# A Phase 1/2a Study to Determine the Dose Response Pharmacokinetics of TSX-011 (Testosterone Undecanoate) in Hypogonadal Males

**TesoRx Pharma, LLC**

TesoRx Study Number: TT-018
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IND Number 135144

**A Phase 1/2a Study to Determine the Dose Response Pharmacokineties of TSX-011 (Testosterone Undeeanoate) in Hypogonadal Males.**

## SIGNATURE PAGE

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct this study:

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# 1. PROTOCOL SYNOPSIS

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| **Title** | A Phase 1/2a Study to Determine the Dose Response Pharmacokinetics of TSX-011 (Testosterone Undecanoate) in Hypogonadal Males |
| **Sponsor** | TesoRx Pharma, LLC. |
| **Investigational Product** | TSX-011 for oral administration |
| **Study Phase** | Phase 1/2a |
| **Study Number** | TT-018 |
| **Study Objectives** | The primary objective of the study is as follows:<br>1. To assess the pharmacokinetics (PK) of total testosterone after oral dosing of TSX-011 in hypogonadal adult male subjects following: 1) single ascending doses, and 2) single or multiple daily doses administered over a 30-day period in a fixed-dose and dose-adjustment adaptive design.<br>The secondary objectives of the study are as follows:<br>1. To assess the safety and tolerability of TSX-011 in hypogonadal adult male subjects by evaluating treatment-emergent adverse events (TEAEs).<br>2. To assess the PK of free testosterone, testosterone undecanoate (TU), dihydrotestosterone (DHT), and dihydrotestosterone undecanoate (DHTU) after oral dosing of TSX-011 in hypogonadal adult male subjects following: 1) single ascending doses, and 2) single or multiple daily doses administered over a 30-day period in a fixed-dose and dose-adjustment adaptive design.<br>The exploratory objectives of the study are as follows:<br>1. To assess the effect of TSX-011 on hypogonadal symptoms as measured by hypogonadal quality of life (QOL) questionnaires: Aging Male Symptom (AMS) scale, Multinational Survey of the Aging Male-7 (MSAM-7; libido questions only), and Psychosexual Daily Questionnaire (PDQ).<br>2. To determine the preferred method of PK specimen collection Serum or enzyme inhibited plasma. |
| **Study Endpoints** | The primary endpoints of the study are PK parameters for testosterone after TSX-011 administration as described below.<br>1. Period 1 (ascending single doses)<br>a. Total (actual measured) testosterone: $AUC_t$ , $C_{max}$, $T_{max}$, $C_{min}$, $T_{min}$, and $C_{max}$ to $C_{min}$ ratio<br>b. Baseline-corrected testosterone: $\lambda_z$, $t_{½}$, CL/F, $V_{ss}/F$, $AUC_{last}$, and $AUC_{0\ \infty}$ |

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| | 2. Period 2 (twice daily dosing) Day 1 and 15 and Period 3 Day 30 (dose adjustment adaptive design)<br>a. Total testosterone: $AUC_t$, $C_{ss,avg}$, $C_{max}$, $T_{max}$, $C_{min}$, $T_{min}$, and $C_{max}$ to $C_{min}$ ratio<br>The secondary endpoints of the study are as follows:<br>1. Number and severity of TEAEs and results of physical examinations, electrocardiograms (ECGs), vital sign measurements, and clinical laboratory tests (serum chemistry, hematology, and urinalysis) following a single dose of TSX-011 and following a single- or multiple-daily dose regimen of TSX-011 using a fixed-dose or a dose-adjustment adaptive design.<br>2. PK parameters (AUC, $C_{max}$, $C_{min}$, $C_{avg}$, $T_{max}$, $T_{min}$) for free testosterone, TU, DHT, and DHTU under fed (or fasted) conditions following 1) ascending single doses of TSX-011, and 2) single- or multiple-daily dose regimen of TSX-011 (1 to 3 doses per day) using a fixed-dose or dose-adjustment adaptive design.<br>The exploratory endpoints of the study are as follows:<br>1. Hypogonadal symptoms as measured by hypogonadal QOL questionnaires: AMS, MSAM-7 (libido questions only), and PDQ.<br>2. Duplicate PK analysis (serum and enzyme inhibited plasma) in the first 9 subjects enrolled. |
| **Study Design** | The study will be conducted as an open-label 3-period investigation as follows:<br>**Period 1.** Ascending single-dose period: 190 mg TSX-011 (fed and fasted), 380 mg TSX-011 (fed), and 570 mg TSX-011 (fed).<br>**Period 2.** 380 mg TSX-011 twice daily dosing period of 15 days in fed conditions.<br>**Period 3.** Dose-adjusted adaptive design period: TSX-011 dose adjustment permitted on Day 16 and Day 26 based on 6 hours postdose (± 15 minutes) testosterone level on Day 8 and Day 19, respectively; dosing period of 15 days.<br>Dosing amounts of TSX-011 in this protocol refer to TU amounts. |
| **Number of Subjects** | Up to 24 subjects will be enrolled in this study to yield 16 evaluable subjects, and it is desired that the same 24 subjects participate in all 3 study periods.<br>The three initial cohorts of 3 subjects each will complete Periods 1, 2, and 3 prior to enrolment of remaining subjects. Interim review of safety and efficacy of TSX-011 will occur prior to enrolment of remaining subjects in the study. Dose response and optimum dosing conditions and PK specimen collection methods (serum vs. enzyme inhibited plasma) will be confirmed prior to remaining subject enrolment. |

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| | Enrolment will be managed to result in at least 10 evaluable native Japanese subjects. Subjects may be replaced at the discretion of the Sponsor in consultation with the Principal Investigator (PI). |
| **Diagnosis and Inclusion Criteria** | **Inclusion Criteria**<br>Subjects will be eligible for the study if they meet the following criteria.<br>1. Men 18 to 75 years of age at time of study enrolment.<br>2. Male subjects (at least 1 serum testosterone level <350 ng/dL, 10 am [± 2 hour] sample). Subjects with a testosterone level ≥350 ng/dL and <400 ng/dL may meet this inclusion criterion with a second sample taken at least 1 week after initial sample.<br>3. Native Japanese subjects (goal of 10 enrolled) must be men born in Japan who have relocated to the United States (US) and continue to practice a predominantly Japanese lifestyle and diet. Japanese men should be first generation in the US with both Japanese parents and grandparents.<br>4. Able to meet the requirements of the study; to give voluntary, written informed consent; and to adhere to dosing and visit schedules for all 3 periods.<br>5. Body mass index (BMI) <35.0 kg/$m^2$ and weight ≥50 kg at screening.<br>6. All sexually active subjects of reproductive potential are required to be sexually abstinent or use a condom with spermicide when engaging in sexual activity throughout the duration of the study and for 90 days after the last dose of study drug.<br>7. Adequate venous access on left or right arm to allow collection of a number of blood samples by venipuncture.<br>8. Adequate hematologic, hepatic, and renal parameters, i.e., hemoglobin >12 g/dL, alkaline phosphatase <130 U/L, and creatinine ≤1.3 mg/dL.<br>9. Agrees not to donate sperm throughout the study from the first dose of study drug to 90 days after the last dose of study drug.<br>**Exclusion Criteria**<br>Subjects will be ineligible for the study if they meet any of the following criteria:<br>1. History of clinically significant renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition that, in the opinion of the PI, could jeopardize the safety of the subject or impact the validity of the study results.<br>2. Significant gastrointestinal or malabsorption conditions (e.g., history of cholecystectomy, gastroparesis, inflammatory bowel disease, pancreatitis, celiac disease, sprue, dumping syndrome, bariatric surgery, short bowel syndrome, lactose intolerance [unless subject avoids dairy products]). Also, previous |

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| | surgery or a medical condition that, in the judgment of the PI, may affect absorption, distribution, metabolism, or elimination of the drug product (e.g., bariatric Roux-en-Y).<br>3. Any man in whom testosterone therapy is contraindicated including the following:<br>a. Known or suspected carcinoma (or history of carcinoma) of the prostate, clinically significant symptoms of benign prostatic hyperplasia, and/or clinically significant symptoms of lower urinary obstruction and International Prostate Symptom Score (IPSS) ≥19. A clinically significant digital rectal examination of the prostate (such as irregularities or nodules palpated, or otherwise suspicious for carcinoma of the prostate) or clinically significant elevated serum prostate-specific antigen (PSA) levels (>4.0 ng/mL).<br>b. Known or suspected carcinoma (or history of carcinoma) of the breast.<br>c. Liver disease defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × upper limit of normal (ULN) or bilirubin >2 × ULN.<br>d. Active deep vein thrombosis or thromboembolic disorder, or a documented history of these conditions.<br>e. Untreated sleep apnea.<br>f. Hematocrit >50%.<br>g. Untreated moderate to severe depression.<br>4. Current use of long-acting testosterone or any of the testosterone esters injectables.<br>5. Topical, oral, or injectable testosterone replacement therapy (any kind including dehydroepiandrosterone [DHEA] and nutritional supplements) within 28 days prior to screening; subjects who have used Testopel are excluded if it was used within the past 2 years, and subjects who have used AVEED are excluded if it was used within the past 6 months.<br>6. Clinically significant changes in any medications (including dosages) or medical conditions in the 28 days before screening.<br>7. Any significant history of allergy and/or sensitivity to the drug product or its excipients, including any history of sensitivity to testosterone or testosterone esters.<br>8. Suspected reversible hypogonadism (e.g., leuprolide injection).<br>9. Is taking concomitant medications that affect testosterone concentrations or metabolism (e.g., gonadotropin-releasing hormone [GnRH], 5α-reductase corticosteroids, or estradiol; see Section 9.1.2) |

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| | 10. Uncontrolled diabetes (screening glycated hemoglobin [HbA1c] ≥9%).<br>11. Any contraindication to blood sampling.<br>12. Intent to have any surgical procedure during the study.<br>13. Taken any investigational product as part of a clinical study within 30 days or 5 half-lives of first administration of the investigational product, whichever is longer.<br>14. Donated blood or blood products or experienced significant blood loss within 90 days before dosing.<br>15. Donated bone marrow within 6 months before dosing.<br>16. History of drug or alcohol abuse in the last 6 months or positive result in urine drug screen.<br>17. Ingested St John's wort within 30 days of screening.<br>18. Subject currently or planning to be on a special low-fat diet during the study.<br>19. Clinically significant positive result in virology tests (HIV, hepatitis). |
| **Study Duration** | The approximate duration of participation for each subject in each study period is as follows:<br>• Period 1: One day for each dose, plus a minimum 3-day and maximum 7-day washout between each single dose, yielding 9 to 21 days from first single dose to last.<br>• Periods 2 and 3: No less than a 3-day washout (no more than 7 days [14 days for the three initial 3 subject cohorts]) following Period 1, followed by 2 consecutive 15-day dosing periods, yielding 33 to 37 days (44 days for initial 3 subject cohorts).<br>The study duration (after enrolment) for each subject will be approximately 8 weeks. |
| **Treatments** | In Period 1, 24 subjects will each receive single oral doses of 190, 380, and 570 mg (TU) TSX-011 (8 am ± 60 minutes) under fed conditions in a sequential dosing, open-label study design. In addition, the 190 mg TU dose will also be administered under fasted conditions as the second of the single doses administered in Period 1. The subjects will be given each of the 4 doses following a minimum 3-day washout from the previous dose.<br>In Period 2, after no less than a 3-day and no more than a 7-day washout (14 days for initial 3 subject cohorts), the same 24 subjects will receive 380 mg (TU) TSX-011 twice daily (8 am ± 60 minutes and 10 hours after morning dose) under fed conditions for 15 days.<br>In Period 3, the same 24 subjects will receive an adjusted dose of TSX-011 (Appendix 2) under fed conditions for 15 days. The first dose adjustment will be based on the 6 hours postdose (± 15 minutes) total testosterone on Day 8 during Period 2, and the second dose adjustment will be based on the |

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| | 6 hours postdose (± 15 minutes) total testosterone on Day 19 during Period 3. |
| **Analysis Populations** | The analysis populations are defined as follows:<br>The Safety population is defined as all randomized subjects who received at least 1 dose of study drug and have at least 1 post-baseline safety assessment.<br>The PK population is defined as all enrolled subjects for whom at least one PK parameter of interest can be calculated. In general, on a parameter by parameter basis, an individual subject's data may be excluded from analysis if insufficient data are available for that subject to calculate the specific parameter in question.<br>The clinical batch population is defined as all enrolled subjects for whom at least one PK parameter of interest can be calculated. This population will be stratified by dosed clinical study drug batch (e.g. first, second batch). |
| **Safety Assessments and Analysis** | Adverse events (AEs), clinical laboratory test results, concomitant medications, vital signs, ECGs, and physical examinations. |
| **Pharmacokinetic Sample Collection and Analysis** | **Period 1**: Blood samples for the determination of endogenous free testosterone, total testosterone, and DHT will be collected for a single 24-hour period before any study subject exposure to TSX-011. This baseline assessment of endogenous androgen production will be assessed over a 24-hour predose interval (Day -1) at hour 0 (8 am ± 60 minutes) and post initial sample intervals of 1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours (Day 1 hour 0 sample). The initial cohort of 3 subjects will have duplicate PK samples (one serum and one plasma) taken prior to each dose and at each postdose collection point following all 4 doses per the instructions in the lab manual. One of the duplicate samples will be serum and the other will be enzyme-inhibited plasma.<br>Blood samples for PK will be collected predose (hour 0) and for 24 hours postdose (1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours) on Day 1 of each dose in Period 1 (190 mg TU fed, 190 mg TU fasted, 380 TU fed, and 570 mg TU fed).<br>In addition, the second and third cohorts of 3 subjects each will have duplicate PK samples taken prior to the 570 mg TU dose and postdose collection points. The serum sample shall be processed initially, and only if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) shall the enzyme inhibited plasma sample undergo PK analysis.<br>**Period 2:** Blood samples for determination of free testosterone, total testosterone, TU, DHT, and DHTU will be collected at 8 am (± 60 minutes) and postdose intervals of 0, 1.5, 3, 4.5, 6, 8, 10, 11.5, 13, 14.5, 16, 18, and 24 hours. In Period 2, a trough PK sample will be obtained before dosing on Day 8.<br>The initial three cohorts of 3 subjects each will have additional PK samples taken. Specifically, duplicate PK samples (one serum and one plasma) will be taken on Day 8 prior to dosing and at 6 hours (± 15 minutes) after the |

