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Long-Term Durability of the Response to Desmopressin in Female and Male Nocturia Patients

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Aims: To explore the durability of efficacy and gender differences during chronic administration of desmopressin in nocturia. **Methods:** This pooled analysis of three short-term efficacy studies, with extensions, of desmopressin administered as orally disintegrating tablet (ODT) or solid tablet in nocturia treatment, comprised 351 patients completing 40–56 weeks' treatment. Efficacy endpoints of change in number of nocturnal voids and duration of initial undisturbed sleep period from baseline were analyzed to determine response durability and gender differences. **Results:** The mean decrease in number of nocturnal voids during short-term treatment was maintained and further reduced during the long term. At 52 weeks, the mean decrease in number of nocturnal voids from baseline reached 1.4–2.1 voids for desmopressin ODT 25–100 μg. Following 40-week tablet treatment, the decrease in number of nocturnal voids was 0.8–1.5 for desmopressin 100–400 μg. The mean decrease in nocturnal voids (25–50 μg ODT) was greater for females than males. For females, the improvement in initial period of undisturbed sleep was 2.5–3 hr for desmopressin ODT 25–100 μg, compared with 1.3–2.6 hr for males. No gender difference in efficacy was seen in the tablet studies. **Conclusions:** The decrease in nocturnal voids and improvement in sleep with short-term desmopressin treatment were maintained throughout long-term treatment. A durable gender difference in efficacy in favor of females was observed with desmopressin ODT 25 μg. Further, large-scale long-term trials are needed to confirm the durability of efficacy with gender-specific doses of desmopressin. *Neurourol. Urodynam. 32:363–370, 2013.*

Key words: desmopressin; durability; nocturia

INTRODUCTION

The efficacy and safety of desmopressin (ODT or tablet) in the treatment of adults with nocturia have been demonstrated in several randomized trials.[1–4] During open-label extension trials, performed primarily to assess the long-term safety and tolerability of desmopressin over 1 year or longer, the long-term durability of the treatment effect was also measured, and the results largely reflected those of short-term studies.

In order to increase knowledge regarding the durability of desmopressin efficacy during chronic administration in nocturia, we conducted this pooled analysis of three short-term efficacy studies, with long-term extensions. Given recent findings of significant pharmacodynamic gender differences in nocturia patients,[5] we also aimed to investigate the degree to which the higher renal sensitivity to desmopressin in women reflected a further reduction of nocturnal voids and prolongation of the initial sleep period during long-term administration of desmopressin compared with male patients. To our knowledge this is the first evaluation of gender differences in the efficacy of desmopressin in long-term nocturia treatment.

It has been suggested that some reports of long-term improvements in efficacy during chronic administration of desmopressin may have been biased due to early withdrawal of poorly responding patients.[3] Thus, a secondary purpose of this analysis was to compare the long-term durability of desmopressin efficacy in nocturia in all patients with that of patients completing the long-term safety extensions, to determine whether patient withdrawals could explain the previously reported improvements in efficacy over time.

MATERIALS AND METHODS

Studies Included

Randomized clinical trials (RCTs) with open-label extensions that measured long-term efficacy (minimum of 40 weeks of treatment) of desmopressin for the treatment of nocturia in male and female adults without severe comorbidities were identified from Ferring's internal databases.

Three RCTs and their open-label extension studies met these criteria, and were included in the analysis. The studies included data from a phase III two-part, randomized, double-blind, placebo-controlled study of desmopressin in the treatment of nocturia[4] (CS29, ClinicalTrials.gov Identifier: NCT00477490). The objective of part I was to investigate the short-term (4-week) efficacy and onset of effect of desmopressin ODT 10, 25, 50, and 100 μg,[4] while part II and the study extension investigated long-term safety and, for the first time reported in this article, the durability of desmopressin efficacy. Placebo patients from part I were manually re-randomized to a treatment group for part II. Part II ended when the last patient completed part I. Part II therefore lasted 4–24 weeks

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depending on when the patient was included. Participation in the open-label extension (CS31, ClinicalTrials.gov Identifier: NCT00615836) was optional. Following unblinding of part II, it became apparent that the 10 μg dose was sub-therapeutic and patients in this group were randomly assigned to 25, 50, or 100 μg desmopressin at the next study visit. Therefore, data from the 10 μg dose group will not be reported in this article.

