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JP. Weiss et al.

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Desmopressin Orally Disintegrating Tablet Effectively Reduces Nocturia: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

Jeffrey P. Weiss,[1]* Norman R. Zinner,[2] Bjarke M. Klein,[3] and Jens Peter Nørgaard[3]
[1]*Department of Urology, SUNY Downstate Medical School, Brooklyn, New York*
[2]*UCLA (Geffen) School of Medicine, Torrance, California*
[3]*Ferring International Pharmascience Center, Copenhagen, Denmark*

Aims: The primary objective was to investigate the efficacy of desmopressin orally disintegrating tablet versus placebo in patients with nocturia. Pharmacodynamics, safety and patient-reported quality of life (QoL) outcomes were also evaluated. One of several benefits of the new formulation is increased bioavailability. Exploring lower doses allows for a better evaluation of therapeutic effect versus tolerability. **Methods:** This was a 4-week, randomized, double-blind study comparing 10, 25, 50, or 100 μg desmopressin versus placebo in adults with defined nocturia. **Results:** The intent to treat population comprised 757 patients experiencing ~3 voids/night and a high prevalence of nocturnal polyuria (~90%). Increasing doses of desmopressin were associated with decreasing numbers of nocturnal voids and voided volume, greater proportions of subjects with >33% reduction in nocturnal voids, and increased duration of first sleep period. The lowest dose reaching statistical significance ($P < 0.05$ vs. placebo) varied by endpoint. Improvements were clinically meaningful, meaning that patients actually had fewer nightly voids. Post hoc analyses by gender suggested a lower minimum effective dose for women. Desmopressin was generally well tolerated. Reductions in serum sodium to <125 mmol/L in six women (taking >25 μg desmopressin) and two men (aged 67 and 82) taking 100 μg, support lower and gender-specific dosing to reduce the small but clinically significant risk of hyponatraemia. Each void reduced/hour of sleep gained was associated with significant improvements in QoL. **Conclusions:** Desmopressin orally disintegrating tablet is an effective and well-tolerated treatment for patients with nocturia. Further exploration of the lower dose range is warranted. *Neurourol. Urodynam.* © 2012 Wiley Periodicals, Inc.

Key words: desmopressin; nocturia; nocturnal polyuria; sleep; urinary bladder

INTRODUCTION

Nocturia is defined as the need to wake to void once or more per night.[1] It is a remarkably prevalent condition[2] that is considered to be clinically significant when ≥2 nightly episodes are experienced.[3,4] Associated chronic fragmentation of sleep and impaired sleep efficiency can have profound consequences for alertness, mood, functioning, cognitive performance and work productivity, and may also affect health and mortality.[5]

Treatment approaches include conservative management via fluid restriction, and pharmacological therapy using anticholinergics and/or drugs for benign prostatic hyperplasia (BPH). However, while these may be effective for daytime overactive bladder (OAB) or BPH symptoms, they are generally ineffective for nocturia.[6,7]

Around 80% of patients with nocturia have nocturnal polyuria (NP), which is reported to be associated with decreased nocturnal secretion of arginine vasopressin (AVP).[8–12] This may be a primary cause of NP or may occur secondary to other conditions (e.g., sleep apnea and third spacing). Desmopressin acetate, a synthetic analog of AVP, mimics the action of the natural hormone, and desmopressin tablets have been shown to be a well-tolerated and effective treatment for nocturia in adults with NP in clinical trials.[13–17]

Desmopressin has most recently been formulated as an orally disintegrating tablet (oral lyophilisate/melt/orodispersible formulation) (MINIRIN® Melt, Ferring Pharmaceuticals A/S, Copenhagen, Denmark), which is administered sublingually without water. This formulation is associated with increased bioavailability, allowing lower dosing than with the original solid tablets. The primary objectives of this study were to evaluate the efficacy and tolerability of desmopressin orally disintegrating tablet versus placebo. The minimum effective dose (MED) was investigated with a view to further optimizing the balance between therapeutic effect and tolerability in patients of all ages.

The study was monitored by an external, independent Data Safety Monitoring Board and was approved by the institutional review board or ethics committee for each site. The study was registered on www.clinicaltrials.gov (NCT00477490, NCT00615836) on 22 May 2007.