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| | morning dose. The plasma sample values will be used to dose titrate according to the adaptive dosing design (Appendix 2).<br>For the first cohort, if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) in the previously collected Day 8 samples, then for PK assessments on Day 15, all blood samples will be collected in duplicate (one serum and one plasma).<br>For the second and third cohorts, Day 15 samples will be collected in duplicate. The serum sample shall be processed initially, and only if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) shall the enzyme inhibited plasma sample undergo PK analysis.<br>**Period 3:** For subjects on a once-daily dosing schedule, blood samples for determination of free testosterone, total testosterone, TU, DHT, and DHTU will be collected at 8 am (± 60 minutes) and postdose intervals of 0, 1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours.<br>For subjects on a twice-daily dosing schedule, blood samples for determination of free testosterone, total testosterone, TU, DHT, and DHTU will be collected at 8 am (± 60 minutes) and postdose intervals of 0, 1.5, 3, 4.5, 6, 8, 10, 11.5, 13, 14.5, 16, 18, and 24 hours.<br>Non-responder subjects ($C_{avg}$ testosterone <350 ng/dL) after 1 dose adjustment (Day 16) will receive TSX-011 three times (thrice) daily. For these subjects on the thrice-daily dosing schedule, blood samples for determination of free testosterone, total testosterone, TU, DHT, and DHTU will be collected at 8 am (± 60 minutes) and postdose intervals of 0, 1.5, 3, 4.5, 6, 8, 9.5, 11, 12.5, 14, 15.5, 17, 18.5, 20, and 24 hours.<br>The three initial cohorts of 3 subjects each will have additional PK samples taken. Specifically, duplicate PK samples (one serum and one plasma) will be taken on Day 19 prior to dosing and at 6 hours (± 15 minutes) after the morning dose. The plasma sample values will be used to dose titrate according to the adaptive dosing design (Appendix 2).<br>For the first cohort, if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) in the previously collected Day 19 samples, then for PK assessments on Day 30, all blood samples will be collected in duplicate (one serum and one plasma).<br>For the second and third cohorts, Day 30 samples will be collected in duplicate. The serum sample shall be processed initially, and only if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) shall the enzyme inhibited plasma sample undergo PK analysis. |
| **Pharmacokinetic Statistics** | Details of the PK data analysis are specified in the statistical analysis plan. PK parameters for free testosterone, total testosterone, TU, DHT, and DHTU given under fed (or fasted) condition after TSX-011 dosing will be determined at all periods of the study. TSX-011 responders are defined as study subjects who are able to achieve a $C_{max}$ testosterone > 350 ng/dL within Period 1 and $C_{avg}$ testosterone > 350 ng/dL in Period 2 and 3. For this protocol, $C_{max}$ testosterone is defined as the testosterone level obtained 6 hours postdose (± 15 minutes) on days designated for dose adjustment. The following PK parameters will be calculated: |

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| | 1) Period 1, ascending single doses of TSX-011: Total testosterone, $AUC_t$, $C_{max}$, $T_{max}$, $C_{min}$, $T_{min}$, and $C_{max}$ to $C_{min}$ ratio. Baseline-corrected testosterone: $\lambda_z$, $t_{½}$, CL/F, Vss/F, $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$.<br>2) Period 2 and 3: Days 1, 15, and 30 total testosterone given as once, twice, or thrice daily dosing of TSX-011 provided in a dose-adjustment adaptive design: $AUC_t$, $C_{ss,avg}$, $C_{max}$, $T_{max}$, $C_{min}$, $T_{min}$, and the $C_{max}$ to $C_{min}$ ratio.<br>PK parameters for free testosterone, TU, DHT, and DHTU following: 1) ascending single doses, and 2) a once, twice, or thrice daily dose adjustment adaptive design of TSX-011: $AUC_t$, $C_{max}$, $C_{min}$, $T_{max}$, $C_{ssavg}$, and $T_{min}$.<br>To assess dose proportionality, analysis of variance will be performed on the ln-transformed PK parameters: AUCs and $C_{max}$.<br>Dose response will be evaluated via a linear mixed model with random subject effect to account for multiple-dose levels per subject.<br>TSX-011 non-responders are defined as study subjects who despite dose adjustments (in Periods 2 and 3) are unable to achieve a $C_{avg}$ testosterone > 350 ng/dL.<br>Interim review of safety and efficacy of TSX-011 for the three initial 3 subject cohorts will occur prior to enrolment of remaining subjects in the study. Protocol amendments may be generated after these initial 3-patient cohorts. |
| **Safety Statistics** | Safety data including laboratory evaluations, physical examinations, AEs, standard 12-lead ECG parameters, and vital signs assessments will be summarized by treatment group and time point of collection, when appropriate.<br>Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA®). A by-patient AE listing by MedDRA system organ class and by preferred term within system organ class, including verbatim term, dose level, severity, and relationship to treatment, will be provided. This listing will include all AEs and serious AEs (SAEs).<br>Descriptive statistics (arithmetic mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and maximum) will be calculated for quantitative safety data as well as for the difference from baseline, when appropriate.<br>Tables summarizing shifts in clinical laboratory results with respect to normal range will be provided, as well as tables summarizing shifts in vital signs and standard 12-lead ECGs with respect to normal and abnormal results.<br>Concomitant medications will be listed by treatment and coded using the most recent version of the World Health Organization Drug Dictionary. |
| **Bioanalytical Method** | See laboratory manual for details. |

# 2. SCHEDULE OF EVENTS

**Table 1: Schedule of Events - Period 1: Ascending Single Doses**

| Event | Screening (Day -30 to -1) | | Single Treatment Doses[1] of 190[2], 380, and 570 mg TU TSX-011 (8 am ± 60 minutes) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 1 | | | | | | | | Day 2 (+4 days) |
| | | | | Post Dose (hours) | | | | | | | | |
| | Screen | Day -2 | Day -1 | 0 | 1.5 | 3 | 4.5 | 6 | 8 | 12 | 16 | 24 |
| Confinement | | | Confined in Study Unit | | | | | | | | | |
| Inclusion/exclusion | ■ | ■ | | | | | | | | | | |
| Informed consent | ■ | | | | | | | | | | | |
| Medical history[3] | ■ | | | | | | | | | | | |
| ECG (12 lead) | ■ | | ■ | | | | | | | | | ■ |
| Vital signs[4,5] | ■ | | ■ | ■ | | | | ■ | | | | ■ |
| Weight/height/BMI | ■ | | | | | | | | | | | |
| Physical examination[4] | ■ | | ■ | | | | | | | | | ■ |
| HbA1c test | ■ | | | | | | | | | | | |
| Testosterone levels | ■ | | | | | | | ■[6] | | | | |
| Virology tests | ■ | | | | | | | | | | | |
| Chemistry/hematology | ■ | | ■ | | | | | | | | | ■ |
| Urinalysis | ■ | | ■ | | | | | | | | | ■ |
| PSA | ■ | | | | | | | | | | | |
| Urine drug\alcohol screen | ■ | | ■ | | | | | | | | | |
| IPSS, QOL questionnaires | ■ | | | | | | | | | | | |
| Drug administration | | | | ■ | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PK sampling[7] | | | ■[8] | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Adverse events | | | | Continual AE monitoring throughout the study duration[9] | | | | | | | | |
| Concomitant medications | | | | Continual concomitant medication monitoring throughout the study | | | | | | | | |

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; HbA1c = glycated hemoglobin; IPSS = International Prostate Symptom Score; PK = pharmacokinetic(s); PSA = prostate-specific antigen; QOL = quality of life

1 There will be a washout period of at least 3 days and up to 7 days between each dose.
2 190 mg dose to be provided in both the fed and fasted state.
3 Demographic information will also be collected.
4 These safety assessments can also be performed at any time at the discretion of the Principal Investigator.
5 Sitting (5 minutes) blood pressure, pulse rate, respiration rate, and temperature; repeat blood pressure 5 minutes later if elevated.
6 Testosterone levels (local lab) needed after each ascending dose; dose escalation permitted if testosterone is < 2500 ng/dL.
7 Three initial cohorts of 3 subjects each will have duplicate PK samples (one serum and the other plasma) taken per the descriptions in Section 11.1.
8 Endogenous baseline testosterone production will be measured before exposure to TSX-011 in Period 1 (per the instruction in the lab manual). With subject confined in study center, a 24-hour blood sample will be obtained at the following time points: hour 0 (8 am ± 60 mins), and 1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours (± 15 minutes for each time point). The last sample can also be used as the Day 1 hour 0 sample.
9 Details on study monitoring of AEs are presented in Section 10.5.2.

**Table 2: Schedule of Events - Period 2: 380 mg bid, Starting 3-7 Days After Last Dose of Period 1**

| Event | Twice Daily 380 mg TSX-011 Dosing (8 am± 60 min and 10 hrs post morning dose ± 15 min) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -1 | Day 1 | | | | | | | | | | | Day 2 | | | Day 8 |
| | | Post Dose (hours) | | | | | | | | | | | | | | |
| | | 0 | 1.5 | 3 | 4.5 | 6 | 8 | 10 | 11.5 | 13 | 14.5 | 16 | 18 | 24 | | |
| Confinement | Confined in Study Unit | | | | | | | | | | | | | | | |
| Vital signs | ■ | ■ | | | | | ■ | | | | | ■ | | | ■ | ■ |
| Physical examination | ■ | | | | | | | | | | | | | | | |
| ECG (12 lead) | | | | | | | | | | | | | | | ■ | ■ |
| Testosterone levels | | | | | | | | | | | | | | | | ■[2] |
| Chemistry/hematology | | | | | | | | | | | | | | | ■ | ■ |
| Urinalysis | | | | | | | | | | | | | | | ■ | ■ |
| Urine drug/alcohol screen | ■ | | | | | | | | | | | | | | | |
| IPSS, QOL questionnaire | ■ | | | | | | | | | | | | | | | |
| Drug administration | | ■ | | | | | | ■ | | | | | | | ■ | ■ |
| PK sampling | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | ■[2,3] |
| Adverse events | Continual AE monitoring throughout the study duration[4] | | | | | | | | | | | | | | | |
| Concomitant meds | Continual concomitant medication monitoring throughout the study duration | | | | | | | | | | | | | | | |

AE = adverse event; bid = twice daily; $C_{max}$ = maximum serum concentration; IPSS = International Prostate Symptom Score; meds = medications; min = minutes; PK = pharmacokinetic(s); QOL = quality of life

1 There will be a washout period of at least 3 days and up to 7 days (14 days for the three initial 3 subject cohorts) between Period 1 and Period 2.

2 Testosterone levels 6 hours postdose (± 15 minutes) on Day 8 will be used to select TSX-011 dose on Period 3, Day 16 per Appendix 2.

3 Day 8 trough PK sample before 8 am dose administration.

4 Details on study monitoring of AEs are presented in Section 10.5.2.

**Table 3: Schedule of Events - Period 2 (continued): 380 mg bid, Starting 3-7 Days After Last Dose of Period 1**

| Event | Twice Daily 380 mg TSX-011 Dosing (8 am ± 60 min and 10 hrs post morning dose ± 15 min) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 15 | | | | | | | | | | | | Day 16[1] | |
| | | Post Dose (hours) | | | | | | | | | | | | | |
| | Day 14 | 0 | 1.5 | 3 | 4.5 | 6 | 8 | 10 | 11.5 | 13 | 14.5 | 16 | 18 | 24 | |
| Confinement | Confined in Study Unit | | | | | | | | | | | | | | |
| ECG (12 lead) | | | | | | | | | | | | | | | ■ |
| Vital signs | ■ | ■ | | | | | ■ | | | | | ■ | | | ■ |
| Physical examination | ■ | | | | | | | | | | | | | | ■ |
| Chemistry/hematology | | | | | | | | | | | | | | | ■ |
| Urinalysis | | | | | | | | | | | | | | | ■ |
| Urine drug/alcohol screen | ■ | | | | | | | | | | | | | | |
| IPSS, QOL questionnaires | | ■ | | | | | | | | | | | | | |
| Drug administration | ■ | ■ | | | | | | ■ | | | | | | | ■ |
| Dose adjustment | | | | | | | | | | | | | | | ■ |
| PK sampling[2] | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| Adverse events | Continual AE monitoring throughout the study duration[3] | | | | | | | | | | | | | | |
| Concomitant meds | Continual concomitant medication monitoring throughout the study duration | | | | | | | | | | | | | | |

AE = adverse event; bid = twice daily; ECG = electrocardiogram; IPSS = International Prostate Symptom Score; meds = medications; min = minutes; PK = pharmacokinetic(s); QOL = quality of life

1 This is the first day of Period 3.

2 On Day 15, duplicate PK samples will be obtained for subjects in Cohorts 2 and 3 (see Section 11.1 for criteria).

3 Details on study monitoring of AEs are presented in Section 10.5.2.

**Table 4: Schedule of Events - Period 3: Adaptive Dose Phase for Once-daily Dosing**

| Event | Once-daily TSX-011 Dosing (8 am ± 60 minutes) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 19[1] | Day 26 | Day 29 | Day 30 | | | | | | | | | Day 31 (exit) |
| | | | | Post Dose (hours) | | | | | | | | | |
| | | | | 0 | 1.5 | 3 | 4.5 | 6 | 8 | 12 | 16 | 24 | |
| Confinement | | | Confined to Study Unit | | | | | | | | | | |
| ECG (12 lead) | | | | | | | | | | | | | ■ |
| Vital signs | | | ■ | | | | | | | | | | ■ |
| Physical examination | | | ■ | | | | | | | | | | ■ |
| Testosterone levels | ■[2] | | | | | | | | | | | | |
| Chemistry / hematology | | | | | | | | | | | | | ■ |
| Urinalysis | | | | | | | | | | | | | ■ |
| PSA | | | | | | | | | | | | | ■ |
| Urine drug/alcohol screen | | | ■ | | | | | | | | | | |
| IPSS, QOL questionnaires | ■ | | | | | | | | | | | | ■ |
| Drug administration | ■ | ■ | ■ | ■ | | | | | | | | | |
| Dose adjustment | | ■[1] | | | | | | | | | | | |
| PK sampling[2] | ■[1] | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| Adverse events | Continual AE monitoring throughout the study duration[3] | | | | | | | | | | | | |
| Concomitant meds | Continual concomitant medication monitoring throughout the study duration | | | | | | | | | | | | |

AE = adverse event; ECG = electrocardiogram; IPSS = International Prostate Symptom Score; meds = medications; PK = pharmacokinetic(s); PSA = prostate specific antigen; QOL = quality of life

1 Testosterone levels 6 hours postdose (± 15 minutes) on Day 19 will be used to select TSX-011 dose on Day 26 per the rules outlined in Appendix 2.

