well as in the sleep/energy domain. Patients receiving 50 μg desmopressin also had significant improvements in 2 sleep quality ratings. No difference was seen in work related domains but the proportion of patients in work was low, resulting in approximately 30% contributing data to the calculation of work productivity loss (post hoc analysis, table 4).

Desmopressin was well tolerated (table 5). Treatment emergent AEs with an incidence of 5% or more in any group included dry mouth and headache. ADRs with an incidence of 2% or more in either treatment group included dry mouth, constipation, serum sodium 125 mmol/L or less and headache. The incidence of ADRs was lower in the 50 μg desmopressin group than in the 75 μg group. Serum sodium levels less than 130 mmol/L were observed in 11 patients, of whom 9 (82%) were 65 years old or older, and 5 of the 6 patients (83%) with a serum sodium of 125 mmol/L or less were 65 years old or

Table 3. *Summary of secondary efficacy end points at 3 months*

	Desmopressin			Comparison vs Placebo					
				Treatment Contrast/OR (CI)				p Value*	
	50 μg	75 μg	Placebo	50 μg		75 μg		50 μg	75 μg
No. pts	119	122	142						
Change from baseline in mean No. nocturnal voids†	−1.29	−1.34	−1.00	−0.29	(−0.52, −0.06)	−0.35	(−0.57, −0.12)	0.013	0.003
33% Responder status:‡									
Probability	0.66	0.68	0.54						
Odds	1.98	2.09	1.15	1.72	(1.03, 2.87)	1.81	(1.08, 3.02)	0.039	0.023
Change from baseline in mean mins to first nocturnal void†	111.8	115.6	72.9	39.0	(11.0, 66.9)	42.8	(15.0, 70.5)	0.006	0.003
Change from baseline in ml nocturnal urine vol	−208.7	−217.1	−130.9§	−77.8	(−135.7, −19.9)	−86.2	(−143.7, −28.6)	0.009	0.003

* Statistically significant difference vs placebo $p \leq 0.05$.

† ANCOVA of change from baseline adjusted for age (younger than 65, 65 years or older) and baseline nocturnal voids.

‡ Logistic regression of 33% responder status adjusted for age (younger than 65, 65 years or older) and baseline nocturnal voids.

§ In 141 patients.

Table 4. *Adjusted treatment differences in mean change from baseline in exploratory end points at month 3*

	No. Desmopressin		No.	Difference in Adjusted Means (95% CI)		p Value	
	50 μg	75 μg	Placebo	50 μg	75 μg	50 μg	75 μg
N-QoL:	103	107	127				
Total score				4.49 (0.24, 8.74)	3.33 (−0.88, 7.54)	0.039*	0.12
Bother/concern domain				2.92 (−1.58, 7.42)	1.82 (−2.62, 6.27)	0.20	0.42
Sleep/energy domain				6.11 (1.42, 10.80)	4.87 (0.23, 9.51)	0.011*	0.040*
Global quality of life				7.21 (3.42, 11.0)	5.35 (1.61, 9.10)	0.0002*	0.005*
Sleep quality:†	102	107	125				
"How do you feel right now?"				0.43 (0.05, 0.82)	0.26 (−0.12, 0.64)	0.027*	0.17
"Rate how refreshed you feel"				0.49 (0.11, 0.87)	0.30 (−0.07, 0.68)	0.011*	0.11
"Rate the quality of your sleep last night"				0.36 (−0.03, 0.75)	0.09 (−0.29, 0.48)	0.068	0.63
WPAI:							
Absenteeism (% work time missed)	33	36	37	−0.92 (−3.45, 1.62)	−0.62 (−3.11, 1.87)	0.47	0.62
Presenteeism (% impairment at work)	34	38	38	2.33 (−5.75, 10.40)	0.56 (−7.35, 8.47)	0.57	0.89
Work productivity loss	33	36	37	2.25 (−6.40, 10.89)	0.87 (−7.63, 9.36)	0.61	0.84
Activity impairment	106	114	131	−3.73 (−9.39, 1.93)	−3.18 (−8.74, 2.37)	0.20	0.26

* Statistically significant difference vs placebo, repeated measures ANCOVA p ≤0.05.
† Mean of scores on 3 consecutive mornings.

older. All recovered to 130 mmol/L or greater. Fewer incidences of a serum sodium less than 130 mmol/L were observed in the 50 μg desmopressin group than in the 75 μg group (2 vs 9). The individual serum sodium profiles of the 2 patients in the 50 μg group are presented in figure 3.