Data from two randomized, double-blind, placebo-controlled, phase III studies (NOCT-2-A and NOCT-3-A) assessing the short-term efficacy and safety of desmopressin tablets (100, 200, or 400 μg) in men[1] and women[2] with nocturia were also included in the analysis. After receiving desmopressin or placebo for 3 weeks, patients were eligible to enroll in long-term extension protocols (NOCT-2-B and NOCT-3-B) with study visits after 4, 16, 28, 40, and 52 weeks of treatment.[3] The last clinic visit was 4 weeks after treatment cessation.

The bioavailability of desmopressin ODT is approximately 60% greater than the solid tablet,[6,7] such that desmopressin ODT 60, 120, and 240 μg are clinically bioequivalent to desmopressin solid tablet 100, 200, and 400 μg (Fig. 1).

For an overview of study specifics, see Table I. All studies were approved by the Institutional Review Board or Ethics Committee for each site, the Declaration of Helsinki was followed, and informed consent was obtained from all patients.

Patient Population, ODT Studies

The patient population has been described elsewhere.[4] Briefly, patients were ≥18 years of age, with ≥2 voids per night determined via a 3-day frequency–volume chart during screening, and a serum sodium >135 mmol/l at time of inclusion. Exclusions included urinary retention and/or post-void residual volume >150 ml, 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/benign prostatic hyperplasia (BPH) had been performed within 6 months. Patients on stable doses of overactive bladder (OAB) and/or BPH medication for 3 months could be included.

Patient Population, Tablet Studies

The patient population has been described elsewhere.[1–3] Briefly, patients were ≥18 years of age with nocturia defined as an average of ≥2 voids per night and with nocturia index scores >1, defined as mean nocturnal volume divided by maximum voided volume, measured at any time. Patients were excluded if they had urge incontinence or other voiding dysfunction, had received treatment with drugs known or suspected to interact with desmopressin (e.g., diuretics, tricyclic antidepressants, indomethacin, carbamazepine, or chlorpropamide), had uncontrolled hypertension or had evidence of clinically relevant cardiac failure.

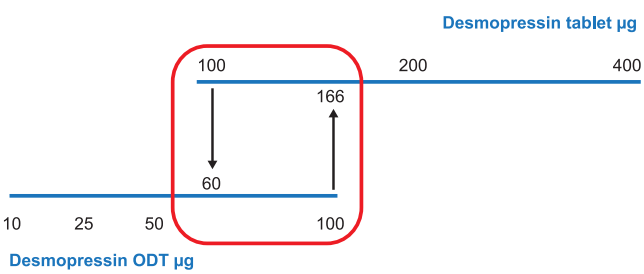

Fig. 1. Bioequivalent dose levels of desmopressin ODT and tablet.

Safety and Tolerability

All subjects who received ≥1 dose of the study drug or placebo and had ≥1 safety assessment were included in the safety analyses. Safety and tolerability were monitored via observation and assessment of adverse events (AEs). AEs were coded by system organ class and preferred term using MedDRA. AEs were recorded from the day of informed consent.

Study Procedures

Diaries and questionnaires. In all studies, patients completed voiding and sleep diaries to record the time and volume of voids and the initial period of undisturbed sleep (time from falling asleep to first nocturnal void).

Endpoints and statistical analysis. Data from all ODT and tablet studies outlined above were combined by formulation type for the efficacy analysis. The durability of desmopressin efficacy over time was summarized by effect on changes from baseline in mean number of nocturnal voids, proportion of patients with >33% and >50% reduction in mean number of nocturnal voids from baseline, and changes in initial period of undisturbed sleep from baseline, overall and stratified by gender. Summarized data are reported as mean ± standard deviation (SD).

Patients receiving placebo or the sub-therapeutic 10 μg dose were excluded from this analysis as insufficient long-term data were available. In ODT trials, missing values from patients who discontinued before Week 4 were imputed using last observation carried forward (LOCF) for the results from the short-term study and these values were used to calculate results from all patients. Observed cases provided similar results as LOCF. In tablet studies, there were no intermediate diaries in the 3-week short-term period, and thus only observed cases were reported. For the study extensions only observed cases were reported.

No formal statistical testing was done comparing desmopressin ODT with tablet since the studies were deemed too different in design, dosing, frequency of efficacy measurements and follow-up time. Any comparison is therefore based on descriptive statistics, supplemented by visual evaluation of the graphs.

SAS version 9.1.3 service pack 4 was used.

RESULTS

Patient Disposition

ODT. A total of 799 patients were randomized, and the intention-to-treat (ITT) population included 757 patients (Table I). Excluding the sub-therapeutic 10 μg dose, 565 patients completed part I, of whom 529 continued into part II. The most common reasons for discontinuation were withdrawal of consent (4%), AEs (2%), and loss to follow-up (2%). 408/529 patients joined the open-label extension, and 248 patients provided data on number of nocturnal voids after 52 weeks of treatment (Table II).

