CLINICAL STUDY PROTOCOL

A Double-Blind, Randomised, Placebo-Controlled, Phase I/IIa, Dose Titration Trial to Evaluate the Safety, Tolerability and Efficacy of Oral Litoxetine up to 30 mg versus Placebo BID in subjects with Urinary Incontinence

Protocol Number:	IXA-CSP-002
Investigational Medicinal Product:	Litoxetine 10 mg, 20 mg
Indication:	Urinary Incontinence
Phase:	I/IIa
Sponsor:	IXALTIS Archamps Technopole Acti'Tech 6 60 avenue Marie Curie 74160 Archamps, France
Principal Scientific Advisor	Pr. Roger Dmochowski MD, MMHC Department of Urology Vanderbilt University Nashville, TN USA
IND:	PIND 132328
Protocol Version and Date:	Version 1 Final Sep 14, 2017 Version 2 Amendment 1, June 28, 2018 Version 3 Amendment 2, October 10, 2018

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Double-Blind, Randomised, Placebo-Controlled, Phase I/IIa, Dose Titration Trial to Evaluate the Safety, Tolerability and Efficacy of Oral Litoxetine up to 30 mg versus Placebo BID in subjects with Urinary Incontinence

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

_____ _____

Elisabeth Svanberg MD, PhD
Chief Development Officer
IXALTIS SA

Date

_____ _____

Jasna Knezevic MD
Independent Medical Safety Expert

Date

Declaration of the Principal Scientific Advisor

Title: A Double-Blind, Randomised, Placebo-Controlled, Phase I/IIa, Dose Titration Trial to Evaluate the Safety, Tolerability and Efficacy of Oral Litoxetine up to 30 mg versus Placebo BID in subjects with Urinary Incontinence

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

Principal Scientific Advisor

Pr. R Dmochowski MD, MMHC Dept of Urology Vanderbilt University Nashville, TN	Date

Declaration of the Investigator

Title: A Double-Blind, Randomised, Placebo-Controlled, Phase I/IIa, Dose Titration Trial to Evaluate the Safety, Tolerability and Efficacy of Oral Litoxetine up to 30 mg versus Placebo BID in subjects with Urinary Incontinence

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, Case Report Forms, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Ethics Committee (EC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study centre

_____ _____

Name Date
Title
Institution

PROTOCOL SYNOPSIS

Title:	**Title:** A Double-Blind, Randomised, Placebo-Controlled, Phase I/IIa, Dose Titration Trial to Evaluate the Safety, Tolerability and Efficacy of Oral Litoxetine up to 30 mg versus Placebo BID in subjects with Urinary Incontinence
Protocol Number:	IXA-CSP-002
Phase:	I/IIa
Sponsor:	IXALTIS
Principal Advisor:	Pr. R Dmochowski
Objectives:	The primary objective of this study is to **evaluate the safety and tolerability of** litoxetine up to 30 mg versus placebo administered orally twice daily (BID) for 8 weeks in subjects with a diagnosis of urinary incontinence (UI). The secondary objectives of this study are to **evaluate the efficacy** of litoxetine up to 30 mg BID compared to placebo in subjects with a diagnosis of UI.
Design:	All subjects will enter the Screening Placebo Run In Period during which eligibility will be assessed, and subjects will receive a single-blind (subject blind) placebo treatment, where subjects must have at least 7 days of daily diary symptom collection (which will include a weekend). Subjects who continue to meet eligibility criteria at the end of the Run-in Period, including collection of diary data, (at least 7 incontinence episodes per week in the diary entries) will enter the Treatment Period. Subjects will be randomly assigned (2:1) to receive study drug (litoxetine for dose titration 10 mg, 20 mg, 30 mg) or placebo BID. Litoxetine treatment will be provided with dose titration, starting with 10 mg BID for 1 week, escalated to 20 mg BID for 1 week, and subsequently escalated to 30 mg BID for 6 weeks for a total litoxetine treatment duration of 8 weeks. Placebo treatment will be matched. If the subject does not tolerate the last dose level escalation (ie can not tolerate 30 mg BID), the dose can be reduced to the previous dose level (20 mg BID). If the patient does not tolerate the lowered dose level (20 mg BID) s/he will be discontinued from the study. After 8 weeks of treatment, doses will be reduced by 50% over 1 week to taper off treatment. A safety follow up visit will occur 4 weeks after treatment is permanently stopped (total study duration 15 weeks)
Inclusion Criteria:	All subjects aged 18 to 70 will be **eligible for inclusion** in this study if all of the following criteria apply: 1. Willing to provide written informed consent 2. Have symptoms of urinary incontinence for at least 3 consecutive months

	3. For male subjects: If subject has undergone any prostate procedure, this must have occurred at least 6 months prior to screening 4. Have at least 7 incontinence episodes per week in the diary entries for the Screening Placebo Run In Period 5. Subject is ambulatory and able to use the toilet independently 6. If subjects use pelvic floor exercises, subjects must have been on a stable exercise and activity regime for at least 3 months prior to screening and that regime must remain stable during the treatment period 7. Subject has a body mass index (BMI) $\geq$ 19 kg/m^2 but $\leq$ 35 kg/m^2 BMI=weight [kg] / height [m^2} 8. Subjects must have a pre-dose mean systolic/diastolic blood pressure of $\leq$ 140/90 mmHg before randomization can occur 9. For female subjects: Must not be pregnant, lactating, or actively trying to become pregnant, Subjects who are premenopausal and of childbearing potential must have a negative pregnancy test at Screening (serum) and at Day 0 (urine) and must use a medically acceptable and effective method of birth control for the duration of the study, which can include: a. Having a male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject b. Use of double-barrier methods of contraception; condoms with the use of caps (with spermicide) and intra-uterine devices are acceptable c. Use of hormonal contraceptives (oral, depots, patches, etc.) with double-barrier methods of contraception as outlined above d. True abstinence: When this is in line with the preferred and usual lifestyle of the subject (period abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception) 10. Subjects taking oral contraceptives or hormone replacement therapy (women) or hormone adjuvant therapy (men) must have a stable dose and regimen for $\geq$ 3 months prior to entry into the study
Exclusion Criteria:	A subject will not be eligible to participate in the study if they meet any of the following criteria: 1. History of anti-incontinence surgery in past 12 months 2. Use of Botox for the treatment of urinary incontinence in the past 12 months

	3. Current or recent (3 months) use of any pharmacologic agent used to treat symptoms of urinary incontinence 4. For women: Grade III/IV pelvic organ prolapse; defined per clinical practice 5. For women: History of pelvic prolapse repair or urethral diverticulectomy within 12 months of Screening For men: urethral surgery within 6 months of Screening. 6. History of interstitial cystitis or bladder-related pain 7. Subjects with concurrent (at Screening), recent (within 30 days), chronic, or recurrent (> 4 per year) urinary tract infections (positive dipstick for urinary tract infection and abnormal microscopic evaluation, signs and symptoms) or unevaluated microhematuria 8. History of diagnosed gastrointestinal obstructive disorders 9. Chronic severe constipation 10. History of radiation cystitis or history of pelvic irradiation 11. Electrostimulation, biofeedback, or bladder training therapy (behavioural therapy), during the previous month prior to Screening, or the intention to initiate such therapies during the study period. Pessaries and implants are also excluded. 12. Postvoid residual (PVR) urine volume > 150 mL 13. Diagnosis of dementia 14. Diagnosis of epilepsy 15. Diagnosis of acute narrow-angle glaucoma 16. History of mania or diagnosis of bipolar disorder and/or seizures 17. Subjects with uncontrolled hypertension 18. Documented history of myocardial infarction, unstable angina, and/or has undergone coronary artery bypass surgery and/or percutaneous transluminal coronary angioplasty in the past year 19. Congestive heart failure (New York Heart Association Class III or IV heart failure; Appendix 3) 20. Any concurrent condition or any clinically significant abnormality on the Screening physical examination, laboratory tests, electrocardiogram (ECG; including ischemic heart disease), Hepatitis B or C, which, in the opinion of the Investigator, may affect the interpretation of safety or efficacy data, or which otherwise contraindicates participation in a clinical study with litoxetine: a. Hypersensitivity to litoxetine or any of its ingredients b. History of clinically significant drug hypersensitivity c. Subjects with current (within 2 years) urogenital neoplasms or malignancies including bladder, uterine or cervical cancer (not

	applicable to male subjects with prostate cancer in whom a prostatectomy has been performed) d. Subjects with neuropathology that could affect the lower urinary tract or nerve supply, including but not limited to multiple sclerosis, stroke, Parkinsonism, or spinal cord injury e. Subjects with diabetes insipidus f. Clinically significant or unstable, endocrine, hepatic, renal, immunologic, or lung disease (ie, active chronic obstructive pulmonary disease), or malignancy other than non-melanomatous skin cancer
	21. Severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m^2)
	22. Severe hepatic impairment (Child-Pugh B or greater)
	23. Current or recent (6 months) treatment for depression, or a current diagnosis of depression or have a state of depression or suicidality at Screening.
	24. History of current or recent (6 months) suicidal ideation and behaviour (SIB), or history of any suicide attempt in the past 12 months.
	25. History of an addiction to drugs or alcohol within 5 years prior to screening, or of alcohol or substance abuse within the past year, as determined by the Investigator.
	26. Current use of the following medications:, any serotonergic medication, nonselective irreversible monoamineoxidase inhibitors (MAOIs), cytochrome P450 (CYP)1A2 inhibitors (such as fluvoxamine, ciprofloxacin, or enoxacin), cytochrome P450 (CYP) 2D6 inhibitors (bupropion, fluoxetine, metoclopromide, paroxetine, quinidine), pimozide and thioridazine, and any other medication that would be considered a safety risk for co-administration with litoxetine (See Section 5.6.2 Prohibited Medications)
	27. Participation in a clinical study within the month prior to Screening, or exposure to an investigational drug which has not washed out for at least 5 half-lives since its last administration, prior to Screening
	28. In the opinion of the Investigator, is at risk of non-compliance with study procedures, or cannot read, understand, or complete study-related materials (including electronic diaries), particularly informed consent
	29. Participation in any clinical study of an investigational drug that may affect urinary function within 3 months prior to Screening

