CLINICAL TRIAL PROTOCOL

Paxerol™ (a Novel Formulation of Acetaminophen and Ibuprofen) for Treatment of Nocturia - A Phase II Placebo-Controlled Trial

Sponsor	**Wellesley Pharmaceuticals, LLC** 3 Valley View Drive Newtown, PA 18940 215-493-0168
Study Phase	Phase II
Protocol Number	CL-Paxerol-002
Investigational Product	Paxerol (an immediate-sustained release oral formulation of combination of acetaminophen 325 mg and ibuprofen 150 mg)
Version Number:	Current: 09.23.2016 Previous: 03.16.2016 02.18.2016 02.02.2016 01.27.2016 December 2015

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INVESTIGATOR SIGNATURE PAGE

I have read this protocol, agree to its contents and, by my signature, confirm that this clinical trial will be conducted according to applicable current guidance of: (i) Institutional Review Board (IRB)/Independent Ethics Committee (IEC), (ii) US and and international regulations (FDA/ICH), and (iii) Good Clincal Practice (GCP).

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Signature: _____

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List of Abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
BMI	Body Mass Index
BPH	Benign prostatic hyperplasia
BUN	Blood urea nitrogen
CBC	Complete blood count
CKD	Chronic Kidney Disease
COX	Cyclooxygenase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DFUS	Duration of First Undisturbed Sleep
DMP	Data Management Plan
DRP	Data Review Plan
ECG	Electrocardiogram
EEG	Electroencephalogram
eCRF	Electronic Case Report Form
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FBG	Fasting blood glucose
FDC	Fixed dose combination
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hgb	Hemoglobin
Hct	Hematocrit
HIV	Human Immunodeficiency Virus
HRP	horse radish peroxidase
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IR	Immediate release
INR	International normalized ratio
KDOQI	Kidney Disease Outcomes Quality Initiative

LDH	Lactate dehydrogenase
LPS	Lipopolysaccharide
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
mg	Milligram
NAPQI	N-acetyl-P-benzoquinone imine
NSAID	Non-steroidal anti-inflammatory drugs
NQOL	Nocturia quality of life
OAB	Overactive bladder
OTC	over-the-counter
P	Placebo
PDE	phosphodiesterase
PFE	Pelvic floor exercises
PRO	Patient-Reported Outcomes
Paxerol	Acetaminophen 325 mg + Ibuprofen 150 mg combination
PGE2	Prostaglandin E2
POX	Peroxidase
PP	Per-Protocol
PSA	Prostate-specific antigen
PT	Preferred Term
PVR	Post-Void Residual
QA	Quality Assurance
QC	Quality Control
RBW	Red blood cell width
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SDV	Source Document Verification
SOC	System organ class designation by MedDRA
SOP	Standard Operating Procedure
SR	Sustained release
SSRI	Selective Serotonin Re-uptake Inhibitor
SUSAR	Suspected unexpected serious adverse drug reaction
TNFα	Tumor necrosis factor alpha
TSH	Thyroid-stimulating hormone
USPI	United States Product Insert
UTI	Urinary tract infection
WBC	White blood cells

1. PROTOCOL SYNOPSIS

Study Title	Paxerol™ (a Novel Formulation of Acetaminophen and Ibuprofen) for Treatment of Nocturia - A Phase II Placebo-Controlled Trial
Protocol No.	CL-Paxerol-002
Study Phase	Phase II
Study Drugs	Paxerol Tablets: Each Paxerol tablet contains acetaminophen 325 mg and ibuprofen 150 mg. It is formulated to release approximately 50% of the acetaminophen and ibuprofen as IR and the other 50% being released as SR over 6-8 hours. Placebo Tablets: Placebo tablets are formulated as Paxerol tablets, except that they do not contain any acetaminophen or ibuprofen.
Study Objectives	The co-primary objectives are: A. To assess the effect of different doses of Paxerol on the reduction in the number of nocturia episodes. B. To assess the clinical benefit of different doses of Paxerol in reducing nocturia via assessment of nocturia quality of life (NQOL). The secondary objectives are to assess the effects of different doses of Paxerol on: A. Duration of First Undisturbed Sleep (DFUS) B. Total hours of nightly sleep C. Safety and tolerability An exploratory assessment is to evaluate baseline urinary PGE2 production on the responsiveness of subjects to Paxerol.
Study Design	This is a multi-center, double-blind, placebo-controlled study with two weeks of daily oral administration of one of three dose levels of Paxerol or placebo in subjects with nocturia. Eligible study subjects will be identified according to inclusion/exclusion criteria (see below), and baseline assessments will be recorded. Due to small sample size of 25 patients per group in this proof-of-principle dosing-finding trial, stratification according to gender and BMI will be difficult. However, similar distribution of patient types to the four treatment groups will be attempted by evenly assigning patients to the four treatment groups according to genders and BMI of <25, 25-30, and >30-<40. Paxerol or placebo will be taken 30 minutes before bedtime daily for two weeks. Nocturia frequency, NQOL, DFUS, total hours of nightly sleep, safety and tolerability will be monitored before and after a two-week treatment period. Results from subjects treated with different doses of Paxerol and placebo will be assessed and compared. Baseline urinary PGE2 production will also be assayed to assess potential correlation between baseline urinary PGE2 production and responsiveness to Paxerol treatment.
Study Duration	Study duration for each subject is approximately 4 weeks, which includes screening, baseline assessment, two weeks of treatment with study drugs, and follow-up.
Study Center(s)	This study is to be conducted in multiple clinical sites with investigators who are experienced in urologic management.
No. of Subjects	It is estimated that approximately 125 study subjects will be enrolled with 100 study subjects (25 subjects per arm) to complete the trial.
Inclusion and Exclusion Criteria	Inclusion: A. Subjects diagnosed with nocturia, as defined by International Continence Society (i.e., the interruption of sleep one or more times at night to void [van Kerrebroeck et al. 2002]), confirmed by evaluation in participating investigator's urology practice: - Nocturia is related to overactive bladder OAB (Diagnosis Code: 2015/16 ICD-10-CM [http://www.icd10data.com/ICD10CM/Codes/N00-N99/N30-N39/N32-/N32.81]) - Nightly ≥2.5 times nocturia present for at least 3 months and not considered caused by persistent or recurrent urinary tract infection. - Post-Void Residual (PVR) urine volume must be <80 cc at the time of screening - Did not respond well to, or unwilling to have, lifestyle modification, behavioral and

	conservative therapies, such as dietary changes, timed voiding, urge suppression (e.g., pelvic floor exercises [PFE] at the time of urge episodes), biofeedback, etc. B. Males or females, ≥18 years of age with Body Mass Index (BMI) <40. C. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and must have a negative serum or urine pregnancy test within 1 week prior to enrollment or Visit 1. D. Ability to understand and sign the study Informed Consent Form (ICF), communicate with the investigators, and understand and comply with the requirements of the protocol, including completion of participation in all phases of the study. E. No current or medical history of: - Gastrointestinal bleeding or malformation - Bleeding diathesis - Restless leg syndrome. F. Not using within 4 weeks before study initiation, or anticipating the use during the study, of the following drugs: - Antiplatelet or anticoagulant drugs (**Note:** Low dose aspirin is allowable if subjects take it in the morning.) - Any Selective Serotonin Re-uptake Inhibitors (SSRIs) (concurrent use of SSRIs and NSAIDs have been reported to increase the risk of upper gastrointestinal bleeding) or anti-diuretic medications (**Note:** Diuretic medication is allowable if the subject is on a stable consistent morning dose.) - Warfarin G. Resting heart rate between 55 and 100 beats per minute, inclusive of both. Exclusion: A. Pregnant or nursing women. B. Known presence of urinary tract infection (UTI) within 4 weeks before study initiation C. Known sleep interruptions due to sleep apnea, dyspepsia or other gastro-intestinal symptoms, seizure disorders or other neurologic symptoms D. Allergy to or intolerance of acetaminophen, ibuprofen, or any inactive component of the study drug formulations. E. A history of allergy to aspirin or other NSAIDs. F. Congenital or acquired structural abnormality of the genitourinary tract. G. Prostate cancer of any stage that has required any treatment. H. Any neurodegenerative disease (including but not limited to Parkinson's Disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Pick's Disease, Multi-Infarct Dementia or recent history of head trauma associated with concussion, stroke or serious cerebrovascular events) which may indicate problems in providing consistent and reliable Patient-Reported Outcomes (PRO) such as diary, Quality-of-Life, etc. required in this study. I. Uncontrolled hypertension (blood pressure >140/90 mm Hg). J. Serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, or New York Heart Association Class II, III or IV), severe debilitating pulmonary disease, or history of stroke (hemorrhagic or thrombotic), A-V malformation, or other cerebrovascular disease. K. Receipt of any investigational drug or participation in any clinical trial within 30 days prior to study participation. L. Use of acetaminophen, ibuprofen, acetylsalicylic acid (ASA) or any NSAID on the day of entry into the study or any anticipated use during the study. (**Note:** Low dose aspirin is allowable if subjects take it in the morning.) In the event of the need for any unanticipated use of such drugs during the trial, the timing and doses of such use should be carefully recorded and reported at the next visit to the clinic. M. Any medical problem requiring uninterrupted use of acetaminophen, ibuprofen, or any NSAIDs, or any other pain medication. N. Daily use of phosphodiesterase (PDE) inhibitors (such as sildenafil, tadalafil, vardenafil, avanafil, and udenafil) within 30 days prior to study or any anticipated daily use during the study. (**Note:** PDE inhibitors are known to have positive effect on voiding dysfunction and

thus can interfere with the assessment of Paxerol [Ückert et al 2010].)

O. Subjects taking ACE inhibitors. (**Note:** Co-administration of NSAIDs with ACE inhibitors may result in deterioration of renal function.) (**Note:** ACE inhibitor medication is allowable if the subject is on a stable consistent morning dose.)
P. History of polyuria or evidence of polyuria (estimation of daily production >2.5 liters of urine).
Q. Uncontrolled Type 1 or 2 diabetes mellitus (HbA1c >7.0%).
R. Diabetes insipidus.
S. Reported significantly impaired renal function (Chronic Kidney Disease [CKD] stage 3 [moderate] of` glomerular filtration rate [GFR] <60 mL/min/1.73kg/m^2, as defined by the US-based Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines)
T. Any visual, motor or other sensory abnormality that might predispose to a fall on nocturnal arising to urinate.
U. Evidence of hyponatremia at baseline.
V. Any significant disease or abnormality of the neurological, visual, gastrointestinal, hepatobiliary, pulmonary, cardiovascular, genitourinary or musculoskeletal system other than those specified above that, in the opinion of the involved investigator, might compromise the ability of the prospective subject to participate in the study or that could confound interpretation of study results.
W. Any abnormality on screening medical history, physical examination or clinical laboratory examination other than those specified above that, in the opinion of the involved investigator, might confound interpretation of study results.
X. Subjects with known hepatitis, HIV-AIDS, or tuberculosis.
Y. Subjects with known dysrhythmia of any form.

