Statistical Analysis Plan

Study 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 No.:	IXA-CSP-002
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Approval SIGNATURE(S)

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 No. IXA-CSP-002

I have read this SAP and confirm that to the best of my knowledge it accurately describes the statistical analyses for this study.

Sponsor Signatory:

Elisabeth Svanberg ..... April 2, 2019 .....
Date

Statistician Signatory:

Gloria Crispino ..... 02/APR/2019 .....
Date

Gloria Crispino, CEO and Director of Biostatistics

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List of abbreviations and definitions of terms

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
BID	Twice daily
CYP	Cytochrome P450
DA	Dopamine
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ICS	International Continence Society
IRAE	Immediately reportable adverse event
ITT	Intent-to-treat (population)
MACR	Missing completely at random
MMRM	Mixed-Effect Model for Repeated Measure
MedDRA	Medical Dictionary for Regulatory Activities
MUI	Mixed urinary incontinence
NE	Norepinephrine
NHS	National Health Service
PP	Per Protocol (population)
PVR	Postvoid residual volume
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUI	Stress urinary incontinence
TEAE	Treatment-emergent adverse event
UI	Urinary incontinence
UK	United Kingdom

Abbreviation	Definition
US	United States
UUI	Urge urinary incontinence
WBC	White blood cell (count)
WHO	World Health Organisation

1. Introduction

This Statistical Analysis Plan (SAP) describes the statistical analysis for IXA-CSP-002 study based on study protocol IXA-CSP-002-protocol amendment 2 issued Oct 10, 2018.

1.1 Background

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). Urinary incontinence, which is defined by the International Continence Society (ICS) as involuntary loss of urine", is estimated to affect 400 million people worldwide (Fultz NH, 2003; Global Forum on Incontinence). Prevalence varies greatly with age and the definition used, and has been reported to be as high as 55%. Not all affected need medical treatment.

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.

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, resulting in social reclusion and also an economic burden.

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). 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).

Women suffer most commonly from stress urinary incontinence (SUI) or a combination of SUI and urge urinary incontinence (UUI) i.e. 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 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.

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, minimally invasive treatment options are available, with intravesical injection of onabotulinum toxin A, sacral neuromodulation, and posterior tibial nerve stimulation available as potential options.

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 is a high 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 3, Feb 2018), which contains comprehensive information on the investigational product.

1.2 Risk/Benefit Assessment

To date, 11 Phase 1 studies in healthy volunteers and 3 Phase 2 studies in subjects suffering from depression have been performed with litoxetine. One in vitro study in human blood has been performed to evaluate plasma protein binding in humans.
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 3, Feb 2018).

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 3, Feb 2018), which contains comprehensive information on the investigational product.

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.

1.4 Statistical Analysis Plan Summary (SAP)

This Statistical Analysis Plan (SAP) describes the statistical analysis for the IXA-CSP-002 study. The SAP provides full details of the analyses, the data displays and the algorithms to be used for data derivations. The analysis will be done using the statistical software SAS version 9.4 or higher.

1.5 Clarifications from Protocol

a. Efficacy analysis of nocturia events has been added, although not specifically laid out in the protocol, since this data is captured in the bladder diary and nocturia episodes are of relevance for the wellbeing of the patient.
b. The protocol includes an mITT population, which has been omitted from analyses since it was determined that the ITT and PP population will adequately describe the data.
c. The methodology described in the protocol for the efficacy analyses is a mixed model with repeated measures (MMRM). In light of the fact that the efficacy measurements were recorded at visit 2 and visit 6 only, there are no repeated measures. Therefore, the MMRM model described in the protocol cannot be applied to these analyses. The efficacy analyses will be conducted as an analysis of covariance (ANCOVA).
d. The description of the efficacy endpoints in the protocol in clarified to be:
    a. Percentage change in number of incontinence episodes that a subject had in a week This analysis is consistent with the analysis conducted for the phase 2 study IXA CSP 001

1.6 Study Summary

This is a Phase 1/2a, double-blind, randomised, placebo-controlled, parallel-group study in subjects, male and female, 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 is a dose titration posology 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 treatment duration of 8 weeks. The Treatment Period will be followed by a 1week Dose-tapering Period and subjects will return to the clinic for a safety Follow up Visit 4 weeks after treatment is completed. This provides a total study duration of 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 at the end of the Placebo Run In period and after 8 weeks of double blind study treatment.

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. This sample size is expected to provide confidence intervals for the most conservative rate of safety events (50%) that are +/- 14% for the widest observed intervals in the treatment arm.

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.

1.7 Version History

SAP version history:
SAP v1.3 – Final (2nd April 2019).
SAP v1.2 – Draft 4 (25th March 2019).
SAP v1.1 – Draft 3 (21th February 2019).
SAP v1.0 – Draft 2 (18th February 2019).
SAP v0.1 – Draft version (8 November 2018).

Study protocol version history:
Version 1 Final Sep 14, 2017
Version 2 Amendment 1, June 28, 2018

Version 3 Amendment 2, October 10, 2018

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 for 1 week - 20 mg for 1 week - 30 mg for 6 weeks BID) compared to corresponding placebo in subjects with a diagnosis of UI.

2.2 Secondary Objective

The secondary objective of this study is to explore efficacy of litoxetine (dose titration 10 mg for 1 week - 20 mg for 1 week - 30 mg for 6 weeks BID) compared to corresponding placebo in subjects with a diagnosis of UI.

2.3 Primary Endpoint(s)

Safety:

1. Incidence and severity of AEs and Adverse Events of interest (urinary retention, withdrawal symptoms) over the course of the study. AEs are recorded at visits 2,3,4,5,6 and 7.
2. 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
3. Suicidal Adverse Events and Adverse Events suggestive of abuse potential will be analysed, and detailed narratives provided
4. Lab parameters: Haematology and chemistry recorded at visit 1,2,6 and 7. Urinalysis recorded at visit 1 and 2.
5. Absolute change from end of the Screening Placebo Run-In Period in ECG readings and Week 8 (Visit 6). ECG parameters of interest include: ventricular rate, QT interval, corrected QT interval, PR interval, and QRS duration
6. Absolute 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

2.4 Secondary Endpoints(s)

Efficacy:

1. Percentage change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes in a week
2. Absolute change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes/24 hours (daily average)
3. Proportion of subjects who become continent at Week 8 (Visit 6)
4. Change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the total number of incontinence pads used per week
5. Percentage change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of nocturia episodes in a week.

3. Study Design

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 and subjects will return to the clinic for a safety Follow up Visit 4 weeks after treatment is completed. This provides 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 single blind placebo run-in medication will be provided. In the latter half of this period, the subject will complete 7 days of bladder diary to capture incontinence events and pad usage. Subjects who continue to meet eligibility criteria after the Screening Placebo Run-In period, will enter the Treatment Period and be randomly assigned (2:1) to receive study drug (litoxetine10 mg, 20 mg, 30mg) or matching placebo BID.
Litoxetine or placebo 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 treatment period of 8 weeks).
If the subject does not tolerate the last dose level escalation (i.e. 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, recorded at Baseline (V2) and endpoint (V6).