MATERIALS AND METHODS

Patients

Patients were ≥18 years of age, with an average of ≥2 voids per night determined via a 3-day frequency–volume chart

Christopher Chapple led the review process.
Conflict of interest: J.P. Weiss has been working with Ferring Pharmascience for more than 10 years acting in the capacity of paid consultant and scientific advisor. N.R. Zinner has been involved in clinical trials and has received speaker honoraria and consultancy fees from Ferring Pharmaceuticals and Astellas. B.M. Klein and J.P. Nørgaard are employees of Ferring Pharmaceuticals.
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*Correspondence to: Jeffrey P. Weiss, Department of Urology, SUNY Downstate Medical School, 445 Lenox Road, Brooklyn, NY 11203. E-mail: urojock@aol.com
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during screening. They were required to have serum sodium ≥135 mmol/L, serum creatinine within normal limits, and estimated glomerular filtration rate ≥60 ml/mm. Exclusions included: urinary retention and/or post-void residual volume >150 ml, or history of urologic malignancies, neurogenic detrusor activity or current genitourinary tract pathology that could interfere with voiding. Males were excluded if there was evidence of bladder outflow obstruction (BOO) and/or urine flow <5 ml/sec, or if surgery for BOO/BPH had been performed within 6 months. Females with potential for pregnancy, use of a pessary for pelvic prolapse, or the presence of unexplained pelvic mass were excluded. Patients on stable doses of OAB and/or BPH medication for 3 months could be included. The study was approved by the institutional review board/ethics committee for each site. All patients provided written informed consent.

Study Design and Procedures

This was a 4-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study, conducted at 78 sites in the USA and Canada between June 2007 and February 2008.

The trial was powered to demonstrate superiority to placebo in a step-down approach simultaneously using two co-primary endpoints. Assuming a baseline nocturia frequency of three episodes/night, and a placebo response of 0.6–1.2 voids (standard deviation 0.8–1.2), the trial had ≥80% power to detect a treatment effect of ≥0.5 voids. These assumptions were based on results from the NOCTUPUS trials.[14–17]

Seven visits were scheduled; three in the first week (visits 2–4) and then at weekly intervals (visits 5–7). At screening (visit 1), investigators recorded demographic data, vital signs, patient history, and conducted a physical examination, and took blood and urine for laboratory tests. Where the patient history led to a clinical suspicion of weak stream or poor emptying, residual volume and Q_{max} were measured. Patients also received a diary in which to record the time and volume of all voids in a 24-hr period for 3 consecutive days.

At visit 2, based on the results of screening and the voiding diary, eligible subjects were randomized to one of five treatment groups (placebo or desmopressin 10, 25, 50, or 100 μg) using a web-based centralized patient randomization system (WebEZ). Desmopressin and placebo were supplied by Ferring Pharmaceutical A/S and were indistinguishable with respect to appearance, smell, taste, and packaging. Treatments were packaged according to the computer generated randomization code to ensure that patients, investigators, and the sponsor remained fully blinded. The tablets were to be taken 1 hr before bedtime. Randomization was initially stratified by age (<65, ≥65 years) and absence/presence of NP (night-time urine volume/24-hr urine volume ≥33%).

Diaries and Questionnaires

At visits 3, 4, and 5 subjects were asked to record times of nocturnal voids for 3 consecutive nights. Vital signs, history taking, and blood tests were repeated at each of these visits. Subjects were instructed to empty their bladder before bed and drink only to satisfy thirst. Evening intake of diuretic fluids (such as drinks containing caffeine or alcohol) was especially discouraged. At visit 6, they recorded the time and volume of all voids in a 24-hr period for 3 consecutive days. They also recorded the initial period of undisturbed sleep (time from falling asleep to first nocturnal void) and self-rated sleep quality (1 [poor]–10 [excellent]). Subjects also completed the Nocturia Quality of Life (N-QoL) questionnaire (13 statements in two domains: sleep/energy and bother/concern) at visits 2 and 7. Patients rated each statement from 0 (lowest QoL) to 4 (highest QoL). The raw scores were then transformed into a standardized score out of 100.

Safety and Tolerability

Adverse events (AEs) were coded by system organ class and preferred term using MedDRA, and categorized by severity, seriousness, and likelihood of causal relationship to study medication rated by the investigator. From the day of informed consent, AEs were monitored at each visit using a standard nonleading question such as "How do you feel since your last visit?" in addition to a specific question regarding dry mouth.