Tablet. Of the patients completing the short-term studies 249 patients (132 of 143 males [92%] and 117 of 141 females [83%]) were enrolled into the long-term extension and received at least one dose of desmopressin (Table I). A total of 98 patients (56 male and 42 female patients) provided data on

TABLE I. Overview of Trials, Patients, and Treatments Included in This Analysis

Study	Number of subjects	Treatments	Duration of exposure
RCT: CS29 ClinicalTrials.gov Identifier: NCT00477490; open-label extension: CS31; ClinicalTrials.gov Identifier: NCT00615836	757 ITT subjects; 268[a] females; 333[a] males; 248 patients provided data on number of voids after 52 weeks of treatment[a]	Placebo; desmopressin administered as ODT (10[a], 25, 50, or 100 μg). Following analysis of the short-term double-blind phase, subjects were unblinded, and those receiving 10 μg were randomly assigned to one of the three higher doses at their next regularly scheduled visit	Short-term: 4 weeks; long-term extension: 52 weeks
RCT: Noct 2A; open-label extension; Noct 2B	Of 143 male patients completing the short-term study (NOCT-2-A), 132 were enrolled into the long-term study (NOCT-2-B); 56 patients provided data on number of voids after 40 weeks of treatment	Placebo; desmopressin administered as tablet (100, 200, or 400 μg)	Short-term: 3 weeks; long-term extension: 40 weeks (52 weeks extension for a subset of patients)
RCT: Noct 3A; Open-label extension; Noct 3B	Of 141 female patients completing the short-term study (NOCT-3-A), 117 were enrolled into the long-term study (NOCT-3-B); 42 patients provided data on number of voids after 40 weeks of treatment	Placebo; desmopressin administered as tablet (100, 200, or 400 μg)	Short-term: 3 weeks; long-term extension: 40 weeks (52 weeks extension for a subset of patients)

ODT, orally disintegrating tablet.
[a]Excluding patients receiving 10 μg desmopressin ODT.

number of voids after 10 months of treatment (Table II). Overall, 37 males (28%) and 30 females (26%) withdrew from long-term treatment.[3]

Long-Term Durability

ODT. Among nocturia patients who remained on desmopressin ODT treatment for 52 weeks, the mean decrease in the number of nocturnal voids steadily increased over time and at the end of the follow-up period reached 1.4 voids in the 25 μg group, 1.8 voids in the 50 μg group, and 2.1 voids in the 100 μg group (Table II, Fig. 2). The overall proportions of patients with >33% reduction in nocturia at 52 weeks were 74% (25 μg), 73% (50 μg) and 88% (100 μg), and the proportions of patients with >50% reduction in nocturia at 52 weeks were 36% (25 μg), 53% (50 μg), and 71% (100 μg; Table III).

The initial period of undisturbed sleep at 52 weeks compared with baseline increased by approximately 2 hr (25, 50 μg) and 2.8 hr (100 μg; Table III). These results indicate that efficacy was maintained (and in some cases increased) after long-term treatment compared with short-term (Table II). Long-term efficacy was generally similar when stratified by age (data not shown).

Tablet. For nocturia patients who remained on desmopressin tablet treatment for 40 weeks, the mean decrease in the number of nocturnal voids was 0.8, 1.5, and 1.5 voids in the 100, 200, and 400 μg group, respectively (Table II, Fig. 3).

The overall proportion of patients with >33% reduction in nocturia compared with baseline was >50% for all tablet strengths (Table III). The initial period of undisturbed sleep at 40–52 weeks increased by approximately 1.1 hr (100 μg) and 2.3 hr (200 and 400 μg; Table III).

Following the 4-week treatment-free period at the end of the tablet studies, the overall mean number of nocturnal voids increased to 2.4, a difference of −0.5 voids compared with baseline (Table II). Thus, cessation of treatment was associated with an increase in the number of nocturnal voids and a return towards baseline values; however, patients in the 200 and 400 μg groups did not experience a complete relapse and maintained a small reduction relative to baseline values (Table II).

Comparing All Patients to Completers of the Long-Term Follow-Up

Comparing the change in number of nocturnal voids from baseline over time between all patients in a given dose group and those patients who completed the long-term open-label studies, no clinically relevant difference in treatment efficacy was observed (Fig. 2 (desmopressin ODT) and Fig. 3 (desmopressin tablet)).

