CLINICAL TRIAL PROTOCOL

IND NUMBER: 126605

Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number: G201002

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Version of Protocol:	4.0
Date of Protocol:	10 April 2018

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number G201002

Protocol Date 10 April 2018

Protocol accepted and approved by:

Vice President, Clinical Development

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Signature

4/11/18
Date

Protocol Approval – Lead Statistician

Study Title Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number G201002

Protocol Date 10 April 2018

Protocol accepted and approved by:

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Protocol Approval – Principal Investigator

Study Title Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number G201002

Protocol Date 10 April 2018

Protocol accepted and approved by:

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4/11/18
Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence" and the accompanying investigator's brochure, version 16, dated 01 Aug 2017.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 4.0, dated 10 April 2018, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with GTx, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

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

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from GTx, Inc.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

Statement of Compliance

This study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- International Council for Harmonization (ICH) E6; 62 Federal Register 25691 (May 9, 1997)

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PROTOCOL SYNOPSIS

Protocol Number:	G201002
Name of Investigational Product:	Enobosarm (GTx-024)
Title of Study:	Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women with Stress Urinary Incontinence
Sponsor:	GTx, Inc.
Phase of Development:	Phase 2
Trial Site(s):	Approximately 70 (US)
Indication:	Stress Urinary Incontinence
Rationale:	GTx-024 is an orally bioavailable and tissue-selective nonsteroidal selective androgen receptor modulator (SARM) that has demonstrated androgenic and anabolic activity and is currently being evaluated as a potential treatment for stress urinary incontinence (SUI) in postmenopausal women. Urinary incontinence and pelvic floor disorders are major health problems for women, especially as they age. Pelvic floor muscle relaxation has been found to correlate with lower urinary tract symptoms including SUI. Muscles of the pelvic floor and lower urinary tract are crucial for supporting the pelvic organs and micturition; however, damage to the muscles or lack of hormonal stimulation are thought to contribute to pelvic organ prolapse and urinary incontinence. Although anabolic steroids may increase muscle mass and strength, lack of oral bioavailability and known potential risks have limited their use. Nonsteroidal SARMs have potential to achieve benefits of anabolic steroid therapy (improved muscle mass, cholesterol/triglyceride levels, glucose metabolism, and bone density) with fewer adverse effects, such as hirsutism and acne, in women. Both nonclinical and clinical data suggest that SARMs may provide a new therapeutic option for pelvic floor and lower urinary tract disorders, as both testosterone and its more potent metabolite, dihydrotestosterone, have anabolic effects on muscle. GTx-024 has demonstrated androgenic and anabolic activity in male and female rat models. GTx-024 has consistently been observed to increase body weight,

	specifically muscle, in female rats. In a male rat model with castrate levels of serum testosterone, GTx-024 has the ability to induce hypertrophy of the levator ani muscle to approximately 120% of a noncastrate male. Another SARM (GSK2849466A), studied in an ovariectomized rat model that mimics SUI by disrupting urethral continence, was shown to increase urethral baseline pressure and the amplitude of urethral responses during sneezing by 64% and 74%, respectively, compared to the vehicle control (Kadekawa et al, AUA Annual Meeting 2015, New Orleans, LA. PD27-11). Furthermore, all of the rats (8/8) in the vehicle-treated group experienced fluid leakage during sneezing whereas only 1 of the rats (1/8) in the SARM-treated group experienced such leakage upon similar challenge. Histologically, the SARM-treated animals had a reversal of the atrophy in urethral muscle observed in the control group. This preliminary in vivo study supports the clinical study of SARMs for the treatment of SUI. A proof-of-concept clinical study is currently ongoing to investigate the effect of GTx-024 on symptoms of SUI in postmenopausal women. Available data from the 18 subjects dosed at 3 mg GTx-024/day for 12 weeks showed a mean reduction in stress incontinence episodes of 81%, with all 18 subjects seeing a clinically significant reduction ($\geq$ 50% reduction in stress leaks) in the number of stress incontinence episodes by Week 12.
Objectives:	**<u>Primary Objective - Efficacy</u>** The primary efficacy objective of this study is to compare the efficacy of GTx-024 (1 mg and 3 mg administered once daily) to that of placebo by evaluating the mean number of subject-reported stress incontinence episodes per day. The primary efficacy endpoint is a responder analysis, where a responder is defined as having a $\geq$ 50% reduction at the end of treatment (Week 12) compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary. Subjects who have missing diary data for the Week 12 visit will be counted as non-responders for this analysis. **<u>Secondary Objectives - Efficacy</u>** The secondary efficacy objectives in this study are to compare, at each visit during the treatment period, the efficacy compared to baseline of 2 doses of GTx-024 (1 mg and 3 mg administered once daily) to that of placebo in relation to the following: • Responder rate, where a responder is defined as

	having a ≥ 50% reduction compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary • Change in the number of stress incontinence episodes per day as measured by the 3-day voiding diary • Change in the total number of voids per day as measured by the 3-day voiding diary • Change in 24-hour pad weight as measured by the 24-hour pad weight test • Change in the Bladder Stress Test (BST) (at Week 12 only) • Change in subject-reported impression of SUI severity as measured by the Patient Global Impression of Severity scale (PGI-S) • Change in subject-reported impression of SUI improvement as measured by the Patient Global Impression of Improvement scale (PGI-I) • Change in subject-reported urogenital distress as measured by the Urinary Distress Inventory questionnaire (UDI-6) • Change in subject-reported impact of urinary incontinence on daily life as measured by the Incontinence Impact Questionnaire (IIQ-7) Short Form • Change in subject-reported impact of urinary incontinence on daily life as measured by the Incontinence Quality of Life questionnaire (I-QOL) • Change in subject-reported sexual function as measured by the Female Sexual Function Index questionnaire (FSFI) • Change in subject-reported assessment of fecal incontinence as measured by the Vaizey Incontinence Severity Score • Change in subject-reported stress incontinence, urge incontinence, and mixed incontinence as measured by the Medical, Epidemiological, and Social Aspects of Aging (MESA) incontinence questionnaire (Week 12 only) **Exploratory Objectives - Efficacy** The exploratory efficacy objectives of this study are to assess the durability of the effect of treatment at Week 16, Week 20, and Week 28 in relation to the following:

	• Responder rate, where a responder is defined as having a ≥ 50% reduction compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary • Number of stress incontinence episodes per day as measured by the 3-day voiding diary • Total number of voids per day as measured by the 3-day voiding diary • Change in 24-hour pad weight as measured by the 24-hour pad weight test • Subject-reported impression of SUI severity as measured by the PGI-S • Subject-reported impression of SUI improvement as measured by the PGI-I • Subject-reported urogenital distress as measured by the UDI-6 • Subject-reported impact of urinary incontinence on daily life as measured by the IIQ-7 Short Form • Subject-reported impact of urinary incontinence on daily life as measured by the I-QOL • Subject-reported sexual function as measured by the FSFI • Subject-reported assessment of fecal incontinence as measured by the Vaizey Incontinence Severity Score. Additional sensitivity analyses may be included in exploratory analyses. **Secondary Objectives - Safety** The safety objectives of this study are to determine the safety and tolerability of 2 doses of GTx-024 (1 mg and 3 mg administered once daily) compared to that of placebo therapy. Safety and tolerability will be assessed in relation to the following: • Incidence of adverse events (AEs) • Change from baseline in clinical laboratory evaluations • Change from baseline in sex hormone binding globulin (SHBG) and testosterone • Change from baseline in vital sign measurements • Change from baseline in endometrial stripe thickness as assessed by transvaginal ultrasound (only in subjects with an intact uterus)

Subject Population:	Inclusion Criteria Each subject must meet all of the following criteria to be enrolled in this study: 1. Able to read, understand, and provide written, dated, informed consent prior to screening, and be likely to comply with the study protocol and communicate with study personnel about AEs and other clinically important information 2. Female, 18 to 80 years of age, inclusive, at screening 3. Subjects must have undergone spontaneous, medically induced, or surgical menopause prior to the start of this study. Postmenopausal subjects are defined as those subjects who meet one of the following criteria: a) greater than or equal to 12 months of spontaneous amenorrhea, or; b) at least 6 months of spontaneous amenorrhea with serum follicle stimulating hormone levels > 40 mIU/ml, or; c) at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, or; d) subjects 60 years of age or older with previous hysterectomy without an oophorectomy with serum follicle stimulating hormone levels > 30 mIU/ml, or; e) subjects less than 60 years of age with previous hysterectomy without an oophorectomy with serum follicle stimulating hormone levels > 40 mIU/ml. 4. SUI symptoms of at least 6 months duration 5. Predominant SUI as determined at the Screening Visit using the MESA incontinence questionnaire. 6. 24-Hour pad weight > 3 g during the screening period 7. A minimum of 1 and no more than 15 SUI episodes on any single day AND no fewer than 9 total SUI episodes over 3 days as reported in the 3-day voiding diary, determined during the screening period 8. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels < 1.5 times the

upper limit of normal at the Screening Visit (Note: laboratory values falling outside of prespecified ranges may be retested once at the discretion of the investigator. Results of the retest must be within prespecified ranges and must be available prior to the baseline visit)

9. Positive bladder stress test conducted during the Screening Visit
10. Subject agrees not to start any new treatment (medication or otherwise) during the treatment and follow-up periods, including vaginal rejuvenation, that is known or suspected to affect lower urinary tract function.
11. Subject agrees to discontinue use of bladder support devices, including but not limited to vaginal pessary, during the screening, treatment, and follow-up periods.
12. Subject agrees to maintain a stable dose of any medication known to affect lower urinary tract function, including but not limited to anticholinergics, tricyclic antidepressants, beta-3 adrenergic agonist, or α-adrenergic blockers, throughout the treatment and follow-up periods.
13. During screening, subject must provide evidence of having received a mammogram examination within the 6 months prior to screening, or she must agree to receive a mammogram examination during screening.

