

CLINICAL STUDY PROTOCOL

IND NUMBER 121245

A Phase 2b, 8-Week, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of 3 Different Dose Levels of IX-01 on Intravaginal Ejaculatory Latency Time (IELT), Patient-Reported Outcomes, and Safety in Men with Lifelong Premature Ejaculation (PE) PROTOCOL NO. IX-0105

Sponsor: **Ixchelsis Ltd.**
Discovery Park House
Discovery Park
Ramsgate Road, Sandwich
Kent CT13 9NJ
United Kingdom

Sponsor Chief Medical Officer: Ian Osterloh MSc, MBBS, MRCP
Chief Medical Officer
Ixchelsis Ltd.
Telephone: +44 (0) 7771 971413

Sponsor Contact and Project Manager: Katie George BSc Hons, PMP
Clinical Project Manager
Ixchelsis Ltd.
Telephone: +44 (0) 7977 008998

24-Hour Safety Hotline: Telephone: +1 800 201 8725
Fax: +1 888 488 9697

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All financial and nonfinancial support for this study will be provided by Ixchelsis Ltd. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Ixchelsis Ltd.

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title A Phase 2b, 8-Week, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of 3 Different Dose Levels of IX-01 on Intravaginal Ejaculatory Latency Time (IELT), Patient-Reported Outcomes, and Safety in Men with Lifelong Premature Ejaculation (PE)

Protocol Number IX-0105

Amendment 1.0 16 January 2017

Protocol accepted and approved by:

Chief Medical Officer

Ian Osterloh MSc, MBBS, MRCP

Ixchelsis Ltd.

Discovery Park House

Discovery Park

Ramsgate Road, Sandwich

Kent CT13 9NJ

United Kingdom

Signature

Date

Protocol Approval – Principal Investigator

Study Title A Phase 2b, 8-Week, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of 3 Different Dose Levels of IX-01 on Intravaginal Ejaculatory Latency Time (IELT), Patient-Reported Outcomes, and Safety in Men with Lifelong Premature Ejaculation (PE)

Protocol Number IX-0105

Amendment 1.0 16 January 2017

Protocol accepted and approved by:

Principal Investigator

Dr Stanley Althof

Center for Marital and Sexual Health of South Florida

1515 North Flagler Drive

Suite 540

West Palm Beach

FL 33401

United States

Signature

Date

Protocol Approval – Biostatistician

Study Title A Phase 2b, 8-Week, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of 3 Different Dose Levels of IX-01 on Intravaginal Ejaculatory Latency Time (IELT), Patient-Reported Outcomes, and Safety in Men with Lifelong Premature Ejaculation (PE)

Protocol Number IX-0105

Amendment 1.0 16 January 2017

Protocol accepted and approved by:

Senior Biostatistician

Nicolas Girard

PPD Development Ltd.

19, rue Docteur Freysz, 67000 Strasbourg

France

Telephone: +33 980 757 587

Signature

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled “A Phase 2b, 8-Week, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of 3 Different Dose Levels of IX-01 on Intravaginal Ejaculatory Latency Time (IELT), Patient-Reported Outcomes, and Safety in Men with Lifelong Premature Ejaculation (PE)” and the accompanying Investigator’s Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1.0, dated 24 October 2016, the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Ixchelsis Ltd or implement protocol changes without institutional review board approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Ixchelsis Ltd.

Signature of Principal Investigator

Date

Stanley Althof

Printed Name of Principal Investigator

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Protocol Synopsis

- Protocol Number:** IX-0105
- Title:** A Phase 2b, 8-Week, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of 3 Different Dose Levels of IX-01 on Intravaginal Ejaculatory Latency Time (IELT), Patient-Reported Outcomes, and Safety in Men with Lifelong Premature Ejaculation (PE)
- Sponsor:** Ixcelsius Ltd.
Discovery Park House, Discovery Park
Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom
- Study Phase:** Phase 2b
- Study Sites:** Approximately 30 sites in the United States
- Indication:** Premature Ejaculation
- Rationale:** In a previous clinical study, the selective oxytocin-receptor antagonist, IX-01 has been shown to prolong intravaginal ejaculatory latency time (IELT) and improve patient-reported outcomes in men with lifelong premature ejaculation (PE). This study is designed to explore the relationship between efficacy and dose.
- Objectives:**
- To determine the efficacy of 3 different dose levels of IX-01 to prolong IELT in men with PE.
 - To determine the efficacy of 3 different dose levels of IX-01 on Clinical Global Impression of Change (CGIC), control of ejaculation, ejaculation-related distress and interpersonal difficulty, and satisfaction with sexual intercourse in men with PE.
 - To determine the toleration and safety of 3 different dose levels of IX-01 taken as required in men with PE.
- Patient Population:**
- Men aged ≥ 18 years and ≤ 60 years in stable (≥ 6 months) heterosexual relationship and who have lifelong PE.
 - PE confirmed by IELT ≤ 1 minute on at least 75% of attempts at sexual intercourse during the run-in period.
 - Men meeting other aspects of International Society for Sexual Medicine (ISSM) definition including inability to delay ejaculation on all or nearly all vaginal penetrations and negative personal consequences such as distress, bother and frustration.

- Patient and partner willing to attempt intercourse at least 4 times during the run-in period and at least 8 additional times during the double-blind part of the study.
- Partner not planning pregnancy and willing to use contraception (unless not of childbearing potential, eg, surgically sterilized).
- Patient willing to limit use of alcohol on days in which he takes study drug (not more than 3 standard drinks as defined in the Informed Consent Form).
- Patient capable of giving written informed consent.
- Key exclusion criteria include any IELT value >2 minutes during the run-in period; any patient making <4 attempts at sexual intercourse during the run-in period; any patient who rates their control of ejaculation as fair, good, or very good (Premature Ejaculation Profile [PEP] question administered at the end of the run-in period); any patient who rates their ejaculation-related “personal distress” as “not at all” or “a little bit” (PEP question administered at the end of the run-in period); coexisting International Index of Erectile Dysfunction (IIEF; Erectile Function domain <22 during the run-in period); concomitant use of phosphodiesterase type 5 inhibitors, selective serotonin reuptake inhibitor (SSRIs)/selective serotonin norepinephrine reuptake inhibitor (SSNRIs), monoamine oxidase inhibitors, alpha blockers, 5-alpha reductase inhibitors, topical anesthetics, and/or tramadol; any history (last 6 months) of use of Botox or similar product to treat PE; any other sexual disorder of patient or partner that could interfere with the results; any current sexually transmitted disease; and being unwilling to stop other treatments including psychotherapy and sex therapy for PE; PHQ-9 total score >9 and/or score of >0 on Question 9 of PHQ-9.

Study Design:

A Phase 2b, 8-week, double-blind, placebo-controlled, parallel-group study to evaluate the effect of 3 different dose levels of IX-01 on IELT and patient-reported outcome in men with lifelong PE.

Men with self-reported lifelong PE (ISSM definition) and in stable heterosexual relationship will undergo a 4-week run-in period during which they will be asked to attempt intercourse at least 4 times. Men with IELT \leq 1 minute on at least 75% of

attempts at intercourse during the no-treatment run-in period will be randomized for the double-blind phase of the study.

In the double-blind phase of the study, men will be asked to take study drug 1 to 6 hours prior to sexual activity. Men and partners will be asked to attempt intercourse a minimum of 8 times during the 8-week double-blind study treatment. The patient or partner will record the IELT on each occasion by use of a stopwatch.

Estimated Study Duration:

Each patient will require a minimum of 6 visits if they do not terminate the study early. The duration of the study for each patient is approximately 4 months (including the 8-week double-blind treatment period).

Efficacy Assessments:

Electronic diary (eDiary) (LogPad) will capture the following:

Sexual activity (date and time)

- IELT
- Level of control of timing of ejaculation and level of ejaculation-related personal distress associated with each event.

Patient Questionnaires/Instruments:

Questionnaires administered at the end of the run-in period and after 4 and 8 weeks of double-blind treatment

- Premature Ejaculation Profile (PEP) including additional question on bother
- Patient Global Impression of Severity (PGIS)

Questionnaire to be administered at end of double-blind treatment only

- Clinical Global Impression of Change (CGIC)

Pharmacokinetic or Pharmacodynamic Assessments:

This protocol does not require sampling for pharmacokinetics.

Safety Assessments:

- Physical examination and vital signs
- Weight and body mass index
- Electrocardiograms
- Laboratory safety tests
- Concomitant medications
- Adverse events
- IIEF

- Patient Health Questionnaire 9 (PHQ-9)
- Columbia-Suicide Severity Rating Scale

Study Drug, Dosage, and Route of Administration:

Study drug will be supplied as 400 mg caplets (IX-01 or matching placebo). One dose is 3 caplets to be taken orally 1 to 6 hours before sexual activity, but not more than once per day. There will be 4 dosage groups (placebo, IX-01 400 mg, IX-01 800 mg, and IX-01 1200 mg). In order to preserve the blind, each dose will be supplied in a blister pack containing 3 caplets (which will comprise placebo and/or IX-01, depending on the treatment group assigned).

Sample Size:

The target total is for 220 patients to be randomized in the study. The randomization ratio will be 2:2:3:3 (placebo, IX-01 400 mg, IX-01 800 mg, and IX-01 1200 mg dose groups, respectively).

Thus, 44 patients each will be randomized to the placebo and IX-01 400 mg dose groups, and 66 patients each will be randomized to the IX-01 800 mg and IX-01 1200 mg dose groups. The 2:3 ratio results in only slight loss of statistical power from 1:1 randomization while increasing the chances that a patient will be randomized to an effective dose of study drug.

Assuming an alpha (2-sided) of 0.05 and an SD of 70 seconds, a sample size of 220 patients randomized in total (44 to the placebo and IX-01 400 mg dose groups and 66 to the IX-01 800 mg and IX-01 1200 mg dose groups) provides approximately 85%, 90%, and 90% power to detect a mean difference of 45 seconds between change from baseline in geometric mean (GM) of IELT for the IX-01 400 mg, IX-01 800 mg, and IX-01 1200 mg dose groups, respectively, compared with the placebo group.

Sequential multiplicity control testing of IX-01 1200 mg dose versus placebo, followed by IX-01 800 mg dose versus placebo and then IX-01 400 mg dose versus placebo will be done in order to control for multiplicity.

Additional patients may be recruited if some patients discontinue from the study with less than 2 postbaseline IELT assessments.

Statistical Methods:

The primary efficacy endpoint of this study is the change in GM IELT over the treatment assessment period compared with baseline, ie, $[GM(IELT_{\text{treatment period}}) - GM(IELT_{\text{baseline}})]$.

Change from baseline in GM IELT over the treatment assessment period will be analyzed using a mixed linear model, including treatment and baseline IELT as fixed factors and site

as a random factor.

The primary comparison of interest is IX-01 1200 mg versus placebo. If it is statistically significant at $\alpha=0.05$, then the following comparisons will be tested in the following order:

- IX-01 800 mg vs placebo group
- IX-01 400 mg vs placebo group

If at any point in the sequence statistical significance is not met, then subsequent analyses in the sequence cannot be deemed statistically significant. In such cases, nominal *P* values and 95% CI will be reported and interpreted in an exploratory manner. Irrespective of whether there are any statistically significant differences between treatment groups, IELT data from all treatment groups will also be used to model a possible dose response relationship.

The same approach to control for multiple comparisons as proposed for the primary endpoint will be used for each secondary endpoint analysis.

The following key secondary efficacy endpoints will be analyzed:

1. Fold change in GM IELT over the treatment assessment period compared with baseline.
2. Proportion of patients with ≥ 2.5 -fold increase in GM IELT over the treatment assessment period compared with baseline, ie, [proportion of subjects with $\text{GM}(\text{IELT}_{\text{treatment period}})/\text{GM}(\text{IELT}_{\text{baseline}}) \geq 2.5$].
3. Proportion of patients rating their PE as improved per the CGIC questionnaire.
4. Proportion of patients achieving mean change in category of ≥ 1 or ≥ 2 on control of timing of ejaculation (PEP), ie, improving control from “very poor” or “poor” to “fair,” “good,” or “very good” at end of treatment.
5. Proportion of patients achieving mean change in category of ≥ 1 or ≥ 2 in ejaculation-related personal distress (PEP), ie, improving rating of ejaculation-related distress to “moderate,” “a bit,” or “not at all” at end of treatment.
6. Proportions of patients achieving change in category of ≥ 2 on control of timing of ejaculation (PEP) and achieving change in category of ≥ 1 in ejaculation-related personal distress (PEP) at end of treatment.

7. Mean change from baseline in score on control of ejaculation (e-diary) over the treatment assessment period.
8. Mean change from baseline in score on ejaculation-related personal distress (e-diary) over the treatment assessment period.

Analyses of e-diary data expressed in change from baseline over the treatment assessment period will be carried out using a mixed linear model. All analyses should include treatment, baseline IELT, and the baseline score of the analyzed endpoint as fixed effects and the site as a random effect.

For each analysis on proportion endpoints, difference in the proportions between each test group and placebo group will be tested using a logistic model. All analyses should include treatment, baseline IELT and the site as factors. *P* values and adjusted odds ratios will be presented.

Amendment 1.0:

16 January 2017

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CGIC	Clinical Global Impression of Change
CNS	Central nervous system
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
GCP	Good Clinical Practice
GGT	Gamma Glutamyltransferase
GM	Geometric mean
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IELT	Intravaginal ejaculatory latency time
IIEF	International Index of Erectile Function
IRB	Institutional review board
ISSM	International Society for Sexual Medicine
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NOAEL	No observed adverse effect level
PDE5	Phosphodiesterase type 5
PE	Premature ejaculation

Abbreviation	Definition
PEP	Premature Ejaculation Profile
PGIS	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire 9
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SSNRI	Selective Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO-DD	WHO Drug Dictionary

1 Introduction

1.1 Disease Under Treatment

Premature ejaculation (PE) is a common male sexual dysfunction, but the etiology is not well understood. Although historically considered to be predominantly a condition of psychological origin, over the last decade, it has been increasingly recognized that men with PE starting and continuing from their earliest sexual experiences may have a genetic predisposition to ejaculate rapidly and that men who acquire PE later in life may have a variety of psychosocial and physical factors that bring on the condition.¹ Thus, PE is subclassified as “lifelong” or “acquired”.² Patients with lifelong PE give a history of rapid ejaculation from the first sexual experience and persistence of rapid ejaculation (before or within 1 to 2 minutes after vaginal penetration) throughout life. Acquired PE is characterized by a gradual or sudden onset following normal ejaculation experiences before onset of the condition, when time to ejaculation becomes short (but often not as short as in lifelong PE).

Until recently, there has been no universally accepted definition of PE. Generally, definitions of PE acknowledge certain core components: short ejaculatory latency, lack of control over ejaculation, and ejaculation-related personal bother or distress. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), published in 2013, defines the condition as persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately one minute following vaginal penetration and before the individual wishes it, and is associated with clinically significant distress in the individual. The International Consultation on Sexual Dysfunctions suggests that men with an intravaginal ejaculatory latency time (IELT) less than 2 minutes qualify as having PE.³ Over the last few years, there has been a new evidence-based definition that has gained widespread acceptance. It is the definition adopted by the International Society for Sexual Medicine (ISSM), and defines PE as a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration (lifelong PE) OR a clinically significant reduction in latency time, often to about 3 minutes or less (acquired PE), and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.⁴ The definition applies to both lifelong and acquired PE but is limited to intravaginal sexual activity. The ISSM definition is similar to the DSM-5.

Premature Ejaculation can have a profoundly negative effect on quality of life, and men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less frequent intercourse than men without PE.^{5,6} PE also diminishes self-confidence and damages the relationship with the partner and may cause mental distress, anxiety, embarrassment, and depression.⁷ Rosen and Althof confirmed a high level of psychological distress associated with PE that can be as impactful as erectile dysfunction on the couple.⁸ They also found that women were impacted as much and possibly more than their partners by PE and were an important reason for men to seek treatment. Another study⁹ confirmed that the partner's satisfaction with the sexual relationship decreased with increasing severity of the man's condition, and a more recent study reported that the detrimental effects of PE often resulted in the termination of the relationship.¹⁰

At present, the only approved prescription oral medication specifically for the management of PE is dapoxetine (Priligy[®]), which has approval in over 60 countries in Europe, Asia, and Latin America.¹¹ Dapoxetine is a selective serotonin reuptake inhibitor (SSRI) taken on demand. When SSRIs are used for the management of depression, they have been associated with the side effect of anorgasmia and hence have been prescribed off-label (often as continuous daily dosing regimens but sometimes on demand) for the treatment of PE. Patients are often reluctant to begin off-label treatment of PE with SSRIs for reasons of not wanting to take an antidepressant, treatment effects below expectations, and cost. Recently, the European Medicines Agency approved a topical prescription-only treatment (PSD502[®]), a local anesthetic containing lidocaine and prilocaine.¹²

In view of the paucity of available treatment options for men with PE, new oral treatments with different modes of action and different benefit/risk profiles are needed.

1.2 Study Drug

IX-01 is a small molecule being developed for the treatment of PE.

IX-01 is a potent, competitive antagonist, which is highly selective for the oxytocin receptor, and exhibits little interaction with the vasopressin receptor family. The chemical name is 5-{3-[3-(2-chloro-4-fluorophenoxy)azetidin-1-yl]-5-(methoxymethyl)-4H-1,2,4-triazol-4-yl}-2-methoxypyridine. IX-01 is a white-to-pale colored solid.

A caplet dosage form of IX-01 has been developed for oral dosing and use in clinical studies. The caplet strength is 400 mg, and the caplet is formulated per Good Manufacturing Practice (GMP) guidelines. Further information on the formulation is provided in the Investigator's Brochure.

