Received: 12 October 2018 | Accepted: 24 November 2018
DOI: 10.1002/nau.23910

ORIGINAL CLINICAL ARTICLE

WILEY Neurourology Urodynamics ICS SUFU

Novel immediate/sustained-release formulation of acetaminophen-ibuprofen combination (Paxerol®) for severe nocturia associated with overactive bladder: A multi-center, randomized, double blinded, placebo-controlled, 4-arm trial

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Aim: To determine short-term efficacy and safety of Paxerol®, novel immediate: sustained (50%:50%) release tablets containing 325 mg acetaminophen and 150 mg ibuprofen per tablet.

Methods: One of three dose levels, corresponding to the amounts in 1, 2, and 3 tablets, of Paxerol and placebo were administered for 14 consecutive days to patients with severe nocturia (defined in this study as an average nocturnal voids [NV] ≥2.5) associated with overactive bladder (OAB). Changes in NV, as well as Nocturia Quality of Life (NQOL), duration of first uninterrupted sleep (DFUS), and total hours of nightly sleep (THNS) associated with treatment were assessed. Short-term safety/tolerability was assessed throughout the study and for at least 30 days post-treatment.

Results: Paxerol at all three doses reduced NV to a greater degree than placebo (average NV −1.1, −1.4, −1.3 voids for low, mid, and high doses, respectively, vs −0.3 void for placebo). NQOL and THNS were similar between baseline and treatment values in all four groups. There were also no between-group differences. Paxerol at high dose tended to (although not statistical significantly) increase DFUS to a greater degree than placebo (1.2 vs 0.4 h, $P = 0.057$). There were no treatment related adverse events in any of the four groups.

Conclusions: This study demonstrates short-term efficacy and short-term safety of Paxerol in patients with severe nocturia associated with OAB. The results warrant further investigation of the long-term efficacy and safety of Paxerol in larger patient populations.

Clinical Trial Number: NCT# 02646826.

Institutions at which work was performed: AccuMed Research Associates, 1305 Franklin Avenue, Garden City, NY 11530; Manhattan Medical Research, 215 Lexington Avenue, 21th Floor, NY, NY 10016; Washington Heights Urology, 286 Fort Washington Ave, NY, NY 10032; A and I Medical PC, 1773 E 19 Street, Suite 1C, Brooklyn, NY 11229; Brightech International, LLC, 285 Davidson Ave, Suite 504, Somerset, NJ 08873.

KEYWORDS
clinical trial, investigational drug, nocturia, prostagladin-E2 inhibitors

1 | INTRODUCTION

Nocturia is defined by International Continence Society (ICS) as the complaint of waking at night to void[1] and has been associated with significant mortality, morbidity and negative economic implications.[2–6] Nocturia is also associated with significantly decreased Nocturia Quality of Life (NQOL), particularly in patients with ≥2 Nocturnal Voids (NV).[7–8] Etiology is multifactorial with three commonly known mechanistic causes: global polyuria, nocturnal polyuria, and decreased nocturnal bladder capacity.[2]

A potential molecular target for treating nocturia may be the prostaglandin (PG) pathway. Evidence includes findings that PGs are local modulators of reflex micturition, increase detrusor muscle tone, and enhance micturition.[9] PG-E2, PG-E2α, PG-E1, and thromboxane A2 have been shown to cause contraction of isolated detrusor muscle in the bladder.[10] Cyclo-oxygenase-2 inhibitors and PG inhibitors such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) reduce urine production, detrusor muscle tone and inflammation, especially in men with benign prostatic hyperplasia (BPH).[11]

Clinical studies have shown how modulation of PG pathway impacts nocturia. PG synthesis inhibitors reduce void frequency and volume in enuresis,[12] indomethacin relieves symptoms of BPH,[4] aspirin and diclofenac relieve nocturnal polyuria symptoms,[13–14] diclofenac improves nocturnal polyuria symptoms,[15] and celecoxib reduces NV and International Prostate Symptom Scores.[16] Tamsulosin and meloxicam combination has been shown to improve symptoms and NQOL scores greater than tamsulosin alone.[17]

The current study used ibuprofen and acetaminophen because they have synergy in analgesic effect,[18–19] which may also alleviate nocturia. Concurrent administrations of ibuprofen and acetaminophen are free of drug-to-drug interactions, and show no changes in pharmacokinetics or bioavailability compared to either drug alone.[18–21]

Ibuprofen (150 mg) and acetaminophen (325 mg) combination was formulated into novel immediate:sustained (50%:50%) release (IR/SR) tablets, referred to as Paxerol. One-half of each tablet is released during the first hour via IR to provide "loading dose" effect, and the other half is released via SR for up to 6 h to coincide with 6-8 h sleep duration. The current study is the first human study of Paxerol, involving a Phase 2, double-blinded, randomized, placebo-controlled design to assess short-term efficacy and safety of three dose levels of Paxerol in OAB patients with severe nocturia.