Serum sodium was measured at baseline and on Days 4 and 8 and then weekly. These intervals were determined in accordance with previous observations,[15,16,18] which demonstrated that[1] serum sodium decreases usually occur shortly after treatment initiation,[2] low sodium increases with age and is rarely seen in subjects <65 years, and[3] low sodium occurs more frequently in men than women, but is often more severe in females. The study was therefore designed to document the early onset of reduction in serum sodium and to ensure the safety of the participants by closely monitoring sodium levels. Subjects with values <130 mmol/L at any point were asked to return the next day for further evaluation. Subjects with values <125 mmol/L were withdrawn from the study immediately.

Reductions in serum sodium were captured as a reported AE of "hyponatremia" or "blood sodium decreased" or as a serum sodium laboratory value <130 mmol/L. It should be noted that investigators used their discretion in assigning AEs and may have assigned an AE of "hyponatremia" or "blood sodium decreased" with serum sodium ≥130 mmol/L.

Endpoints

There were two co-primary endpoints: change in mean number of nocturnal voids from baseline, and proportion of subjects with >33% reduction in mean number of nocturnal voids from baseline. Secondary endpoints included change in diuresis (total and nocturnal volumes), change in initial period of undisturbed sleep, and change in N-QoL. Safety variables included AEs and serum sodium values, as well as a standard battery of blood and urine analyses, vital signs, and physical examinations.

Statistical Analysis

The intent to treat (ITT) dataset included all randomized subjects who received ≥1 dose of study drug and provided ≥1 post-baseline primary efficacy measure. All subjects who received ≥1 dose of the study drug or placebo and had ≥1 safety assessment were included in the safety analyses.

Change in nocturnal voids was analyzed by analysis of covariance (ANCOVA) with voids as the dependent variable, age (<65, ≥65 years), presence/absence of NP, and treatment group as independent variables and baseline number of nocturnal voids as a covariate. The same covariate and factors were used in the logistic regression model for the proportion of subjects with >33% reduction in nocturnal voids. The first period of undisturbed sleep and nocturnal urine volumes were analyzed in an identical manner.

The impact of change in nocturnal voids on QoL was investigated by an ANCOVA model using change from baseline in QoL as the dependent variable, main effects for age and NP,

and change from baseline in nocturnal voids and the baseline QoL score as covariates. This analysis was performed for the overall score and for each of the two domains. The impact of the change in initial period of undisturbed sleep on QoL was analyzed in a similar manner.

Two-sided tests using a step-down strategy from highest to lowest dose were used for all efficacy endpoints. Missing values for nocturnal voids at Days 8, 15, 22, and 28 were imputed using last observation carried forward.

SAS version 9.1.3 service pack 4 was used.

RESULTS

Patient Disposition and Demographics

Only 799/1,412 subjects were randomized (Fig. 1). The most common reasons for screening failure were renal insufficiency (15%) and averaging <2 nocturnal voids during screening (10%). Other reasons included diabetes insipidus (5%), hyponatremia (4%), suspected urinary disorders (4%), and uncontrolled diabetes mellitus (4%) or hypertension (3%). Reasons for exclusion were not given in 35% of cases.

The ITT population included 757 subjects and 710 (89%) completed the study. Across treatment groups, 6–16% of subjects discontinued prematurely. The most common reasons for discontinuation were withdrawal of consent (4%), AEs (2%), and lost to follow-up (2%).

Overall, treatment groups were well balanced (Table I).

Change in Mean Number of Nocturnal Voids

A greater decrease in nocturnal voiding was observed with increasing dose of desmopressin (−0.83 to −1.43) (Table II). Reductions were significant versus placebo for 100 μg