1.3 Preclinical Experience

Detailed information regarding the nonclinical pharmacology and toxicology of IX-01 may be found in the Investigator's Brochure.

1.3.1 Nonclinical Pharmacology

In Vitro Pharmacology

IX-01 is a potent, competitive antagonist, which is highly selective for the oxytocin receptor, and exhibits little interaction with the vasopressin receptor family. Its potency is similar for human and rat oxytocin receptors. The functional inhibition constants (K_B) for the human and rat native uterine smooth muscle oxytocin receptors are 5.7 nM and 8.9 nM, respectively.

IX-01 has little activity against the human recombinant V_{1B} receptor, with an $IC_{50} > 10 \mu M$ for the receptor-binding assay. It is equally inactive against the V_2 receptor in the V_2 receptor β -lactamase reporting assay (agonist format: $EC_{50} > 10 \mu M$; antagonist format: $IC_{50} > 1 \mu M$). The compound is more than 100-fold selective against the V_{1A} receptor in either native or recombinant human oxytocin receptor assays and > 85 -fold selective over the V_{1A} receptor in rat native assays.

In Vivo Pharmacology

IX-01 has been evaluated in 2 in vivo pharmacological models. In the anesthetized rat electromyography model of ejaculation, IX-01 interrupted the expulsion phase of ejaculation. In the anesthetized rat central nervous system (CNS) neuronal firing model, IX-01 demonstrated CNS penetration and modulation of an oxytocin-mediated response in the nucleus tractus solitarius.

1.3.2 Safety Pharmacology

The biochemical activity of IX-01 was screened in different assays for enzymes, receptors, and transporters. Activities were observed in 3 of 60 for the receptors, channels, and transporters tested. There was no activity detected in enzyme assays.

In isolated dog Purkinje fibers, dose-dependent reductions in action potential duration at 50% and 90% repolarization occurred at IX-01 concentrations of 10 and 30 μM . IX-01 also reduced peak hERG potassium current amplitude at high concentration. It was devoid of any biologically relevant hemodynamic or electrocardiogram (ECG) effects in conscious dogs up to the dose of 20 mg/kg (total C_{max} of 9007 nM).

IX-01 does not affect respiratory function in male rats up to doses of 150 mg/kg. The only effects were a small reduction in respiratory rate and a nonstatistically significant decrease in minute volume at 450 mg/kg.

IX-01 had no adverse effects on neurofunctional assessment in male rats.

IX-01 at dose levels up to 20 mg/kg (C_{max} 9007.5 nM, 3780 ng/mL) does not adversely affect cardiovascular function in conscious male dogs.

1.3.3 Toxicology

Administration of IX-01 to male rats and male dogs were performed per Good Laboratory Practice.

In the toxicology program, IX-01 was orally administered to male rats and dogs for up to 90 days. Adaptive changes related to liver enzyme induction were noted in the liver as well as in the thyroid and pituitary. Deaths observed at doses ≥ 750 mg/kg in the 1-month studies and exploratory rat studies were likely due to hypothermia. In addition to low core body temperature, these deaths were preceded by clinical signs such as decreased blood pressure, decreased respiration rate, and neurological signs in the animals. At 200 mg/kg of IX-01, dogs exhibited potential neurological signs consisting of titubation, prostration, whining, partially closed eyes, tremors, and occasional diarrhea. The no observed adverse effect levels (NOAELs) with repeated administration were 450 mg/kg in rats and 120 mg/kg in dogs. The corresponding C_{max} and AUC values in rats were 10 100 ng/mL (525 ng/mL free) and

140 000 ng × h/mL (7280 ng × h/mL free), respectively, and in dogs were 52 900 ng/mL (5660 ng/mL free) and 778 000 ng × h/mL (83 246 ng × h/mL free), respectively. The NOAEL is based on adverse clinical effects apparently associated with the CNS observed at higher doses.

IX-01 was negative in genetic toxicology testing and presented no phototoxic potential in vitro.

1.3.4 Pharmacokinetics and Product Metabolism in Animals

Pharmacokinetic studies were done in rats and dogs, and in vitro. It was found that 87.4% to 94.8% of IX-01 was bound to rat, dog, and human and dog plasma proteins in vitro. IX-01 penetrated the CNS. Clearance predominantly occurred through cytochrome P450 (CYP) 3A4 metabolism, with minor contributions from CYP2C19, CYP2D6, and glucuronidation. The overall potency of IX-01 as an inhibitor of CYP metabolism is weak; however, CYP3A4 inhibitors or inducers may alter the pharmacokinetics of IX-01.

1.3.5 Clinical Data

To date, 162 male subjects have received one or more doses of IX-01. Clinical safety and pharmacokinetic data are available from four completed Phase 1 studies (A8651001, IX-0101, IX-0102, and IX-0104). Also, preliminary clinical safety and kinetic data are available from recently completed study IX-0106. A Phase 2a proof-of-concept study (IX-0103) has also been completed and demonstrated the efficacy of IX-01 (doses 400 to 800 mg as needed) to prolong IELT, improve ejaculation-related control, and reduce ejaculation-related distress in men with lifelong PE.

Single-Ascending Dose Study

The first-in-human study (A8651001) recruited 30 healthy male volunteers in 3 sequential cohorts and evaluated 11 different dose levels of IX-01 ranging from 0.3 mg to 2400 mg. The overall incidence of adverse events (AEs) was similar across all treatment groups, including placebo. The most common treatment-emergent adverse events (TEAEs) were nasopharyngitis, headache, insomnia, and nightmares. The most frequent treatment-related AE was headache. All of the AEs were considered mild to moderate in severity. Three subjects who had received IX-01 and one subject who had received placebo reported events

of nightmare after dosing. These events were single episodes with the exception of one subject who reported 3 episodes of nightmare after 2 different doses of IX-01 (one episode while receiving 400 mg and 2 episodes while receiving 800 mg). All events of nightmare were mild in intensity.

There was no evidence of a drug- or dose-related effect on laboratory test results, and there were no clinically significant changes in vital signs or ECGs. One subject in Cohort 2 discontinued from the study due to mild, asymptomatic, non-sustained ventricular tachycardia (IX-01, 400 mg) that appeared approximately 7 hours post-dose and lasted only 3 seconds. Although it is impossible to completely exclude a relationship to the study drug, the short episode resolved without requiring any treatment and was not accompanied by symptoms or hemodynamic changes.

There was no effect of IX-01 on core body temperature at any dose studied. The mean maximum exposure reached (1.9 µg/mL total, 452 nM total) was similar to that which resulted in mild hypothermia in rats (1-10 µg/mL; 238-2380 nM total).

Peak plasma concentrations (T_{max}) of IX-01 occurred approximately 1 to 2 hours after oral dosing. Overall, exposure (AUC) increased subproportionally with dose. The terminal half-life was approximately 12 hours. Under fed conditions (800 mg), both peak concentration and overall exposure were increased (1.8-fold and 1.3-fold, respectively). Urinary excretion of intact drug was negligible, with < 0.05% of the dose excreted over 24 hours after dosing.

Multiple-Ascending Dose Study (1)

The multiple-ascending dose study (IX-0101) recruited 48 volunteers in 4 cohorts of 12 subjects each. Within each cohort, subjects were randomized (1:3) to receive placebo or IX-01 in the fasted state once daily for 10 consecutive days. The final cohort received the maximum dose (1200 mg daily) permitted by the protocol. The protocol required monitoring of vital signs and the recording of 12-lead ECGs at frequent intervals postdose on Days 1 and 10 and predose on Days 1, 5, 8, and 10. Continuous Holter ECG monitoring was performed on all subjects from 2 hours predose to 8 hours postdose on Days 1 and 10. In addition, aural temperature was recorded at frequent intervals postdose on Days 1 and 10, and predose and 12 hours postdose on Days 2 to 9.

All 48 subjects completed the study, and there were no serious adverse events (SAEs) and no severe AEs. There was no evidence of any treatment-related changes in aural temperature at any of the doses administered. The mean maximum plasma concentration of IX-01 reached in this study (2.2 µg/mL total at C_{max} on Day 10 in the 1200 mg dose group) was higher than the mean maximum exposure achieved with a single 2400 mg dose of IX-01 in Study A8651001, and thus, the clinical safety data provide further evidence that hypothermia observed in some rat studies does not translate to a similar finding in human.

The overall number of AEs reports was low with no clear evidence of a dose-related increase in incidence. No particular AE occurred in more than one subject per treatment group apart from headache (2 of 9 subjects receiving 1200 mg IX-01). Two subjects (one receiving placebo and one receiving 800 mg IX-01) reported intermittent vivid dreams (coded as abnormal dreams) throughout most of the dosing phase of the study. There were no reports of nightmares.

There were no clinically significant changes in vital signs, 12-lead ECGs, or ECG monitoring by telemetry reported by the investigator for any of the subjects in any of the dose groups.

The Day 10 pharmacokinetic profiles were similar to those observed on Day 1. IX-01 was rapidly absorbed, reaching C_{max} at approximately 1.5 hours (T_{max}) postdose (range 0.5-4 hours) across the dose range. Post- C_{max} , plasma concentrations declined in a biphasic manner. The terminal half-life ($t_{1/2}$) was similar across all dose groups, with mean estimates of 11.6 to 12.3 hours. The geometric mean (GM) steady-state C_{max} values increased subproportionally compared with dose, with a 6.2-fold increase over a 12-fold dose range. Accumulation ratios (C_{max} and AUC_{0-24h} values on Day 10/Day 1) were 1.24 and 1.34, respectively, for the 1200 mg dose.

Semen samples were collected from all subjects at 2 to 4 hours postdose on Day 9, and the concentrations of drug were subsequently measured. The mean amount of IX-01 in the ejaculate (2 µg or less) constituted <0.0003% of the administered dose, and as such, the intravaginal dose to the partner of a subject taking IX-01 is negligible.

Multiple-Ascending Dose Study (2)

A maximally tolerated dose was not identified in Study IX-0101, and therefore, a second multiple-ascending doses study (IX-0104) was performed. This study recruited 24 volunteers in 2 cohorts of 12 subjects each. Within each cohort, subjects were randomized (1:2) to receive placebo or IX-01 in the fasted state once daily for 10 consecutive days. The final cohort received the maximum dose (2400 mg daily) permitted by the protocol. The protocol required monitoring of vital signs and the recording of 12-lead ECGs at frequent intervals postdose on Days 1 and 10 and predose on Days, 1, 5, 8, and 10. Continuous Holter ECG monitoring was performed on subjects from 2 hours predose to 8 hours postdose on Days 1 and 10. In addition, aural temperature was recorded at frequent intervals postdose on Days 1 and 10, and predose and 12 hours postdose on Days 2 to 9.

Both cohorts of Study IX-0104 completed with no SAEs and no severe AEs reported. In Cohort 1, there were 2 AEs that were considered possibly related to treatment by the investigator. One subject in the placebo group reported headache of moderate severity on Day 1. It lasted for 4 hours and required treatment with paracetamol but fully resolved. Another subject who received 1600 mg IX-01 reported pruritic rash of moderate severity on Day 8. Dosing with study drug was discontinued, and the subject was given one application of antihistamine ointment. The AE was fully resolved at follow-up. In Cohort 2, there was only one AE reported and was for a subject who received 2400 mg IX-01 and was noted to have urticaria of moderate severity starting approximately one hour after dosing on Day 1. Dosing was discontinued in this subject as a precaution, but the urticaria had fully resolved without treatment less than 3 hours after first being noted. There were no clinically significant changes in vital signs, 12-lead ECGs, or ECG monitoring by telemetry reported by the investigator for any of the subjects in any of the dose groups.

IX-01 was rapidly absorbed, reaching C_{max} at approximately 2 hours (T_{max}) postdose. The GM C_{max} values on Day 1 were 1883 and 2622 ng/mL for the 1600 mg and 2400 mg treatment groups, respectively. The GM AUC_{tau} values on Day 1 were 14 953 and 25 926 h \times ng/mL for the 1600 mg and 2400 mg treatment groups, respectively.

The Day 10 pharmacokinetic profiles were similar to those observed on Day 1. IX-01 was rapidly absorbed, reaching C_{max} at approximately 2 hours (T_{max}) postdose (range 1.5 to

4 hours) across the dose range. The GM C_{\max} values on Day 10 were 2552 and 2516 ng/mL for the 1600 mg and 2400 mg treatment groups, respectively. The GM AUC_{τ} values on Day 10 were 28 623 and 27 862 h \times ng/mL for the 1600 mg and 2400 mg treatment groups, respectively.

The terminal half-life ($t_{1/2}$) was similar in both dose groups, with mean estimates of 11.6 to 11.7 hours. This study confirmed subproportional increases in the absorption of IX-01 when administered as a dispersion in the fasted state.

Relative Bioavailability Study (200mg capsules)

In Study IX-0102, 12 subjects were randomized to receive IX-01 800 mg dispersion in the fasted state, IX-01 800 mg (4 \times 200 mg capsules) in the fasted state, and IX-01 800 mg (4 \times 200 mg capsules) administered after a high-fat meal.

The bioavailability of the capsule formulation was similar to that of the dispersion formulation when both are administered in the fasted state. Administration of a high-fat meal immediately prior to the capsules increased the bioavailability of IX-01.

In this study, the subjects also underwent lumbar puncture 1 to 6 hours after receiving the dispersion formulation. The results confirmed that IX-01 is present in the cerebrospinal fluid; CNS penetration of IX-01 is important for the potential to treat PE.

Relative Bioavailability Study (400mg caplets)

In Study IX-0106, 12 subjects were randomized to receive IX-01 1600 mg dispersion in the fasted state, IX-01 1600 mg (4 \times 400 mg caplets) in the fasted state, and IX-01 1600 mg (4 \times 400 mg caplets) administered after a high-fat meal.

The preliminary results indicate that the GM C_{\max} values were 2152 ng/ml for the caplet formulation administered in the fasted state, and that the caplet has an improved bioavailability compared to the dispersion, with GM C_{\max} and AUC 1.8 fold those of the dispersion. In addition, food increased the bioavailability (AUC) of the caplet (1.5 fold), which is comparable to the effect of food seen with the capsule and dispersion formulations previously. However, unlike the capsule and dispersion formulations, the rate of absorption was not significantly delayed for the caplet formulation with C_{\max} increasing 2.7 fold in the

presence of food. There were no treatment-related adverse events or safety issues reported in this study.

Proof-of-Concept Study

IX-0103 was an 8-week, double-blind, placebo-controlled, Phase 2a clinical study that recruited 88 men with lifelong PE at 10 study centers in the United States and Australia.

Eligible patients (men fulfilling the ISSM definition of lifelong PE with $\geq 75\%$ of intercourses lasting ≤ 60 seconds during a 4-week run-in period without treatment) were randomized (2:1 ratio) to an 8-week treatment period with IX-01, 400 mg (2 capsules), or equivalent double-blind placebo, with the medication being taken as required, 1 to 6 hours prior to sexual activity. If treatment was poorly tolerated, the dose could be reduced to 200 mg or equivalent placebo. From Week 2 onwards, the investigator could increase the dose to 800 mg or equivalent placebo (4 capsules) if toleration was acceptable and optimal efficacy had not been obtained.

During the treatment period, patients were required to return to the study site at Weeks 2, 4, and 8 and use their electronic diary (LogPad) to complete the Premature Ejaculation Profile (PEP) and other patient-reported outcomes. A follow-up visit was to be performed 2 weeks after the end of treatment.

The mean age of men in this study was 43 years, and the baseline GM IELT was < 30 seconds in both treatment groups. Patients randomized to IX-01 took a mean of 14.6 (range 1-59) doses during the study. Patients randomized to placebo took a mean of 13.0 (range 1-51) doses. Fifty (89.3%) and 23 (76.7%) patients (IX-01 and placebo, respectively) took the permitted maximum dose of 4 capsules at least once during the study.

Mean IELT values increased 3.6-fold from baseline for IX-01, compared with 1.8-fold for placebo. Mean IELT values increased by over 1 minute (61.0 seconds) for IX-01 compared with 16.4 seconds for placebo. The results also showed clinically and statistically significant improvements in perceived control of ejaculation and ejaculation-related personal distress at end of treatment for IX-01 compared with placebo. Twenty-one (44%) patients randomized to IX-01 rated their PE as improved at the end of treatment compared with 3 (13%) of patients randomized to placebo. There were also clinically and statistically significant

improvements for some of the results of the 4-week recall PEP, with 17 (33%) patients randomized to IX-01 improving their control of ejaculation to “fair,” “good,” or “very good” compared with one (3%) patient randomized to placebo. There was also a clinically and statistically significant difference in favor of IX-01 for the proportion of patients whose level of ejaculation-related distress improved to “moderate,” “a bit,” or “not at all,” 24 (46%) for patients randomized to IX-01 versus 4 (16%) for patients randomized to for placebo.

There were no serious and no severe AEs reported during this study. The proportions of patients reporting AEs were similar for IX-01 and placebo, with no AE reported by more than 2 patients in any treatment group. Two patients were discontinued from IX-01 for possibly treatment-related AEs: one for AE of increased transaminases that normalized during treatment and one for AE of nausea. There were no safety signals arising from review of vital signs, laboratory function test results, 12-lead ECGs, and other safety assessments.

This study has demonstrated the ability of IX-01 (taken as required prior to sexual activity) to improve all the 3 key features (short ejaculation time, lack of control, and ejaculation-related distress) of the condition in men with most severe form of lifelong PE. IX-01 was effective while maintaining a toleration and safety profile indistinguishable from placebo in this study. Post hoc exploratory analyses indicated that the 800 mg dose was more effective than the initial 400 mg dose, and thus, there is likely to be potential for increased efficacy when larger doses are administered in future studies.