Number of Subjects:	Approximately 95 subjects are expected to be enrolled into a 2-week, single-blind (subject blind), Screening Placebo Run-In Period. It is expected that 20% of subjects will not qualify for randomization after Screening Placebo Run-In. The study is expected to randomize approximately 78 subjects into the double-blind treatment where subjects will be allocated to litoxetine (dose titration 10 mg, 20 mg, 30 mg) or matched placebo BID in a 2:1 ratio. A post randomisation dropout rate of 30% has been estimated, resulting in 60 evaluable subjects.
Countries/Number of Sites:	Up to 15 sites in the US
Investigational Medicinal Product:	Litoxetine 10 mg, 20 mg, Batch number for active pharmaceutical ingredient: 100193-01
Reference Therapy:	Placebo
Duration of Participation:	The study will include a 2-week single-blind (subject blind) Screening Placebo Run-In Period; and a 8-week double-blind Treatment Period. The Treatment Period will be followed by a 1-week Dose-tapering Period. Subjects will be return to the clinic for a safety Follow-up Visit 4 weeks after treatment is completed, for a total study duration of 15 weeks.
Criteria for Evaluation: **Safety Assessments:**	Safety assessments will be conducted throughout the trial and will include physical examinations, vital signs, clinical laboratory evaluations, 12-lead electrocardiograms (ECGs), and adverse events (AEs).
Efficacy Assessments:	Efficacy will be assessed by numbers of urinary incontinence episodes and number of incontinence pads used
Endpoints:	**Primary:** • Incidence and severity of AEs and Adverse Events of interest (urinary retention, withdrawal symptoms) over the course of the study. • Adverse Events of special psychiatry interest (nervousness, anxiety, panic attacks, insomnia, aggression, mania, suicidal ideation, development/worsening of depression) over the course of the study • Suicidal Adverse Events and Adverse Events suggestive of abuse potential (described in Section 6.2.2.3) will be analysed, and detailed narratives provided • Haematology, chemistry, and urinalysis • Actual change from end of the Screening Placebo Run-In Period in ECG readings and Week 8. ECG parameters of interest include: ventricular rate, QT interval, corrected QT interval, PR interval, and QRS duration • Actual change from end of the Screening Placebo Run-In Period to each visit in standardised cuff systolic and diastolic blood pressure and radial heart rate **Secondary:** The following Efficacy endpoints will be explored

	• Percentage change from end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence episodes/24 hours • Absolute change from end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence episodes/24 hours • Proportion of subjects who become continent at Week 8 • Change from end of the Screening Placebo Run-In Period in the number of incontinence pads used per week
Statistical Methods:	**Study Populations:** The Safety Population (SP) is defined as all subjects who are randomised and receive the study drug, and undergo at least 1 visit. The intent-to-treat (ITT) population includes all subjects who are randomized The modified intent-to-treat (mITT) population includes all subjects who are randomized, receive at least 1 dose of study drug, and provide an end of study primary efficacy endpoint. The Per Protocol (PP) population is defined as those subjects who meet the ITT criteria and have completed the trial without a major protocol violation. The efficacy analysis will be performed on the ITT, mITT, and PP populations. The primary efficacy analysis will be performed on the ITT population with the analysis of the primary end-point on the mITT and PP populations as part of the secondary efficacy analysis. The efficacy analysis planned is a mixed effects model with repeated measure (MMRM). Percent reduction in incontinence episodes as the response variable is the first efficacy endpoint. The factor variable will be dose and centre. The covariate will be end of the Screening Placebo Run-In Period episodes of incontinence. Visits within subjects will provide the random effects of the mixed model. There is only one hypothesis so there will be no adjustment for multiplicity. Further efficacy analysis will be conducted similarly, with appropriate baseline measures. There will not be an adjustment for multiple comparisons for these secondary endpoint analyses. **Safety Analyses:** Safety data will be presented and analysed using the Safety Population. • Serious adverse events (SAEs) will be listed and summarised in a table, including a description of each event, the time to onset, the severity, and the relationship to trial drug. • All AEs (excluding SAEs) will be listed, and their time to onset, frequency, severity, and relationship to the trial drug will be tabulated by treatment. Adverse events that occur before the time of the first treatment with the trial drug will be considered a non-treatment- emergent AE (non-TEAE), and all AEs that occur after the time of the first treatment with trial drug will be considered TEAEs. Non-TEAEs will be summarised separately from TEAEs. • Adverse Events of Special Interest (AESI) include urinary retention, psychiatric adverse events (nervousness, anxiety, panic attacks, insomnia, aggression, mania, suicidal ideation, development/worsening of depression) and withdrawal symptoms will be specifically summarized.

	• Suicidal adverse events and abuse related events will be specifically summarized • Premature withdrawals from the trial will be displayed and summarised by primary reason and treatment. • Abnormal laboratory values will be listed and their incidence, severity and relationship to the trial drug will be tabulated by treatment. Change from Screening will be summarised by treatment. Individual changes (shift tables), individual clinically significant abnormalities, and modified World Health Organisation (WHO) ratings will also be presented. • While total white blood cell (WBC) count will be expressed in absolute values, differential count will be expressed as both absolute count and percentage of WBCs. • Abnormal physical examination findings will be summarised over time. • Concomitant medications will be presented in summary tables and listings. They will be classified according to whether they were taken before the trial (and ongoing into the trial), or started during the trial period. • Vital signs will be summarised by treatment group and listed by subject. • Any AE/SAE which occurs during the 30-day Follow-up Period or following discontinuation of treatment will be listed and summarized separately, and include a description of the event, time to onset, frequency, severity and relationship to treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE inhibitors	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
BID	Twice daily
CRA	Clinical Research Associate
CYP	Cytochrome P450
DA	Dopamine
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
ICF	Informed consent form
ICH	International Council on Harmonization
ICS	International Continence Society
IRAE	Immediately reportable adverse event
IRB	Institutional Review Board
ISF	Investigative site file
ITT	Intent-to-treat (population)
IWR-IM	Interactive Web-based Randomization and Inventory Management System
MACR	Missing completely at random
MMRM	Mixed-Effect Model for Repeated Measure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat (population)
MUI	Mixed urinary incontinence

Abbreviation	Definition
NE	Norepinephrine
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
PP	Per Protocol (population)
PVR	Postvoid residual volume
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SNRI	Selective norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUI	Stress urinary incontinence
TEAE	Treatment-emergent adverse event
UI	Urinary incontinence
UK	United Kingdom
US	United States
UUI	Urge urinary incontinence
WBC	White blood cell (count)
WHO	World Health Organisation

1 INTRODUCTION

1.1 Background

1.1.1 Urinary Incontinence

Urinary incontinence (UI) is a common and chronic condition affecting both males and females, although it is more commonly seen in women. For both genders, prevalence increases with age, occurring frequently in the geriatric population (65 years and older) (Adams P, 2010).

While not life-threatening, urinary incontinence can have a significant negative impact on the psychological well-being, social functioning and overall quality of life of those affected. Prevalence varies greatly with age and the definition used, although not all affected patients are in need of medical treatment (Adams P, 2010).

Women suffer most commonly from stress urinary incontinence (SUI) or a combination of SUI and urge urinary incontinence (UUI) ie, Mixed Urinary Incontinence (MUI). Men suffer primarily from urgency, due to obstruction from prostate hypertrophy, and have a higher incidence of 'dry' symptoms (urgency, frequency without urinary incontinence). Stress incontinence in men accounts for less than 10%, mainly occurring post prostate surgery (Adams P, 2010).

Urinary incontinence is estimated to affect 400 million people worldwide (Fultz NH, Burgio K, Diokno AC et al. Burden of stress urinary incontinence for community dwelling women. Am J Obstet Gynaecol 2003; 189: 1275-1282.

Global Forum on Incontinence). The prevalence is variable but has been reported to be as high as 55%.

The International Continence Society (ICS) defines incontinence as "involuntary loss of urine." which leads to a significant impact on quality of life, social seclusion, psychological stress, and economic burden. This condition is often underreported since many people avoid discussing the problem with their doctor due to embarrassment, lack of knowledge about treatment options, or a belief that urinary incontinence is an inevitable part of ageing. The burden of urinary incontinence is high in financial terms, with the total annual cost of urinary incontinence in the United States (US) estimated to be as high as $32 billion (Wood LN, 2014), and similar costs have been described also in other countries; Total cost of managing urinary incontinence in women over the age of 40 years in the United Kingdom (UK) in 2004 was £301 million, 0.3% of the total National Health Service (NHS) budget (Turner DA, 2004). Costs borne by women in out-of-pocket expenses was £230 million (Fultz NH, 2003) or £290 per woman per year (Papanicolaou S, 2005).

Urinary incontinence can be managed initially by lifestyle modifications, with reduction of excessive fluid intake, timed voiding, weight loss if required, and bladder and pelvic floor muscle training. Drug treatments are available for over-active bladder, with anticholinergic drugs the mainstay of treatment for cases that do not respond to lifestyle modification. Several agents

are currently available including oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, and darifenacin (Adams P, 2010).

Many women are unable to tolerate anticholinergic drugs and 30-91% discontinue them after 1 year. If patients do not respond to a treatment attempt of anticholinergic drugs, beta3 agonists or minimally invasive treatment options are available, with intravesical injection of onabotulinum toxin A, sacral neuromodulation, and posterior tibial nerve stimulation available as potential options (Adams P, 2010).

1.1.2 Litoxetine for the Treatment of Urinary Incontinence

Serotonin plays an important role in centrally modulating the reflexes of continence/micturition; 5-HT potentiates the guarding reflex which allows continence by increasing urethral pressure and inhibits the micturition reflex responsible for voiding. Animal studies have shown that increased levels of 5-HT and norepinephrine (NE), in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle during the storage phase of the micturition cycle. Studies with duloxetine support a similar mechanism in women, believed to result in stronger urethral closure during urine storage with physical stress.

Animal studies have confirmed that litoxetine increases the urethral sphincter pressure, and also demonstrated that litoxetine improves bladder capacity through a relaxation effect of the detrusor. Taken together these effects suggest that litoxetine could have therapeutic benefit in Urinary Incontinence, a condition for which there remain an unmet medical need.

The 5-HT selectivity of litoxetine, and the weaker affinity for NE and epinephrine (E) as well as for dopamine (DA) transporters has the potential to provide a good cardiovascular safety profile, and reduce the risk of nausea which is the most frequent side effect following treatment with 5-HT reuptake inhibitors.

Further details can be found in the Investigator's Brochure (edition 2), which contains comprehensive information on the investigational product.

1.2 Risk/Benefit Assessment

To date, 10 Phase 1 studies and 3 Phase 2 studies have been performed with litoxetine. Litoxetine has been evaluated in 154 healthy subjects and 445 patients with depression either as a capsule or a tablet containing litoxetine drug substance with excipients. Clinical pharmacology data has shown that doses up to 50 mg BID were acceptable, the open-label Phase 2 study in depression explored doses up to 100 mg daily, and subsequent double-blind, placebo-controlled studies explored doses up to 60 mg daily for a duration of 6 weeks. While study effects were observed in subjects with depression, the efficacy of litoxetine compared to placebo was negligible. In these studies, litoxetine safety information did not show any negative cardiovascular effects. The most common AEs were headache, nausea, and dyspepsia. The safety profile of litoxetine is acceptable and in line with the known and well established safety profile of 5-HT reuptake inhibitors. No AEs in the clinical studies have been reported which would

preclude development of litoxetine in the new indication of Urinary Incontinence and Adverse Events will continue to be monitored throughout the study, including AEs of special interest (i.e., urinary retention, psychiatric adverse events and withdrawal effects).

Non-clinical studies have demonstrated effects of litoxetine on urethral sphincter and bladder capacity, which are key features for micturition and continence. The “dual action”-inhibitory effect on detrusor muscle activity and excitatory effect on urethral sphincter- provides a scientific rationale to evaluate whether litoxetine treatment may be a treatment option for subjects with UI. One phase 2 study is currently ongoing with litoxetine in women suffering from MUI, and, while early in its conduct, the adverse events reported to date confirm the data previously reported.