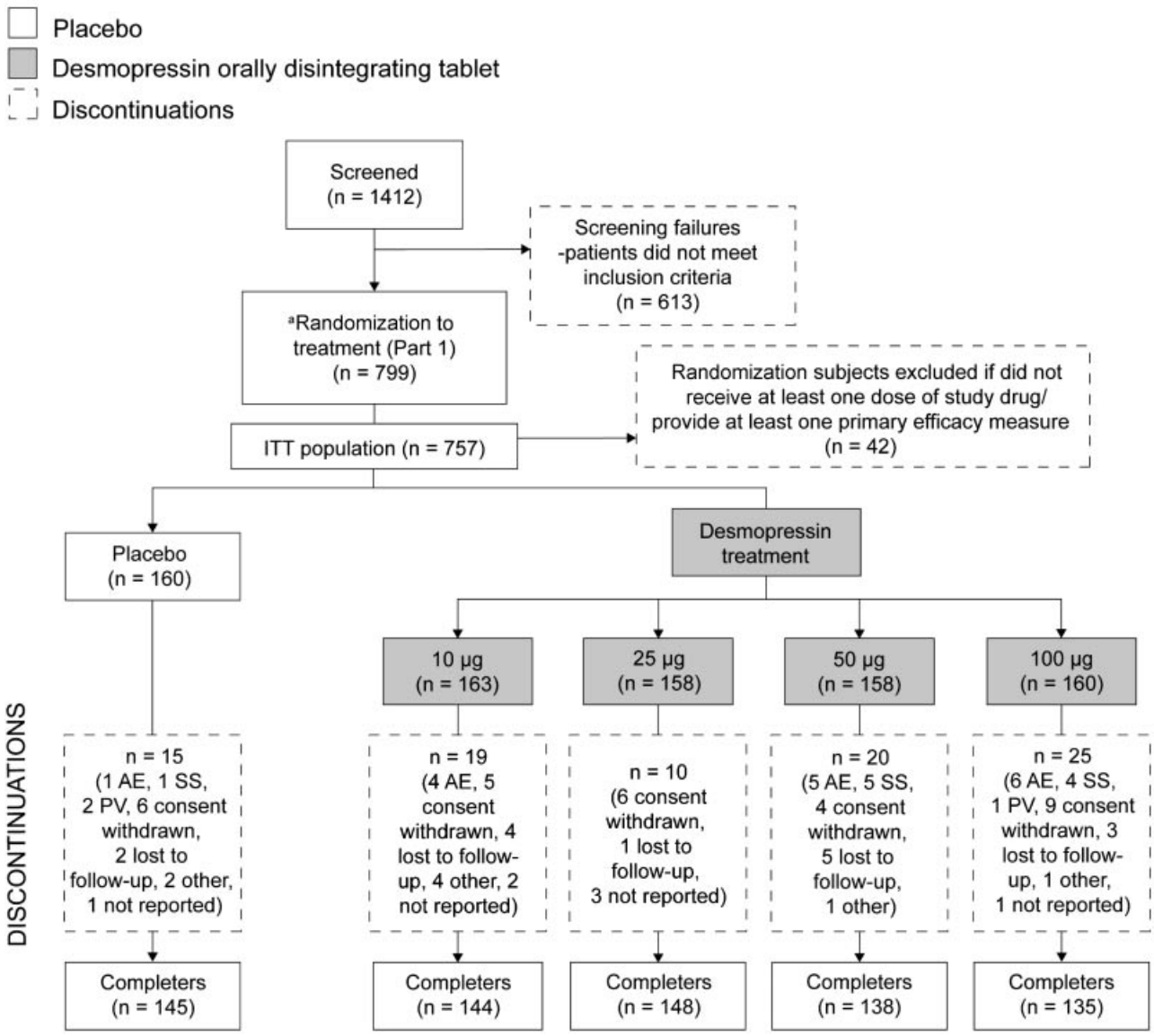

Fig. 1. Patient disposition. [a]Randomization stratified by age (<65, ≥65 years), presence/absence NP. ITT, intent to treat; AE, adverse event; SS, serum sodium; PV, post-void residual volume.

TABLE I. Baseline Demographics (Part I)

Demographic characteristic	Placebo (n = 156)	Desmopressin orally disintegrating tablet			
		10 μg (n = 155)	25 μg (n = 152)	50 μg (n = 148)	100 μg (n = 146)
Age (years)					
Mean (SD)	62.1 (13.4)	61.7 (14.4)	62.4 (13.2)	61.6 (11.8)	62.1 (12.3)
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%)
Other	1 (1%)	9 (6%)	2 (2%)	2 (1%)	2 (1%)
Baseline number of voids[a], Mean (SD)	3.27 (1.16)	3.21 (1.03)	3.35 (1.32)	3.39 (1.07)	3.22 (1.10)
Presence of nocturnal polyuria, n (%)	142 (91.0)	137 (88.4)	139 (91.4)	135 (91.2)	130 (89.0)
Ever diagnosed with OAB? (% of treatment group)	29	25	24	27	34
Ever diagnosed with BPH? (% of treatment group)	53	45	41	53	51

[a]Overall, 54% of subjects averaged ≤3 nocturnal voids, 28% averaged >3–4 nocturnal voids, 11% averaged >4–5 nocturnal voids.