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

Figure 1: Schedule of Assessment

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 **post Randomization Post-Treatment Safety F/U**[(3)] **(End of Study Visit)**
Study Day [(2)]	**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

Figure 1: Schedule of Assessment

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 **post Randomization Post-Treatment Safety F/U**[3] **(End of Study Visit)**
Study Day [2]	**Day 0**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 70**	**Day 105**
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]
Evaluation of eligibility/randomization	X	X						
Dispensing/collection of trial drug	X	X	X	X			X[14]	X

Figure 1: Schedule of Assessment

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 **post Randomization Post-Treatment Safety F/U**[3] **(End of Study Visit)**
Study Day [2]	**Day 0**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 70**	**Day 105**
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. Subjects who continue to be eligible after the Screening Placebo Run-In Period will be randomised (Treatment Period).

(2) Visit window ± 2 days

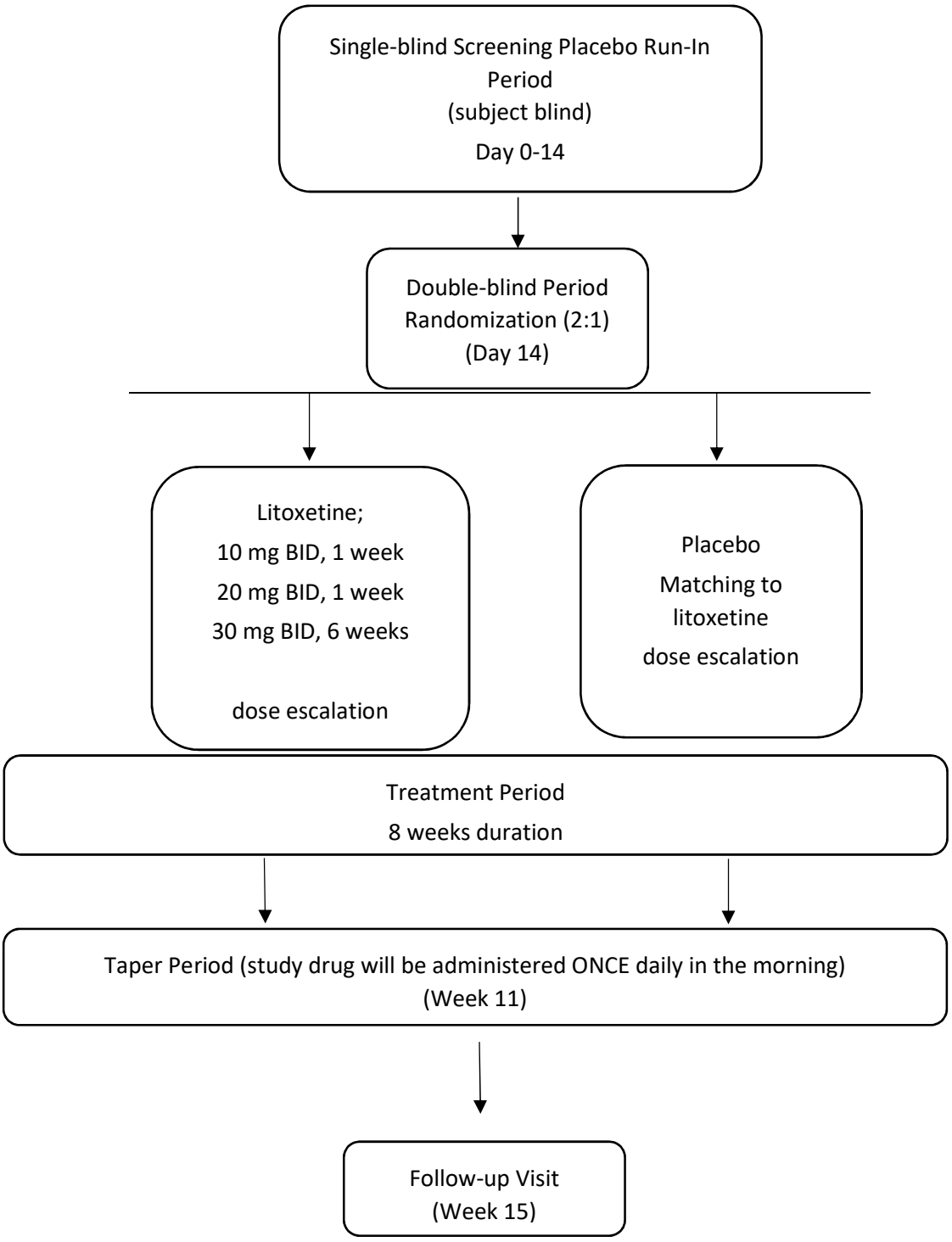
(3) AEs must be followed for a minimum of 30 days and until complete resolution or stabilization of the event, or as deemed appropriate by the Investigator on consultation with the Sponsor medical responsible.

(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).

Figure 2: Study Design



BID = twice daily

3.1 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.

A sample size of 60 subjects is expected to provide a 95% confidence interval for a rate of safety events of 50% with a width +/- 14%. The sample size calculation is based on the precision of the estimate of the primary outcome, safety events, using a rate of 50% which would provide the most conservative sample size.

3.2 Randomisation

The patient number will be an 8 digits code: 3 digits country code (the study is only conducted in the US, US Country Code is 840), 2 digits site number and 3 digits patient number. 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.

For subjects who remain eligible after the Screening Placebo Run-In period, randomization numbers (which are separate from the screening 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.

4. Analysis Sets

4.1 Study Populations

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.
A valid efficacy measurement is defined as a valid number of incontinence episodes as recorded in the bladder diary and uploaded in the eCRF at Visit 2 and Visit 6, i.e. either as 0 or greater than 0.

There are 4 analysis populations for this study:
Randomised population:
Defined as all subjects randomised to treatment (Visit 2).

Safety population:
Defined as all subjects who are randomised to treatment (Visit 2), receive study drug, and undergo at least 1 visit.

Intent-to-Treat (ITT) population:
Defined as all subjects who are randomized to treatment (Visit 2), receive at least one dose of study drug and have a valid efficacy measurement at Baseline (Visit 2).

Per Protocol (PP) population:
Defined as those subjects who are randomised, receive at least one dose of study drug, provide a valid efficacy measurement at Baseline (Visit 2) and a valid end of study primary efficacy endpoint (Visit 6), and have completed the study without a major protocol deviation.

The following populations are defined for analysis purposes:

1. Enrolled Population: each subject that signed the Informed Consent form and entered the Screening Period.
2. Completers Population: each subject that completed the trial, per protocol.
3. Full Analysis Set Population: each subject which is in either ITT or PP population.

4.2 Disposition of Subjects

Subjects randomised and who receive study drug will be identified as completing the study or withdrawn from the study.

