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ORIGINAL ARTICLE

Low-dose Desmopressin and Tolterodine Combination Therapy for Treating Nocturia in Women with Overactive Bladder: A Double-blind, Randomized, Controlled Study

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Objective: Evaluation of safety and efficacy of desmopressin/tolterodine combination therapy in women.
Methods: This double-blind, randomized, proof-of-concept study enrolled 106 patients (≥18 years), with overactive bladder (OAB) and nocturia, with ≥2 nocturnal voids, receiving a 3-month once-daily combination (desmopressin 25 µg, orally-disintegrating tablets [ODT]/tolterodine 4 mg [Detrol® LA]; $n = 49$) or monotherapy (tolterodine 4 mg/placebo ODT; $n = 57$). Primary endpoint was change from baseline in mean number of nocturnal voids. Secondary endpoints were change from baseline in nocturnal voided volume, time to first nocturnal void, and quality-of-life. *Post-hoc* exploratory analysis were performed for patients with and without baseline nocturnal polyuria (NP, $n = 47$ each).
Results: Overall population showed a non-significant reduction in mean number of nocturnal voids with combination *versus* monotherapy (full analysis set: adjusted treatment contrast [TC], −0.34; $P = 0.112$). Change in mean nocturnal void volume (TC, −64.16 mL; $P = 0.103$), mean time to first nocturnal void (TC, 18.00 min; $P = 0.385$) and Nocturia Impact (NI) Diary© scores were comparable. In *post-hoc* analysis, NP patients showed a benefit with combination *versus* monotherapy for nocturnal void volume ($P = 0.034$) and time to first nocturnal void ($P = 0.045$), and a non-significant improvement in NI Diary© scores. Safety profile was comparable between treatments. A single transient event of asymptomatic clinically significant hyponatremia in combination group resolved subsequently.
Conclusion: Low-dose desmopressin could be safely combined with tolterodine for treating nocturia in women with OAB, with a significant benefit in women with NP. Further, prospective validation studies of combination therapy are warranted in mixed NP/OAB population, based on this favorable proof-of-concept finding.

Key words antimuscarinics, desmopressin, nocturia, overactive bladder, tolterodine

1. INTRODUCTION

Overactive bladder (OAB) is characterized by urgency, with or without urge urinary incontinence, usually with frequency and nocturia.[1] More than 70% of women with OAB are bothered by nocturia,[2] and nearly 40% experience an average of two or more voids every night.[3] Of late, the impact of nocturia on chronic sleep disruption is being increasingly recognized, both in terms of effect on quality-of-life (QoL),[4] and long-term morbidity and mortality outcomes.[5] However, patients with OAB and nocturia are often treated with antimuscarinics or anticholinergics, which mostly address the day-time symptoms such as urgency, frequency and incontinence due to bladder overactivity but do not reduce nocturia frequency,[6−9] especially nocturia due to nocturnal polyuria (NP), which is the case in >60% of the patients with OAB.[10,11] Even among those without NP, a reduction of only 0.18 nocturia episodes per night compared with placebo was demonstrated – this was reported to be a statistically significant difference, though its clinical significance is questionable. There is some evidence that anticholinergics have greatest, though still modest effect in patients with significant urgency-related nocturia but without NP.[12] Therefore, it is important to explore the treatment options that address both day-time and night-time symptoms in these patients.

Combination pharmacotherapy for lower urinary tract symptoms (LUTS) is a well-accepted concept for a number of conditions, often using agents that address different mechanisms of actions.[13−15] Using this idea, we evaluated the combination therapy for OAB and nocturia, with tolterodine – an antimuscarinic, and desmopressin – a synthetic analogue of arginine vasopressin. Desmopressin is the first-line pharmacological therapy for patients with

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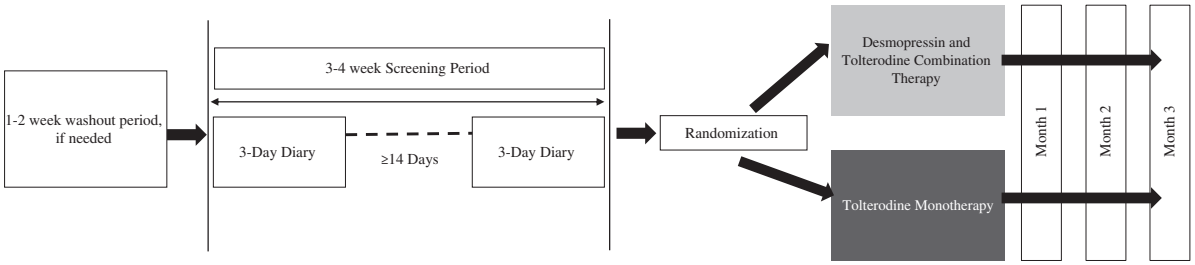

Fig. 1 Study design.

bothersome nocturia due to NP.[16,17] It is efficacious in controlling nocturia[18] by reducing nocturnal urine output,[19] and has a positive benefit/risk profile, even in elderly patients at risk of hyponatremia.[20] Desmopressin is the only drug approved for the treatment of nocturia due to NP.