<u>Exclusion Criteria</u>

A subject meeting any of the following criteria will be excluded from the study:

1. Pelvic floor physical therapy, including muscle training and/or electrostimulation, in a clinical setting within 30 days prior to screening
2. History of pelvic radiation treatment
3. History of urethral diverticula
4. History of surgery for incontinence, including urethral sling, anterior prolapse repair, intra-detrusor botulinum toxin injection, sacral nerve stimulation, and percutaneous tibial nerve stimulation
5. Treatment with urethral bulking agents within the 6 months prior to the Screening Visit

	6. Known vesicoureteral reflux, vaginal prolapse beyond the introitus, or other significant pelvic floor abnormalities that, in the investigator's opinion, may impact the subject's response 7. Vaginal rejuvenation treatment, including laser treatments and radiofrequency therapy, within the 6 months prior to the Screening Visit 8. Subject has urinary incontinence of neurogenic etiology 9. Subject is morbidly obese (defined as body mass index 40 or greater) 10. Chronic hepatitis (i.e., inflammation of the liver that has been ongoing for at least 6 months) 11. Hepatic cirrhosis due to, for example, sustained excessive alcohol consumption, hepatitis B virus, hepatitis C virus, or fatty liver disease 12. Evidence of active infection with hepatitis B or hepatitis C as determined by serology 13. History of human immunodeficiency virus (HIV) infection 14. Subject is currently taking systemic sex-hormone products (excludes intravaginal application of estradiol topical/tablet agents and hormones delivered via vaginal rings). The following washout periods are required if systemic hormonal products are discontinued prior to screening: a) minimum of 4 weeks for prior transdermal products or products with systemic absorption applied topically; b) minimum of 8 weeks for prior oral products; c) minimum of 8 weeks for prior intrauterine products, and; d) minimum of 3 months for prior hormonal implants or injectable drug therapy. 15. Subject has current cancer diagnosis (with the exception of non-melanoma skin cancer) or any history of breast or endometrial cancer 16. Known history or current episode of: • New York Heart Association ≥ Stage 2 hypertension (systolic blood pressure [BP] > 160 mmHg or diastolic BP > 100 mmHg) at screening and/or baseline. Subjects with hypertension that has been treated and

	controlled with medication for at least 2 weeks prior to screening are eligible for participation • Recent myocardial infarction or arterial or venous thromboembolic event (within 1 year) or a history of more than 1 myocardial infarction or arterial or venous thromboembolic event • Cardiac-related syncopal event within the past year • Cardio or cerebral vascular disease requiring surgical intervention (e.g., bypass surgery, angioplasty). For subjects with previous stent placement, please contact the medical monitor • Congestive heart failure (CHF) New York Heart Association Criteria > Stage 2 • Angina pectoris • QT Fridericia-corrected ≥ 450 msec at screening (If QTcF is above this range, a repeat ECG can be done at the discretion of the investigator, and if the value is in range, the patient may be enrolled in the study.) 17. For subjects with an intact uterus, > 5 mm endometrial stripe thickness as measured at screening by transvaginal ultrasound 18. Clinically confirmed urinary tract infection, requiring treatment as determined by the investigator, at the Screening Visit 19. Current or past history of any physical condition that, in the investigator's opinion, might put the subject at risk, impact the absorption of the study drug, or interfere with study results interpretation.
Study Design	This is a double-blind, placebo-controlled, parallel design, randomized, multicenter, Phase 2 study. The study consists of the following periods: screening period, treatment period, follow-up period, and durability period. **Screening Period (4 Weeks)** Potential subjects will be evaluated during a screening period lasting no more than 4 weeks. After written informed consent is obtained, Screening Visit procedures will be performed as specified in the schedule of events for the study.

	Treatment Period (12 Weeks) At Baseline (Visit 1, Week 0), subjects who continue to meet all eligibility criteria will be randomly assigned to one of the three treatment arms in a 1:1:1 ratio for a 12-week, double-blind treatment period. Subjects will be assigned to one of the following treatment groups: 1 mg GTx-024, 3 mg GTx-024, or matching placebo. Randomized subjects will take their first dose of study drug during the Baseline visit. Following the Baseline visit, subjects will attend the clinic at Weeks 4, 8, and 12 during the treatment period. At each clinic visit, study procedures will be performed as specified in the schedule of events for the study. All unused study drug will be collected at Week 12 (Visit 5), the end of the treatment period. **Follow-up Period (4 Weeks) and Durability Period (16 Weeks)** Upon completion of Week 12 (Visit 5), all subjects will enter either a 4-week Follow-up Period or a 16-week Durability Period. The first 225 randomized subjects only will enter the 16-week Durability Period of the study. Visit 5, 12 weeks after the start of treatment, is the baseline for the 16-week durability period, during which time no study drug will be administered. During the durability period, there will be clinic visits at Week 16, Week 20, and Week 28. At each visit, study procedures will be performed as specified in the schedule of events for the study. Data from the follow-up period will be used to assess the durability of the effect of GTx-024. All other randomized subjects will complete a 4-week Follow-up Period following Week 12 (Visit 5) during which time no study drug will be administered. The Follow-up Period includes a clinic visit at Week 16 where study procedures will be performed as specified in the schedule of events for the study. **Extension Studies** Two extension studies are planned and will be conducted under separate protocols. Subjects who complete the 16-week Durability Period will be offered the opportunity to enter into a 20-week durability extension study under a separate protocol. Data from this extension study will be used to further assess the durability of effect of GTx-024. No study drug will be administered during this durability extension study.

	Subjects who complete the required treatment period and durability or follow-up periods of this study may be offered the opportunity to enter into an open-label extension study under a separate protocol. Subjects will receive study drug during this open-label extension study.
Estimated Study Duration:	Subject completion is defined as completing all phases of the study: through follow-up (Week 28) for the first 225 randomized subjects and through follow-up (Week 16) for all other randomized subjects. The maximum duration of each subject's participation will be ≤ 32 weeks.
Efficacy Assessments:	The following assessments will be conducted to evaluate efficacy: • 3-Day Voiding Diary The 3-day voiding diary is a study tool for subjects to report each episode of urinary void. The subject will be asked to record each episode of urinary leakage, the type (stress or urge) of leakage, and the severity of leakage. Subjects will also be asked to record each episode of voluntary urinary void and fluid intake. • Bladder Stress Test The Bladder Stress Test (BST) is used to confirm stress incontinence by simulating the accidental release of urine when a patient coughs, sneezes, laughs, or exercises. • PGI-S The PGI-S is a global rating of subject-reported impression of severity using a 4-point scale. Validity of the PGI-S has been established for application in SUI. • PGI-I The PGI-I is a global rating of subject-reported impression of improvement using a 7-point scale. Validity of the PGI-I has been established for application in SUI. • UDI-6 and IIQ-7 The UDI-6 and IIQ-7 are validated subject questionnaires used to assess symptom distress and the impact of urinary incontinence on daily life. • I-QOL The I-QOL is a validated subject questionnaire used to assess the impact of urinary incontinence and treatments. • FSFI The FSFI is a self-administered questionnaire to

	assess overall sexual experience that consists of 19 questions that are scored from 0 to 5. The scale contains 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI total score is a weighted average of the 6 domains with each contributing a maximum of 6 points to the total (maximum score of 36). • Vaizey Incontinence Severity Score The Vaizey Incontinence Severity Score is a self-administered questionnaire to assess a subject's bowel symptoms and the impact of these symptoms on daily life. • 24-hour Pad Weight Test The 24-hour pad weight test is a quantitative test intended to provide information on the severity of incontinence. The amount of urine leaked over the 24 hours of testing is quantified by measuring the change in weight of perineal pads used during testing. • MESA The MESA incontinence questionnaire consists of 15 items divided into stress incontinence (9 items) and urge incontinence (6 items) subscales. Based on their responses, subjects can be characterized as having predominant stress incontinence, urge incontinence, or mixed incontinence (Herzog and Fultz 1990).
Safety Assessments:	Safety assessments will include: • Adverse events • Clinical laboratory analyses • Levels of SHBG and testosterone • Endometrial stripe thickness as assessed by transvaginal ultrasound (only for subjects with an intact uterus) Other standard safety assessments will include vital sign, height, and weight measurements, concomitant medications, medical history, and physical examination findings.
Study Drug:	Study drug will be provided as softgel capsules in blister packaging, labeled and designed to protect study blinding. Subjects will be randomized to one of three dosing groups: 1 mg GTx-024, 3 mg GTx-024, or matching placebo. All subjects will take 2 softgel capsules orally, once daily.