2 On Day 30, duplicate PK samples will be obtained for subjects in Cohorts 2 and 3 (see Section 11.1 for criteria).

3 Details on study monitoring of AEs are presented in Section 10.5.2.

**Table 5: Schedule of Events - Period 3: Adaptive Dose Phase for Twice-daily Dosing**

| Event | | Twice-daily TSX-011 Dosing (8 am ± 60 minutes and 10 hrs post morning dose ± 15 minutes) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 30 | | | | | | | | | | | | Day 31 (exit) | |
| | | | | Post Dose (hours) | | | | | | | | | | | | | |
| | Day 19[1] | Day 26 | Day 29 | 0 | 1.5 | 3 | 4.5 | 6 | 8 | 10 | 11.5 | 13 | 14.5 | 16 | 18 | 24 | |
| Confinement | | | Confined to Study Unit | | | | | | | | | | | | | | |
| ECG (12 lead) | | | | | | | | | | | | | | | | | ■ |
| Vital signs | | | ■ | | | | | | | | | | | | | | ■ |
| Physical examination | | | ■ | | | | | | | | | | | | | | ■ |
| Testosterone levels | ■[1] | | | | | | | | | | | | | | | | |
| Chemistry / hematology | | | | | | | | | | | | | | | | | ■ |
| Urinalysis | | | | | | | | | | | | | | | | | ■ |
| PSA | | | | | | | | | | | | | | | | | ■ |
| Urine drug/alcohol screen | | | ■ | | | | | | | | | | | | | | |
| IPSS, QOL questionnaire | ■ | | | | | | | | | | | | | | | | ■ |
| Drug administration | ■ | ■ | ■ | ■ | | | | | | ■ | | | | | | | |
| Dose adjustment | | ■[1] | | | | | | | | | | | | | | | |
| PK sampling[2] | ■[1] | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| Adverse events | Continual AE monitoring throughout the study duration[3] | | | | | | | | | | | | | | | | |
| Concomitant medications | Continual concomitant medication monitoring throughout the study duration | | | | | | | | | | | | | | | | |

AE = adverse event; ECG = electrocardiogram; IPSS = International Prostate Symptom Score; PK = pharmacokinetic(s); PSA = prostate specific antigen; QOL = quality of life
1 Testosterone levels 6 hours postdose (± 15 minutes) on Day 19 will be used to select TSX-011 dose on Day 26 per the rules outlined in Appendix 2.
2 On Day 30, duplicate PK samples will be obtained for subjects in Cohorts 2 and 3 (see Section 11.1 for criteria).
3 Details on study monitoring of AEs are presented in Section 10.5.2.

**Table 6: Schedule of Events - Period 3, Adaptive Dose Phase for Thrice-daily Dosing**

| Event | Thrice-daily TSX-011 Dosing (8 am± 60 mins, 8 hrs post morning dose ± 15 mins, and 14 hrs post morning dose ± 15 mins) | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 30 | | | | | | | | | | | Day 31 (exit) | | | |
| | | | | Post Dose (hours) | | | | | | | | | | | | | | |
| | Day 19[1] | Day 26 | Day 29 | 0 | 1.5 | 3 | 4.5 | 6 | 8 | 9.5 | 11 | 12.5 | 14 | 15.5 | 17 | 18.5 | 20 | 24 | |
| Confinement | | | Confined to Study Unit | | | | | | | | | | | | | | | | |
| ECG (12 lead) | | | | | | | | | | | | | | | | | | | ■ |
| Vital signs | | | ■ | | | | | | | | | | | | | | | | ■ |
| Physical examination | | | ■ | | | | | | | | | | | | | | | | ■ |
| Testosterone levels | ■[1] | | | | | | | | | | | | | | | | | | |
| Chemistry / hematology | | | | | | | | | | | | | | | | | | | ■ |
| Urinalysis | | | | | | | | | | | | | | | | | | | ■ |
| PSA | | | | | | | | | | | | | | | | | | | ■ |
| Urine drug\alcohol screen | | | ■ | | | | | | | | | | | | | | | | |
| IPSS, QOL questionnaire | ■ | | | | | | | | | | | | | | | | | | ■ |
| Drug administration | ■ | ■ | ■ | ■ | | | | | ■ | | | | ■ | | | | | | |
| Dose adjustment | | ■[1] | | | | | | | | | | | | | | | | | |
| PK sampling[2] | ■[1] | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| Adverse events | Continual AE monitoring throughout the study duration[3] | | | | | | | | | | | | | | | | | | |
| Concomitant medications | Continual concomitant medication monitoring throughout the study duration | | | | | | | | | | | | | | | | | | |

AE = adverse event; ECG = electrocardiogram; IPSS = International Prostate Symptom Score; mins = minutes; PK = pharmacokinetic(s); PSA = prostate specific antigen; QOL = quality of life

1 Testosterone levels 6 hours postdose (± 15 minutes) on Day 19 will be used to select TSX-011 dose on Day 26 per the rules outlined in Appendix 2.

2 On Day 30, duplicate PK samples will be obtained for subjects in Cohorts 2 and 3 (see Section 11.1 for criteria).

3 Details on study monitoring of AEs are presented in Section 10.5.2.

# 3. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of daily living |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ALT | L-alanine aminotransferase |
| AST | L-aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{last}$ | Area under the concentration versus time curve from time 0 to the last measurable concentration |
| $AUC_t$ | Area under the concentration versus time curve, from time 0 to the last measurable concentration on or before time t |
| $AUC_\infty$ | Area under the concentration versus time curve from time 0 to infinity |
| BC | Baseline corrected |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| $C_{avg,ss}$ | Steady-state average drug concentration |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CL/F | Apparent total body clearance after oral dosing |
| $C_{max}$ | Maximum drug concentration |
| $C_{min}$ | Minimum drug concentration |
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| DHT | Dihydrotestosterone |
| DHTU | Dihydrotestosterone undecanoate |
| DSPC | Distearoylphosphatidylcholine |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GnRH | Gonadotropin-releasing hormone |
| HbA1c | Glycated hemoglobin |
| HIV | Human immunodeficiency virus |
| ICH | International Conference on Harmonisation |
| IPSS | International Prostate Symptom Score |
| MedDRA® | Medical Dictionary of Regulatory Activities® |
| NF | National Formulary |
| PDQ | Psychosexual Daily Questionnaire |
| PI | Principal Investigator |

| | |
|---|---|
| PK | Pharmacokinetic(s) |
| PSA | Prostate specific-antigen |
| REC | Research ethics committee |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SOP | Standard operating procedure |
| SUSAR | Suspect unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time of the maximum measured concentration over the specified interval. If the maximum value occurs at more than one time point, $T_{max}$ is defined as the first time point with this value. |
| $T_{min}$ | Time of the minimum measured concentration over the specified interval |
| TU | Testosterone undecanoate |
| $t_{1/2}$ | Apparent elimination half-life |
| ULN | Upper limit of normal |
| US | United States |
| USP | United States Pharmacopeia |
| $V_{ss}/F$ | Volume of distribution at steady state after oral dosing |
| WHO | World Health Organization |
| $\lambda z$ | Apparent elimination rate constant |

# 4. INTRODUCTION

Native testosterone is not bioavailable after oral administration because of low aqueous solubility, presystemic enterocyte-based cytochrome P450 (CYP) metabolism, and extensive first-pass hepatic metabolism after absorption via the portal vein. Commercial testosterone products address this problem by providing testosterone for parenteral routes of administration (e.g., transdermal patches or gels and intramuscular injections or implants), or by providing a chemical derivative of the testosterone molecule that hinders hepatic uptake and decreases the rate of hepatic metabolism.

Currently approved formulations have significant drawbacks, such as:

1. Testosterone injection and implants: inflammation and pain at the site of administration
2. Testosterone gels: issues with secondary exposure and adverse events (AEs) associated with supraphysiologic doses
3. Testosterone patches: skin irritation and elevated dihydrotestosterone (DHT)

Several androgenic therapies employing testosterone and testosterone ester formulations have been developed to increase serum testosterone levels. Oral testosterone undecanoate (TU) has been marketed for testosterone replacement therapy outside of the US for over 20 years as Andriol Testocaps®. The Nebido® or Reandron® product (injectable TU) has recently become available in 36 countries. Other esterified testosterone products have been approved for injection by the Food and Drug Administration (FDA), including testosterone cypionate, testosterone enanthate, and testosterone propionate.

TesoRx Pharma, LLC (TesoRx) has developed a novel approach for the oral administration of testosterone based on TSX-011, a novel proliposomal formulation of TU that achieves significant oral bioavailability.

After passing through the intestinal epithelium, TSX-011 is absorbed into the lymphatic system rather than into the capillaries of the portal system. Thus, the testosterone derived from TSX-011 enters the systemic circulation via the lymphatics instead of via the portal vein to the liver (Hirano and Hunt, 1985). This allows the testosterone derived from TSX-011 to bypass presystemic hepatic metabolism, which can improve oral bioavailability of drugs that undergo extensive first-pass metabolism (Vorshosaz et al., 2010).

The drug substance in TSX-011 is testosterone undecanoate United States Pharmacopeia (USP). Testosterone undecanoate (17β-undecanoyloxy-4-androsten-3-one) is an inactive prodrug ester of the androgen testosterone that has very weak binding affinity for the androgen receptor. Testosterone is formed by nonspecific esterase cleavage of the ester side chain of TU.

For detailed information on TSX-011 and its excipients, refer to the Investigator's Brochure.

Dosing amounts of TSX-011 in this protocol refer to TU amounts.

## 4.1. Pharmacologic Profile

TSX-011 is a novel proliposomal formulation of TU that achieves significant oral bioavailability by enhancing lymphatic uptake of the drug from the gastrointestinal tract, thereby limiting passage of the drug through the portal vein to the liver and, hence, hepatic metabolism of testosterone.

## 4.2. Toxicology

The active ingredient in the TSX-011 formulation is testosterone undecanoate USP, for which decades of clinical and nonclinical experience exist. Testosterone undecanoate is currently marketed in the United States (US) for the intramuscular route of administration at doses of up to 750 mg every 10 weeks (e.g., AVEED®, New Drug Application [NDA] #22-219). According to the FDA review of the pharmacology and toxicology of AVEED, the overall results of the nonclinical program were similar to what would be expected for testosterone.

Exogenous exposure to testosterone or testosterone esters has resulted in common adverse responses in men including: elevated DHT and estradiol (metabolites of testosterone), reduced fertility, gynecomastia, behavioral changes, sleep apnea, edema (retention of sodium, chloride, potassium, and inorganic phosphates), increased prostatic hyperplasia, increased platelet aggregation and thrombogenicity, altered serum lipid profile, polycythemia, and liver and kidney toxicity.

## 4.3. Pharmacokinetic Profile

The TSX-011 pharmacokinetic (PK) profile in humans is unknown; however, the TSX-011 PK profile in beagle dogs indicates a gradual, broad increase in plasma testosterone concentration, with dose proportionality observed over the dosing range 3.75, 7.5, and 11.25 mg/kg, and no evidence of significant exposure difference following a regular-fat meal versus a high-fat meal. Optimal dosing conditions in the beagle dog are in the fed condition.

The PK profile of the injectable AVEED formulation of TU is described in the AVEED label. AVEED delivers physiologic amounts of testosterone when administered in accordance with the prescribing information; circulating testosterone concentrations approximate normal concentrations in healthy men (approximately 300 to 1000 ng/dL). Following intramuscular injection of 750 mg of AVEED, serum testosterone concentrations reach a maximum after a median of 7 days (range 4 to 42 days) and then slowly decline. Steady-state serum testosterone concentration is achieved with the third injection of AVEED at 14 weeks.

AVEED is the only marketed formulation of TU in the US; no oral formulations are approved for use. TSX-011 has been designed to provide dosing via oral administration. This study is designed to determine the daily oral dose of TSX-011 needed to achieve normal concentrations (300 to 1000 ng/dL) of testosterone in males with serum testosterone level <350 ng/dL.

## 4.4. Clinical Experience

No clinical trials have been conducted with TSX-011.

TesoRx has conducted clinical studies with a similar proliposomal formulation of testosterone (TSX-002; IND 110712). The composition of TSX-002 is almost identical to TSX-011; testosterone is replaced with TU to improve bioavailability, reduce venous uptake from the intestine and thereby decrease first-pass hepatic metabolism, and cholesterol has also been removed from the formulation. In 3 studies, a total of 171 subjects were treated with TSX-002. One serious adverse event (rhabdomyolysis; deemed not related by the principal investigator [PI] and sponsor) and no serious adverse reactions occurred during the studies. Although no clinical trials in humans have been completed with TSX-011, 2 oral non-GLP toxicology studies in dogs demonstrated that oral TSX-011 was well tolerated for up to 7 days of continuous twice daily dosing. TesoRx believes that TSX-011 will have a similar safety profile to TSX-002.