The safety and tolerability of litoxetine was mainly determined on data from 445 subjects included in depression studies, receiving daily doses up to 100 mg daily, up to 6 weeks duration, to support the current use of litoxetine at doses 20, 40, and 60 mg daily (10, 20 and 30 BID) for the currently proposed 8-week treatment period, while the non- clinical pharmacology supports the scientific rationale to evaluate litoxetine in the indication of UI. The safety data from the comprehensive nonclinical study program support the proposed Phase I/IIa study. Further details can be found in the Investigator's Brochure (edition 1).

Taken together the Risk/Benefit for the use of litoxetine in the proposed study phase 1/2a is considered acceptable.

1.3 Rationale

Urinary incontinence is a condition which can have a significant negative impact on the psychological well-being, social functioning and overall quality of life of those affected. There remains an unmet medical need to identify treatment options for patients suffering from UI. The “dual action”-inhibitory effect on detrusor muscle activity and excitatory effect on urethral sphincter- provides a scientific rationale to evaluate whether litoxetine treatment may be a treatment option for UI.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of litoxetine (dose titration 10 mg, 20 mg, 30 mg) compared to placebo administered orally twice daily (BID) for 8 weeks in subjects with a diagnosis of UI.

2.2 Secondary Objectives

The secondary objective of this study is to explore efficacy of litoxetine (dose titration 10 mg, 20 mg, 30 mg) compared to placebo administered orally twice daily (BID) for 8 weeks in subjects with a diagnosis of UI.

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a Phase 1/2a, double-blind, randomised, placebo-controlled, parallel-group study in subjects 18 to 70 years old diagnosed with UI.

The study will include a 2-week, single-blind (subject blind) Screening Placebo Run-In Period and an 8-week double-blind Treatment Period. The Treatment Period will be followed by a 1-week Dose-tapering Period. Subjects will return to the clinic for a safety Follow-up Visit 4 weeks after treatment is completed for a total study duration of 15 weeks. No interim analysis is planned.

All subjects will enter the Screening Placebo Run-In Period during which eligibility will be assessed and placebo run in medication will be provided. During this period, 7 days daily diary symptoms will be collected. Subjects who continue to meet eligibility criteria after the Screening Placebo Run-In period, including collection of diary data will enter the Treatment Period and be randomly assigned (2:1) to receive study drug (litoxetine 10 mg, 20 mg, 30mg, or placebo) BID.

Litoxetine treatment will be provided with dose titration, starting with 10 mg BID for 1 week, escalated to 20 mg BID for 1 week, and subsequently escalated to 30 mg BID for 6 weeks' duration (for a total litoxetine treatment period of 8 weeks). Placebo treatment will be matched.

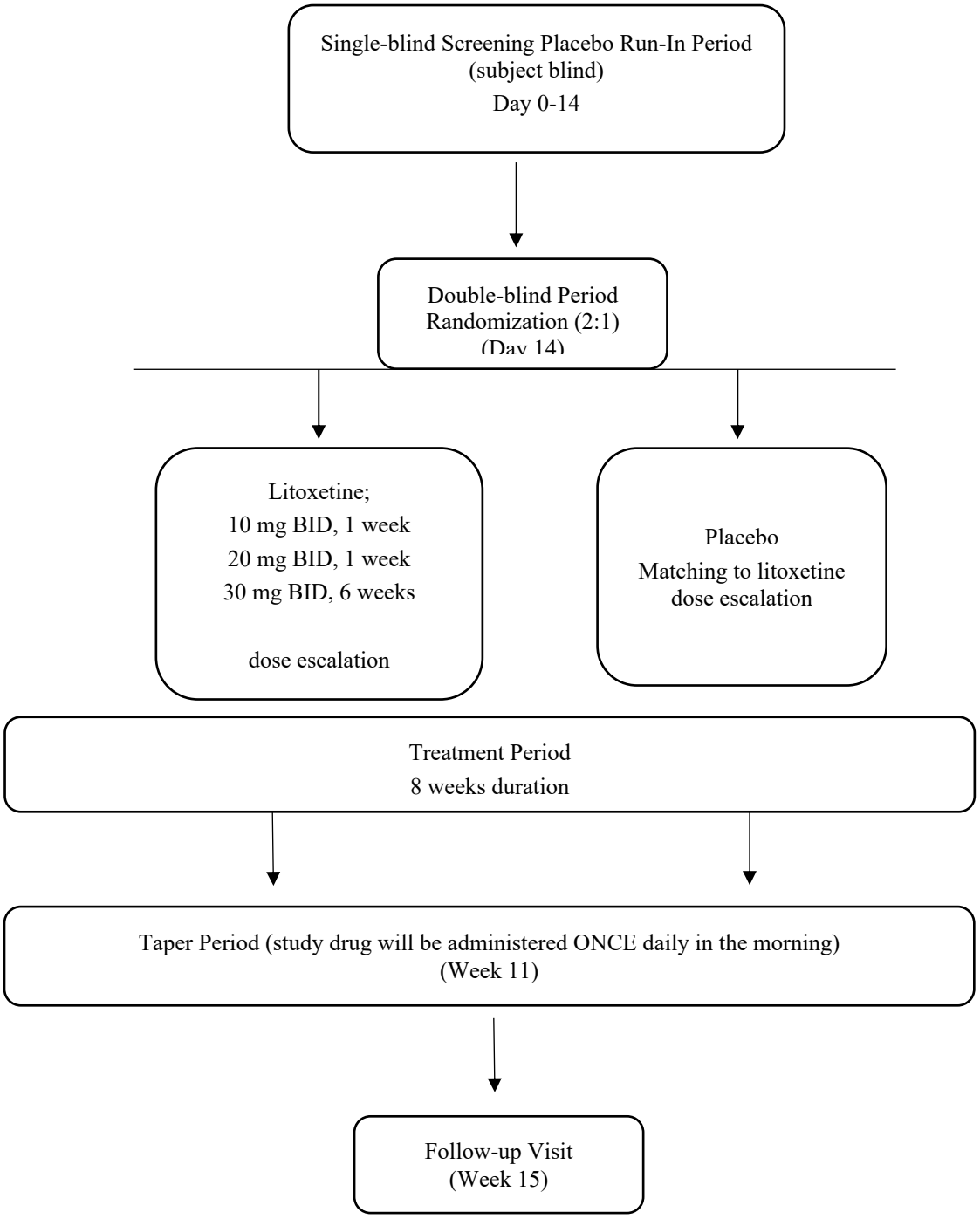
If the subject does not tolerate the last dose level escalation (ie cannot tolerate 30 mg BID), the dose can be reduced to the previous dose level (20 mg BID). If the patient does not tolerate the lower dose level (20 mg BID) s/he will be discontinued from the study. After 8 weeks of treatment, doses will be reduced by 50% over 1 week to taper off treatment. A safety follow up visit will occur 4 weeks after treatment is permanently stopped (total study duration 15 weeks)

Safety assessments will be conducted throughout the trial and will include physical examinations, vital signs, evaluation of psychiatric status (suicidality, depression symptoms, anxiety and sleep related symptoms), clinical laboratory evaluations, 12-lead electrocardiograms (ECGs), and adverse events (AEs).

Efficacy will be assessed by number of urinary incontinence episodes and the number of incontinence pads used.

A schedule of assessments is provided in Appendix 2. A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



BID = twice daily

3.2 Discussion of Study Design

Litoxetine' s initial development as an antidepressant (discontinued in the 1990's due to absence of effect) has included 12 phase 1 studies in HVs. The current development in Urinary

Incontinence (UI) is based on the scientific rationale and preclinical data showing effect on both detrusor and sphincter, and the definition of the condition used in this protocol adheres to clinical practice and ICS guidelines. The present study, for which safety is the primary endpoint, will include patients diagnosed with UI and is designed as a phase 1/2a study. The inclusion of a placebo arm is based on recent European Medicines Agency (EMA) guidelines for the development of medications for UI (European Medicines Agency, UI Guideline 2013). The dose titration posology serves to explore safety and tolerability following a sequential increase in dose, rather than as a fixed dose regimen. The selection of safety parameters for determination of subject eligibility and for safety analysis reflect the FDA's recommendation for evaluation of SSRIs, including attention to psychiatric adverse events and events indicative of abuse potential. Inclusion of subjects in the age range 18-70 is reflective of the expectation that UI may affect all age groups, with increasing prevalence with age (FDA Guidance General Consideration for the Clinical Evaluation of Drugs). The choice of efficacy endpoint (percentage change from end of the Placebo Run-in Period to Week 8 in the number of incontinence episodes/24 hours) is a clinical measure to explore whether litoxetine has a clinically relevant treatment effect on patients' reported symptomatology and patient reported outcome measures in a clinical practice setting. The 2-week Screening Placebo Run-In Period serves to control for the placebo effect which is anticipated to be relatively large.

4 STUDY POPULATION

The study population will consist of subjects with UI. Subjects must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

In addition, to assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the litoxetine Investigator Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational products being used in the study.

4.1 Inclusion Criteria

Subjects aged 18 to 70 will be **eligible for inclusion** in this study if all the following criteria apply:

1. Willing to provide written informed consent
2. Have symptoms of urinary incontinence for at least 3 consecutive months
3. For male subjects: If subject has undergone any prostate procedure, this must have occurred at least 6 months prior to screening
4. Have at least 7 incontinence episodes per week in the diary entries for the Screening Placebo Run-In Period
5. Subject is ambulatory and able to use the toilet independently
6. If subjects use pelvic floor exercises, subjects must have been on a stable exercise and activity regime for at least 3 months prior to screening and that regime must remain stable during the treatment period
7. Subject has a body mass index (BMI) ≥ 19 kg/m^2 but ≤ 35 kg/m^2 (BMI=weight [kg] / height [m^2})
8. Subjects must have a pre-dose mean systolic/diastolic blood pressure of $\leq 140/90$ mmHg before randomization can occur
9. For female subjects: Must not be pregnant, lactating, or actively trying to become pregnant. Subjects who are premenopausal and of childbearing potential must have a negative pregnancy test at Screening (serum) and at Day 0 (urine) and must use a medically acceptable and effective method of birth control for the duration of the study, which can include:
    a. Having a male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject
    b. Use of double-barrier methods of contraception; condoms with the use of caps (with spermicide) and intra-uterine devices are acceptable
    c. Use of hormonal contraceptives (oral, depots, patches, etc.) with double-barrier methods of contraception as outlined above

d. True abstinence: When this is in line with the preferred and usual lifestyle of the subject (period abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)

10. Subjects taking oral contraceptives or hormone replacement therapy (women) or hormone adjuvant therapy (men) must have a stable dose and regimen for ≥ 3 months prior to entry into the study

4.2 Exclusion Criteria

Individuals who meet any of the following criteria are not eligible to participate in the study.