Sample Size Calculation:	The sample size calculation was performed using PASS v12.0.1 for binary outcomes. The sample size calculation was performed for a binary response (i.e., a responder is defined as having a ≥ 50% reduction at the end of treatment compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary). The assumptions were a 60% active treatment response and 40% placebo response. The overall discontinuation rate was anticipated to be approximately 25%. Given these assumptions, a randomized sample size of approximately 400 subjects (randomized in a 1:1:1 ratio for placebo, 1 mg GTx-024, 3 mg GTx-024, respectively) will have 80% power to detect a treatment difference of 20%. A 2-sided hypothesis test with 5% significance is used for each pairwise comparison between GTx-024 and placebo (i.e., alternatively using a 1-sided significance level of 2.5%).

Analysis Sets:	Data analysis will be performed on a full analysis set (FAS), a per protocol set (PPS), an intent-to-treat (ITT) set, a durability set (DS), and a safety analysis (SA) set. The FAS is used for the primary analysis. The FAS consists of all randomized subjects who receive at least 1 dose of study drug and have at least 1 post baseline primary efficacy assessment (3-day voiding diary). All analyses using the FAS will group participants according to randomized treatment. The PPS is used for a supportive analysis and will also be defined as all subjects included in the FAS who do not have any significant protocol deviations. All analyses using the PPS will group subjects according to treatment actually received. The ITT set consists of all randomized subjects who receive at least 1 dose of study drug. All analyses using the ITT set will group subjects according to randomized treatment. Subjects who do not have any postbaseline assessments will be treated as non-responders for ITT analyses. The DS is used for exploratory analyses to assess the durability of the effect of treatment and will be defined as the first 225 randomized subjects who complete a Week 12 final visit and at least one assessment during the Durability period. The SA set contains all subjects randomized in the study who receive at least 1 dose of study drug. All efficacy analyses performed on the FAS will be repeated on the PPS and the ITT set.
Methods of Analysis:	Before unblinding, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for all endpoints. In general, summary statistics (n, mean, standard deviation, median, minimum and maximum values for continuous variables, and number [%] of subjects in each category for categorical variable) will be provided by treatment group and visit. Source data for summary tables and statistical analyses will be presented as subject data listings. All statistical analyses will be performed using SAS (v9.4 or higher). Unless stated otherwise, all statistical tests will be 2-sided using a 5% significance level, leading to 95% (2-sided) confidence intervals. No adjustment will be made for multiplicity due to 2 dose levels of GTx-024 being compared with placebo. The trial is not powered to show a statistical difference between the 2 dose arms of GTx-024.

	The primary efficacy period is defined as baseline (Day 0) through Week 12. Change from baseline and determination of responder rate status will be between baseline and visits through Week 12. The durability period is defined as Week 12 to Week 16, Week 20, and/or Week 28. **Analysis of the Primary Efficacy Endpoint** The primary analysis will be conducted on the primary endpoint using the FAS. The primary efficacy endpoint (i.e., a binary response indicator where a responder is defined as having a ≥ 50% reduction at the end of treatment compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary) will be evaluated using a logistic regression model. The logistic regression model will include treatment group as a covariate. The odds ratio of response between each dose level of GTx-024 and placebo (together with the corresponding 95% confidence interval) will be reported. The null hypothesis is that there is no treatment effect for either dose level of GTx-024. This will be tested against the alternative hypothesis that there is a treatment effect for at least 1 of the dose levels of GTx-024. The corresponding *P*-value for the comparison between each dose level of GTx-024 and placebo will be derived using the standard normal distribution. Subjects who have missing values at these visits will be counted as non-responders for this analysis. Sensitivity analyses will be specified in the SAP. **Analysis of Secondary Efficacy Endpoints** For binary secondary endpoints (responders), the treatment effect will be estimated using a logistic regression model with treatment as a covariate. For continuous secondary endpoints, treatment effects will be estimated using a mixed model repeated measures analysis (MMRM). The MMRM model will specify an unstructured variance/covariance matrix and will include treatment group, visit, and baseline as covariates. For ordinal endpoints, treatment effects will be estimated using a proportional odds model. Further details on the analysis of secondary efficacy endpoints will be provided in the SAP. **Analysis of Exploratory Efficacy Endpoints** Durability of treatment effect will be examined in the DS for the exploratory efficacy endpoints. Additional sensitivity analyses of exploratory and secondary efficacy

	endpoints may also be conducted as exploratory analyses, including sensitivity analyses with regard to missing data. Further details of the exploratory analyses will be provided in the SAP. **Safety Analyses** All safety parameters (including AEs, vital signs, laboratory evaluations, SHBG, testosterone, and endometrial stripe thickness) will be summarized using the SA set. No formal hypothesis testing will be performed. All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent AEs (TEAEs) will be summarized and presented in the listings by the number of subjects reporting an event, the percentage of subjects with that event, the number of events, and the grade, duration, and relationship to treatment. Percentages will be based on the number of subjects who received each treatment during the study. Clinical laboratory safety tests will be performed, and normal ranges will be provided for each lab test. Values outside the normal range will be assessed for clinical significance by the investigator. Shift tables (change from baseline value to on-treatment values) will be presented for each laboratory measurement and assessment time. Each parameter outside the normal range will be designated as high (H) or low (L) in the individual data listings.

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BST	bladder stress test
CFR	Code of Federal Regulations
DS	durability set
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	US Food and Drug Administration
FSFI	Female Sexual Function Index questionnaire
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IIQ-7	Incontinence Impact Questionnaire
INR	international normalized ratio
I-QOL	Incontinence Quality of Life questionnaire
IRB	institutional review board
ITT	intent to treat
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MESA	Medical, Epidemiological, and Social Aspects of Aging
OTC	over-the-counter
PGI-I	Patient Global Impression of Improvement Scale
PGI-S	Patient Global Impression of Severity Scale
PPS	per protocol set
SAE	serious adverse event
SARMS	selective androgen receptor modulators
SA	safety analysis
SHBG	sex hormone binding globulin

Abbreviation	Definition
SUI	stress urinary incontinence
TEAE	treatment-emergent adverse event
UDI-6	Urinary Distress Inventory Questionnaire
ULN	Upper Limit of Normal

1 Introduction

1.1 Background and Rationale

Enobosarm (GTx-024) is an orally bioavailable and tissue-selective nonsteroidal selective androgen receptor modulator (SARM) that has demonstrated androgenic and anabolic activity and is currently being evaluated as a potential treatment for stress urinary incontinence (SUI) in postmenopausal women.

Urinary incontinence and pelvic floor disorders are major health problems for women, especially as they age (Luber 2004). Pelvic floor muscle relaxation has been found to correlate with lower urinary tract symptoms including SUI. Muscles of the pelvic floor and lower urinary tract are crucial for supporting the pelvic organs and micturition; however, damage to the muscles and/or lack of hormonal stimulation are thought to contribute to pelvic organ prolapse and urinary incontinence.

Although anabolic steroids may increase muscle mass and strength, lack of oral bioavailability and known potential risks have limited their use (Mohler et al 2009). Nonsteroidal SARMs have potential to achieve benefits of anabolic steroid therapy (improved muscle mass, cholesterol/triglyceride levels, glucose metabolism, and bone density) with fewer adverse effects, such as hirsutism and acne, in women.

Both nonclinical and clinical data suggest that SARMs may provide a new therapeutic option for pelvic floor and lower urinary tract disorders, as both testosterone and its more potent metabolite, dihydrotestosterone, have anabolic effects on muscle.

GTx-024 has demonstrated androgenic and anabolic activity in male and female rat models. GTx-024 has consistently been observed to increase body weight, specifically muscle, in female rats. In a male rat model with castrate levels of serum testosterone, GTx-024 has the ability to induce hypertrophy of the levator ani muscle to approximately 120% of a noncastrate male.

Another SARM (GSK2849466A), studied in an ovariectomized rat model that mimics SUI by disrupting urethral continence, was shown to increase urethral baseline pressure and the amplitude of urethral responses during sneezing by 64% and 74%, respectively, compared to the vehicle control (GTx, Inc. 2017; Kadekawa et al 2015). Furthermore, all of the rats (8/8) in the vehicle-treated group experienced fluid leakage during sneezing whereas only 1 of the

rats (1/8) in the SARM-treated group experienced such leakage upon similar challenge. Histologically, the SARM-treated animals had a reversal of the atrophy in urethral muscle observed in the control group. This preliminary in vivo study supports the clinical study of SARMs for the treatment of SUI.

A proof-of-concept study is currently ongoing to investigate the effect of GTx-024 on symptoms of SUI in postmenopausal women. Available data from the 18 subjects dosed at 3 mg GTx-024/day for 12 weeks showed a mean reduction in stress incontinence episodes of 81%, with all 18 subjects seeing a clinically significant reduction ($\geq$ 50% reduction in stress leaks) in the number of stress incontinence episodes by Week 12.

2 Study Objectives

2.1 Primary Objective

The primary efficacy objective of this study is to compare the efficacy of GTx-024 (1 mg and 3 mg administered once daily) to that of placebo by evaluating the mean number of subject-reported stress incontinence episodes per day through a responder analysis, where a responder is defined as having a ≥ 50% reduction at the end of treatment (Week 12) compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary. Subjects who have missing diary data for the Week 12 visit will be counted as non-responders for this analysis.