Desmopressin orally disintegrating tablets (ODT) were demonstrated to be safe and efficacious at a low-dose (25 μg) in women, without additional clinical benefits at higher doses (50 and 100 μg).[21,22] A low-dose (60 μg) formulation was safely combined with tamsulosin for controlling LUTS/benign prostatic hyperplasia in men.[23]

The logical principle of using combination therapy to address combined LUTS etiologies have been widely discussed,[7,24,25] but to our knowledge, no randomized controlled trials (RCTs) have been conducted in patients with OAB and nocturia. In this study, which is the first of its kind, we evaluated the safety and efficacy of a combination of low-dose desmopressin (25 μg ODT) and tolterodine (4 mg extended-release capsules) for treating nocturia in women with OAB. In order to explore the effect of combination therapy on a broad clinical sample of patients with OAB and nocturia, and to establish whether outcomes were improved using combination therapy, patients with nocturia due to any cause were included. Since OAB patients with nocturia due to NP may have insufficient benefit from anticholinergic therapy,[10] we performed a *post-hoc* analysis to specifically evaluate the effect of combination therapy in patients with NP.

2. MATERIALS AND METHODS

2.1. Patients

Women ≥18 years of age, with OAB and nocturia, and symptomatic for ≥6 months prior to study entry, were enrolled. Patients had ≥2 nocturnal voids/night, ≥6 daytime voids/day, and at least one urgency episode/24 h as documented in two consecutive 3-day diaries completed 14 days apart during screening. Patients with nocturia due to other treatable medical conditions (urinary tract infections, interstitial cystitis, bladder related pain, bladder/urethra stone, diabetes insipidus, gastric retention, myasthenia gravis, obstructive sleep apnea), severe daytime dysfunction (>20 daytime voids/24 h), >10 nocturnal voids/24 h, and those with hyponatremia were excluded.

Sample size was based on the hypothesis that tolterodine monotherapy would have an effect similar to placebo on nocturnal voids. The study was powered to observe a treatment contrast (TC) of 0.5 voids/night with 85% power at a significance level of 5% (0.05). Therefore, a total of 50 patients/arm were required to demonstrate superiority of combination over monotherapy in the full sample.

2.2. Study design and setting

This randomized, double-blind, active-controlled, multi-center study was conducted across 33 sites in the USA, and eligible patients from 20 sites were randomized to a treatment. The study design is presented in Figure 1.

2.3. Study treatment

Patients were randomized 1:1 to receive either combination therapy (desmopressin ODT 25 μg and tolterodine 4 mg [Detrol® LA]) or monotherapy (tolterodine 4 mg [Detrol® LA] and placebo ODT) approximately 1 h prior to bedtime. Desmopressin ODT for sublingual administration was blinded while tolterodine capsules for oral administration were not blinded. All patients received behavioral therapy, and were instructed to limit their fluid intake to a minimum from 2 h before and up until 7 h after taking study drug, and to empty their bladder before going to the bed.

2.4. Study endpoints

The primary efficacy endpoint was the change from baseline in mean number of nocturnal voids during 3 months of treatment. The secondary efficacy endpoints were change from baseline in the mean time to first nocturnal void, mean nocturnal void volume, and responder status during 3 months of treatment. Patients experiencing ≥33% reduction from baseline in the mean number of nocturnal voids, and at least one night with no voids during the 3-day diary period were designated as responders. In addition, the impact of nocturia on QoL endpoints were evaluated, which included change from baseline during 3 months of treatment using the Nocturia Impact (NI) Diary©, EuroQoL Group 5 Dimensions Questionnaire (EQ-5D-5L™), and impact on sleep quality using Sleep Rating Scale.[26] For the *post-hoc* subgroup analyses, NP was defined as nocturnal urine volume ≥33% of total daily urine volume at baseline.[27]

Safety was evaluated by recording adverse events (AEs), vital signs, laboratory parameters, and physical examination. AEs were coded using the medical dictionary

for regulatory activities (MedDRA). Patients were evaluated for hyponatremia during screening, Day 8, Day 29, Day 57, and Day 85 (±7 days). Hyponatremia was reported as clinically significant if serum sodium levels were ≤130 mmol/L.