Investigational Product and Test Articles, Dose, Route, and Administration

Eligible subjects will be given one of the four treatment types, as outlined in Table A (below):

Table A: Four Treatment Arms

Treatment Arm	Treatment	Tablets to be Taken By Subjects at Each Dose		
		Paxerol Tablet	Placebo Tablet	Total Number of Tablets
1	Low Dose Paxerol	1	2	3
2	Mid Dose Paxerol	2	1	3
3	High Dose Paxerol	3	0	3
4	Placebo	0	3	3

Paxerol and placebo are provided in tablet formulation. Paxerol is formulated to release approximately 50% of the acetaminophen and ibuprofen as IR formulation and the other 50% being released as SR over 6-8 hours. It is important that the subjects not cut or bite into the tablet, since that would destroy the tablet's SR capabilities. Paxerol and placebo tablets are to be taken orally 30 minutes before bedtime daily for 2 weeks during the treatment period. Drinking fluids should generally be avoided just before retiring, but a small amount of water may be taken to facilitate swallowing of the study drug.

Subjects should void immediately after taking the study drug and again just prior to bedtime. This should provide improved results for those with significant post-void residual urine.

Study Procedures

The study procedures are outlined in Table B (below):

Table B: Study Procedures - Overview

Procedures	Visit 1 (Consent, Eligibility & Baseline, Day 1)	Visit 2 [a] (Pre-Treat-ment, Day 15)	Visit 3 [a] (End of Study, Day 29, or Early Termination)
Obtain written ICF from the subject, before any screening procedures.	√		
Investigator reviews and assures subject eligibility according to inclusion and exclusion criteria, including:	√		
- assessment of PVR <80 cc	√		
- subject's nocturia diary showing an average nightly void ≥2.5 times during the 14 days pretreatment period.		√	
Record demographic data including date of birth and age, sex, and race/ethnicity.	√		
Record medical history, including treatment of the lower urinary tract (duration of symptoms	√		

	of urgency, frequency and urge incontinence, medical and surgical).			
	Record urinary symptoms based on I-PSS.		√	√
	Record concurrent diseases and symptoms, concomitant medications, and any non-drug treatments/procedures.	√	√	√
	Collect urinary sample for assessment of PGE2 production (see Section 8.3 of the protocol).	√	√ [h]	
	Perform physical exam (including body weight and height [baseline only]) and measure vital signs (blood pressure and heart rate), temperature and respiratory rate.	√		√
	Clinical laboratory evaluation and urinalysis [d]	√		√
	Pregnancy test for women of child-bearing potential	√ [f]		
	Provide nocturia diary and instructions for completion	√ [e]	√ [e]	
	NQOL		√ [c]	√ [c]
	Randomization and dispense study drugs [b]		√ [b]	
	Collect unused study drug, perform Drug Accountability Reconciliation/Assess subject compliance for taking study drug, quantify subject compliance and record on CRF.			√
	Collect subject's nocturia diary. Review with subject for completeness.		√	√
	Assess the occurrence of AEs. Record all directly observed AEs and all AEs spontaneously reported by the subject since the first dose of randomized study drug. Record any changes in the subject's medical conditions, concurrent diseases or symptoms on the Adverse Event form of the CRF.			√
	Schedule the next appointment	√	√	
	Study Disposition Form			√
	Estimate the average amount of fluid consumed with the 3 tablets each night.		√ [g]	√ [g]

AE = adverse event; CRF = Case Report Form; FBG = fasting blood glucose; I-PSS = International Prostate Symptom Score; NQOL = Nocturia quality of life survey; PGE2 = prostaglandin E2; and PVR = Post-Void Residual.

[a] If a subject is withdrawn from study participation, the subject's enrollment in the study will be terminated, study drug will be discontinued and no further data will be collected on the subject. However, efforts will be made to perform all assessments scheduled for the end-of-study visit (i.e., Visit 3) prior to subject withdrawal and complete the Subject Disposition form. The Subject Disposition form is used to record the primary reason for withdrawal from the study.

[b] The study drug is different dose levels of Paxerol or Placebo for use 14 days on Days 15 through 28.

[c] Instruct subject to complete NQOL survey during Visits 2 and 3.

[d] Clinical lab tests include hematology (complete blood count, including RBC, Hgb, Hct, WBC, WBC differential, MCV, MCH, and platelet count); blood coagulation (INR); and electrolytes and chemistry (Na+, K+, Cl-, HCO3-, Ca++, BUN, creatinine (and derived creatinine clearance), AST, ALT, alkaline phosphates, LDH, total bilirubin, albumin, and HbA1c. Urinalysis includes pH, specific gravity, glucose, protein, blood, ketones and urine culture. Urine culture is not needed if other urinalysis test results are negative and there are no symptoms of urinary tract infection.

[e] When dispensing nocturia diary, instruct subject regarding completion of the nocturia diary. Ensure that they know that a bathroom visit that coincidences with the intention of getting up in the morning should not be considered nocturia. A bathroom visit that is followed by the intention of going back to sleep should be considered as nocturia. In this latter case, it should be considered nocturia even if the subject fails to fall sleep due to insomnia or some other issue. Explain to subjects that accurate reporting of the results will be critical in order to ensure the success of the study. Advise subject that nocturia symptoms may change by a small or a large amount at various times. Remind subjects about the importance of accurate reporting responses for all diary questions and review the expectations for diary completion. Remind subjects to void just after taking the study drug and once again just prior to bedtime for best results. Remind them that what they drink and when they drink it will affect urine output, so they should if possible try to remain

	consistent in their drinking habits each day, especially regarding drinking after 5 p.m. each day. [f] For women of child-bearing potential, they must have a negative serum or urine pregnancy test within 1 week prior to enrollment or Visit 1. [g] During Visit 2, instruct subject that at Visit 3 he/she will be asked to estimate the average amount of fluid consumed with the 3 tablets each night. If possible, an estimate in terms of ounces would be preferable. (**Note:** A cup of fluid is 8 ounces and a large glass of fluid could be 12-16 ounces.) Subject should also be instructed to use the smallest amount of fluid that he/she can in order to swallow the tablets comfortably. During Visit 3, ask subject to estimate the average amount of fluid consumed with the 3 tablets each night. [h] Collection of urinary sample for assessment of PGE2 production during Visit 2 is needed only if this process was not successful during Visit 1.

2. BACKGROUND INFORMATION

2.1 Nocturia

Nocturia or Nocturnal Micturition is defined by the International Continence Society as the interruption of sleep one or more times at night to void (van Kerrebroeck et al. 2002). Nocturia is a major health problem for benign prostatic hyperplasia (BPH) and overactive bladder (OAB) patients. Nocturia is a symptom which interrupts sleep by the urge to void. Nocturia is thought to be caused by volume-related reasons (excess intake of alcohol or diuretics, endocrine or metabolic disorders, peripheral edema), sleep-related reasons (insomnia, pain, dyspnea, depression, drugs) and lower urinary tract-related reasons (small bladder capacity, detrusor hyperactivity, prostate-related, overflow incontinence, decreased bladder compliance, sensory urgency) (Resnick et al. 2002). Multiple factors may result in nocturia, including pathological conditions, such as cardiovascular disease, diabetes mellitus, lower urinary tract obstruction, anxiety or primary sleep disorders, and behavioural and environmental factors (Weiss 2000).

The prevalence of nocturia is higher with increasing age (Fitzgerald et al. 2007). Although nocturia is relatively uncommon among younger adults, by 80 years of age, the prevalence rises to 80 to 90% in both men and women (Weiss 2000). Occasional nocturia is present in 50% of men and women aged 50 to 59 years. Among 18 to 49 year olds, more women than men have nocturia; the sex ratio reverses after 60 years of age, with prevalence greater in men than women. The prevalence of twice nightly or greater nocturia among men between 70 and 79 is nearly 50% (Liew et al. 2006).

Nocturia disrupts sleep, leading to daytime somnolence, depressive symptoms, cognitive dysfunction, and a reduced sense of well being and quality of life. Moreover, nocturia is associated with a dramatically increased risk of morbidity and mortality (Stewart et al. 1992; Asplund 1999). While it may take years to have data to conclusively show that reduction in nocturia episodes can improve nocturia-induced reduction in lifespan and overall health, the correlations between nocturia incidence with longevity, quality of life, and a variety of serious medical conditions in these patients is undeniable. Nocturia is a serious medical condition, especially in the elderly and especially when it occurs 2 or more times per night.

A reduced nocturnal bladder capacity alone related to OAB and abnormal bladder function can rarely be effectively managed with anti-muscarinics. Nocturnal polyuria is associated with abnormalities of the secretion of arginine vasopressin, lifestyle or dietary factors, and other medical conditions (e.g., congestive heart failure, venous stasis disease, sleep apnea). The first approach to treatment is changes in lifestyle and behavioural changes, including the elimination of fluid intake in the evening and reducing alcohol and caffeine. However, these initial measures alone are rarely effective. Moreover, the available medical therapies for nocturnal polyuria are limited to antidiuretic agents, which can cause complications, such as hyponatremia, in older persons. In addition, the presence of common comorbidities can be associated with potentially adverse interactions between the antidiuretics and other medications. Alpha-blockers and 5-alpha-reductase inhibitors are used for men with BPH. However, the effectiveness of these drugs for nocturia is reported to be only 25-39%. Novel and second-line therapies include diuretics such as furosemide, cyclooxygenase (COX)-2 inhibitors, as well as botulinum toxin injected directly into the detrusor muscle for overactive bladder. Medical therapy for BPH and OAB is able to decrease

this symptom by more than 50% in only 25-39% of patients. The low response rate and significant side effects cause most users of these drugs to abandon them within 2-3 months.

2.1 Prostaglandins and Nocturia

Cyclo-oxygenase-2 inhibitors and other nonsteroidal anti-inflammatory drugs (NSAID) have been shown to decrease urine production, detrusor muscle tone, and inflammation, especially in men with BPH (Varilla et al. 2011). There is increasing evidence that NSAIDs are effective for the treatment of nocturia. Recent reports indicated that NSAIDs are effective for patients with nocturia. Larsen (1995) reported that indomethacin relieves symptoms of BPH. Le Fanu (2001) reported that aspirin is effective for symptoms of nocturnal polyuria.