Gender Difference

The mean decrease in number of nocturnal voids was greater for females than males at the lower doses of desmopressin ODT 25 and 50 μg at all times during the entire study duration (Fig. 2). No gender difference was found in mean decrease in number of nocturnal voids for those receiving desmopressin ODT 100 μg. In the tablet studies, no gender difference in mean decrease in number of nocturnal voids was seen at any dose level (Table III, Fig. 3).

For females receiving desmopressin ODT 25–100 μg the increase in initial period of undisturbed sleep was 2.4–3 hr, whereas for males the increase was 1.3 hr (25 μg), 1.8 hr (50 μg), and 2.6 hr (100 μg; Table III).

At the lower dose levels of desmopressin ODT (25 and 50 μg) a clear gender difference was observed in the proportion of patients with >33% and >50% reduction in the mean number of nocturnal voids from baseline, whereas at higher doses (desmopressin ODT 100 μg and all tablet doses) no gender difference in the proportion of patients with >33% and >50% reduction in the mean number of nocturnal voids from baseline was seen.

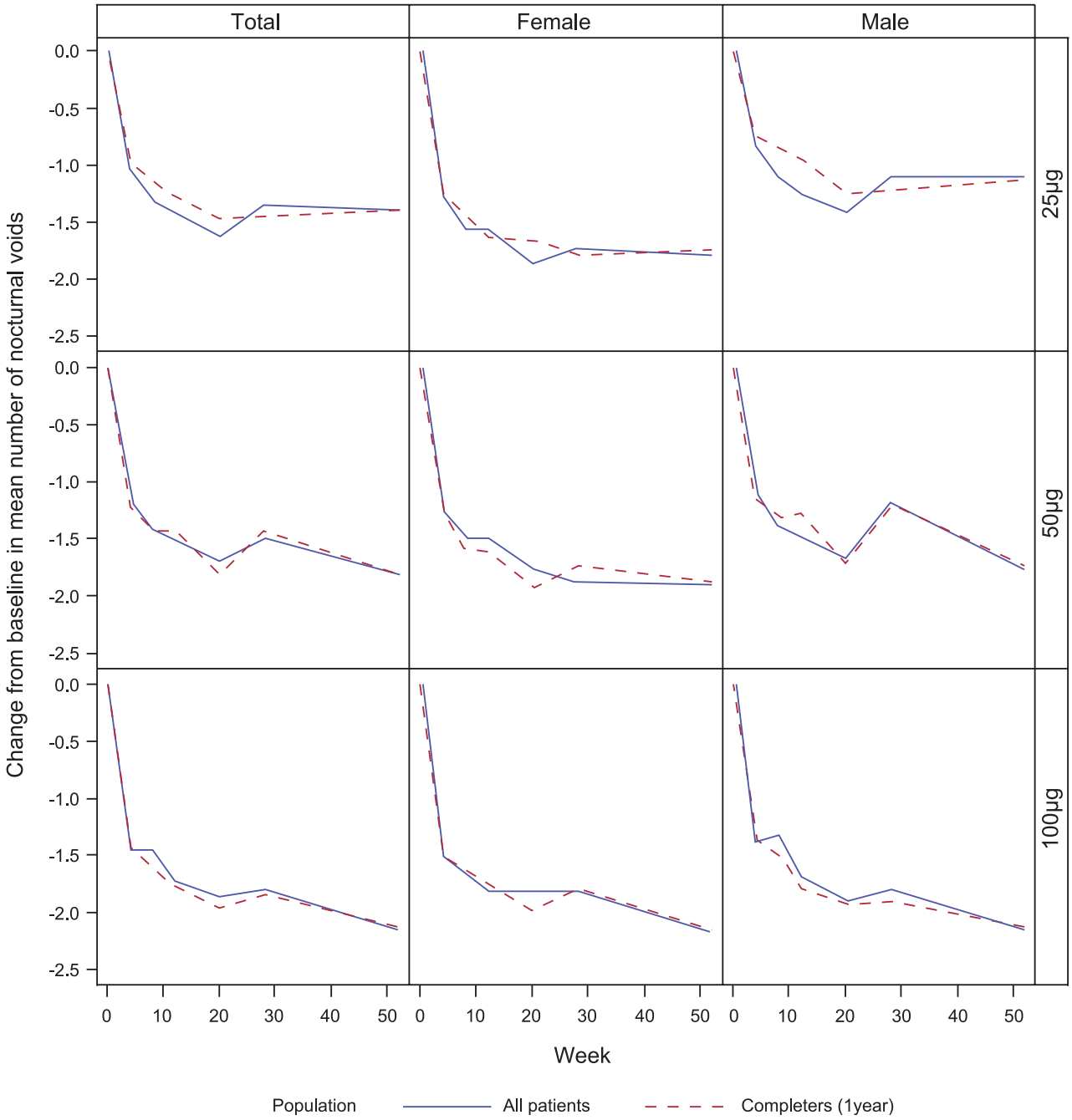

Fig. 2. Change from baseline in the mean number of nocturnal voids in all patients and patients completing long-term treatment (up to 12 months) receiving desmopressin ODT 25, 50, and 100 µg, reported stratified by gender and total.