## 4.5. Study Rationale

The rationale for this study is to determine the feasibility of oral testosterone replacement therapy with proliposomal TSX-011. The premise of the TSX-011 development program is that delivering TU in a proliposomal formulation will enable a safer (e.g., less risk of hepatic events; more flexible dosing) and more convenient treatment for hypogonadism than is available with currently marketed testosterone formulations and modified testosterone products.

# 5. STUDY OBJECTIVES

## 5.1. Study Objectives

The primary objective of the study is as follows:

1. To assess the PK of total testosterone after oral dosing of TSX-011 in hypogonadal adult male subjects following: 1) single ascending doses, and 2) single or multiple daily doses administered over a 30-day period in a fixed-dose and dose-adjustment adaptive design.

The secondary objectives of the study are as follows:

1. To assess the safety and tolerability of TSX-011 in hypogonadal adult male subjects by evaluating treatment-emergent adverse events (TEAEs).
2. To assess the PK of free testosterone, TU, DHT, and DHTU after oral dosing of TSX-011 in hypogonadal adult male subjects following: 1) single ascending doses, and 2) single or multiple daily doses administered over a 30-day period in a fixed-dose and dose-adjustment adaptive design.

The exploratory objectives of the study are as follows:

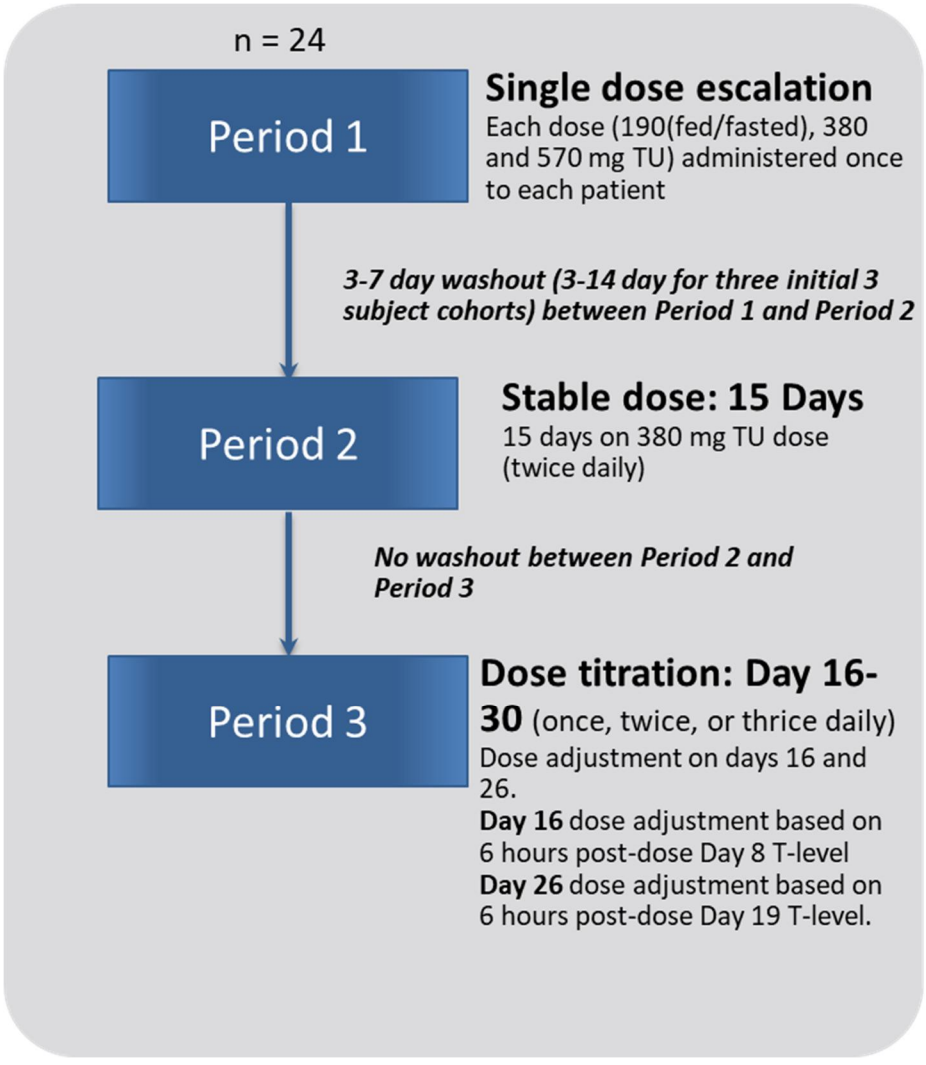
1. To assess the effect of TSX-011 on hypogonadal symptoms as measured by hypogonadal quality of life (QOL) questionnaires: Aging Male Symptom (AMS) scale, Multinational Survey of the Aging Male-7 (MSAM-7; libido questions only), and the Psychosexual Daily Questionnaire (PDQ).
2. To determine the preferred method of PK specimen collection Serum or enzyme inhibited plasma.

# 6. INVESTIGATIONAL PLAN

## 6.1. Overall Study Design

This will be a phase 1/2a, open-label, single-center study with 3 periods. The aims of the study are to: 1) evaluate the dose-response curve following ascending single doses of TSX-011; 2) confirm optimum dosing conditions; 3) evaluate the efficacy of single or multiple daily adaptive dosing; and 4) evaluate the safety and tolerability of TSX-011. Up to 24 hypogonadal men will be enrolled in this study to yield 16 evaluable subjects, and it is desired that the same 24 subjects participate in all 3 study periods. A diagram of the study design is presented in Figure 1. The schedule of events is presented in Table 1 (Period 1), Table 2 (Period 2 up to Day 8), Table 3 (Period 2 from Day 14 to Day 16), Table 4 (Period 3 for single-daily dosing), Table 5(Period 3 for twice-daily dosing), and Table 6 (Period 3 for thrice-daily dosing).

**Figure 1: Study Design for Study TT-018**




T = testosterone

Period 1 (Figure 1 and Table 1) is an ascending single-dose study of TSX-011 at 3 doses, with the lowest dose administered under fed and fasted conditions: 190 mg TSX-011 in the fed state, 190 mg TSX-011 in the fasted state, 380 mg TSX-011 in the fed state, and 570 mg TSX-011in the fed state. Before exposure to TSX-011, a 24-hour baseline measurement of testosterone and DHT will be performed for each subject. Samples for analysis of testosterone will be obtained at the following time points on Day -1: hour 0 (8 am ± 60 minutes) and 1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours (± 15 minutes for each time point).

The day following the sampling for endogenous testosterone (Day 1) in Period 1, each subject will receive the first single dose of TSX-011 (190 mg) under fed conditions. Following administration of TSX-011, blood samples will be obtained over a 24-hour period for PK analysis. Subjects will undergo a minimum 3-day and up to 7-day washout period between each of the doses of TSX-011 in Period 1. After the 570 mg TSX-011 dose in Period 1, a minimum 3-day and up to 7-day (14 day for three initial 3 subject cohorts) washout period will occur before the start of Period 2.

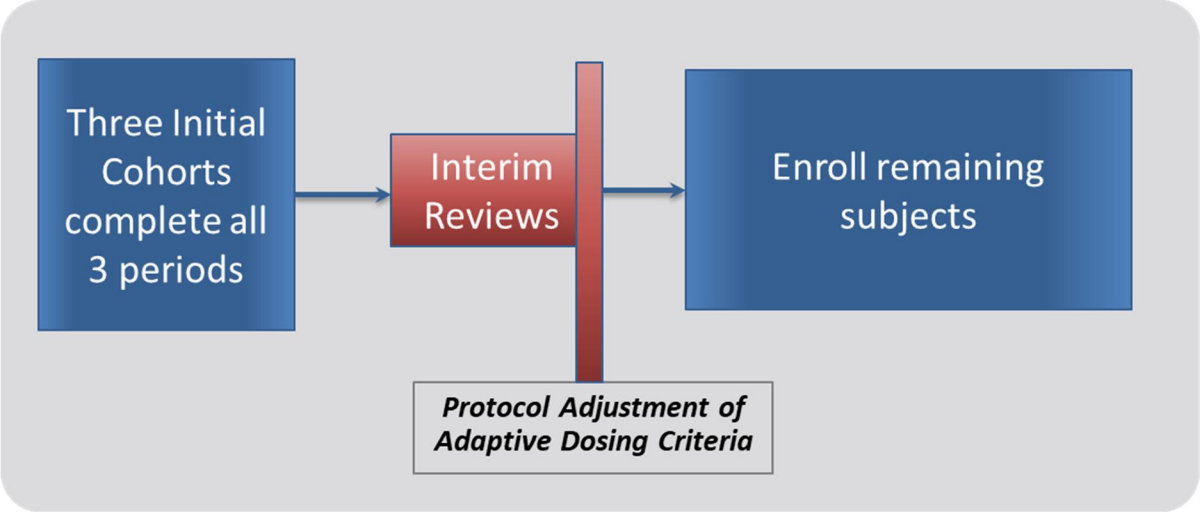
Period 2 is a twice-daily dosing period (Figure 1, Table 2, and Table 3), where fed subjects will be dosed with 380 mg TSX-011 twice daily (at 8 am and 6 pm ± 60 minutes) for 15 days (Days 1 through 15). Pharmacokinetic assessments over 24 hours will occur on Days 1 and 15. On Day 8 in Period 2, before the morning dose, a trough PK blood sample will be drawn. In addition, on Day 8, 6 hours (± 15 minutes) after the morning dose, testosterone levels will be obtained and used to dose titrate according to the adaptive dosing design (Appendix 2). The TSX-011 dose will be titrated up or down beginning with the Day 16 (Period 3) morning dose, based on established dosing rules (see Appendix 2).

Period 3 is a dose-adjusted adaptive design period that begins on Day 16, with the first adjusted TSX-011 dose (see Appendix 2 and randomization scheme) administered in the fed state on a once-daily or twice-daily schedule. The 6-hour postdose (± 15 minutes) testosterone level on Day 19 will be used to perform the second and final TSX-011 dose adjustment, based on established criteria. As specified by the dose adjustment rules in Appendix 2, Day 26 begins with either a once-daily, twice-daily, or thrice-daily fed dose schedule (Table 4, Table 5, and Table 6, respectively). The thrice-daily dose schedule will be administered only to non-responders ($C_{avg}$ testosterone <350 ng/dL despite 1 dose adjustment). On Day 30, a 24-hour PK assessment will be performed, and the subject's participation in the study is completed the morning of Day 31.

Three starting cohorts of 3 subjects each will complete Periods 1, 2, and 3 prior to enrolment of the remaining subjects (see Figure 2). For purpose of this protocol 'enrolment' is the subject first dose (i.e., 190 mg fed Day 1). An interim review of TSX-011 safety and efficacy data (including PK data) will occur prior to enrolling the remaining subjects in the study. Any subject in these cohorts who fails to complete all 3 study periods or is determined to be a non-responder will be replaced. For the first cohort, duplicate PK samples (one serum and one plasma) will be taken prior to each dose and at each postdose collection point following all 4 period 1 doses and analyzed per instruction in the lab manual. One of the duplicate samples will be serum and the

other will be enzyme-inhibited plasma. Additional duplicate samples will be collected per the descriptions in Section 11.1.

**Figure 2: Study Cohort Enrolment Design**




## 6.2. Study Endpoints

The primary endpoints of the study are PK parameters for testosterone after TSX-011 administration under fed (or fasted [Period 1, 190 mg dose only]) conditions as described below:

1. Period 1 (ascending single doses):
    a. Total (actual measured) testosterone, $AUC_t$, $C_{max}$, $T_{max}$, $C_{min}$, $T_{min}$, and $C_{max}$ to $C_{min}$ ratio.
    b. Baseline-corrected (BC) testosterone: $\lambda z$, $t½$, CL/F, $V_{ss}/F$, $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$.
2. Period 2 (twice-daily dosing) Days 1 and 15 and Period 3 (dose-adjustment adaptive design) Day 30:
    a. Total testosterone: $AUC_t$, $C_{ss,avg}$, $C_{max}$, $T_{max}$, $C_{min}$, $T_{min}$, and $C_{max}$ to $C_{min}$ ratio.

The secondary endpoints of the study are as follows:

1. Number and severity of TEAEs and results of physical examinations, electrocardiograms (ECGs), vital sign measurements, and clinical laboratory tests (serum chemistry, hematology, and urinalysis) following a single dose of TSX-011 and following a single- or multiple-daily dose regimen of TSX-011 using a fixed-dose or a dose-adjustment adaptive design.

2. PK parameters ($AUC_t$, $C_{max}$, $T_{max}$, $C_{min}$, and $C_{avg}$) for free testosterone, TU, DHT, and DHTU under fed (or fasted [Period 1, 190 mg dose only]) conditions following: 1) ascending single doses of TSX-011, and 2) single- or multiple-daily dose regimen of TSX-011 using a fixed-dose and dose-adjustment adaptive design.

The exploratory endpoints of the study are as follows:

1. Hypogonadal symptoms as measured by the hypogonadal QOL questionnaires: AMS scale, MSAM-7 (libido questions only), and PDQ.
2. Duplicate PK analysis (serum and enzyme inhibited plasma) in the first 9 subjects enrolled.

## 6.3. Treatments

**Period 1:**

Eligible subjects will receive ascending doses of TSX-011 at 8 am (± 60 minutes) in the following order: 190 mg fed, 190 mg fasted, 380 mg fed, and 570 mg fed. The second dose will follow an overnight fast of at least 6 hours duration, and food will be given 2 hours after dosing. Fed doses will be followed by a breakfast 15 minutes (± 15 minutes) after dosing. A minimum 3-day and up to 7-day washout will occur between doses. Up to 24 subjects will be tested, to yield at least 16 evaluable subjects.