2.2 Secondary Objectives

The secondary efficacy objectives in this study are to compare, at each visit during the treatment period, the efficacy compared to baseline of two doses of GTx-024 (1 mg and 3 mg administered once daily) to that of placebo in relation to the following:

- Responder rate, where a responder is defined as having a ≥ 50% reduction compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary
- Change in the number of stress incontinence episodes per day as measured by the 3-day voiding diary
- Change in the total number of voids per day as measured by the 3-day voiding diary
- Change in 24-hour pad weight as measured by the 24-hour pad weight test
- Change in the Bladder Stress Test (BST) (at Week 12 only)
- Change in subject-reported impression of SUI severity as measured by the Patient Global Impression of Severity scale (PGI-S)
- Change in subject-reported impression of SUI improvement as measured by the Patient Global Impression of Improvement scale (PGI-I)
- Change in subject-reported urogenital distress as measured by the Urinary Distress Inventory questionnaire (UDI-6)

- Change in subject-reported impact of urinary incontinence on daily life as measured by the Incontinence Impact Questionnaire (IIQ-7) Short Form
- Change in subject-reported impact of urinary incontinence on daily life as measured by the Incontinence Quality of Life questionnaire (I-QOL)
- Change in subject-reported sexual function as measured by the Female Sexual Function Index questionnaire (FSFI)
- Change in subject-reported assessment of fecal incontinence as measured by the Vaizey Incontinence Severity Score
- Change in subject-reported stress incontinence, urge incontinence, and mixed incontinence as measured by the Medical, Epidemiological, and Social Aspects of Aging (MESA) incontinence questionnaire (Week 12 only)

2.3 Exploratory Efficacy Objectives

The exploratory efficacy objectives of this study are to assess the durability of the effect of treatment at Week 16, Week 20, and Week 28 in the first 225 randomized subjects in relation to the following:

- Responder rate, where a responder is defined as having a ≥ 50% reduction compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary
- Number of stress incontinence episodes per day as measured by the 3-day voiding diary
- Total number of voids per day as measured by the 3-day voiding diary
- Change in 24-hour pad weight as measured by the 24-hour pad weight test
- Subject-reported impression of SUI severity as measured by the PGI-S
- Subject-reported impression of SUI improvement as measured by the PGI-I
- Subject-reported urogenital distress as measured by the UDI-6
- Subject-reported impact of urinary incontinence on daily life as measured by the IIQ-7 Short Form

- Subject-reported impact of urinary incontinence on daily life as measured by the I-QOL
- Subject-reported sexual function as measured by the FSFI
- Subject-reported assessment if fecal incontinence as measured by the Vaizey Incontinence Severity Score

Additional sensitivity analyses may be included in exploratory analyses.

2.4 Safety Objectives

The safety objectives of this study are to determine the safety and tolerability of 2 doses of GTx-024 (1 mg and 3 mg administered once daily) compared to that of placebo therapy. Safety and tolerability will be assessed in relation to the following:

- Incidence of adverse events (AEs)
- Change from baseline in clinical laboratory evaluations
- Change from baseline in sex hormone binding globulin (SHBG) and testosterone
- Change from baseline in vital sign measurements
- Change from baseline in endometrial stripe thickness as assessed by transvaginal ultrasound (in subjects with an intact uterus)

3 Investigational Plan

3.1 Study Design

This is a double-blind, placebo-controlled, parallel design, randomized, multicenter, Phase 2 study to assess the clinical activity and safety of GTx-024 in postmenopausal women with SUI. The study consists of the following periods: screening period, treatment period, follow-up period, and durability period.

Screening Period (4 Weeks)

Potential subjects will be evaluated during a screening period lasting no more than 4 weeks. After written informed consent is obtained, Screening Visit procedures will be performed as specified in the schedule of events (Table 12–1).

Treatment Period (12 Weeks)

At Baseline (Visit 1, Week 0), subjects who continue to meet all eligibility criteria will be randomly assigned to one of the three treatment arms in a 1:1:1 ratio for a 12-week, double-blind treatment period. Subjects will be assigned to one of the following treatment groups: 1 mg GTx-024, 3 mg GTx-024, or matching placebo.

Enrolled subjects will take their first dose of study drug during the Baseline visit.

Following the Baseline visit, subjects will have a phone call follow up at Week 1 and attend the clinic at Weeks 4, 8, and 12 during the treatment period. At each clinic visit, study procedures will be performed as specified in the schedule of events (Table 12–1). All unused study drug will be collected at Week 12 (Visit 5), the end of the treatment period.

Follow-up Period (4 Weeks) and Durability Period (16 Weeks)

Upon completion of Week 12 (Visit 5), all subjects will enter either a 4-week Follow-up Period or a 16-week Durability Period.

The first 225 randomized subjects only will enter the Durability Period of the study. Visit 5, 12 weeks after the start of treatment, is the baseline for the 16-week durability period, during which time no study drug will be administered. During the Durability period, there will be clinic visits at Week 16, Week 20, and Week 28. At each visit, study procedures will be

performed as specified in the schedule of events (Table 12–1). Data from the follow-up period will be used to assess the durability of the effect of GTx-024.

All other randomized subjects (those not included in the first 225) will complete a 4-week follow-up period following Week 12 (Visit 5) during which time no study drug will be administered. The follow-up period includes a clinic visit at Week 16 where study procedures will be performed as specified in the schedule of events (Table 12–1).

Subject completion is defined as completing all phases of the study through durability (Week 28) for the first 225 randomized subjects and through follow-up (Week 16) for all other randomized subjects. The maximum duration of each subject's participation will be ≤ 32 weeks.

Extension Studies

Two extension studies are planned and will be conducted under separate protocols.

Subjects who complete the 16-week Durability Period will be offered the opportunity to enter into a 20-week durability extension study under a separate protocol. Data from this extension study will be used to further asses the durability of effect of GTx-024. No study drug will be administered during this durability extension study.

Subjects who complete the required treatment period and durability or follow-up periods of this study may be offered the opportunity to enter into an open-label extension study under a separate protocol. Subjects will receive study drug during this open-label extension study.

3.1.1 Rationale of Study Design

A double-blind, placebo-controlled, parallel design study with a 12-week duration of treatment has demonstrated the efficacy of duloxetine for the treatment of North American women with SUI, using data from a voiding diary as the primary outcome variable (Norton et al 2002, Dmochowski et al 2003).

In prior clinical studies, GTx-024 has been generally well tolerated, including single doses up to 100 mg and multiple doses up to 30 mg once daily for up to 14 days. In longer studies, GTx-024 has also been generally well tolerated at 1, 3, and 9 mg daily doses for up to 833 days (GTx, Inc. 2017). The selection of the 3 mg GTx-024 maximum daily dose in this

study was informed by early data from a proof-of-concept study of 3 mg GTx-024 per day for 12 weeks in subjects with SUI, wherein all 18 subjects a clinically meaningful (≥ 50% reduction in stress leaks) decrease in the frequency of SUI episodes by 12 weeks of treatment.

A 16-week durability period for a subset of subjects is included in the study design to assess the durability of effect after cessation of treatment.

3.1.1.1 Risk Mitigation

This study has been designed to mitigate known risks associated with the use of GTx-024. Clinical study G200501 observed the effects of administering doses of 0.1, 0.3, 1, and 3 mg of GTx-024 (or placebo) for 86 days to healthy subjects: postmenopausal women and elderly men. A dose-dependent increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase was observed. A higher incidence of transient, asymptomatic increases in ALT reported as adverse events occurred in the group receiving 3 mg GTx-024 (20.8%) compared to placebo (0%). One subject receiving 3 mg per day of GTx-024 was discontinued for an ALT level > 3 times the upper limit of normal. The ALT levels returned to normal with continued exposure to GTx-024 in most cases and, further, in instances when dosing was not continued, levels returned to normal. No significant increases in total bilirubin, gamma glutamyl transferase, alkaline phosphatase, or lactate dehydrogenase have been observed in subjects with elevated ALT levels. Consistent with the effects of other orally administered anabolic agents, GTx-024 causes a dose dependent reduction in high-density lipoprotein (HDL), the clinical significance of which is unknown at this time. The proposed mechanism for reduction in HDL is due to stimulation of reverse cholesterol transport and increased HDL catabolism by hepatic lipase. Reductions in HDL are temporary and typically return to baseline 12 months after treatment initiation.

In an ongoing Phase 2 study of GTx-024 in ER+/AR+ breast cancer examining daily doses of GTx-024 at 9 mg and 18 mg, several cases of clinically significant hypercalcemia have been observed that were assessed by the investigators as possibly related to GTx-024. Patients with hypercalcemia had ER+ breast cancer with bone metastases. Hypercalcemia has not been observed in previous studies of healthy individuals or at doses less than 9 mg.

Subjects will be monitored at each visit for health changes since the previous visit and adverse effects of treatment. Since elevations of ALT have been observed in prior studies,

serum ALT and other liver function analytes will be monitored at each visit during treatment (Table 12–1). Stopping rules have been included for severe elevations of LFTs or other signs of hepatotoxicity (Section 6.3.2). Patients will also be monitored for changes in lipid profile and serum calcium.