2.5. Study assessments

The threshold of treatment compliance was set at 80% of study drug taken. A 3-day electronic diary (eDiary) was used to document voiding behavior (voiding diary), and the daily impact of nocturia was assessed using the NI Diary© at baseline, as well as throughout the study. The outcomes were assessed at baseline, Week 4, Week 8 and then at 3 months (Week 12). The NI Diary© was used in conjunction with the voiding diary to capture real-life consequences of nocturia and its treatment.[21] The QoL was evaluated using the EQ-5D-5L, which comprises evaluation of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depressions), and a visual analogue scale with a single rating of ''how good or bad your health is TODAY?'' The distribution of patients across these dimensions, combined with the US utility weights was used to generate Quality Adjusted Life Years (QALYs). The impact on sleep was evaluated by the Sleep Rating Scale,[28] a validated and standardized tool.[29]

2.6. Statistical analysis

Endpoints were assessed for the full analysis set (FAS), which comprised all randomized and exposed patients with at least an efficacy assessment after treatment initiation. Changes from baseline in efficacy variables were analyzed using a repeated measures analysis of covariance (ANCOVA). QALY was derived as a cumulative measure for treatment duration as the area under the curve (AUC) of US EQ-5D index values *versus* time. Treatment contrasts, adjusted for baseline values and visit were presented for treatment differences. Similar analyses were repeated for the NP subgroup. For the NI Diary©, the minimally important difference for total scores (unidimensional) was set at half the baseline standard deviation for each measure.[30]

2.7. Ethics and study registration

The study was conducted in accordance with the Declaration of Helsinki, with applicable United States Food and Drug Administration Code of Federal Regulations, and the International Conference on Harmonization Guidelines for Good Clinical Practice. Study protocol and amendments were approved by appropriate Institutional Review Boards for each site. All patients provided written, informed consent. The study is registered at clinicaltrials.gov (NCT01729819).

3. RESULTS

The study was conducted from January 2013 to November 2014. A total of 913 patients with OAB were screened, of which 807 patients could not be randomized. This was mainly due to non-fulfillment of inclusion/exclusion criteria, where most patients did not meet the definition of nocturia based upon two 3-day voiding diaries during the screening. A total of 49 patients were randomized to combination therapy and 57 patients to monotherapy. Patient disposition is presented in Figure 2. Treatment compliance in combination and monotherapy groups was 96 and 100%, respectively. Demographics and baseline characteristics of total study population and NP subgroup are summarized in Tables 1 and 2. In the NP subgroup, a significant difference between combination and monotherapy was observed at baseline, in the mean number of nocturnal voids ($P = 0.0409$). There was a non-significant improvement in all parameters of combination *versus* monotherapy (Fig. 3a–d). More patients tended to achieve a responder status with combination *versus* monotherapy though this was non-significant (Odds Ratio 1.36, 95% confidence interval [CI] 0.71, 2.62; $P = 0.352$). The change in the EQ-5D Visual Analogue Scale (VAS) scores seemed to be favoring the monotherapy *versus* combination therapy, but did not reach statistical significance during 3 months of treatment (Fig. S1). No differences between treatment groups were detected in QALYs. The change in mean quality of sleep from baseline with respect to all the three questions seemed to be favoring the combination therapy *versus* monotherapy, but did not reach statistical significance (Fig. S2).

Results of the *post-hoc* exploratory analysis in NP and non-NP subgroups are shown in Figure 4a–d. For all the parameters, non-NP patients had a similar response, whether using combination therapy or monotherapy, and there were no significant differences between the treatments groups. In the NP subgroup, however, there were greater differences between the treatment groups, suggesting a differential effect of combination therapy *versus* monotherapy. There was a trend towards reduction in mean number of nocturnal voids with combination therapy *versus* monotherapy (TC, −0.62; $P = 0.064$; Fig. 4a) while the reduction in mean nocturnal void volume (TC, −166.0 mL; $P = 0.034$) and increase in mean time to first nocturnal void (TC, 65.11 min; $P = 0.045$) was significantly greater with combination *versus* monotherapy (Fig. 4b,c). Consistent with this, there was a trend towards greater improvement from baseline to Month 3 in NI Diary© total scores (Q1–Q11) (TC, −10.58; $P = 0.059$) and overall QoL impact question score (Q12) (TC, −13.85; $P = 0.062$) with combination *versus* monotherapy. The treatment contrast was >10 points for NI Diary© total and overall impact scores (Q1–Q11 and Q12) (Fig. 4d). Significantly more patients achieved responder status with combination *versus* monotherapy (Odds Ratio 4.21; 95% CI 1.38, 12.82; $P = 0.0114$).

Additionally, in the NP subgroup, EQ-5D VAS scores seemed to be favoring monotherapy over combination therapy, but the difference was not significant (Fig. S3). Numerical improvements were observed in mean sleep quality with combination *versus* monotherapy in this subgroup (TC 0.48–0.62; $P > 0.05$) (Fig. S4).