Long-Term Safety

Desmopressin was well tolerated during long-term exposure (Table IV). The frequency and type of adverse events was similar to those in short-term studies.[1,2,4]

DISCUSSION

Our analysis has shown that the decrease in number of nocturnal voids and improvement in sleep observed with short-term desmopressin treatment were maintained for the full duration of treatment, with an indication of increasing efficacy with increasing time on treatment. A dose–response relationship was seen with the ODT formulation, which was less pronounced with the tablet. A gender difference in efficacy in favor of females was observed with desmopressin ODT 25 µg, which persisted over time.

One of the objectives of this pooled analysis of long-term efficacy data from trials in nocturia patients was to investigate whether the reduction in the number of night-time voids with both oral formulations of desmopressin achieved during short-term treatment (3–4 weeks) was maintained

TABLE II. Baseline Number of Nocturnal Voids and Change From Baseline Post-Treatment

Treatment	Placebo ODT		25 μg ODT		50 μg ODT		100 μg ODT	
Period	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline week 0	156	3.3 (1.16)	152	3.3 (1.32)	147	3.4 (1.07)	146	3.2 (1.10)
Change from baseline (number of nocturnal voids)								
Week 4	156	−0.9 (1.05)	152	−1.0 (1.13)	147	−1.2 (1.19)	146	−1.4 (1.22)
Week 8			96	−1.3 (1.18)	91	−1.4 (1.28)	104	−1.5 (1.08)
Week 12			81	−1.4 (1.25)	76	−1.5 (1.16)	81	−1.7 (1.04)
Week 20			58	−1.6 (1.17)	63	−1.7 (1.17)	64	−1.9 (1.08)
Week 28			85	−1.4 (1.14)	61	−1.5 (1.28)	62	−1.8 (0.90)
Week 52			91	−1.4 (1.22)	80	−1.8 (1.33)	77	−2.1 (1.11)

Treatment	Placebo tablet		100 μg tablet		200 μg tablet		400 μg tablet	
Period	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	133	3.0 (1.10)	28	3.0 (0.91)	54	2.9(0.75)	73	3.0(0.88)
Change from baseline (number of nocturnal voids)								
Washout	133	−0.3 (0.77)	28	−0.1 (0.78)	54	−0.3 (0.65)	72	−0.4 (0.63)
Double-blind	133	−0.5 (0.84)	28	−1.1 (0.61)	54	−1.4 (0.72)	73	−1.3 (0.72)
Week 4			20	−1.1 (0.56)	42	−1.6 (0.93)	59	−1.5 (0.76)
Week 16			17	−1.1 (0.45)	43	−1.6 (0.77)	57	−1.5 (0.70)
Week 28			13	−1.0 (0.74)	40	−1.4 (0.69)	50	−1.6 (0.74)
Week 40			13	−0.8 (0.83)	37	−1.5 (0.82)	48	−1.5 (0.80)
Week 52			5	−1.0 (1.32)	27	−1.6 (0.72)	27	−1.8 (0.80)
Treatment-free			12	0.0 (1.30)	34	−0.5 (0.87)	47	−0.6 (1.56)

during long-term treatment.[3,4] In general, open-label extension studies create challenges in data analysis and interpretation, particularly with regard to the fact that the characteristics of the study participants who chose to continue may differ significantly from the individuals who drop out of the trial.[8] Also, patients in placebo-controlled RCTs may report improved efficacy following enrollment in the open-label phase, knowing that they now receive active treatment. Furthermore, nocturia severity fluctuates over time,[9] and spontaneous alleviation of symptoms may occur in some patients, negating the requirement for long-term treatment. However, none of these valid issues fully explain why efficacy not only endured but also improved further with increasing dose and time on treatment. Also, the decrease in nocturnal voids for all patients and for patients who completed the long-term study was not different (Figs. 2

TABLE III. Changes From Baseline for Patients Completing Long-Term Treatment With Desmopressin ODT (52–56 Weeks) and Tablet (40 Weeks), in Total and by Gender