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

1. Withdrawal of written informed consent
2. Required treatment with any medication known or suspected to interfere with the study drug
3. Pregnancy
4. Lack of study compliance
5. Treatment unblinding (treatment unblinding for the purpose of expedite reporting of SUSARs will not by default lead to withdrawal of subjects from the study)
6. Any other condition which in the opinion of the Investigator no longer permits safe participation in the study
7. Protocol Deviation
8. AE
9. Other

4.3 Protocol Deviations

In addition to clinical and study conduct protocol deviations which may include deviations to visit procedure, lab testing and patient safety, the following criteria will be considered as protocol deviations:

1. Study drug compliance less than 80% during Treatment Period of the study
2. Not valid efficacy Endpoint value: Number of incontinence episodes not available at Visit 6 (Endpoint).
3. Not valid efficacy Baseline value: Number of incontinence episodes not available at Visit 2 (Baseline).
4. Prohibited medication and medications to be used with caution taken 30 days prior to study entry (Visit 1) onwards. During the Blinded Data Review meeting the Sponsor will evaluate the medications taken from each patient on a case by case basis, determining if major protocol deviations are found, and if so exclude such subject from the ITT or PP population analysis. The adjudication of prohibited and to be used with caution medications will be provided by the Medical monitor. They include:
    a. Prohibited medications:
        - 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
    b. Medications to be used with caution:
        - 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.
5. Days outside the protocol timeframe (protocol allowed time window is ±2 days) at Visit 6 greater or equal to 8 days will be considered a major protocol deviation. If the number of days outside the protocol timeframe is smaller or equal to 7 the deviation is considered minor.

5. Definitions and Data Conventions

This section contains definitions and conventions that will be used for analysis.

5.1 General, demographic and baseline characteristics

Age (years)

The age will not be recalculated. The values automatically derived in the CRF will be used in the analysis.

Body Mass Index (BMI) (kg/m2)
BMI will not be recalculated. The values automatically derived in the CRF will be used in the analysis.

Previous and Concomitant Medication
Any medication the subject takes from the signature of informed consent and through the duration of the study, other than the study drug, is considered a concomitant medication.
The CRF records all concomitant medications and all medications taken within 30 days prior to Screening.
The medications labelled as 'ongoing' in the 'Prior and Concomitant Medications and Procedures' page in the eCRF will be considered concomitant medications. All other medications are evaluated based on the date: all records with start or end date after the date of signature of the informed consent are labelled as concomitant, other medications are labelled as past.

Past and Concomitant disease
Medical history will be recorded in the CRF. A disease is concomitant if ongoing at Screening visit (i.e. it ended after Screening visit).
A disease is considered as past if it ended prior to the Screening visit.
The diseases labelled as 'ongoing' in the 'Medical and Surgical procedure history' page in the eCRF will be considered concomitant diseases, all other diseases will be defined as past.

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

Date of first randomised study drug intake is the Study Visit 2 date, at which the trial drug is dispensed.

Date of last randomised study drug intake is the date of study visit 6. If this date is missing, the last Study Visit date available will be considered (excluding Visit 1 and Visit 7 dates). The tapering period will not be included to assess the last intake.

5.2 Compliance

All subjects will enter the Screening Placebo Run-In Period (2 weeks) during which they will receive the placebo treatment twice daily.
After randomisation, subjects are instructed to take the study drug or the matched Placebo orally twice daily (BID) for 8 weeks. Study treatment (litoxetine or placebo) 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.
After 8 weeks of treatment, doses will be reduced by 50% over 1 week to taper off treatment.

Compliance will be computed for treatment period only, ie. from Visit 2 to Visit 6 (8 weeks).

During the treatment period, patients are instructed to take two capsules in the morning and two capsules in the evening. The two capsules will be taken as follows: one from jar A and one from jar B.
The CRF captures the actual medication taken based on quantitative pill count at the site. The CRF data is therefore to be used as the source to determine patient treatment compliance.

The Investigational Site personnel will collect the study drug containers and will count and record unused study drug. This information will be used to compute compliance according to the following formula:

$$Compliance = \left(\frac{Total\ number\ of\ Capsules\ taken}{Number\ of\ days\ between\ Visit\ 2\ and\ Last\ study\ drug\ intake\ \times 4}\right) \times 100$$

The above formula takes into account the fact that four capsules are taken each day (number of days × 4).
If the date of last study drug intake is not available, the date of the latest available visit will be considered in the formula above (excluding Visit 1 and Visit 7 dates).

To compute the compliance for Jar A and Jar B separately, the following formula will be used:

$$Compliance\ Jar\ i = \left(\frac{Total\ number\ of\ Capsules\ taken\ from\ Jar\ i}{Number\ of\ days\ between\ Visit\ 2\ and\ Last\ study\ intake\ \times 2}\right) \times 100$$

Where i = A, B.
The formula takes into account that two capsules from each Jar are taken at each day.

The total number of capsules taken during the treatment period will be derived from the eCRF as:

$$Capsules\ taken = capsules\ dispensed - capsules\ returned - capsules\ not\ taken/not\ returned$$

Treatment duration will be calculated as:

$$Treatment\ Duration = Date\ of\ last\ study\ drug\ intake - Date\ of\ first\ drug\ intake$$

The date of the first study drug intake is the date of Visit 2, after randomisation to treatment (it excludes the Placebo Run-in period). Date of last randomised study drug intake is the date of Study Visit 6. If this date is missing, the date of last Study Visit available will be considered (excluding Visit 1 and Visit 7 dates).

5.3 Safety variables

All safety variables will be derived from the eCRF.

Adverse Event (AE) 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.

Non-Treatment-Emergent Adverse Event (non-TEAE)
When an AE occurs after written consent has been obtained but before the first dose of treatment study drug (Visit 2 date), the AE will be considered a non-treatment emergent AE. Adverse Events, related to abnormal laboratory parameters, that were identified at Visit 2, when blood samples were collected before the first dose of the study drug, are considered non- TEAEs.

Treatment-Emergent Adverse Event (TEAE)
An AE that occurs from the time the subject receives his first dose of treatment study drug (Visit 2 date) until his last study visit (Follow-up Visit date) will be considered a treatment-emergent AE (TEAE) regardless of the assessed relationship to the administration of the study drug.

Immediately Reportable Adverse Event (IRAE)
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.

Immediately reportable AEs include:

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

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.

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

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- 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 hospitalisation, 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.

Adverse Event of Special Interest (AESI)
Adverse events of special interest are:

1. Adverse Events of Interest include urinary retention and withdrawal symptoms.
2. Adverse Events of Special Psychiatric Interest include nervousness, anxiety, panic attacks, insomnia, aggression, mania, suicidal ideation and development/worsening of depression.

Suicidal Adverse Event
Suicidal Adverse Events and Adverse Events suggestive of abuse potential will be recorded.
Adverse Events suggestive of abuse potential are the events listed in the FDA Guidance for Industry (see Appendix 6). In particular, the following AEs are defined as adverse events suggestive of abuse potential:

1. Euphoria-related terms (Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination; Inappropriate affect)
2. Terms indicative of impaired attention, cognition, and mood (Somnolence; Mood disorders and disturbances)
3. Dissociative/psychotic terms (Psychosis; Aggression; Confusion and disorientation)
4. Related terms not captured elsewhere (Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders)

The following special types of events should be recorded as AEs:

1. Pregnancy - Occurrence of pregnancy in a subject during a clinical study must be recorded.
2. 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.

12-lead ECG
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 duration, QT, corrected QT, RR, and PR intervals.

Physical examination
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).