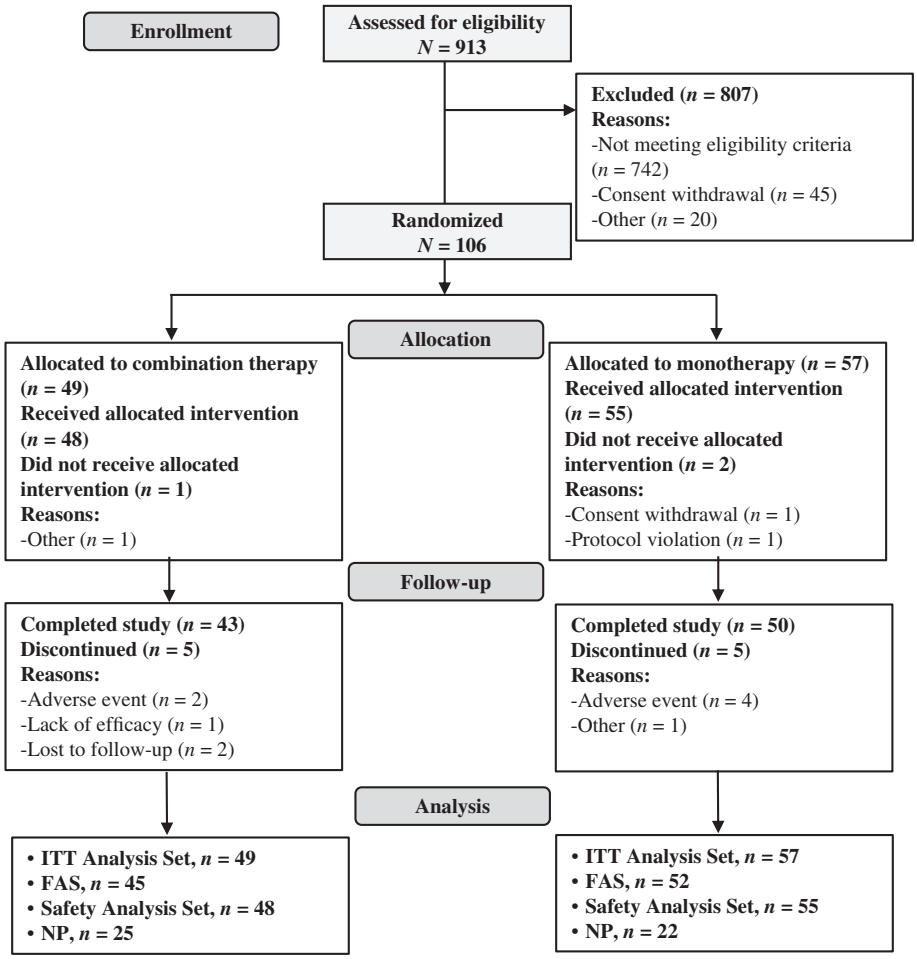

Fig. 2 CONSORT flowchart- patient disposition. NP, nocturnal polyuria, nocturnal volume ≥33% of total daily urine volume at baseline; ITT, intention-to-treat, all randomized patients were included in the ITT analysis set; FAS, full analysis set, all randomized and exposed patients with at least one efficacy assessment after treatment initiation were included in FAS; safety analysis set, all patients who received at least one dose of IMP and had at least one safety assessment were included in safety analysis set.

Safety analysis demonstrated a greater incidence of AEs in the combination therapy group for all AEs affecting ≥5% of patients, except one that affected both groups equally (Table 3). In particular, AEs known to be associated with tolterodine such as dry mouth and headache were more frequent with monotherapy. There were no deaths or serious AEs. There was one case of clinically significant asymptomatic hyponatremia with combination therapy, leading to treatment discontinuation, which resolved during subsequent follow-up, and was considered unlikely to be related to study medication.

4. DISCUSSION

We report the first RCT of combination therapy using low-dose desmopressin and an antimuscarinic for the treatment of women with OAB and nocturia. In order to closely mimic the real-world clinical practice, women with nocturia due to NP and due to other urological causes were included. It is important to note that although the primary objective of this study was not statistically met in this broad population, the results of this study clearly indicate that the combination therapy may benefit OAB patients where nocturia is due to NP. This benefit seems to be in-line with the antidiuretic mechanism of action of desmopressin.

The lack of a significant difference in efficacy between the two treatment groups could be due to several reasons. First, 50% of patients in this study did not have NP, and it is a possibility that in these patients, nocturia was due to urgency or detrusor overactivity[31] rather than NP, which, based on the mode of action, would not be expected to be improved by desmopressin. Therefore, it is plausible that in 50% women without NP, nocturia was addressed by tolterodine as in previous studies.[10,12] Second, both the treatment groups received behavioral therapy, which is the first-line management strategy for nocturia, while pharmacotherapy is an add-on therapy in those with failed behavioral therapy. Behavioral therapy has been reported to have similar to better efficacy than pharmacotherapy in older women with incontinence,[32] and men with OAB.[33,34] Antimuscarinics with behavioral therapy may therefore adequately address nocturia due