Prostaglandins play a role as local modulators of reflex micturition. By stimulation of sensory nerves they cure bladder motility disorders. Prostaglandins increase the tone of detrusor muscle and enhance micturition (Maggi 1992). Prostaglandin E2 (PGE2), PGE2α, PGE1 and thromboxane A2 cause contraction of the isolated detrusor muscle of the human bladder (Andersson 1997). A study showed that prostaglandins synthesis inhibitors reduced the frequency of voiding and decreased the urine volume in enuresis (Al-Waili 2002). A pilot observational study indicated the possible role of NSAIDs in the treatment of nocturnal polyuria and the significant symptomatic improvement (Addla et al. 2014). NSAIDs may play a role in inhibiting OAB by inhibition of prostaglandin synthesis via inhibition of COX.

Ibuprofen [(±)-2-(p-isobutyl phenyl) propionic acid] and acetaminophen [N-(4-hydroxyphenyl) acetamide] are among the most widely used non-prescription medications. Ibuprofen is a commonly used and frequently prescribed NSAID. Through non-selective inhibition of COX-1 and COX-2, ibuprofen decreases the synthesis of pain- and inflammation-promoting prostaglandins (Chavez et al. 2003). Likewise, acetaminophen is a selective COX-2 inhibitor that is synergistic with ibuprofen by inhibiting prostaglandin production at the peroxidase (POX) site within COX 1/2 enzymes (Chavez et al. 2003; Anderson 2008).

There is no evidence of drug-drug interactions between acetaminophen and ibuprofen so they can be administered concurrently. The steady state kinetics of acetaminophen and ibuprofen are not changed when the two drugs are co-administered. The combination of both drugs does not affect the bioavailability of either drug (Merry et al. 2010; Wright et al. 1983). Pharmacokinetic studies also have demonstrated that administration of ibuprofen and acetaminophen in a fixed-dose combination tablet does not significantly alter the pharmacokinetic profiles of either drug (Tanner et al. 2010). Since ibuprofen and acetaminophen have different metabolic pathways and do not have drug-drug interactions between them, the combination product is not expected to have additional safety concerns compared to either of drugs alone.

2.3 Preclinical Data

2.3.1 Non-clinical Pharmacology (Pharmacodynamics)

Ibuprofen is a NSAID. Through non-selective inhibition of COX-1 and COX-2, ibuprofen decreases the synthesis of pain- and inflammation-promoting prostaglandins (Chavez 2003). Acetaminophen is a selective COX-2 inhibitor that is additive, if not synergistic, with ibuprofen by inhibiting prostaglandin production at the POX site within COX 1/2 enzymes (Chavez et al.

2003). It may also involve COX inhibition in the central nervous system and activation of central serotonergic pathways (Chavez et al. 2003; Anderson 2008).

2.3.1.1 Pharmacokinetics of Ibuprofen

The absorption of ibuprofen was studied *in vivo* and *in vitro*. The main site of absorption of ibuprofen occurs is the intestine, though some absorption of drug normally occurs in the stomach (Adams et al. 1969). Tissue accumulation and distribution of ibuprofen was investigated in rats and dogs. The levels of radioactivity in dog tissues did not exceed those in plasma after repeated doses of 8 mg/kg twice daily, but extremely high concentrations occurred in bile. Measurement of radioactivity in urine and faeces from dogs revealed that initially 60% of the dose was eliminated after 3-5 days.

2.3.1.2 Pharmacokinetics of acetaminophen

The absorption of acetaminophen by rat small intestine, colon and stomach was studied *in vivo* and *in vitro*. Small intestinal *in vivo* studies, using a wide range of drug concentrations, showed that absorption was efficient and uniform throughout the small bowel, no site showing preferential absorption and it occurs by passive transport (Bagnall et al. 1979). In a study that determined the concentrations of acetaminophen in blood and other tissues of dog and man, it was found that unconjugated acetaminophen is rapidly and uniformly distributed throughout the body fluids (Anderson 2008).

2.4 Clinical Data

2.4.1 Pharmacokinetics

The pharmacokinetic parameters for ibuprofen and acetaminophen were similar for the both fixed dose combination and monotherapy. The rate of absorption of both ibuprofen and acetaminophen was significantly delayed when the combination tablet was administered in the fed versus fasted state; median delay was 25 minutes for ibuprofen ($p > 0.05$) and 55 minutes for acetaminophen ($p < 0.001$). The pharmacokinetic parameters of ibuprofen (200 mg) and acetaminophen (500 mg) FDC tablet were compared with ibuprofen (200 mg) and acetaminophen (500 mg) monotherapy in an open-label, randomized study (Tanner et al. 2010). The multi-dose pharmacokinetics of the fixed-dose combination tablet are comparable to the single-dose pharmacokinetics and three times daily dosing may offer enhanced therapeutic effect for longer than twice daily dosing (Tanner et al. 2010).

2.4.2 Overview of Potential Efficacy, Safety and Benefit of Acetaminophen/Ibuprofen Combination

The efficacy of acetaminophen and ibuprofen combination in the treatment of nocturia is yet to be established. However, several clinical trials have shown that different NSAIDs may be effective against nocturia (Araki et al. 2004 and 2008; Addla et al. 2006 and 2014; 2006; Falahatkar et al. 2008).

An acetaminophen and ibuprophen combination has been found to be more effective than individual drugs in other indications such as analgesia (Mehlisch et al. 2010; Merry et al. 2010).

This is possibly because acetaminophen and ibuprophen inhibit prostaglandin production at different locations of the synthetic pathway (Chavez et al 2003; Anderson et al 2008). This combination may also be more effective than individual drugs in the treatment of nocturia, which is one of the objectives of the current study.

There were no changes in the adverse event (AE) profiles when the combination was compared to either drug alone (Mehlisch et al 2010).

2.5 Dose Justification and Risk Assessment

2.5.1 Dose Justification

The current clinical study involves subjects with nocturia being administered Paxerol tablets 30 minutes before bedtime daily for 2 weeks. The starting doses for acetaminophen and ibuprofen are considered the lowest effective dose, based on an *in vitro* study investigating the inhibitory effects of these agents on bladder smooth muscle cells (the site of action for anti-nocturia activities) stimulated by the inflammatory reaction to lipopolysaccharide (LPS) of *Salmonella typhymurium* (Report from Ohio State Univ. 2012). The concentrations of acetaminophen and ibuprofen used in this *in vitro* study were 5 and 50 μM, which are below the plasma Cmax concentrations after oral administration at therapeutic doses of these drugs in humans (see Table 2.5.1-1, below).

Table 2.5.1-1: Plasma Cmax After Oral Therapeutic Doses of Acetaminophen or Ibuprofen in Humans

Test Drugs			Plasma Cmax		
Drugs	**Dose (mg)**	**Molecular Weight (a.m.u.)**	**mg/L**	**μM**	**References**
Acetaminophen	500-1000	151.16	11-18	72-119	Tanner et al. 2010; van der Westhuizen et al. 2011
Ibuprofen	200-1,400	206.29	24-32	116-155	Tanner et al. 2010; Shah et al. 2001

Cmax = maximum plasma concentration post-administration.

This *in vitro* study showed that COX2, PGE2 and Tumor necrosis factor alpha (TNFα) secretions were inhibited by both acetaminophen and ibuprofen at both 5 and 50 μM (Table 2.5.1-2, next page). However, the degrees of inhibition were equivalent at these concentrations for both acetaminophen and ibuprofen. Since the inhibitory effect was not dependent on the concentrations between 5-50 μM, doses of acetaminophen and ibuprofen that can provide plasma concentrations around 5 μM (the lowest effective concentrations) of these drugs were chosen for the current clinical trial, suggesting doses of 325 mg and 150 mg for acetaminophen and ibuprofen for Paxerol, respectively.

Note that there are acetaminophen/ibuprofen combination dosage forms with doses higher than those of Paxerol (see next section). These combination high dosage forms are for relieving pain and decreasing the production of prostaglandins. It is a more subtle process in the attenuation of the activities of bladder smooth muscle cells, and the lower doses of these drugs chosen for Paxerol should be effective, as shown with the *in vitro* study on bladder smooth muscle cells.

Table 2.5.1-2: Autocoid Secretion by Normal Human Bladder Smooth Muscle Cells After *In Vitro* Stimulation with Inflammatory Stimulus, LPS, in the Presence and Absence of Acetaminophen or Ibuprofen

Stimuli	Drugs Used to Inhibit Autocoid Secretion	Subject 1	Subject 2	Mean	% Reduction Compared to Sham Treatment
COX2 Levels (normalized RFU's)					
None	None	230	199	214.5	--
LPS (10 µg/mL)	None	672	633	652.5	--
	Acetaminophen (5 µM)	428	457	442.5	32%
	Acetaminophen (50 µM)	399	509	454.0	30%
	Ibuprofen (5 µM)	417	456	436.5	33%
	Ibuprofen (50 µM)	427	466	446.5	32%
PGE2 Levels (pg/mL)					
None	None	<20.5	<20.5	<20.5	--
LPS (10 µg/mL)	None	1125	998	1061.5	--
	Acetaminophen (5 µM)	817	542	679.5	36%
	Acetaminophen (50 µM)	803	540	671.5	37%
	Ibuprofen (5 µM)	824	527	675.5	36%
	Ibuprofen (50 µM)	821	501	661.0	38%
TNFα Secretion (pg/mL)					
None	None	<5	<5	<5	--
LPS (10 µg/mL)	None	5725	4107	4916.0	--
	Acetaminophen (5 µM)	2338	2267	2302.5	53%
	Acetaminophen (50 µM)	2184	2056	2120.0	57%
	Ibuprofen (5 µM)	2733	2288	2510.5	49%
	Ibuprofen (50 µM)	2603	1997	2300.0	53%

RFU = relative fluorescence unit; LPS = lipopolysaccharide of *Salmonella typhymurium*, used as the inflammatory stimulus.

2.5.2 Risk Assessment

Maxigesic® is an immediate release (IR) dosage form of acetaminophen and ibuprofen combination, with the amount of acetaminophen (500 mg) being higher whereas that of ibuprofen (150 mg) being the same as Paxerol. This combination is an approved product in New Zealand and other non-US countries for temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. The approval of Maxigesic in these non-US countries was based on the safety and efficacy profile of this combination.

The fixed dose combination of two other IR dosage forms containing even higher doses of acetaminophen and ibuprofen have been investigated in a randomized, double-blind, placebo-controlled, parallel-group clinical trial (Mehlisch et al 2010). These two higher dose forms were: (i) ibuprofen 400 mg + acetaminophen 1,000 mg and (ii) ibuprofen 200 mg + acetaminophen 500 mg. These 2 higher combination dosage forms were compared to ibuprofen 400 mg alone, acetaminophen 1,000 mg alone, and to placebo. The results showed that the study drugs were well tolerated, with a similar frequency of all adverse events in all treatment arms including the placebo arm (Table 2.5.2-1, next page). There was no evidence that the study drugs had any clinically meaningful effects on vital signs. These results indicated that the combination of ibuprofen and acetaminophen in an IR formulation at doses higher than those of Paxerol, the investigational drug, were safe and well tolerated. Accordingly, Paxerol is not expected to induce any unexpected risk of adverse events due to its low doses, and because approximately 50% of Paxerol consist of IR and the other 50% is released over 6-8 hours via the sustained release (SR) formulation.

