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DESMOPRESSIN ORALLY DISINTEGRATING TABLET EFFECTIVELY REDUCES SYMPTOMS OF NOCTURIA AND PROLONGS UNDISTURBED SLEEP IN PATIENTS WITH NOCTURIA: RESULTS OF A RANDOMIZED PLACEBO-CONTROLLED STUDY

Hypothesis / aims of study
Nocturia, the need to wake at night to void, is one of the most bothersome of the lower urinary tract symptoms (LUTS) (1). It is a major cause of sleep disturbance in adults (2) and is associated with poor quality of life, functioning and health. Key urological causes of nocturia include overproduction of urine at night (nocturnal polyuria [NP]) and reduced bladder storage capacity (e.g. due to overactive bladder [OAB] or benign prostatic hyperplasia [BPH]). Up to 88% of nocturia cases are at least partially attributable to NP (3). Desmopressin, a synthetic analogue of the antidiuretic hormone AVP, is an effective and generally well-tolerated treatment for nocturia in adults with NP. This study investigates 4 doses of a new orally disintegrating formulation of desmopressin in adults with nocturia, aiming to investigate: 1) efficacy and impact on sleep, 2) safety and tolerability, and 3) baseline characteristics that may affect treatment success in patients with/without additional LUTS (OAB/BPH).

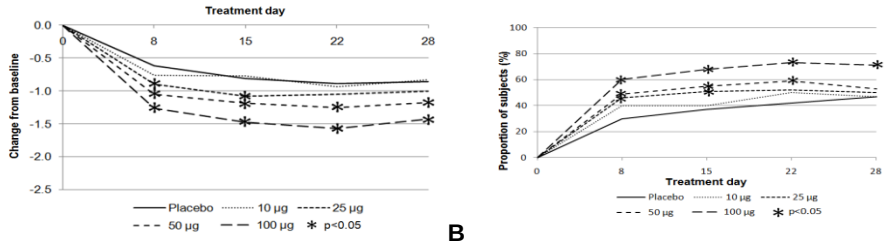
Study design, materials and methods
Adults with an average of ≥2 voids/night and a serum sodium >135 mmol/L were recruited from 78 study centers in the USA and Canada. In Part I (28 days), subjects received in a double-blind, parallel design placebo or desmopressin (10, 25, 50 or 100 µg) administered orally ~1 hour before bedtime. In Part II (1–6 months), subjects on desmopressin continued the same treatment while subjects on placebo were re-randomized to one of the active groups. On completing Part II (blind maintained), subjects could join an open-label extension (ongoing; 1-year data included) on the same dose. Co-primary endpoints of Part I were the change in mean number of nocturnal voids from baseline to final visit (Day 28) and the proportion of subjects with >33% reduction in the mean number of nocturnal voids from baseline to Day 28. In Part I, efficacy was assessed weekly using 3-day voiding-frequency diaries. Durability of effect was assessed at intervals in Part II and the extension. Secondary endpoints included change in initial period of undisturbed sleep, defined as the time from sleep onset until the first void, and assessed using 3-night sleep diaries completed at baseline and Day 28 (Part I), monthly (first 2 months) then every other month (Part II) and 6 monthly (extension). Treatment differences were analyzed by ANCOVA with change from baseline as the outcome (dependent) variable – age, NP, treatment group and baseline (covariate) were independent variables. Safety was assessed by monitoring AEs and analyzing serum sodium (including early sampling on Day 4) throughout the study. Baseline demographics and voiding characteristics were summarized for 5 groups: all randomized subjects (n=799), those who received concomitant treatment for OAB only (n=54), BPH only (n=74), OAB and BPH (n=15), OAB, BPH or both conditions (n=143), and no concomitant treatment (n=656). Exploratory 1st co-primary endpoint analysis was done by subgroup for the purpose of criterion validation (50 and 100 µg doses only).