1. History of anti-incontinence surgery in past 12 months
2. Use of Botox for the treatment of urinary incontinence in the past 12 months
3. Current or recent (3 months) use of any pharmacologic agent used to treat symptoms of urinary incontinence
4. For women: Grade III/IV pelvic organ prolapse; defined per clinical practice
5. For women: History of pelvic prolapse repair or urethral diverticulectomy within 12 months of Screening.
   For men: urethral surgery within 6 months of Screening.
6. History of interstitial cystitis or bladder-related pain
7. Subjects with concurrent (at Screening), recent (within 30 days), chronic, or recurrent (> 4 per year) urinary tract infections (positive dipstick for urinary tract infection and abnormal microscopic evaluation, signs and symptoms) or unevaluated microhematuria
8. History of diagnosed gastrointestinal obstructive disorders
9. Chronic severe constipation
10. History of radiation cystitis or history of pelvic irradiation
11. Electrostimulation, biofeedback, or bladder training therapy (behavioural therapy), during the previous month prior to Screening, or the intention to initiate such therapies during the study period. Pessaries and implants are also excluded.
12. Postvoid residual (PVR) urine volume > 150 mL
13. Diagnosis of dementia
14. Diagnosis of epilepsy

15. Diagnosis of acute narrow-angle glaucoma
16. History of mania or diagnosis of bipolar disorder and/or seizures
17. Subjects with uncontrolled hypertension
18. Documented history of myocardial infarction, unstable angina, and/or has undergone coronary artery bypass surgery and/or percutaneous transluminal coronary angioplasty in the past year
19. Congestive heart failure (New York Heart Association Class III or IV heart failure; Appendix 3)
20. Any concurrent condition or any clinically significant abnormality on the Screening physical examination, laboratory tests, electrocardiogram (ECG; including ischemic heart disease), Hepatitis B or C, which, in the opinion of the Investigator, may affect the interpretation of safety or efficacy data, or which otherwise contraindicates participation in a clinical study with litoxetine:
    a. Hypersensitivity to litoxetine or any of its ingredients
    b. History of clinically significant drug hypersensitivity
    c. Subjects with current (within 2 years) urogenital neoplasms or malignancies including bladder, uterine or cervical cancer (not applicable to male subjects with prostate cancer in whom a prostatectomy has been performed)
    d. Subjects with neuropathology that could affect the lower urinary tract or nerve supply, including but not limited to multiple sclerosis, stroke, Parkinsonism, or spinal cord injury
    e. Subjects with diabetes insipidus
    f. Clinically significant or unstable, endocrine, hepatic, renal, immunologic, or lung disease (ie, active chronic obstructive pulmonary disease), or malignancy other than non-melanomatous skin cancer
21. Severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m^2)
22. Severe hepatic impairment (Child-Pugh B or greater)
23. Current or recent (6 months) treatment for depression, or a current diagnosis of depression or have a state of depression or suicidality at Screening
24. History of current or recent (6 months) suicidal ideation and behaviour (SIB), or history of any suicide attempt in the past 12 months.
25. History of an addiction to drugs or alcohol within 5 years prior to screening, or of alcohol or substance abuse within the past year, as determined by the Investigator

26. Current use of the following medications:, any serotonergic medication, nonselective irreversible monoamineoxidase inhibitors (MAOIs) , cytochrome P450 (CYP)1A2 inhibitors (such as fluvoxamine, ciprofloxacin, or enoxacin), cytochrome P450 (CYP) 2D6 inhibitors (buproprion, fluoxetine, metoclopramide, paroxetine, quinidine), pimozide and thioridazine, and any other medication that would be considered a safety risk for co-administration with litoxetine (See Section 5.6.2 Prohibited Medications)
27. Participation in a clinical study within the month prior to Screening, or exposure to an investigational drug which has not washed out for at least 5 half-lives since its last administration, prior to Screening
28. In the opinion of the Investigator, is at risk of non-compliance with study procedures, or cannot read, understand, or complete study-related materials (including electronic diaries), particularly informed consent
29. Participation in any clinical study of an investigational drug that may affect urinary function within 3 months prior to Screening

4.3 Subject Withdrawal and Replacement

The participation of an individual subject may be discontinued prematurely for reasons such as:

- Withdrawal of written informed consent
- Required treatment with any medication known or suspected to interfere with the study drug
- Pregnancy
- Lack of study compliance
- Treatment unblinding (treatment unblinding for the purpose of expedite reporting of SUSARs will not by default lead to withdrawal of subjects from the study)
- Any other condition which in the opinion of the Investigator no longer permits safe participation in the study

A subject may discontinue participation in the clinical study at their own request at any time without stating a reason.

The Investigator can stop a subject's participation in the study at any time if continuation could lead to disadvantages for the subject which cannot be justified by the Investigator.

The reason for withdrawal of the subject must be documented by the Investigator. All data collected until the day of premature study discontinuation including laboratory results and assessment of AEs will be evaluated. AEs will be followed up until resolution of the symptoms or until they reach a stable chronic condition.

Abrupt discontinuation of litoxetine should be avoided; the dose should be reduced over a period of 1 week to reduce the risk of withdrawal reactions. If intolerable symptoms occur following this decrease in dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the Investigator may continue decreasing the dose. Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. The risk of withdrawal symptoms seen with selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Generally, these symptoms are mild to moderate; however, in some subjects they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more).

Subjects who withdraw from the study will be asked to taper the dose of study drug. If they refuse, that refusal will be recorded. The subject will be asked to return for the Post-treatment Follow-up Visit and if symptomatic of withdrawal, will be followed up until the resolution of such symptoms or until they reach a stable chronic condition.

4.4 Subject Identification and Randomization

Each country will be assigned a 3-digit country code. Each participating investigative study centre will be assigned a 2-digit investigative study centre number (eg, 01, 02, 03, and up) on enrolment. Each subject will receive a 3-digit Screening number in sequential order at the Screening Visit after the consent form is signed (eg, 001, 002, 003), regardless of the investigative study centre at which the subject is enrolled.

Enrolled subjects who fail Screening or discontinue study participation early, regardless of whether treatment was received or not, will retain their Screening number and a new number will be assigned to the next enrolled subject.

Randomization numbers will be assigned by the Interactive Response Randomization System, which is integrated into the Electronic Data Capture (EDC) system. Details of assignment of subject numbers will be provided as a separate document.

Subjects will be randomly assigned to receive litoxetine or matched placebo BID in a 2:1 ratio.

See Section 5.4 for information on blinding and breaking the blind.

5 STUDY DRUG

5.1 Identity

Litoxetine is a selective inhibitor of serotonin (5-HT) reuptake. Litoxetine is formulated as an immediate release capsule. The formulated product is a dry-blend containing either 10 mg or 20 mg litoxetine (free base equivalents) in orange hard gelatine capsules. The composition of litoxetine is presented in Table 5.1. The batch number for active pharmaceutical ingredient is 100193-01.

Table 5.1 Composition of Litoxetine and Placebo Capsules

Ingredient	mg/capsule		
	10 mg Free Base Equivalents	**20 mg Free Base Equivalents**	**Placebo**
Litoxetine benzoate [a]	15.1	30.2	–
Microcrystalline cellulose	272.9	257.8	288.00
Sodium starch glycolate	9.00	9.00	9.00
Magnesium stearate	3.00	3.00	3.00
Total fill weight	300.0	300.0	300.0

[a] Conversion factor from base to benzoate salt is 1.51.

Matching placebo capsules will be manufactured without the active ingredient.

5.2 Administration

Study drug will be administered orally BID with 240 mL water.

During the tapering period, the study drug will be administered ONCE daily in the morning with 240 mL water.

5.3 Packaging, Labelling and Storage

Litoxetine benzoate capsules (10 and 20 mg of free base equivalents) are packaged in high-density polyethylene (HDPE) jars with tamper evident and child-resistant closures.

Study drug will be packaged according to local legal requirements. Study drug will be labelled in accordance with applicable regulatory requirements.

All study drug supplies must be stored in accordance with the manufacturer's instructions (between 15 and 25ºC). Temperature excursions between 8ºC to 15ºC and 30ºC to 25ºC are allowed for up to 3 days. This is a conservative estimate based on accelerated stability data. Until dispensed to the subjects, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

Packaging and labelling of study drug will comply with Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) rules, Annex 13, and country specific regulatory requirements.

5.4 Blinding and Breaking the Blind

The study will be performed in a single-blind ([subject blind] Screening Placebo Run-In Period) and a double-blind (Treatment Period) manner. All study drugs will be supplied in identical HDPE bottles and will be similar in colour, smell, taste, and appearance, thereby enabling single- and double-blind conditions.

During the Treatment Period, the study blind should not be broken except in a medical emergency (where knowledge of the study drug received is essential for the treatment of the emergency) or due to a regulatory requirement (eg, expedited reporting). If required for medical emergency, the EDC system will be used to break the blind.

If the blind is broken, the date, time and reason will automatically be recorded in the subject's electronic case report form (eCRF). An automated email notification from EDC will be sent to the Sponsor/Medical Monitor in the event that the blind is broken.

If an Investigator, site personnel performing assessments, or subject, is unblinded, the subject must be withdrawn from the study and procedures accompanying withdrawal are to be performed. In cases where there are ethical reasons for the subject to remain in the study, the Investigator must obtain specific approval from the appointed CRO for the subject to continue in the study.

The overall randomization code will be broken only for reporting purposes. This will occur once all interim/final (as appropriate) clinical data have been entered onto the database and all data queries have been resolved and database lock has been approved.

5.5 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

Each dispensing of study drug will be documented in the eCRF.

At the end of the study, the Investigator is responsible for return or destruction of all unused or partially used study drugs, as agreed with the Sponsor and must verify that all unused or partially used drug supplies have been returned by the subject and that no remaining supplies are in the Investigator's possession. Destruction will only be performed in accordance with the Investigators institutional procedures, by authorised personnel who are aware of any possible hazardous effects and following receipt and written approval from the Sponsor. The procedure should be documented in full, in writing.

5.6 Concomitant Medications

Any medication the subject takes other than the study drug is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route

of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Detailed medication history will be collected during Screening. Details regarding concomitant medications taken since previous visit will be collected at every study visit.

5.6.1 Allowed Medications

Chronic medications, other than those listed as **Prohibited Medications** (Section 5.6.2), are permitted. However, dosages changes in these medications should, if medically appropriate, not occur while the subject is enrolled in the study. If a dosage change in medication is necessary, information pertaining to the change must be documented in the eCRF. Conventional once-daily multivitamins, acetylsalicylic acid (aspirin) and acetaminophen (Tylenol®), or occasional over-the-counter non-steroidal anti-inflammatory drug (NSAID) compounds (ibuprofen) are permitted during the study.

If a subject is receiving anti-hypertensive medication, then their blood pressure must have been stable over the last 4 weeks on the same dose of anti-hypertensives including, but not limited to, angiotensin-converting enzyme (ACE) inhibitors, diuretics, or ß-blockers. If a subject does not meet blood pressure eligibility at Screening, but is otherwise eligible to participate in the study, medication may be added or the dose of medication may be modified if medically appropriate, and the subject rescreened 1 month after the dose adjustment. The change in dosage must be documented according to the instructions in the previous paragraph.

While in the study, doses of anti-hypertensives therapy must not be changed. The only exception to this is a change in dosage that occurs between initial Screening and rescreening as discussed above (ie, the subject's dose of medication changed a month before officially entering the study). The subject should be withdrawn if doses of antihypertensive and/or lipid lowering medications are changed during the study.