Table 2.5.2-1: Frequency (expressed as %) of Adverse Events That Occurred in >5% of Patients in the 5 Treatment Groups of Patients Undergoing Surgical Removal of Impacted Molars (Mehlisch et al 2010)

AE	Ibuprofen 400 mg/ APAP 1000 mg (n = 67)	Ibuprofen 200 mg/ APAP 500 mg (n = 33)	Ibuprofen 400 mg (n = 69)	APAP 1,000 mg (n = 34)	Placebo (n = 31)
Any AE	38 (56.7)	14 (42.4)	39 (56.5)	24 (70.6)	21 (67.7)
Treatment-related AE	10 (14.9)	6 (18.2)	19 (27.5)	12 (35.3)	13 (41.9)
Severe AE	11 (16.4)	6 (18.2)	14 (20.3)	11 (32.4)	11 (35.5)
Nausea	15 (22.4)	7 (21.2)	18 (26.1)	10 (29.4)	11 (35.5)
Vomiting	9 (13.4)	4 (12.1)	13 (18.8)	10 (29.4)	8 (25.8)
Headache	5 (7.5)	1 (3.0)	9 (13.0)	7 (20.6)	2 (6.5)
Dizziness	2 (3.0)	1 (3.0)	6 (8.7)	7 (20.6)	3 (9.7)

AE = adverse event; APAP = acetaminophen; n = sample size

2.6 Drug-Drug Interactions and Side effects

2.6.1 Acetaminophen

Interactions

Isoniazid: Isoniazid induces the cytochrome P-450 system, resulting in increased metabolism of acetaminophen, formation of toxic metabolites, depletion of glutathione stores, and subsequent hepatocellular injury. Subjects on isoniazid should use caution when taking acetaminophen since the potentially hepatotoxic effects may be amplified due to induction of the cytochrome P-450 system (Crippin 1993).

Anticoagulants: Acetaminophen may potentiate the anticoagulant effect of oral anticoagulants, increasing haemorrhagic risk in subjects receiving this combination of drugs (Mahé et al. 2004; Ornetti et al. 2005). Acetaminophen potentiates the anticoagulant effect of warfarin and therefore such subjects will be excluded from the trial (Mahé et al. 2005).

Metoclopramide: The absorption of acetaminophen is accelerated by metoclopramide, a drug that stimulates gastric emptying (Nimmo et al. 1973).

Chloramphenicol: Acetaminophen accelerates the clearance of chloramphenicol (Spika et al. 1986).

Cholestyramine: Simultaneous oral administration of cholestyramine reduces the absorption of acetaminophen (Dordoni et al. 1973).

Side effects

Few clinically significant drug interactions have been documented. There is probable potentiation of hepatotoxicity following an overdose from the acetaminophen metabolite N-Acetyl-P-Benzoquinone Imine (NAPQI) by enzyme-inducing drugs. The absorption of acetaminophen is dependent on gastric emptying; other drugs that alter gastric emptying can change its pharmacokinetics, but would not cause serious adverse effects (SAEs). Although animal experiments have demonstrated that many compounds can modify acetaminophen hepatotoxicity, these are unlikely to be important at therapeutic doses (Toes et al. 2005).

2.6.2 Ibuprofen

Interactions:

Angiotensin Coverting Enzyme (ACE) inhibitors: NSAIDs reduce the renal excretion of ACE inhibitors and may attenuate the hemodynamic actions of ACE inhibitors (Shionoiri 1993). These activities may explain the renal side effects of NSAIDs (see below).

Aspirin: Ibuprofen can interfere with the antiplatelet effect of low dose aspirin, potentially rendering aspirin less effective when used for cardio protection and stroke prevention (Information of Healthcare Professionals at FDA website). As a result, subjects using Paxerol should be instructed that if they are taking low dose aspirin it should be taken in the morning instead of at night.

Diuretics: NSAIDs attenuates the antihypertensive effect of thiazide and loop diuretics. NSAIDs may also inhibit the natriuretic response to diuretics with resultant adverse effects in subjects with heart failure and other forms of oedema (Webster 1985; Herchuelz et al. 1989).

Lithium: The administration of ibuprofen can increase steady-state plasma lithium concentrations and decrease lithium clearance (Kristoff et al. 1986; Ragheb 1987).

Side effects:

Gastrointestinal: Long term use of ibuprofen is associated with gastrointestinal (GI) bleeding. Upper GI bleeding is infrequent with prescription doses of ibuprofen and occurs with high doses on long term usage (Bjarnason 2007; Michels 2012). Ibuprofen at the maximum dose of 1200 mg/day for 7-10 days is also found to be well-tolerated (Doyle et al. 1999; Rampal et al. 2002).

Central nervous system: Side effects of NSAIDS include aseptic meningitis, psychosis, and cognitive dysfunction. Aseptic meningitis is found most commonly in subjects with lupus treated with ibuprofen, but it should be considered in any subject with meningitis if the subject has used NSAIDs. Psychosis, although infrequently reported with NSAIDs, should be suspected in an elderly subject started on a regimen of indomethacin who acutely develops disorientation, paranoia, or hallucinations. There appears to be some potential for memory dysfunction and attention deficits in elderly subjects treated with NSAIDs (Hoppmann et al. 1991). Drowsiness, tiredness, dizziness, light-headedness, nervousness, irritability and unsteadiness are reported with the use of ibuprofen (Furey et al. 1992).

Cardiovascular: Ibuprofen at low doses is least likely to increase cardiovascular risk. At doses more than 1200 mg/d and above, ibuprofen increases the risk (McGettigan et al. 2011; Trelle et al. 2011).

In 2015, FDA strengthened the labeling of all NSAIDs regarding increased cardiovascular risk, per FDA review of new safety information and the advisory committee's recommendations (http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm). The revised NSAID labels include the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease, or risk factors for it, have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors, because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

Renal: Ibuprofen can cause renal impairment in elderly subjects and subjects with coronary artery disease. Therefore renal function should be monitored when ibuprofen and other nonsteroidal anti-inflammatory drugs are prescribed (Murray et al. 1990). Use of ibuprofen may cause acute renal failure in subjects with asymptomatic, mild chronic renal failure (Welton et al. 1990).

2.6.3 Overdose

Acetaminophen over dose in children 10 years of age or younger can cause hepatotoxicity (Rivera-Penera et al. 1997). Acetaminophen overdose causes acute liver failure. Acetaminophen overdose subjects recover with early N-acetylcysteine (NAC) therapy and supportive care (Fontana 2008). The frequency of life-threatening complications from ibuprofen overdose is low. Mild gastrointestinal disturbances and central nervous system depression were the most common adverse effects (McElwee et al. 1990).

3. STUDY OBJECTIVES

The co-primary objectives are:

A. To assess the effect of different doses of Paxerol on the reduction in the number of nocturia episodes.
B. To assess the clinical benefit of different doses of Paxerol in reducing nocturia via assessment of nocturia quality of life (NQOL).

The secondary objectives are to assess the effects of different doses of Paxerol on:

A. Duration of First Undisturbed Sleep (DFUS)
B. Total hours of nightly sleep
C. Safety and tolerability

An exploratory assessment is to evaluate baseline urinary PGE2 production on the responsiveness of subjects to Paxerol.

4. STUDY DESIGN

This is a multi-center, double-blind, placebo-controlled study with two weeks of daily oral administration of one of three dose levels of Paxerol or placebo in subjects with nocturia. Eligible study subjects will be identified according to inclusion/exclusion criteria (see Section 5.0), and baseline assessments will be recorded.

Due to small sample size of 25 patients per group in this proof-of-principle dosing-finding trial, stratification according to gender and BMI will be difficult. However, similar distribution of patient types to the four treatment groups will be attempted by evenly assigning patients to the four treatment groups according to genders and BMI of <25, 25-30, and >30-<40.

Paxerol or placebo will be taken 30 minutes before bedtime daily for two weeks. Nocturia frequency, NQOL, DFUS, total hours of nightly sleep, safety and tolerability will be monitored before and after a two-week treatment period. Results from subjects treated with different doses of Paxerol and placebo will be assessed and compared. Baseline urinary PGE2 production will also be assayed to assess potential correlation between baseline urinary PGE2 production and responsiveness to Paxerol treatment.

5. SUBJECT SELECTION AND WITHDRAWAL

It is estimated that approximately 125 study subjects will be enrolled with 100 study subjects (25 subjects per arm) to complete the trial. The study will be conducted in multiple study sites.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

5.1 Inclusion Criteria

A. Subjects diagnosed with nocturia, as defined by International Continence Society (i.e., the interruption of sleep one or more times at night to void [van Kerrebroeck et al. 2002]), confirmed by evaluation in participating investigator's urology practice:
   - Nocturia is related to OAB (Diagnosis Code: 2015/16 ICD-10-CM [http://www.icd10data.com/ICD10CM/Codes/N00-N99/N30-N39/N32-/N32.81])
   - Nightly ≥2.5 times nocturia present for at least 3 months and not considered caused by persistent or recurrent urinary tract infection.
   - Post-Void Residual (PVR) urine volume must be <80 cc at the time of screening
   - Did not respond well to, or unwilling to have, lifestyle modification, behavioral and conservative therapies, such as dietary changes, timed voiding, urge suppression (e.g., pelvic floor exercises [PFE] at the time of urge episodes), biofeedback, etc.

B. Males or females, ≥18 years of age with Body Mass Index (BMI) <40.

C. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and must have a negative serum or urine pregnancy test within 1 week prior to enrollment or Visit 1.

D. Ability to understand and sign the study Informed Consent Form (ICF), communicate with the investigators, and understand and comply with the requirements of the protocol, including completion of participation in all phases of the study.

E. No current or medical history of:
   - Gastrointestinal bleeding or malformation
   - No bleeding diathesis
   - Restless leg syndrome.