**Period 2:**

Subjects in a fed state will receive 380 mg TSX-011 twice daily (8 am ± 60 minutes and 10 hours ± 15 minutes post morning dose) for 15 days. Subjects will be permitted to eat breakfast and dinner 15 minutes (± 15 minutes) after the morning and evening doses, respectively. In addition, a snack will be permitted between 2 and 3 pm. On Day 8, a predose blood sample for trough PK will be obtained. On Day 8, 6 hours post dose (± 15 minutes), a blood sample will be drawn for testosterone analysis, and the results will be used to determine dose adjustment for Period 3 (beginning on Day 16).

**Period 3:**

On Day 16, subjects will receive an adjusted dose of TSX-011 (see Appendix 2), fed (8 am ± 60 minutes and 10 hours post morning dose ± 15 minutes). The second TSX-011 dose adjustment will be based on a blood sample for testosterone analysis obtained 6 hours (± 15 minutes) after the morning dose on Day 19, and will start with the morning dose on Day 26. The dose adjustment will be based on criteria specified in Appendix 2. Subjects will receive the adjusted dose of TSX-011 either once daily fed (8 am ± 60 minutes), twice daily fed (8 am ± 60 minutes and 10 hours post morning dose ± 15 minutes), or, for non-responders only ($C_{avg}$ testosterone <350 ng/dL after 1 dose adjustment), thrice daily fed (8 am ± 60 minutes, 8 hours post morning dose ± 15 minutes, and 14 hours post morning dose ± 15 minutes) for the final 5 days of Period 3.

## 6.4. Stopping Rules of Dose Escalation

Interim review of safety and PK data will be performed at the following times during the study:

- On completion of Period 3 by the initial three cohorts of 3 subjects each. Interim reviews to be completed prior to enrolment of remaining subjects.

Informal safety reviews will be conducted in between the dose escalations of Period 1 and Period 3. The informal reviews may include a safety meeting, but it is not required. Dose escalation will be halted for a subject in the event of any of the following:

- An incidence of a serious/severe adverse drug reaction (ADR) among subjects that, in the opinion of the PI or the Sponsor, necessitates discontinuation of dose escalation.
- An incidence of a treatment-related, clinically significant laboratory event that, in the opinion of the PI or the Sponsor, necessitates discontinuation of dose escalation.
- A serum testosterone $C_{max}$ exceeding 2500 ng/dL. Subjects experiencing testosterone levels >2500 ng/dL will be discontinued from further dose escalation treatment with TSX-011 and be followed until testosterone levels normalize or return to baseline; subject will be eligible to continue at TSX-011 dose that did not result in supra-physiological $C_{max}$ values.
- If any subject develops a hemoglobin of 18 g/dL or higher, or a hematocrit of 54% or higher, the drug should be discontinued.

Prior to each interim review, the following data will be reviewed by the Sponsor and/or Sponsor representative(s) and the PI:

- Vital signs assessments
- ECG assessments
- Safety laboratory analysis
- AEs assessment
- PK analysis

Study progression will be permitted only if adequate safety and tolerability have been demonstrated at the previous lower dose, as agreed by the PI and the Sponsor.

# 7. SELECTION, EXCLUSION AND WITHDRAWAL CRITERIA

## 7.1. Inclusion Criteria

Subjects will be eligible for the study if they meet the following criteria.

1. Men 18 to 75 years of age at time of study enrolment.
2. Male subjects (at least 1 serum testosterone level <350 ng/dL, 10 am [± 2 hour] sample). Subjects with testosterone level ≥350 ng/dL and <400 ng/dL may meet this inclusion criterion with a second sample taken at least 1 week after initial sample.
3. Native Japanese subjects (goal of 10 enrolled) must be men born in Japan who have relocated to the US and continue to practice a predominantly Japanese lifestyle and diet. Japanese men should be first generation in the US with both Japanese parents and grandparents.
4. Able to meet the requirements of the study; to give voluntary, written informed consent; and to adhere to dosing and visit schedules for all 3 periods.
5. Body mass index (BMI) <35.0 kg/$m^2$ and weight ≥50 kg at screening.
6. All sexually active subjects of reproductive potential are required to be sexually abstinent or use a condom with spermicide when engaging in sexual activity throughout the duration of the study and for 90 days after the last dose of study drug.
7. Adequate venous access on left or right arm to allow collection of a number of blood samples by venipuncture.
8. Adequate hematologic, hepatic, and renal parameters, i.e., hemoglobin >12 g/dL, alkaline phosphatase <130 U/L, and creatinine ≤1.3 mg/dL.
9. Agrees not to donate sperm throughout the study from the first dose of study drug to 90 days after the last dose of study drug.

## 7.2. Exclusion Criteria

Subjects will be ineligible for the study if they meet any of the following criteria:

1. History of clinically significant renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition that, in the opinion of the PI, could jeopardize the safety of the subject or impact the validity of the study results.
2. Significant gastrointestinal or malabsorption conditions (e.g., history of cholecystectomy, gastroparesis, inflammatory bowel disease, pancreatitis, celiac disease, sprue, dumping syndrome, intestinal bypass bariatric surgery (lap band and gastric sleeve will not exclude subjects), short bowel syndrome, lactose intolerance [unless subject avoids dairy products]). Also, previous surgery or a

medical condition that, in the judgment of the PI, may affect absorption, distribution, metabolism, or elimination of the drug product (e.g., bariatric Roux-en-Y).

3. Any man in whom testosterone therapy is contraindicated including the following:
    a. Known or suspected carcinoma (or history of carcinoma) of the prostate, clinically significant symptoms of benign prostatic hyperplasia, and/or clinically significant symptoms of lower urinary obstruction and International Prostate Symptom Score (IPSS) ≥19. A clinically significant digital rectal examination of the prostate (such as irregularities or nodules palpated, or otherwise suspicious for carcinoma of the prostate) or clinically significant elevated serum prostate-specific antigen (PSA) levels (>4.0 ng/mL).
    b. Known or suspected carcinoma (or history of carcinoma) of the breast.
    c. Liver disease defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × upper limit of normal (ULN) or bilirubin >2 × ULN.
    d. Active deep vein thrombosis or thromboembolic disorder, or a documented history of these conditions.
    e. Untreated sleep apnea.
    f. Hematocrit >50%.
    g. Untreated moderate to severe depression.
4. Current use of long-acting testosterone or any of the testosterone esters injectables.
5. Topical, oral, or injectable testosterone replacement therapy (any kind including dehydroepiandrosterone [DHEA] and nutritional supplements) within 28 days prior to screening; subjects who have used Testopel are excluded if it was used within the past 2 years, and subjects who have used AVEED are excluded if it was used within the past 6 months.
6. Clinically significant changes in any medications (including dosages) or medical conditions in the 28 days before screening.
7. Any significant history of allergy and/or sensitivity to the drug product or its excipients, including any history of sensitivity to testosterone or testosterone esters.
8. Suspected reversible hypogonadism (e.g., leuprolide injection).
9. Is taking concomitant medications that affect testosterone concentrations or metabolism (e.g., gonadotropin-releasing hormone [GnRH], 5α-reductase corticosteroids, or estradiol; see Section 9.1.2).
10. Uncontrolled diabetes (screening HbA1c ≥9%).
11. Any contraindication to blood sampling.

12. Intent to have any surgical procedure during the study.
13. Taken any investigational product as part of a clinical study within 30 days or 5 half-lives of first administration of the investigational product, whichever is longer.
14. Donated blood or blood products or experienced significant blood loss within 90 days before dosing.
15. Donated bone marrow within 6 months before dosing.
16. History of drug or alcohol abuse in the last 6 months or positive result in urine drug screen.
17. Ingested St John's wort within 30 days of screening.
18. Subject currently or planning to be on a special low-fat diet during the study.
19. Clinically significant positive result in virology tests (HIV, hepatitis).

## 7.3. Subject Withdrawal and Replacement

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or subinvestigator, for example in cases of:

- Intolerable AEs
- Difficulties in blood collection
- Protocol violation
- ECG abnormality
- Any other clinically significant abnormality as deemed by the PI and/or the Sponsor

The clinical study report will include reasons for subject withdrawals as well as details relevant to the subject withdrawal.

Should any subject withdraw or be withdrawn from the study, all the follow-up evaluations (Day 31 Exit visit procedures) should be performed. Subjects experiencing adverse reactions will be followed until the reaction has resolved. Appropriate supportive and/or definitive therapy will be administered as required.

Subjects withdrawn from this study cannot re-enter.

Subjects who drop out or are withdrawn will be replaced at the discretion of the Sponsor in consultation with the PI.

# 8. STUDY CONDUCT

For an overview of test scheduling, see the study design diagram in Figure 1. For a detailed description of the study assessments per visit, please refer to the schedule of events (Section 2).

### 8.1.1. Screening

During the screening period, all prospective subjects will have the study explained in non-technical terms by a member of the clinic staff. The nature of the drug substance to be evaluated will be explained together with potential hazards. Subjects will be informed of the study restrictions. Prior to performing any study-related procedures on a subject, the subject's acknowledgement of the receipt of this information and his informed consent to participate in the study will be obtained in writing. The subject will be given a copy of the signed informed consent form (ICF).

Subjects must meet all eligibility and no exclusion criteria before being enrolled in the study.

The following procedures will be performed during screening:

- Medical history
- 12-lead ECG
- Vital signs, sitting (5 minutes): blood pressure, pulse rate, respiration rate, and temperature. If blood pressure is elevated, repeat at least 5 minutes later per site procedures.
- Height (centimeters) and weight (kilograms)
- Physical examination
- Urine drug and alcohol screens
- Glycated hemoglobin (HbA1c) determination
- Screening determination of testosterone levels (central laboratory): one sample at 10 am (± 2 hours), must be less than 350 ng/dL; one repeat sample is allowed at least 1 week later if testosterone level is ≥350 ng/dL and <400 ng/dL.
- Human immunodeficiency virus (HIV) and hepatitis screens
- Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis; see Section 10.4)
- Prostate-specific antigen (PSA)
- International Prostate Symptom Score (IPSS) and testosterone deficiency-specific questionnaires: AMS scale, MSAM-7 (libido questions only), PDQ (see Appendix 3)

### 8.1.2. Subject Confinement

In Period 1, subjects will be admitted into the study unit on Day -1 prior (Day -2 for first treatment) to each of the 4 ascending treatment doses. Prior to the first dose of TSX-011, subjects will undergo 24-hour blood sampling for endogenous testosterone measurements. Each study subject will remain in the treatment facility from Day -1 until after the 24-hour postdose safety evaluation and blood sample collection on Day 2, at which time they will be discharged. There will be a washout period of at least 3 days and up to 7 days between each dose in Period 1.

There will be a washout period of at least 3 days and up to 7 days (14 days for initial 3 subject cohorts) between Periods 1 and 2. In Period 2, subjects will be admitted into the study unit from Day -1 to Day 2 and from Day 14 to Day 16. Subjects will return to clinic on Day 8 for morning drug dose and for 6-hour postdose blood draw to measure testosterone level. After receiving study drug on Day 1 and Day 14, subjects will undergo 24-hour PK blood sampling. During these admissions to the study unit, subjects will also have assessments of vital signs, physical examination, urine drug/alcohol screen, IPSS and testosterone deficiency-specific questionnaires, AEs, concomitant medications, and clinical laboratory tests.

In Period 3, Day 16, the subject will leave the study unit with dose adjustment per Appendix 2. Subjects will be admitted into the study unit for confinement on Day 29, undergo PK blood sampling following administration of study drug on Day 30, and be discharged on Day 31. Other assessments during this admission include vital signs, physical examination, urine drug/alcohol screen, IPSS and testosterone deficiency-specific questionnaires, AEs, concomitant medications, ECG, clinical laboratory tests, and PSA.

Subjects may return to the study unit for a safety follow-up visit up to 30 days from check-out.

See Section 8.1.3 for duration details if all planned study arms proceed.

### 8.1.3. Study Duration

The approximate duration for each subject in each study period is as follows.

Period 1: One day for each dose, plus a minimum 3-day and maximum 7-day washout between each single dose, yielding a minimum of 9 days and a maximum of 21 days from first single dose to last.

Periods 2 and 3: A minimum 3-day and maximum 7-day washout (maximum 14-day washout for initial 3 subject cohorts) followed by 2 consecutive 15-day dosing periods, yielding a minimum of 33 days and a maximum of 37 days (maximum of 44 days for initial 3 subject cohorts).

The study duration (after enrolment) for each subject will be approximately 8 weeks, with a range of 6 to 9½ weeks.

# 9. TREATMENT OF SUBJECTS

### 9.1.1. Prohibited Food and Beverages

Consumption of foods and beverages containing the following substances are prohibited as indicated:

- Xanthines / caffeine: 24 hours before dosing and during the study confinement period
- Alcohol: No more than 3 units per day of alcoholic beverages from the beginning of screening through the end of study
- Grapefruit / Seville orange: 14 days before dosing and throughout the study period
- Smokers will be restricted to scheduled smoking breaks during confinement days to facilitate conduction of study events
- *Tribulus alatus* plant extracts

**Table 7: Prohibitions**

| Prohibition | Metrics for Prohibition | Reason for Prohibition | Classification of Reason for Prohibition [1] |
|---|---|---|---|
| Alcohol | No more than 3 units per day of alcoholic beverages from the beginning of screening through the EOS; a unit is defined as 4 oz of wine, 8 oz of beer, or 1.5 oz of hard liquor | To avoid cognitive impairment and study subject mistakes in following study drug administration and procedures | Subject compliance |
| Grapefruit/Seville orange | Prohibited from 14 days before dosing and during the treatment period | Potential CYP3A interaction | Potential CYP3A interaction |
| Herbal supplements (particularly those affecting testosterone levels such as *Tribulus alatus* plant extracts) | Prohibited from 48 hours from the beginning of screening through the EOS | Affecting testosterone levels | Affecting testosterone levels |
| St John's wort | Prohibited from 28 days before the first dose of study drug through the EOS | Potential CYP3A interaction | Potential CYP3A interaction |

CYP = cytochrome P450; EOS = end of study; T = testosterone
1 TSX-011 interaction or confounding effect.