Women are permitted to take oestrogen if the dose has been stable over the last 3 months. Men are permitted to take hormone adjuvant therapy if the dose has been stable dose over the last 3 months.

5.6.2 Prohibited Medication

The following medications are prohibited during the study and within 30 days prior to study entry:

- Nonselective, irreversible monoamine oxidase inhibitors: eg, moclobemide or linezolid
- CYP1A2 inhibitors like fluvoxamine, ciprofloxacin, or enoxacin since the combination may result in elevated plasma concentrations of litoxetine
- CYP2D6 inhibitors like bupropion, fluoxetine, metoclopromide, paroxetine or quinidine since the combination may result in elevated plasma concentrations of litoxetine

- Pimozide and thioridazine since the combination with litoxetine may result in elevated plasma concentration of these compounds
- Medicinal products containing duloxetine
- St John's wort or herbal preparations containing St John's wort (Hypericum perforatum)
- Other serotonergic agents: SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, triptans, tramadol, pethidine, and tryptophan
- Administration of any other medication that would be considered a safety risk for co-administration with litoxetine
- Any pharmacologic agent used to treat symptoms of urinary incontinence

5.6.3 Medications to be Used with Caution

The following medications should be used with caution during the study:

- Warfarin or digoxin
- Benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines
- 1c antiarrhythmics (propafenone, flecainide) and metoprolol
- Herbal preparations (other than St John's wort mentioned above). However, subjects who have been on a stable dose of these preparations prior to entering the study may continue to take these drugs. No new herbal preparations may be introduced or dosage changes initiated while participating in the study.

6 PARAMETERS AND METHODS OF ASSESSMENT

6.1 Safety Parameters

6.1.1 Demographics/Medical History

The medical history should include demographic information, urinary and incontinence history (with date of onset), past treatment(s) for incontinence, current co-morbidities, relevant past illnesses, surgical procedures performed within the prior 6 months, all current medications (including those taken within 30 days prior to Screening), and smoking history (including current usage, if applicable).

At the screening visit and at each study visit, the Investigator must conduct the following psychiatric monitoring:

- suicide monitoring through the use of Columbia-Suicide Severity Rating Scale (C-SSRS)
- monitor for depression symptoms through the use of the Beck Depression Inventory-II (BDI-II)
- monitor for anxiety and sleep-related symptoms through the use of Beck Anxiety Inventory (BAI) and Pittsburgh Sleep Quality Index (PSQI)

In addition to the visit assessments detailed above, suicide monitoring using the C-SSRS will also be performed by a telephone contact with the subject 4 weeks post randomization (study day 42).

6.1.2 Adverse Events

6.1.2.1 Definitions

Per the International Council on Harmonization (ICH), an AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The AE may be any of the following:

- A new illness
- An exacerbation of a sign or symptom or of the underlying condition or of a concomitant illness under treatment
- Unrelated to participation in the clinical study or an effect of the study medication or comparator drug

- A combination of 1 or more of the above factors

No causal relationship with the study medication is implied by the use of the term AE.

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

When an AE occurs after written consent has been obtained but before the first dose of study drug, the AE will be considered a non-treatment emergent AE. An AE that occurs from the time the subject receives their first dose of study drug until their last study visit will be considered a treatment-emergent AE (TEAE) regardless of the assessed relationship to the administration of the study drug.

For the recording of pregnancy and relevant laboratory data see Section 6.1.2.2.

6.1.2.1.1 Immediately Reportable Adverse Event

Immediately reportable AEs (IRAEs) are AEs that must be reported to the Sponsor within 24 hours of the study site being informed of the IRAE (reporting requirements are detailed in Section 6.1.2.3).

Immediately reportable AEs include:

- All SAEs
- Overdose
- Pregnancy
- AEs that result in a subject's withdrawal from the study

6.1.2.1.2 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another medically important condition

An important medical event that is not immediately life-threatening or will result in death or hospitalization, but which may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above, should be reported as "serious" as well.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

"Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event.

6.1.2.1.3 Severity of Adverse Event

The severity of an AE refers to the extent to which an AE affects the subject's daily activities. Severity will be categorized according to the following criteria:

Mild:	The AE does not interfere with the subject's routine activities.
Moderate:	The AE interferes with the subject's daily routine, but usual routine activities can still be carried out.
Severe:	The AE results in the inability to perform routine activities.

The term "severity" is used to describe the intensity of an event. This is not the same as "serious." Seriousness, not severity, refers to results or consequences of an adverse event and serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

6.1.2.1.4 Causality of Adverse Event

The causality of an AE refers to the relationship of the AE to study drug. Causality will be categorized according to the following criteria:

Certain:	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probably/ Likely:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possible:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be

	explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely:	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

6.1.2.1.5 Action Taken Regarding Adverse Events

The Investigator must assess the action taken with regards to each AE as:

- None
- Dosing interrupted
- Dose reduction
- Use of concomitant medication
- Discontinuation from the study drug

6.1.2.1.6 Outcome of Adverse Events

The Investigator must assess the outcome of each AE as:

- Unresolved
- Resolving
- Resolved
- Resolved with sequelae
- Death
- Unknown

Every effort should be made to determine the outcome of any AE that occurs at any point in the study.

6.1.2.1.7 Overdose

An overdose is defined as administration of a quantity of a medicinal product given per administration or per day, which is above the maximal recommended dose according to the authorised product information. This shall also take into account cumulative effects due to overdose. Therefore, for litoxetine in the current study and with the current posology, an overdose should be considered as any dose above 60 mg taken per day, since the maximum dose in this study will be 30 mg BID.

6.1.2.2 Recording Adverse Events

Period – Subject Enrolment to the First Administration of Study Drug: Non-treatment emergent AEs will be recorded from the time when the subject is enrolled into the study (date of signature of the informed consent) until first administration of study drug.

Period – First Administration of Study Drug to Subject's Last Study Visit: In this period, all AEs are TEAEs (see Definitions, Section 6.1.2.1) and will be recorded until the final Follow-up Visit has been performed.

Period – After Last Study Visit: Any SAE occurring after the subject's last study visit but considered by the Investigator to be related to the study drug will be recorded.

If an AE (serious or not) started during the study but did not end before the final Follow-up Visit, the Investigator should make a reasonable effort to establish the outcome (resolution of symptoms, stable condition) and the end date. If this is not possible, the outcome recorded at the final Follow-up Visit will be assumed to be the final outcome.

If an event stops and later restarts, all the occurrences must be reported. Adverse events assessed as related to study medication by the Investigator and all SAEs must be followed up until resolution, or until they reach a stable chronic condition.

Signs/symptoms should be documented if a definite diagnosis cannot be established. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the symptoms have to be reported separately.

In addition to the definition as given, the following special types of events should be recorded:

a) **Pregnancy -** Occurrence of pregnancy in a subject during a clinical study must be recorded.

b) **Laboratory values that are outside the normal range** and if, in the opinion of the Investigator, these values represent a clinically relevant change versus pre-treatment values are also defined as AEs.

If abnormal laboratory values are signs of an AE (eg, an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE.

Wherever reasonable the reporting Investigator will use the clinical term rather than the laboratory term (eg, anaemia versus low haemoglobin value).

6.1.2.3 Responsibilities of the Investigator

Adverse event data should be obtained through observation of the subject, from any information volunteered by the subject, or through subject questioning. The general type of question asked could be similar to: “Do you have any health problems?” or “Have you had any health problems since your last clinic visit?”

Specific emphasis should be given to explore the occurrence of psychiatric events (nervousness, anxiety, panic attacks, insomnia, aggression, mania, suicidal ideation, development/worsening of depression). The patient should be routinely monitored by the C-SSRS, BDI-II, BAI and PSQI, as laid out in section 6.1.1.

If any patient experience suggestive suicidal ideation/behaviour as per the C-SSRS s/he will be submitted for psychiatric evaluation. The outcome of the psychiatric evaluation will determine the patient's suicidal state and whether the patient will continue in the study or prematurely withdrawn from participation.

Adverse Event terms such as euphoria, dissociative effects, hallucinosis, psychosis, impaired cognition, attention, mood and psychomotor effects, inappropriate affect, patient dropouts, overdoses, misuse and lost or unaccounted for medication and unjustified dose increases will result in detailed narratives, as they may be indicative of abuse potential.

Adverse events are to be documented/recorded accurately and completely on the AE pages of the respective eCRF and in the subject's source data.

All non-treatment and treatment-emergent AEs will be recorded. This is true even if the study drug was not administered according to study protocol.

For conditions leading to unplanned surgical procedures, the underlying condition, but not the procedure, should be documented as an AE.

Reporting Immediately Reportable Adverse Events (IRAEs):

For AEs that are "serious" (SAEs) additional separate documentation is required using the electronic SAE Forms.

The following variables will be recorded on the electronic SAE Form and on the eCRFs provided in accordance to the eCRF completion guidelines:

- Description of the event, including its duration (date of onset and resolution),
- Whether the event constitutes a SAE or not (if yes, see event seriousness criteria in Section 6.1.2.1.2)
- Any action taken (eg, changes to study treatment, other treatment given, and follow up tests)
- Outcome of the event
- Investigator's assessment of causality (the relationship to the study treatment and study procedures)
- Severity

For all SAEs where important or relevant information is missing, active follow-up should be undertaken.

The assumption of a causal relationship between the study medication/study conduct and the AE is irrelevant to the obligation to record AEs and notifying IRAEs to the Sponsor.

For subject withdrawal due to AEs the eCRF page "Study completion / Study termination Form" and a copy of the eCRF AE page needs to be completed and forwarded to INC Research's Pharmacovigilance Department.

Pregnancy Reporting: Patients who become pregnant during the study must be withdrawn from study medication and Early Termination visit assessments should be performed. Each pregnancy that starts during the study must be reported by the Investigator to INC Research's Pharmacovigilance Department within 24 hours of the Investigator's knowledge of the pregnancy by using the Pregnancy Reporting Form. Any adverse outcome of the pregnancy must be recorded and notified on the "Drug Exposure via Parent Report Form." The Investigator should make any reasonable effort to follow any pregnancy until birth of the child.

Overdose needs to be reported to INC Research's Pharmacovigilance Department following the criteria for SAE reporting.

If additional information is required by INC Research's Pharmacovigilance Department, then as a representative of the Sponsor. INC Research must be granted access to the medical records.

After subject's last study visit:

The Investigator records and forwards to the Sponsor all SAEs that she or he becomes aware of and she or he considers related to the study drug.

6.1.2.4 Responsibilities of the Sponsor

For purposes of safety analyses, all AEs will be recorded in the clinical database. To ensure expedited and periodic notification of authorities, SAEs will also be recorded in the drug safety database.

6.1.2.5 Evaluation of Adverse Events

6.1.2.5.1 Responsibilities of the Investigator

The Investigator will assess the seriousness, severity, and causality of each AE in accordance with the definitions in Section 6.1.2.1. Notification of IRAEs must follow the procedure described in Section 6.1.2.3.

Causality of AE:

For all AEs a causality assessment must be provided and documented on the respective form (eCRF AE page for all AEs, SAE form for SAEs and eCRF page "Study completion / termination Form" for withdrawals due to AEs) even if it is preliminary information.