	Desmopressin ODT						Desmopressin tablet					
	25 μg		50 μg		100 μg		100 μg		200 μg		400 μg	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Mean decrease in number of nocturnal voids												
All	91	−1.4 (1.22)	80	−1.8 (1.33)	77	−2.1 (1.11)	13	−0.8 (0.83)	37	−1.5 (0.82)	48	−1.5 (0.80)
Males	51	−1.1 (1.24)	48	−1.7 (1.58)	39	−2.1 (0.86)	10	−0.9 (0.91)	18	−1.7 (0.74)	28	−1.5 (0.83)
Females	40	−1.7 (1.13)	32	−1.9 (0.86)	38	−2.1 (1.33)	3	−0.7 (0.66)	19	−1.4 (0.88)	20	−1.6 (0.77)
Proportion of patients with >33% reduction in nocturia (%)												
All	91	74	80	73	77	88	13	54	37	81	48	75
Males	51	63	48	63	39	87	10	50	18	89	28	79
Females	40	88	32	88	38	89	3	67	19	74	20	70
Proportion of patients with >50% reduction in nocturia (%)												
All	91	36	80	53	77	71	13	23	37	57	48	60
Males	51	29	48	46	39	69	10	30	18	56	28	61
Females	40	45	32	63	38	74	3	0	19	58	20	60
Mean increase in initial period of undisturbed sleep (min)												
All	88	111 (114)	74	124 (128)	71	168 (118)	13	66 (66)	37	134 (119)	48	141 (118)
Males	50	79 (99)	43	108 (115)	35	155 (105)	10	69 (72)	18	143 (116)	28	126 (110)
Females	38	152 (119)	31	146 (144)	36	181 (130)	3	55 (48)	19	125 (125)	20	161 (128)

ODT, orally disintegrating tablet.