The effect of GTx-024 on a fetus has not been evaluated; therefore, the subjects in the current investigation will be postmenopausal.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 400 subjects will be enrolled at approximately 70 sites in the United States. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

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

1. Able to read, understand, and provide written, dated, informed consent prior to screening, and be likely to comply with study protocol and communicate with study personnel about AEs and other clinically important information.
2. Female, 18 to 80 years of age, inclusive, at screening
3. Subjects must have undergone spontaneous, medically induced, or surgical menopause prior to the start of this study. Postmenopausal subjects are defined as those subjects who meet one of the following criteria:
    a) greater than or equal to 12 months of spontaneous amenorrhea, or;
    b) at least 6 months of spontaneous amenorrhea with serum follicle stimulating hormone levels > 40 mIU/ml, or;
    c) at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, or;
    d) subjects 60 years of age or older with previous hysterectomy without an oophorectomy with serum follicle stimulating hormone levels > 30 mIU/ml, or;
    e) subjects less than 60 years of age with previous hysterectomy without an oophorectomy with serum follicle stimulating hormone levels > 40 mIU/ml.
4. SUI symptoms of at least 6 months duration

5. Predominant SUI as determined at the Screening Visit using the MESA incontinence questionnaire.
6. 24-Hour pad weight > 3 g during the screening period
7. A minimum of 1 and no more than 15 SUI episodes on any single day AND no fewer than 9 total SUI episodes over 3 days as reported in the 3-day voiding diary, determined during the screening period
8. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels < 1.5 times the upper limit of normal at the Screening Visit (Note: laboratory values falling outside of prespecified ranges may be retested once at the discretion of the investigator. Results of the retest must be within prespecified ranges and must be available prior to the baseline visit)
9. Positive bladder stress test (BST) conducted during the Screening Visit
10. Subject agrees not to start any new treatment (medication or otherwise) during the treatment and follow-up periods, including vaginal rejuvenation, that is known or suspected to affect lower urinary tract function.
11. Subject agrees to discontinue use of bladder support devices, including but not limited to vaginal pessary, during the screening, treatment, and follow-up periods.
12. Subject agrees to maintain a stable dose of any medication known to affect lower urinary tract function, including but not limited to anticholinergics, tricyclic antidepressants, beta-3 adrenergic agonist, or α-adrenergic blockers, throughout the treatment and follow-up periods.
13. During screening, subject must provide evidence of having received a mammogram examination within the 6 months prior to screening, or she must agree to receive a mammogram examination during screening.

4.1.2 Exclusion Criteria

A subject meeting any of the following criteria will be excluded from the study:

1. Pelvic floor physical therapy, including muscle training and/or electrostimulation, in a clinical setting within 30 days prior to screening
2. History of pelvic radiation treatment

3. History of urethral diverticula
4. History of surgery for incontinence, including urethral sling, anterior prolapse repair, intra-detrusor botulinum toxin injection, sacral nerve stimulation, and percutaneous tibial nerve stimulation
5. Treatment with urethral bulking agents within the 6 months prior to the Screening Visit
6. Known vesicoureteral reflux, vaginal prolapse beyond the introitus, or other significant pelvic floor abnormalities that, in the investigator's opinion, may impact the subject's response
7. Vaginal rejuvenation treatment, including laser treatments and radiofrequency therapy, within the 6 months prior to the Screening Visit
8. Subject has urinary incontinence of neurogenic etiology
9. Subject is morbidly obese (defined as body mass index 40 or greater)
10. Chronic hepatitis (i.e., inflammation of the liver that has been ongoing for at least 6 months)
11. Hepatic cirrhosis due to, for example, sustained excessive alcohol consumption, hepatitis B virus, hepatitis C virus, or fatty liver disease
12. Evidence of active infection with hepatitis B or hepatitis C as determined by serology
13. History of human immunodeficiency virus (HIV) infection
14. Subject is currently taking systemic sex-hormone products (excludes intravaginal application of estradiol topical/tablet agents and hormones delivered via vaginal rings). The following washout periods are required if systemic hormonal products are discontinued prior to screening:
    a) minimum of 4 weeks for prior transdermal products or products with systemic absorption applied topically;
    b) minimum of 8 weeks for prior oral products;
    c) minimum of 8 weeks for prior intrauterine products, and;
    d) minimum of 3 months for prior hormonal implants or injectable drug therapy.

15. Subject has current cancer diagnosis (with the exception of non-melanoma skin cancer) or any history of breast or endometrial cancer
16. Known history or current episode of:
    - New York Heart Association ≥ Stage 2 hypertension (systolic blood pressure [BP] > 160 mmHg or diastolic BP > 100 mmHg) at screening and/or baseline. Subjects with hypertension that has been treated and controlled with medication for at least 2 weeks prior to screening are eligible for participation.
    - Recent myocardial infarction or arterial or venous thromboembolic event (within 1 year) or a history of greater than 1 myocardial infarction or arterial or venous thromboembolic event
    - Cardiac-related syncopal event within the past year
    - Cardio or cerebral vascular disease requiring surgical intervention (e.g., bypass surgery, angioplasty). For subjects with previous stent placement, please contact the medical monitor
    - Congestive heart failure (CHF) New York Heart Association (NYHA) Criteria > Stage 2
    - Angina pectoris
    - QT Fridericia-corrected ≥ 450 msec at screening (If QTcF is above this range, a repeat ECG can be done at the discretion of the investigator, and if the value is in range, the patient may be enrolled in the study.)
17. For subjects with an intact uterus, > 5 mm endometrial stripe thickness as measured at screening by transvaginal ultrasound
18. Clinically confirmed urinary tract infection, requiring treatment as determined by the investigator, at the Screening Visit
19. Current or past history of any physical condition that, in the investigator's opinion, might put the subject at risk, impact the absorption of the study drug, or interfere with study results interpretation.

4.2 Withdrawal of Subjects From the Study

The duration of the study is defined for each subject as the date signed written informed consent is provided through the last follow-up visit (Visit 8 at Week 28).

4.2.1 Reasons for Withdrawal/Discontinuation

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 Principal Investigator (PI) in consultation with GTx, Inc. for any of the following reasons:

- AEs that require treatment with a prohibited medication or procedure
- Development of any condition that may pose an additional risk to the subject or that the PI decides is in the best interest of the subject to withdraw from the study
- Sponsor's decision
- Subject is unable to follow Investigators' instructions and/or to comply with the study procedures
- Protocol deviation
- Disease progression

The clinical study report will include reasons for all subject withdrawals from treatment as well as details relevant to violations of Study Prohibitions and Concomitant Therapy.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the Sponsor.

Subjects who discontinue study treatment or active participation in the study will no longer receive GTx-024 or placebo (study drug) and will be considered to have withdrawn from the study. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Those subjects who receive study drug will be monitored for AEs for 30 days after stopping treatment with study drug. Every effort will be made to obtain all end-of-treatment measures

(Visit 5), as outlined in Table 12–1, in the event that a subject withdraws, or is withdrawn, from the study before completing treatment. Subjects who are not returning for final assessments will be contacted (2 documented telephone calls followed by 1 registered letter) by the site in an attempt to improve their compliance.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety follow-up procedures. All data collected from all subjects, including early withdrawals and early discontinuations of treatment, will be used in the reporting and analysis of the study.

4.2.3 Replacements

Subjects who have been randomly assigned to receive study drug and who subsequently discontinue prematurely from the study will not be replaced. Subjects who fail to satisfy inclusion and exclusion criteria at screening may be rescreened 1 additional time at the discretion of the Sponsor.

5 Study Treatments

Refer to Section 3.1 for a full description of the study design and randomization scheme. Investigational product will be administered orally once daily and supplied as opaque, white to off-white, size 5, oval Softgel capsules.

Subjects assigned to receive GTx-024 1 mg will be required to take two (2) 0.5 mg GTx-024 capsules once daily. Subjects assigned to receive GTx-024 3 mg will be required to take one (1) 3 mg GTx-024 capsule and one (1) placebo capsule once daily. Subjects assigned to receive placebo will be required to take two (2) placebo capsules once daily.

5.1 Method of Assigning Subjects to Treatment Groups

Subjects meeting all eligibility criteria will be randomized to receive placebo, 1 mg GTx-024, or 3 mg GTx-024 in a 1:1:1 ratio.

An interactive web response system (IWRS) will be used to administer the randomization schedule. Biostatistics will generate the randomization schedules using SAS software Version 9.4 (SAS Institute Inc., Cary, North Carolina) or later. The IWRS will link sequential subject randomization numbers to treatment codes.

5.2 Treatments Administered

Study drug (Section 5) will be taken orally with water at approximately the same time each day, with or without food. Subjects will be instructed to take 2 capsules each day.

5.3 Identity of Study Drug

The GTx-024 study drug is an opaque, white to off-white, size 5, oval Softgel capsule containing the active ingredient GTx-024 (0.5 mg or 3 mg) dissolved in the inactive excipient polyethylene glycol 400. The placebo study drug is identical in appearance to the GTx-024 study drug and contains polyethylene glycol 400 but not GTx-024. All study drug capsules will be imprinted with “GTx” in black ink on the outer shell of the capsule.