2 | MATERIALS AND METHODS

2.1 | Study oversight

The study was preceded by Institutional Review Board (IRB) approval and conducted under an Investigational New Drug application of Food and Drug Administration (FDA). IRB-approved Informed Consent was received from all patients before participating. Clinical investigation was conducted according to Declaration of Helsinki principles and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and per Good Clinical Practices.

2.2 | Study drug and placebo

Paxerol and placebo tablets were obtained from Wellesley Pharmaceuticals, LLC (Newtown, PA). Paxerol is a novel proprietary IR/SR (50%:50%) formulation of PG inhibitors (acetaminophen and ibuprofen). Each Paxerol tablet contains 325 mg acetaminophen and 150 mg ibuprofen. One-half of each Paxerol tablet is IR with release duration of ~1 h. The other half is SR with release for ~6 h (Appendix S1). Placebo tablets were identical in color, size, and shape to Paxerol, but contained neither drug.

2.3 | Patients' eligibility criteria

Major inclusion criteria included nocturia related to OAB, age ≥18 years of both sexes; ≥2.5 voids/night for >3 months; no history of persistent or recurrent urinary tract infections (UTIs); Post-Void Residual urine volume of <80 mL; and poor response to or unwilling to have lifestyle modifications or behavioral and conservative therapies. Additional criteria were: Body Mass Index <40; heart rate 55-100 beats/min; negative pregnancy test prior to enrollment and practice contraceptive methods during study (for childbearing age women); ability to give informed consent and communicate with investigators; ability to understand and comply with protocol requirements. Major exclusion criteria were: pregnancy or nursing; UTI within 4 weeks; history of sleep interruptions due to sleep apnea, gastrointestinal (GI) symptoms (eg, dyspepsia), or restless legs; history of seizures or other neurologic disorders (eg, neurodegenerative disorders, recent concussion, or stroke); inability to provide consistent and reliable Patient-Reported Outcomes (NQOL

score data); allergy or intolerance to acetaminophen, any NSAIDs, or any inactive component of Paxerol; history of GI bleeding; GI tract structural abnormality; history of prostate cancer; uncontrolled hypertension; serious medical illness; participation in any clinical trial within 30 days; anticipated use of acetaminophen, NSAIDs, ACE inhibitors, anticoagulants, or full acetylsalicylic acid dose (>81 mg) during study period; daily use of phosphodiesterase (PDE) inhibitors within 30 days prior to study or any anticipated daily use during the study; history or evidence of polyuria; uncontrolled Types 1 or 2 diabetes mellitus; diabetes insipidus; significantly impaired renal function; predisposition to falls; evidence of hyponatremia; hepatitis; HIV-AIDS; tuberculosis; uncontrolled known cardiac dysrhythmia; any significant disease or abnormality that the involved investigator believed might compromise subject's ability to participate in the study or that could confound result interpretation.

2.4 | Study design, procedures, and assessments

This was prospective, multi-center, randomized, double-blind, placebo-controlled, four-arm parallel Phase 2 study. It was conducted between March 21, 2016 and September 11, 2017. The objectives were to evaluate short-term efficacy in reducing NV, as well as the safety and tolerability, of different doses of Paxerol compared to placebo. The exploratory objectives included assessing the effects of different Paxerol doses on NQOL, Duration of First Uninterrupted Sleep (DFUS), and Total Hours of Nightly Sleep (THNS) compared to placebo.

A schematic outline of study procedures is provided in Figure 1A. Potentially eligible patients were screened and, if eligible, given a 2-week diary for recording times they went to sleep, woke up for the first nocturnal void, concluded sleeping, and NV (excluding the first void after concluding sleeping). Patients with average NV ≥2.5 who met all eligibility criteria were enrolled and asked to complete baseline NQOL questionnaires. The average NV ≥2.5 was used because this study investigated effects of Paxerol in patients with severe nocturia associated with OAB. NV more than 2-3 times/night is considered "severe."[2,22]

Patients were randomly assigned into four groups: Paxerol at low, mid, and high doses and placebo, based on random assignment (ie, proportional or quota randomization) performed by randomly assigning subjects to the four treatment groups using a Clinical Information Management System (CIMS). To ensure proper blinding, all patients received three tablets nightly—the placebo group received three placebo tablets, the low-dose group two placebo + 1 Paxerol tablets, the mid-dose group one placebo + 2 Paxerol tablets, and the high-dose group three Paxerol tablets. Patients were instructed to take the tablets nightly, 30 minutes before bed. NV, DFUS, and THNS were recorded by subjects nightly using a 14-day nightly diary at baseline and during treatment periods. After the 14-day treatment, subjects were asked to complete post-treatment NQOL questionnaires.