### 9.1.2. Prohibited Medications

Prohibited medications are summarized below.

- Any form of testosterone replacement
- Finasteride
- Dutasteride
- St. John's wort
- Luteinizing hormone-releasing hormone (LHRH) agonist or antagonist
- Estrogens

### 9.1.3. Concomitant Medications

No subject may take medications or herbal products during the study except if allowed by the PI.

All medications taken by subjects during the study will be recorded. If drug therapy other than that specified in the protocol is required (over the counter and/or prescription), a decision to continue or discontinue the subject will be made, based on the time the medication was administered and its pharmacology and PK.

### 9.1.4. Level of Activity During the Confinement Period

Subjects will remain ambulatory or seated upright for the first 4 hours after drug administration, except when they are supine or semi-reclined for study procedures (e.g., ECGs). However, should AEs occur at any time, subjects may be placed in an appropriate position for comfort or safety. Subjects will not engage in strenuous activity at any time during the confinement period.

# 10. SAFETY ASSESSMENTS

Safety of TSX-011 will be determined by evaluating physical examination findings, ECGs, vital signs, clinical laboratory parameters, and AEs (see the Schedules of Events in Section 2 for details). The PI may order any test at any time for evaluation and management of an AE.

Vital signs and ECG assessments have a window of ± 15 minutes around each scheduled time point.

If deemed necessary, additional safety measurements will be performed at the discretion of the PI.

## 10.1. ECGs

For study subjects, 12-lead ECGs will be performed and evaluated for all subjects as presented in the Schedule of Events (Section 2).

## 10.2. Vital Signs

For study subjects, sitting (5 minutes) vital signs including blood pressure, pulse rate, respiration rate, and temperature will be evaluated as presented in the Schedule of Events (Section 2).

## 10.3. Physical Examination

A physical examination will be conducted for all subjects presented in the Schedule of Events (Section 2).

The physical examination will include evaluation of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, genitourinary system, extremities, neurological status, and skin. Digital rectal examination is required only at screening.

## 10.4. Clinical Laboratory Tests

Samples for hematology (excluding HbA1c), serum chemistry (excluding testosterone and PSA), and urinalysis evaluations will be obtained as presented in the Schedule of Events (Section 2).

A certified and accredited facility will perform the safety laboratory tests.

Laboratory parameters for hematology, serum chemistry, urinalysis, virology, and urine drug screen are detailed in Table 7.

**Table 7: Clinical Laboratory Tests**

**Hematology**

- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count
- White blood cell count
- HbA1c**

**Urine drug screen** ***

- Cocaine
- Cannabinoids
- Alcohol
- Opiates
- Barbiturates
- Amphetamines
- Benzodiazepines

**Urinalysis**

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte esterase
- Microscopic assessment for cells and casts

**Serum Chemistry**

- Albumin
- Alkaline phosphatase
- AST
- ALT
- Blood urea nitrogen
- Creatinine
- Creatine kinase
- Lactate dehydrogenase
- Glucose
- Total bilirubin*
- Total protein
- Sodium
- Potassium
- Chloride
- Calcium
- Triglycerides
- Total cholesterol
- Uric acid
- High-density lipoprotein (HDL)
- Low-density lipoprotein (LDL)
- Testosterone (per Schedule of Events)
- PSA (per Schedule of Events)

**Virology**

- HIV test**
- Hepatitis B surface antigen**
- Hepatitis C virus**

* If total bilirubin results are above the upper limits of normal, direct and indirect bilirubin analysis will be performed.
** To be performed at screening only.
*** To be performed at screening and at each confinement check-in.
After screening, safety laboratory tests will be performed in the fasted state (at least 8 hours fasted).

## 10.5. Adverse Events

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21 Code of Federal Regulations (CFR) 312, International Conference on Harmonisation (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and ICH Guideline E-6: Guidelines for Good Clinical Practice (GCP).

The investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the investigational product. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as a serious adverse event (SAE) or a serious and unexpected suspected adverse reaction (SUSAR) requiring immediate notification to the Sponsor or its designated representative.

### 10.5.1. Definitions of Adverse Events

#### 10.5.1.1. Adverse Event (AE)

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (ICH E6 Guidelines for GCP). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

#### 10.5.1.2. Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor whether it is considered treatment related or not.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered "life-threatening" if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of investigational product dependency or abuse.
- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to the Sponsor as described in Section 10.5.3.

Adverse events associated with hospitalization or prolongation of hospitalization are considered serious. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard of care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities, or respite care (e.g., caregiver relief)
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g., for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject.

Medical and scientific judgment should be exercised in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition. These should also usually be considered serious, and reported.

#### 10.5.1.3. Serious and Unexpected Suspected Adverse Reactions (SUSARs)

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE. A SAR implies a lesser degree of certainty about causality than an ADR (21 CFR 312.32(a)).

The Sponsor is responsible for assessing AEs for expectedness. With regards to reporting to the Health Authority, an AE is considered "unexpected" when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the protocol/package insert/investigator's brochure/prescribing information for the study drug. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the investigator's brochure as

occurring with a class of drug or as anticipated from the pharmacological properties of the study drug but are not specifically mentioned as occurring with the particular study drug under investigation (21 CFR 312.32(a)).

For a comparator product with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the Prescribing Information.

Adverse events that meet all three criteria (i.e., serious, unexpected and SAR; SUSAR) are reported to FDA as described in Section 10.5.3.3.

### 10.5.2. Adverse Event Monitoring

Adverse events will be continually monitored for the duration of the study. During confinement, subjects will be monitored throughout confinement until the poststudy follow-up visit for adverse reactions to the study formulation and/or procedures. Subjects will be asked an open question, such as "How have you been feeling since you were last asked?" at the following time points:

- Period 1: predose (Day 1), 24 hours post dose (Day 2), and for each ascending dose
- Period 2: Day 1 predose, Day 8 postdose, and Day 15 post dose
- Period 3: Day 19 postdose, and Day 30 after last dose

The subjects will also be instructed to inform the PI/investigator's designee or clinic staff of any AEs and undercurrent illnesses experienced during the study.

All AEs ongoing at the follow-up visit will be followed up until resolution, stabilization, or determination that the subject is lost to follow-up (for up to 30 days) by the investigator or designee. Unresolved AEs at the follow-up visit will be followed up for a further 30 days. For AE status to be considered lost to follow-up, the site must attempt to contact the subject by phone twice, followed by a registered letter; if no contact is made within 5 days of receipt of the registered letter or return of the letter as undeliverable, a status of lost to follow-up is entered.

A physician will administer treatment for AEs and/or SAEs as appropriate.

### 10.5.3. Reporting Adverse Events (AEs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARS)

#### 10.5.3.1. Reporting Adverse Event (AEs)

All AEs occurring from signature of the informed consent until completion of the clinical study will be recorded in the case report form (CRF) and coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA®).

An AE is any unwarranted medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH/World Health Organization [WHO]). Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory

finding, for example), symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medical product (ICH/WHO).

The investigator will make a determination of the relationship of the AE to the study drug using a 4-category system (not related, possible, probable, and definite) according to the guidelines in Table 8.

**Table 8: Relationship to Study Drug**

| | |
|---|---|
| Not Related | An AE that does not follow a reasonable temporal sequence from administration of the drug or that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment. |
| Possible | The AE follows a reasonable temporal sequence from drug administration; is unlikely to have been produced by the patient's underlying medical conditions, environmental or toxic factors or other therapeutic interventions. |
| Probable | The AE follows a reasonable temporal sequence from drug administration, or is associated with established drug concentration in body tissues; improves on stopping or reducing drug dosage (de-challenge); and could not reasonably be explained by the study patient's underlying medical conditions, environmental or toxic factors, or other therapeutic interventions. |
| Definite | Same as for "probable" - but AE reappears on repeated exposure (re-challenge). |

Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), according to Table 9.

**Table 9: Severity Scale**

| | |
|---|---|
| Mild (Grade 1) | Experience is minor and does not cause significant discomfort to subject/patient or change in activities of daily living (ADLs); subject/patient is aware of symptoms but symptoms are easily tolerated. |
| Moderate (Grade 2) | Experience is an inconvenience or concern to the patient and causes interference with ADLs but the patient is able to continue with ADLs. |
| Severe (Grade 3) | Experience significantly interferes with ADLs and the patient is incapacitated and/or unable to continue with ADLs.<br>Note: An experience may be severe but may not be serious (e.g., severe headache). |

The date and time of onset, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

#### 10.5.3.2. Reporting Serious Adverse Events (SAEs)

Safety reporting, including suspected "unexpected" serious adverse reactions (SUSARs) reporting, will be performed in line with European Clinical Trial Directive (2001/20/EC) and United Kingdom guidelines, as applicable.

If an SAE occurs to a patient on this study, the Sponsor will be contacted and SAEs will be reported to the appropriate regulatory authority in accordance with local laws and regulations and in accordance with site standard operating procedures (SOPs).

All SAEs will be reported to the contract research organization (CRO), and subsequently in redacted format to Sponsor, the Medical Monitor, and Rho, Inc., which is acting on behalf of the Sponsor as the holder of the safety database. All SAEs must be communicated within 24 hours and followed by written reports within 48 hours of first knowledge of the event, whether or not the SAEs are deemed drug related.

A paper SAE report form will be submitted to the following as a fax or as a scan that is emailed. The initial SAE notification should provide the following information:

- Study number
- Subject number
- Gender
- Date of birth
- PI or designated physician name and investigational site address
- Date of SAE onset
- Details of SAE
- Criterion of SAE classification
- Study drug name, or code if blinded
- Treatment start date
- Causality assessment

Initial reports of SAEs must be later followed with detailed descriptions, including photocopies of other documents where applicable (e.g., hospital reports, laboratory reports, hospital consultant reports, autopsy reports, etc.) with the subject's personal identifiers removed. All relevant information obtained by the PI will be reviewed and as appropriate recorded in the subject's CRF or where applicable, and a new SAE form will be generated.

#### 10.5.3.3. Reporting Suspected Unexpected Serious Adverse Reactions (SUSARS)

If applicable, the Sponsor must ensure that the research ethics committee (REC), the appropriate Competent Authority, and the licensing authority are informed of all SUSARs within 15 days of the event in accordance with Directive 2001/20/EC. All SUSARs leading to death or which are life-threatening should be reported by the Sponsor

to the REC, the appropriate Competent Authority, and the licensing authority within 7 days of the event. The Sponsor should present all SUSARs to the appropriate Competent Authority once a year, or on request.

This activity is delegated by the Sponsor to the CRO. In the event of a SUSAR, the CRO will submit the relevant data to the REC and the Medicines and Healthcare Products Regulatory Agency (MHRA).

### 10.5.4. Pregnancy Reporting

If any study subject's female partner becomes pregnant while the study participant is enrolled in the study or within 90 days following the last dose, the PI should submit a pregnancy report form within 24 hours of the PI becoming aware of the pregnancy confirmation.

If permission is granted, pregnancies will be followed up by the PI. If the pregnancy is to be terminated, the date of termination should be provided. If the pregnancy ends for any reason before the anticipated date, the PI will notify the Sponsor immediately.

If the PI becomes aware of an AE (maternal or infant), a birth defect/congenital abnormality, or other adverse pregnancy outcome (e.g., miscarriage or stillbirth) that occurred during pregnancy or delivery and that fulfills the definition of a SAE, the PI should complete and submit a SAE report form.

Following birth, the progress of any live infants, where permissible, will be followed as deemed appropriate by the PI.

# 11. PHARMACOKINETIC ASSESSMENTS

## 11.1. PK Blood Samples

Blood samples for PK will be collected according to the schedule of events in blood collection tubes as detailed in the laboratory manual. All PK blood samples will be collected for central bioanalytical laboratory analysis. The initial cohort of 3 subjects will have additional PK samples taken. Specifically, duplicate PK samples (one serum and one plasma) will be taken prior to each dose (i.e., 0 hr) and at each postdose collection point following all 4 period 1 doses and analyzed per instructions in the lab manual.

In addition, the second and third cohorts of 3 subjects each will have duplicate PK samples taken prior to the 570 mg TU dose and postdose collection points following the instructions in the lab manual. The serum sample shall be processed initially, and only if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) shall the enzyme inhibited plasma sample undergo PK analysis.

**Period 1:** Blood samples for the determination of endogenous testosterone and DHT (4-6 mL per time point) will be collected for a single 24-hour period before any study subject exposure to TSX-011. This baseline assessment of endogenous testosterone and DHT will be assessed over a 24-hour predose interval (Day -1) at 0, 1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours.

Blood samples (4-6 mL per time point) for 24-hour post-dosing will be collected on Day 1 of each dosing PK (190, 380, 570 mg TU) at 0, 1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours.

**Period 2:** Blood samples (4-6 mL per time point) for determination of PK measurements will be collected at 0, 1.5, 3, 4.5, 6, 8, 10, 11.5, 13, 14.5, 16, 18, and 24 hours on Day 1 and Day 15. The three initial cohorts of 3 subjects each will have additional PK samples taken. Specifically, duplicate PK samples (one serum and one plasma) will be taken on Day 8 prior to dosing and at 6 hours (± 15 minutes) after the morning dose. The plasma sample values will be used to dose titrate according to the adaptive dosing design (Appendix 2).

For the first cohort, if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) in the previously collected Day 8 samples, then for PK assessments on Day 15, all blood samples will be collected in duplicate (one serum and one plasma).

For the second and third cohorts, Day 15 samples will be collected in duplicate. The serum sample shall be processed initially, and only if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) shall the enzyme inhibited plasma sample undergo PK analysis.

**Period 3:**

On Day 30, PK samples for a 24-hour PK profile will be obtained at the following sampling times based upon the daily dosing regimen.