5.4 Management of Clinical Supplies

GTx, Inc. will provide adequate supplies of study drug through a central distribution center to clinical sites.

5.4.1 Study Drug Packaging and Storage

Study drug will be packaged in blister packaging that is designed and labeled in a manner to protect study blinding. Each blister pack will contain assigned dosing for 1 subject and will contain a sufficient quantity for each 4-week dispensing period plus 1 week of overage.

Each blister pack will be a carton containing 5 blister cards. Each blister card will be composed of 2 blister strips encased in a child-resistant heat-sealed card. The blister strips are composed of a PVC/ACLAR base and an aluminum foil/PVC/PVAC copolymer and polymethacrylate lidding. Perforations on the back of the heat-seal card overlay the foil lidding. To remove study drug, subjects will release the appropriate perforation by depressing a release button on the inside of the card. Once released, the perforation can be removed and the study drug pushed through the foil.

A clinical label will be affixed to the outside of each blister card and carton. The label will specify storage and dosing information.

At the study site, study drug must be stored in a secure area (e.g., a locked cabinet), protected from moisture, and kept at a controlled room temperature 15^{o}C-25^{o}C (59^{o}F-77^{o}F) with excursions permitted to 30^{o}C (86^{o}F).

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed to and used by each subject in the study. Reasons for departure from the expected dispensing regimen must be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations and Sponsor requirements.

5.4.3 Other Supplies

Test kits for the 24-hour pad weight test will be provided to sites by the Sponsor. Test kits will include sanitary pads and subject instructions.

5.5 Overdose Management

Subjects in this study will be dispensed a maximum of 105 mg of GTx-024 at any visit; this is therefore the maximum amount available to any subject at any time. In Phase 1 studies, subjects have safely received single doses of up to 100 mg GTx-024. The likelihood of a need for other than symptomatic treatment of overdose is considered extremely low. In the event of an overdose reported to the study site, the medical monitor should be contacted immediately.

5.5.1 Medication Errors

Dispensing study drug to subjects for self-administration in an outpatient study increases the risk of medication errors. All errors in medication dispensing or administration must be carefully documented. These errors may include (but are not limited to) providing the wrong dose, medication loss, or administration at the wrong time of day. Adherence to medication protocol will be emphasized at every visit.

5.5.2 Treatment of Medication Errors

The treatment of medication errors should be discussed with the medical monitor on a case by case basis.

5.6 Blinding

The study will be performed in a double-blind manner. All study drug will be supplied in identical packaging and will be similar in color, smell, taste, and appearance to enable double-blind conditions.

5.6.1 Breaking the Blind

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study treatment the subject received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation. As soon as possible, the investigator should first contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that subject. The treatment assignment will be unblinded through IWRS. Reasons for treatment unblinding must be clearly explained and

justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

5.7 Treatment Compliance

Individual subject compliance in taking study drug will be monitored by counting unused medication returned by the subject at visits. Compliance will be documented. If compliance is less than 80% or more than 120%, the Investigator or designee is to counsel the subject and ensure that steps are taken to improve compliance. Subjects who are less than 80% or more than 120% compliant with the dosage regimen for any 2 consecutive visit periods during the study may be withdrawn from the study.

5.8 Prior and Concomitant Medications

The Investigator or designee must record the use of prior medications (all medication taken within 30 days prior to Visit 1) and current treatment (including both drug and nondrug therapies and all prescribed, over-the-counter [OTC], and alternative medicines) in the eCRFs. The minimum requirement is that the drug name and dates of administration are to be recorded. This also includes drugs used on a chronic or as-needed basis. Subjects must be instructed not to start any new medication, either prescribed or OTC, without consulting the Investigator, unless the new medication is required for emergency use. Subjects must be instructed to notify the Investigator immediately if medications are required for emergency use.

Any changes in concomitant medications also will be recorded in the subject's eCRF.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

5.8.1 Prohibited Concomitant Medications and Treatments

Prohibited medications and treatments during the study duration include the following:

- Systemic hormonal products including but not limited to estrogens, progestins, testosterone, methyltestosterone, oxandrolone (Oxandrin®), oxymetholone, danazol, fluoxymesterone (Halotestin®), other androgenic compounds, including herbals such as fenugreek, Korean ginseng, goat weed, forskolin, ashwagandha, and Testro-X®. Intravaginal application of estradiol topical/tablet agents and hormones delivered via vaginal ring are allowed.
- Any new treatment (medication or otherwise), including vaginal rejuvenation, that is known or suspected to affect lower urinary tract function throughout the treatment and follow-up periods
- Treatment with any investigational agent within the 30 days before the first dose of study treatment
- New pelvic floor exercises (including Kegel) throughout the treatment and follow-up period

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an informed consent form (ICF). Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator will also sign the ICF.

6.1 Study Visits

The schedule of events for this study is presented in Table 12–1.

6.1.1 Screening

6.1.1.1 Screening Visit, Days –28 to 0

The study will be explained in detail and adequate time will be allowed for answering questions from a potential subject before she signs the institutional review board (IRB)-approved informed consent document. Informed consent will be obtained from those potential subjects meeting initial inclusion/exclusion criteria and expressing willingness to participate before study site personnel conduct any study assessments of such subjects.

Once informed consent is obtained, a subject number will be assigned and a detailed interview will be conducted with the subject about her medical history, including past gynecological and obstetric history (gravida, para, prior abortions and deliveries) and about her concomitant medications. The subject will complete the MESA incontinence questionnaire to determine if she has predominant stress incontinence. If the urinary continence type is stress predominant, a BST will be conducted to confirm SUI. Height and weight will be measured, and vital signs will be assessed. A gynecologic pelvic examination and a physical examination will be conducted. A dipstick urinalysis will be performed and blood will be drawn for laboratory tests as presented in Table 12–1. The subject's eligibility criteria will be reviewed and, if the subject is considered to be provisionally qualified, she will undergo the additional screening procedures described in Section 6.1.1.2.

6.1.1.2 Additional Screening Procedures

If the subject has provisionally qualified for the study during the Screening Visit, the following procedures will be performed between the Screening Visit and Visit 1 (Baseline):

- A mammography examination will be performed, unless the subject provides evidence of a mammography examination performed within the 6 months prior to the Screening Visit
- A transvaginal ultrasound examination will be performed in subjects with an intact uterus
- A 12-lead electrocardiography examination will be performed
- The subject will complete a 24-hour pad weight test
- The subject will complete a 3-day voiding diary

6.1.2 Study Visit 1: Week 0, Clinic Visit

Concomitant medications and AEs will be reviewed. The results of the 24-hour pad weight test and the 3-day voiding diary will be reviewed, and continued eligibility for enrollment will be evaluated, also considering the results of laboratory tests during screening. A subject meeting the inclusion and exclusion criteria after all screening study measures have been completed and reviewed will be randomly assigned to treatment (randomization).

Vital signs will be obtained, a dipstick urinalysis will be performed, and the subject will complete the UDI-6, IIQ-7 Short Form, I-QOL, FSFI, PGI-S, and Vaizey Incontinence Severity questionnaires.

Study drug will be dispensed with administration instructions, and each package will be preprinted with a medication identification number. The medication identification number assigned to the subject will be noted in the eCRF for study drug. The subject will take the first dose of study drug during this visit.

6.1.3 Study Visit 2: Week 1, Phone Visit

Approximately 1 week after beginning treatment, the subject will be contacted by phone to assess for concomitant medications and AEs (which will be recorded in the eCRF). The subject will be instructed to complete a 24-hour pad weight and 3-day voiding diary within the week preceding her next study visit. The subject will be reminded to bring all unused study drug (in its original packaging) to her next clinic visit.

6.1.4 Study Visit 3: Week 4, Clinic Visit

Approximately 4 weeks after beginning treatment, the subject will return to the study site for a clinic visit. Unused study drug will be collected. Concomitant medications and AEs will be reviewed. Weight and vital signs will be measured, and a physical examination will be performed. A dipstick urinalysis will be performed, and blood will be drawn for a comprehensive metabolic panel (CMP). Completion of a 24-hour pad weight test and a 3-day voiding diary will be verified.

The subject will complete the UDI-6, IIQ-7 Short Form, I-QOL, FSFI, PGI-S, PGI-I, and Vaizey Incontinence Severity questionnaires.

Study drug will be dispensed with administration instructions, and each package will be preprinted with a medication identification number. The medication identification number assigned to the subject will be noted in the eCRF for study drug.

The subject will be instructed to complete a 24-hour pad weight and 3-day voiding diary within the week preceding her next study visit. The subject will be reminded to bring all unused study drug (in its original packaging) to her next clinic visit.

6.1.5 Study Visit 4: Week 8, Clinic Visit

Approximately 8 weeks after beginning treatment, the subject will return to the study site for a clinic visit. Unused study drug will be collected. Concomitant medications and AEs will be reviewed. Weight and vital signs will be measured, and a physical examination will be performed. A dipstick urinalysis will be performed, and blood will be drawn for a CMP. Completion of a 24-hour pad weight test and a 3-day voiding diary will be verified.

The subject will complete the UDI-6, IIQ-7 Short Form, I-QOL, FSFI, PGI-S, PGI-I, and Vaizey Incontinence Severity questionnaires.

