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

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Abbreviations and Acronyms

ADR = adverse drug reaction
AEs = adverse events
MED = minimum effective dose
NP = nocturnal polyuria
N-QoL = nocturia quality of life
OAB = overactive bladder
ODT = orally disintegrating tablet
QoL = quality of life
WPAI = work productivity and activity impairment

Accepted for publication February 13, 2013.
Study received institutional review board approval.
Supported by Ferring Pharmaceuticals.
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‡ Financial interest and/or other relationship with Merck, Ferring, Johnson & Johnson and Allergan.
§ Financial interest and/or other relationship with Ferring Pharmaceuticals.

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Purpose: Previous studies suggest a lower dose of desmopressin orally disintegrating tablet may be effective in females compared to males with nocturia. We confirm the efficacy and safety of 25 μg desmopressin orally disintegrating tablet compared to placebo in female patients.

Materials and Methods: In this 3-month, randomized, double-blind, parallel group study 25 μg desmopressin once daily was compared to placebo in women with nocturia (2 or more nocturnal voids). The co-primary efficacy end points were change from baseline in mean number of nocturnal voids and proportion of patients achieving at least a 33% reduction from baseline in the mean number of nocturnal voids (33% responders).

Results: The full analysis set comprised 261 patients (age range 19 to 87 years). Desmopressin significantly reduced the mean number of nocturnal voids and increased the odds of a 33% or greater response compared to placebo during 3 months, assessed by longitudinal analysis (−0.22, $p = 0.028$ and OR 1.85, $p = 0.006$, respectively). Desmopressin increased the mean time to first nocturnal void by 49 minutes compared to placebo at 3 months ($p = 0.003$). The response to desmopressin was seen by week 1 of treatment and was sustained throughout the trial. Significant increases in health related quality of life and sleep quality were observed compared to placebo. Desmopressin was well tolerated. Serum sodium levels remained greater than 125 mmol/L throughout the trial and 3 transient decreases to less than 130 mmol/L were recorded.

Conclusions: At a dose of 25 μg, desmopressin orally disintegrating tablet is an effective and well tolerated treatment for women with nocturia. Treatment provides rapid and sustained improvement in nocturia and quality of life.

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

NOCTURIA is defined by the International Continence Society and the International Urogynecological Association as the need to wake to void once or more per night.[1,2] It is a highly prevalent condition[3] that has a clinically significant impact on morbidity, mortality, quality of life and productivity.[4–7] The detrimental impact on health is considered mainly to be due to sleep fragmentation[8,9] when 2 or more nocturnal voids are experienced.[5,7,10]

The etiology of nocturia is multifactorial. Treatment based on advice re-

0022-5347/13/1903-0958/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.02.037
Vol. 190, 958-964, September 2013
Printed in U.S.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 the study drug or placebo and had 1 or more safety assessments 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 various points based on data from females in a previous trial,[10] simulations demonstrated that a sample size of 130 patients per group yielded at least 95% power to detect 0.5 or more voids constant treatment effect as well as a statistically significant subsequent time averaged odds ratio of 33% responder status.

All end points were analyzed based on the full analysis set that 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 (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 the respective baseline as covariate, and age stratification and treatment as factors. Missing values were imputed using last observation carried forward. 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 39 primary and secondary care centers across the United States and Canada from November 2010 to November 2011. Of 649 screened subjects 268 were randomized to treatment (fig. 1). The most common reason for screening failure was nonfulfillment of the inclusion/exclusion criteria (49%), such as evidence of severe daytime voiding dysfunction, renal impairment and averaging less than 2 nocturnal voids during screening. Overall, 96% of randomized patients took greater than 80% of the planned doses (based on returned medication) and 89% completed the study. An equal percentage of patients prematurely discontinued in the desmopressin and placebo treatment groups (fig. 1). Two patients were randomized to placebo but received desmopressin, and they are included in the placebo group in the full analysis set. Baseline characteristics are summarized in table 1. Overall, treatment groups were well balanced. All patients had a previous diagnosis of nocturia. Daytime frequency of 6 or more voids was reported by 40% to 50% of patients in the treatment groups and 5 patients were included despite having 8 or more voids at baseline. The most common concomitant medications were vitamins, lipid modifying agents, analgesics, anti-inflammatory agents and antirheumatic agents.

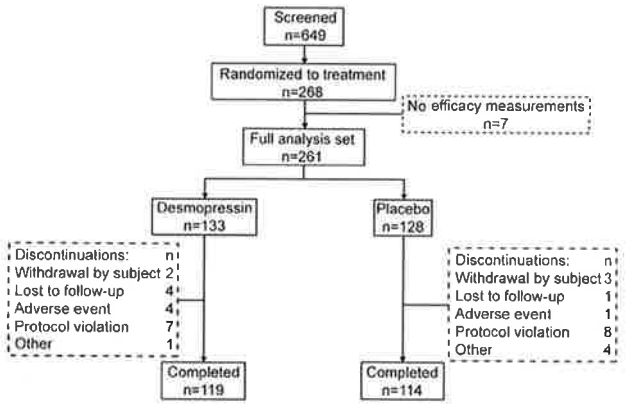

Figure 1. Patient disposition

The trial met its primary objective as statistically significant differences, favoring desmopressin compared with placebo, were shown for the co-primary end points of change from baseline in mean number of nocturnal voids (treatment effect −0.22 voids, $p = 0.028$) and the odds of achieving a 33% or greater responder status (odds ratio 1.85, $p = 0.006$) during 3 months as assessed by longitudinal analysis (table 2). The treatment difference was similar for patients younger than 65 and 65 years old or older (test for interaction $p = 0.25$ and 0.60, respectively). The dose of 25 μg desmopressin ODT rapidly reduced the number of nocturnal voids from baseline and maintained the reduction with a trend for further reduction with time (fig. 2, *A*). Similarly, the proportion of 33% responders increased from baseline by week 1 and was maintained throughout the trial (fig. 2, *B*).