F. Not using within 4 weeks before study initiation, or anticipating the use during the study, any of the following drugs:
   - antiplatelet or anticoagulant drugs (**Note:** Low dose aspirin is allowable if subjects take it in the morning.)
   - Any Selective Serotonin Re-uptake Inhibitors (SSRIs) (concurrent use of SSRIs and NSAIDs have been reported to increase the risk of upper gastrointestinal bleeding) or anti-diuretic medications. (Note: Diuretic medication is allowable if the subject is on a stable consistent morning dose.)
   - Warfarin

G. Resting heart rate between 55 and 100 beats per minute, inclusive of both.

5.2 Exclusion Criteria

A. Pregnant or nursing women.

B. Known presence of urinary tract infection (UTI) within 4 weeks before study initiation

C. Known sleep interruptions due to sleep apnea, dyspepsia or other gastro-intestinal symptoms, seizure disorders or other neurologic symptoms

D. Allergy to or intolerance of acetaminophen, ibuprofen, or any inactive component of the study drug formulations.
E. A history of allergy to aspirin or other NSAIDs.
F. Congenital or acquired structural abnormality of the genitourinary tract.
G. Prostate cancer of any stage that has required any treatment.
H. Any neurodegenerative disease (including but not limited to Parkinson's Disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Pick's Disease, Multi-Infarct Dementia or recent history of head trauma associated with concussion, stroke or serious cerebrovascular events) which may indicate problems in providing consistent and reliable "Patient-Reported Outcomes" (PRO) such as diary, Quality-of-Life, etc. required in this study.
I. Uncontrolled hypertension (blood pressure >140/90 mm Hg).
J. Serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, or New York Heart Association Class II, III or IV), severe debilitating pulmonary disease, or history of stroke (hemorrhagic or thrombotic), A-V malformation, or other cerebrovascular disease.
K. Receipt of any investigational drug or participation in any clinical trial within 30 days prior to study participation.
L. Use of acetaminophen, ibuprofen, acetylsalicylic acid (ASA) or any NSAID on the day of entry into the study or any anticipated use during the study. (**Note:** Low dose aspirin is allowable if subjects take it in the morning.) In the event of the need for any unanticipated use of such drugs during the trial, the timing and doses of such use should be carefully recorded and reported at the next visit to the clinic.
M. Any medical problem requiring uninterrupted use of acetaminophen, ibuprofen, or any NSAIDs, or any other pain medication.
N. Daily use of phosphodiesterase (PDE) inhibitors (such as sildenafil, tadalafil, vardenafil, avanafil, and udenafil) within 30 days prior to study or any anticipated daily use during the study. (**Note:** PDE inhibitors are known to have positive effect on voiding dysfunction and thus can interfere with the assessment of Paxerol [Ückert et al 2010].)
O. Subjects taking ACE inhibitors. (**Note:** Co-administration of NSAIDs with ACE inhibitors may result in deterioration of renal function.) (**Note:** ACE inhibitor medication is allowable if the subject is on a stable consistent morning dose.)
P. History of polyuria or evidence of polyuria (estimation of daily production >2.5 liters of urine).
Q. Uncontrolled Type 1 or 2 diabetes mellitus (HbA1c >7.0%).
R. Diabetes insipidus.
S. Reported significantly impaired renal function (Chronic Kidney Disease [CKD] stage 3 [moderate] of` glomerular filtration rate [GFR] <60 mL/min/1.73kg/m^2, as defined by the US-based Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines)
T. Any visual, motor or other sensory abnormality that might predispose to a fall on nocturnal arising to urinate.
U. Evidence of hyponatremia at baseline.
V. Any significant disease or abnormality of the neurological, visual, gastrointestinal, hepatobiliary, pulmonary, cardiovascular, genitourinary or musculoskeletal system other than those specified above that, in the opinion of the involved investigator, might compromise the ability of the prospective subject to participate in the study or that could confound interpretation of study results.

W. Any abnormality on screening medical history, physical examination or clinical laboratory examination other than those specified above that, in the opinion of the involved investigator, might confound interpretation of study results.
X. Subjects with known hepatitis, HIV-AIDS, or tuberculosis.
Y. Subjects with known dysrhythmia of any form.

5.3 Early Withdrawal of Subjects

Subjects who complete the two-week treatment and have all data collected by study personnel are considered to have completed the study. Subjects who do not complete the study will follow the procedures described in subsequent sections per visit.

5.3.1 When and How to Withdraw Subjects

If a subject is withdrawn from study participation, the subject's enrollment in the study will be terminated, study drug will be discontinued and no further data will be collected on the subject. However, efforts will be made to perform all assessments scheduled for the end-of-study visit (i.e., Visit 3) prior to subject withdrawal and complete the Subject Disposition form.

A subject may be withdrawn from further study participation under the following circumstances:

- At the subject's own request.
- Noncompliance with protocol procedures, as determined by the investigators.
- AE, with decision to be removed from study made by either the investigator or subject. (The investigator must notify the sponsor immediately if a subject is withdrawn because of an AE.)
- Decision by the investigator or sponsor that termination is in the subject's best medical interest or administrative decision for a reason other than that of an AE.
- General or specific changes in the subject's condition that renders the subject ineligible for further investigational treatment
- Lost to follow-up
- Sponsor decision to halt the entire study.

Subjects who withdraw should have end of trial procedures completed at the time of discontinuation. In all cases, the reason for withdrawal must be recorded in the Subject Disposition form and in the subject's medical records.

5.3.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. In case of withdrawal of a subject from the study, the primary reason for withdrawal should be clearly specified and the subject should, whenever possible, irrespective of the reason for withdrawal, as soon as possible be examined. All relevant assessments should be completed according to the schedule for the final visit (Visit 3), using a Subject Disposition form. The Subject Disposition Form supplements all assessments per Visit 3, and record the primary reason for withdrawn from the study.

5.3.3 Lost-to-Follow-Up

A subject is considered lost-to-follow-up if he/she misses one study visit or more, without a major reason agreed upon by the sponsor.

6. TREATMENT

6.1 Study Drugs

The study drugs are:

Paxerol Tablets: Each Paxerol tablet contains acetaminophen 325 mg and ibuprofen 150 mg. It is formulated to release approximately 50% of the acetaminophen and ibuprofen as IR and the other 50% being released as SR over 6-8 hours.

Placebo Tablets: Placebo tablets are formulated as Paxerol tablets, except that they do not contain any acetaminophen or ibuprofen.

It is important that the subjects not cut or bite into the tablets, since that would destroy the tablet's SR capabilities. Paxerol and placebo tablets are to be taken orally 30 minutes before bedtime daily for two weeks during the 2-week treatment period. Drinking fluids should generally be avoided just before retiring, but a small amount of water may be taken to facilitate swallowing of the study drug.

Subjects should void immediately after taking the study drug and again just prior to bedtime. This should provide improved results for those with significant post void residual urine.

Paxerol and placebo tablets will only be shipped to investigators who have been provided with all the required study documents, IEC/IRB approval, and have signed a final study agreement with the Sponsor (or an authorized representative).

6.2 Treatments to be Administered

Eligible subjects will be assigned to one of the four treatment groups, as outlined in Table 6.2-1 (below).

Table 6.2-1: Four Treatment Arms

Treatment Arm	Treatment	Tablets to be Taken By Subjects at Each Dose		
		Paxerol Tablet	Placebo Tablet	Total Number of Tablets
1	Low Dose Paxerol	1	2	3
2	Mid Dose Paxerol	2	1	3
3	High Dose Paxerol	3	0	3
4	Placebo	0	3	3

Paxerol and placebo are provided in tablet formulation. Paxerol is formulated to release approximately 50% of the acetaminophen and ibuprofen as IR and the other 50% being released as SR over 6-8 hours. It is important that the subjects not cut or bite into the tablet, since that would destroy the tablet's SR capabilities. Paxerol and placebo tablets are to be taken orally 30 minutes before bedtime daily for 2 weeks during the treatment period. Drinking fluids should generally be avoided just before retiring, but a small amount of water may be taken to facilitate swallowing of the study drug.

Subjects should void immediately after taking the study drug and again just prior to bedtime. This should provide improved results for those with significant post void residual urine.

6.3 Packaging and Labeling

Paxerol and placebo tablets are identical in appearance per double-blinding of the study design, and they are to be administered in the same manner. Paxerol and placebo are coded, and only the statistician will have the key to the code.

Labeling of Paxerol and placebo is consistent with 21 CFR 312.6 for investigational drugs.

6.4 Storage and Dispensing of Study Drug

All clinical drug supplies are to be stored in a secure, monitored, limited-access area in accordance with labeled storage conditions. Paxerol and matching placebo will be stored at room temperature at 20 to 25°C (68 to 77°F). The Investigator is to maintain accurate records related to dispensing of all clinical trial supplies during the study. These records shall include the amounts of drug supplied and the dates on which drug supplies are received from the Sponsor (or an authorized representative), dispensed to the subject, returned by the subject and returned to the Sponsor (or an authorized representative). If errors or damages in the clinical drug supply shipments occur, the Investigator must contact the Sponsor (or an authorized representative) immediately.

6.5 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a Screening number and if eligible for treatment, a Randomization number will be assigned. Due to small sample size of 25 patients per group in this proof-of-principal dosing-finding trial, stratification according to gender and BMI will be difficult. However, similar distribution of patient types to the four treatment groups will be attempted by evenly assigning patients to the four treatment groups according to genders and BMI of <25, 25-30, and >30-<40.

6.6 Blinding and Treatment Code Information

Neither the investigator nor the subject will be aware of which treatment is being administered. Coded and packaged medication will be provided to the investigational site and dispensed to the subjects. Paxerol and placebo tablets will be identical in appearance, shape, smell and taste, and packaged in the proper proportion to assure desired dosages and maintenance of the blinding. An investigator may request unblinding of a subject's treatment in case of a SAE the care of which requires knowledge of the treatment group. Treatment codes will be available to the study Medical Monitor. The investigator will document the request for unblinding and inform the Sponsor (or an authorized representative) when a code is broken.

For emergency and urgent unblinding of a subject, the investigator (or designee) should contact Dr. John Whisnant (Phone: 908-790-8888; Cell: 609-505-3162; E-mail: jwhisnant@brightech-intl.com).

6.7 Concomitant and Prohibited Medications

At the screening visit, the investigator will obtain any information about concomitant drug and non-drug treatments. In particular, the investigator will document all information regarding previous nocturia treatments, recording the generic name, and the start dates and stop dates. All nocturia treatments must be discontinued at screening.

All prior and concomitant treatments within 30 days of screening will be recorded for all enrolled subjects. At each study visit, the investigator will obtain and record any information about

concomitant illnesses and any therapeutic interventions, e.g., concomitant drug treatment/non-drug treatment, surgery, etc.
Where applicable, the following will be included:

(1) the names (generic preferably) of all drug treatments, non-drug treatments or procedures;
(2) start and stop date; and
(3) indication.

Any medication the subject takes, other than the study drugs specified in the protocol, is considered concomitant medication. All concomitant medications and non-drug treatments/procedures must be recorded in the subject's medical record and on the CRFs.