($P < 0.0001$) and 50 μg ($P = 0.02$) (Table II). Significant mean decreases were observed by Day 8 with doses of ≥25 μg ($P = 0.03$, 0.0011, <0.0001, respectively), demonstrating a rapid onset of effect.

When primary endpoints were analyzed by gender (Table II), the mean change in females was significant versus placebo for 100 μg ($P < 0.0001$), 50 μg ($P = 0.009$), and 25 μg ($P = 0.02$). For males, 100 μg was superior to placebo ($P = 0.005$).

TABLE II. Change From Baseline to Final Visit (Day 28) in: Mean Number of Nocturnal Voids, Duration of First Period of Sleep, Nocturnal and Total Urine Volume; Also the Proportion of Subjects With >33% Reduction From Baseline to Final Visit (Day 28) (Responder Rate Is Rate Only, Not a Change Score); All Categories Analyzed Overall and by Gender

	All				Women				Men			
Endpoint	n	mean	SD	*P*	n	mean	SD	*P*	n	mean	SD	*P*
Nocturnal voids												
Pbo	156	−0.86	1.05	—	66	−0.88	1.01	—	90	−0.84	1.09	—
10 μg	155	−0.83	1.07	0.93	73	−1.15	1.07	0.07	82	−0.54	0.99	0.09
25 μg	152	−1.00	1.13	0.31	65	−1.22	1.06	0.02*	87	−0.83	1.15	0.6
50 μg	148	−1.18	1.19	0.02*	71	−1.23	1.06	0.009*	77	−1.13	1.3	0.4
100 μg	146	−1.43	1.22	<0.0001*	66	−1.51	1.14	<0.0001*	80	−1.38	1.28	0.005*
33% Responder rate, n (%)												
Pbo	156	73 (47)	—	—	66	28 (42)	—	—	90	45 (50)	—	—
10 μg	155	73 (47)	—	0.94	73	41 (56)	—	0.09	82	32 (39)	—	0.2
25 μg	152	76 (50)	—	0.55	65	40 (62)	—	0.02*	87	36 (41)	—	0.2
50 μg	148	79 (53)	—	0.27	71	42 (59)	—	0.04*	77	37 (48)	—	0.7
100 μg	146	103 (71)	—	<0.0001*	66	51 (77)	—	<0.0001*	80	52 (65)	—	0.05*
Initial period of undisturbed sleep (minutes)												
Pbo	126	39	89	—	49	37	94	—	77	40	86	—
10 μg	126	51	111	0.36	60	54	117	—	66	48	107	—
25 μg	121	83	106	0.001*	51	113	118	0.0012*	70	61	90	0.18
50 μg	123	85	109	0.0008*	61	98	125	0.0048*	62	72	90	0.07
100 μg	121	107	116	<0.0001*	57	114	130	0.0002*	64	100	103	0.0006*
Urinary volume, nocturnal (ml)												
Pbo	140	−109	246	—	66	−86	278	—	90	−125	219	—
10 μg	137	−164	277	0.078	73	−207	292	0.011*	82	−125	257	0.96
25 μg	144	−224	264	0.0001*	65	−307	276	<0.0001*	87	−163	238	0.15
50 μg	138	−272	296	<0.0001*	71	−257	282	<0.0001*	77	−286	309	0.0029*
100 μg	135	−313	275	<0.0001*	66	−321	239	<0.0001*	80	−306	302	<0.0001*
Urinary volume, total (ml)												
Pbo	139	−155	427	—	66	−127	529	—	90	−176	335	—
10 μg	137	−220	474	0.37	73	−242	481	0.23	82	−200	470	0.86
25 μg	142	−249	429	0.11	65	−350	456	0.019*	87	175	396	0.76
50 μg	137	−264	515	0.16	71	−236	449	0.22	77	290	571	0.49
100 μg	132	−346	543	0.0015*	66	−279	400	0.097	80	−398	631	0.0055*

*Statistically significant difference versus Pbo, $P \leq 0.05$.

TABLE III. Change in N-QoL for Each Reduction of One in Number of Nocturnal Voids and for Each Increase of 1 hr in First Period of Undisturbed Sleep

	Change in N-QoL for each change of 1 in number of nocturnal voids estimate [95% CI]	Change in N-QoL for each change of 1 hr in first period of undisturbed sleep ESTIMATE [95% CI]
Sleep/energy domain	4.25 [3.11; 5.38]*	3.27 [2.52; 4.03]*
Bother/concern domain	5.03 [3.82; 6.24]*	4.05 [3.25; 4.85]*
Total score	4.68 [3.61; 5.75]*	3.68 [2.98; 4.38]*

*Statistically significant ($P \leq 0.05$, 95% CI does not contain 0).