TABLE 1. Demographics and baseline characteristics-overall population

	Combination therapy $n = 45$	Monotherapy $n = 52$	Total $n = 97$
Age (years)			
Mean ± SD	55.3 ± 12.6	51.8 ± 10.3	53.4 ± 11.5
Median (range)	57 (24–84)	54 (28–72)	55 (24–84)
Age category, n (%)			
<65 years	32 (71)	48 (92)	80 (82)
≥65 years	13 (29)	4 (8)	17 (18)
Baseline BMI (kg/m^2)			
Mean ± SD	31.3 ± 7.08	29.6 ± 5.62	30.4 ± 6.35
Median (range)	29.5 (18.4–51.6)	28.4 (20.5–43.2)	29.2 (18.4–51.6)
Ethnicity, n (%)			
Hispanic or Latino	12 (27)	10 (19)	22 (23)
Not Hispanic or Latino	33 (73)	42 (81)	75 (77)
Race, n (%)			
Black or African American	10 (22)	14 (27)	24 (25)
White	35 (78)	38 (73)	73 (75)
Mean number of nocturnal voids			
Mean ± SD	3.38 ± 0.97	3.11 ± 1.06	3.24 ± 1.02
Median (range)	3 (2–5.83)	2.75 (1.5–6.67)	2.83 (1.5–6.67)
Mean number of day-time voids			
Mean ± SD	9.69 ± 1.35	10.1 ± 1.97	9.91 ± 1.71
Median (range)	9.33 (8–13.7)	9.5 (7.5–16)	9.42 (7.5–16)
Mean time to first nocturnal void (min)			
Mean ± SD	125 ± 44.6	143 ± 56.1	135 ± 51.6
Median (range)	121 (65– 251)	131 (37.9–275)	128 (37.9–275)
Mean nocturnal urine volume (mL)			
Mean ± SD	546 ± 281	537 ± 278	541 ± 278
Median (range)	445 (175–1306)	468 (105–1487)	466 (105–1487)

n, number of patients; NP, nocturnal polyuria; SD, standard deviation; %, percentage of patients.

to urgency and excessive fluid load, in some patients,[33] though in others it may not respond due to the multifactorial etiology of nocturia.[35]

Importantly, however, the *post-hoc* exploratory analysis in this study where the subgroup with nocturia due to NP was analyzed, potentially provides some options for these patients. In the NP subgroup, reduction in mean number of nocturnal voids did not reach statistical significance but, importantly, the effect size was almost twice as large as that seen in the total population (−0.62 *vs* −0.34, respectively), demonstrating an increased effect in OAB patients with NP. Additionally, patients with NP had more severe nocturia at baseline (3.56 *vs* 2.94 voids), but the scale of improvement with treatment (−1.72 voids/night) means that nocturia was reduced to below two voids/night, which is commonly considered a threshold for significant bother associated with the condition.[36] Consistent with this, there was also a trend for QoL scores to improve with combination therapy, with mean NI Diary© improvement >10 points, which is above the clinically important difference of 5–10 points.[26] It should be noted that the study was underpowered for these *post-hoc* comparisons. Despite this and a small sample size, our results provide support for the efficacy of desmopressin in patients with OAB and nocturia due to NP, as well as demonstrate the lack of efficacy of antimuscarinic monotherapy in this subgroup. As such, desmopressin may be a treatment option not only for patients with ''pure NP'' but also in those with LUTS of mixed etiology.

Safety analysis demonstrated no safety concerns with concomitant use of tolterodine and desmopressin in women with OAB and nocturia, consistent with clinical experience of this combination therapy for the treatment of enuresis.[37] A rare but potentially serious AE associated with desmopressin use is hyponatremia, the risk of which is reduced by using low-dose desmopressin.[38] In this study, there was one case of clinically-significant hyponatremia, which was reported unlikely to be related to study drugs.

This study has some limitations that should be considered when interpreting the results. There were a large number of screening failures, mostly due to patients failing to fulfill nocturia criteria of ≥2 voids/night. Unlike many studies of nocturia, we used two 3-day diaries completed 14 days apart during the screening period, and a small fluctuation during one diary period could have forced the exclusion of patients who would have qualified based on their other diary results. Possibly, there were some misassumptions too with respect to sample size calculations. Sample size was based on previous nocturia studies, where patients with OAB were excluded due to the daytime voiding inclusion criteria. The differences between the target populations of these studies, for example, within-patient variability of nocturnal voids, may have impacted the power of the study. Additionally, our power calculations were based on the assumption that tolterodine compared to placebo, would have a similar effect on nocturia, but it may have been more appropriate to assume a small effect, notably in patients without

TABLE 2. Demographics and baseline characteristics- patients with and without nocturnal polyuria