2.5 | Statistical analysis

Changes in NV, NQOL, DFUS, and THNS values from baseline vs. treatment were evaluated. For NV, DFUS, and THNS, 14-day averaged treatment-associated changes from baseline were calculated. NQOL included a 7-question Sleep/Energy domain and a 5-question Bother/Concern domain, and each question was scored from 0 (best NQOL) to 4 (worst NQOL). NQOL scores were re-scaled to 0-100, then Sleep/Energy and Bother/Concern domains for each patient were averaged to obtain the patient's Sleep/Energy and Bother/Concern scores. The conversion from 0-4 to 0-100 scale is consistent with the NQOL analysis guidelines, as it enables easy assessments with 0 being the best and 100 being the worst. The Sleep/Energy and Bother/Concern scores were averaged to get a 0-100 NQOL score. Analysis of Variance was performed on the 14-day averaged NV, DFUS, and THNS, as well as on 100-point scaled NQOL values for inter-treatment group comparison. Dunnett's test was used to adjust for multiple comparisons of Paxerol treatment groups with the Placebo group. For percentage change of NV from baseline, 14 days of non-averaged individual data were analyzed with a Mixed Model of Repeated Measurements to examine the change of treatment effect with study day.

Safety and tolerability were assessed throughout the study and for 30 days post-treatment. Adverse events were examined descriptively without statistical inference. Treatment differences were considered significant if P-values were <0.05. There are multiple endpoints in this study. While no hierarchical test was applied, P-values are interpreted as "descriptive" instead of taken at face value. As a Phase 2, proof-of-concept, first-time in human, dose-ranging trial, the sample size was not pre-calculated and could not be powered for statistical significance.

3 | RESULTS

3.1 | Patient disposition and demographics

Of 133 screened patients, 86 (65%) were eligible and enrolled, as shown in Figure 1B. Demographic and baseline voiding characteristics of patients are summarized in Table 1. There were no significant differences in baseline characteristics amongst the groups. Of the 86 patients enrolled, 80 (93%) completed 14 treatment days. All patients were analyzed based on an intention-to-treat basis.

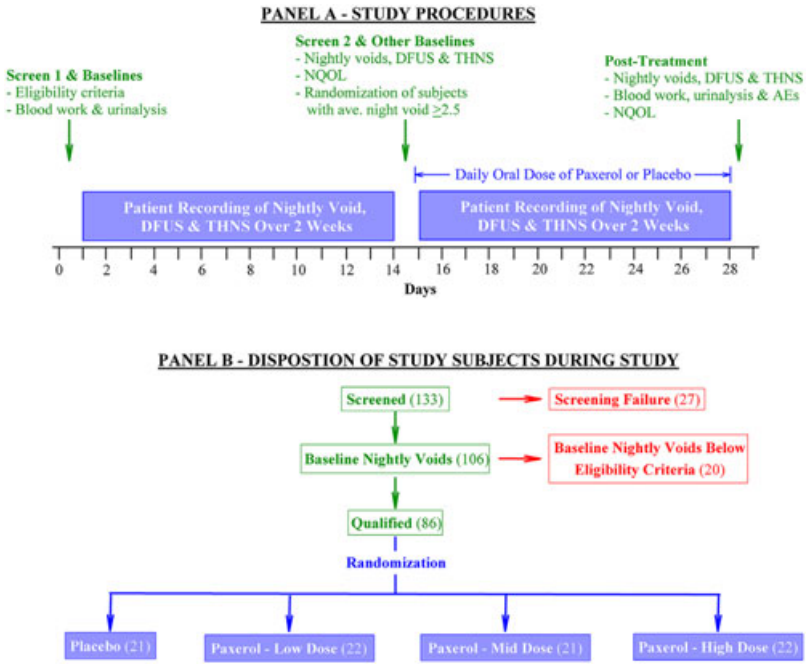

FIGURE 1 A, Schematic outline of the study procedures for the prospective, multi-center, double blind, placebo-controlled, four-arm Phase 2 trial of Paxerol. B, Disposition of study subjects during the study in the prospective, multi-center, double-blind, placebo-controlled, four-arm Phase 2 trial of Paxerol. AE, adverse event; Ave, average; DFUS, duration of first undisturbed sleep; NQOL, nocturia-quality-of-life; THNS, total hours of nightly sleep

3.2 | Efficacy

Reductions in NV were seen on the first day of treatment and were maintained throughout the treatment period in all four groups (Figure 2), with average reductions of −0.3, −1.1, −1.4, −1.3 voids per night for placebo, and low, mid, and high doses of Paxerol, respectively (Table 2). Paxerol patients averaged a 6% improvement in NV during the second week beyond the first week's improvement. The reductions in NV during treatment in all three Paxerol groups were significantly greater than the placebo group. These results indicated that the three dose levels of Paxerol were equi-effective in reducing NV. An average of ∼80% of patients at the three dose groups of Paxerol had reduction to ≤1 void/night and ∼100% had reduction to ≤2 void/night.