1.4 Study Rationale

IX-01 is a CNS-penetrant, selective oxytocin receptor antagonist that has shown to be effective in treating men with lifelong PE when doses of 400 to 800 mg have been administered prior to intercourse. The present study is to determine the efficacy and safety of 3 different dose levels (administered as required prior to intercourse) of IX-01 to prolong IELT in patients with lifelong PE. The design of the study including the choice of efficacy instruments is consistent with the latest recommendations by experts in PE.¹³

1.4.1 Rationale for Dose Selection

The results of study IX-0103 indicated that single doses of IX-01 (400 to 800 mg administered as capsules), taken 1 to 6 hours prior to intercourse in the fasted state, prolong

IELT and improve ejaculation-related control and distress. A post hoc analysis indicated that 400 mg is less effective than the 800 mg dose. However, even at 800 mg, less than half of the patients reported benefit, and therefore, the objective of this study is to explore the efficacy and safety of 1200 mg (3 x 400 mg caplets) and to compare the response at this dose with placebo, 400 mg, and 800 mg doses. In the previous efficacy study, doses of 400 to 800 mg were taken one hour before or after food and 1 to 6 hours prior to sexual activity. In this study, it is also recommended to take the study drug at least one hour before or after food, and 1 to 6 hours prior to sexual activity. A 400 mg caplet formulation has been developed to improve bioavailability and to allow a reduced number of caplets to be taken per dose of IX-01.

1.5 Potential Risks and Benefits

The nonclinical toxicology, pharmacology, and pharmacokinetic data generated to date and the clinical safety, pharmacokinetic, and pharmacodynamic data generated in studies A8651001 and IX-0101 to IX-0104 support an acceptable risk-benefit profile to evaluate the efficacy and toleration of single doses of orally administered IX-01 (taken as required but not more than once per day) in adult males, aged 18 to 60 years, inclusive, with PE. The maximum dose to be administered in this study is 1200 mg (3 x 400 mg caplets) taken prior to sexual activity but not more than once per day. Doses up to and including 2400 mg administered as a dispersion and taken in the fasted state once daily for 10 consecutive days have been well tolerated by healthy volunteers. Small reductions in mean systolic and diastolic blood pressure between active and placebo groups were not of clinical significance. Two subjects have been discontinued from IX-01 because of skin AEs: a subject who had a pruritic skin rash after 8 days of consecutive dosing with 1600 mg, and a subject with transient urticaria after a single dose of 2400 mg. In Study IX-0106 twelve subjects have received 1600mg administered as 4 x 400 caplets in fasted state and 11 subjects also received 4 x 400 mg caplets after a high fat meal. No treatment-related adverse events were observed. As in the previous Phase 2 study, the safety of the patients will be assessed at frequent intervals by physical examination and laboratory safety tests. Although preclinical and clinical data generated to date with IX-01 provide no evidence of adverse effects on mood, this protocol includes questionnaires and interviews to screen for depression and suicidality, which is in accordance with other clinical studies of new treatments for PE.

Formal teratology and reproductive studies have not been performed with IX-01. The amount of IX-01 in human ejaculate has been measured and is <0.0003% of the administered dose. This study will only recruit patients who are not attempting to father a child.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to determine the efficacy of three different dose levels of IX-01 to prolong IELT in men with lifelong PE.

2.2 Secondary Objectives

- To determine the efficacy of three different dose levels of IX-01 on Clinical Global Impression of Change (CGIC), control of ejaculation, ejaculation-related distress and interpersonal difficulty, and satisfaction with sexual intercourse in men with PE.
- To determine the toleration and safety of three different dose levels of IX-01 taken as required in men with PE.

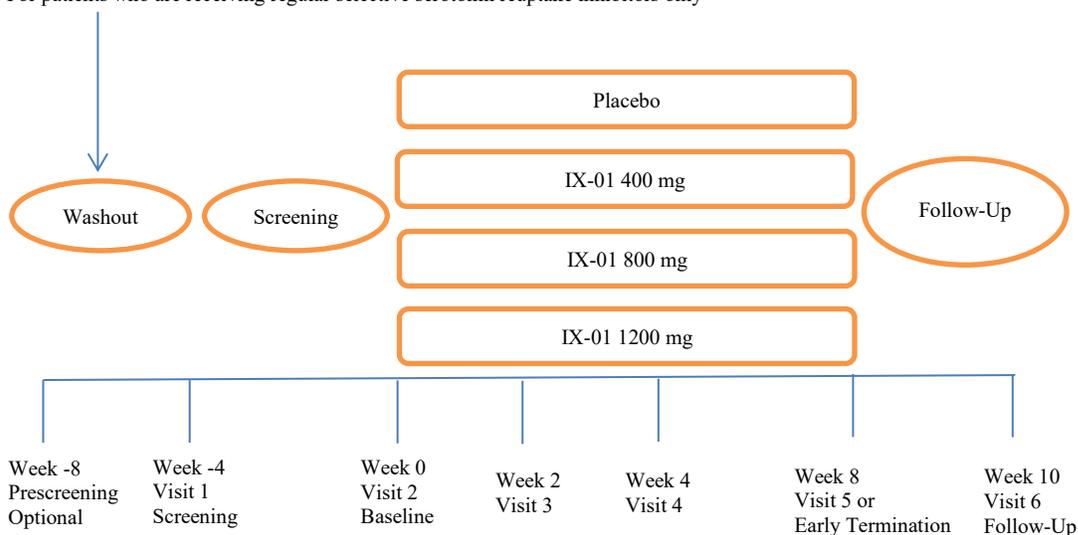
3 Investigational Plan

3.1 Study Design

The design of this study is illustrated in Figure 3-1. This will be a randomized, double-blind, placebo-controlled study in men with lifelong PE to determine the efficacy, safety, and tolerability of three different dose levels of IX-01 compared with placebo. The study will be performed in multiple centers in the United States. The patient population will consist of male adults aged 18 to 60 years in stable heterosexual relationship and who have lifelong PE. A target of 220 patients with IELT \leq 1 minute on \geq 75% of attempts at intercourse during the no-treatment run-in period will be randomized.

Figure 3-1 Study Design

For patients who are receiving regular selective serotonin reuptake inhibitors only



Screening (Visit 1) will occur approximately 4 weeks before dosing (Visit 2). During screening, patients will undergo the measurements and examinations detailed in the Schedule of Events (Table 13-1). Eligible patients will be provided with a LogPad (electronic diary) and stopwatch. Patients will be asked to attempt sexual intercourse at least 4 times during the 4-week run-in period.

Note: Patients taking chronic SSRIs for the treatment of PE must have an additional 4-week washout prior to the 4-week run in period. Patients taking CYP3A4 inducers or moderate and potent CYP3A4 inhibitors must be excluded from the study or stop and refrain from their use at Visit 1.

At the end of the run-in period, patients will undergo their baseline measurements and examinations detailed in the Schedule of Events (Table 13-1), which includes a PEP, International Index of Erectile Function (IIEF), Patient Health Questionnaire 9 (PHQ-9), and mandatory Columbia-Suicide Severity Rating Scale (C-SSRS) assessment. The patient's LogPad is used for completing the questionnaires and providing results to the Investigator regarding the eligibility of the patient, based on IELT and patient-reported outcome criteria. The C-SSRS is a face-to-face interview that must be administered by the Investigator or his/her designate. If the patient does not meet eligibility to remain in the study, the Investigator must not randomize the patient and may suggest alternate treatment.

Eligible patients will undergo one 8-week treatment period, during which time they are randomized to take IX-01, 400, 800, or 1200 mg or matching placebo. In order to maintain the double-blind, each dose will be presented as 3 caplets in blisters in single-dose units. Thus, for example, a patient randomized to 400 mg IX-01 will receive blister cards with each dose comprising one IX-01 400 mg caplet and two matching placebo caplets. Patients will complete an e-diary (LogPad) on all days during the treatment period that sexual activity is performed with or without the use of the study drug.

During the treatment period, patients will be expected to return to the study site and use their LogPad to complete the following questionnaires according to the study schedule:

- Premature Ejaculation Profile (PEP)
- International Index of Erectile Function (IIEF)
- Patient Health Questionnaire (PHQ-9)
- Patient Global Impression of Severity (PGIS)
- Clinical Global Impression of Change (CGIC) – Early Termination/Visit 5 only

The LogPad will provide results to the Investigator regarding whether or not the patient is required to complete the C-SSRS. The C-SSRS is mandatory at baseline, and is only mandatory at all other visits if the PHQ-9 total score is >9 , and/or the PHQ-9 Question 9 score is >0 ; it may also be administered at any time if clinically indicated, in the opinion of the Investigator. A final follow-up visit is conducted 2 weeks after the end of double-blind treatment. For more details of the procedures at each study visit, please refer to Section 6.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Men aged ≥ 18 years and ≤ 60 years in stable (≥ 6 months) heterosexual relationship and who have lifelong PE.
2. Premature ejaculation confirmed by IELT ≤ 1 minute on $\geq 75\%$ attempts at sexual intercourse during the run-in period.
3. Patient meets other aspects of ISSM definition including inability to delay ejaculation on all or nearly all vaginal penetrations and negative personal consequences such as distress, bother, and frustration.
4. Patient and partner willing to attempt intercourse at least 4 times during the run-in period and at least 8 additional times during the double-blind part of the study.
5. Partner not planning pregnancy and willing to use contraception (unless not of childbearing potential, eg, surgically sterilized).
6. Patient willing to limit use of alcohol on days in which he takes study drug (not more than 3 standard drinks as defined in the Informed Consent Form).
7. Patient capable of giving written informed consent.

4.1.2 Exclusion Criteria

1. Any IELT value > 2 minutes during the run-in period.
2. Any patient making < 4 attempts at sexual intercourse during the run-in period (screening may be extended or patient may be rescreened if there are extenuating circumstances).
3. Any patient who rates his control of ejaculation as fair, good, or very good (PEP question administered at the end of the run-in period).
4. Any patient who rates his ejaculation-related “personal distress” as “not at all” or “a little bit” (PEP question administered at the end of run-in period).

5. Coexisting Erectile Dysfunction (IIEF Erectile Function domain <22 during the run-in period).
6. Concomitant use of phosphodiesterase type 5 (PDE5) inhibitors, SSRIs/selective serotonin norepinephrine reuptake inhibitor (SSNRIs), monoamine oxidase inhibitors, alpha blockers, 5-alpha reductase inhibitors, topical anesthetics, and/or tramadol.
7. Any history (last 6 months) of use of Botox or similar product to treat PE.
8. Any patient who has received IX-01 in a previous clinical study.
9. Any patient who is unwilling to stop other treatments for PE (including but not limited to pharmacological, sex therapy, psychotherapy multiple condoms, and prior masturbation).
10. Any other sexual disorder of patient or partner that could interfere with results.
11. Any current sexually transmitted disease.
12. Any major medical condition of patient that could interfere with ability to have sexual activity and/or require hospital treatment.
13. Body mass index (BMI) >40 kg/m² or weight <60 kg.
14. Participation in a clinical drug study anytime during the 30 days prior to screening.
15. History of or positive test results for Human immunodeficiency virus (HIV), hepatitis B.
16. History of prostate disease or clinically significant prostate disease.
17. History of myocardial infarction, coronary bypass surgery, coronary artery angioplasty, unstable angina, clinically evident congestive heart failure, cardiac pacemaker, or cerebrovascular accident.
18. Cardiac arrhythmia: significant cardiac arrhythmia shown on screening ECG, or a known or suspected history of significant cardiac arrhythmias.
19. History of drug-induced allergic reactions including skin reactions.
20. History of congenital QT prolongation and/or corrected QT interval >450 msec at screening visit using the Bazett formula.
21. Mean systolic cuff blood pressure >140 mm Hg, as assessed by 3 measurements taken in sequence within 5 to 10 minutes of last measure.

22. Mean diastolic cuff blood pressure >90 mm Hg, as assessed by 3 measurements taken in sequence within 5 to 10 minutes of the last measure.
23. Significant psychiatric disease and/or risk of suicidal tendency as assessed by clinical evaluation and PHQ-9 and C-SSRS.
 - PHQ-9 total score >9 and/or score of >0 on Question 9 of PHQ-9 would be exclusion criterion.
24. Any other major medical or psychological or psychiatric condition that could cause the patient to be unsuitable for the study or could interfere with interpretation of the study results.
25. Clinically significant abnormal laboratory function test results (including liver enzymes $>2 \times$ the upper limit of normal [ULN] or bilirubin $>1.5 \times$ ULN).
26. Patients taking CYP3A4 inducers, or moderate and potent CYP3A4 inhibitors.
27. History of or other evidence of recent alcohol or drug abuse.

4.2 Withdrawal of Patients From the Study

Patients will be discontinued from the investigational product and/or from the study in the following circumstances:

1. Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
2. The patient requests to be discontinued from the study.
3. Sponsor decision to stop the study or to stop the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).
4. If a clinically significant event occurs that is considered related to the study drug, then the investigational product is to be discontinued and appropriate measures taken. A clinically significant event will be defined as a moderate to severe AE (eg, rash), abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the patient.

5. The results of the PHQ-9 and C-SSRS indicate a change in mental condition and a risk to the patient by continuing in the study. (see Section 13.2)
6. Certain laboratory test criteria are fulfilled:
 - a. Discontinuation of the investigational product for abnormal liver tests must occur when a patient meets one of the following conditions after consultation with the designated medical monitor:
 - i. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>8 \times$ ULN
 - ii. ALT or AST $>5 \times$ ULN for more than 2 weeks
 - iii. ALT or AST $>3 \times$ ULN and total bilirubin level $>2 \times$ ULN or prothrombin time $>1.5 \times$ ULN
 - iv. ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$)
 1. Liver function tests should be repeated if ALT and or AST $>3 \times$ ULN and/or bilirubin $>1.5 \times$ ULN (or $1.5 \times$ baseline value if baseline value was $>ULN$)

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented. Patients who are discontinued early from the study should complete the Early Termination visit (see Section 6.1). Every effort will be made to follow up all patients for safety.

Study site participation may be discontinued if the sponsor or its designee, the Investigator, or the Institutional Review Board (IRB) of the study site judges it necessary for any reason consistent with applicable laws, regulations, and GCP.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

The study will be conducted in a double-blind manner using a placebo matching the active drug in appearance, labelling, and packaging. Randomization numbers will be assigned according to the randomization schedule that contains patient identification numbers with a corresponding assignment of active drug or placebo. Assignment of study medication as well as site investigational product inventory control and emergency unblinding will be managed by an automated system (Interactive Web Response System).

The randomization ratio of the target 220 patients is 2:2:3:3 (0, 400, 800, 1200 mg dose groups). Thus, 44 patients will each to be randomized to placebo and IX-01 400 mg dose groups, and 66 patients will each to be randomized to IX-01 800 mg and 1200 mg dose groups. The sponsor retains the option to replace any patients who drop out without any postbaseline efficacy data.

5.2 Treatments Administered

Study drug will be supplied as 400 mg caplets (IX-01 or matching placebo), and treatment allocation will be composed of 4 dosage groups (placebo, IX-01 400 mg, IX-01 800 mg, and IX-01 1200 mg). One dose is 3 caplets (placebo and/or IX-01, depending on the dosage) to be taken orally at least one hour before or after food, 1 to 6 hours before sexual activity, but not more than once per day.

5.3 Management of Clinical Supplies

5.3.1 Study Drug Packaging and Storage

In order to preserve the blind, each dose will be supplied in a blister card containing 3 caplets (which will comprise placebo and/or IX-01, depending on the treatment group assigned). Seven single-dose cards will then be packed into a tamper sealed carton, in line with the visit schedules. Supplies will be shipped at ambient temperature with temperature-monitoring devices (TempTale[®]). On arrival, the site will check if the temperature-monitoring device has alarmed; if not, the supplies are approved for use. If the alarm has been triggered following a temperature excursion, supplies will be placed in quarantine while the TempTale[®] data are

returned and reviewed by Ixcelsius or delegate. The site will then be informed if the excursion warrants the supplies being destroyed and/or replaced or if they are cleared for use.

All supplies will be packed, labelled, and released in accordance with GMP and GCP guidelines. The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secure area, under recommended storage conditions 59°F-86°F (15°C-30°C) and in accordance with applicable regulatory requirements. Any excursions from the recommended storage conditions should be reported to the sponsor within 24 hours of the finding.

5.3.2 Test Article Accountability

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product.

Unless otherwise notified, all investigational product both used and unused must be saved for study treatment accountability. The investigational product accountability records must be available for verification by the study monitor at each monitoring visit. At the completion of the study, a final reconciliation of all investigational product will be performed and Ixcelsius will provide instructions regarding the disposition of any unused investigational product. If Ixcelsius authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policies, and any special instructions provided by Ixcelsius including written confirmation that the supplies can be destroyed. Destruction must be adequately documented and the documentation provided to Ixcelsius.

5.3.3 Product Complaints and Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify or suspect a potential product complaint should immediately contact Ixcelsius or designee and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from an Ixcelsius or a designated quality representative.

The Investigator or his/her designee is responsible for handling the product complaint process in accordance with the instructions provided for this study in the Study Training Manual.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Ixcelsius or designee.

5.4 Blinding

5.4.1 Breaking the Blind

All study medication will be administered in a double-blind manner. Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the patient, the Investigator may unblind a patient's treatment assignment. If the blind is broken for any reason, the Investigator must notify the Sponsor or designee immediately after the unblinding incident without revealing the patient's study treatment assignment. In addition, the Investigator will record the date and reason for revealing the blinded treatment assignment for that patient in the electronic case report form (eCRF).

5.5 Treatment Compliance

There is no requirement for the patient to take medication every day. However, he should only take a maximum of one dose (3 caplets) per day and record this in the LogPad. The Investigator should record the amounts of study drug dispensed and returned at each visit during the treatment period. The patient should always take the 3 caplets from the same blister card with each dose. He should never take more or less than these 3 caplets per dose.