Results of the secondary efficacy end points at 3 months are presented in supplementary table 2 (http://jurology.com/). While a significant difference compared with placebo was seen in the change from baseline in the number of nocturnal voids after desmopressin treatment ($p = 0.01$), the 33% responder rate did not reach statistical significance. A significant increase in time to first void and a reduction in nocturnal urine volume from baseline were seen

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

	No. 25 μg Desmopressin*	No. Placebo*	Difference in Adjusted Means (95% CI)	p Value
N-QoL:	133	128		
Total score			5.34 (0.76, 9.92)	0.02†
Bother/concern domain			5.69 (0.72, 10.65)	0.03†
Sleep/energy domain			4.90 (0.06, 9.75)	0.05†
Global quality of life			1.26 (−2.97, 5.49)	0.56
Sleep quality:‡	133	128		
"How do you feel right now?"			0.43 (−0.01, 0.87)	0.06
"Rate how refreshed you feel"			0.46 (0.02, 0.90)	0.04†
"Rate the quality of your sleep last night"			0.53 (0.06, 1.00)	0.03†
WPAI:				
Absenteeism (% work time missed)	32	30	−0.12 (−8.46, 8.23)	0.98
Presenteeism (% impairment at work)	32	31	−2.93 (−13.10, 7.24)	0.57
Work productivity loss	32	30	−3.37 (−14.75, 8.01)	0.56
Activity impairment	124	126	−6.68 (−12.66, −0.70)	0.03†

* Number of patients completing questionnaire/questionnaire subsection.
† Statistically significant difference vs placebo, repeated measures ANCOVA $p \leq 0.05$.
‡ Mean of scores on 3 consecutive mornings.

tract infection, headache and upper respiratory tract infection. ADRs with an incidence of 2% or more in either treatment group included dry mouth, headache, medication error, somnolence and rash. AEs that led to discontinuation were headache, somnolence and hypertension in the desmopressin group and pulmonary embolism in the placebo group. No serum sodium values of 125 mmol/L or less were observed. All 3 patients whose serum sodium reached less than 130 mmol/L recovered to greater than 130 mmol/L within 2 to 4 days without discontinuing treatment (fig. 3). Of these 3 patients 2 had a serum sodium level of less than 135 mmol/L at baseline.

DISCUSSION

This study confirms the efficacy of 25 μg desmopressin ODT in the treatment of nocturia in adult female patients. It was conducted to confirm the findings of a recently published large trial of 10, 25, 50 and 100 μg desmopressin ODT,[10] where post hoc analyses by gender indicated a difference in the MED as well as safety benefits of targeting the gender specific MED.[22] These findings demonstrate an improved therapeutic window and risk-to-benefit ratio for the more bioavailable desmopressin ODT compared with standard tablet in the treatment of nocturia in female patients.

Table 4. *Summary of treatment emergent AEs and serum sodium values (safety analysis set)*

	No. 25 μg Desmopressin (%)		No. Placebo (%)	
No. pts	135		126	
All AEs	60	(44)	57	(45)
Severe AEs	1	(less than 1)	3	(2)
ADRs*	26	(19)	15	(12)
AEs leading to discontinuation	4	(3)	1	(less than 1)
ADRs leading to discontinuation*	3	(2)	0	
Serious AEs	0		2	(2)†
Serum sodium (mmol/L):				
125 or Less	0		0	
126–129	3	(2)‡	0	
130–134	11	(8)	2	(2)

* An AE assessed by the investigator as possibly/probably related to study drug.
† Cellulitis and pulmonary embolism.
‡ Two patients were included with baseline serum sodium less than 135 mmol/L.

Compared with baseline, the desmopressin group had a clinically relevant reduction of approximately 1.5 nocturnal voids. Desmopressin demonstrated statistically significant benefits compared to placebo, with reduction in nocturnal voids and nocturnal urine output, and increase in time to first void and proportion of 33% responders. The notable placebo effect is worth discussing. It may be partly linked to advice on fluid restriction given during screening. The regular, extended completion of voiding diaries may increase awareness of drinking and voiding habits and exert similar influences to those reported with behavioral training.[23] Large responses to placebo have been reported for studies in urological indications such as OAB and benign prostatic hyperplasia.[23–25] In a meta-analysis of placebo responses across different disorders, placebo responses were largest in urogenital disorder trials.[23] Participation in a trial may improve patient knowledge to a larger extent than for other conditions that are more widely and openly discussed. Indeed, large placebo effects have been reported even in trials of nonpharmacological interventions for the treatment of OAB, such as pelvic floor training.[23]

In other therapeutic areas the placebo effect tends to decrease with time. However, the placebo effect persisted throughout this study. Durable placebo re-

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