There were no obvious improvements in NQOL scores between baseline versus treatment in all groups or differences among the four groups (Table 2).

There was an increase in DFUS during treatment compared to baselines in all four groups (Table 2). The high-dose Paxerol group was, although not statistical significantly, larger compared to placebo (mean values of 1.2 vs 0.4 h, $P = 0.057$). There were no significant differences in THNS between baselines versus during treatment in all groups, or differences among the four groups.

3.3 | Short-term safety and tolerability

Of 86 enrolled patients, 9 had 15 adverse events (3 placebo patients and 2 in each Paxerol group, 10.5%) (Table 3). The events included UTI, nausea, abdominal pain, vomiting, abdominal pain, glycosuria, hematuria, pain, and increased glycosylated hemoglobin. The most common event was UTI (1 in placebo, 3 in mid-dose group, and 1 in high-dose group, or 6% incidence). None of the events was severe or considered treatment-related.

4 | DISCUSSION

This multi-center, double-blinded, placebo-controlled, 4-arm Phase 2 clinical trial evaluated three doses of Paxerol in patients with nocturia associated with OAB. The objectives were to evaluate short-term efficacy in reducing NV, as well as safety and tolerability, of different doses of Paxerol when compared to placebo. The exploratory objectives included assessing effects of different doses of Paxerol on NQOL, DFUS, and THNS compared to placebo. The results suggest that Paxerol may be an efficacious and safe short-term therapy for nocturia. The long-term efficacy and safety of Paxerol remain to be investigated.

4.1 | Paxerol designed specifically for nocturia

Paxerol is a novel proprietary IR/SR (50%:50%) formulation of PG inhibitors (acetaminophen and ibuprofen). Inhibition of the PG pathway is expected to alleviate nocturia because PGs are local modulators of reflex micturition, increase detrusor muscle tone, enhance micturition,[10] and inhibit antidiuretic

TABLE 1 Demographics and baseline characteristics of the four treatment groups

Parameters	Placebo ($N = 21$)	Paxerol Low dose ($N = 22$)	Paxerol Mid dose ($N = 21$)	Paxerol High dose ($N = 22$)	Total ($N = 86$)	*P*-values[a]
Demographics—number (% of group total)						
Sex						0.360
Female	2 (9.5%)	5 (22.7%)	4 (19.0%)	7 (31.8%)	18 (20.9%)	
Male	19 (90.5%)	17 (77.3%)	17 (81.0%)	15 (68.2%)	68 (79.1%)	
Age (yrs)						0.945
Mean ± SD (range)	58.4 ± 12.8 (34-87)	60.3 ± 7.9 (50-76)	59.9 ± 13.8 (34-85)	59.9 ± 8.9 (46-75)	59.6 ± 10.9 (34-87)	
Race						0.651
White	9 (42.9%)	9 (40.9%)	11 (52.4%)	13 (59.1%)	42 (48.8%)	
African American	9 (42.9%)	12 (54.5%)	8 (38.1%)	7 (31.8%)	36 (41.9%)	
Asian	1 (4.8%)	1 (4.5%)	0 (0%)	0 (0%)	2 (2.3%)	
Other	2 (9.5%)	0 (0%)	2 (9.5%)	2 (9.1%)	6 (7.0%)	
Ethnicity						0.282
Hispanic or Latino	3 (14.3%)	2 (9.1%)	3 (14.3%)	7 (31.8%)	15 (17.4%)	
Not Hispanic or Latino	18 (85.7%)	20 (90.9%)	18 (85.7%)	15 (68.2%)	71 (82.6%)	
Baseline characteristics—mean ± SD (range)						
BMI (kg/m^2)	29.1 ± 3.9 (22-38)	29.5 ± 5.1 (24-39)	29.4 ± 5.3 (22-39)	28.6 ± 5.6 (21-39)	29.2 ± 4.9 (21-39)	0.928
PVR (mL)	21.5 ± 20.7 (0.0-76.0)	19.5 ± 22.5 (0.0-73.2)	16.6 ± 16.2 (0.0-54.4)	18.0 ± 15.4 (0.0-55.0)	18.9 ± 18.7 (0.0-76.0)	0.857
Nightly voids	3.6 ± 0.7 (2.5-5.0)	3.3 ± 1.0 (2.5-7.1)	3.9 ± 1.4 (2.5-8.8)	3.6 ± 1.0 (2.6-6.6)	3.6 ± 1.0 (2.5-8.8)	0.453
DFUS (h)	1.8 ± 0.7 (0.5-3.0)	2.2 ± 0.9 (0.9-4.8)	2.0 ± 1.1 (1.0-4.4)	2.1 ± 0.8 (0.5-3.8)	2.0 ± 0.9 (0.5-4.8)	0.513
THNS (h)	8.5 ± 1.0 (6.9-10.5)	7.9 ± 1.0 (5.5-10.4)	8.6 ± 1.6 (6.0-12.0)	8.6 ± 1.3 (6.8-11.7)	8.4 ± 1.2 (5.5-12.0)	0.224
NQOL						
Sleep/energy domain	49.0 ± 17.2 (17.9-85.7)	48.9 ± 22.3 (7.1-85.7)	59.0 ± 18.4 (17.9-92.9)	59.4 ± 20.5 (25.0-100.0)	54.1 ± 20.1 (7.1-100.0)	0.127
Bother/concern domain	56.0 ± 18.6 (30-90)	55.7 ± 21.8 (5-90)	68.1 ± 23.9 (20-100)	60.0 ± 24.7 (15.0-100.0)	59.9 ± 22.6 (5.0-100.0)	0.244
Average	52.5 ± 15.2 (31.1-87.9)	52.3 ± 20.4 (6.1-82.9)	63.6 ± 19.6 (24.0-94.0)	59.7 ± 20.7 (20.0-100.0)	57.0 ± 19.4 (6.1-100.0)	0.153