5.6 Prior and Concomitant Therapy

Use of SSRIs must be stopped, and patients who were previously taking SSRIs regularly require an additional 4-week washout prior to the 4-week run-in period. Patients who require SSRI treatment for depression or other illnesses (not PE) should not be included in the study.

Concomitant treatment with PDE5 inhibitor (eg, sildenafil, tadalafil, vardenafil), topical anesthetics, and/or tramadol is prohibited. Additionally, any history (current or last 6 months) of use of Botox or similar product to treat PE is not allowed.

The following treatments are also prohibited during the study: monoamine oxidase inhibitors, alpha blockers, 5-alpha reductase inhibitors (including finasteride [Propecia] for hair loss). Herbal supplements are also prohibited.

Concomitant use of potent or moderate CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir) and inducers (eg, bosentan, carbamazepine, phenytoin, phenobarbital, St John's Wort, and rifampicin) is not allowed from at least 4 weeks before the start of dosing until the end of the study.

6 Study Assessments and Procedures

6.1 Study Visits

A complete listing of study measurements and evaluations may be found in the Schedule of Events (Table 13-1).

Screening Visit 1

Approximately 28 days (± 3 days) prior to the first dosing, patients will attend the center for assessment of eligibility for the study. Written informed consent must be obtained from each potentially eligible patient by study site personnel prior to the initiation of screening procedures as outlined in this protocol.

Note: Patients taking chronic SSRIs for the treatment of PE must have an additional 4-week washout prior to the 4-week run-in period.

After providing signed written informed consent, patients will complete screening assessments. Each patient who undergoes screening for study enrollment will be assigned an identification number, which will provide a means of identifying each patient. Information and data collected will include the following:

- Assessment of patient eligibility according to the entry criteria, including clinical interview by the Investigator or his/her qualified designee to indicate that the patient meets the ISSM definition of PE. In particular, the investigator should ask the patient about the duration of the symptoms of PE, since lifelong PE can only be diagnosed if ejaculation always or nearly always occurred prior to or within about 1 minute of vaginal penetration from the earliest sexual experience.
- Medical history and assessment of concomitant medication.
- Year and month of birth, gender at birth, and race (ethnicity).
- Height, weight and physical examination. A physical examination will be conducted by the Investigator or other licensed study site personnel to establish an overall profile of the

patient's health and to identify and document any abnormal physical findings prior to the patient's participation in the study.

- Recording of vital sign data (heart rate and blood pressure measurements).
- 12-lead ECG.
- Blood sampling for laboratory safety tests (including hematology and clinical chemistry analyses) and serology for HBsAg, HCV Ab, HIV 1, and HIV 2.
- Urinalysis.
- Urine drug screen.

Patients willing to take part in the study and who are eligible according to the criteria already assessed during the screening visit will be provided with a LogPad and stopwatch. They will complete training on how to use the LogPad during this visit. Once the training is completed, patients will be asked to attempt intercourse with their partners at least 4 times during the 4-week run-in period, to use the stopwatch to time the attempt, and to record the relevant details in the LogPad including whether alcoholic drinks were taken prior to intercourse. At the next study visit (Visit 2), the patient must bring the LogPad to the study site. Further details for LogPad use and instructions are found in the Study Training Manual.

Baseline Visit 2

On Visit 2 (Day 0, Week 0 \pm 7 days from screening), patients will attend the study center, and information and data collected will include the following:

- Assessment of patient eligibility according to the IELT entry criteria. The patient will return the LogPad to the investigator. The LogPad will provide a summary of the IELT data collected during the run-in period and will indicate whether the patient is eligible to continue in the study based on the IELT criteria. (Note: Refer to the Study Training Manual for instructions if a patient does not remember to return the LogPad.)
- The investigator will provide the LogPad back to the patient for completion of the PEP, PGIS, IIEF, and PHQ-9. After completion of these questionnaires, the patient will return

the LogPad to the investigator. The LogPad will provide a further summary that will indicate whether the patient is eligible to continue in the study based on the results of the PEP, IIEF, and PHQ-9. If the patient is not eligible based on these assessments, then he should not be randomized or continued in the study, and the investigator may discuss alternate treatment options.

- Weight.
- Physical examination.
- Recording of vital sign data (heart rate, blood pressure, and oral temperature measurements) and 12-lead ECG.
- Blood sampling for laboratory safety tests (including hematology, clinical chemistry, and coagulation analyses).
- Urinalysis.
- Urine drug screen.
- C-SSRS.
- Adverse events and concomitant medication update.
- The patients who meet all of the eligibility criteria will be randomized and assigned a treatment number. Eligible patients will be provided with at least 7 doses of study drug (IX-01 or placebo). Further supplies can be dispensed at this visit based on a discussion between the Investigator and patient but the maximum allowed dose is 1 dose (3 caplets) per day. Each dose of study drug comprises 3 caplets contained within a discrete blister card. Patients must be informed that 1 dose is all 3 caplets, and the dose should be taken with water at least one hour before or after food. Patients should attempt sexual intercourse approximately 1 to 6 hours after taking the dose. The patients will also be provided with a LogPad. Patients should be reminded on the instructions for using the stopwatch and also the LogPad to record their usage of the study medication, as well as all occasions that they attempt sexual intercourse and whether alcoholic drinks were

taken. Patients will be asked if they are willing to try intercourse with their partner approximately 8 times or more between Visit 2 and Visit 5 although less than 8 attempts will not be classified as a protocol deviation. Patients should be reminded to bring their LogPad and any unused study medication back to the study site for Visit 3.

Visit 3

- Patients will return to the study center on Day 14 \pm 3 days (Week 2). The patients will be asked for information on any AEs that have occurred or are occurring and concomitant medication usage since Visit 2. The remaining study medication will be collected, and a check of the quantity remaining will be performed. After completion of all assessments, the patient will receive enough medication to take at least 7 doses of study drug (IX-01 or placebo). Further supplies can be dispensed at this visit based on a discussion between the Investigator and patient but the maximum allowed dose is 1 dose (3 caplets) per day. (Note: Refer to the Study Training Manual for instructions if a patient does not remember to return the LogPad.)
- The patient will return the LogPad.
- The investigator will provide the LogPad back to the patient for completion of the PHQ-9. Once complete, the patient will return the LogPad to the investigator.
- If the results of the PHQ-9 indicate a change in mental condition and/or if the investigator suspects a deleterious change in mood (see Section 13.2), the investigator must administer the C-SSRS.
- Physical examination. Any changes in physical findings that meet the definition for an AE and that occur after the patient initiates investigational product will be recorded as AEs in the eCRF.
- Blood sampling for laboratory safety tests (including hematology and clinical chemistry analyses).
- Adverse events and concomitant medication update.

Visit 4

- Patients will return to the study center on Day 28 \pm 7 days (Week 4). The patients will be asked for information on any AEs that have occurred or are occurring and concomitant medication usage since Visit 3. The remaining study medication will be collected, and a check of the quantity remaining will be performed. After completion of all assessments, the patient will receive enough medication to take at least another 14 doses of study drug (IX-01 or placebo). Further supplies can be dispensed at this visit based on a discussion between the Investigator and patient but the maximum allowed dose is 1 dose (3 caplets) per day. (Note: Refer to the Study Training Manual for instructions if a patient does not remember to return the LogPad.)
- The patient will return the LogPad.
- The investigator will provide the LogPad back to the patient for completion of the PEP, PGIS, IIEF, and PHQ-9. Once complete, the patient will return the LogPad to the investigator.
- If the results of the PHQ-9 indicate a change in mental condition (or the investigator suspects an adverse change), the investigator should administer the C-SSRS and determine if the patient may remain in the study.
- Physical examination.
- Recording of vital signs data (heart rate and blood pressure measurements).
- Blood sampling for laboratory safety tests (including hematology and clinical chemistry analyses).
- Urinalysis.
- Adverse events and concomitant medication update.

Visit 5 (End of Treatment or Early Termination)

Note that if a patient is discontinued from the study at any time during the treatment period earlier than expected, then he must return to the study site and complete an early termination visit (Visit 5).

- Patients will return to the study center on Day 56 ± 7 days (Week 8). The patients will be asked for information on any AEs that occurred or are occurring and concomitant medication usage since Visit 4. The patient must return the LogPad. The remaining study medication will be collected. The LogPad will be checked and retained at the study center. (Note: Refer to the Study Training Manual for instructions if a patient does not remember to return the LogPad.)
- The investigator will provide the LogPad back to the patient for completion of the PEP, IIEF, PHQ-9, PGIS and CGIC. After completion, the patient will return the LogPad to the investigator.
- If the results of the PHQ-9 indicate a change in mental condition (or the investigator suspects an adverse change), the investigator should administer the C-SSRS.
- Weight.
- Physical examination.
- Recording of vital sign data (heart rate and blood pressure measurements) and 12-lead ECG.
- Blood sampling for laboratory safety tests (including hematology and clinical chemistry analyses).
- Urinalysis.
- Urine drug screen.
- Adverse events and concomitant medication update.

End of Study Visit 6 (Follow Up)

Patients will return to the study center for a follow-up visit on Day 70 \pm 7 days (Week 10), and the following assessments will be performed approximately 2 weeks after the last visit:

- Weight.
- Physical examination.
- Recording of vital sign data (heart rate and blood pressure measurements) and 12-lead ECG.
- Blood sampling for laboratory safety tests (including hematology and clinical chemistry analyses).
- Urinalysis.
- Adverse events and concomitant medication update.
- C-SSRS, only if clinically indicated per the protocol.

6.2 Efficacy Assessments

Outcome measures included during treatment include results from the use of the following:

- Stopwatch to measure IELT.
- LogPad (e-diary) to record summary of study drug intake and details of sexual intercourse attempts (including IELT and two PEP questions (control and ejaculation-related personal distress)).
- Responses to the PEP questionnaire.
- Responses to PGIS questionnaire.
- Responses to the CGIC questionnaire.

IELT

The IELT is the time from the start of intercourse (penetration) until ejaculation and is recorded by the patient or partner using the stopwatch provided. At the start of the run-in phase, the patient and partner should decide who will activate the stopwatch and subsequently stop the stopwatch to record the timing of intercourse. The same person should start and stop the stopwatch with every intercourse attempt throughout the study until Visit 5.

LogPad

The LogPad has been specifically designed to enable patients to record details of sexual intercourse attempts and study drug use throughout the study. The key data to be recorded by the patients are date and time of study drug caplets taken, date and time of any intercourse attempt, IELT, level of control of timing of ejaculation; and level of ejaculation-related personal distress. The patient also will use the LogPad at each study visit to complete the PEP, PGIS, IIEF, and PHQ-9 (PEP, PGIS and IIEF are not completed at Visit 3/Week 2). At the final treatment visit (Visit 5 or Early Termination), the CGIC is also collected via the LogPad. For further details of the LogPad design and function, refer to the Study Training Manual.

PEP

The PEP is a widely used self-administered tool that includes measures of perceived control over ejaculation, ejaculation-related personal distress, ejaculation-related interpersonal difficulty, and satisfaction with intercourse. It has been used in many previous studies of PE and is considered validated for this purpose. All of the domains are relevant to a patient with PE, and the instrument has the advantage of being simple and quick to use.¹⁴ In this study an additional exploratory question on bother will be included in the 4-week recall version used at baseline, week 4 and week 8.

PGIS

The Patient Global Impression of Severity is a questionnaire that asks the patient to assess the severity of their condition (categories of response are no PE, mild, moderate, severe).

CGIC

The Clinical Global Impression of Change (CGIC) (also referred to as PGIC) is a simple and validated instrument that allows the patient to rate the change in his condition (PE) at the end of treatment on a 7-point scale ranging from “much worse” to “much better.”¹⁵ In this study the CGIC will be administered after the PEP at the final visit and will include two additional questions. See Appendix 2.

6.3 Safety Assessments

Adverse Events

The Investigator and study personnel will monitor each patient for AEs occurring throughout the study treatment period. The process of collection and reporting of AEs is described in Section 6.3.1.

Vital Signs

Vital sign measurements will be taken after the patient has been resting in the sitting position for at least 5 minutes and will include diastolic and systolic blood pressure and heart rate. Vital signs may be repeated if clinically significant values are measured. Out-of-range blood pressure or heart rate measurements will be repeated at the Investigator’s discretion especially if the investigator believes that the initial measurements are due to insufficient relaxation or error. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

Electrocardiogram (ECG)

A single 12-lead ECG will be collected after a 5-minute period of rest and should be completed before any blood collection. If any clinically significant changes in findings are observed versus the predose or baseline visits, they must be documented. If a clinically significant abnormal finding occurs after the patient initiates use of the study drug, then it will be recorded as an AE in the eCRF.

IIEF

The IIEF is a validated 15-item questionnaire that was designed to evaluate sexual function in men with possible erectile dysfunction. The main purpose of including this instrument in this study is to exclude men with coexisting erectile dysfunction at baseline and to check whether erectile dysfunction occurs during the study.¹⁶ As this instrument was designed for use in men with possible erectile dysfunction, the investigator should clarify the meaning of Questions 4, 5, and 15 before the patient completes the questionnaire. The patient should be told that he is being asked to assess whether he can maintain his erection until ejaculation occurs (Questions 4 and 5) and about his confidence to get and keep an erection until ejaculation occurs (Question 15).

Psychological Assessments

The following questionnaire will be self-completed by each patient using the LogPad (e-diary).

- Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a reliable and valid screening tool for depression severity. The module scores each of the 9 Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria as “0” (not at all) to “3” (nearly every day). A PHQ-9 score ≥ 10 had a sensitivity of 88% and a specificity of 88% for major depression. PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively.¹⁷ The questionnaire will be completed at each study visit during the treatment period.

The Investigator will administer the following instrument at baseline and at other times thereafter throughout the study as required by the protocol.

- C-SSRS

The C-SSRS is a structured clinical interview used to assess an individual’s behavior to exhibit thoughts or intent to commit suicide.¹⁸ Investigators and other designated staff performing the interview must be trained in its use.

6.3.1 Adverse Events

6.3.1.1 Definitions of Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and 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. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect. After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

An SAE or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- results in death;
- is life threatening (immediate risk of death);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

Serious adverse event collection begins after the patient has signed informed consent and has received investigational product through to 28 calendar days after last administration of the investigational product.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

The investigator does not need to actively monitor patients for AEs once the study has ended (after follow-up visit), unless stipulated otherwise in the protocol. However, if an investigator becomes aware of any SAEs occurring after the patient's participation in the study has ended, the investigator should report the SAEs to Ixcelsius or designated representative regardless of the investigator's opinion of causation. In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must notify Ixcelsius or designated representative within 24 hours of the study site staff becoming aware of the SAE.

6.3.1.2 Eliciting and Documenting Adverse Events

For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Ixcelsius or designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE.

6.3.1.3 Reporting Adverse Events

All observed AEs and their suspected causal relationship to the study product will be reported. Adverse events and SAEs should be reported using concise medical terminology as appropriate in the eCRF.

For all AEs, the Investigator must obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as an SAE requiring immediate notification to Ixcelsius or designated representative.

If an SAE occurs, expedited reporting to regulatory authorities will follow local regulations, as appropriate. The Investigator must report all SAEs to Ixcelsius or designated representative within 24 hours of the Investigator's awareness of the event. This timeframe also applies to additional new information on previously reported SAEs. The contact details for reporting SAEs by telephone and fax are as follows:

PPD 24-Hour Safety Hotline:

+1 800 201 8725

PPD 24-Hour Safety Hotline Fax:

+1 888 488 9697

6.3.1.4 Assessment of Severity

Severity describes the intensity of a specific event:

- Mild – Symptom(s) barely noticeable to the patient or does not make the patient uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate – Symptom(s) of a sufficient severity/intensity to make the patient uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
- Severe – Symptom(s) of a sufficient severity to cause the patient severe discomfort. Severity may cause cessation of treatment with the investigational product. Treatment for symptom(s) may be given.
- Life-threatening – Symptom(s) of a sufficient severity/intensity to cause the patient to be at immediate risk of death. Treatment for symptom(s) may be given.

6.3.1.5 Assessment of Causality

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (serious and nonserious). An Investigator's causality assessment is the

determination of whether there exists a reasonable possibility that the study product caused or contributed to an AE. If the Investigator's final determination of causality is unknown because the Investigator does not know whether or not the study product caused the AE, then the AE will be handled as "related to investigational product" for reporting purposes and reporting expedited according to local regulations. If the Investigator's final determination of causality is "unknown but not related to investigational product," this information should be clearly documented in the study records.

In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

6.3.1.6 Follow-Up of Patients Reporting Adverse Events

For all AEs, follow up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator. The medical monitor will monitor safety data throughout the course of the study.

6.4 Pregnancy

If the partner of a patient is of childbearing potential, then at least one reliable form of contraception must be used.

If a patient used condoms during the run-in period when engaging in sexual intercourse, then he must continue to use the same brand and type of condom for every sexual intercourse attempt. If the condom is the main method of contraception, then it should be used with spermicide (or similar product according to availability). If the patient did not use a condom during the run-in period, then his partner must use a form of contraception such as intrauterine device, diaphragm with spermicide (or similar product according to availability), oral contraceptives, injectable progesterone, subdermal implants, or tubal ligation when engaging in sexual intercourse, unless the patient has had a documented vasectomy or confirmed azoospermia.

This criterion must be followed from the time of the run-in period until 30 days after the last dose of study medication.

If a patient reports that his partner is pregnant, the patient must be withdrawn from the study and the Investigator will inform Ixcelsius or designee, who will endeavor to collect any relevant information on the outcome of the pregnancy unless there is confirmation that the patient was not exposed to study drug prior to or during the pregnancy. Cases of pregnancy that occur after a patient has been consented should be reported. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and drug safety evaluation.

The Investigator must report the pregnancy to Ixcelsius or designee with 24 hours of the study site staff becoming aware of the pregnancy.