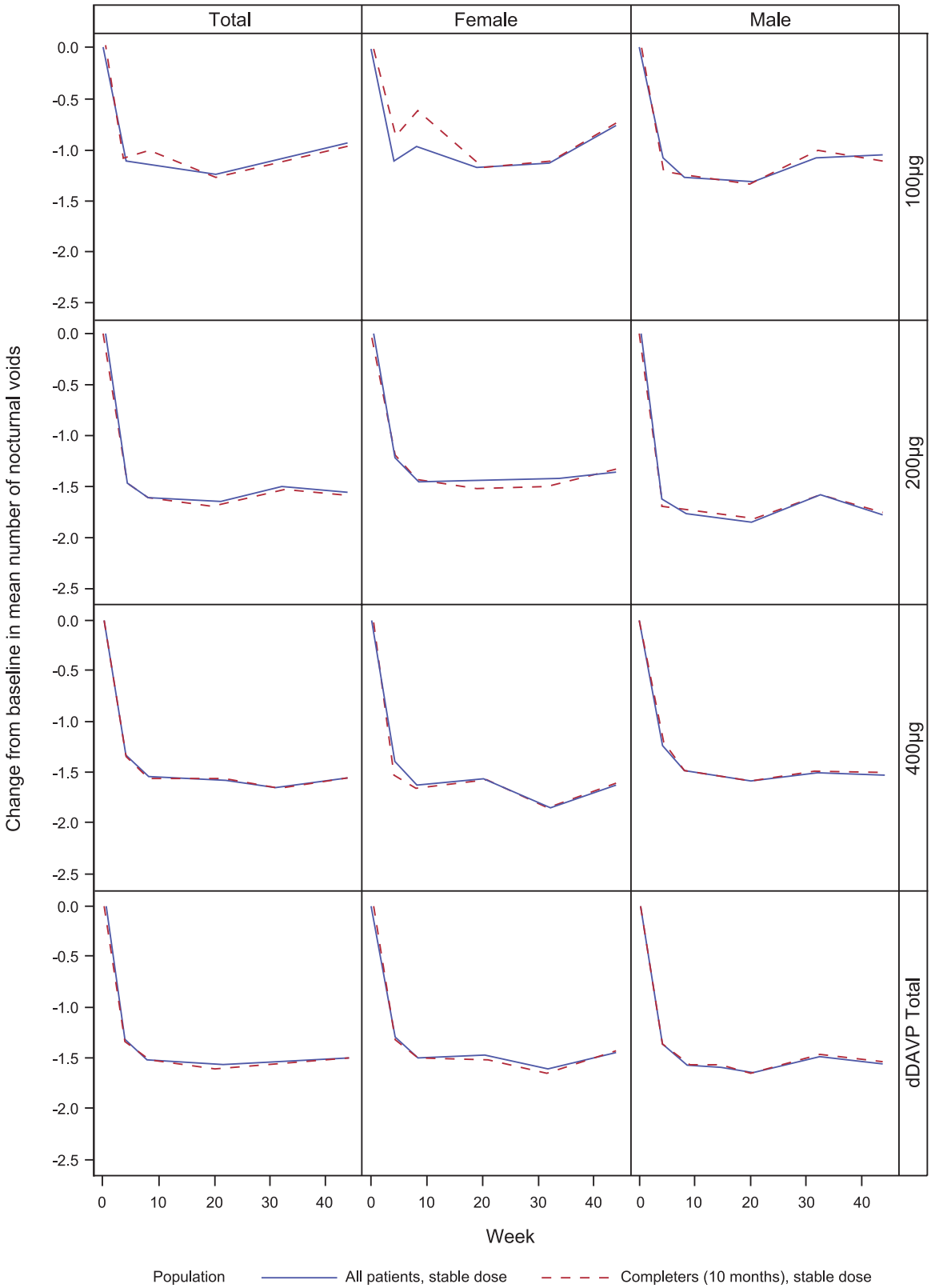

Fig. 3. Change from baseline in the mean number of nocturnal voids in all patients and patients completing long-term treatment (up to 10 months) receiving desmopressin tablet 100, 200, 400 µg and all doses combined, reported stratified by gender and total.

TABLE IV. Summary of Common (≥5% of Patients in Any Treatment Group) Treatment-Emergent Adverse Events During Long-Term Treatment With Desmopressin ODT and Tablet

	Desmopressin ODT		Desmopressin tablet	
Adverse events	Males (%)	Females (%)	Males (%)	Females (%)
Abdominal pain			6	9
Accident/injury			5	9
Arthralgia			5	7
Back pain	9	6	5	9
Bronchitis	5	8	5	2
Cough	5	8		
Diarrhea	2	5		
Dizziness			6	5
Dry mouth[a]	18	13		
Gastroesophageal reflux disease	3	6		
Headache	5	11	6	15
Hypertension	7	12	5	3
Influenza like symptoms	5	3	9	10
Insomnia	4	5		
Nasopharyngitis	7	10		
Nausea	3	5	2	5
Peripheral edema			2	5
Pharyngolaryngeal pain	<1	5		
Sinusitis	7	10		
Upper respiratory tract infection	6	17	8	21
Urinary tract infection	4	13		

Incidences <5% in given trial are not reported.
[a]A specific question regarding dry mouth, in addition to a standard non-leading question was used in the desmopressin ODT trials only.

and 3), indicating that the efficacy increase over time was not due only to high responders completing the long-term follow-up and patients with lack of effect withdrawing from treatment.

The initial period of undisturbed sleep was 2.4–3 hr, increasing by 1.3–2.6 hr depending on dose. The clinical relevance of prolongation of undisturbed sleep is supported by quality of life (QoL) data. A 1-hr increase in the first period of undisturbed sleep has been associated with a significant increase in QoL scores.[4]

The long-term durability of desmopressin efficacy in nocturia is sparsely described in the scientific literature, thus confirming the need for this analysis. Although the multiple sclerosis (MS) patient population is clinically very different from the population in our analysis, our findings are, with some caution, supported by a report in 19 MS patients reporting continued benefit from desmopressin treatment for their nocturia symptoms without any "wearing off."[10] Another analogous observation was made in a review of several pediatric studies evaluating long-term use of desmopressin in primary nocturnal enuresis, indicating that desmopressin efficacy improved steadily and that long-term treatment may accelerate cure rates compared to the spontaneous cure rate of 15% annually.[11] Thus, our results, supported by findings in similar indications, underline that additional clinical relief of nocturia symptoms can be expected with persistence in antidiuretic treatment.

Desmopressin tablets and desmopressin ODT are considered to be clinically bioequivalent at doses of 200/400 μg for the tablet and 120/240 μg for the ODT formulation.[7] However, in this analysis the increased short-term and long-term reduction of nocturnal voids with desmopressin ODT compared with desmopressin tablet were achieved at much lower doses of 25–100 μg. This suggests a difference between the two formulations in clinical efficacy, at least in certain real-world clinical circumstances. One possible reason could be less interference of nutrition with desmopressin ODT compared with the tablet as recently suggested, resulting in more stable exposure to desmopressin and thus a prolonged and more predictable duration of antidiuretic action.[12,13] We speculate that differences in exposure to desmopressin may influence long-term alterations in the hormonal control of water homeostasis,[14] thereby providing greater efficacy with time. Prolonged changes in hydration status trigger adaptational changes, modulating the acute response to V2 receptor stimulation and abundance of aquaporin-2 (AQP2) in the kidney.[15] Furthermore, recent animal research suggests that desmopressin influences the long-term regulation of AQP2.[16]