Use of the following medications is prohibited during the study period:

- Treatment with acetaminophen, ibuprofen, non-ibuprofen NSAID, or any other pain medication within 24 hours of study entry, and during participation in the study. (**Note:** Low dose aspirin is allowable if subjects take it in the morning.) In the event of need for any unanticipated use of such drugs during the trial, the timing and doses of such use should be carefully recorded and reported at the next visit to the clinic. This is important due to the possibility that Paxerol's efficacy could be impacted by such use, in which case the resulting data may need to be isolated from the overall results.
- Treatment with diuretic medication, anti-diuretic medication or SSRIs within 4 weeks of study entry, and during participation in the study. (**Note:** Diuretic medication is allowable if the subject is on a stable consistent morning dose.)
- Daily use of PDE inhibitors (such as sildenafil, tadalafil, vardenafil, avanafil, and udenafil) within 30 days prior to or during the study.
- Treatment with any investigational drug within 30 days prior to or during study participation
- Use of antiplatelet drugs, warfarin or other anticoagulant drugs within 4 weeks prior to or during participation in the study. (**Note:** Low dose aspirin is allowable if subjects take it in the morning.)

6.8 Treatment Compliance

Subject will be asked to return the remaining medication at the end of the treatment period. The quantity of returned study drugs will be counted for compliance. If compliance is less than 100%, the subject should report on which night he/she failed to use the drug. The treatment compliance data will be summarized and analyzed vs. efficacy and safety.

6.9 Drug Accountability

The Investigator is accountable for all clinical drug supplies shipped to the study site for the duration of the study. A final accounting of the clinical drug supplies will be required at the completion/termination of the study. The Investigator is required to provide written explanation for any discrepancies. All unused clinical drug supplies (except required retention samples) will be inventoried and returned to the Sponsor (or an authorized representative) by a designated study monitor. The Investigator will not be permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by the Sponsor (or authorized representative).

7. STUDY PROCEDURES

This investigation is a multi-center, randomized, double-blind, placebo-controlled study in adults with nocturia. Study duration for each subject is approximately 4 weeks, which includes screening, baseline assessment, two weeks of treatment with study drugs, and follow-up. On a case-by-case basis and in discussion with the Medical Monitor, some shifts for visit schedule may be permitted.

The study scheme is outlined in Table 7-1 (below).

Table 7-1: Study Design Schematic

	Events			
	Subject Consent, Eligibility and Baseline Assessments	**Pre-Treatment**	**Treatment with 1 of 3 Dose Levels of Paxerol or Placebo over 2 weeks**	**End of Study**
Study Day	Day 1	Day 15	Days 15-28	Day 29
Visit #	1	2		3

The study requires a total of 3 in-clinic visits. Each study visit may deviate by ± 1 working day or 2 weekend days. The window for each visit day will be recorded in real calendar time, and the total study treatment regimens will remain two weeks, and study days for assessments will be adjusted accordingly. For deviations greater than the visit window specified, subject continuation needs to be discussed with Medical Monitor (or designee). For subjects out of window, study treatment regimens will remain consistent with Appendix 1 and study days for assessments will be adjusted accordingly.

A signed and dated ICF must be obtained by the investigator prior to any screening procedures at this visit. The purpose and design of the study as well as the risks and benefits of the investigational product will be explained to the subjects. Subjects will be given time and opportunity to ask questions and decide about participation.

The procedures for conduct of the study are provided in Appendix 1, and they are outlined below:

Prior to trial entry, the following screening procedures will be performed:

Visit 1 (Day 1 - Subject Consent, Eligibility and Baseline Assessments):

1. Obtain written ICF from the subject, which must be obtained prior to any screening procedures.
2. Investigator reviews and assures subject eligibility according to applicable inclusion and exclusion criteria, including assessment of PVR <80 cc.
3. Record demographic data including date of birth and age, sex, and race/ethnicity.
4. Record medical history, including treatment of the lower urinary tract (duration of symptoms of urgency, frequency and urge incontinence, medical and surgical).
5. Record concurrent diseases and symptoms, concomitant medications, and any non-drug treatments/procedures.
6. Collect urinary sample for assessment of PGE2 production (see Section 8.3).
7. Perform physical examination (including body weight and height) and measure vital signs (blood pressure and heart rate), temperature and respiratory rate.

8. Clinical laboratory evaluation and urinalysis (see Section 8.2.4).
9. Dispense nocturia diary. Instruct subject regarding completion of the nocturia diary. Ensure that they know that a bathroom visit which coincides with the intention of getting up in the morning should not be considered nocturia. A bathroom visit that is followed by the intention of going back to sleep should be considered a nocturia event. In this latter case, it should be considered nocturia even if the subject fails to fall sleep due to insomnia or some other issue. Explain to subject that accurate reporting of the results will be critical in order to ensure success of the study. Advise subject that nocturia symptoms may change by a small or a large amount at various times. Remind subjects the importance of providing the required information accurately and review completion of diary by subjects. Remind subjects to void immediately after taking the study drug and once again just prior to bedtime for best results. Remind subjects that what they drink and when they drink it will affect urine output, so they should if possible try to remain consistent in their drinking habits each day, especially regarding drinking after 5 p.m. each day.
10. Schedule the next appointment, Study Visit 2 on Day 15±1 working day or ±2 weekend day.

Visit 2 (Day 15 - Pre-Treatment):

1. For women of child-bearing potential, a serum or urine pregnancy test. (The pregnancy test is to be performed within 1 week prior to enrollment or Visit 1.)
2. Record urinary symptoms based on International Prostate Symptom Score (I-PSS) (see Appendix 2).
3. Record concurrent diseases and symptoms, concomitant medications, and any non-drug treatments/procedures.
4. Collect the subject's nocturia diary. Review the diary with subject for completeness. If the subject's average nightly void when not using the study drug is on average less than 3 times per night, the subject should be removed from the trial.
5. Instruct subject to complete NQOL survey during the office visit.
6. Dispense nocturia diary. Instruct subject regarding completion of the nocturia diary. Ensure that they know that a bathroom visit that coincides with the intention of getting up in the morning should not be considered nocturia. A bathroom visit that is followed by the intention of going back to sleep should be considered a nocturia event. In this latter case, it should be considered nocturia even if the subject fails to fall sleep due to insomnia or some other issue. Explain to the subject that accurate reporting of the results will be critical in order to ensure success of the study. Advise subject that nocturia symptoms may change by a small or a large amount at various times. Remind subjects the importance of providing the required information accurately and review the completion of diary by subjects. Remind subjects to void immediately after taking the study drug and once again just prior to bedtime for best results. Remind subjects that what they drink and when they drink it will affect urine output, so they should if possible try to remain consistent in their drinking habits each day, especially regarding drinking after 5 p.m. each day.
7. Dispense study drugs, to be taken on Days 15-28, 30 minutes before bed.
8. Schedule the next appointment, Study Visit 3, on Day 29±1 working day or ±2 weekend day.
9. Instruct subject that at Visit 3 he/she will be asked to estimate the average amount of fluid consumed with the 3 tablets each night. If possible, an estimate in terms of ounces would be preferable. (**Note:** A cup of fluid is 8 ounces and a large glass of fluid could be 12-16 ounces.) Subject should also be instructed to use the smallest amount of fluid that he/she can in order to swallow the tablets comfortably.

Visit 3 (Day 29 - End of Study):

1. Record urinary symptoms based on International Prostate Symptom Score (I-PSS) (see Appendix 2).
2. Record concurrent diseases and symptoms, concomitant medications, and any non-drug treatments/procedures.
3. Perform physical examination (including body weight) and measure vital signs (blood pressure and heart rate), temperature and respiratory rate.
4. Clinical laboratory evaluation and urinalysis (see Section 8.2.4).
5. Instruct subject to complete NQOL survey during the office visit.
6. Collect unused study drug, perform Drug Accountability Reconciliation/Assess subject's compliance for taking study drug, quantify subject compliance and record on CRF.
7. Collect subject's nocturia diary. Review with subject for completeness.
8. Assess the occurrence of AEs. Record all directly observed AEs and all AEs spontaneously reported by the subject since the first dose of randomized study drug. Record any changes in the subject's medical conditions, concurrent diseases or symptoms on the Adverse Event form of the CRF.
9. Complete Subject Disposition Form.
10. Ask subject to estimate the average amount of fluid consumed with the 3 tablets each night. If possible, an estimate in terms of ounces would be preferable. (**Note:** A cup of fluid is 8 ounces and a large glass of fluid could be 12-16 ounces.)

8. ASSESSMENTS

8.1 Efficacy Assessments

8.1.1 Nocturia Diary

The subject will be asked to complete details of micturitions (timing and frequency) in the nocturia diary (see Appendix 3) for two weeks prior to treatment and during the two weeks of treatment on Days 15-28. Results from the diaries will be collected during Study Visit 2 (Pre-Treatment Visit) and Visit 3 (End of Study visit). Any ambiguities should be reviewed and clarified by the investigator in cooperation with the subject.

8.1.2 NQOL Questionnaire

Subjects will be required complete NQOL questionnaires during Visits 2 and 3. The questionnaires will assess certain aspects of micturition symptoms and their impact on the subjects' quality of life. The site study coordinator will review these questionnaires for completeness with the subject at each visit and prior to the subject leaving the study site. Subjects' responses to these questionnaires must be entered into the CRF by study coordinator or appropriate designee for all randomized subjects.

NQOL questionnaire (Appendix 4) is a self-administered, 15-item, validated questionnaire that assesses how much the subject has been bothered by nocturia symptoms recently. It consists of two distinct components. The first 9 questions constitute the domains sleep and energy. Questions 10-14 constitute the domains of coping, concern, and social function. Question 15 constitutes overall rating. Subjects will rate each statement from 0 (lowest NQOL) to 4 (highest NQOL).

8.2 Safety Assessments

8.2.1 Vital Signs (Blood Pressure and Heart Rate), Temperature and Respiratory Rate

Blood pressure, heart rate, temperature and respiratory rate will be recorded during Visits 1 and 3. The sitting blood pressure and heart rate will be measured after being seated and relaxed for 5 minutes. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the non-dominant arm. Heart rate will be measured in the brachial/radial artery for at least 30 seconds.

8.2.2 Physical Examination

Physical examination (including body weight and height [only Visit 1]) will be performed during Visits 1 and 3.

8.2.3 Clinical Laboratory Testing and Urinalysis

Clinical laboratory tests will include hematology, coagulation, and chemistry panels and urinalysis at Visits 1 and 3.

Clinical laboratory tests include:

- Complete blood count (CBC), which includes: RBC, Hgb, Hct, WBC, WBC differential, and platelet count
- blood coagulation: INR
- Electrolytes and chemistry: Na+, K+, Cl-, HCO3-, Ca++, BUN, creatinine (with estimated clearance), AST, ALT, alkaline phosphatase, LDH, total bilirubin, albumin, and HbA1c.

Urinalysis includes pH, specific gravity, glucose, protein, blood, ketones and urine culture. Urine culture is not needed if other urinalysis test results are negative and there are no symptoms of urinary tract infection.