6.1.2.5.2 Responsibilities of the Sponsor

The Sponsor will not downgrade the causality assessment provided by the Investigator. If the Sponsor disagrees with the Investigator's causality assessment, both the opinion of the Investigator and the Sponsor will be recorded.

6.1.2.6 Notifying of Adverse Events

6.1.2.6.1 Responsibilities of the Investigator

For IRAEs (SAEs, overdose, pregnancy, and AEs leading to withdrawal), the Investigator must inform the INC Research's Pharmacovigilance Department via e-mail or fax using the SAE report/eCRF page within 24 hours of the study site being informed of the IRAE. At a later date, the INC Research Safety Contact will report to IXALTIS, the INC Research Clinical Study Manager, and the INC Research Medical Monitor.

For any new SAE, the following minimum information is required as initial notification:

- Clear identification of the Investigator/Reporter with full contact information,
- Subject identification details (study number, site number, date of birth),
- Investigational Medicinal Product administration details (dates),
- Diagnosis of the event with the description (or a brief description of signs/symptoms/clinical course if the diagnosis is not available) and the date of onset,
- Reason(s) for considering the event serious, and
- Relationship of the event with the Investigational Medicinal Product or with the trial procedure (eg, the causality according to the Investigator).

In addition, the Investigator/Reporter must respond to any request for follow-up information or questions the Sponsor may have regarding the AE within the same timelines as for initial reports.

Adverse Event Reporting Contact:

INC Research Pharmacovigilance

Fax: 1-877-464-7787

E-mail: INCDrugSafety@incresearch.com

For questions regarding IRAEs, or to provide information that cannot be provided electronically, or to notify the Sponsor of an IRAE in the event of technical failure, the Investigator should contact INC Research's Pharmacovigilance Department. Details for contacting the Pharmacovigilance Department if this occurs will be provided in the Safety Plan.

Investigators or other site personnel should inform INC Research's Pharmacovigilance Department of any follow-up information that becomes available for a previously reported SAE immediately but no later than 24 hours of becoming aware of the information. Follow-up reports (as many as required) should be completed and faxed or e-mailed following the same procedure

above. Any requested supporting documentation (eg, ECG, laboratory results, autopsy report) should be sent to the INC Research's Pharmacovigilance Department.

Prior to forwarding any personal data for safety reporting, the documents need to be coded in a way that keeps the subject's identity confidential (eg, by using the subject's identification code, randomization number, etc.).

For fatal and life-threatening SAEs, INC Research's Pharmacovigilance Department will work with the Investigator to ensure that any additional information is provided by the Investigator within 1 business day. The Investigator will ensure that all the necessary information for all other SAEs will be provided within the timelines stipulated by the Sponsor when the request for information is made.

If required, the Investigator is responsible for informing local Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the Investigator Site File (ISF)/Regulatory Binder.

Subject Enrolment to the First Administration of Study Drug:

Only serious procedure-related AEs will be reported to the Sponsor using the IRAE reporting process (SAE report form) as described above.

After Subject's Last Study Visit:

The Investigator will notify INC Research's Pharmacovigilance Department of any SAE that she or he becomes aware of and considers related to the study drug.

Following-up AEs / SAEs:

At the subject's last study visit (including Early Termination Visit, if applicable), a Safety Follow-up Visit should be scheduled up to 30 days after the final examination only for those subjects who experienced not resolved related AEs, laboratory parameters showing not normalized clinical relevant changes, or SAEs. The assessments measured will be determined by the Investigator. All data must be documented in the eCRF.

6.1.2.7 Responsibilities of the Sponsor

The Sponsor is responsible for fulfilling all obligations regarding notification of Regulatory Authorities and IECs/IRBs according to applicable regulatory requirements (eg, expedited and periodic reporting, serious unexpected suspected adverse reactions, Development Safety Update Report). In addition, the Sponsor will provide safety information to Investigators according to the current regulations.

6.1.3 Laboratory Parameters

Laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel (Appendix 1) at the time points outlined in Appendix 2.

The tests listed in Table 6.1 will be conducted on samples collected and analysed by standard laboratory procedures at the time points outlined on the Schedule of Assessments (Appendix 2). Blood draws that are not done must be reported as such on the eCRFs.

Table 6.1: Laboratory Parameters

Haematology		
Haemoglobin Haematocrit Red blood cell count Platelets	White blood cell count with differential(neutrophils,neutrophil bands, lymphocytes, monocytes, eosinophils, basophils)	Mean corpuscular volume Mean corpuscular haemoglobin concentration Red cell morphology
Chemistry		
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin	Total protein Blood urea nitrogen Albumin Glucose[a]	Creatinine Gamma glutamyl transpeptidase Electrolytes (sodium, potassium, chloride) Cholesterol (total, HDL, LDL)
Urine [b]		
Appearance Specific gravity pH	Glucose Ketones	Occult blood Macroscopic haematuria
Other Tests		
Pregnancy tests for women of childbearing potential: Serum at Screening (Visit 1), the ET Visit (if the subject is discontinuing from the study), or the End of Study Visit (Visit 7) and urine (at all other visits)		

AE = adverse event; ET = early termination; HDL = high-density lipoprotein; LDL = low-density lipoprotein

a Glucose should be measured fasting. If for any reason a subject is not able to follow this recommendation, then there should be a 2-hour gap between a meal and the blood sample.

b Microscopic evaluations will be performed if dipstick is positive. At Screening, if dipstick is positive and microscopic evaluation is abnormal, the subject must be excluded from participating in the study. If during the study, the dipstick is positive and the microscopic evaluation is abnormal these results will be recorded as an AE with the follow-up of the AE reported to the Medical Monitor.

6.1.4 Vital Signs

Vital signs will be measured and recorded at the time points outlined on the Schedule of Assessments (Appendix 2). The following measurements must be performed: systolic/diastolic blood pressure, heart rate, and body temperature. Vital signs will be measured after the subject has been in the supine position for at least 5 minutes. At the Randomization Visit (Visit 3), vital signs will be measured 3 times in order to determine the mean blood pressure. All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion

of the Investigator and must be reported on the corresponding eCRF. When vital signs and ECGs occur at the same time, vital signs should be performed before ECGs.

6.1.5 Electrocardiograms

During the study, 12-lead ECGs will be performed at the time points designated on the Schedule of Assessments (Appendix 2).

The subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. All ECGs should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: ventricular rate, QRS, QT, corrected QT, RR, and PR intervals.

The Investigator or designated site physician will review and sign all ECGs. Results must be summarized in writing and classified as normal; abnormal; abnormal, clinically relevant; or abnormal, not clinically relevant. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the Sponsor, a copy of the original ECG will be made available.

6.1.6 Physical Examinations

The Investigator or qualified designee will perform a complete physical examination at the time points outlined on the Schedule of Assessments (Appendix 2). Pre-dose abnormal findings will be reported on the medical history eCRF. Any adverse change from the baseline physical examination (Day 0 examination) will be documented on the AE eCRF. Weight will be measured at Screening, at Visit 6 (Eight weeks Postrandomization/ Early Termination Visit) and Visit 7 (Week 15, Post-Treatment Safety Follow-up Visit).

A full physical examination will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, urinary system, musculoskeletal system, and nervous system, (including the central nervous system).

6.1.7 Prior and Concomitant Medication

Prior and concomitant medication will be recorded at the time points outlined on the Schedule of Assessments (Appendix 2). All prior and concomitant medications taken by the subject will be recorded in the appropriate eCRF along with dose, dates of administration, and reason for use.

6.1.8 Postvoid Residual Volume

Bladder scans (ultrasound) for postvoid residual volume will be recorded at the time points outlined on the Schedule of Assessments (Appendix 2). Measurements should be performed within 15 minutes of the void. The time of the bladder scan and the time of the preceding void will also be recorded. Subjects who demonstrate a PVR >150 mL at Screening or at Day 0

(Visit 3), will require a repeat bladder scan. If the PVR is >150 mL, the subject will be ineligible for study.

Catheterization should not be used to capture post void residual volume.

6.2 Efficacy Parameters

6.2.1 Bladder Diary Questions

The bladder diary will be completed daily for the 7 days prior to visit 2 and visit 6, to record the number of incontinence episodes and whether these were nocturia events. If a subject has multiple events in 1 day, each event will preferably be entered separately. The number of incontinence pads used will also be recorded in the diary.

Subjects will be instructed on how to use the bladder diary and complete the assessments.

7 STUDY CONDUCT

7.1 Observations by Visit

Visits should occur within ±2 days of the scheduled visit. All times should be recorded using the 24-hour clock (eg, 23:20, not 11:20 PM).

7.1.1 Screening/Placebo Run-In Visit – Visit 1 (Days 0)

The following procedures are to be completed during the Screening/washout period at time points outlined on the Schedule of Assessments (Appendix 2).

- Provide informed consent and request informed consent form (ICF) signature
- Record demographic data including sex, age, race, and ethnicity
- Record medical/surgical history (including urinary and incontinence history and symptoms); record smoking history and current usage, if applicable)
- Record previous and current medications
- Measure and record vital signs (blood pressure, heart rate, and body temperature)
- Complete full physical examination (including height and weight)
- Complete the C-SSRS, BDI-II, BAI, PSQI
- Determine subject's PVR
- Draw blood for pregnancy test in women of childbearing potential
- Collect urine for dipstick test (If test is positive for nitrates and leukocyte esterase, take history of signs and symptoms of urinary tract infection and perform urine culture. If urine culture and clinical signs and symptoms are positive, the subject cannot be enrolled in the study, but can be re-screened at a later date, as long as s/he does not meet exclusion criterion 11 [chronic, or recurrent (> 4 per year) urinary tract infections]. Microscopic evaluations will be performed if the dipstick test is positive. If the dipstick test is positive at Screening, the subject must be excluded from the study.)
- Draw blood for haematology and biochemistry tests
- Perform 12-lead ECG
- Verify eligibility (inclusion/exclusion criteria)
- Dispense single-blind study drug for Placebo Run-In Period
- Dispense bladder diary and instruct subject in its use

7.1.2 Eligibility Assessment Visit – Visit 2 (Day 14)

The following procedures are to be completed during the Eligibility Assessment Visit at time points outlined on the Schedule of Assessments (Appendix 2).

- Record current medications
- Measure and record vital signs (blood pressure, heart rate, and body temperature)
- Complete full physical examination
- Complete the C-SSRS, BDI-II, BAI, PSQI
- Determine subject's PVR
- Collect urine for pregnancy test in women of childbearing potential
- Collect urine for dipstick test (If test is positive for nitrates and leukocyte esterase, take history of signs and symptoms of urinary tract infection and perform urine culture. If urine culture and clinical signs and symptoms are positive, the subject cannot be enrolled in the study, but can be re-screened at a later date, as long as s/he does not meet exclusion criterion 11 [chronic, or recurrent (> 4 per year) urinary tract infections]. Microscopic evaluations will be performed if the dipstick test is positive. If the dipstick test is positive and the microscopic evaluation is abnormal these results will be recorded as an AE with the follow-up of the AE reported to the Medical Monitor.)
- Draw blood for haematology and biochemistry tests
- Perform 12-lead ECG
- Review bladder diary
- Verify eligibility (inclusion/exclusion criteria)
- Randomise subject
- Collect single-blind study drug for Run-in Period and perform drug accountability
- Dispense double-blind study drug
- Query for AEs

7.1.3 One Week Post-randomisation Visit – Visit 3 (Day 21)

The following procedures are to be completed during the 1 Week Post-randomisation Visit at time points outlined on the Schedule of Assessments (Appendix 2).