BMI, body mass index; DFUS, duration of first undisturbed sleep; N, sample size; NQOL, nocturia-quality-of-life; PVR, post-void residual; SD, standard deviation; THNS, total hours of nightly sleep. All NQOL scores are re-scaled to 0-100 from the original 0-4 scores.

[a]*P*-values for the differences in the baseline values among the four treatment groups for the categorical variables (ie, sex, race, and ethnicity) were from Fisher's Exact test, and those for these continuous variables (ie, age, BMI, PVR, nightly voids, DFUS, THNS, and NQOL) were from Analysis of Variance.

hormone.[11] One-half of the drugs is released via IR during the first hour to provide "loading dose" effect. The other half is released via SR for up to 6 h to coincide with the normal 6-8 h of sleep. This low-dose IR/SR dosage form is unlike the modified-release formulations of acetaminophen and/or ibuprofen, which are high-dose prolonged release formulations. The acetaminophen-containing modified release formulations were suspended from marketing by the European Union regulatory agencies in 2017 due to safety concerns for providing uninterrupted steady presence of high dose of acetaminophen in the body for a very prolonged time period.

Patients could take Over-the-Counter (OTC) products (eg, Tylenol and an Advil) at bedtime to have initial attenuation of nocturia during early bedtime. However, due

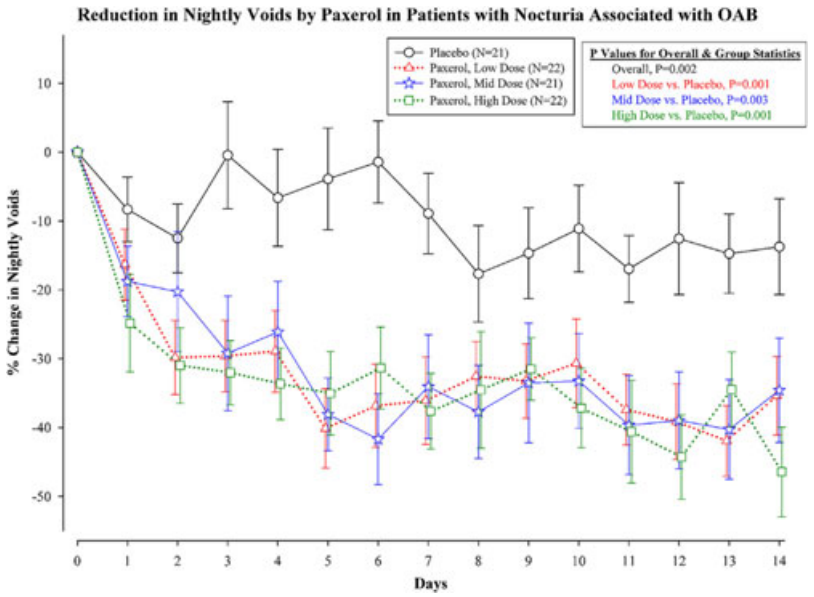

FIGURE 2 Percent changes (mean ± SEM) in nightly voids by study day in the four treatment groups: placebo and Paxerol at low, mid and high doses. N, sample size; SEM, standard error of the mean. The *P*-values were from a mixed-effect model repeated measures, adjusted for multiple comparisons with Dunnett's method

to the short half-life of approximately 2 h, these agents are not able to provide benefit for 6-8 h of normal sleep duration. Furthermore, OTC drugs are packaged at doses suitable for analgesia and anti-inflammation, which are beyond the dose for nocturia (~3× and ~4×, respectively, higher than Paxerol). Long-term exposure to OTC dose levels increase risks of cardiovascular and GI toxicities with ibuprofen, and hepatotoxicity secondary to inadvertent overdose with acetaminophen. They are not suitable for treatment of a chronic condition like nocturia, which is consistent with the National Institute for Health and Clinical Excellence guidelines of not recommending NSAIDs for nocturia. The toxicity risks with chronic use may be one of the reasons that the work of NSAIDs on nocturia did not result in NSAID products for nocturia. Paxerol is different from OTC products for analgesia or anti-inflammation. Paxerol contains only ~6% and ~8%, respectively, of maximum OTC doses, and release from Paxerol tablets lasts over 6 h. Toxicity risks associated with chronic use should be minimal.