	NP Subgroup			Non-NP Subgroup		
	Combination therapy $n = 25$	Monotherapy $n = 22$	Total $n = 47$	Combination therapy $n = 20$	Monotherapy $n = 27$	Total $n = 47$
Age (years)						
Mean ± SD	58 ± 12.8	55 ± 9.26	56.6 ± 11.3	51.9 ± 11.8	49 ± 10.6	50.3 ± 11.1
Age category, *n* (%)						
<65 years	16 (64)	19 (86)	35 (74)	16 (80)	27 (100)	43 (91)
≥65 years	9 (36)	3 (14)	12 (26)	4 (20)		4 (9)
Baseline BMI (kg/m^2)						
Mean ± SD	32.2 ± 7.12	31.2 ± 6.06	31.7 ± 6.59	30.1 ± 7.03	28.5 ± 5.2	29.2 ± 6.02
Ethnicity, *n* (%)						
Hispanic or Latino	7 (28)	4 (18)	11 (23)	5 (25)	6 (22)	11 (23)
Not Hispanic or Latino	18 (72)	18 (82)	36 (77)	15 (75)	21 (78)	36 (77)
Race, *n* (%)						
Black or African American	5 (20)	8 (36)	13 (28)	5 (25)	5 (19)	10 (21)
White	20 (80)	14 (64)	34 (72)	15 (75)	22 (81)	37 (79)
Number of nocturnal voids†						
Mean ± SD	3.99 ± 1.270	3.26 ± 1.190	3.65 ± 1.275	3.03 ± 0.756	2.89 ± 0.676	2.95 ± 0.706
Median (range)	3.67 (2.3–7.0)	3.17 (1.3–6.0)	3.67 (1.3–7.0)	3.00 (2.0–4.5)	2.67 (2.0–5.0)	2.67 (2.0–5.0)
Number of day-time voids						
Mean ± SD	9.52 ± 1.705	9.66 ± 2.271	9.58 ± 1.969	9.40 ± 1.732	10.42 ± 1.954	9.98 ± 1.912
Median (range)	9.33 (7.0–12.7)	8.67 (7.7–16.0)	8.67 (7.0–16.0)	9.00 (7.7–15.7)	10.33 (8.0–15.3)	9.33 (7.7–15.7)
Time to first nocturnal void (min)						
Mean ± SD	107.00 ± 35.006	130.44 ± 56.723	117.97 ± 47.412	145.71 ± 68.569	152.14 ± 99.378	149.40 ± 86.801
Median (range)	108.33 (31.7– 180.0)	124.58 (21.7–232.5)	110.00 (21.7–232.5)	154.17 (43.3–298.3)	143.33 (36.7–505.0)	145.00 (36.7–505.0)
Nocturnal urine volume (mL)						
Mean ± SD	690.43 ± 321.799	563.21 ± 273.331	630.88 ± 303.731	391.79 ± 200.632	442.33 ± 245.988	420.82 ± 226.860
Median (range)	700.00 (222.5–1506.7)	500.83 (200.0–1276.7)	587.50 (200.0–1506.7)	333.33 (141.7–875.0)	400.00 (86.7–1043.3)	361.67 (86.7–1043.3)

†Significant difference between combination and monotherapy in the NP subgroup ($P = 0.0409$).
n, number of patients; NP, nocturnal polyuria; SD, standard deviation; %, percentage of patients.