Psychiatric monitoring
The following psychiatric monitoring will be conducted at the screening visit and at each study visit:

1. suicide monitoring through the use of Columbia-Suicide Severity Rating Scale (C-SSRS)
2. monitor for depression symptoms through the use of the Beck Depression Inventory-II (BDI-II)
3. 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).

5.4 Efficacy Variables

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.

Percentage change in number of incontinence episodes in a week
The number of incontinence episodes entered into the eCRF is the total number of events a subject recorded during the 7day period prior to visit 2 and visit 6. This number will be directly used in the calculation of % change in number of incontinence episodes in a week

Number of Incontinence Episodes/24 hours (daily average)
The number of incontinence episodes entered in the eCRF will be divided by 7 to compute the number of episodes/24 hours (daily average). This consideration follows the assumption that the bladder diary will be filled by the subject for the 7 days prior to Visit 2 and Visit 6 and that the patient entered all episodes occurred in this period. Therefore, the following formula will be used:

$$Number\ of\ Incontinence\ episodes\ /\ 24\ hours = \frac{Number\ of\ incontinence\ episodes\ recorded}{7}$$

Number of Nocturia Episodes in a week
The number of nocturia episodes entered in the eCRF is the total number of nocturia episodes a subject recorded during the 7day period prior to Visit 2 and Visit 6. The value entered in the eCRF will be used in the efficacy analysis of nocturia episodes without any adjustment.

Number of Incontinence Pads per week
The number of incontinence pads entered in the diary represents the number of pads used in a week, therefore the value entered in the eCRF will be used in the analysis without any adjustment.

This consideration follows the assumption that the bladder diary is completed by the subject for the 7 days prior to Visit 2 and Visit 6 and that the patient entered all pads used in this period.

Proportion of subjects who become continent
A subject is defined as continent if he/she has no incontinence episodes.

5.4.1 Sensitivity Efficacy Variables

Sensitivity Analyses will be performed on the number of incontinence episodes in a week as defined in section 5.4.

One set of sensitivity analysis runs efficacy analyses without imputation.

A second set of sensitivity analysis compares the placebo group with the patients in the litoxetine arm at 30 mg who did not have a dose reduction.

A third set of tables will analyse the absolute change of the number of incontinence episodes in a week and the percentage change in the number of incontinence episodes/24 hours.

5.4.2 Exploratory Efficacy Variables

Exploratory Analyses will be performed on the number of incontinence episodes in a week and on the number of incontinence episodes/24 hours as defined in section 5.4.

Based on previous study results with litoxetine, an exploratory analysis will be conducted in subjects with less and more severe UI. Less severe is defined as the population who has incontinence episode frequency below the study median at baseline, while more severe is defined as the population who has incontinence episode frequency above the study median at baseline.

5.5 Baseline

Baseline for all Safety variables including the laboratory parameters will be defined as Visit 2 date.
Baseline for all efficacy endpoints will be defined as the last week of the Screening Placebo Run-in Period.

6. Statistical Methodology

6.1 Handling of Missing Data

Missing Data for the Safety Analysis

Partial dates for medications will be imputed. In case of incomplete date, if day and month are missing the first of January is imputed, if only the day is missing the first of the month will be imputed. Completely missing dates will not be imputed.
No other imputation methods are used for missing values in safety variables.

Missing Data for the Efficacy Analysis

The cases where the total number of incontinence episodes is missing will be addressed prior to unblinding with the following multiple imputation process:

1. The imputation method will be applied to the total number of incontinence episodes missing at Visit 6 only.
2. The imputation method will be applied to the number of incontinence episodes only, it will not be applied to the number of pads or to the number of nocturia episodes.
3. The number of imputations will be based on the percentage of missing data.
4. The seed will be set to 1.
5. The imputation process will be applied to the ITT population.

The method of Predictive Mean Matching is proposed for the imputation process. The method imputes the total number of incontinence episodes for each subject with missing value at visit 6. This method does not make an assumption about the distribution of the variables, thereby minimising the risk of assuming normality when not applicable.

With this method a predictive value is computed via a regression model using a set of observed values from cases deemed to be similar to the missing case based on a set of covariates. This methodology is consistent with an assumption of Missing at Random.

For all analyses where the imputation method is used, analyses without imputation will also be performed as sensitivity analyses.

6.2 Covariate and Subgroups

Safety
Age (under 65, over 65) is used as subgroup for the analysis of treatment emergent adverse event.

Efficacy
The methodology described in the protocol for the efficacy analyses is a mixed model with repeated measures (MMRM). In light of the fact that the efficacy measurements were recorded at visit 2 and visit 6 only, there are no repeated measures. Therefore, the MMRM model described in the protocol cannot be applied to these analyses. The efficacy analyses will be conducted as an analysis of covariance (ANCOVA).
The model will include Baseline values as a covariate and dose and site as factor variables.

Baseline is defined as end of Screening Placebo Run-in for all efficacy analyses (Visit 2).

Exploratory efficacy analysis will be performed based on the baseline severity of incontinence episodes, as defined in section 5.4.2. Patients will be divided in 2 groups according to the median number of incontinence episodes.

6.3 General Methodology

Safety
Safety data will be presented and analysed using the Safety Population.
The primary safety analyses include all treatment emergent adverse events defined as any AE started after Visit 2. The analysis will be carried out with point estimates and Clopper Pearson 95% confidence intervals.

Descriptive statistics will be provided for all variables in the summary tables by treatment group according to the type of variable summarised.

Quantitative variables will be summarised by using n (number of subjects per group), arithmetic mean, standard deviation (SD), median and range (minimum and maximum).

Categorical variables will be summarised by using frequency distributions and percentages.
The number of Adverse Events and the number and the percentage of patients experiencing those events, will be summarised by treatment group. Differences between groups will be evaluated using Chi-square test or Fisher's exact test. Subgroup analysis of differences between groups of AEs will be performed separately for patients who had an adverse event while on the 10mg dose (AE started from Visit 2 and Visit 3), 20 mg dose (AE started from Visit 3 and Visit 4) and 30 mg dose (AE started from Visit 4 and Visit 6). Subjects with adverse events who deviated from the protocol dosage will be highlighted in the footnotes.
Shift tables will be used to describe the evaluation of clinical significance for laboratory values, 12-Lead ECG and physical examination.

For all analyses, hypothesis testing will be carried out at the alpha = 0.05 level (two-sided) when comparing treatments. P-values will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.05.

Efficacy
For the PP efficacy analysis of incontinence episodes, only valid efficacy endpoints at Visit 6 will be used. For the ITT efficacy analysis of incontinence episodes, valid and imputed endpoints at Visit 6 will be used. The imputation method is described in section 6.1. No LOCF from baseline will be used for any efficacy analysis.

Descriptive statistics will be provided for all variables in the summary tables by treatment group according to the type of variable summarised.

Quantitative variables will be summarised by using n (number of subjects per group), arithmetic mean, standard deviation (SD), median and range (minimum and maximum).

Categorical variables will be summarised by using frequency distributions and percentages.

For all analyses, hypothesis testing will be carried out at the alpha = 0.05 level (two-sided) when comparing treatments. P-values will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.05.