DISCUSSION

Previously published post hoc analyses of data from a large randomized clinical trial indicated that low dose desmopressin ODT (25 to 100 μg) is effective, the minimum effective dose is lower in women than in men and the small but clinically noteworthy risk of severe hyponatremia with desmopressin is further reduced by the use of the gender specific minimum effective dose.[8,18] Gender differences in sensitivity to desmopressin are also supported by a study

Table 5. *Summary of treatment emergent AEs and serum sodium values (safety analysis set)*

	No. 50 μg Desmopressin (%)	No. 75 μg Desmopressin (%)	No. Placebo (%)
No. pts	119	122	143
All AEs	46 (39)	49 (40)	58 (41)
Severe AEs	2 (2)	2 (2)	2 (1)
ADRs*	23 (19)	20 (16)	22 (15)
AEs leading to discontinuation	4 (3)	7 (6)	7 (5)
ADRs leading to discontinuation*	4 (3)	5 (4)	4 (3)
Serious AEs	4 (3)†	5 (4)‡	1 (less than 1)§
Serum sodium (mmol/L):			
125 or Less	2 (2)	4 (3)	0 (0)
126–129	0 (0)	5 (4)	0 (0)
130–134	9 (8)	12 (10)	2 (1)

* An AE assessed by the investigator as possibly/probably related to study drug.
† Two patients with hyponatremia, 1 with acute myocardial infarction and 1 with osteoarthritis.
‡ Four patients with hyponatremia and 1 with transient global amnesia.
§ Pyrexia.

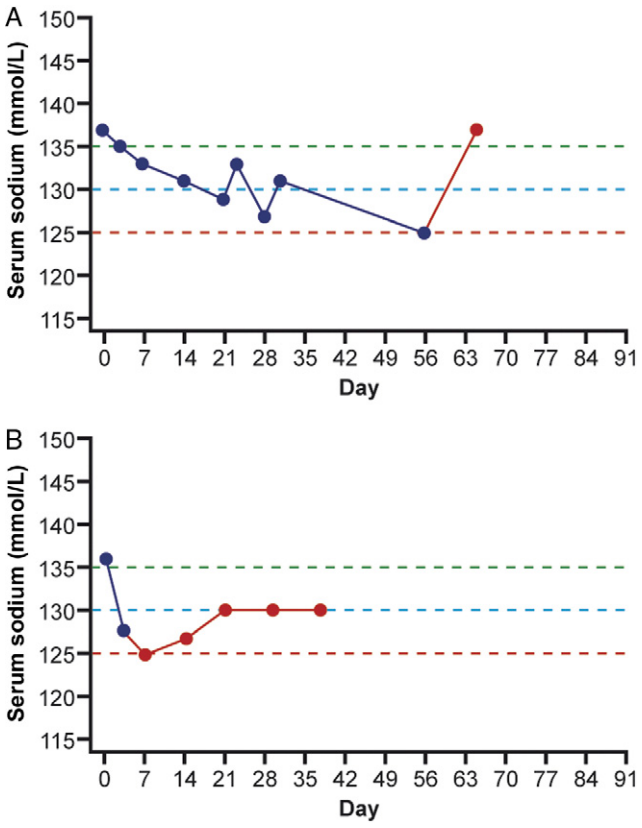

Figure 3. Serum sodium profiles of patients receiving 50 μg desmopressin with a post-baseline serum sodium level less than 130 mmol/L. Red indicates measurements after withdrawal of treatment. *A*, patient was also taking enalapril and lovastatin, which may contribute to hyponatremia. On cessation of desmopressin, enalapril and lovastatin, serum sodium normalized within 1 week.

of Japanese patients with nocturia[19] and a post hoc analysis of study extensions to trials of desmopressin.[20] We report a new study demonstrating the efficacy of 50 and 75 μg desmopressin ODT as well as the relevance of exploring the lower dose range to optimize safety in the treatment of nocturia in men.

This study demonstrated statistically significant clinical benefits of 50 and 75 μg desmopressin ODT compared to placebo, with rapid reduction in nocturnal voids and nocturnal urine output, and increase in time to first void and proportion of 33% responders. The magnitude of improvement from baseline was clinically relevant, similar for both doses, and comparable to those previously reported with desmopressin ODT in men with nocturia, with similar end points.[8] A notable placebo response was also observed, which is common in trials of urological indications including overactive bladder and BOO.[21–23]

Reduction in nocturnal voids and nocturnal urine output are key end points for documenting the clinical efficacy of antidiuretic treatment, but sleep, health related QoL, and daytime activity/productivity demonstrate the benefits to patients. In this study desmopressin increased the time to first void from baseline by almost 2 hours (approximately 40 minutes more than placebo), resulting in a mean total initial undisturbed sleep period of approximately 4.5 hours after desmopressin treatment. The importance of prolonging the initial undisturbed sleep period was supported by the post hoc analysis showing significant treatment differences in N-QoL total score, sleep/energy domain and global QoL as well as in 2 of 3 sleep quality scales.

The WPAI questionnaire is a productivity instrument that has been assessed extensively[24,25] and has been used to show significant productivity loss due to nocturia.[26] In this study no difference was observed in work related domains. This finding may be attributable to insufficient power as only approximately a third of the study population was working.

The safety data obtained in this study support previous findings that hyponatremia is the only clinically significant AE with desmopressin.[8,27,28] The most prevalent ADR was dry mouth. However, the incidence was similar in active treatment compared with placebo, and dry mouth is a common complaint in patients with nocturia.[29] This study confirms that higher desmopressin doses and age older than 65 years are predictors of clinically significant reductions in serum sodium,[8,18] that the risk is low at doses of 50 to 75 μg, and that confirming a normal serum sodium value before treatment initiation and 4 to 8 days and 1 month after treatment initiation will minimize that risk.