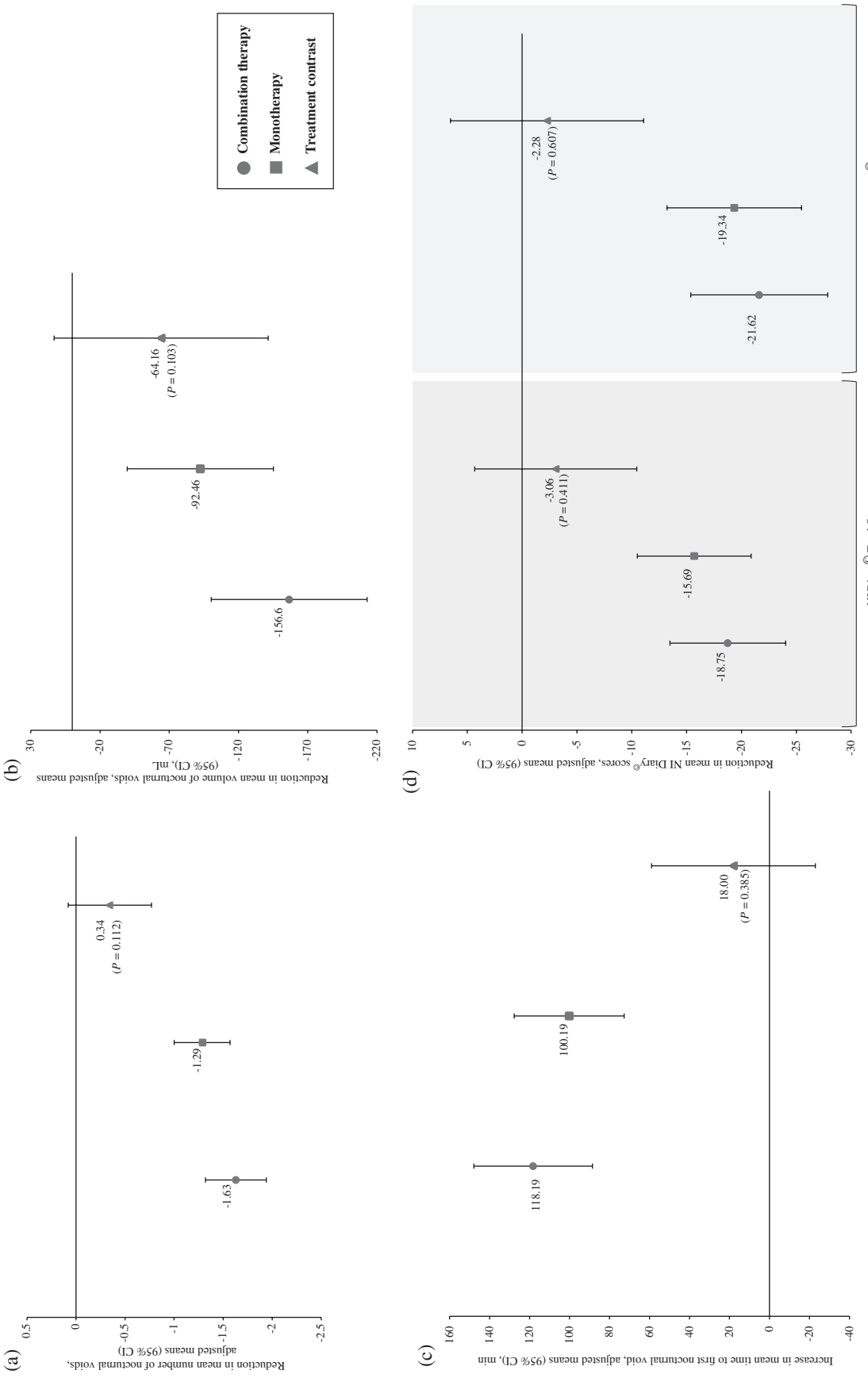

Fig. 3 Adjusted treatment contrasts for change from baseline in efficacy variables for FAS. (a) Mean number of nocturnal voids. (b) Mean volume of nocturnal voids. (c) Mean time to first nocturnal void. (d) Mean Nocturia Impact Diary Scores. CI, confidence interval; FAS, full analysis set; NI Diary©, nocturia impact diary.