For subjects on once daily dosing, blood samples for determination of PK measurements (4-6 mL blood per time point) will be collected at 0, 1.5, 3, 4.5, 6, 8, 12, 16, and 24 hours.

For subjects on twice daily dosing, blood samples for determination of PK measurements (4-6 mL blood per time point) will be collected at 0, 1.5, 3, 4.5, 6, 8, 10, 11.5, 13, 14.5, 16, 18, and 24 hours.

For subjects on thrice daily dosing, blood samples for PK determination will be collected at 0, 1.5, 3, 4.5, 6, 8, 9.5, 11, 12.5, 14, 15.5, 17, 18.5, 20, and 24 hours.

The three initial cohorts of 3 subjects each will have additional PK samples taken. Specifically, duplicate PK samples (one serum and one plasma) will be taken on Day 19 at 6 hours (± 15 minutes) after the morning dose. The plasma sample values will be used to dose titrate according to the adaptive dosing design (Appendix 2).

For the first cohort, if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) in the previously collected Day 19 samples, then for PK assessments on Day 30, all blood samples will be collected in duplicate (one serum and one plasma).

For the second and third cohorts, Day 30 samples will be collected in duplicate. The serum sample shall be processed initially, and only if TU is detectable at a level 5 times above the LLOQ (i.e. 10 ng/ml) shall the enzyme inhibited plasma sample undergo PK analysis.

A dosing window of ± 60 minutes is allowed; however, this window establishes time 0 and subsequent sampling times will be followed as indicated above. For example, if subject is dosed at 7:45 am, this is time 0; 1 hour postdose is 8:45 am and so on.

The exact time the PK blood sample is obtained must be recorded. PK samples should be taken as close to their allotted sampling times as practical to minimize bias in the baseline corrected PK parameters; however a window of ± 15 minutes will be permitted.

Cannulae may be used for blood sample withdrawal. Before withdrawing blood for PK, the cannula must be aspirated to permit removal of the “dead space” blood, which is discarded, and then the PK blood may be withdrawn using a new syringe.

The actual times of each sample draw will be recorded to the nearest minute. The recorded actual sample times will be used in conjunction with the actual time of dose administration for calculation of PK parameters as appropriate, as denoted above.

## 11.2. Blood Volume, Pharmacokinetic Blood Sample Processing/ Analysis, and Bioanalytical Method

Total blood volumes per individual subject, PK blood sample processing and analysis, and bioanalytical methods in each study period are detailed in the laboratory manual.

# 12. EXPLORATORY ASSESSMENTS

The exploratory assessments of the study are:

1) measurements of QOL related to hypogonadal symptoms. These QOL questionnaires include the IPSS, AMS scale, MSAM-7 (libido questions only), and PDQ, and are administered as follows.

- Screening
- Period 2: Day -1, Day 15
- Period 3: Day 31

2) To determine the preferred method of PK specimen collection Serum or enzyme inhibited plasma. Method of PK collection (serum vs enzyme inhibited plasma) shall be performed to assess consistency of bioanalytical assay reporting.

# 13. STUDY DRUG MATERIALS AND MANAGEMENT

## 13.1. Investigational Products

| | |
|---|---|
| TSX-011 | Active ingredient: testosterone undecanoate USP<br>Example approximate doses:<br>(190 mg TU) 3 × 63.2 mg TSX-011 capsule<br><br>(380 mg TU) 6 × 63.2 mg TSX-011 capsule<br><br>(570 mg TU) 9 × 63.2 mg TSX-011 capsule |

## 13.2. Drug Identification

The TSX-011 formulation will be composed of pharmaceutical grade synthetic testosterone undecanoate USP powder purchased from Pfizer (Kalamazoo, MI), which maintains a Drug Master File with the FDA containing stability data for testosterone drug substance. The excipients used in the manufacture of the encapsulated TSX-011 formulation are distearoylphosphatidylcholine (DSPC), microcrystalline cellulose National Formulary (NF), sodium starch glycolate NF, and alcohol USP. The excipients used in the enteric coating are methacrylic acid copolymer NF, triethyl citrate NF, talc NF, and purified water USP. Alcohol and purified water are removed during processing.

## 13.3. Drug Supply

Please refer to the pharmacy manual.

## 13.4. Drug Accountability, Storage, and Retention

The study site must maintain accurate records demonstrating dates and amount of study treatment dispensed (patient-by-patient accounting) and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all drug products, including the empty packaging if applicable, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to TesoRx Pharma LLC. A written explanation will be provided for any discrepancies.

At the conclusion of the study, any unused study drug in addition to used and unused packaging will be returned to the Sponsor.

## 13.5. Randomization and Blinding

### 13.5.1. Randomization: Based on Day 8 Testosterone Level

If Period 2 Day 8 (6 hours postdose ± 15 minutes) total testosterone is >800 ng/dL, subjects will be randomized in a 1:1 ratio to receive:

- Schedule A: 317 mg (TU) TSX-011 twice daily OR
- Schedule B: 507 mg (TU) TSX-011 once daily

Subjects will be stratified during randomization per Japanese/non-Japanese classification. Enrolment will be managed to result in at least 10 evaluable Japanese subjects. Stratification and randomization will be managed within the electronic data capture system.

The study is an open-label study, and as such, no blinding will be performed.

## 13.6. Dosage and Administration

TSX-011 capsule(s) will be administered orally with at least 240 mL of water. The drinking containers will be examined by the clinic staff immediately after dosing to ensure all study drug and water was taken. Dosing (swallowing capsules) should be completed within 5 minutes of starting. Study drug containers will be returned to the pharmacy after dosing is complete. All drug administration procedures will be performed at the clinical study unit during confinement. The actual time of each dose administration will be recorded to the nearest minute, and this will be used in conjunction with the actual sample times to determine PK parameters as appropriate.

## 13.7. Meal Schedule

Meals and/or snacks will be provided as appropriate (breakfast, lunch, and dinner) on predose days (e.g., Day -1); thereafter, the meal schedule will be as follows.

Subjects under fed conditions will be dosed after at least one hour fasted and 15 minutes before a standard reference meal (30% fat), except for Period 1, 190 mg dose fasted, which will be dosed after an overnight fast of at least 6 hours duration, and no food for 2 hours after dosing. Standard reference (30% fat) meals will be provided at no sooner than 15 minutes after dosing, and at appropriate times thereafter. During housing, postdose meal plans will be consistent for all periods.

In Period 3, subjects assigned to a twice-daily dosing regimen may have a standard snack (e.g., granola bar) between 2:00 and 3:00 pm (e.g., if 8:00 am dosing). The study subjects randomized to the thrice-daily dosing schedule may have a snack (e.g., fruit) no sooner than 2 hours after dosing (e.g., between 4:00 and 5:00 pm if 2:00 pm dosing).

Foods and beverages containing alcohol, caffeine, or grapefruit will not be served in the clinic during any study part.

## 13.8. Water Administration

Water/liquid will not be allowed to be consumed (except for study drug administration) in the study facility from 1 hour before dosing until 1 hour post dosing in all study arms; thereafter, subjects can consume water freely.

# 14. STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP).

Interim review of safety and efficacy of TSX-011 for the initial 9 subjects will occur prior to enrolment of the remaining subjects in the study.

The SAP will be prepared by an appropriate vendor, agreed upon with the Sponsor, and finalized before database lock.

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint's definition and/or analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed, if deemed appropriate, and included in the plan.

## 14.1. Sample Size Calculation

The study is a proof-of-concept study with adaptive dosing. The sample size chosen for this study was selected without statistical considerations but has been determined adequate to meet the study objectives.

## 14.2. Analysis Populations

The analysis populations are defined as follows:

- The Safety population is defined as all randomized subjects who received at least one dose of study drug and have at least one post-baseline safety assessment.
- The PK population is defined as all randomized subjects for whom at least one PK parameter of interest can be calculated. In general, on a parameter-by-parameter basis, an individual subject's data may be excluded from analysis if insufficient data are available for that subject to calculate the specific parameter in question.
- The clinical batch population is defined as all enrolled subjects for whom at least one PK parameter can be calculated. This population will be stratified by dosed clinical study drug batch (e.g. first, second batch).

## 14.3. Statistical Analyses

### 14.3.1. Safety Analyses

Safety data including laboratory evaluations, physical examinations, AEs, standard 12-lead ECG parameters, and vital signs assessments will be summarized by treatment group and time point of collection, when appropriate.

Adverse events will be coded using the most recent version of MedDRA. A by-patient AE listing by MedDRA system organ class and by preferred term within system organ class, including verbatim term, dose level, severity, and relationship to treatment, will be provided. This listing will include all AEs and SAEs.

Descriptive statistics (arithmetic mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and maximum) will be calculated for quantitative safety data as well as for the difference from baseline, when appropriate.

Tables summarizing shifts in clinical laboratory results with respect to normal range will be provided, as well as tables summarizing shifts in vital signs and standard 12-lead ECGs with respect to normal and abnormal results.

Concomitant medications will be listed by treatment and coded using the most recent version of the World Health Organization Drug Dictionary.

## 14.4. Pharmacokinetic Analyses

### 14.4.1. Pharmacokinetic Parameters

The following PK parameters will be calculated using both actual and/or BC testosterone, free testosterone, TU, DHTU, and DHT concentrations following dose administration of TSX-011:

| | |
|---|---|
| $AUC_t$: | The area under the concentration versus time curve, from time 0 to the last measurable concentration on or before time t, as calculated by a linear trapezoidal method. |
| BC: | Baseline-corrected T of single-dose data in Period 1. For AUC, this is the total AUC after each dose subtracted from the corresponding total AUC of endogenous testosterone. For estimation of $\lambda z$, $t_{½}$, CL/F, and $V_{ss}/F$, the discrete total endogenous testosterone concentrations are first subtracted from total testosterone concentrations obtained at the same nominal time point after single-dose TSX-011. Differences of zero or less than zero are ignored in this determination. |
| $C_{max}$: | Maximum measured concentration over the time span specified. |
| $C_{avg}$: | Average measured concentration over the time span specified. |
| $C_{min}$: | Minimum measured concentration over the time span specified. |
| $T_{max}$: | Time of the maximum measured concentration. If the maximum value occurs at more than one time point, $T_{max}$ is defined as the first time point with this value. |
| CL/F: | The apparent total body clearance (measured for BC testosterone only). |
| $V_{ss}/F$: | Total steady-state volume of distribution (measured for BC testosterone only). |
| $\lambda z$: | Apparent terminal elimination rate constant calculated from a semi-log plot of the single-dose BC testosterone concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., 3 or more non-zero serum concentrations). |
| $t_{½}$: | Apparent terminal elimination half-life will be calculated as $0.693/\lambda z$ (measured for BC testosterone only). |

$T_{min}$: Time of the minimum measured concentration. If the minimum value occurs at more than one time point, $T_{min}$ is defined as the first time point with this value.

For all study arms, other PK parameters may be calculated and will be appropriately described in the SAP.

### 14.4.2. Method for Baseline-Adjustment of Pharmacokinetic Parameters

An adjustment will be made on every serum testosterone, free testosterone, and DHT concentrations as follows: BC testosterone of single-dose data in Period 1. For AUC this is the total AUC after each dose subtracted from the corresponding total AUC of endogenous testosterone. For estimation of $\lambda z$, $t_{½}$, CL/F, and $V_{ss}/F$, the discreet total endogenous testosterone concentrations are first subtracted from total endogenous testosterone concentrations obtained at the same nominal time point at the baseline PK determined at Period 1. Differences of zero or less than zero are ignored in this determination.

This adjustment is hence subject- and period-specific.

### 14.4.3. Pharmacokinetic Data Analyses

Details of the PK data analyses are specified in the SAP. An overview of the data analysis is provided below.

The PK sample concentrations for all subjects within each dose level and dosing regimen will be summarized for each nominal sample time using min, max, median, mean (SD), and geometric mean (confidence interval [CI]).

Noncompartmental analysis will be performed on serum free testosterone, total testosterone, TU, DHT, and DHTU levels using the actual recorded time of sample withdrawals. The following actual PK parameters for serum testosterone, free testosterone, TU, DHT, and DHTU following single-dose administration of TSX-011 will be calculated: AUC, $C_{max}$, $C_{min}$ (actual testosterone), $T_{max}$, and $T_{min}$. Baseline-corrected values for testosterone, free testosterone, and DHT will also be calculated using the same PK parameters. In addition, BC $\lambda z$ and $t_{½}$ will be collected for testosterone, free testosterone, and DHT. In addition, the fraction of time within the therapeutic window and the fraction of time above the therapeutic threshold will be reported for Period 2, Day 15 and Period 3, Day 30.

Pharmacokinetic parameters from Periods 1, 2, and 3 will be summarized using statistics appropriate for the PK parameter (means, geometric means, frequencies, etc.). Continuous PK parameters will also be summarized using least squares means or least squares geometric means estimated using mixed models statistical analyses.

Dose proportionality of the BC PK parameters: AUCs and $C_{max}$ will be assessed among the once-daily dosing regimens of Period 1 using the CI criteria (Smith et al., 2000).

# 15. STUDY ADMINISTRATION

## 15.1. Basic Principles

This research will be carried out in accordance with the principles enunciated in the Declaration of Helsinki (Seoul 2008), the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996), and the SOPs of clinical sites.

## 15.2. Data Capture

A customized electronic source data capture system will be developed and used. Each electronic source data capture form will be reviewed and approved by the PI. The CRO will ensure complete and accurate entries on the forms.

## 15.3. Study Report

The final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports). The report includes a description of the clinical conduct of the study, analytical methods and results, and the statistical analysis of the PK and safety parameters described in the statistical methodology section of the protocol.