6.4 Patient Disposition

Disposition of patients will be presented by treatment group and overall for all patients.

The number of patients included in each of the randomised, safety, ITT, and PP populations will be summarised for each treatment group and overall.
Randomised patients who discontinued from the study prematurely will also be presented with a breakdown of the reasons for discontinuation by treatment group and overall for the randomised population.

Major and minor protocol violations will be presented in the listings only.

The number of patients who need a dose reduction will be presented with means of descriptive statistics. Frequencies and percentages will be used to describe the number of subjects who took a given amount of study drug (10/20/30 mg) at each visit.

6.5 Demographic and Screening/Baseline Characteristics

The baseline demographic characteristics recorded during Screening visit (Visit 1) will be summarised by treatment group and overall by means of descriptive statistics.
The following characteristics will be provided for the Safety population:

1. Age (years)
2. Sex
3. Race (White, Black or African American, Asian, Native Hawaiian or Pacific Islander, Other)
4. Weight (kg)
5. Height (m)
6. BMI (kg/m2)
7. Vital sign – blood pressure (systolic and diastolic), heart rate, Temperature (C)
8. ECG result at Screening visit (Normal, Abnormal NCS, Abnormal CS)
9. Smoking history and current usage, if applicable

Demographic characteristics will also be summarised by site.

Prior and Concomitant medications
Medications will be coded using WHO Drug Dictionary, B3 WHO DDE-March17, using the following Anatomical Therapeutic Classification (ATC) codes;

1. Anatomical Main Group (ATC 1st level code);
2. Chemical subgroup (ATC 4th level code);
3. Preferred name.

Prior and concomitant medications will be summarised separately for safety population by anatomical main group, chemical subgroup and preferred name by treatment group.
Subjects experiencing more than one previous (or concomitant) medication within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

Past disease and concomitant disease
Past disease and concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary (version 20.1) and frequency distributions and percentages will be summarised by treatment group for the safety population by System Organ Class (SOC) and PT.

6.6 Compliance

Overall compliance to study treatment during the treatment period will be summarised using descriptive statistics by treatment group. Compliance will also be presented separately for jars A and B.
Total number of capsules taken from each jar and overall, as well as the treatment duration will also be summarised by treatment group.
Compliance will be analysed in the safety population.

6.7 Safety Analysis

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. All safety analyses will be conducted on the safety population.

All AEs will be coded using the MedDRA dictionary (version 20.1).

1. Incidence and severity of Treatment Emergent Adverse Events and Treatment Emergent Adverse Events of interest (urinary retention, withdrawal symptoms) over the course of the study.

The Treatment Emergent Adverse Events (TEAEs) and the TEAEs of Interest will be summarised by treatment group. The SOCs and PTs will be used for tabulation. The number of TEAEs/TEAEs of interest and the number and the percentage of patients with at least one AE will be presented by SOC and PT for each treatment group. Within each SOC and PT, the highest severity grade attained will be reported, for AEs with divergent severities.

TEAEs/TEAEs of interest will be described with point estimates and Clopper Pearson 95% confidence intervals.
The analysis of treatment emergent adverse events is the primary safety endpoint, the analysis of TEAEs of interest is considered as part of the secondary safety analysis.

2. Treatment Emergent 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

The Treatment Emergent Adverse Events of special psychiatry interest will be summarised by treatment group. The SOCs and PTs will be used for tabulation. The number of AEs and the number and the percentage of patients with at least one AE will be presented by SOC and PT for each treatment group. Within each SOC and PT, the highest severity grade attained will be reported, for AEs with divergent severities.
Adverse events will be described with point estimates and Clopper Pearson 95% confidence intervals.

3. Treatment Emergent Suicidal Adverse Events and Adverse Events suggestive of abuse potential

Suicidal Adverse Events and Adverse Events suggestive of abuse potential will be summarised by treatment group. The SOCs and PTs will be used for tabulation. The number of AEs and the number and the percentage of patients with at least one AE will be presented by SOC and PT for each treatment group. Within each SOC and PT, the highest severity grade attained will be reported, for AEs with divergent severities.
Adverse events will be described with point estimates and Clopper Pearson 95% confidence intervals.

4. Laboratory parameters (Haematology, chemistry, and urinalysis)

Abnormal laboratory values will be listed and their incidence, severity, and relationship to the trial drug will be tabulated by treatment. Change from baseline will be summarised by treatment. Individual changes (shift tables) and individual clinically significant abnormalities 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.
Haematology and chemistry parameters will be summarised by treatment at each visit (visit 2 and visit 6) by means of descriptive statistics. At each visit, mean of the change from baseline will be calculated by treatment group. For Electrolytes only, values at visit 3, visit 4 and visit 5 will also be summarised. In special cases, other parameters may be collected at visit 3, visit 4 and visit 5. In that case the results will be included in the summary statistics.

Shift tables presenting the number and the percentage of patients in each bivariate category (Baseline (Visit 2) versus Endpoint (Visit 6)) with regards to normal range (Low, Normal, High) will be provided for all laboratory parameters (Haematology and chemistry) by treatment group.

For liver enzymes (ALT, AST) and total bilirubin additional analysis will be performed with values expressed in ULN (upper limit of normal) in incidence tables (>3xULN, >5xULN, and >10xULN for aminotransferase activities, and for total bilirubin >2xULN).

The pregnancy test and the urinalysis will be listed only. In particular, the serum pregnancy test is performed at visit 1, visit 6 and visit 7, while the urine (dipstick) pregnancy test is performed at visit 2, visit 3, visit 4,visit 5 and visit 6. Urinalysis is performed at visit 1 and 2.

5. Absolute 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

Absolute values and also change from baseline (Screening Placebo Run-In Period) in ECG readings at Week 8 (Visit 6) will be summarised by descriptive statistics.
ECG parameters of interest include:

a. Ventricular rate
b. QT interval

c. Corrected QT interval
d. PR interval
e. RR interval
f. QRS duration.

6. Absolute change from end of the Placebo Run-In Period to each visit in standardised cuff systolic and diastolic blood pressure and radial heart rate

Absolute change form baseline (Visit 2) to each visit (Visits 3, 4, 5 and 6) for Systolic and Diastolic blood pressure will be summarised by treatment group. The average value of 3 recordings will be considered in the analysis.
A t-test will be used to test a difference between arms only for the change of systolic and diastolic blood pressure from Baseline (Visit 2) to Endpoint (Visit 6). Hypothesis testing will be carried out at the alpha = 0.05 level (two-sided) when comparing treatments. P-value and 95% Confidence Interval will be reported. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.05.

6.8 Additional Safety Analyses

Adverse Events
The number of treatment-emergent AEs, non-TEAEs, AEs occurring during follow-up or following discontinuation, AEs leading to death, AEs leading to discontinuation and SAEs, and the number and the percentage of patients experiencing those events, will be summarised by treatment group. Differences between groups will be evaluated using Chi-square test or Fisher's exact test (if more than 20% of the cells in a contingency table have counts less than 5).