6.5 Laboratory Analyses

The central laboratory will process all samples collected for laboratory safety function tests. Section 13.3 provides a full list of tests, and the details regarding the laboratory safety tests and sampling can be found in the Study Training Manual.

Collection of blood and urine samples for clinical laboratory analysis will occur per the Schedule of Events (Table 13-1). Whole blood samples will be collected at each of these time points for hematology and clinical chemistry with coagulation testing being performed at baseline. An additional collection of blood sample for serology testing (hepatitis B surface antigen, hepatitis C virus antibody, HIV 1, HIV 2) will be performed at screening only.

Urine samples will be collected for urinalysis (Screening, Visit 2, Visits 4-6) and urine drug screen (Screening, Visit 2 and Visit 5 only).

7 Statistical and Analytical Plan

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the change in GM IELT over the treatment assessment period compared with baseline, ie, $[GM(IELT_{\text{treatment period}}) - GM(IELT_{\text{baseline}})]$.

7.2 Secondary Efficacy Endpoints

7.2.1 Key Secondary Efficacy Endpoints

The following key secondary efficacy endpoints will be analyzed:

1. Fold change in GM IELT over the treatment assessment period compared with baseline.
2. Proportion of patients with ≥ 2.5 -fold increase in GM IELT over the treatment assessment period compared with baseline, ie, $[\text{proportion of subjects with } GM(IELT_{\text{treatment period}})/GM(IELT_{\text{baseline}}) \geq 2.5]$.
3. Proportion of patients rating their PE as improved per the CGIC questionnaire.
4. Proportion of patients achieving mean change in category of ≥ 1 or ≥ 2 on control of timing of ejaculation (PEP), ie, improving control from “very poor” or “poor” to “fair,” “good,” or “very good” at end of treatment.
5. Proportion of patients achieving mean change in category of ≥ 1 or ≥ 2 in ejaculation-related personal distress (PEP), ie, improving rating of ejaculation-related distress to “moderate,” “a bit,” or “not at all” at end of treatment.
6. Proportions of patients achieving change in category of ≥ 2 on control of timing of ejaculation (PEP) and achieving change in category of ≥ 1 in ejaculation-related personal distress (PEP) at end of treatment
7. Mean change from baseline in score on control of ejaculation (e-diary) over the treatment assessment period.
8. Mean change from baseline in score on ejaculation-related personal distress (e-diary) over the treatment assessment period.

7.2.2 Other Secondary Efficacy Endpoints

The following other secondary efficacy endpoints will be analyzed:

1. Fold change from baseline in (arithmetic) mean IELT over the treatment assessment period.
2. Change from baseline in (arithmetic) mean IELT over the treatment assessment period.
3. Proportion of patients with GM IELT of ≥ 1 minute over the treatment assessment period.
4. Proportion of patients with GM IELT of ≥ 2 minutes over the treatment assessment period.
5. Proportion of patients with GM IELT of ≥ 3 minutes over the treatment assessment period.
6. Proportion of patients with GM IELT of ≥ 4 minutes over the treatment assessment period.
7. Proportion of patients with GM IELT of ≥ 5 minutes over the treatment assessment period.
8. Proportion of patients with GM IELT increase over the treatment assessment period of ≥ 45 seconds compared with baseline.
9. Proportion of patients with GM IELT increase over the treatment assessment period of ≥ 1 minute compared with baseline.
10. Percentage of intercourse attempts lasting > 1 minute over the treatment assessment period.
11. Percentage of intercourse attempts lasting > 2 minutes over the treatment assessment period.
12. Percentage of intercourse attempts lasting > 3 minutes over the treatment assessment period.
13. Percentage of intercourse attempts lasting > 4 minutes over the treatment assessment period.
14. Percentage of intercourse attempts lasting > 5 minutes over the treatment assessment period.
15. Proportion of patients improving on PGIS
16. Proportion of patients achieving ≥ 1 category of improvement from baseline to end of treatment in each of the following (from 4-weekly PEP questionnaire):

- a. Satisfaction with sexual intercourse
 - b. Control over ejaculation during sexual intercourse
 - c. Ejaculation-related distress
 - d. Ejaculation-related interpersonal difficulty
 - e. Ejaculation-related bother
17. Change in score from baseline in each of the following (from 4-weekly PEP questionnaire):
- a. Satisfaction with sexual intercourse
 - b. Control over ejaculation during sexual intercourse
 - c. Ejaculation-related distress
 - d. Ejaculation-related interpersonal difficulty
 - e. Ejaculation-related bother

7.3 Sample Size Calculations

The target total is for 220 patients to be randomized in the study.

The randomization ratio will be 2:2:3:3 (placebo, IX-01 400 mg, IX-01 800 mg, and IX-01 1200 mg dose groups, respectively).

Thus, 44 patients each will be randomized to placebo and IX-01 400 mg dose groups, and 66 patients each will be randomized to IX-01 800 mg and IX-01 1200 mg dose groups. The 2:3 ratio results in only slight loss of statistical power from 1:1 randomization, while increasing the chances that a patient will be randomized to an effective dose of study drug.

Assuming an alpha (2-sided) of 0.05 and an SD of 70 seconds, a sample size of 220 patients randomized in total (44 to the placebo and IX-01 400 mg dose groups and 66 to the IX-01 800 mg and IX-01 1200 mg dose groups) provides approximately 85%, 90%, and 90% power to detect a mean difference of 45 seconds between change from baseline in GM of IELT for the IX-01 400 mg, IX-01 800 mg, and IX-01 1200 mg dose groups, respectively, compared with the placebo group.

Sequential multiplicity control testing of IX-01 1200 mg dose versus placebo, followed by IX-01 800 mg dose versus placebo and then IX-01 400 mg dose versus placebo will be done in order to control for multiplicity. See details below.

Additional patients may be recruited if some patients discontinue from the study with less than 2 postbaseline IELT assessments.

7.4 Analysis Sets

The following 4 populations, defined as below, will be used in the analyses:

Intent-to-Treat (ITT) Set: The ITT Set is defined as all randomized patients who have taken at least 1 dose of study medication. Patients will be analyzed according to the treatment arm to which they were randomized.

Modified Intent-to-Treat (mITT) Set: The mITT Set is defined as all randomized patients who have taken at least 1 dose of study medication and with at least 2 postbaseline analyzable IELT assessments. Patients will be analyzed according to the treatment arm to which they were randomized.

Safety Set: The Safety Set consists of all randomized patients who have taken at least 1 dose of study medication. Patients will be analyzed according to the treatment arm for the study drug that they actually received.

Per-Protocol Set: The Per-Protocol Set is defined as all patients from the mITT without any major protocol deviation that could affect the evaluability of the primary efficacy parameter. Patients will be analyzed according to the treatment arm to which they were randomized.

The allocation of patients to analysis sets will be done in a blinded way prior to database lock.

7.5 Description of Subgroups to be Analyzed

Details will be provided in the Statistical Analysis Plan (SAP) for any proposed subgroup analyses (e.g. patients with all baseline IELTs were ≤ 60 seconds).

7.6 Statistical Analysis Methodology

Summary statistics will be provided for all study endpoints. For continuous endpoints n (number of patients included in the analysis), mean, SD, median, minimum, maximum, Quartile 1, and Quartile 3 will be provided. For categorical endpoints, the number and frequency in each category will be provided. Adjusted effect size and 95% CI will be displayed for all treatment comparisons.

For the purpose of e-diary data analyses, the treatment assessment period will include all assessments done between end of treatment and end of treatment minus 28 days, if patients have a sufficient amount of assessments within this time window. The time window may be extended back for patients without a sufficient amount of assessments within the predefined time window. Additional details will be provided in the SAP regarding the derivation of the treatment assessment period.

7.6.1 Analysis of Primary Efficacy Endpoint

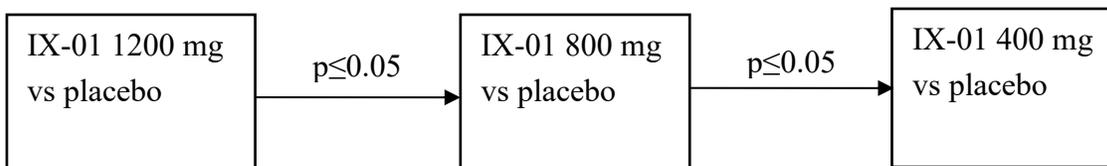
The primary efficacy analysis of the primary endpoint will be performed on the mITT population. Change from baseline in GM IELT over the treatment assessment period will be analyzed using a mixed linear model, including treatment and baseline IELT as fixed factors and type of site as a random factor.

The primary comparison of interest is IX-01 1200 mg versus placebo. If it is statistically significant at $\alpha=0.05$, then the following comparisons will be tested in the following order:

- IX-01 800 mg vs placebo group
- IX-01 400 mg vs placebo group

An overview of the approach to control for multiple comparisons is provided in Figure 7-1.

Figure 7-1 Overview of the Multiplicity Control



If at any point in the sequence statistical significance is not met, then subsequent analyses in the sequence cannot be deemed statistically significant. In such cases, nominal P values and 95% CI will be reported and interpreted in an exploratory manner. Irrespective of whether there are any statistically significant differences between treatment groups, IELT data from all treatment groups will also be used to model a possible dose response relationship. Further details on dose response analysis will be provided in the SAP.

The analyses above will be repeated using the Per-Protocol and ITT populations to examine the robustness of the primary results.

As a sensitivity analysis of the primary endpoint, a nonparametric approach will be carried out on the mITT population in order to obtain the median treatment effect and 95% CI.

7.6.2 Analysis of Secondary Efficacy Endpoint

All secondary analyses will be carried out testing each dose group versus the placebo group on for the ITT population.

The same approach to control for multiple comparisons as proposed for the primary endpoint will be used for each secondary endpoint analysis.

7.6.2.1 Change From Baseline Endpoints

Analyses of e-diary data expressed in change from baseline over the treatment assessment period will be carried out using a mixed linear model. All analyses should include treatment, baseline IELT, and the baseline score of the analyzed endpoint as fixed effects and the site as a random effect. In addition to the mixed linear model, a nonparametric approach may be carried out for specific secondary endpoints. Further details will be provided in the SAP.

Change in score from baseline in each of the PEP questions (ie, Endpoint 17 of Section 7.2.2) will be carried out using a mixed-effect model repeated measure model. All analyses should include treatment, baseline IELT, the baseline score of the analyzed endpoint, the visit, and the interaction between visit and treatment as fixed effects and the site as a random effect. Visit will be considered as the repeated measurement.

7.6.2.2 Proportion Endpoints

For each analysis on proportion endpoint, difference in the proportions between each test group and placebo group will be tested using a logistic model. All analyses should include treatment, baseline IELT, and the type of site as factors. *P* values and adjusted odds ratios will be presented.

7.6.2.3 Percentage Endpoints

The percentage of intercourse attempts lasting longer than a predefined threshold during the treatment assessment period will be analyzed by treatment as continuous data.

Analyses will be carried out using a mixed linear model. All analyses should include treatment and baseline IELT as fixed effects and the type of site as a random effect.

7.6.2.4 Missing Data

Sensitivity analyses for the primary endpoint with methods of handling missing data will be specified in the SAP.

7.6.3 Safety Analyses

Safety analyses will be based on all patients included in the safety population.

Changes from baseline will be the absolute changes from baseline:

Change from baseline = raw value – baseline value

Study Drug Administration and Exposure: Study drug administration and exposure will be summarized and listed. Further details on study drug administration and exposure calculation will be given in the SAP.

Medical History: Medical history details recorded at screening will be summarized and listed according to the coded Medical Dictionary for Regulatory Activities (MedDRA) (latest version) by system organ class, preferred term, and treatment group.

Concomitant Medications: Previous and concomitant medications will be summarized according to the WHO Drug Dictionary (WHO-DD). The number and percentage of patients for each treatment group will be presented for previous and concomitant medications.

The patient will record in the LogPad whether he had any alcoholic drinks within 4 hours prior to sexual intercourse.

Adverse Events: Adverse events will be coded according to the coded MedDRA (latest version). Treatment-emergent AEs will be tabulated by system organ class, preferred term, and treatment group. Further details will be given in the SAP on the definition of TEAEs.

The following summary tables will be produced:

- TEAEs
- Serious TEAEs
- TEAEs leading to study drug discontinuation
- Treatment-related TEAEs leading to study drug discontinuation
- Treatment-related TEAEs
- Treatment-related serious TEAEs

All AEs recorded during the study (including non-treatment-emergent AEs) will be listed.

Physical Examination and Vital Signs: Abnormal physical examinations will be listed. Descriptive by-visit summaries of vital signs data will be presented by treatment group (including raw values and change from baseline). Vital signs will include blood pressure, heart rate, and temperature.

Height, Weight, and BMI: Baseline height, weight, and BMI will be summarized and listed. Weight and BMI as well as mean change from baseline will be summarized for Week 8 and end-of-study visits.

ECGs: Descriptive summaries of change in overall assessment of ECG data from baseline to Week 8 and end of study will be presented in a shift table (normal, abnormal [not clinically significant], and abnormal [clinically significant]) by treatment group.

Laboratory Safety Tests: Hematology and clinical chemistry safety tests will be summarized by treatment and visit. Postbaseline visit will include change from baseline. Shift tables displaying baseline versus worst postbaseline results will be provided by treatment group.

PHQ-9: The PHQ-9 is comprised of 9 questions and is used to monitor depression symptoms. All questions elicit responses on an ordered 4-point scale (0-3), which are added together to generate a single summary score. Higher summary scores indicate an increase in depression severity. The questionnaire is administered at baseline, Week 2, Week 4, and Week 8 visits. Total PHQ-9 scores will be summarized by treatment and visit, with the postbaseline visit displaying raw values as well as change from baseline. In addition, responses to the final question “If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?” will be summarized by visit as frequency data.

Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a structured clinical interview used to assess an individual’s behavior to exhibit thoughts or intent to commit suicide. The questionnaire will be completed at baseline and may be administered at other visits thereafter if clinically indicated. Baseline results will be summarized and listed. Postbaseline results will be listed.

International Index of Erectile Function (IIEF): The IIEF is a questionnaire that comprises 15 questions assessing the effect that erection problems have had on the patient’s sex life over the previous 4 weeks. It is administered at baseline, Week 4, and Week 8. Summary statistics will be provided by visit, and questionnaires will be listed in detail.

7.6.4 Other Analyses

Not applicable.

7.6.5 Interim Analyses

No formal interim analyses of unblinded data are planned.

8 Data Quality Assurance

The study will be conducted in accordance with the International Council for Harmonisation (ICH) GCP and the appropriate regulatory requirement(s). The investigator will receive training regarding the appropriate use of the investigational product as described in the protocol and the Investigator's Brochure.

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 patient. Study data will be entered on a electronic case report form (eCRF) by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Ixcelsius and Ixcelsius-authorized representatives will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator so these can be resolved. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

8.1 Case Report Forms and Source Documents

The term CRF should be understood to refer to either a paper form or electronic data record or both, depending on the data collection method used in this study. This study is expected to use a web-based EDC application. Ixcelsius or designee will supply eCRFs for each patient screened. Historical information and study data, specified in the protocol, will be recorded on the eCRFs by the investigator or designee. All patient data from each study visit must be collected on source documents and must be promptly entered on the eCRFs in accordance with the specific instructions given. Case report form entries will be performed by an investigator or designee and the study coordinator, who are authorized to complete such documentation. It is the investigator's responsibility to ensure completion and to review and approve all eCRFs. Case report forms must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs.

Patient source documents are the physician's patient records maintained at the study site.

In some cases, the eCRF may also serve as the source document. In these cases, Ixcelsius (or designee) and the investigator must prospectively document which items will be recorded in the source documents and for which items the eCRF will stand as the source document.

If queries are generated by Ixcelsius or designee to the participating medical institutions for resolution, the eCRF data will be changed or a response will be recorded in accordance with the specific instructions given.

The investigator must maintain source documents, such as all original signed ICFs, laboratory reports, and complete medical history. All source documents should be accessible for verification by the site monitor, auditor, IRB, or for inspections by regulatory authorities. Direct access to these documents must be guaranteed by the investigator or designee. If electronic records are maintained at the medical institution, the method of verification must be specified in documents within that medical institution.

9 Ethics

9.1 Institutional Review Board

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent, and other relevant documents, eg, recruitment advertisements, if applicable from the IRB. The study will commence only after the IRB has given full approval and the investigator has received the approval documents. All correspondence with the IRB should be retained in the investigator file. Copies of IRB approvals will be forwarded to Ixchelsis Ltd. Documentation of the IRB compliance with ICH GCP will be maintained by the site and will be available for review by Ixchelsis Ltd or its designee.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with all appropriate regulatory requirements, local laws, and under the IRB-approved protocol. The study will be conducted in accordance with current ICH GCP, all appropriate patient privacy requirements, and the ethical principles outlined in the Declaration of Helsinki.

9.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations Part 50 shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. The investigator or subinvestigator (designated by the investigator) will fully explain the nature of the study to each patient using the IRB-approved informed consent document prior to each patient entering the study. The investigator or subinvestigator will explain the nature, purpose and methods, reasonably anticipated benefits, and potential hazards of the study to each patient in simple terms using the IRB-approved consent document. The investigator or subinvestigator will obtain written informed consent from each patient before any study specific activity is performed. The investigator will retain the original of each patient's signed consent form.

The ICF must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The ICF and any changes made during the course of the study must be prospectively approved by both the IRB and Ixchelsis before use.

10 Investigator's Obligations

10.1 Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the US Food and Drug Administration and applicable laws.