## 15.4. Confidentiality

All members of the PI's staff will sign confidentiality agreements with the CRO. All information provided to the PI dealing with the study and all information obtained during the course of the study will be regarded by CRO as confidential. Subjects will be informed that all study findings will be stored on computers and handled in a strictly confidential way. Subjects will be identified throughout documentation and evaluation by the individual subject number and initials (where appropriate), whereas all subjects' names will be kept secret. The PI must guarantee the privacy of the subjects taking part in the study. Any information concerning the volunteers (clinical notes, identification codes, etc.) must be kept on file by the PI, who will ensure that it is revealed only to the applicable regulatory authorities and to the Sponsor and its designated agent for the purposes of study monitoring, auditing, or official inspections.

## 15.5. Publication Policy

All data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only with the Sponsor's written agreement and in collaboration with participating personnel from the Sponsor.

## 15.6. Procedure for Amendments to Protocol

No deviations from this protocol will be permitted, except in a medical emergency, without the approval of the Sponsor and the institutional review board (IRB). The PI and the Sponsor will discuss any amendment to this study. If an agreement is reached concerning the need for modification, this agreement will be made in a formal

amendment to the protocol. Any protocol amendments must be reviewed by the Sponsor, the PI, applicable regulatory authorities, and the IRB.

The IRB must approve all revisions and/or amendments to the protocol in writing.

## 15.7. Institutional Review Board

This protocol, ICFs, and any amendments to the protocol will be reviewed by the IRB and the study will not start until the committee has approved the protocol or a modification thereof. The committee is constituted and operates in accordance with the principles and requirements described in the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996). Notice that the protocol and informed consent have been reviewed and approved by the IRB and will be in the final study report.

## 15.8. Termination of Study

The Sponsor reserves the right to discontinue this study for administrative reasons at any time. The PI, in collaboration with the Sponsor, reserves the right to discontinue the study for safety reasons at any time.

## 15.9. Study Records

All raw data generated in connection with this study, together with the original copy of the final report, will be retained in the archives of the CRO or designee until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in a ICH region, or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by applicable regulatory requirements or by agreement with the Sponsor. It is the responsibility of the Sponsor to inform the CRO as to when these documents no longer need to be retained.

## 15.10. Quality Assurance/Quality Control

The study will be conducted in compliance with ICH GCP and all local laws and regulations. Standard operating procedures will be adhered to for all activities relevant to the quality of the study. All clinical data will undergo 100% monitoring prior to clinical database lock. Edit checks will then be performed as a validation routine using SAS to check for missing data, data inconsistencies, data ranges, etc. Corrections will be made prior to database lock.

# 16. REFERENCES

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# APPENDIX 1. INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

| | Not at all | Less than 1 time in 5 | Less than half the time | About half the time | More than half the time | Almost always | Score |
|---|---|---|---|---|---|---|---|
| **Incomplete Emptying** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating? | 0 | 1 | 2 | 3 | 4 | 5 | |
| **Frequency** Over the past month, how often have you had to urinate again less than two hours after you finish urinating? | 0 | 1 | 2 | 3 | 4 | 5 | |
| **Intermittency** Over the past month, how often have you found you stopped and started again several times when you urinated? | 0 | 1 | 2 | 3 | 4 | 5 | |
| **Urgency** Over the past month, how difficult have you found it to postpone urination? | 0 | 1 | 2 | 3 | 4 | 5 | |
| **Weak stream** Over the past month, how often have you had a weak urinary stream? | 0 | 1 | 2 | 3 | 4 | 5 | |
| **Straining** Over the past month, how often have you had to push or strain to begin urination? | 0 | 1 | 2 | 3 | 4 | 5 | |
| | | | | | | | |
| | none | 1 time | 2 times | 3 times | 4 times | 5 times or more | Score |
| **Nocturia** Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? | 0 | 1 | 2 | 3 | 4 | 5 | |
| | | | | | | | |
| **Total IPSS Score** | | | | | | | |
| **Quality of life due to urinary symptoms** | Delighted | Pleased | Mostly satisfied | Mixed - about equally satisfied and dissatisfied | Mostly dissatisfied | Unhappy | Terrible |
| If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |

**Total score:** 0 7 mildly symptomatic
8 19 moderately symptomatic
20 35 severely symptomatic

# APPENDIX 2. ADAPTIVE DOSING CRITERIA

Table 10 summarizes the adaptive design and adjustment criteria.

If the total testosterone subject report is delayed past the dose adjustment day, the subject should remain on the existing dose until availability of the new testosterone value.

## *Dose adjustment number 1 (Period 3, Day 16):*

In Period 2, the subjects will receive 380 mg of TSX-011 twice daily (8 am ± 60 minutes and 10 hours after morning dose) under fed conditions for 15 days.

If Period 2 Day 8 (6 hours postdose ± 15 minutes) total testosterone is <350 ng/dL, adjust dose to 570 mg (TU) TSX-011 twice daily.

If Period 2 Day 8 (6 hours postdose ± 15 minutes) total testosterone is ≥350 ng/dL and <500 ng/dL, adjust dose to 443 mg (TU) TSX-011 twice daily.

If Period 2 Day 8 (6 hours postdose ± 15 minutes) total testosterone is 500 to 800 ng/dL, inclusive, maintain 380 mg (TU) TSX-011 twice daily.

If Period 2 Day 8 (6 hours postdose ± 15 minutes) total testosterone is >800 ng/dL, randomize subjects in a 1:1 ratio to receive:

- Schedule A: 317 mg (TU) TSX-011 twice daily OR
- Schedule B: 507 mg (TU) TSX-011 once daily.

Subjects will be stratified during randomization per Japanese/non-Japanese classification. Stratification and randomization will be managed within the electronic data capture system.

If imbalance in randomization occurs, study subjects may be manually assigned to schedule A or B to balance dosing schedule.

## *Dose adjustment number 2 (Day 26):*

If Period 3 Day 19 (6 hours postdose ± 15 minutes) total testosterone is <350 ng/dL, dose adjust subjects to 570 mg TU dosing thrice daily. Dosing times should be (8 am ± 60 minutes, 8 hours post morning dose ± 15 minutes, and 14 hours post morning dose ± 15 minutes):

If Period 3 Day 19 (6 hours postdose ± 15 minutes) total testosterone is ≥350 ng/dL and <500 ng/dL:

a. Dose adjust subjects on once-daily dosing from 507 mg TU daily to 570 mg TU daily.
b. Dose adjust subjects on twice daily dosing as follows:
    - If dose is 570 mg TU twice daily, increase to 633 mg TU twice daily.
    - If dose is 443 mg TU twice daily, increase to 507 mg TU twice daily.
    - If dose is 380 mg TU twice daily, increase to 443 mg TU twice daily.
    - If dose is 317 mg TU twice daily, increase to 380 mg TU twice daily.

If Period 3 Day 19 (6 hours postdose ± 15 minutes) total testosterone is 500 to 800 ng/dL inclusive, continue current dose.

If Period 3 Day 19 (6 hours postdose ± 15 minutes) total testosterone is >800 ng/dL, decrease TSX-011 dose as follows:

a. Dose-adjust subjects on once-daily dosing from 507 mg TU daily to 380 mg TU daily.

b. For the twice-daily dosing group:

- If dose is 570 mg TU twice daily, decrease to 507 mg TU twice daily.
- If dose is 443 mg TU twice daily, decrease to 380 mg TU twice daily.
- If dose is 380 mg TU twice daily, decrease to 317 mg TU twice daily.
- If dose is 317 mg TU twice daily, decrease to 253 mg TU twice daily.

**Table 10: Adaptive Design and Dose Adjustment Criteria**

| **Period 2 - Days 1-15** | | | **Period 2 - Dose Adjustment on Day 16** | | |
|---|---|---|---|---|---|
| **Day 8 T level (ng/dL)** | **Starting Dose** | **Frequency** | **Dose Change** | **New Dose** | **Frequency** |
| <350 | 380 | BID | Increase | 570 | BID |
| 350-499 | 380 | BID | Increase | 443 | BID |
| 500-800 | 380 | BID | No change | 380 | BID |
| >800 | 380 | BID | Decrease (randomization 1:1) | 317 | BID |
| >800 | 380 | BID | Decrease (randomization 1:1) | 507 | QD |
| | | | | | |
| **Period 3 - Day 16-30** | | | **Period 3 - Dose Adjustment on Day 26** | | |
| **Day 19 T level (ng/dL)** | **Starting Dose** | **Frequency** | **Dose Change** | **New Dose** | **Frequency** |
| <350 | all | | Increase | 570 | TID |
| 350-499 | 570 | BID | Increase | 633 | BID |
| 350-499 | 443 | BID | Increase | 507 | BID |
| 350-499 | 380 | BID | Increase | 443 | BID |
| 350-499 | 317 | BID | Increase | 380 | BID |
| 350-499 | 507 | QD | Increase | 570 | QD |
| | | | | | |
| 500-800 | 570 | BID | No change | 570 | BID |
| 500-800 | 443 | BID | No change | 443 | BID |
| 500-800 | 380 | BID | No change | 380 | BID |
| 500-800 | 317 | BID | No change | 317 | BID |
| 500-800 | 507 | QD | No change | 507 | QD |
| | | | | | |
| >800 | 570 | BID | Decrease | 507 | BID |

| | | | | | |
|---|---|---|---|---|---|
| >800 | 443 | BID | Decrease | 380 | BID |
| >800 | 380 | BID | Decrease | 317 | BID |
| >800 | 317 | BID | Decrease | 253 | BID |
| >800 | 507 | QD | Decrease | 380 | QD |

BID = twice-daily; QD = once-daily; TID = thrice-daily

# APPENDIX 3. HYPOGONADAL QUALITY OF LIFE (QOL) QUESTIONNAIRES

## AMS Questionnaire

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

| | Symptoms: | none | mild | moderate | severe | extremely severe |
|---|---|---|---|---|---|---|
| | Score = | 1 | 2 | 3 | 4 | 5 |
| 1. | **Decline in your feeling of general well-being** (general state of health, subjective feeling) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. | **Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. | **Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. | **Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. | **Increased need for sleep, often feeling tired** | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. | **Irritability** (feeling aggressive, easily upset about little things, moody) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. | **Nervousness** (inner tension, restlessness, feeling fidgety) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. | **Anxiety** (feeling panicky) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. | **Physical exhaustion / lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. | **Decrease in muscular strength** (feeling of weakness) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. | **Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. | **Feeling that you have passed your peak** | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13. | **Feeling burnt out, having hit rock-bottom** | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. | **Decrease in beard growth** | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. | **Decrease in ability/frequency to perform sexually** | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16. | **Decrease in the number of morning erections** | ☐ | ☐ | ☐ | ☐ | ☐ |
| 17. | **Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse) | ☐ | ☐ | ☐ | ☐ | ☐ |

**Have you got any other major symptoms?** Yes ☐ No ☐

**If Yes, please describe:** _____

_____

**THANK YOU VERY MUCH FOR YOUR COOPERATION**

**Male Sexual Dysfunction Multinational Survey of the Aging Male (MSAM-7; libido questions only)**

*The next 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.*

**Q22. Over the past 4 weeks, how often have you felt sexual desire?**

*Please tick one box only.*

Almost always or always ☐1
Most times (much more than half the time) ☐2
Sometimes (about half the time) ☐3
A few times (much less than half the time) ☐4
Almost never or never ☐5

**Q23. Over the past 4 weeks, how would you rate your level of sexual desire?**

*Please tick one box only.*

Very high ✓1
High ✓2
Moderate ✓3
Low ✓4
Very low or none at all ✓5

***Division of Endocrinology, Harbor-UCLA Research and Education Institute***

# Psychosexual Daily Questionnaire

(a) Center No.: ☐ (b) Subject No.: ☐ (c) Visit No.: ☐ (d) Day: ☐ (e) Date: ☐

1. Please rate your overall level of sexual desire today by circling the appropriate number below:

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7
none | very low | very high

2. Please rate highest level of enjoyment or pleasure of any sexual activity that you experienced today.
(a) without a partner (e.g., masturbationl sexual fantasies) and/or (b) with a partner (e.g., kissing, intercourse) by circling the appropriate number below.

(a) Without a partner
0 — 1 — 2 — 3 — 4 — 5 — 6 — 7
none | very high enjoyment/pleasure

(b) With a partner
0 — 1 — 2 — 3 — 4 — 5 — 6 — 7
none | very high enjoyment/pleasure

(c) Please indicate if partner is available ☐ yes ☐ no

3. Please rate your mood by writing the number that corresponds to the scale below. For each item 0 indicates that the descriptor is not at all true; 7 indicates that the descriptor is very true for you today.

not at all true 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 very true

(a) Angry? ___ (d) Full of pep/energetic?___ (g) Friendly?_____
(b) Alert? ___ (e) Sad or Blue?_____ (h) Nervous?_____
(c) Irritable?___ (f) Tired? _____ (i) Well/good?_____

4. For all of the items below check yes if you have experienced (or are experiencing) today, otherwise check no.

| | Yes | No | | Yes | No | | Yes | No | |
|---|---|---|---|---|---|---|---|---|---|
| (a) | ☐ | ☐ | sexual daydreams | (e) | ☐ | ☐ | orgasm | (i) | ☐ | ☐ | masturbation |
| (b) | ☐ | ☐ | anticipation of sex | (f) | ☐ | ☐ | flirting (by others toward you) | (j) | ☐ | ☐ | night spontaneous erection |
| (c) | ☐ | ☐ | sexual interactions with partner | (g) | ☐ | ☐ | ejaculation | (k) | ☐ | ☐ | day spontaneous erection |
| (d) | ☐ | ☐ | flirting (by you) | (h) | ☐ | ☐ | intercourse | (l) | ☐ | ☐ | erection in response to sexual activity |

**Answer the following two questions only if you experienced an erection as shown in No. 4. j-l above.**

5. If you experienced an erection today, indicate the % full erection that you experienced by circling the appropriate number below (make a reasonable estimate):

%= 0 10 20 30 40 50 60 70 80 90 100

6. If you experienced an erection today, indicate whether it was maintained for a satisfactory duration by circling the appropriate number below:

not satisfactory 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 very satisfactory

Day is the relative day of the reporting period/week (i.e., 1,2,3,4,5,6, or 7)