Proportion With >33% Reduction in Mean Number of Nocturnal Voids

The proportion of subjects with >33% reduction in nocturnal voids increased with increasing dose (47–71%) (Table II). The effect was significantly greater versus placebo with 100 μg ($P < 0.0001$) and demonstrated a rapid onset. In females, the effect was significantly greater versus placebo for 100 μg ($P < 0.0001$), 50 μg ($P = 0.04$) and 25 μg ($P = 0.02$); in males, 100 μg was superior to placebo ($P < 0.05$). The results were consistent in both age groups.

The results of all analyses of voiding data are mutually supportive, indicating that the MED for desmopressin orally disintegrating tablets is 100 μg in men and 25 μg in women. Ten micrograms was sub-therapeutic for the co-primary endpoints (Table II).

Diuresis (Volumes)

At Day 28, nocturnal urine volume had decreased in all groups (Table II). Overall reductions were greater in the treatment groups than with placebo, being significant versus placebo ($P < 0.05$) at 25–100 μg. For females the difference was significant at 10–100 μg, and for males at 50–100 μg.

Sleep (Time From Falling Asleep to Waking for First Nocturnal Void)

The initial period of undisturbed sleep increased with desmopressin dose in all groups (Table II). Increases versus placebo were significant at 25, 50, and 100 μg (83, 85, and 107 min, respectively) (Table II). A significant increase was noted at 25–100 μg in females, and 100 μg in males.

QoL

One less nocturnal void was associated with an increase of 4.68 in total N-QoL score (5.03 for bother/concern, 4.25 for sleep/energy; $P < 0.05$) (Table III). Similarly, a 1-hr increase in first period of undisturbed sleep was associated with an increase of 3.68 in total N-QoL (4.05 for bother/concern score, 3.27 for sleep/energy; $P < 0.05$) (Table III). These changes support the notion that reducing nocturia increases QoL.

Safety and Tolerability

AE reporting. Table IV summarizes AE categories by treatment group. The four serious AEs reported were considered unrelated or unlikely to be related to the study drug and none were related to reductions in serum sodium. The incidence of AEs leading to discontinuation was highest in the 50 μg (8%) and 100 μg (9%) groups, primarily as a result of the protocol-defined withdrawal of patients with serum sodium <125 mmol/L. Individual AE terms did not reveal any unexpected findings, with respect to their prevalence. A relation to desmopressin dose was suggested for the following reported AEs: "nausea" (<1% in placebo group vs. 2–5% in desmopressin groups), "diarrhea" (1% vs. 1–6%), "dizziness" (0 vs. 2–4%), "blood sodium decreased" (<1% vs. 1–5%), and "hyponatremia" (<1% vs. 0–6%).

Laboratory serum sodium levels. Overall, 24 patients (3.0%) had serum sodium levels <130 mmol/L during the study. Of these, nine (1.1% of total), including six women and two men on active treatment, had reductions in serum sodium to <125 mmol/L. These drops all occurred within a week of treatment initiation. Patients ≥65 years were more frequently affected than those <65 years (Table V). No woman receiving 25 μg desmopressin had serum sodium <125 mmol/L. No man under the age of 65 years had serum sodium <130 mmol/L.

DISCUSSION

The objectives of this large randomized trial were to investigate whether a new formulation of desmopressin was superior

TABLE IV. Summary of Treatment-Emergent Adverse Events

		Active				
	Placebo	10 μg	25 μg	50 μg	100 μg	Total
n	160	163	158	158	160	799
All AEs, n (%)	76 (48%)	92 (56%)	78 (49%)	92 (59%)	99 (62%)	437 (55%)
Serious AEs, n (%)	1 (<1%)[a]	1 (<1%)[b]	1(<1%)[c]	1 (<1%)[d]	—	4 (<1%)
AEs leading to discontinuation, n (%)	7 (4%)	6 (4%)	2 (1%)	13 (8%)	14 (9%)	42 (5%)
Severe AEs, n (%)	2 (1%)	6 (4%)	3 (2%)	11 (7%)	7 (4%)	29 (4%)
ADRs, n (%)	47 (29%)	55 (34%)	57 (36%)	69 (44%)	73 (46%)	301 (38%)

[a]Prostate cancer.
[b]Diverticulitis.
[c]Myalgia.
[d]Metastasis.