The following adverse events will be specifically summarized by treatment:
1. TEAEs 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
2. Treatment Emergent Suicidal Adverse Events and Adverse Events suggestive of abuse potential
3. SAEs
4. TEAEs
5. Non-TEAEs
6. AEs/SAEs which occurred during the 30-day Follow-up Period or following discontinuation

The SOCs and PTs will be used for tabulation. The number of AEs and the number and the percentage of patients with at least one AE will be presented by SOC and PT for each treatment group. Within each SOC and PT, the highest severity grade attained will be reported, for AEs with divergent severities.

A comparison of treatment-emergent AE rates between litoxetine and placebo will be performed using an exact logistic regression model with the treatment-emergent AE ("1"=At least one treatment-emergent AE occurred for the patient; "0"=otherwise) as dependent variable and litoxetine dose as fixed effects. The probability modelled will be treatment-emergent AE="1".
The number of patients and the number of patients considered in the model will be provided. The exact odds ratio of the fixed effects will be calculated as the number of patients with/without AEs in all arms. If the omnibus test is significant, comparisons between arms will be tested individually, with the relative 95% CI and p-value.
The same model will be repeated by considering SAE ("1"=At least one SAE occurred for the patient; "0"=otherwise) as dependent variable.

AEs leading to study drug discontinuation and AEs leading to death will be presented in the listings only.

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. Non-TEAEs will be summarised separately from TEAEs.

A subgroup analysis of TEAEs will be presented. Subjects will be divided according to age (under 65, over 65). The SOCs and PTs will be used for tabulation. The number of TEAEs and the number and the percentage of patients with at least one TEAE will be presented by SOC and PT for each treatment group and according to the patient's age.

An additional analysis will explore the TEAEs that lead to study drug reduction. Results will be presented as listings as well as with means of descriptive statistics.

Withdrawals
Premature withdrawals from the trial will be displayed and summarised by primary reason and treatment.

Physical examination
Abnormal physical examination findings will be summarised. For each physical examination a shift table presenting the number and the percentage of patients in each bivariate category (baseline versus Week 8 (Visit 6)) with regards to investigator's interpretation (Normal, Abnormal NCS, Abnormal CS, Not done) will be provided by treatment group.
The other results of targeted physical examination will be only listed.

Concomitant Medications
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. A medication will be defined as concomitant if taken after the date of informed consent.
The following information will be reported for each concomitant medication: generic name, route of administration, start date, stop date, frequency, dosage, and indication.

Prior Medications
Prior medications will be presented in summary tables and listings. Medications will be classified as prior medications if taken before the date of informed consent.

Vital signs
Vital signs will be summarised by treatment group at each visit (Baseline, Visit 3, Visit 4, Visit 5, Visit 6) by means of descriptive statistics and listed by subject.
Parameters collected include:

1. Heart Rate (bpm)
2. Body Temperature (Degree Centigrade)

An additional analysis will be performed also on radial heart rate. The actual change from baseline to each visit (Visit 3, Visit 4, Visit 5, Visit 6) in radial heart rate will be computed.

Past and Concomitant Diseases
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).

Past and concomitant diseases will be coded using MedDRA dictionary (version 20.1) and frequency distributions and percentages will be summarised by treatment group for the safety population by SOC and PT.

Counts will be given for both SOC and PT by subject. Subjects experiencing more than one past disease (or concomitant disease) event within a given SOC category will be counted only once within that SOC. Similarly, subjects experiencing more than one past disease (or concomitant disease) event fitting a given PT will be counted only once for that PT.

Summary tabulations for the Safety Population, including the number and percentage of subjects with past and concomitant diseases by SOC and PT, and further categorised by treatment arm will be added.

12-Lead ECG

Actual values and also change from baseline in ECG readings at Visit 2 (baseline), Visit 3, Visit 4, Visit 5, Visit 6 will be summarised by descriptive statistics.
ECG parameters of interest include:

1. Ventricular rate
2. QT interval
3. Corrected QT interval
4. PR interval
5. RR interval
6. QRS duration.

All three measurements for each parameter will be reported. A shift table presenting the number and the percentage of patients in each bivariate category (Baseline to Endpoint) with regards to investigator's interpretation (Normal, Abnormal NCS, Abnormal CS, Not done) will be provided by treatment group.

QT will be corrected for HR using the following formulas:

- Fridericia's correction ($QTc=QT/RR^{0.33}$),
- Bazett's correction ($QTc=QT/RR^{0.5}$)
- Framingham correction (QTc=QT+0.154(1-RR))

Change in QT and QTc for each correction method, will be analysed by central tendency and as categorical analyses. The mean of the QT and HR (obtained in triplicate) will be used.

Central tendency analysis will include:

- Change from baseline (V2) at all time points.
- The change from baseline to Visit 6 in active treatment group will be compared to placebo with a two-sided t-test. The level of significance alpha will be set equal to 5%.
- Results will be reported by 95% CI

Categorical analysis will be conducted based on predetermined thresholds (Visit 2, Visit 3, Visit 4, Visit 5, Visit 6):

- Number of subjects with 450 < QT <= 480 ms, 480 ms < QT <= 500 ms and QT > 500 ms
- Number of subjects with 450 < QTc <= 480 ms, 480 ms < QTc <= 500 ms and QTc > 500 ms

- Number of subjects with increase in QT from baseline >30 ms and <= 60 ms, as well as >60 ms
- Number of subjects with increase in average QTc from baseline >30 ms and <= 60 ms, as well as >60 ms

Tabulation of the results will follow Appendix 1, Guide for the analysis and review of QT and QTc Interval data, Health Canada, 2010.

Psychiatric monitoring

Answers of the questionnaires for psychiatric monitoring will be listed.
In particular, answers for the following questionnaires will be reported:

1. Columbia-Suicide Severity Rating Scale (C-SSRS)
2. Beck Depression Inventory-II (BDI-II)
3. Beck Anxiety Inventory (BAI)
4. Pittsburgh Sleep Quality Index (PSQI)

For the Columbia-Suicide Severity Rating Scale (C-SSRS), summary tables will be used to present the results at visit 1, visit 2, visit 3, visit 4, visit 5, telephone contact at day 42, visit 6 and visit 7. Patients will be classified into 3 categories of subjects with suicidal behaviour, suicidal ideation and suicidal ideation or behaviour according to the Columbia Scoring and Data Analysis Guide (see Appendix 2). Subcategories will also be included. A subject has a suicidal ideation if she/he reports "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS; a suicidal behaviour if there is a "yes" answer to any one of the five suicidal behaviour questions (Categories 6-10); a suicidal ideation or behaviour is the subject has either suicidal ideation or behaviour.
The Suicidal Ideation Score corresponds to the 'Most severe Ideation' score reported in the eCRF and it will be presented as listings. A missing suicidal ideation score means no ideation is present. A shift table will be provided to demonstrate changes in C-SSRS categories from Baseline to Visit 6.

The BDI-II is a widely used 21-item self-report inventory measuring the severity of depression in adolescents and adults. BDI-II items are rated on a 4-point scale ranging from 0 to 3 based on the severity of each item. The maximum total score is 63. The total score derived in the eCRF will be summarized. Patients will also be classified according to the following rules: total scores of 0 to 13 indicates minimal depression, 14 to 19 indicates mild depression, 20 to 28 indicates moderate depression, and 29 to 63 indicates severe depression. A summary table will be used to describe the results at visit 1, visit 2, visit 3, visit 4, visit 5, visit 6 and visit 7. See Appendix 3 for more details on this questionnaire. A shift table will be provided to demonstrate changes in BDI-II categories from Baseline (Visit 2) to end of study (Visit 6).