- Record current medications
- Measure and record vital signs (blood pressure, heart rate, and body temperature)
- Complete full physical examination
- Complete the C-SSRS, BDI-II, BAI, PSQI
- Collect urine for pregnancy test in women of childbearing potential
- Draw blood for analysis of electrolytes (including sodium)

- Perform 12-lead ECG
- Collect unused study drug and perform drug accountability
- Dispense study drug
- Query for AEs, including adverse events of special psychiatric interest

7.1.4 Two Weeks Post-randomisation Visit – Visit 4 (Day 28)

The following procedures are to be completed during the 2 Weeks Post-randomisation Visit at time points outlined on the Schedule of Assessments (Appendix 2).

- Record current medications
- Measure and record vital signs (blood pressure, heart rate, and body temperature)
- Complete full physical examination
- Complete the C-SSRS, BDI-II, BAI, PSQI
- Collect urine for pregnancy test in women of childbearing potential
- Draw blood for analysis of electrolytes (including sodium)
- Perform 12-lead ECG
- Collect unused study drug and perform drug accountability
- Dispense study drug
- Query for AEs including adverse events of special psychiatric interest

7.1.5 Three Weeks Post-randomisation Visit – Visit 5 (Day 35)

The following procedures are to be completed during the 3 Weeks Post-randomisation Visit at time points outlined on the Schedule of Assessments (Appendix 2).

- Record current medications
- Measure and record vital signs (blood pressure, heart rate, and body temperature)
- Complete full physical examination
- Complete the C-SSRS, BDI-II, BAI, PSQI
- Collect urine for pregnancy test in women of childbearing potential
- Draw blood for analysis of electrolytes (including sodium)
- Perform 12-lead ECG
- Collect unused study drug and perform drug accountability
- Dispense study drug

- Query for AEs including adverse events of special psychiatric interest

7.1.6 Eight Weeks Post-randomisation/Early Termination Visit – Visit 6 (Day70)

The following procedures are to be completed during the 8 Weeks Post-randomisation/Early Termination Visit at time points outlined on the Schedule of Assessments (Appendix 2).

If this is the Early Termination Visit, the Investigator should use every effort to encourage the subject to taper study medication for 1 week and to return for the Safety Follow-up Visit (Visit 7).

- Record current medications
- Measure and record vital signs (blood pressure, heart rate, and body temperature)
- Complete full physical examination (including weight)
- Complete the C-SSRS, BDI-II, BAI, PSQI
- Determine subject's PVR
- Collect urine for pregnancy test in women of childbearing potential if the subject is continuing in the study or collect blood for the pregnancy test if this is the ET Visit
- Draw blood for haematology and biochemistry tests
- Perform 12-lead ECG
- Collect unused study drug and perform drug accountability
- Dispense study drug for the 1-week tapering period (half of the dose to which the subject is randomized)
- Review and collect bladder diary
- Query for AEs including adverse events of special psychiatric interest

7.1.7 Post-treatment Visit/End of Study Visit – Visit 7 (Day 105)

The following procedures are to be completed during the Post-treatment Visit at time points outlined on the Schedule of Assessments (Appendix 2).

- Measure and record weight
- Record current medications
- Measure and record vital signs (blood pressure, heart rate, and body temperature)
- Complete full physical examination (including weight)
- Complete the C-SSRS, BDI-II, BAI, PSQI

- Draw blood for pregnancy test in women of childbearing potential
- Draw blood for haematology and biochemistry tests (only if abnormal values were seen at Visit 6)
- Perform 12-lead ECG (only if any abnormality seen at Visit 6 represents a clinically significant worsening from baseline)
- Collect unused study drug and perform drug accountability
- Query for AEs including adverse events of special psychiatric interest

7.2 Monitoring by telephone contact

- In addition to the visit assessments detailed above, suicide monitoring using the C-SSRS will also be performed by a telephone contact with the subject 4 weeks post randomization (study day 42).

8 STATISTICAL METHODS

8.1 General Considerations

The general objectives of this study are to establish the safety, tolerability and efficacy of litoxetine in men and women who suffer from UI. The primary analyses will focus on safety, describing the adverse events with point estimates and Clopper Pearson 95% confidence intervals. Efficacy will be explored with regards to number of incontinence episodes and will use a mixed effects model with repeated measure (MMRM). Additional statistical considerations will be addressed in the Statistical Analysis Plan (SAP).

8.2 Analysis Populations

There are 4 analysis populations for this study:

Safety population:	Defined as all subjects who are randomised, receive study drug, and undergo at least 1 visit
Intent-to-Treat (ITT) population:	Defined as all subjects who are randomized
Modified Intent-to-Treat (mITT) population:	Defined as all subjects who are randomised, receive at least 1 dose of study drug, and provide an end of study primary efficacy endpoint
Per Protocol (PP) population:	Defined as those subjects who meet the ITT criteria and have completed the study without a major protocol deviation

8.3 Disposition of Subjects

Subjects randomised and who receive study drug will be identified as completing the study or withdrawn from the study. Reasons for withdrawal will include: AE, failure to return, protocol deviation, subject request, and other.

8.4 Protocol Deviations

In addition to clinical and study conduct protocol deviations, subjects that fail to provide valid measurements **of the bladder diary** at the end of the Placebo Run-In Period and at the end of the Treatment Period will be considered protocol deviations. Additionally, subjects that do not meet compliance criteria will be considered protocol deviations.

8.5 Demographics, Baseline Characteristics, and Concomitant Medications

Demographics, baseline characteristics (including smoking history and current usage, if applicable), medical history, and concomitant medications will be reported for the subjects in the study.

8.6 Treatment Compliance

Treatment compliance will be defined as all subjects that take at least 80% of the study drug during the Treatment Period of the study.

8.7 Safety Endpoints and Analyses

8.7.1 Safety Endpoints

- Incidence and severity of AEs and Adverse Events of interest (urinary retention, withdrawal symptoms) over the course of the study.
- Adverse Events of special psychiatry interest (nervousness, anxiety, panic attacks, insomnia, aggression, mania, suicidal ideation, development/worsening of depression) over the course of the study
- Suicidal Adverse Events and Adverse Events suggestive of abuse potential will be analysed, and detailed narratives provided
- Haematology, chemistry, and urinalysis
- Actual change from end of the Screening Placebo Run-In Period in ECG readings and Week 8. ECG parameters of interest include: ventricular rate, QT interval, corrected QT interval, PR interval, and QRS duration
- Actual change from end of the Placebo Run-In Period to each visit in standardised cuff systolic and diastolic blood pressure and radial heart rate

8.7.2 Safety Analyses

- SAEs will be listed and summarised in a table, including a description of each event, the time to onset, the severity, and the relationship to trial drug.
- All AEs (excluding SAEs) will be listed, and their time to onset, frequency, severity, and relationship to the trial drug will be tabulated by treatment. Adverse events that occur before the time of the first treatment with the trial drug will be considered a non-treatment-emergent AE (non-TEAE), and all AEs that occur after the time of the first treatment with trial drug will be considered TEAEs. Non-TEAEs will be summarised separately from TEAEs.
- AEs of Special Interest include urinary retention, psychiatric adverse events ((nervousness, anxiety, panic attacks, insomnia, aggression, mania, suicidal ideation, development/worsening of depression) and withdrawal symptoms will be specifically summarized by treatment
- Suicidal adverse events and abuse related adverse events will be specifically summarized by treatment
- Premature withdrawals from the trial will be displayed and summarised by primary reason and treatment.

- Abnormal laboratory values will be listed and their incidence, severity, and relationship to the trial drug will be tabulated by treatment. Change from Screening will be summarised by treatment. Individual changes (shift tables), individual clinically significant abnormalities, and modified World Health Organization (WHO) ratings will also be presented.
- While total white blood cell (WBC) count will be expressed in absolute values, differential count will be expressed as both absolute count and percentage of WBCs.
- Abnormal physical examination findings will be summarised over time.
- Concomitant medications will be presented in summary tables and listings. They will be classified according to whether they were taken before the trial (and ongoing into the trial), or started during the trial period.
- Vital signs will be summarised by treatment group and listed by subject.
- Any AE/SAE which occurs during the 30-day Follow-up Period or following discontinuation of treatment will be listed and summarized separately, and include a description of the event, time to onset, frequency, severity and relationship to treatment.

8.8 Efficacy Endpoints and Analyses

8.8.1 Efficacy Endpoints

Baseline for all efficacy endpoints will be defined as the last week of the Screening Placebo Run-In Period.

- Percentage change from the end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence episodes/24 hours
- Absolute change from the end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence episodes/24 hours

Number of incontinence episodes/24 hours will be computed as Total Number of incontinence episodes recorded over the 7 days/7.

- Proportion of subjects who become continent at Week 8
- Change from end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence pads used per week

8.8.2 Efficacy Analyses

The efficacy analysis will be performed on the ITT, mITT, and PP populations. The efficacy analysis will be performed on the ITT population, with the analysis on the mITT and PP populations as part of secondary efficacy analysis.

The efficacy analysis planned is a mixed effects model with repeated measures (MMRM). Percent reduction in incontinence episodes as the response variable is the first efficacy endpoint. The factor variable will be dose and the covariate will be baseline episodes (end of placebo run

in) of incontinence. Visits within subjects will provide the random effects of the mixed model. There is only one hypothesis so there will be no adjustment for multiplicity. Further efficacy analysis will be conducted similarly, with appropriate baseline measure. There will not be an adjustment for multiple comparisons for these secondary analyses.

8.9 Interim Analyses

No interim analyses are planned for this study.

8.10 Determination of Sample Size

Approximately 95 subjects are expected to be enrolled into the 2-week, single-blind (subject blind) Screening Placebo Run-In Period. It is expected that 20% of subjects will not qualify for randomization after Screening Placebo Run-In.

The study is expected to randomize approximately 78 subjects into the double-blind treatment where subjects will be allocated to litoxetine (dose titration over 10 mg, 20 mg, 30mg) or matched placebo BID in a 2:1 ratio. A post randomisation dropout rate of 30% has been estimated, resulting in 60 evaluable subjects.

This sample size will provide confidence intervals for the rate of safety events that are +/- 14% for the widest observed intervals in the treatment arm.

8.11 Missing Data

As a sensitivity analysis, missing data will be addressed with a multiple imputation method for the efficacy endpoints only. Details of the imputation method will be identified in the SAP prior to unblinding the data which will include the seed for the imputation, the number of imputations, and how the imputations will be randomly selected. As the only term in the efficacy analysis that should be missing is the change from baseline, the imputation will be a simple imputation on this variable with no covariates. In the event other values are missing, they too will be imputed using simple multiple imputation methods with no covariates in the imputation algorithm. This is consistent with an assumption of missing completely at random (MCAR). This method is selected over single imputation methods as the anticipated placebo effect is expected to be considerable.