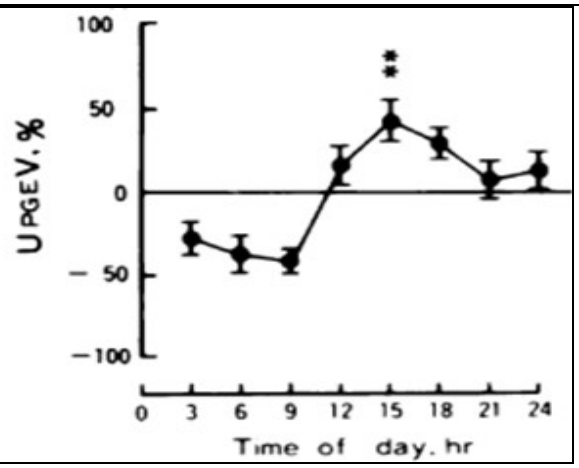
8.3 Assessments of Baseline Urinary PGE2 Production

8.3.1 Background, Introduction and Rationale

As an exploratory assessment, baseline urinary PGE2 production will be assayed, and potential correlation between baseline urinary PGE2 production and the degree of nocturia reduction induced by Paxerol treatment will be evaluated. The rationale for this exploratory assessment is that subjects with nocturia and OAB average approx. 5 times above normal levels of urinary PGE2 production (Kim et al. 2005 and 2006; Cho et al. 2013; Liu et al. 2010). Prostaglandins, the locally derived regulatory factor, play an important role in regulating renal water excretion (Kramer et al. 1981) and rhythmic contraction of detrusor muscle of the bladder wall (Collins et al. 2009, Klausner et al 2011; Takagi-Matsumoto et al. 2004, Tsukimi et al. 2004; Olesen & Fenton 2013). Therefore, nocturia may be related to high urinary prostaglandins production.

It is our speculation that Paxerol responders will be those who have elevated urinary PGE2 production (thus resulting in low nocturnal bladder capacity), since the two drugs that comprise Paxerol synergistically inhibit the production of PGE2 in the bladder (Collins et al. 2009, Klausner et al 2011; Takagi-Matsumoto et al. 2004, Tsukimi et al. 2004). For patients whose nocturia is caused by polyuria or causes other than low nocturnal bladder capacity caused by excessive urinary PGE2 production, Paxerol may not provide any benefit. Since published articles have reported that subjects with nocturia and OAB average approx. 5x above normal levels of PGE2 (Kim et al. 2005 and 2006; Cho et al. 2013; Liu et al. 2010), most eligible study subjects in this trial (i.e., subjects with OAB) should benefit from Paxerol.

Urinary PGE2 production naturally follows a circadian pattern (see Figure 8.3-1, next page). In order to accurately assay urinary PGE2 production, we need to collect a timed urine sample, including the total volume of urine that comprises the sample, the time since the last complete bladder void, and the time of day. Also, the levels are significantly higher for men (average 278-431 pgs/minute or 400-620 ng/24 hours, according to Mayo Clinic reports) than for women (average 115-124 pgs or 166-178 ng/24 hours, according to an NIH publication). Therefore, assessment should subdivided according to the genders.

Figure 8.3-1: Circadian variations of urinary prostaglandin E excretion. Each point represents % deviation from mean value of 24 hours calculated as follows: (average value of each time - mean value of 24 hours) x 100/mean value of 24 hours. Vertical bar represents standard error of the mean (SEM). Information is derived from Abe et al. (1981).	

8.3.2 Procedures

The procedures in assaying urinary PGE production are outlined below.

A. Collection of Urinary Sample

During Visit 1 (and Visit 2, if collection of urinary sample is not successful during Visit 1), ask each subject to drink 16 ounces of water upon arrival. Each subject is to have two separate but consecutive voids in association with collection of the urinary sample. For the first void, it is to be done upon arrival at the clinic and the exact time of the void must be noted. This void is to attempt to empty the subject's bladder as much as possible, and no urinary sample will be collected. For the second void, it is the very next void by the subject. This can be the void that the subject naturally intends to have while he/she is still in the clinic during the visit. If the subject does not plan to void while in the clinic, he/she is to be asked to void before leaving the clinic. In the second void, all of the urine needs to be collected for the measurement of urinary volume (see Section B below), and the actual time between these two voids is to be precisely recorded.

B. Measurement of Urinary Sample Volume

Once collected, the urine sample (in its pre-weighted container) is to be weighed, and the weight of the urine sample is the difference between the weight of the urinary sample in its pre-weighted container and the weight of the container. The volume of urine (in mL) is the weight (1 gm = 1 mL) of the urinary sample collected. This weight should be recorded.

C. Handling and Storage of Urinary Sample for PGE2 Measurement

Once the weight of the urinary sample has been recorded, approximately 2-3 mL of the urine sample should be retained in plastic tube with a screw on top. (**Note:** The exact volume of the urine sample is not important, as long as it is at least 1 mL in volume.) The rest of the urine may be discarded unless it is needed for some other purpose. The urine sample tube must be labeled according to subject ID and date of sample collection. Records should be kept so that each urinary sample vial is linked to patient's name, the date and time of collection, time between voids, and total sample volume collected. The vial should be stored frozen at -20°C

until it is ready for shipment to the lab for PGE2 measurement. Urine samples can be safely stored in a frozen state for up to 180 days.

D. Shipment of Urinary Sample

After all patients have provided urine samples or before 180 days after urinary sample collection, all samples should be shipped to:

Raj Pandian, Ph.D.
Director of Scientific Affairs
Pan Laboratories, LLC
15375 Barranca Parkway, Suite E-101
Irvine, CA 92618

The return address should be:

Mr. David Dill
Wellesley Pharmaceuticals
3 Valley View Drive
Newtown, PA 18940

The proper return address will ensure that the proper testing is completed and the invoice and results are sent to the right place.

After each shipment, email Mr. David Dill at ddill@wellesleypharma.com and provide tracking number information in the email so that the shipment can be tracked.

The sample containers should be packaged in Styrofoam box, or a box lined with Styrofoam, of at least ¾ inch thick. The box should also contain 15 pounds of dry ice that is contained in a plastic bag that is not perfectly sealed at the top. Likewise, the box should not be perfectly sealed since otherwise cracking of the Styrofoam box can occur as the dry ice evaporates. The box should be prepared in a Monday through Thursday afternoon and should be sent for next morning delivery to Pan Laboratories. It is important that shipment that results in potential arrival on a Saturday, Sunday or holiday should not be made, as Pan Laboratories is closed on these days and the dry ice will only last about 30 hours.

E. Description of the Urinary PGE2 Assay

ANALYTICAL PRINCIPLE

Urine samples are diluted and assayed by an immunoassay. PGE2 is measured by a competitive enzyme immunoassay (EIA), using goat anti-mouse immunoglobulin coated to microtiter plates. PGE2 antibody (monoclonal) and PGE2 peroxidase are incubated with calibrators and samples. The color is developed using tetramethylbenzidine (TMB) substrate and read at 450 nm. The color is low when the concentration of PG-E2 is high.

REAGENTS

PGE2 multiformat EIA kit (Research Use only kit will be used).

PROCEDURES

1. Bring all the required reagents to room temperature, including microtiter plate coated with goat anti-rabbit gamma globulin.
2. Dilute the standard in assay diluent from 1.9 to 500 pg/mL.
3. Pipette 100 µL of diluted standard, diluted controls and diluted samples (1:10) as per protocol. Add 25 µL of horse radish peroxidase (HRP) conjugated PGE2 and 25 ul of anti-PGE2. Incubate at room temperature, shaking in a rotator at 400 RPM for 2 hours.
4 Following incubation, the plates are washed with wash buffer 4 times (manually).
5. Add 100 µL of substrate (TMB) to develop the color. Substrate is incubated for 30 min at room temperature, without shaking. At the end of the incubation, 50ul of stop solution is added. The color turns into yellow. The Developed color is read at 450 nm, within 20 minutes, in a Multiskan enzyme-linked immunosorbent assay (ELISA) reader.

CALCULATION

A standard curve (four-parameter curve) is produced using the calibrator concentrations and the optical density for respective calibrator. The sample optical density is read using the standard curve. The results for the samples are corrected for dilution and expressed in pg/ml of urine.

8.4 Data Management

8.4.1 Case Report forms

Electronic case report forms (eCRF) will be used to record all data as well as other data that will be transferred electronically from an external source. The investigator or an authorized person will record subject data in the eCRF in a precise and accurate manner. The data should be recorded as soon as they are available.

8.4.2 Data Management Plan and Database Design

The CRO will generate a study specific Data Management Plan (DMP) to detail the data handling guidelines and procedures related to managing the data for the lifecycle of the study. As applicable, other study specific plans, guidelines, or specifications will be generated. For example, a Data Review Plan (DRP) will be generated to specify the checks that are to be performed on patient data to raise data discrepancies/queries. Additionally specifications and study specific documents will be generated to detail database development and testing activities. The DMP will also include data handling guidelines for protocol deviations and details to complete database finalization and lock activities.

8.4.3 Handling of External Data

External data consists of data that is not recorded in eCRFs. Data may be received in electronic format or paper printout. As applicable a Data Transfer Plan will be generated and agreed upon with each Vendor to document the key variables used uniquely identify each sample record, file

and data formats, and data handling. Any data transferred between the 2 vendors must contain origin, date created, date sent and number of records at minimum.

8.4.4 Medical Encoding

Medical encoding will be performed by trained personnel at the CRO and approved by Wellesley Pharmaceuticals, LLC. Adverse Events and Medical History verbatim terms are encoded using MedDRA, latest version available when approving the DMP.

Concomitant Medications verbatim terms are encoded using WHODD codes.

8.5 Justification of Sample Size

This is a Phase II dose-ranging study consisting of four treatment groups - 3 dose levels of Paxerol and placebo. Due to the dose-finding nature of the trial, the sample size will be 25 subjects per treatment group.

8.6 Statistical Analysis

8.6.1 General Consideration

The co-primary objectives of assessing effects of different doses of Paxerol, when compared to placebo, on the reduction in the number nocturia episodes and clinical benefit of the reduction in nocturia on quality of life. The secondary objectives are to assess the effects of different doses of Paxerol, when compared to placebo, on DFUS, total hours of nightly sleep, and the safety and tolerability. An exploratory assessment is to evaluate baseline urinary PGE2 production on the responsiveness of subjects to Paxerol.

Due to the small sample size of 25 subjects per treatment arms in this dose-ranging proof-of-concept trial, outcome from any statistical analysis will be limited. As such, the analyses of the results from this trial will be primarily descriptive, including the numerical change from baseline in frequency of nocturia vs. placebo.

Summary statistics for continuous variables will include mean, standard deviation, median and range. Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier plots. Data listings will be created to support tables and present data.

All statistical analyses will be conducted using SAS® Version 9.2 or above (SAS Institute, Cary, NC). All probability values under the null hypotheses shown in the tables will be rounded to 3 decimal places. If a rounded p-value is equal to 0.000, the result will be displayed as "< 0.001" in the tables.