4.2 | Efficacy parameters assessed

In this study, NV decreased during treatment in all groups compared to baselines. The decrease in the placebo group was small, and the decrease was significantly greater in the Paxerol groups versus placebo. Patients might have been cognizant of their fluid intake before bed during the study period, leading to lower nocturia.

Exploratory endpoints included NQOL, DFUS, and THNS. There were no obvious changes in these endpoints except for possible improvement in DFUS in the high dose group. A lack of statistical improvement in these exploratory endpoints may be because this was a short-term study with a small sample size. Whether these efficacy parameters will improve in larger long-term studies remains to be investigated.

4.3 | Patient population characteristics

The current study used OAB patients with nocturia. Some of these patients also had BPH, as OAB and BPH are not exclusive etiologies. Approximately 35% of those in this trial had BPH. Based on subgroup analysis, Paxerol appears to be effective for those with and without BPH.

Recent ICS Nocturia Guidelines White Paper does not distinguish nocturnal voiding from nocturia, as it is difficult to discern "reason for waking" and to confirm that waking was for "passing urine." Hence, nocturia and nocturnal voiding are referenced as the same in this study, as we did not attempt to determine whether sleep interruption was due to bladder filling sensation or involuntary contractions sufficient to awaken a sleeping person.[23]

4.4 | Safety and tolerability

Paxerol at all dose levels was safe and well-tolerated. There were only limited number of adverse events and all were of mild to moderate severity, incidental and unrelated to Paxerol, and occurred in both placebo and Paxerol groups. There was no adverse renal effect, a side effect associated with NSAIDs. These results suggest that Paxerol has great short-term safety

TABLE 2 NV, NQOL, DFUS, and THNS values

		Paxerol		
Variables	**Placebo ($N = 21$)**	**Low dose ($N = 22$)**	**Mid dose ($N = 21$)**	**High dose ($N = 22$)**
14-day averaged nocturnal voids (NV)				
Baseline	3.6 ± 0.7	3.3 ± 1.0	3.9 ± 1.4	3.6 ± 1.0
During treatment	3.2 ± 1.0	2.2 ± 1.0	2.5 ± 1.0	2.4 ± 1.0
Change from baseline	−0.3 ± 0.7	−1.1 ± 0.7	−1.4 ± 1.4	−1.3 ± 0.8
P-value compared to Placebo		0.002	0.003	0.001
Nocturia qualify of life (NQOL) score				
Sleep/energy domain score				
Baseline	49.0 ± 17.2	48.9 ± 22.3	59.0 ± 18.4	59.4 ± 20.5
Post-treatment	39.1 ± 18.4	37.3 ± 21.1	34.5 ± 23.7	37.0 ± 23.4
Change from baseline	−9.9 ± 16.8	−11.5 ± 25.1	−24.5 ± 24.5	−22.4 ± 20.1
P-value compared to Placebo		0.989	0.086	0.157
Bother/concern domain score				
Baseline	56.0 ± 18.6	55.7 ± 21.8	68.1 ± 23.9	60.0 ± 24.7
Post-treatment	45.0 ± 21.2	44.1 ± 23.5	46.4 ± 25.1	37.7 ± 26.7
Change from baseline	−11.0 ± 16.3	−11.6 ± 24.9	−21.7 ± 17.5	−22.3 ± 28.2
P-value compared to Placebo		0.999	0.286	0.237
Average scores of sleep/energy and bother/concern domains				
Baseline	52.5 ± 15.2	52.3 ± 20.4	63.6 ± 19.6	59.7 ± 20.7
Post-treatment	42.1 ± 18.3	40.7 ± 21.4	40.5 ± 18.1	37.4 ± 23.4
Change from baseline	−10.4 ± 15.1	−11.6 ± 23.5	−23.1 ± 15.7	−22.3 ± 22.0
P-value compared to Placebo		0.995	0.096	0.119
14-day averaged duration of first uninterrupted sleep (DFUS, hours)				
Baseline	1.8 ± 0.7	2.2 ± 0.9	2.0 ± 1.1	2.1 ± 0.8
During treatment	2.2 ± 0.9	2.8 ± 1.3	2.7 ± 1.4	3.3 ± 1.5
Change from baseline	0.4 ± 0.6	0.6 ± 1.1	0.7 ± 1.2	1.2 ± 1.4
P-value compared to Placebo		0.783	0.766	0.057
14-day averaged total hours of nightly sleep (THNS, hours)				
Baseline	8.5 ± 1.0	7.9 ± 1.0	8.6 ± 1.6	8.6 ± 1.3
During treatment	8.3 ± 1.0	7.7 ± 0.9	8.5 ± 1.4	8.4 ± 1.3
Change from baseline	−0.3 ± 0.6	−0.3 ± 0.6	−0.2 ± 1.0	−0.2 ± 0.6
P-value compared to Placebo		0.997	0.886	0.921