As the efficacy observed with 50 and 75 μg desmopressin was similar and the lower dose group had fewer incidences of serum sodium 125 mmol/L or less (reversible reductions in 2 patients age 74 and 79 years), this study supports a 50 μg desmopressin ODT dose recommendation for the treatment of nocturia in men.

ACKNOWLEDGMENTS

Medical writing and editorial assistance provided by Dr. Kerry af Forselles, ApotheCom ScopeMedical Ltd, funded by Ferring Pharmaceuticals.

REFERENCES

1. van Kerrebroeck P, Abrams P, Chaikin D et al: The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; **21:** 179.

2. Bosch JL and Weiss JP: The prevalence and causes of nocturia. J Urol 2010; **184:** 440.

3. Kupelian V, Wei JT, O'Leary MP et al: Nocturia and quality of life: results from the Boston area community health survey. Eur Urol 2012; **61:** 78.

4. Kupelian V, FitzGerald MP, Kaplan SA et al: Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol 2011; **185:** 571.

5. Lightner DJ, Krambeck AE, Jacobson DJ et al: Nocturia is associated with an increased risk of coronary heart disease and death. BJU Int 2012; **110:** 848.

6. Nakagawa H, Niu K, Hozawa A et al: Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol 2010; **184:** 1413.

7. Ancoli-Israel S, Bliwise DL and Nørgaard JP: The effect of nocturia on sleep. Sleep Med Rev 2011; **15:** 91.

8. Weiss JP, Zinner NR, Klein BM et al: Desmopressin orally disintegrating tablet effectively reduces nocturia: results of a randomized, double-blind, placebo-controlled trial. Neurourol Urodyn 2012; **31:** 441.

9. Weiss JP, Van Kerrebroeck PE, Klein BM et al: Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. J Urol 2011; **186:** 1358.

10. Smith AL and Wein AJ: Outcomes of pharmacological management of nocturia with non-antidiuretic agents: does statistically significant equal clinically significant? BJU Int 2011; **107:** 1550.

11. Weiss JP, Blaivas JG, Bliwise DL et al: The evaluation and treatment of nocturia: a consensus statement. BJU Int 2011; **108:** 6.

12. van Kerrebroeck P, Hashim H, Holm-Larsen T et al: Thinking beyond the bladder: antidiuretic treatment of nocturia. Int J Clin Pract 2010; **64:** 807.

13. Nørgaard JP, Hashim H, Malmberg L et al: Antidiuresis therapy: mechanism of action and clinical implications. Neurourol Urodyn 2007; **26:** 1008.

14. Abrams P, Andersson KE, Birder L et al: Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn 2010; **29:** 213.

15. Thüroff JW, Abrams P, Andersson KE et al: EAU guidelines on urinary incontinence. Eur Urol 2011; **59:** 387.

16. Oelke M, Bachmann A, Descazeaud A et al: Guidelines on the Management of Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO). European Association of Urology. Available at www.uroweb.org/gls/pdf/12_Male_LUTS_LR.pdf. Accessed October 2012.

17. Rembratt A, Riis A and Nørgaard JP: Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia. Neurourol Urodyn 2006; **25:** 105.

18. Juul KV, Klein BM, Sandström R et al: Gender difference in antidiuretic response to desmopressin. Am J Physiol Renal Physiol 2011; **300:** F1116.

19. Yamaguchi O, Nishizawa O, Juul KV et al: Gender difference in efficacy and dose response in Japanese patients with nocturia treated with four different doses of desmopressin orally disintegrating tablet in a randomized, placebo-controlled trial. BJU Int 2013; **111:** 474.

20. Juul KV, Klein BM and Nørgaard JP: Long-term durability of the response to desmopressin in female and male nocturia patients. Neurourol Urodyn 2013; **32:** 363.

21. Lee S, Malhotra B, Creanga D et al: A meta-analysis of the placebo response in antimuscarinic drug trials for overactive bladder. BMC Med Res Methodol 2009; **9:** 55.

22. Mangera A, Chapple CR, Kopp ZS et al: The placebo effect in overactive bladder syndrome. Nat Rev Urol 2011; **8:** 495.

23. van Leeuwen JH, Castro R, Busse M et al: The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. Eur Urol 2006; **50:** 440.

24. Reilly MC, Zbrozek AS and Dukes EM: The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993; **4:** 353.

25. Prasad M, Wahlqvist P, Shikiar R et al: A review of self-report instruments measuring health-related work productivity: a patient-reported outcomes perspective. Pharmacoeconomics 2004; **22:** 225.

26. Kobelt G, Borgström F and Mattiasson A: Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. BJU Int 2003; **91:** 190.

27. Mattiasson A, Abrams P, Van Kerrebroeck P et al: Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. BJU Int 2002; **89:** 855.

28. Lose G, Mattiasson A, Walter S et al: Clinical experiences with desmopressin for long-term treatment of nocturia. J Urol 2004; **172:** 1021.

29. Asplund R: Nocturia in the elderly in relation to thirst, dry mouth and dry eyes. Can J Urol 2004; **11:** 2322.