Following the 4-week treatment-free period at the end of the desmopressin tablet studies, the number of nocturnal voids increased, as expected, but remained 0.5 voids below baseline. Thus, cessation of treatment was associated with a return of nocturnal voids towards baseline values, but not a complete relapse. Whether this is due to long-term alterations in hormonal control of water homeostasis under the influence of desmopressin[14] remains to be investigated. Even if the prevalence of nocturia generally increases over time and with increasing age, nocturia by natural history shows considerable fluctuation; in older men fluctuation may be as high as 21.6–51.2% after approximately 2 years.[9] In contrast, in a long-term study of 15 elderly male patients with severe nocturia (>3 voids per night), voiding symptoms and nocturnal urine production returned to baseline levels after stopping desmopressin tablet treatment.[17] Further exploration is needed to determine the optimal duration of desmopressin treatment and which patients with nocturia require chronic treatment. Studies measuring time to return of symptoms following cessation of treatment in matched cohorts to account for fluctuation of nocturia symptoms over time are required to support recommendations of optimal treatment duration.

In our analysis no significant dose-related differences were observed with the tablet in long-term efficacy, confirming earlier reports.[3,18] We suggest that this lack of a clear dose–response is due to reaching the upper asymptote of the dose–response curve with doses above 100 μg desmopressin tablet, a relatively high dose, especially for female patients, considering the recently reported significant pharmacodynamic gender differences in sensitivity to desmopressin's antidiuretic action in nocturia patients.[5] In contrast, gender differences in the response to desmopressin ODT were clearly seen with the 25 μg dose during the 52-week follow-up period. Thus, the increased female renal sensitivity to desmopressin previously observed with the 25 μg ODT dose seems to be a durable effect, and translates into the clinically relevant endpoints of reduction in number of nocturnal voids, proportion of responders and increased duration of initial sleep period.[5] Our findings are in accordance with previous modeling of pharmacokinetic and pharmacodynamic data that revealed a 2.7 male/female dose ratio for desmopressin's antidiuretic effect and a suggestion of an optimal dose of 25 μg desmopressin ODT for treatment of female nocturia patients, and an estimated 67 μg desmopressin ODT as the optimal dose for treatment of male nocturia patients.[5] The reasons for this gender effect are not fully understood and require further investigation. Possible explanations include sex hormones altering the sensitivity to vasopressin and desmopressin,[19–21] and vasopressin receptor (V2) receptor density, since the vasopressin receptor gene (AVPR2) is located on the X chromosome and

may escape X inactivation.[22] Thus, females may have higher levels of V2 receptor expression than males, thereby increasing their response to desmopressin.[23]

The long-term data presented here demonstrate that good tolerability was maintained over the longer term as previously reported.[3] As patients were specifically queried about dry mouth in the desmopressin ODT study, it is not unexpected that this was a common AE, with high incidence in the placebo as well as desmopressin groups. Desmopressin ODT has a good long-term safety profile, and offers an effective and well-tolerated treatment for chronic nocturia.

Due to eligibility criteria applied in the studies in our analysis, the durability of desmopressin efficacy in nocturia cannot be claimed in all patient groups. In particular, men who underwent surgery for BPH within 6 months of the study, or those with evidence of BOO or urine flow <5 ml/sec were excluded. Therefore this analysis does not support the use of desmopressin in patients with severe prostate-driven nocturia.

In summary, our findings on the long-term durability of desmopressin efficacy support gender-specific dose recommendations. However, further large-scale long-term trials are needed to confirm that desmopressin ODT 25 μg in female nocturia patients and the 50–100 μg dose range in male nocturia patients offer a beneficial gender-specific therapeutic window, maintaining the durability of long-term treatment efficacy with a lower risk of dose-related safety issues such as hyponatremia.

CONCLUSIONS

The mean decrease in the number of nocturnal voids and increase in initial undisturbed sleep period that were observed with short-term desmopressin ODT treatment were maintained throughout the full duration of the open-label study, with an indication of larger mean decreases in the number of nocturnal voids with increasing time on treatment. In the desmopressin tablet studies the mean decrease in number of nocturnal voids with increasing time on treatment were less pronounced compared with those seen with the ODT formulation. Lower doses of desmopressin, as supported by recent gender-specific sensitivity findings, favored females in terms of the long-term efficacy of desmopressin ODT 25 μg, offering the prospect of an improved therapeutic window in female nocturia patients; maintaining durability of efficacy with lower risk of dose-related safety issues.

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