The Beck Anxiety Inventory (BAI) is a widely used 21-item self-reported inventory used to assess anxiety levels in adults and adolescents. Summary tables will be used to present the total score at visit 1, visit 2, visit 3, visit 4, visit 5, visit 6 and visit 7. The total score will be computed summing up the score to each question.
The total score ranges from 0–63. The following categories for the interpretation of scores will be used: 0–7, minimal; 8-15, mild; 16-25, moderate; and 26–63, severe anxiety. A shift table will be provided to demonstrate changes in BAI categories from Baseline (Visit 2) to end of study (Visit 6).
See Appendix 4 for more details on this questionnaire.

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality (question 6), sleep latency (question 2 and 5A), sleep duration

(question 4), habitual sleep efficiency (questions 1, 3, 4), sleep disturbances (question 5B to 5J inclusive), use of sleeping medications (question 7), and daytime dysfunction over the last month (questions 8 and 9). In scoring the PSQI, seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality. The global score reported in the eCRF will be summarized at visit 1, visit 2, visit 3, visit 4, visit 5, visit 6 and visit 7. A global sum greater than "5" indicates a "poor" sleeper, therefore patients will be classified according to the global score into "good" or "poor" sleepers, a summary table will be provided to describe those results. A shift table will be provided to demonstrate changes in PSQI categories from Baseline to end of study (Visit 6).
See Appendix 5 for more details on this questionnaire.

6.9 Efficacy Analyses

Efficacy will be assessed by the number of urinary incontinence episodes. There is only one hypothesis so there will be no adjustment for multiplicity.

The efficacy analysis will be performed on the ITT and PP populations.
There will not be an adjustment for multiple comparisons for these efficacy analyses.
Baseline for all efficacy endpoints will be defined as the last week of the Screening Placebo Run-In Period (Visit 2). The final measurement (endpoint) will be defined as Week 8 (Visit 6).

1. Percentage change from end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence episodes in a week

The efficacy analysis planned is an analysis of covariance model (ANCOVA). Percentage change in the number incontinence episodes/week is the response variable. The factor variables will be dose and centre. If the center effect is significant, summary statistics will be presented to describe the effect. The covariate will be end of the Screening Placebo Run-In Period episodes of incontinence.

The percentage change, $\%UIE_i$, for subjects in each arm, is expressed as the ratio of the total number of urinary incontinence episodes in a week between final measurement ($UIE_{i,\,end}$) and baseline ($UIE_{i,\,base}$)

$$\%UIE_{\mathrm{i}} = \frac{UIE_{\mathrm{i},end}}{UIE_{\mathrm{i},base}}$$

Since percentage change from baseline does not have the properties of additivity and symmetry, it will be log-transformed, and the response variable will be the natural logarithm of the ratio of Week 8 (Visit 6) to Baseline, as shown below:

$$\log(\%UIE_{\mathrm{i}}) = \log\left(\frac{UIE_{i,end}}{UIE_{i,base}}\right)$$

The hypothesis test being conducted is as follows:

H_0: $\log(\%UIE_{Litoxetine}) - \log(\%UIE_{Placebo}) = 0$
H_1: $\log(\%UIE_{Litoxetine}) - \log(\%UIE_{Placebo}) \neq 0$,

This is equivalent to testing the hypothesis:

$$H_0: \log\left(\frac{\%UIE_{\text{Litoxetine}}}{\%UIE_{\text{Placebo}}}\right) = 0$$

The result of the ANCOVA model will be expressed as log % and then back transformed to percentage change. Therefore, H_0 can be interpreted as:

$$H_0: \frac{\%UIE_{Litoxetine}}{\%UIE_{\text{Placebo}}} = 1$$

This makes the actual statistics:

$$\delta = \log(\%UIE_{Litoxetine}) - \log(\%UIE_{Placebo}) = \log\left(\frac{\%UIE_{Litoxetine}}{\%UIE_{\text{Placebo}}}\right)$$

When back-transformed, this is expressed as follows:

$$\Delta = \exp\left(\log\left(\frac{\%UIE_{Litoxetine}}{\%UIE_{\text{Placebo}}}\right)\right) = \frac{\%UIE_{Litoxetine}}{\%UIE_{\text{Placebo}}}$$

$\%UIE_i$ is the ratio of the total number of urinary incontinence episodes in a week at endpoint (Visit 6) ($UIE_{i,end}$) to the total number of urinary incontinence episodes in a week at baseline ($UIE_{i,base}$) for arm *i*, with *i* equal to Litoxetine or Placebo.

An ANCOVA will be performed to compare δ to 0; the test will provide an appropriate p-value with a significance level alpha equal to 0.05. This p-value will be computing the probability of observing a difference among arms.

Numbers of incontinence episodes equal to 0 (not missing) will be imputed as 0.4 to allow for the log transformation.

2. Absolute change from end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence episodes/24 hours (daily average)

The analysis planned is an analysis of covariance model (ANCOVA). Absolute change in the total number of incontinence episodes/24 hours is the response variable. The factor variables will be dose and centre. The covariate will be end of the Screening Placebo Run-In Period episodes of incontinence.

Number of incontinence episodes/24 hours will be computed as Total Number of incontinence episodes recorded during the 7-day period and entered in the eCRF divided by 7, as defined in Section 5.4.

The hypothesis test being conducted is as follows:

$H_0: \Delta UIE_{\text{Litoxetine}} - \Delta UIE_{\text{Placebo}} = 0$
$H_1: \Delta UIE_{\text{Litoxetine}} - \Delta UIE_{\text{Placebo}} \neq 0$

Where ΔUIE_i is the absolute change, for subjects in arm *i*, in the number of incontinence episodes/24 hoursas defined above from baseline ($UIE_{i,base}$) to the final measurement ($UIE_{i,end}$):

$$\Delta UIE_i = UIE_{i,end} - UIE_{i,base}\ .$$

Where *i* goes from 1 to 2 and it represents the 2 arms: Litoxetine and Placebo.

3. Proportion of subjects who become continent at Week 8

A subject is defined as continent if s/he has no incontinence episodes at Visit 6 (Week 8). Frequencies will be used to describe the proportion of subjects who are continent at Week 8. The proportion will be computed on the total number of subjects for each arm at baseline. The category Missing will be included in the analysis, to consider subjects who do not attend the visit or who have missing values for that visit.

Differences between groups will be evaluated using Chi-square test or Fisher's exact test (if more than 20% of the cells in a contingency table have counts less than 5).

4. Change from end of the Screening Placebo Run-In Period to Week 8 in the number of incontinence pads used per week

The analysis planned is an analysis of covariance model (ANCOVA). Absolute change in the number of incontinence pads used per week is the response variable. The factor variables will be dose and centre. The covariate will be the number of pads used at the end of the Screening Placebo Run-In Period.

Number of incontinence pads used per week will be derived for the eCRF, as defined in Section 5.4.