Results
799 subjects were randomized to treatment and dosed –these formed the safety population; 757 subjects received ≥1 dose and had ≥1 post-baseline efficacy observation – these formed the intent to treat (ITT) population. 710 (89%) subjects completed Part I. 665 subjects continued into Part II and 508 entered the extension. 367 subjects had ≥1 year of exposure. Approximately 20% of patients (143/799) received concomitant treatment for OAB, BPH or both conditions. NP was present in the vast majority of patients across all groups (range 87–93%), regardless of whether OAB, BPH or both conditions were present. Desmopressin ≥25 µg reduced the mean number of nocturnal voids within 1 week of treatment (Figure 1A). A dose-response trend was evident in the overall study population; the difference between placebo and the 50 and 100 µg doses was significant ($p<0.05$) at the primary endpoint (Day 28) but the 25 µg dose, while exerting some clinical effect, was not significant. The 10 µg dose was sub-therapeutic. Similar results were obtained for the co-primary endpoint 33% responder rate (Figure 1B). The exploratory analyses suggested that in patients with OAB, BPH or both conditions, desmopressin reduces nocturia to the same extent as in patients without these conditions (mean 1.3 void reduction).Treatment efficacy was maintained beyond Part I. At 1 year, the mean decrease in the number of nocturnal voids was 1.4 (3.4 at baseline), 1.8 (3.4 at baseline) and 2.1 (3.2 at baseline) for 25, 50 and 100 µg, respectively. Table 1 summarizes the ITT analysis of change in initial period of undisturbed sleep in Part I and for those providing data at 1 year. Table 2 summarizes key safety data. Hyponatremia tended to occur early in treatment (usually during the first week), and at similar rates to placebo in lower dose groups (≤25 µg), but increased ≥50 µg. Ten of the 12 subjects with s serum sodium level <125 mmol/L at anytime during the study were ≥65 years.

Interpretation of results
In adults with nocturia, desmopressin in doses ≥25 µg was effective in significantly reducing nocturia and the effect was rapid and durable. A clear dose-response effect was observed. Duration of the initial period of undisturbed sleep was significantly prolonged ≥25 µg. Compared with placebo a mean of up to 1 hour was gained during Part I, extending the initial period of undisturbed sleep to ~4 hours which may increase the period of deep slow-wave restorative sleep. Desmopressin was generally well tolerated. Early sodium monitoring in elderly patients should be undertaken. The validity of using antidiuretic therapy in nocturia related to nocturnal polyuria, also in the presence of OAB/BPH, was confirmed.

Concluding message
Treatment of nocturia must aim to address NP in addition to normalizing bladder storage capacity. Desmopressin orally disintegrating tablet reduces nocturia and prolongs the important initial period of undisturbed sleep in adults with nocturia.

Figure 1: (A) Change in mean number of nocturnal voids with 4 doses of desmopressin orally disintegrating tablet compared with placebo (ITT; n=757); (B) Proportion of subjects with >33% reduction from baseline to final visit (Day 28) in mean number of nocturnal voids



A **B**

Table 1: Baseline values and change from baseline (min) to Day 28 in initial period of undisturbed sleep and results for those with 1-year data

	Placebo	**10 µg**	**25 µg**	**50 µg**	**100 µg**
Baseline (all; n=715)	117	117	114	111	114
Change from baseline					
Part I (all; n=617)	39	51	83*	85**	107***
1 year (all; n=264)	N/A	121	119	126	161

Mean; *p<0.01, **p<0.001, ***p<0.0001 vs placebo

Table 2: Overall AE rates and 'Hyponatremia'; Part I and Part II + extension (in parenthesis)

	Placebo	**Desmopressin orally disintegrating tablet (µg)**			
		10	25	50	100
Incidence (%)	n=160	n=163 (135)	n=159 (135)	n=157 (132)	n=160 (127)
Any AE	48	56 (76)	49 (74)	59 (82)	62 (83)
Serious AE	<1	<1 (7)	<1 (3)	<1 (8)	0 (8)
AE withdrawal	4	4 (4)	1 (6)	8 (8)	9 (6)
'Hyponatremia'	<1	0 (2)	<1 (<1)	5 (3)	6 (4)

Note: Part I is 4 weeks for both placebo and active treatment; Part II and extension includes all patients continuing on active treatment (i.e. re-randomized placebo patients are excluded for purity of sample); exposure is ≥1 year.

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Specify source of funding or grant	**Funded by Ferring Pharmaceuticals**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**The study was registered on www.clinicaltrials.gov (NCT00477490, NCT00615836)**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Study was approved by the institutional review board or ethics committee for each site**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**