TABLE V. Incidence of Low Serum Sodium During Study, Stratified by Age Group

	Placebo, n (%)		10 μg, n (%)		25 μg, n (%)		50 μg, n (%)		100 μg, n (%)	
Serum sodium (mmol/L)	<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 (100)	76 (100)	85 (100)	78 (100)	80 (100)	78 (100)	82 (100)	76 (100)	75 (100)	85 (100)
125–130	0	1 (1.3)	0	1 (1.3)	0	2 (2.6)	2 (2.4)	5 (6.6)	2 (2.7)	12 (14.1)
<125	0	1 (1.3)	0	0	0	0	2 (2.4)	2 (2.6)	0	4 (4.7)

to placebo for treating nocturia and if the treatment was well tolerated.

Overall, the highest doses of desmopressin gave rapid, clinically relevant, and statistically significant reductions in mean number of nocturnal voids versus placebo. Dose-dependent increases in the proportions of patients achieving >33% reduction in mean number of night voids and decreases in diuresis were also observed. Importantly, desmopressin 25–100 μg was associated with statistically significant increases in duration of initial sleep period versus placebo, which amounted to an additional 44–68 min of uninterrupted sleep per night. The 10 μg dose had a notable (although less pronounced in men) pharmacodynamic effect on nocturnal urine production, but this did not translate into improvement in nocturia over placebo, probably because the lower dose is insufficient to address all factors involved in the etiology of nocturia. Reductions in nocturnal diuresis in the placebo group suggest that patients were following advice to limit fluids and empty their bladder at bedtime.

The safety data obtained in this study are generally consistent with that from studies with the solid desmopressin tablet[14–18] and support previous findings that hyponatraemia is the only safety issue with desmopressin. Age ≥65 years and higher desmopressin dosing are predictors of clinically significant drops in serum sodium. It is therefore recommended that only patients with normal serum sodium at baseline should be treated. Treatment should be discontinued if serum sodium drops below 130 mmol/L. A phase III study is currently investigating doses that provide an optimal risk–benefit profile in elderly males.

A supplemental analysis revealed that females were more sensitive to desmopressin than males. Doses of 25 μg upwards were significantly superior ($P \leq 0.05$) to placebo for both primary efficacy endpoints in females, whereas a statistically significant reduction was only achieved with the 100 μg dose in males. This suggests MEDs of 25 μg for females and 100 μg for males (since results for all analyses are mutually supportive). These doses, which are lower than those required with desmopressin tablets, are supported by the safety analyses, which found no hyponatremia at the MED in women. In males ≥65 years, additional monitoring is recommended on Days 4[19] and 28 following treatment initiation. The reasons for this gender effect are not fully understood. Sex-specific hormonal mechanisms may alter sensitivity to vasopressin, and possibly, also to desmopressin.[20–22] Alternatively, since the relevant vasopressin receptor gene (*AVPR2*) is located on the X chromosome, it is possible that it is one of few X-linked genes to escape X inactivation,[23] meaning females have higher levels of *AVPR2* expression, and increased response to desmopressin than males[24]. This hypothesis requires further investigation.[25]

A decrease of one nocturnal void was associated with a statistically significant increase of ~5 in total N-QoL score. This is a relatively new questionnaire, and the extent of clinically relevant changes in score has not been established. A few studies have indicated differences in N-QoL score of between 2.9 and 11 for each void/night.[4,19,26] Our findings are comparable with these scores.

Nocturia is acknowledged to be a nontrivial condition that can have serious effects on patients' morbidity, mortality and QoL.[27] The findings of this study not only support the efficacy and safety findings of previous studies with desmopressin in nocturia, but also indicate areas of research to further optimize the risk–benefit ratio for the drug in patients of both genders and all ages.

CONCLUSIONS

Desmopressin orally disintegrating tablet is a well-tolerated and effective treatment for nocturia. It prolongs the first sleep period and thereby improves patients' QoL. Early monitoring is recommended in males aged ≥65 years due to increased risk of serum sodium reductions with age and higher dosing. Further risk–benefit analyses are required to confirm the MED findings and any advantages of moving to a lower recommended dose based on them.

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