The hypothesis test being conducted is as follows:

H_0: $\Delta\text{Pads}_{\text{Litoxetine}} - \Delta\text{Pads}_{\text{Placebo}} = 0$
H_1: $\Delta\text{Pads}_{\text{Litoxetine}} - \Delta\text{Pads}_{\text{Placebo}} \neq 0$

Where ΔPads_i is the absolute change, for subjects in arm *i*, in the number of incontinence pads used per week from baseline ($\text{Pads}_{i,base}$) to the final measurement ($\text{Pads}_{i,end}$):

$$\Delta\text{Pads}_i = \text{Pads}_{i,end} - \text{Pads}_{i,base} .$$

Where *i* goes from 1 to 2 and it represents the 2 arms: Litoxetine and Placebo.

5. Percentage change from end of the Screening Placebo Run-In Period to Week 8 in the number of nocturia episodes in a week

The analysis planned is an analysis of covariance model (ANCOVA). Percentage change in the total number of nocturia episodes in a week is the response variable. The factor variables will be dose and centre. The covariate will be end of the Screening Placebo Run-In Period episodes of incontinence.

The number of nocturia episodes in a week is the total number of nocturia episodes recorded over the 7-day period and entered in the eCRF, as defined in Section 5.4.

The analysis will be carried out as described in section 6.9 point 1.

6.9.1 Sensitivity Efficacy Analyses

For the Efficacy Analyses relating to the number of incontinence episodes, a sensitivity analysis without imputation will be performed.
The sensitivity analyses will be performed on the ITT only, since the imputation method is not used in the PP population.
As with the Efficacy Analysis, baseline for all sensitivity endpoints will be defined as the last week of the Screening Placebo Run-In Period. The final measurement (endpoint) will be defined as Week 8 (Visit 6).

A second set of sensitivity analysis compares the placebo group with the patients in the litoxetine arm at 30 mg who did not have a dose reduction.

A third set of tables will analyse the absolute change of the number of incontinence episodes in a week and the percentage change in the number of incontinence episodes/24 hours.

1. Percentage change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes in a week (without imputation)

This sensitivity analysis will use an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 1.
The imputation method will not be applied.

2. Change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes/24 hours (daily average) (without imputation)

The change in the total number of incontinence episodes in a week will be analysed with an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 2.
The imputation method will not be applied.

3. Percentage change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes in a week for patients without a dose reduction

The percentage change in the total number of incontinence episodes in a week will be analysed with an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 1. In the litoxetine group, only patients who did not have a dose reduction will be considered. Therefore, subjects who are dispensed the 30 mg dose at visit 5 will be considered in the litoxetine group.

4. Change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes/24 hours (daily average) for patients without a dose reduction

The change in the total number of incontinence episodes/24 hours will be analysed with an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 2. In the litoxetine group, only patients who did not have a dose reduction will be considered. Therefore, subjects who took the 30 mg dose at visit 6 will be considered in the litoxetine group.

5. Percentage change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes/24 hours (daily average)

This exploratory analysis will use an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 1.
The number of incontinence episodes/24 hours (daily average) will be used as endpoint.

6. Change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes in a week

The change in incontinence episodes in a week will be analysed with an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 2.
The total number of incontinence episodes in a week will be used as endpoint.

6.9.2 Exploratory Efficacy Analyses

The severity of incontinence episodes will be explored dividing the population in subjects with less/more severe UI. Less severe is defined as the population who has incontinence episode frequency below the study median at baseline, while more severe is defined as the population who has incontinence episode frequency above the study median at baseline.

Based on the assessment of the variability of the data and the size of each subgroup, the efficacy analysis will be performed on the subgroups.
Baseline severity threshold is defined as the median value of incontinence episodes at baseline.

These analyses will be performed on the PP population only.

1. Percentage change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes in a week as a function of degree of incontinence

The percentage change in the total number of incontinence episodes in a week will be analysed with an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 1. Patients will be divided in two groups depending on the baseline severity of incontinence episodes.
The median number of incontinence episodes at baseline will be computed on the randomised population. Two analyses will be performed, one on subjects whose baseline number of incontinence episodes is less than the median, and the other on subjects whose baseline number of incontinence episodes is greater than or equal to the median.

2. Change from end of the Screening Placebo Run-In Period to Week 8 (Visit 6) in the number of incontinence episodes/24 hours (daily average) as a function of degree of incontinence.

The change in the number of incontinence episodes/24 hours (daily average) will be analysed with an ANCOVA model. It will follow the efficacy analysis described in section 6.9 point 2. Patients will be divided in two groups depending on the baseline severity of incontinence episodes.
The median number of incontinence episodes at baseline will be computed on the randomised population. Two analyses will be performed, one on subjects whose baseline number of incontinence episodes is less than the median, and the other on subjects whose baseline number of incontinence episodes is greater than or equal to the median.

7. General Considerations

7.1 Software to be used

All statistical analyses and data processing will be performed using SAS version 9.4 or higher.

7.2 Programs and Tables Quality Control

The following procedures will be implemented as quality control measures:

- Double-blind programming, ensuring that the code gives the required output and the programming is in compliance with any applicable specifications from the analysis plan
- Check for errors and warning messages
- Check of the layout of the listings and tables

Additionally, in the course of data collection, eCRF data will be reviewed and queries raised if needed.

8. Data Storage

Relevant study documentation will be stored in the “Buncro” – private StatisticaMedica cloud hosted by Radix Technologies, in IXA2-Ixaltis Prostate and SUI/Programming for the scripts and IXA2-Ixaltis Prostate and SUI/Reports for the delivered documentation, in the corresponding subfolders for the SAP, TFLs and CSR.

9. References

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2. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence. 27 June 2013.
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5. Wood LN, Anger JT. Urinary incontinence in women. BMJ: 2014;349: g4531.
6. Papanicolaou S. Pons ME, Hampel C et al. Medical resource utilization and cost of care for women seeking treatment for urinary incontinence in an outpatient setting. Examples from three countries in the PURE study. Maturitas 2005; 52. Suppl 2:S35-47.

10. Appendix 1

Guide for the analysis and review of QT and QTc Interval data, Health Canada, 2010.

11. Appendix 2

Nilsson, Mary E., et al. "Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide." CSSRS Scoring Version 2 (2013): 1-13.

12. Appendix 3

Beck Depression Inventory-Second Edition published on *The National Child Traumatic Stress Network* (Source URL: https://www.nctsn.org/measures/beck-depression-inventory-second-edition)

13. Appendix 4

Beck, Aaron T., et al. "An inventory for measuring clinical anxiety: psychometric properties." Journal of consulting and clinical psychology 56.6 (1988): 893.

Clinical Psychology, 56, 893–897. Beck, A. T., & Steer, R. A. (1990). Manual for the Beck Anxiety Inventory. San Antonio, TX: Psychological Corporation. Jolly, J.

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14.Appendix 5

Buysse, Daniel J., et al. "The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research." *Psychiatry research* 28.2 (1989): 193-213.

15. Appendix 6

Food and Drug Administration Center for Drugs Evaluation Research, Guidance for Industry: Assessment of Abuse Potential of Drugs (2017)