Study drug will be dispensed with administration instructions, and each package will be preprinted with a medication identification number. The medication identification number assigned to the subject will be noted in the eCRF for study drug.

The subject will be instructed to complete a 24-hour pad weight and 3-day voiding diary within the week preceding her next study visit. The subject will be reminded to bring all unused study drug (in its original packaging) to her next clinic visit.

6.1.6 Study Visit 5: Week 12 or Early Withdrawal, Clinic Visit

Approximately 12 weeks after beginning treatment, the subject will return to the study site for a clinic visit. Unused study drug will be collected and accounted for. Concomitant medications and AEs will be reviewed. Weight and vital signs will be measured, and both a gynecologic pelvic examination and a physical examination will be performed. A dipstick urinalysis will be performed and blood will be drawn for laboratory testing as presented in Table 12–1. Completion of a 24-hour pad weight test and a 3-day voiding diary will be verified. A BST and, in subjects with an intact uterus, a transvaginal ultrasound examination will be performed.

The subject will complete the MESA, UDI-6, IIQ-7 Short Form, I-QOL, FSFI, PGI-S, PGI-I, and Vaizey Incontinence Severity questionnaires.

The subject will be instructed to complete a 24-hour pad weight and 3-day voiding diary within the week preceding her next study visit.

6.1.7 Study Visit 6: Week 16, Clinic Visit

Approximately 16 weeks after beginning treatment and 4 weeks after the last dose of study drug, the subject will return to the study site for a clinic visit. Concomitant medications and AEs will be reviewed. Weight and vital signs will be measured, and a physical examination will be performed. Blood will be drawn for laboratory testing as presented in Table 12–1. Completion of a 24-hour pad weight test and a 3-day voiding diary will be verified.

The subject will complete the UDI-6, IIQ-7 Short Form, I-QOL, FSFI, PGI-S, PGI-I, and Vaizey Incontinence Severity questionnaires.

Subjects continuing to Week 20 will be instructed to complete a 24-hour pad weight and 3-day voiding diary within the week preceding her next study visit.

6.1.8 Study Visit 7: Week 20, Clinic Visit

Approximately 20 weeks after beginning treatment and 8 weeks after the last dose of study drug, the subject will return to the study site for a clinic visit. Concomitant medications and AEs will be reviewed. Blood will be drawn for laboratory testing as presented in Table 12–1. Completion of a 24-hour pad weight test and a 3-day voiding diary will be verified.

The subject will complete the UDI-6, IIQ-7 Short Form, I-QOL, FSFI, PGI-S, PGI-I, and Vaizey Incontinence Severity questionnaires.

The subject will be instructed to complete a 24-hour pad weight and 3-day voiding diary within the week preceding her next study visit.

6.1.9 Study Visit 8: Week 28, Clinic Visit

Approximately 28 weeks after beginning treatment and 16 weeks after the last dose of study drug, the subject will return to the study site for a clinic visit. Concomitant medications and AEs will be reviewed. Blood will be drawn for laboratory testing as presented in Table 12–1. Completion of a 24-hour pad weight test and a 3-day voiding diary will be verified.

The subject will complete the UDI-6, IIQ-7 Short Form, I-QOL, FSFI, PGI-S, PGI-I, and Vaizey Incontinence Severity questionnaires.

6.2 Efficacy Assessments

Efficacy assessments will include a 3-day voiding diary, PGI-S, PGI-I, UDI-6, IIQ-7, I-QOL, FSFI, Vaizey Incontinence Severity Score, and 24-hour pad weight test. Changes in subject-reported impressions will be noted.

6.2.1 Three-Day Voiding Diary

Subjects will record all urinary voids, specifying each episode of urinary leakage including type. Fluid intake will also be recorded as well as any episode of vaginal discharge or spotting.

In each 3-day voiding diary, subjects are to record voiding data for 3 consecutive days in a paper diary. To be considered valid, each 3-day voiding diary must be recorded within 7 days on either side of a planned visit, based on the date of randomization.

Three-day voiding diaries are reliable measures of the mean number of urinary incontinence episodes per day, incontinence type, mean voids per 24 hours, and mean voids during sleeping hours.

6.2.2 Bladder Stress Test (BST)

Before the BST, a bladder scan will be performed by ultrasound to verify that the subject's bladder contains at least 150 ml of urine. The volume of urine present in the bladder should be captured. Once the urine volume has been determined, the subject will stand over an absorbent pad and be instructed to cough forcefully and/or perform a Valsalva maneuver to elicit a urinary stress leak. If there is no observable urine loss on the absorbent pad, a paper towel will be placed lightly against the perineum to detect any urine leakage that may not have dropped onto the pad. Any urine loss observed by the research staff is indicative of a positive BST.

After completion of the BST, subjects will be asked to void and the volume of urine remaining in the bladder after voiding (post void residual) will be measured via ultrasound bladder scan. The volume of urine present in the bladder post voiding should be captured.

A BST will be conducted for each subject at the Screening Visit and at Visit 5 (Table 12–1).

6.2.3 Patient Global Impression of Severity

The PGI-S is a global rating of subject-reported impression of SUI severity using a 4-point scale (Appendix 12.3). Validity of the PGI-S has been established for application in SUI.

6.2.4 Patient Global Impression of Improvement

The PGI-I is a global rating of subject-reported impression of SUI improvement using a 7-point scale (Appendix 12.4). Validity of the PGI-I has been established for application in SUI.

6.2.5 Urogenital Distress Inventory and Incontinence Impact Questionnaire Short Form

The UDI-6 (Appendix 12.5) and IIQ-7 Short Form (Appendix 12.6) are validated subject questionnaires used to assess symptom distress and the impact of urinary incontinence on daily life (Shumaker et al 1994; Uebersax et al 1995). The UDI-6 and IIQ-7 are both ‘‘A

grade'' recommended by the Fourth International Consultation on Incontinence (Shumaker et al 1994; Uebersax et al 1995; Staskin et al 2008, 2009).

6.2.6 Incontinence Quality of Life

The I-QOL (Appendix 12.7) is a validated subject questionnaire used to assess the impact of urinary incontinence and treatments.

6.2.7 Female Sexual Function Index

The FSFI (Appendix 0) is a self-administered questionnaire to assess overall sexual experience that consists of 19 questions scored from 0 to 5. The scale contains 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain (Rosen et al 2000). The FSFI total score is a weighted average of the 6 domains with each contributing a maximum of 6 points to the total (maximum score of 36).

6.2.8 Vaizey Incontinence Severity Score

The Vaizey Incontinence Severity Score is obtained through a self-administered questionnaire to assess a subject's bowel symptoms and the impact if these symptoms of daily life.

6.2.9 Twenty-Four Hour Pad Weight Test

The 24-hour pad weight test is a quantitative test intended to provide information on the severity of incontinence. The amount of urine leaked over the 24 hours of testing is quantified by measuring the change in weight of perineal pads used during testing.

The 24-hour pad test should be completed during 1 day of each scheduled 3-day voiding diary. Subjects will be instructed to record pad weight on a day that is typical for them in terms of activity level and fluid intake. Subjects must use the incontinence pads provided in the 24-hour pad weight test kit for the 24-hour test; no other pads are to be used. Subjects should receive 8 incontinence pads for use during each 24-hour test period. Pads will be returned before or at the next scheduled study visit.

6.2.10 Medical, Epidemiological, and Social Aspects of Aging Questionnaire

The MESA incontinence questionnaire (Appendix 12.2) consists of 15 items divided into stress incontinence (9 items) and urge incontinence (6 items) subscales. Based on their responses, subjects can be characterized as having predominant stress incontinence, urge incontinence, or mixed incontinence (Herzog and Fultz 1990).

6.3 Safety Assessments

6.3.1 Adverse Events

6.3.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study regardless of their possible relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug and within the 30 days following discontinuation of drug treatment

An SAE is defined as any event that results in one of the following conditions:

- Death
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization
- An event that results in persistent or significant disability/incapacity
- An event that results in a congenital anomaly/birth defect

- Any other important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 drug dependency or drug abuse.

6.3.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed beginning at enrollment (date of signed informed consent) through the completion of the durability or follow up period.

Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the investigator considers them to be related to study drug.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, electrocardiogram [ECG] changes) or identified from review of other documents (e.g., subject diaries) that are relevant to subject safety will be documented on the AE page in the eCRF.

6.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened should not be reported as an AE. However, if a pre-existing condition changes in intensity or frequency at any time during the study, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 6.3.1.1) must be entered into the electronic data capture (EDC) system immediately (i.e., within 1 business day) after site personnel first learn of the event. Once the qualifying SAE data are entered, pharmacovigilance will be notified by an email alert, which will contain high level safety information. Additional safety information will be obtained from the EDC system via applicable eCRF pages. If the EDC system is not available, the site should send a completed paper SAE report form to pharmacovigilance by fax or email:

- Safety Fax Line: 1-866-966-2970 (US toll-free)
- Safety Email: sae@cmedresearch.com

When the EDC system is again available, the site must enter all applicable information into the EDC system. All supporting source information concerning the SAE (e.g., hospital records) should be provided by fax or email.