9 DATA MANAGEMENT

9.1 Data Collection

The trained Investigator site staff will enter the data required by the protocol into the eCRFs from source documents (eg, medical records and study-specific data capture tools as needed) directly into the study database on a central server. All information in the eCRFs must be traceable to these source documents. Data recorded directly into the eCRFs will be defined before study start and the eCRFs will be considered the source data. Clinical Research Associates (CRAs) and a Data Manager will review eCRFs entered by investigational staff for completeness and accuracy. Automatic quality programs check for data discrepancies in the eCRFs and the resulting queries will be notified to the investigational site using an electronic data query process within the EDC system. Designated Investigator site staff are required to respond to queries and make any necessary changes to the data. Details of the data correction process will be specified in the Data Quality Check specification.

A validated, electronic database will be employed from the EDC system. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a Data Management Plan together with a description of the personnel responsible for data entry.

The bladder diary will be used to collect daily bladder information (incontinence episodes, pad usage) for 7 days prior to visit 2 and visit 6.

9.2 Data Correction

Automatic and manual queries will be defined according to the Data Quality Check specification. These queries will be generated by the INC Research Data Management Department and CRAs and sent through the EDC system for clarification. Corrections will be entered directly into the system. This procedure will be repeated until all queries are resolved. All query forms will be linked to the eCRF in the EDC system.

9.3 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding of AEs and concomitant diseases. Concomitant medication will be coded using the WHO Drug Dictionary **A**natomical **T**herapeutic **C**hemical code.

9.3.1 Deviations from the Protocol

Deviations from the protocol will be judged during the study and/or when an individual subject's eCRF is completed (monitored).

9.4 Data Quality Assurance

INC Research will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRFs for this study must be consistent with the subjects' source documentation (ie, medical records).

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Study Initiation Activities

The Investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at a Pre-Study Visit by the CRA (if necessary), an Investigators' meeting, or during the Site Initiation Visit by the CRA.

10.2 Training of Site Staff

The Investigator will ensure that everyone assisting with the clinical study is adequately informed about the protocol, the study drugs, and their study-related duties and functions. Furthermore, the Investigator will maintain a list of qualified persons to whom the Investigator has delegated study-related duties.

10.3 Documentation and Filing

10.3.1 eCRF System

The Investigator and persons authorized by the Investigator will be instructed about how to complete the eCRF. Entries in the eCRF must only be made by the Investigator or persons authorized by the Investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site.

The Investigator must verify that all data entries in the eCRF are accurate and correct. Entries will be checked against appropriate source documentation by the monitor.

10.3.2 Bladder diary

Bladder diary data are uploaded into the EDC at visit 2 and visit 6.

10.3.3 List of Subjects (subject identification log)

The Investigator will keep a confidential list of names of all subjects participating in the study, so that the subjects' records can be identified if necessary.

In addition, the Investigator will keep a list of all subjects screened on a Screening log to document identification of subjects who entered pre-study Screening. If a subject is not eligible to participate in the study, a reason must be provided.

10.3.4 Source Data

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or

magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

10.3.5 Investigator Site File / Regulatory Binder

Before site initiation INC Research will provide an ISF/Regulatory Binder to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements.

The Investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the CRA. These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to legal requirements.

Prior to destruction of study-related documents, the Investigator will contact IXALTIS for approval and confirmation.

10.4 Monitoring

The monitor is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the monitor ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

The interval between monitoring visits will depend on the recruitment rate and the site needs.

Source data verification is an essential part of the monitoring process and the Investigator must grant direct access to the subject’s source data.

The extent and nature of monitoring will be described in detail in the monitoring plan.

10.5 Audits and Inspections

Audits will be performed according to the corresponding audit program. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the CRA will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IECs/IRBs are possible at any time, even after the end of study. The Investigator is to notify the Sponsor immediately of any such inspection. The Investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or Regulatory Authorities, and will allow direct access to source data and source documents for monitoring, audits, and inspections.

11 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

11.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH, and of the current version of the Declaration of Helsinki. The study also will be carried out in keeping with local legal requirements.

11.2 Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject (or their legally authorized representative) according to the regulatory and legal requirements of the participating country and the current version of the Declaration of Helsinki. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

The explicit wish of a mentally incapacitated adult, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be considered by the Investigator.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC/IRB/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

11.4 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years 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 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these

documents should be retained for a longer period if required by the applicable legal requirements.

11.5 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be temporarily or permanently discontinued after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure to enrol subjects at an acceptable rate
- A decision on the part of the Sponsor to suspend or discontinue development of the drug

11.6 End of the Trial

For administrative and safety reporting purposes, the end of the trial will be defined as the date of the final clinical database lock. This provides for a single and conservative definition across all trial sites.

11.7 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on eCRFs and other documents by their subject number, and/or birth date, not by name. Documents that identify the subject (eg, the signed informed consent) must be maintained in confidence by the Investigator.

11.8 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

11.9 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

12 REFERENCE LIST

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13 APPENDICES

Appendix 1: List of Institutions Involved in the Study

Sponsor	IXALTIS Archamps Technopole Acti'Tech 6 60 avenue Marie Curie 74160 Archamps, France
Principal Scientific Advisor	Pr. Roger Dmochowski Vanderbilt University Nashville, TN
Contract Research Organization	INC Research International
Adverse Event Reporting	INC Research Pharmacovigilance Fax: 1-877-464-7787 E-mail: INCDrugSafety@incresearch.com
Central Laboratory	TBD

Appendix 2: Schedule of Assessments

Visit Number	**Visit 1**[1]	**Visit 2**[1]	**Visit 3**	**Visit 4**	**Visit 5**	**Telephone contact**	**Visit 6**	**Visit 7**
Visit Name	Screening/ Placebo Run In	Eligibility assessment/ Randomization (start 10 mg litoxetine or Placebo BID)	1 week **Post Randomization** First dose escalation (start 20 mg or Placebo BID)	2 weeks **Post Randomization** Second dose escalation (start 30 mg or Placebo BID)	3 weeks **Post Randomization**		8 weeks **post Randomization Final Treatment Visit**[4] **(ET Visit)**	13 weeks **po Randomiza Post-Treatn Safety F/U**[3] **(End of Stu Visit)**
Study Day	**Day 0**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 70**	**Day 105**
Signed informed consent	X							
Demographics (incl body weight and height, BMI)	X						X[13]	X[13]
Complete C-SSRS, BDI-II, BAI, PSQI[16]	X	X	X	X	X	X (C-SSRS only)	X	X
Medical / surgical/ smoking history	X							
Urinary and incontinence history	X							
Prior and concomitant medication recording	X	X	X	X			X	X
Vital signs[11]	X	X	X	X	X		X	X
Physical examination	X	X	X	X	X		X	X
PVR	X	X					X	
Pregnancy test[5,6]	X	X	X	X			X	X
Urinalysis (dipstick)[10]	X	X						
Haematology and biochemistry[8]	X	X	X[15]	X[15]	X[15]		X	X[9]
ECG (resting, 12-lead)	X	X	X	X	X		X	X[7]

Appendix 2: Schedule of Assessments

Visit Number	**Visit 1**[1]	**Visit 2**[1]	**Visit 3**	**Visit 4**	**Visit 5**	**Telephone contact**	**Visit 6**	**Visit 7**
Visit Name	Screening/ Placebo Run In	Eligibility assessment/ Randomization (start 10 mg litoxetine or Placebo BID)	1 week **Post Randomization** First dose escalation (start 20 mg or Placebo BID)	2 weeks **Post Randomization** Second dose escalation (start 30 mg or Placebo BID)	3 weeks **Post Randomization**		8 weeks **post Randomization Final Treatment Visit**[4] **(ET Visit)**	13 weeks **po Randomiza Post-Treatn Safety F/U**[3] **(End of Stu Visit)**
Study Day	**Day 0**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 70**	**Day 105**
Evaluation of eligibility/randomization	X	X						
Dispensing/collection of trial drug	X	X	X	X			X[14]	X
Patient bladder diary review/collection[12]	X	X					X	
Recording of AEs		X	X	X	X		X	X

Abbreviations: AEs = adverse events; BMI = body mass index; ECG = electrocardiogram; ET = early termination; PVR = postvoid residual urine volume; UTI = urinary tract infection

(1) Eligible subjects will undergo a 2-week Screening Placebo Run-In Period with 7 days bladder daily diary symptom collection (e-diaries). Subjects who continue to be eligible after the Screening Placebo Run-In Period will be randomised (Treatment Period).

(2) Visit window ± 2 days

(3) AEs must be followed for a minimum of 30 days and until complete resolution or stabilization of the event, or as deemed appropriate by the Investigator on consultation with the Sponsor medical responsible.

(4) If a subject is withdrawn prematurely from the trial, all procedures indicated for the Week 8 (Visit 6) visit must be performed. The Investigator should use every effort to encourage the subject to taper study medication for 1 week and to return for the Safety Follow-up Visit (Visit 7).

(5) Serum pregnancy tests will be performed prior to entry into the trial (Visit 1), the ET Visit (Visit 6; if the subject is discontinuing the study) and at the End of Study Visit (Visit 7) for all female subjects of childbearing potential. Only those female subjects with a negative pregnancy test at Visit 1 will receive trial medication.

(6) Urine (dipstick) pregnancy tests will be performed at Visits 2, 3, 4, 5, and 6 (if it is not the ET Visit) for all female subjects of childbearing potential. Only those female subjects with a negative pregnancy test will receive trial medication.

(7) ECG at Follow-up (Visit 7) is only required if ECG was abnormal at Week 8 (Visit 6) and the abnormality represents a clinically significant worsening from baseline.

(8) Blood samples will be taken in a fasting state at Screening, Day 14 (Visit 2) and Week 8 (Visit 6).

(9) Laboratory tests at Follow-up (Visit 7) are only required if labs were abnormal at Week 8 (Visit 6) and the abnormality represents a clinically significant worsening from baseline.

(10) If Urine Dipstick is positive for nitrates and leukocyte esterase, take history of signs and symptoms of UTI, and perform urine culture. If urine culture and clinical signs and symptoms are positive, the subject cannot be included, but can be re-screened at a later date as long as the subject does not meet exclusion criterion 3 (4 or more UTIs in the past 12 months).

(11) Vital signs include blood pressure, heart rate, and body temperature.

(12) At Visit 1, the patient is in formed how to use the bladder diary. During the 7 days prior to Visit 2 and Visit 6 the following urinary incontinence information will be recorded in the bladder diary: the number of incontinence episodes/pads used daily.

(13) Weight only.

(14) Dispense study drug for the 1-week tapering period (half of the dose to which the subject is randomized).

(15) Electrolytes (including sodium) only.

(16) In addition to the visit assessments detailed above, suicide monitoring using the C-SSRS will also be performed by a telephone contact with the subject 4 weeks post randomization (study day 42).

Appendix 3: New York Heart Association Heart Failure Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix 4: Psychiatric monitoring: Columbia-Suicide Severity Rating Scale (C-SSRS), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Pittsburgh Sleep Quality Index (PSQI)