10.2 Study Conduct

The investigator will conduct the study in compliance with the protocol provided by Ixcelsius and given approval/favorable opinion by the IRB and the appropriate regulatory authority. Modifications to the protocol are not to be made without agreement of both the investigator and Ixcelsius. Changes to the protocol will require written IRB approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Ixcelsius or a designee will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Ixcelsius or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

10.3 Records Retention

To enable evaluations and/or audits from regulatory authorities or Ixcelsius, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs, hospital records), all original signed ICFs, source documents, and detailed records of treatment disposition. The study documents should be retained until at least 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. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement

with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator and institution should take measures to prevent accidental or premature destruction of these documents.

If the investigator relocates, retires, or for any reason withdraws from the study, Ixcelsius should be prospectively notified. The study documents must be transferred to an acceptable designee, such as another investigator, another institution, or to Ixcelsius. The investigator must obtain Ixcelsius's written permission before disposing of any records, even if the retention requirements have been met.

10.4 Publications

All information regarding IX-01 supplied by Ixcelsius to the Investigator is privileged and confidential information and Ixcelsius retains ownership of all data.

Following completion of the study, the data from the entire study may be considered for reporting at a scientific meeting or for publication in a scientific journal, in which case Ixcelsius will be responsible for these activities and will work with the Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. Authorship will be based on criteria stipulated by leading clinical journals (eg, contribution to 1 or more areas of study design, data analysis and interpretation, and manuscript preparation and review).

11 Study Management

11.1 Monitoring

Monitoring and auditing procedures will be followed to comply with ICH GCP guidelines. All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained. The investigator and institution will allow Ixcelsius monitors or designee and appropriate regulatory authorities direct access to source documents to perform this verification.

It is important that the investigator(s) and relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11.2 Study Termination

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB, drug safety problems, or at the discretion of Ixcelsius.

If the study is prematurely terminated or suspended, Ixcelsius will promptly inform all of the investigators. The relevant regulatory authorities and IRBs will be informed in accordance with local regulations. The investigator or designee should promptly inform the participating patients. As directed by Ixcelsius, all study materials must be collected and all CRFs completed to the greatest extent possible.

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13 Appendices

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events

IX-0105 Study Schedule and Events							
	For Patients on Chronic SSRIs only Prescreening Visit ¹ (Week -8)	Visit 1 ¹ Screening (Week -4)	Visit 2 ² Baseline (Week 0)	Visit 3 ² (Week 2)	Visit 4 ² (Week 4)	Visit 5 or Early Termination ² (Week 8)	Visit 6 Follow Up (Week 10)
Days Post First Dose (Window)	-56	-28 (±3)	0 (±7)	14 (±3)	28 (±7)	56 (±7)	70 (±7)
Informed Consent	X	X ¹					
Medical History and Demography	X	X ¹					
Inclusion/Exclusion Criteria and Eligibility Review	X	X	X ³				
Physical Examination		X	X	X	X	X	X
Height		X					
Weight		X	X			X	X
Blood Pressure and Heart Rate		X	X		X	X	X
Oral Temperature			X				
12-lead ECG (single)		X	X			X	X
Safety Laboratory Tests (Clinical Chemistry, Hematology, and Coagulation ⁴)		X	X	X	X	X	X
Urinalysis		X	X		X	X	X
Serology (HBsAg, HCV Ab, HIV 1, HIV 2)		X					
Urine Drug Screen		X	X			X	
Randomization			X				
e-Diary Supply ⁵		X	X	X	X		
Diary Evaluation ⁵			X	X	X	X	
Study Drug Supply			X	X	X		
Study Drug Compliance				X	X	X	
IIEF ⁶			X		X	X	
PEP ⁶ (with additional question)			X		X	X	

IX-0105 Study Schedule and Events							
	For Patients on Chronic SSRIs only Prescreening Visit ¹ (Week -8)	Visit 1 ¹ Screening (Week -4)	Visit 2 ² Baseline (Week 0)	Visit 3 ² (Week 2)	Visit 4 ² (Week 4)	Visit 5 or Early Termination ² (Week 8)	Visit 6 Follow Up (Week 10)
Days Post First Dose (Window)	-56	-28 (±3)	0 (±7)	14 (±3)	28 (±7)	56 (±7)	70 (±7)
PGIS			X		X	X	
CGIC						X	
PHQ-9			X	X	X	X	
Columbia-Suicide Severity Rating Scale ⁷			X	(X)	(X)	(X)	(X)
Adverse Events			X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X

Abbreviations: CGIC, Clinical Global Impression of Change; ECG, electrocardiogram; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; IELT, intravaginal ejaculatory latency time; IIEF, International Index of Erectile Function; PEP, Premature Ejaculation Profile; PHQ-9, Patient Health Questionnaire 9; SSRI, selective serotonin reuptake inhibitor.

1. Only patients taking chronic SSRIs will have an additional 4-week washout prior to the 4-week run-in period. They will attend a Prescreening Visit and will return to the site for a complete screening (Visit 1) once their washout period is complete. Informed consent and medical history will be obtained at the Prescreening Visit for patients who are receiving chronic SSRIs.
2. Refer to the Study Training Manual for instructions if a patient does not remember to return the LogPad.
3. The patient will return the LogPad to the investigator. The LogPad will provide a summary of the IELT data collected during the run-in period, and will indicate whether the patient is eligible to continue in the study based on the IELT criteria
4. Coagulation (prothrombin time and activated partial thromboplastin time) will be tested at baseline (Visit 2). Only prothrombin time will be taken at other time points if certain laboratory test criteria defined in Section 4.2 are fulfilled.
5. Medication use, IELT, ejaculation control, and ejaculation-related distress and alcohol intake are collected after each event via e-diary.
6. IIEF and PEP have 4-week recall periods, and so these questionnaires are completed by the patients at study visits as above.
7. Columbia-Suicide Severity Rating Scale is only mandatory at baseline but may be administered at other visits if clinically indicated.

13.2 Appendix 2: Evaluation Instruments

13.2.1 Clinical Global Impression of Change (CGIC)

This patient-completed questionnaire is often referred to as PGIC (Patient Global Impression of Change). The following questions will be asked after the patient has completed the PEP at the final visit:

Compared to the start of the study, would you describe your premature ejaculation problem as:

-3 = Much worse

-2 = Worse

-1 = Slightly worse

0 = No change

1 = Slightly better

2 = Better

3 = Much better

Compared to the start of the study did you experience a meaningful change in the time you took to ejaculate (cum)? (Yes/No)

Compared to the start of the study did you experience a meaningful change in your level of distress related to your premature ejaculation? (Yes/No)

13.2.2 Premature Ejaculation Profile (PEP)

1. Over the past month, was your control over ejaculation during sexual intercourse:

1 – Very Poor 2 – Poor 3 – Fair 4 – Good 5 – Very Good

2. Over the past month, was your satisfaction with sexual intercourse:

1 – Very Poor 2 – Poor 3 – Fair 4 – Good 5 – Very Good

3. Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

4. Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

Additional Question

5. Over the past month, how bothered were you by how fast you ejaculated during sexual intercourse:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

Patient Global Impression of Severity (PGIS)

This questionnaire will be completed after the patient has completed the PEP.

How would you rate your premature ejaculation (PE) now? 1 No PE (none), 2 Mild 3 Moderate 4 Severe

13.2.3 International Index of Erectile Function (IIEF)

These questions ask about the effect your erection problems have had on your sex life **over the past 4 weeks**. Please answer these questions as honestly and as clearly as possible. Please answer every question by checking the appropriate box. If you are unsure about how to answer, please give the best answer you can.

In answering these questions, the following definitions apply:

* **Sexual intercourse**

Is defined as sexual penetration of the partner.

** **Sexual Activity**

Includes intercourse, caressing, foreplay and masturbation.

***** Ejaculate**

Is defined as the ejection of semen from the penis (or the sensation of this).

****** Sexual stimulation**

Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

1. **Over the past 4 weeks** how often were you able to get an erection during sexual activity**?

Please check one box only.

- No sexual activity
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

2. **Over the past 4 weeks** when you had erections with sexual stimulation****, how often were your erections hard enough for penetration?

Please check one box only.

- No sexual stimulation
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

The next 3 questions will ask about the erections you may have had during sexual intercourse*.

- 3. **Over the past 4 weeks** when you attempted sexual intercourse* how often were you able to penetrate (enter) your partner?

Please check one box only.

- Did not attempt intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

- 4. **Over the past 4 weeks** during sexual intercourse* **how often** were you able to maintain your erection after you had penetrated (entered) your partner?

Please check one box only.

- Did not attempt intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

5. **Over the past 4 weeks** during sexual intercourse* **how difficult** was it to maintain your erection to completion of intercourse?

Please check one box only.

- Did not attempt intercourse
- Extremely difficult
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

6. **Over the past 4 weeks** how many times have you attempted sexual intercourse*?

Please check one box only.

- No attempts
- 1-2 attempts
- 3-4 attempts
- 5-6 attempts
- 7-10 attempts
- 11 + attempts

7. **Over the past 4 weeks** when you attempted sexual intercourse* how often was it satisfactory for **you**?

Please check one box only.

- Did not attempt intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

8. **Over the past 4 weeks** how much have you enjoyed sexual intercourse*?

Please check one box only.

- No intercourse
- Very highly enjoyable
- Highly enjoyable
- Fairly enjoyable
- Not very enjoyable
- Not enjoyable

9. **Over the past 4 weeks** when you had sexual stimulation**** **or** intercourse* how often did you ejaculate***?

Please check one box only.

- No sexual stimulation or intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

10. **Over the past 4 weeks** when you had sexual stimulation**** **or** intercourse* how often did you have the feeling of orgasm with or without ejaculation***?

Please check one box only.

- No sexual stimulation or intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

The next 2 questions ask about sexual desire. Let’s define sexual desire as a feeling that may include wanting to have a sexual experience (e.g. masturbation or intercourse*), thinking about sex, or feeling frustrated due to lack of sex.

11. **Over the past 4 weeks** how often have you felt **sexual desire**?

Please check one box only.

- No sexual stimulation or intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

12. **Over the past 4 weeks** how would you rate your level of **sexual desire**?

Please check one box only.

- Very high
- High
- Moderate
- Low
- Very Low
- None at all

13. **Over the past 4 weeks** how satisfied have you been with your overall **sex life**?

Please check one box only.

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

14. **Over the past 4 weeks** how satisfied have you been with your **sexual relationship** with your partner?

Please check one box only.

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

15. **Over the past 4 weeks** how would you rate your **confidence** that you could get and keep an erection?

Please check one box only.

- Very high
- High
- Moderate
- Low
- Very Low

13.2.4 Patient Health Questionnaire 9 (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE – 9				
Over the last 2 weeks, how often have you been bothered by any of the following problems?				
<i>(Use “✓” to indicate your answer)</i>	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
For OFFICE CODING <u> 0 </u> + <u> </u> + <u> </u> + <u> </u> Total Score: <u> </u>				
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?				
Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display, or distribute.

13.2.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS¹⁸ is intended to be used by individuals who have received training in its administration. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

SUICIDAL IDEATION		
<i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i>	Lifetime: Time He Felt Most Suicidal	Past ____ Months
<p>1. Wish to be Dead Patient endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> If yes, describe:</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
<p>2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i> If yes, describe:</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
<p>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Patient endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes a person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i> If yes, describe:</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
<p>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and patient reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i> If yes, describe:</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
<p>5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and patient has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i> If yes, describe:</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>

INTENSITY OF IDEATION		
<p><i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he was feeling the most suicidal.</i></p> <p><u>Lifetime</u> Most Severe Ideation: _____ _____ Type # (1-5) Description of Ideation</p> <p><u>Past X Months</u> Most Severe Ideation: _____ _____ Type # (1-5) Description of Ideation</p>	Most Severe	Most Severe
<p>Frequency How many times have you had these thoughts? (1) Less than once a week (2) Once a week (3) 2-5 times (4) Daily or almost daily (5) Many times each day</p>	_____	_____
<p>Duration When you have the thoughts how long do they last? (1) Fleeting – a few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time</p>	_____	_____
<p>Controllability Could/can you stop thinking about killing yourself or wanting to die if you want to? (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts</p>	_____	_____
<p>Deterrents Are there things-anyone or anything (e.g., family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide? (1) Deterrents definitely stopped you from committing suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply</p>	_____	_____
<p>Reasons for Ideation What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both? (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply</p>	_____	_____

SUICIDAL BEHAVIOR <i>(Check all that apply, so long as these are separate event; must ask about all types)</i>	Lifetime	Past _____ Years
<p>Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Were you trying to end your life when you _____?</i> <i>Or Did you think it was possible you could have died from _____?</i> Or did you do it purely for other reasons/without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:</p> <p>Has patient engaged in Non-Suicidal Self-Injurious Behavior?</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of Attempts</p> <p>_____</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of Attempts</p> <p>_____</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>
<p>Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of interrupted</p> <p>_____</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of interrupted</p> <p>_____</p>
<p>Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of aborted</p> <p>_____</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of aborted</p> <p>_____</p>

<p>Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:</p>		Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	
<p>Suicidal Behavior Suicidal behavior was present during the assessment period?</p>		Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	
<p>Answer for Actual Attempts Only</p>		Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
<p>Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches. 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>		Enter Code _____	Enter Code _____	Enter Code _____
<p>Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0. Behavior not likely to result in injury 1. Behavior likely to result in injury but not likely to cause death 2. Behavior likely to result in death despite available medical care</p>		Enter Code _____	Enter Code _____	Enter Code _____

13.3 Appendix 3: Laboratory Safety Tests

Hematology Profile

Hemoglobin
Hematocrit
Platelets
Neutrophils
Lymphocytes
Monocytes
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Eosinophils
Basophils
Red blood cell count
White blood cell count

Other Blood Screens and Coagulation

Hepatitis B surface antigen. Screening Only
Hepatitis C virus antibody. Screening Only
HIV 1 and HIV 2 EIA antibody. Screening Only
Prothrombin time (international normalized ratio value). Baseline Only
Activated partial thromboplastin time. Baseline Only

Clinical Chemistry Profile

Sodium
Potassium
Magnesium
Chloride
Calcium
Alkaline phosphate
Glucose, random, serum
Bicarbonate
Creatinine, enzymatic
Total bilirubin
Direct bilirubin
Indirect bilirubin
Alkaline phosphatase
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma glutamyl transpeptidase (GGT)
Cholesterol
High-density lipoprotein cholesterol

Ixchelsis Ltd

IX-01

Protocol: IX-0105 Final Protocol Amendment 1.0

16 January 2017

Low-density lipoprotein cholesterol (CALC)

Triglycerides

Urea (blood urea nitrogen)

Urine Drug Screen

Amphetamines

Barbiturates

Benzodiazepines

Cannabinoids

Cocaine metabolite

Ethanol

Opiates

Phencyclidine

Propoxyphene

13.4 Appendix 4 Amendment 1.0

Reasons for Amendment

- Inclusion of new data from recently complete caplet bioavailability study IX-0106
- 1600 mg dose changed to 1200 mg dose thus number of caplets required per single dose reduced from four caplets to three caplets
- Inclusion of additional information to be collected in LogPad as suggested by FDA

Protocol Sections Amended

The amended protocol sections are detailed below. The format is as follows:

- The “change from” section represents the current text in the protocol
- The “change to” section represents the revised text. Bolded text is used to indicate the addition of information to the current text, and strike-out text (e.g. ~~text~~) is used to show the deletion of information from the current text

Summary of Changes

All references to 1600 mg dose have been changed to 1200 mg throughout the protocol with the exception of pages 25 and 26 which refer to the 1600 mg dose in the Multiple-Ascending Dose Study (2)

All references to 4 caplets have been changed to 3 caplets throughout the protocol

All references to ‘type of site’ have been replaced with ‘site’ throughout the protocol

Protocol Synopsis

Efficacy Assessments

Change From

Patient Questionnaires/Instruments:

Questionnaires administered at the end of the run-in period and after 4 and 8 weeks of double-blind treatment

- Premature Ejaculation Profile (PEP)

Questionnaire to be administered at end of double-blind treatment only

- Clinical Global Impression of Change (CGIC)

Change To

Patient Questionnaires/Instruments:

Questionnaires administered at the end of the run-in period and after 4 and 8 weeks of double-blind treatment

- Premature Ejaculation Profile (PEP) **including additional question on bother**
- **Patient Global Impression of Severity (PGIS)**

Questionnaire to be administered at end of double-blind treatment only

- Clinical Global Impression of Change (CGIC)

List of Abbreviations

Add Text

PGIS Patient Global Impression of Severity

1.3.5 Clinical Data

Change From

To date, 150 male subjects have received one or more doses of IX-01. Clinical safety and pharmacokinetic data are available from four completed Phase 1 studies (A8651001, IX-0101, IX-0102, and IX-0104). A Phase 2a proof-of-concept study (IX-0103) has also been completed and demonstrated the efficacy of IX-01 (doses 400 to 800 mg as needed) to prolong IELT, improve ejaculation-related control, and reduce ejaculation-related distress in men with lifelong PE.

Change To

To date, **150 162** male subjects have received one or more doses of IX-01. Clinical safety and pharmacokinetic data are available from four completed Phase 1 studies (A8651001, IX-0101, IX-0102, and IX-0104). **Also, preliminary clinical safety and kinetic data are available from recently completed study IX-0106.** A Phase 2a proof-of-concept study (IX-0103) has also been completed and demonstrated the efficacy of IX-01 (doses 400 to 800 mg

as needed) to prolong IELT, improve ejaculation-related control, and reduce ejaculation-related distress in men with lifelong PE.

1.3.5 Clinical Data

Change From

Relative Bioavailability Study

Change To

Relative Bioavailability Study (200 mg capsules)

1.3.5 Clinical Data

Add Text

Relative Bioavailability Study (400mg caplets)

In Study IX-0106, 12 subjects were randomized to receive IX-01 1600 mg dispersion in the fasted state, IX-01 1600 mg (4 × 400 mg caplets) in the fasted state, and IX-01 1600 mg (4 × 400 mg caplets) administered after a high-fat meal.