Values shown in table are mean ± Standard Deviation. The Dunnett's test was used to adjust for multiple comparisons of Paxerol treatment group with the Placebo group. All NQOL scores are re-scaled to 0-100 from the original scores.

and tolerability profiles, although long-term safety and tolerability are to be investigated.

The contraindications, warnings and limitations in the use of Paxerol should be consistent with the product labels of acetaminophen and ibuprofen. For example, patients with the following conditions should not use Paxerol: (i) GI bleeding or malformation, bleeding diathesis, dyspepsia, or other GI symptoms; (ii) on antiplatelet or anticoagulant drugs, or Selective Serotonin Re-uptake Inhibitors (SSRIs); (iii) allergy to or intolerance of acetaminophen, ibuprofen, or any inactive component of Paxerol; (iv) a history of allergy to NSAIDs; (v) have any medical problem requiring uninterrupted use of acetaminophen, ibuprofen, or any NSAIDs; (vi) on ACE inhibitors; and (vii) impaired renal function. Also, pregnant or nursing women should not use Paxerol.

4.5 | Current nocturia therapies unsatisfactory

Current therapies for nocturia, especially severe nocturia, are limited and unsatisfactory. The first approach is lifestyle and behavioral modifications, including elimination of evening fluid intake and reducing alcohol and caffeine. However,

TABLE 3 Adverse event incidence in the four treatment groups during and after the study

Adverse events				Treatment groups			
					Paxerol		
System	Type	Drug related?	Severity	Placebo ($N = 21$)	Low dose ($N = 22$)	Mid dose ($N = 21$)	High dose ($N = 22$)
Infections/infestations	Urinary tract infection	No	Mild	1 (5%)		3 (14%)	1 (5%)
Gastrointestinal	Nausea	No	Mild			1 (5%)	
	Pain, abdominal	No	Mild	1 (5%)			
	Vomiting	No	Mild		1 (5%)		
Renal and urinary	Glycosuria	No	Moderate				1 (5%)
	Hematuria	No	Mild		1 (5%)		
Musculoskeletal and connective tissues	Pain, flank	No	Moderate	1 (5%)			
Metabolic	Hemoglobin A1c, increase	No	Mild				1 (5%)
General	Pain, chest, non-cardiac	No	Mild	1 (5%)			
	Pain, general	No	Mild			1 (5%)	

these initial measures are rarely completely effective, especially for severe nocturia.

First-line medical therapies are use of antidiuretic agents, which can cause complications such as hyponatremia, especially in older persons who constitute the larger portion of nocturia patients. The presence of common comorbidities associated with nocturia can be associated with adverse interactions with these agents. Second-line medical therapies include potent diuretics such as furosemide, COX-2 inhibitors, as well as botulinum toxin injected directly into the detrusor muscle for OAB. Alpha-blockers and 5-alpha-reductase inhibitors are used for men with BPH, the improvement of which can alleviate nocturia somewhat.

The only FDA approved nocturia drugs are Desmopressin nasal spray (Noctiva) and sublingual tablet (Nocdurna). Unfortunately, Desmopressin has limited efficacy, with approximately 0.2 and 0.3-0.4 NV reduction compared to placebo for the nasal spray and sublingual tablet, respectively. NV reduction by Paxerol was ~1 void/night compared to placebo. Desmopressin's modest efficacy comes with substantial risks, as indicated by black-box warning for potentially life-threatening hyponatremia. For a higher desmopressin dosage form for a different indication, there were 61 cases of hyponatremia-related seizures reported, 2 of which resulted in death. In nocturia treatment, although the lower dose versions had lower hyponatremia incidence, it remains the most frequent adverse event and led to treatment discontinuation in some cases.

Nocturia is frequently associated with BPH and OAB. Reduction in symptoms by OAB drugs, which can alleviate nocturia slightly, occurs only in 25-39% of patients. Low response rates and significant side effects cause most OAB drug users to abandon them within 2-3 months.

Due to limited effectiveness of current nocturia therapies, a safe and effective therapy, especially for severe nocturia, is of great medical need. Paxerol may potentially be a safe and effective alternative to current therapies.