8.6.2 Efficacy Endpoints

Co-Primary Efficacy Endpoints:

The co-primary objectives of assessing effects of different doses of Paxerol, when compared to placebo, on:

A. Reduction in the number nocturia episodes, based on the number of nightly voids as recorded by the subjects in the nocturia diary
B. Clinical benefit of the reduction in nocturia, based on NQOL survey

Additionally, the rate of responders who achieve at least 33% of reduction in mean number of nocturia in compared to baseline in each treatment arm, and potential dose-related effects will also be evaluated.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints for this study are change from baseline in the mean values of the following variables in each treatment arm, when compared to placebo:

A. DFUS (the time between bedtime and when the subject first go to the bathroom after bedtime begins, as recorded by the subjects in the nocturia diary)
B. total hours of nightly sleep (the time between bedtime and wakeup time, as recorded by the subjects in the nocturia diary)

8.6.3 Safety Endpoints

One of the secondary endpoints is safety for assessing the safety and tolerability of different doses of Paxerol, compared to placebo.

Safety variables include AEs; discontinuations; vital sign (blood pressure and heart rate); clinical lab (hematology, chemistry, and coagulation); urinalysis; physical examinations including weight); and body temperature. All safety endpoints will be summarized descriptively. No statistical inference will be applied to the safety endpoints.

8.6.4 Exploratory Assessment

An exploratory assessment is to examine if there is a relationship between baseline urinary PGE2 production and the responsiveness of subjects to Paxerol. Potential correlation between baseline urinary PGE2 production and the degree of reduction in nocturia will be examined via regression analysis.

9. ADVERSE EVENTS - RECORDING AND REPORTING

9.1 Adverse Events and Adverse Drug Reactions

Definition of Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom (including an AE occurring from drug abuse, an AE occurring from drug withdrawal and any failure of expected pharmacological action), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definition of Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

An unexpected ADR is an ADR, the nature or severity of which is not consistent with the applicable product information, such as the Investigator's Brochure (IB) or the United States Product Insert (USPI).

9.2 Recording of Adverse Events

AEs will be recorded from the start of Paxerol administration through 30 days after the final visit (Visit 3 or early discontinuation). Any AE should be recorded on the Adverse Events form in the CRF and source documents. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should group together into a single term signs and symptoms, which constitute a single diagnosis.

The existence of or change in an AE may be concluded due to the necessity to administer a concomitant medication, from a spontaneous report of the subject, from the physical examination or from special tests like electroncardiograms (ECGs), electroencephalograms (EEGs), laboratory assessments or other study specified tests (source of AE).

AEs that occur at the start of treatment and those that occur up to 30 days after the last dose of study drug will be handled as any other AE occurring during treatment with study drug.

Each AE is to be evaluated for severity, seriousness, duration and causal relationship to the investigational drug. The action taken with study drug, the concomitant treatment/therapy introduced and the outcome as well as whether the event led to study termination will also be recorded.

Severity:

The severity of the AE should be graded according to Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. The website is:

evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Drug-Event Relationship:

The causal relationship between the study drug and the AE should be characterized according to the following:

- Unrelated – there is not a reasonable possibility that the study drug caused the AE.
- Possible – the association of the AE with the study drug is unknown, however the event is not reasonably supported by other conditions.
- Probable – a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of the disease state, or concomitant medication reactions) do not appear to explain the AE.
- Related - there is a reasonable causal relationship between study drug and the AE.

Outcome:

The outcome of the AE should be classified according to the following definitions:

- Recovered / resolved: the event has resolved (no further symptoms are present and no treatment is being received by the subject).
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Fatal: the subject died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the subject's death. Fatal events require immediately reporting to the Sponsor (or an authorized representative).
- Unknown: may only be used in the event that the subject is lost to follow-up and no reliable data can be obtained.

All efforts should be made to classify the AE according to the above categories.

(**Note:** When the AE is ongoing, provide appropriate wording such as "not yet recovered", "not yet resolved", "ongoing", etc. in the outcome section of the Adverse Events form in the CRF. Do not leave the outcome section blank.)

9.3 Follow-up of Adverse Events

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved or judged no longer clinically significant, or if a chronic condition, until fully characterized. All follow-up results are to be reported to the Sponsor (or an authorized representative).

9.4 Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions (SADRs)

Definitions of Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADRs)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of an existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether other conditions should also be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. These should also be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.5 Reporting Serious Adverse Events

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the study drug, must be reported immediately (within 24 hours of the study site's knowledge of the event) by telephone or fax to the Sponsor or the Sponsor's authorized representative at the following numbers:

John Whisnant, MD
Brightech International, LLC
285 Davidson Ave
Somerset, NJ 08873
Phone: 908-790-8888; Cell: 609-505-3162; E-mail:jwhisnant@brightech-intl.com

The report will contain as much available information concerning the SAE to enable the Sponsor (or an authorized representative) to file a report, which satisfies regulatory reporting requirements. In addition to the initial 24-hour report, a completed, separate SAE Report form is to be sent to the

Sponsor (or an authorized representative) via fax or mail within 48 hours of the event. These timelines apply to initial reports of SAEs and to all follow-up reports.

All SAEs will be recorded on the SAE Report form, the Adverse Events form in the CRF, and source documents. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described.

SAEs that are spontaneously reported within 30 days of a subject's last visit are to be collected and reported as previously described.

9.6 Reporting of Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) to Regulatory Authorities and Investigators

Adverse reactions will be considered as unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference safety information.

All SUSARs will be subject to expedited reporting. Additionally, SUSARs that occur within 30 days of the last dose of the investigation drug qualify for expedited reporting.

The Sponsor (or an authorized representative) is responsible for submitting reports of SUSARs to the appropriate national regulatory authorities within the required reporting period. All Investigators participating in ongoing clinical studies with the study drug will be notified by the Sponsor (or an authorized representative) of all SUSARs that require prompt submission to the IEC/IRB. The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for notifying the IECs/IRBs in writing of the SUSARs within the required reporting timelines. Copies of the notification will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

10. DATA HANDLING AND RECORD KEEPING

The investigator must maintain all documentation relating to this study. Essential documents (as defined in the ICH Guideline of GCP) must be retained until after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or at least 5-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Sponsor.

In any case, all study records such as but not limited to CRFs, regulatory documents, the subject identification code list, subject files and other source data that support CRFs must be retained for at least 15-years after the completion or discontinuation of the study. If the investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred and Sponsor notified in writing. Sponsor will notify the investigator in writing when the study-related records are no longer needed.

11. RANDOMIZATION AND BLINDING

Subject will be administered each treatment according to the randomization scheme produced by the statistic group of the Sponsor.

12. PROTOCOL AMENDMENTS

Any prospective change to the protocol will be agreed between the investigator and the Sponsor prior to its implementation. Any such amendments will be submitted for consideration to the approving IRB/IEC. Ethical approval will be requested for any change to this protocol which could affect the safety of the subjects, the scope/design of the study, any increase in dosage or duration of exposure to the trial medication, an increase in the number of subjects treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

During the trial, a Clinical Research Associate (CRA) will have regular contact with the site, including monitoring visits. Monitoring will be undertaken as described in the monitoring manual. The CRA will be available between visits if the investigator or other staffs at the center need information and advice.

13.2 Source Document Verification

Source documents are original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, x-rays, subject files and records kept at the pharmacy, recorded data from automated instruments etc.). All information in original records and certified copies of clinical findings, observations, or other activities in the study are considered Source Data.

The location of source data will be registered on a form specifying where the source data can be located, e.g. medical record, CRF, lab reports etc.

Unless precluded by the list below, the CRF may be the source document.
The following information must be available for Source Data Verification (SDV) in source documents other than the CRF:

- Date of ICF.
- Gender and date of birth.
- Clinical Trial Protocol number.
- Statement that the subject is participating in the clinical trial.
- Data for evaluation of eligibility criteria.
- Relevant medical history and diagnosis.
- Screening Number and Subject Number.
- Administration of trial drug.
- All study visit dates.
- Adverse Events.
- Concomitant Medication.
- Date and reason for exclusion or withdrawal.

Source data verification will require direct access to all original records for each subject. During the first monitoring visits, 100% SDV will be performed. At later monitoring visits, SDV will be done for the items during the first monitoring where discrepancies was found and on few data randomly chosen before the monitoring visit.

13.3 Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority or an IEC both national and foreign, may visit the center to perform audits or inspections. The purpose of an audit or inspection is to systematically and independently examine all trial related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The

investigators should contact the sponsor/Contract Research Organization (CRO) immediately if contacted by a regulatory agency about an inspection at their centre. The sponsor has the right to perform an audit of the study site and the CRO. Such audit will be conducted according to a specific audit plan.

14. ETHICAL CONSIDERATIONS

14.1 Independent Ethics Committee or Institutional Review Board

The trial will be conducted in accordance with Good Clinical Practice (ICH-GCP) guidelines and the World Medical Association's Declaration of Helsinki and applicable regulatory requirements.

The study will not commence until favourable opinion has been obtained from the appropriate IEC or IRB.

14.2 Ethical Conduct of the Trial

The investigator(s) will respect and protect the confidentiality of the subject in all possible ways. Subject identification, other than subject number and initials, will not appear in any CRF pages or other documents given to the Sponsor. Only the investigator and the persons authorized to verify the quality and integrity of the study (inspector/auditor) will have access to subject records where the subject can be identified.

14.3 Subject Information and Informed Consent

The investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the trial. Subjects must also be notified that they are allowed to discontinue from the trial at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subjects' signed and dated ICF must be obtained before conducting any trial related procedure.

The signed and dated ICFs will be kept by the investigator and will be available for inspection by the sponsor and the authorities. A copy of the signed Written ICF must be given to the subject.

The written ICF will explain that the trial data will remain confidential in accordance with national data legislation. Initials and subject number will solely identify subjects in the database. The written ICF will also explain that data verification purposes, authorized representatives of the sponsor, a regulatory authority, or an IEC, require direct access to parts of the hospital or practice records relevant to the trial, including the subject's medical history.

15. FINANCE AND INSURANCE

The involved parties will be insured, in accordance with applicable laws and regulations, against financial loss resulting from personal injury and/or other damages, which may arise as a consequence of this study.

The sponsor will provide adequate insurance for the investigator according to regulatory requirement(s). If required by local law, study subjects enrolled into this clinical trial will also be insured against any injury resulting from the clinical study.

16. PUBLICATION POLICY

The CRO and investigator agree to keep strictly confidential all unpublished information and results concerning this study. Unpublished information must not be published or disclosed without Sponsor's prior written approval. Sponsor reserves all the rights to declare any of its data confidential or of business importance and will provide it only to the regulatory authorities of concern on request/demand.

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