The preliminary results indicate that the GM C_{max} values were 2152 ng/ml for the caplet formulation administered in the fasted state, and that the caplet has an improved bioavailability compared to the dispersion, with GM C_{max} and AUC 1.8 fold those of the dispersion. In addition, food increased the bioavailability (AUC) of the caplet (1.5 fold), which is comparable to the effect of food seen with the capsule and dispersion formulations previously. However, unlike the capsule and dispersion formulations, the rate of absorption was not significantly delayed for the caplet formulation with C_{max} increasing 2.7 fold in the presence of food. There were no treatment-related adverse events or safety issues reported in this study.

1.4.1 Rationale for Dose Selection

Change From

The results of study IX-0103 indicated that single doses of IX-01 (400 to 800 mg), taken 1 to 6 hours prior to intercourse in the fasted state, prolong IELT and improve ejaculation-related control and distress. A post hoc analysis indicated that 400 mg is less effective than the 800 mg dose. However, even at 800 mg, less than half of the patients reported benefit, and therefore, the objective of this study is to explore the efficacy and safety of 1600 mg and to compare the response at this dose with placebo, 400 mg, and 800 mg doses. In the previous efficacy study, doses of 400 to 800 mg were taken one hour before or after food and 1 to 6 hours prior to sexual activity. In this study, it is also recommended to take the study drug one hour before or after food and 1 to 6 hours prior to sexual activity. A 400 mg caplet formulation has been developed to allow a reduced number of caplets to be taken per dose of IX-01.

Change To

The results of study IX-0103 indicated that single doses of IX-01 (400 to 800 mg **administered as capsules**), taken 1 to 6 hours prior to intercourse in the fasted state, prolong IELT and improve ejaculation-related control and distress. A post hoc analysis indicated that 400 mg is less effective than the 800 mg dose. However, even at 800 mg, less than half of the patients reported benefit, and therefore, the objective of this study is to explore the efficacy and safety of 16200 mg (**3 x 400 mg caplets**) and to compare the response at this dose with placebo, 400 mg, and 800 mg doses. In the previous efficacy study, doses of 400 to 800 mg were taken one hour before or after food and 1 to 6 hours prior to sexual activity. In this study, it is also recommended to take the study drug **at least** one hour before or after food and 1 to 6 hours prior to sexual activity. A 400 mg caplet formulation has been developed **to improve bioavailability and** to allow a reduced number of caplets to be taken per dose of IX-01.

1.5 Potential Risks and Benefits

Change From

The nonclinical toxicology, pharmacology, and pharmacokinetic data generated to date and the clinical safety, pharmacokinetic, and pharmacodynamic data generated in studies A8651001 and IX-0101 to IX-0104 support an acceptable risk-benefit profile to evaluate the efficacy and toleration of single doses of orally administered IX-01 (taken as required but not

more than once per day) in adult males, aged 18 to 60 years, inclusive, with PE. The maximum dose to be administered in this study is 1600 mg taken prior to sexual activity but not more than once per day. Doses up to and including 2400 mg administered as a dispersion and taken in the fasted state once daily for 10 consecutive days have been well tolerated by healthy volunteers. Small reductions in mean systolic and diastolic blood pressure between active and placebo groups were not of clinical significance. Two subjects have been discontinued from IX-01 because of skin AEs: a subject who had a pruritic skin rash after 8 days of consecutive dosing with 1600 mg, and a subject with transient urticaria after a single dose of 2400 mg. As in the previous Phase 2 study, the safety of the patients will be assessed at frequent intervals by physical examination and laboratory safety tests. Although preclinical and clinical data generated to date with IX-01 provide no evidence of adverse effects on mood, this protocol includes questionnaires and interviews to screen for depression and suicidality, which is in accordance with other clinical studies of new treatments for PE.

Change To

The nonclinical toxicology, pharmacology, and pharmacokinetic data generated to date and the clinical safety, pharmacokinetic, and pharmacodynamic data generated in studies A8651001 and IX-0101 to IX-0104 support an acceptable risk-benefit profile to evaluate the efficacy and toleration of single doses of orally administered IX-01 (taken as required but not more than once per day) in adult males, aged 18 to 60 years, inclusive, with PE. The maximum dose to be administered in this study is 16200 mg (**3 x 400 mg caplets**) taken prior to sexual activity but not more than once per day. Doses up to and including 2400 mg administered as a dispersion and taken in the fasted state once daily for 10 consecutive days have been well tolerated by healthy volunteers. Small reductions in mean systolic and diastolic blood pressure between active and placebo groups were not of clinical significance. Two subjects have been discontinued from IX-01 because of skin AEs: a subject who had a pruritic skin rash after 8 days of consecutive dosing with 1600 mg, and a subject with transient urticaria after a single dose of 2400 mg. **In Study IX-0106 twelve subjects have received 1600mg administered as 4 x 400 caplets in fasted state and 11 subjects also received 4 x 400 mg caplets after a high fat meal. No treatment-related adverse events were observed.** As in the previous Phase 2 study, the safety of the patients will be assessed at frequent intervals by physical examination and laboratory safety tests. Although preclinical and clinical data generated to date with IX-01 provide no evidence of adverse effects on

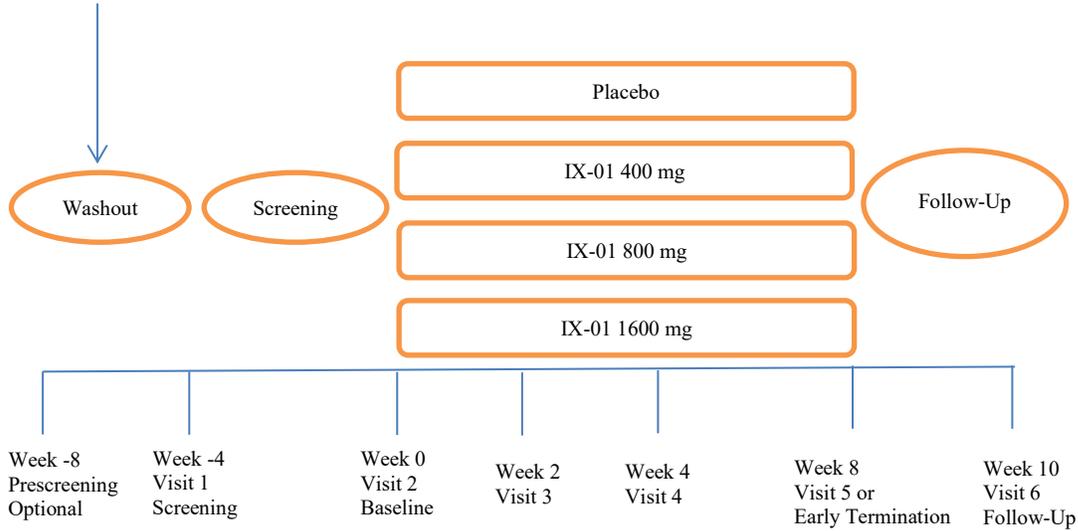
mood, this protocol includes questionnaires and interviews to screen for depression and suicidality, which is in accordance with other clinical studies of new treatments for PE.

3.1 Study Design

Change From

Figure 13-1 Study Design

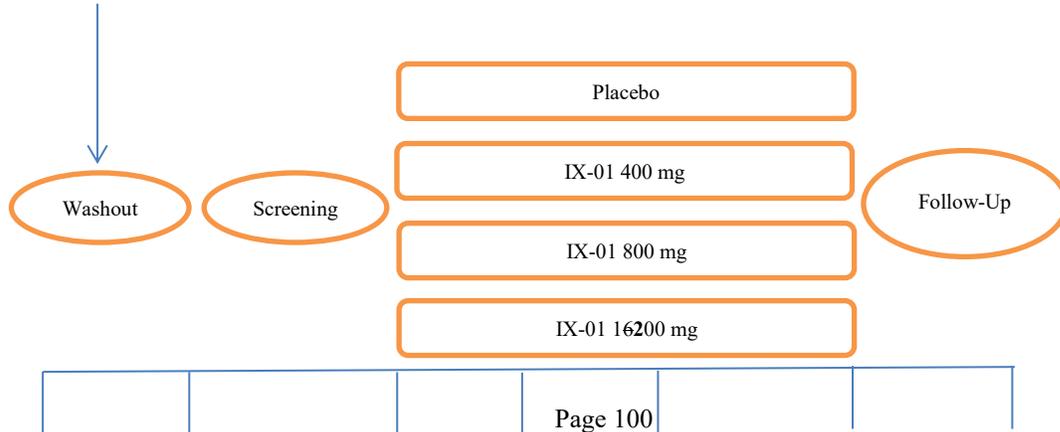
For patients who are receiving regular selective serotonin reuptake inhibitors only



Change To

Figure 13-2 Study Design

For patients who are receiving regular selective serotonin reuptake inhibitors only



Week -8 Prescreening Optional	Week -4 Visit 1 Screening	Week 0 Visit 2 Baseline	Week 2 Visit 3	Week 4 Visit 4	Week 8 Visit 5 or Early Termination	Week 10 Visit 6 Follow-Up
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3.1 Study Design

Change From

Eligible patients will undergo one 8-week treatment period, during which time they are randomized to take IX-01, 400, 800, or 1600 mg or matching placebo. In order to maintain the double-blind, each dose will be presented as 4 caplets in blisters in single-dose units. Thus, for example, a patient randomized to 400 mg IX-01 will receive blister cards with each dose comprising one IX-01 400 mg caplet and three matching placebo caplets. Patients will complete an e-diary (LogPad) on all days during the treatment period that sexual activity is performed with or without the use of the study drug.

Change To

Eligible patients will undergo one 8-week treatment period, during which time they are randomized to take IX-01, 400, 800, or 16200 mg or matching placebo. In order to maintain the double-blind, each dose will be presented as 34 caplets in blisters in single-dose units. Thus, for example, a patient randomized to 400 mg IX-01 will receive blister cards with each dose comprising one IX-01 400 mg caplet and ~~two three~~ matching placebo caplets. Patients will complete an e-diary (LogPad) on all days during the treatment period that sexual activity is performed with or without the use of the study drug.

3.1 Study Design

Change From

During the treatment period, patients will be expected to return to the study site and use their LogPad to complete the following questionnaires according to the study schedule:

- Premature Ejaculation Profile (PEP)
- International Index of Erectile Function (IIEF)
- Patient Health Questionnaire (PHQ-9)

- Clinical Global Impression of Change (CGIC) – Early Termination/Visit 5 only

Change To

During the treatment period, patients will be expected to return to the study site and use their LogPad to complete the following questionnaires according to the study schedule:

- Premature Ejaculation Profile (PEP)
- International Index of Erectile Function (IIEF)
- Patient Health Questionnaire (PHQ-9)
- **Patient Global Impression of Severity (PGIS)**
- Clinical Global Impression of Change (CGIC) – Early Termination/Visit 5 only

5.3.1 Study Drug Packaging and Storage

Change From

All supplies will be packed, labelled, and released in accordance with GMP and GCP guidelines. The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secure area, under recommended storage conditions (15°C-30°C) and in accordance with applicable regulatory requirements. Any excursions from the recommended storage conditions should be reported to the sponsor within 24 hours of the finding.

Change To

All supplies will be packed, labelled, and released in accordance with GMP and GCP guidelines. The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secure area, under recommended storage conditions **59°F-86°F** (15°C-30°C) and in accordance with applicable regulatory requirements. Any excursions from the recommended storage conditions should be reported to the sponsor within 24 hours of the finding.

Section 6.1 Study Visits

Screening Visit 1

Change From

Patients willing to take part in the study and who are eligible according to the criteria already assessed during the screening visit will be provided with a LogPad and stopwatch. They will complete training on how to use the LogPad during this visit. Once the training is completed, patients will be asked to attempt intercourse with their partners at least 4 times during the 4-week run-in period, to use the stopwatch to time the attempt, and to record the relevant details in the LogPad. At the next study visit (Visit 2), the patient must bring the LogPad to the study site. Further details for LogPad use and instructions are found in the Study Training Manual.

Change To

Patients willing to take part in the study and who are eligible according to the criteria already assessed during the screening visit will be provided with a LogPad and stopwatch. They will complete training on how to use the LogPad during this visit. Once the training is completed, patients will be asked to attempt intercourse with their partners at least 4 times during the 4-week run-in period, to use the stopwatch to time the attempt, and to record the relevant details in the LogPad **including whether alcoholic drinks were taken prior to intercourse**. At the next study visit (Visit 2), the patient must bring the LogPad to the study site. Further details for LogPad use and instructions are found in the Study Training Manual.

Baseline Visit 2

Change From

- The investigator will provide the LogPad back to the patient for completion of the PEP, IIEF, and PHQ-9. After completion of these questionnaires, the patient will return the LogPad to the investigator. The LogPad will provide a further summary that will indicate whether the patient is eligible to continue in the study based on the results of the PEP, IIEF, and PHQ-9. If the patient is not eligible based on these assessments, then he should not be randomized or continued in the study, and the investigator may discuss alternate treatment options.

- The patients who meet all of the eligibility criteria will be randomized and assigned a treatment number. Eligible patients will be provided with at least 7 doses of study drug (IX-01 or placebo). Further supplies can be dispensed at this visit based on a discussion between the Investigator and patient but the maximum allowed dose is 1 dose (3 caplets) per day. Each dose of study drug comprises 3 caplets contained within a discrete blister card. Patients must be informed that 1 dose is all 3 caplets, and the dose should be taken with water at least one hour before or after food. Patients should attempt sexual intercourse approximately 1 to 6 hours after taking the dose. The patients will also be provided with a LogPad. Patients should be reminded on the instructions for using the stopwatch and also the LogPad to record their usage of the study medication, as well as all occasions that they attempt sexual intercourse. Patients will be asked if they are willing to try intercourse with their partner approximately 8 times or more between Visit 2 and Visit 5 although less than 8 attempts will not be classified as a protocol deviation. Patients should be reminded to bring their LogPad and any unused study medication back to the study site for Visit 3.

Change To

- The investigator will provide the LogPad back to the patient for completion of the PEP, PGIS, IIEF, and PHQ-9. After completion of these questionnaires, the patient will return the LogPad to the investigator. The LogPad will provide a further summary that will indicate whether the patient is eligible to continue in the study based on the results of the PEP, IIEF, and PHQ-9. If the patient is not eligible based on these assessments, then he should not be randomized or continued in the study, and the investigator may discuss alternate treatment options.
- The patients who meet all of the eligibility criteria will be randomized and assigned a treatment number. Eligible patients will be provided with at least 7 doses of study drug (IX-01 or placebo). Further supplies can be dispensed at this visit based on a discussion between the Investigator and patient but the maximum allowed dose is 1 dose (3 caplets) per day. Each dose of study drug comprises 3 caplets contained within a discrete blister card. Patients must be informed that 1 dose is all 3 caplets, and the dose should be taken with water at least one hour before or after food. Patients should attempt sexual intercourse approximately 1 to 6 hours after taking the dose. The patients will also be

provided with a LogPad. Patients should be reminded on the instructions for using the stopwatch and also the LogPad to record their usage of the study medication, as well as all occasions that they attempt sexual intercourse **and whether alcoholic drinks were taken**. Patients will be asked if they are willing to try intercourse with their partner approximately 8 times or more between Visit 2 and Visit 5 although less than 8 attempts will not be classified as a protocol deviation. Patients should be reminded to bring their LogPad and any unused study medication back to the study site for Visit 3.

Section 6.1 Study Visits

Visit 4

Change From

- The investigator will provide the LogPad back to the patient for completion of the PEP, IIEF, and PHQ-9. Once complete, the patient will return the LogPad to the investigator.

Change To

- The investigator will provide the LogPad back to the patient for completion of the PEP, **PGIS**, IIEF, and PHQ-9. Once complete, the patient will return the LogPad to the investigator.

Section 6.1 Study Visits

Visit 5 (End of Treatment or Early Termination)

Change From

- The investigator will provide the LogPad back to the patient for completion of the PEP, IIEF, PHQ-9, and CGIC. After completion, the patient will return the LogPad to the investigator.

Change To

- The investigator will provide the LogPad back to the patient for completion of the PEP, IIEF, PHQ-9, **PGIS** and CGIC. After completion, the patient will return the LogPad to the investigator.

6.2 Efficacy Assessments

Change From

Outcome measures included during treatment include results from the use of the following:

- Stopwatch to measure IELT.
- LogPad (e-diary) to record summary of study drug intake and details of sexual intercourse attempts (including IELT).
- Responses to the PEP questionnaire.
- Responses to the CGIC questionnaire.

Change To

Outcome measures included during treatment include results from the use of the following:

- Stopwatch to measure IELT.
- LogPad (e-diary) to record summary of study drug intake and details of sexual intercourse attempts (including IELT **and two PEP questions (control and ejaculation-related personal distress)**)).
- Responses to the PEP questionnaire.
- **Responses to PGIS questionnaire.**
- Responses to the CGIC questionnaire.

Change From

LogPad

The LogPad has been specifically designed to enable patients to record details of sexual intercourse attempts and study drug use throughout the study. The key data to be recorded by the patients are date and time of study drug caplets taken, date and time of any intercourse attempt, IELT, level of control of timing of ejaculation; and level of ejaculation-related personal distress. The patient also will use the LogPad at each study visit to complete the PEP, IIEF, and PHQ-9 (PEP, and IIEF are not completed at Visit 3/Week 2). At the final treatment visit (Visit 5 or Early Termination), the CGIC is also collected via the LogPad. For further details of the LogPad design and function, refer to the Study Training Manual.