5 | CONCLUSIONS

This Phase 2 clinical trial demonstrated that the proprietary novel IR/SR (50%:50%) formulation of ibuprofen/acetaminophen, Paxerol, is effective compared to placebo as a short-term therapy in reducing NV in patients with severe nocturia associated with OAB. Paxerol at all tested doses was safe and well-tolerated when used short-term. These results warrant further studies with larger sample size and for longer treatment duration to validate the efficacy and safety of Paxerol as a potential treatment option for nocturia.

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REFERENCES

1. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence

Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010;29:4–20.
2. Bosch JL, Weiss JP. The prevalence and causes of nocturia. *J Urol*. 2010;184:440–446.
3. Coyne KS, Zhou Z, Bhattacharyya SK, et al. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. *BJU Int*. 2003;92: 948–954.
4. Holm-Larsen T. The economic impact of nocturia. *Neurourol Urodyn*. 2014;33:S10–S14.
5. Kupelian V, Fitzgerald MP, Kaplan SA, et al. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. *J Urol*. 2011;185: 571–577.
6. Lowenstein L, Brubaker L, Kenton K, et al. Prevalence and impact of nocturia in a urogynecologic population. *Int Urogynecol J Pelvic Floor Dysfunct*. 2007;18:1049–1052.
7. Tikkinen KA, Johnson TM, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol*. 2010;57:488–496.
8. Weiss JP. Introduction. In: Weiss JP, Blaivas JG, VanKerrebroeck PEV, Wein AJ, editors. *Nocturia* (1st ed.). New York: Springer; 2012. 1–10.
9. Maggi CA. Prostanoids as local modulators of reflex micturition. *Pharmacol Res*. 1992;25:13–20.
10. Andersson KE, Ek A, Persson CG. Effects of prostaglandins on the isolated human bladder and urethra. *Acta Physiol Scand*. 1977; 100:165–171.
11. Varilla V, Samala RV, Galindo D, Ciocon J. Nocturia in the elderly: a wake-up call. *Cleve Clin J Med*. 2011;78:757–764.
12. Al-Waili NS. Increased urinary nitrite excretion in primary enuresis: effects of indomethacin treatment on urinary and serum osmolality and electrolytes, urinary volumes and nitrite excretion. *BJU Int*. 2002;90:294–301.
13. Le Fanu J. The value of aspirin in controlling the symptoms of nocturnal polyuria. *BJU Int*. 2001;88:126–127.
14. Presti JC. Indomethacin and symptomatic relief of benign prostatic hyperplasia. *JAMA*. 1995;273:347.
15. Addla SK, Adeyoju AB, Neilson D, et al. Diclofenac for treatment of nocturia caused by nocturnal polyuria: a prospective, randomised, double-blind, placebo-controlled crossover study. *Eur Urol*. 2006;49:720–725.
16. Falahatkar S, Mokhtari G, Pourreza F, et al. Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study. *Urology*. 2008;72:813–816.
17. Gorgel SN, Sefik E, Kose O, et al. The effect of combined therapy with tamsulosin hydrochloride and meloxicam in patients with benign prostatic hyperplasia symptoms and impact on nocturia and sleep quality. *Int Braz J Urol*. 2013;39:657–662.
18. Mehlisch DR, Aspley S, Daniels SE, et al. Comparison of the analgesic efficacy of concurrent ibuprofen and paracetamol with ibuprofen or paracetamol alone in the management of moderate to severe acute postoperative dental pain in adolescents and adults: a randomized, double-blind, placebo-controlled, parallel-group, single-dose, two-center, modified factorial study. *Clin Ther*. 2010;32:882–895.
19. Merry AF, Gibbs RD, Edwards J, et al. Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. *Br J Anaesth*. 2010;104:80–88.
20. Tanner T, Aspley S, Munn A, Thomas T. The pharmacokinetic profile of a novel fixed-dose combination tablet of ibuprofen and paracetamol. *BMC Clin Pharmacol*. 2010;10:10.
21. Wright CE, Antal EJ, Gillespie WR, et al. Ibuprofen and acetaminophen kinetics when taken concurrently. *Clin Pharmacol Ther*. 1983;34:707–710.
22. Nassau D, Avulova S, Friedman FM, et al. Prediction of nocturia severity in men: nocturnal urine overproduction vs race or metabolic risk factors. *JAMA Surg*. 2015;150:125–128.
23. Addla SK, Adeyoju AB, Neilson D, et al. Diclofenac for treatment of nocturia caused by nocturnal polyuria: a prospective, randomised, double-blind, placebo-controlled crossover study. *Eur Urol*. 2006;49:720–725.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Lee KC, Rauscher F, Kaminesky J, et al. Novel immediate/sustained-release formulation of acetaminophen-ibuprofen combination (Paxerol®) for severe nocturia associated with overactive bladder: A multi-center, randomized, double blinded, placebo-controlled, 4-arm trial. *Neurourology and Urodynamics*. 2019;38:740–748. https://doi.org/10.1002/nau.23910