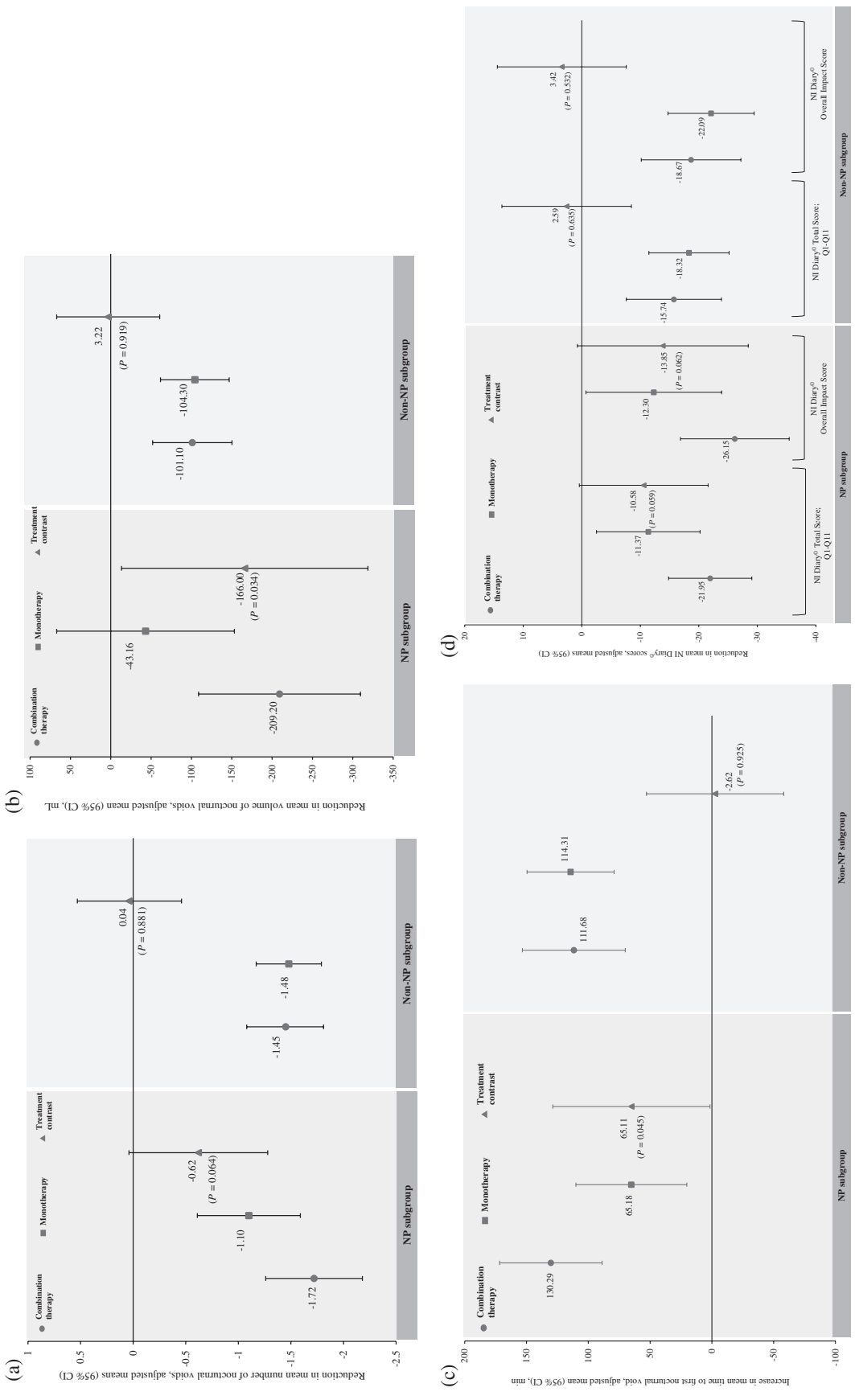

Fig. 4 Adjusted treatment contrasts for change from baseline in efficacy variables in NP and Non-NP subgroup analysis for FAS. (a) Mean number of nocturnal voids. (b) Mean volume of nocturnal voids. (c) Mean time to first nocturnal void. (d) Mean Nocturia Impact Diary Scores. CI, confidence interval; FAS, full analysis set; NI Diary©, nocturia impact diary; NP, nocturnal polyuria.

TABLE 3. Treatment-emergent adverse events with an incidence of ≥5% by MedDRA preferred term (Safety Analysis Set)

	Combination therapy		Monotherapy		Total	
	n = 48		*n* = 55		*n* = 103	
	n (%)	E	*n* (%)	E	*n* (%)	E
Any non-serious AE	21 (44)	36	28 (51)	55	49 (48)	91
ADRs	7 (15)	11	14 (25)	32	21 (20)	43
Gastrointestinal disorders	4 (8)	4	12 (22)	17	16 (16)	21
Dry mouth	1 (2)	1	6 (11)	6	7 (7)	7
General disorders and administration site conditions	2 (4)	2	3 (5)	5	5 (5)	7
Infections and infestations	3 (6)	3	6 (11)	6	9 (9)	9
Investigations	7 (15)	13	8 (15)	10	15 (15)	23
Nervous system disorders	4 (8)	5	6 (11)	8	10 (10)	13
Headache	2 (4)	2	5 (9)	5	7 (7)	7

ADR, AE assessed by investigator as reasonable possibly related to investigational product; AE, adverse event; E, number of adverse events; MedDRA, Medical Dictionary for Regulatory Activities; *n*, number of patients with adverse events; %, percentage of patients with adverse events; 5% incidence, at least 5% of patients in any treatment group.

NP, as studies have been inconsistent in this respect.[6] Nevertheless, the results of this study provide exploratory data that can help to inform the design of prospective studies of combination therapy in OAB patients, where selection of the patient populations and prospective analyses can be based on nocturia severity, NP status and/or failure to respond to behavioral therapy. This might allow firmer conclusions on treatment effect to be drawn in future.

The study concludes that low-dose desmopressin ODT can be safely combined with tolterodine for the treatment of nocturia in women with OAB. While combination therapy was not significantly more effective in reducing nocturia than tolterodine monotherapy in the overall patient population, subgroup analyses confirmed significant clinical benefits of combination therapy in patients with NP. These data may help to guide future research into combination therapy for nocturia and LUTS, which should seek to confirm treatment effects in specific patient populations and to clarify best practice in patient selection.

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Disclosure

Raymond K and Juul KV are employees of Ferring Pharmaceuticals. Rovner ES has received travel expenses for scientific meetings from Ferring Pharmaceuticals, and is a part of an advisory board. There are no other conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web site:

Fig. S1. Change in EQ-5D VAS score and EQ-5D QALY from baseline during 3 months in total population.

Fig. S2. Change in mean quality of sleep rating scales from baseline during 3 months in overall population.

Fig. S3. Change in EQ-5D VAS score and EQ-5D QALY from baseline during 3 months in NP and Non-NP subgroups.

Fig. S4. Change in mean quality of sleep rating scales from baseline during 3 months in NP and non-NP subgroups.