PEP

The PEP is a widely used self-administered tool that includes measures of perceived control over ejaculation, ejaculation-related personal distress, ejaculation-related interpersonal difficulty, and satisfaction with intercourse. It has been used in many previous studies of PE and is considered validated for this purpose. All of the domains are relevant to a patient with PE, and the instrument has the advantage of being simple and quick to use.¹⁴

CGIC

The Clinical Global Impression of Change (CGIC) is a simple and validated instrument that allows the patient to rate the change in his condition (PE) at the end of treatment on a 7-point scale ranging from “much worse” to “much better.”¹⁵

Change To**LogPad**

The LogPad has been specifically designed to enable patients to record details of sexual intercourse attempts and study drug use throughout the study. The key data to be recorded by the patients are date and time of study drug caplets taken, date and time of any intercourse attempt, IELT, level of control of timing of ejaculation; and level of ejaculation-related personal distress. The patient also will use the LogPad at each study visit to complete the PEP, **PGIS**, IIEF, and PHQ-9 (PEP, **PGIS** and IIEF are not completed at Visit 3/Week 2). At the final treatment visit (Visit 5 or Early Termination), the CGIC is also collected via the

LogPad. For further details of the LogPad design and function, refer to the Study Training Manual.

PEP

The PEP is a widely used self-administered tool that includes measures of perceived control over ejaculation, ejaculation-related personal distress, ejaculation-related interpersonal difficulty, and satisfaction with intercourse. It has been used in many previous studies of PE and is considered validated for this purpose. All of the domains are relevant to a patient with PE, and the instrument has the advantage of being simple and quick to use.¹⁴ **In this study an additional exploratory question on bother will be included in the 4-week recall version used at baseline, week 4 and week 8.**

PGIS

The Patient Global Impression of Severity is a questionnaire that asks the patient to assess the severity of their condition (categories of response are no PE, mild, moderate, severe).

CGIC

The Clinical Global Impression of Change (CGIC) (**also referred to as PGIC**) is a simple and validated instrument that allows the patient to rate the change in his condition (PE) at the end of treatment on a 7-point scale ranging from “much worse” to “much better.”¹⁵ **In this study the CGIC will be administered after the PEP at the final visit and will include two additional questions. See Appendix 2.**

Section 7.2.2 Other Secondary Efficacy Endpoints

Change From

The following other secondary efficacy endpoints will be analyzed:

1. Fold change from baseline in (arithmetic) mean IELT over the treatment assessment period.
2. Change from baseline in (arithmetic) mean IELT over the treatment assessment period.
3. Proportion of patients with GM IELT of ≥ 1 minute over the treatment assessment period.
4. Proportion of patients with GM IELT of ≥ 2 minutes over the treatment assessment period.
5. Proportion of patients with GM IELT of ≥ 3 minutes over the treatment assessment period.
6. Proportion of patients with GM IELT of ≥ 4 minutes over the treatment assessment period.
7. Proportion of patients with GM IELT of ≥ 5 minutes over the treatment assessment period.
8. Proportion of patients with GM IELT increase over the treatment assessment period of ≥ 45 seconds compared with baseline.
9. Proportion of patients with GM IELT increase over the treatment assessment period of ≥ 1 minute compared with baseline.
10. Percentage of intercourse attempts lasting > 1 minute over the treatment assessment period.
11. Percentage of intercourse attempts lasting > 2 minutes over the treatment assessment period.
12. Percentage of intercourse attempts lasting > 3 minutes over the treatment assessment period.
13. Percentage of intercourse attempts lasting > 4 minutes over the treatment assessment period.
14. Percentage of intercourse attempts lasting > 5 minutes over the treatment assessment period.
15. Proportion of patients achieving ≥ 1 category of improvement from baseline to end of treatment in each of the following (from 4-weekly PEP questionnaire):
 - a. Satisfaction with sexual intercourse
 - b. Control over ejaculation during sexual intercourse

- c. Ejaculation-related distress
 - d. Ejaculation-related interpersonal difficulty
16. Change in score from baseline in each of the following (from 4-weekly PEP questionnaire):
- a. Satisfaction with sexual intercourse
 - b. Control over ejaculation during sexual intercourse
 - c. Ejaculation-related distress
 - d. Ejaculation-related interpersonal difficulty

Change To

The following other secondary efficacy endpoints will be analyzed:

1. Fold change from baseline in (arithmetic) mean IELT over the treatment assessment period.
2. Change from baseline in (arithmetic) mean IELT over the treatment assessment period.
3. Proportion of patients with GM IELT of ≥ 1 minute over the treatment assessment period.
4. Proportion of patients with GM IELT of ≥ 2 minutes over the treatment assessment period.
5. Proportion of patients with GM IELT of ≥ 3 minutes over the treatment assessment period.
6. Proportion of patients with GM IELT of ≥ 4 minutes over the treatment assessment period.
7. Proportion of patients with GM IELT of ≥ 5 minutes over the treatment assessment period.
8. Proportion of patients with GM IELT increase over the treatment assessment period of ≥ 45 seconds compared with baseline.
9. Proportion of patients with GM IELT increase over the treatment assessment period of ≥ 1 minute compared with baseline.
10. Percentage of intercourse attempts lasting > 1 minute over the treatment assessment period.
11. Percentage of intercourse attempts lasting > 2 minutes over the treatment assessment period.

12. Percentage of intercourse attempts lasting >3 minutes over the treatment assessment period.

13. Percentage of intercourse attempts lasting >4 minutes over the treatment assessment period.

14. Percentage of intercourse attempts lasting >5 minutes over the treatment assessment period.

15. Proportion of patients improving on PGIS

16. Proportion of patients achieving ≥ 1 category of improvement from baseline to end of treatment in each of the following (from 4-weekly PEP questionnaire):

- a. Satisfaction with sexual intercourse
- b. Control over ejaculation during sexual intercourse
- c. Ejaculation-related distress
- d. Ejaculation-related interpersonal difficulty
- e. Ejaculation-related bother**

19. Change in score from baseline in each of the following (from 4-weekly PEP questionnaire):

- a. Satisfaction with sexual intercourse
- b. Control over ejaculation during sexual intercourse
- c. Ejaculation-related distress
- d. Ejaculation-related interpersonal difficulty
- e. Ejaculation-related bother**

Section 7.5 Description of Subgroups to be Analyzed

Change From

Details will be provided in the Statistical Analysis Plan (SAP) for any proposed subgroup analyses

Change To

Details will be provided in the Statistical Analysis Plan (SAP) for any proposed subgroup analyses (**e.g patients with all baseline IELTs were ≤ 60 seconds**)

7.6.2.1 Change From Baseline Endpoints

Change From

Analyses of e-diary data expressed in change from baseline over the treatment assessment period will be carried out using a mixed linear model. All analyses should include treatment, baseline IELT, and the baseline score of the analyzed endpoint as fixed effects and the type of site as a random effect. In addition to the mixed linear model, a nonparametric approach may be carried out for specific secondary endpoints. Further details will be provided in the SAP.

Change in score from baseline in each of the 4 PEP questions (ie, Endpoint 17 of Section 7.2.2) will be carried out using a mixed-effect model repeated measure model. All analyses should include treatment, baseline IELT, the baseline score of the analyzed endpoint, the visit, and the interaction between visit and treatment as fixed effects and the type of site as a random effect. Visit will be considered as the repeated measurement.

Change To

Analyses of e-diary data expressed in change from baseline over the treatment assessment period will be carried out using a mixed linear model. All analyses should include treatment, baseline IELT, and the baseline score of the analyzed endpoint as fixed effects and the ~~type of~~ site as a random effect. In addition to the mixed linear model, a nonparametric approach may be carried out for specific secondary endpoints. Further details will be provided in the SAP.

Change in score from baseline in each of the **4** PEP questions (ie, Endpoint 177 of Section 7.2.2) will be carried out using a mixed-effect model repeated measure model. All analyses should include treatment, baseline IELT, the baseline score of the analyzed endpoint, the visit, and the interaction between visit and treatment as fixed effects and the ~~type of~~ site as a random effect. Visit will be considered as the repeated measurement.

Section 7.6.3 Safety Analyses

Change From

Concomitant Medications: Previous and concomitant medications will be summarized according to the WHO Drug Dictionary (WHO-DD). The number and percentage of patients for each treatment group will be presented for previous and concomitant medications.

Change To

Concomitant Medications: Previous and concomitant medications will be summarized according to the WHO Drug Dictionary (WHO-DD). The number and percentage of patients for each treatment group will be presented for previous and concomitant medications.

The patient will record in the LogPad whether he had any alcoholic drinks within 4 hours prior to sexual intercourse.

Table 13-2 Schedule of Events**Change From**

IX-0105 Study Schedule and Events							
	For Patients on Chronic SSRIs only Prescreening Visit ¹ (Week -8)	Visit 1 ¹ Screening (Week -4)	Visit 2 ² Baseline (Week 0)	Visit 3 ² (Week 2)	Visit 4 ² (Week 4)	Visit 5 or Early Termination ² (Week 8)	Visit 6 Follow Up (Week 10)
Days Post First Dose (Window)	-56	-28 (±3)	0 (±7)	14 (±3)	28 (±7)	56 (±7)	70 (±7)
Informed Consent	X	X ¹					
Medical History and Demography	X	X ¹					
Inclusion/Exclusion Criteria and Eligibility Review	X	X	X ³				
Physical Examination		X	X	X	X	X	X
Height		X					
Weight		X	X			X	X
Blood Pressure and Heart Rate		X	X		X	X	X
Oral Temperature			X				
12-lead ECG (single)		X	X			X	X
Safety Laboratory Tests (Clinical Chemistry, Hematology, and Coagulation ⁴)		X	X	X	X	X	X
Urinalysis		X	X		X	X	X
Serology (HBsAg, HCV Ab, HIV 1, HIV 2)		X					
Urine Drug Screen		X	X			X	
Randomization			X				
e-Diary Supply ⁵		X	X	X	X		
Diary Evaluation ⁵			X	X	X	X	
Study Drug Supply			X	X	X		
Study Drug Compliance				X	X	X	

IX-0105 Study Schedule and Events							
	For Patients on Chronic SSRIs only Prescreening Visit ¹ (Week -8)	Visit 1 ¹ Screening (Week -4)	Visit 2 ² Baseline (Week 0)	Visit 3 ² (Week 2)	Visit 4 ² (Week 4)	Visit 5 or Early Termination ² (Week 8)	Visit 6 Follow Up (Week 10)
Days Post First Dose (Window)	-56	-28 (±3)	0 (±7)	14 (±3)	28 (±7)	56 (±7)	70 (±7)
IIEF ⁶			X		X	X	
PEP ⁶			X		X	X	
CGIC						X	
PHQ-9			X	X	X	X	
Columbia-Suicide Severity Rating Scale ⁷			X	(X)	(X)	(X)	(X)
Adverse Events			X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X

Abbreviations: CGIC, Clinical Global Impression of Change; ECG, electrocardiogram; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; IELT, intravaginal ejaculatory latency time; IIEF, International Index of Erectile Function; PEP, Premature Ejaculation Profile; PHQ-9, Patient Health Questionnaire 9; SSRI, selective serotonin reuptake inhibitor.

1. Only patients taking chronic SSRIs will have an additional 4-week washout prior to the 4-week run-in period. They will attend a Prescreening Visit and will return to the site for a complete screening (Visit 1) once their washout period is complete. Informed consent and medical history will be obtained at the Prescreening Visit for patients who are receiving chronic SSRIs.
2. Refer to the Study Training Manual for instructions if a patient does not remember to return the LogPad.
3. The patient will return the LogPad to the investigator. The LogPad will provide a summary of the IELT data collected during the run-in period, and will indicate whether the patient is eligible to continue in the study based on the IELT criteria
4. Coagulation (prothrombin time and activated partial thromboplastin time) will be tested at baseline (Visit 2). Only prothrombin time will be taken at other time points if certain laboratory test criteria defined in Section 4.2 are fulfilled.
5. Medication use, IELT, ejaculation control, and ejaculation-related distress are collected after each event via e-diary.
6. IIEF and PEP have 4-week recall periods, and so these questionnaires are completed by the patients at study visits as above.
7. Columbia-Suicide Severity Rating Scale is only mandatory at baseline but may be administered at other visits if clinically indicated.

Change To**Table 13-3 Schedule of Events**

IX-0105 Study Schedule and Events							
	For Patients on Chronic SSRIs only Prescreening Visit ¹ (Week -8)	Visit 1 ¹ Screening (Week -4)	Visit 2 ² Baseline (Week 0)	Visit 3 ² (Week 2)	Visit 4 ² (Week 4)	Visit 5 or Early Termination ² (Week 8)	Visit 6 Follow Up (Week 10)
Days Post First Dose (Window)	-56	-28 (±3)	0 (±7)	14 (±3)	28 (±7)	56 (±7)	70 (±7)
Informed Consent	X	X ¹					
Medical History and Demography	X	X ¹					
Inclusion/Exclusion Criteria and Eligibility Review	X	X	X ³				
Physical Examination		X	X	X	X	X	X
Height		X					
Weight		X	X			X	X
Blood Pressure and Heart Rate		X	X		X	X	X
Oral Temperature			X				
12-lead ECG (single)		X	X			X	X
Safety Laboratory Tests (Clinical Chemistry, Hematology, and Coagulation ⁴)		X	X	X	X	X	X
Urinalysis		X	X		X	X	X
Serology (HBsAg, HCV Ab, HIV 1, HIV 2)		X					
Urine Drug Screen		X	X			X	
Randomization			X				
e-Diary Supply ⁵		X	X	X	X		
Diary Evaluation ⁵			X	X	X	X	
Study Drug Supply			X	X	X		
Study Drug Compliance				X	X	X	

IX-0105 Study Schedule and Events							
	For Patients on Chronic SSRIs only Prescreening Visit ¹ (Week -8)	Visit 1 ¹ Screening (Week -4)	Visit 2 ² Baseline (Week 0)	Visit 3 ² (Week 2)	Visit 4 ² (Week 4)	Visit 5 or Early Termination ² (Week 8)	Visit 6 Follow Up (Week 10)
Days Post First Dose (Window)	-56	-28 (±3)	0 (±7)	14 (±3)	28 (±7)	56 (±7)	70 (±7)
IIEF ⁶			X		X	X	
PEP ⁶ (with additional question)			X		X	X	
PGIS			X		X	X	
CGIC						X	
PHQ-9			X	X	X	X	
Columbia-Suicide Severity Rating Scale ⁷			X	(X)	(X)	(X)	(X)
Adverse Events			X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X

Abbreviations: CGIC, Clinical Global Impression of Change; ECG, electrocardiogram; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; IELT, intravaginal ejaculatory latency time; IIEF, International Index of Erectile Function; PEP, Premature Ejaculation Profile; PHQ-9, Patient Health Questionnaire 9; SSRI, selective serotonin reuptake inhibitor.

1. Only patients taking chronic SSRIs will have an additional 4-week washout prior to the 4-week run-in period. They will attend a Prescreening Visit and will return to the site for a complete screening (Visit 1) once their washout period is complete. Informed consent and medical history will be obtained at the Prescreening Visit for patients who are receiving chronic SSRIs.
2. Refer to the Study Training Manual for instructions if a patient does not remember to return the LogPad.
3. The patient will return the LogPad to the investigator. The LogPad will provide a summary of the IELT data collected during the run-in period, and will indicate whether the patient is eligible to continue in the study based on the IELT criteria
4. Coagulation (prothrombin time and activated partial thromboplastin time) will be tested at baseline (Visit 2). Only prothrombin time will be taken at other time points if certain laboratory test criteria defined in Section 4.2 are fulfilled.
5. Medication use, IELT, ejaculation control, and ejaculation-related distress **and alcohol intake** are collected after each event via e-diary.
6. IIEF and PEP have 4-week recall periods, and so these questionnaires are completed by the patients at study visits as above.
7. Columbia-Suicide Severity Rating Scale is only mandatory at baseline but may be administered at other visits if clinically indicated.

Appendix 2: Evaluation Instruments

13.2.1 Clinical Global Impression of Change (CGIC)

Change From

The CGIC question is the following:

Compared to the start of the study, would you describe your premature ejaculation problem as:

-3 = Much worse

-2 = Worse

-1 = Slightly worse

0 = No change

1 = Slightly better

2 = Better

3 = Much better

Change To

This patient-completed questionnaire is often referred to as PGIC (Patient Global Impression of Change). The following questions will be asked after the patient has completed the PEP at the final visit:

Compared to the start of the study, would you describe your premature ejaculation problem as:

-3 = Much worse

-2 = Worse

-1 = Slightly worse

0 = No change

1 = Slightly better

2 = Better

3 = Much better

Compared to the start of the study did you experience a meaningful change in the time you took to ejaculate (cum)? (Yes/No)

Compared to the start of the study did you experience a meaningful change in your level of distress related to your premature ejaculation? (Yes/No)

13.2.1 Premature Ejaculation Profile (PEP)

Change From

1. Over the past month, was your control over ejaculation during sexual intercourse:

1 – Very Poor 2 – Poor 3 – Fair 4 – Good 5 – Very Good

2. Over the past month, was your satisfaction with sexual intercourse:

1 – Very Poor 2 – Poor 3 – Fair 4 – Good 5 – Very Good

3. Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

4. Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

Change To

1. Over the past month, was your control over ejaculation during sexual intercourse:

1 – Very Poor 2 – Poor 3 – Fair 4 – Good 5 – Very Good

2. Over the past month, was your satisfaction with sexual intercourse:

1 – Very Poor 2 – Poor 3 – Fair 4 – Good 5 – Very Good

3. Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

4. Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

Additional Question

5. Over the past month, how bothered were you by how fast you ejaculated during sexual intercourse:

1 – Extremely 2 – Quite a bit 3 – Moderately 4 – A little bit 5 – Not at all

Patient Global Impression of Severity (PGIS)

This questionnaire will be completed after the patient has completed the PEP.

**How would you rate your premature ejaculation (PE) now? 1 No PE (none), 2 Mild
3 Moderate 4 Severe**