If there is a question concerning an SAE, the site needs guidance regarding reporting of an SAE, the site is returning a call from a safety specialist, or the site urgently needs to report an SAE or make pharmacovigilance aware of an SAE, the Safety Hotline should be used:

- Safety Hotline: 1-866-966-8429 (US toll free)

If a site makes an initial report of an SAE by the safety hotline, the site must subsequently enter all applicable information into the EDC system immediately thereafter.

6.3.1.4 Assessment of Severity

All AEs will be assessed by the Investigator according to NCI-CTCAE, Version 4.0. For any AE that is not specifically covered in NCI-CTCAE, Version 4.0, the criteria below should be used:

Grade	Description
0	No AE or within normal limits
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.3.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.3.1.6 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and be monitored to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

6.3.2 Halting Rules

If in the opinion of the Investigator, the participation in the study is or is becoming detrimental to the well-being of a particular subject, this issue should be discussed with the medical monitor for this study and the subject's participation in the study may be discontinued.

Discontinuation of treatment should be considered if:

- ALT or AST > 8 × upper limit of normal (ULN)

- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (differential count > 5%)

In the event that ALT or AST is > 3 × ULN, the subject will return for an unscheduled clinic visit and blood will be drawn for a coagulation panel to determine the INR. The INR will be determined at a local laboratory.

All subjects discontinued from the study should be followed until abnormal values return to normal, and all discontinuations should be discussed with the medical monitor prior to discontinuation.

6.3.3 Safety Assessments

The safety assessments will include AEs (Section 6.3.1), vital sign measurements, height and weight, concomitant medications, medical history, physical examination findings, transvaginal ultrasound, and clinical laboratory analyses (Section 6.6). Refer to Table 12–1 for a detailed schedule of the timing of study procedures.

6.3.3.1 Vital Sign Measurements

Vital sign measurements include oral temperature, seated BP, pulse rate, and respiration rate. Vital sign measurements will be collected as indicated in Table 12–1.

6.3.3.2 Height and Weight

Height will be measured at screening only and weight will be measured as indicated in Table 12–1.

6.3.3.3 Prior and Concomitant Medications

At the Screening Visit, the Investigator or designee must record the use of prescription and OTC medication taken within the prior 30 days. Concomitant medications (including

prescription and OTC medications) will be assessed and recorded throughout the study (Table 12–1).

6.3.3.4 Medical History

A detailed review of medical history, conducted at the Screening Visit, will include review of gravida, prior abortions, parity, deliveries, and history of gynecological conditions, surgeries, and cancer.

6.3.3.5 Physical Examination

The purpose of the physical examination is to identify any medical conditions that would impact eligibility of the subject at screening, and to identify any changes that occur as a result of treatment. Physical examination will include visual inspection, chest auscultation, organ and lymph node palpation, skin turgor, and brief neurologic exam (muscle strength, reflexes, sensation). The visual inspection should include a visual skin examination with specific attention to any androgenic changes (acne, hirsutism). Physical examinations will be performed as indicated in Table 12–1.

6.3.3.6 Transvaginal Ultrasound

Only for subjects with an intact uterus, transvaginal ultrasound will be performed at screening and at the end of treatment (Visit 5) to observe changes in the endometrial stripe thickness (mm). Transvaginal ultrasound examinations will be evaluated locally.

6.4 Other Assessments

6.4.1 Pelvic Examination

Gynecologic pelvic examination of each subject will be conducted at the Screening Visit and at Visit 5 (Table 12–1). The purpose of the pelvic examination at screening is to identify any gynecologic findings that might impact the patient's participation in the trial, and at the end of the treatment period to note whether any changes have occurred. The pelvic exam should include external inspection, speculum, and bimanual examinations.

6.4.2 Mammography

Mammography is the process of using low-energy x-rays to examine the human breast, which is used as a diagnostic and screening tool. The goal of mammography is the early

detection of breast cancer, typically through detection of characteristic masses and/or microcalcifications. Mammography examination of each subject will be conducted during the screening period unless the subject provides evidence of a mammography examination performed within the 6 months prior to screening (Table 12–1). Mammograms will be read locally.

6.4.3 Electrocardiography

A standard 12-lead ECG will be obtained at screening. Tracings must be dated and signed by the Investigator (or his/her designee) and filed with the subject's source documentation. Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), and subject number. Interpretation of the tracing must be made by a qualified physician. Results from 12-lead ECG examination should be captured in the ECG Evaluation eCRF. Clinically significant abnormalities present at screening should be reported on the Medical History eCRF page. Clinically significant findings should be discussed with the medical monitor prior to randomizing the subject in the study. The PI will make the final decision if any observed deviations in the ECG are sufficient to require that the subject be excluded from the study. The ECG may be repeated at the discretion of the Investigator at any time during the study as clinically indicated, and any clinically relevant findings should be added to the AE eCRF.

6.5 Pregnancy

This study will enroll only postmenopausal women who are not taking hormone products. In the unlikely event of a pregnancy, any pregnancy must be reported to pharmacovigilance within 2 weeks of learning of its occurrence, using the EDC system (Section 6.3.1.3). The pregnancy must be followed-up to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to pharmacovigilance.

6.6 Laboratory Analyses

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, or vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Laboratory analyses include the following:

- Comprehensive metabolic panel (Chem 14): includes calcium, carbon dioxide, glucose, potassium, sodium, total protein, and kidney and liver function tests (serum ALT, AST, γ-glutamyl transpeptidase, and total and direct bilirubin) will be performed (the investigator may repeat these checks if clinically indicated).
- Serum follicle stimulating hormone
- Complete blood count with differential
- Urinalysis dipstick testing for blood, protein, and leukocytes will be performed on a clean catch midstream voided urine specimen. If results or clinical symptoms indicate a possible urinary tract infection (UTI), the specimen will be sent for culture. If the culture is positive, the subject will receive appropriate treatment for UTI per standard of care. If the subject has a positive urine culture at the time of screening, she will be considered a screening failure and will not be enrolled until she has been treated for a UTI, the UTI symptoms disappear, and a dipstick urinalysis is consistent with the absence of a UTI. The subject will then be eligible for rescreening 1 additional time at the discretion of the Sponsor. After a subject has qualified for enrollment based on a negative urinalysis and the absence of clinical symptoms of a UTI, any subsequent UTI will be treated and the subject will continue in the study.
- Fasting lipid panel: including total cholesterol, low-density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, and HDL particle composition
- C-reactive protein (CRP)

- Serology for evidence of active infection with hepatitis B or hepatitis C
- Hormone panel: includes testosterone, free testosterone, and estradiol.
- SHBG

6.7 Sample Collections

Instructions for sample collection, handling, and shipping will be presented in a separate laboratory manual that will be provided to study sites as a separate document. Required blood samples should be 12-hour fasting samples.

7 Statistical and Analytical Plan

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is a responder analysis, where a responder is defined as having a ≥ 50% reduction at the end of treatment (Week 12) compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary. Subjects who have missing diary data for the Week 12 visit will be counted as non-responders for this analysis. Rules for recording valid diary data are presented in Section 6.2.1.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are the following assessments compared to baseline at each visit during the treatment period:

- Responder rate, where a responder is defined as having a ≥ 50% reduction compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary
- Change in the number of stress incontinence episodes per day as measured by the 3-day voiding diary
- Change in the total number of voids per day as measured by the 3-day voiding diary
- Change in the mean number of stress incontinence episodes per day as measured by the 3-day voiding diary
- Change in 24-hour pad weight as measured by the 24-hour pad weight test
- Change in the results of the Bladder Stress Test (BST)
- Change in subject-reported impression of SUI severity as measured by the PGI-S
- Change in subject-reported impression of SUI improvement as measured by the PGI-I
- Change in subject-reported urogenital distress as measured by the UDI-6
- Change in subject-reported impact of urinary incontinence on daily life as measured by the IIQ-7 Short Form

- Change in subject-reported impact of urinary incontinence on daily life as measured by the I-QOL
- Change in subject-reported sexual function as measured by the FSFI
- Change in subject-reported assessment of fecal incontinence as measured by the Vaizey Incontinence Severity Score.
- Change in subject-reported stress incontinence, urge incontinence, and mixed incontinence as measured by the MESA incontinence questionnaire (Week 12 only)

7.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints in this study are the following assessments compared to Week 12 for all treatments at Week 16, Week 20, and Week 28:

- Responder rate, where a responder is defined as having a ≥ 50% reduction compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary
- Number of stress incontinence episodes per day as measured by the 3-day voiding diary
- Total number of voids per day as measured by the 3-day voiding diary
- Change in 24-hour pad weight as measured by the 24-hour pad weight test
- Subject-reported impression of SUI severity as measured by the PGI-S
- Subject-reported impression of SUI improvement as measured by the PGI-I
- Subject-reported urogenital distress as measured by the UDI-6
- Subject-reported impact of urinary incontinence on daily life as measured by the IIQ-7 Short Form
- Subject-reported impact of urinary incontinence on daily life as measured by the I-QOL
- Subject-reported sexual function as measured by the FSFI
- Subject-reported assessment of fecal incontinence as measured by the Vaizey Incontinence Severity Score

Additional sensitivity analyses may be included in exploratory analyses. These analyses will be described in further detail in the SAP.

7.4 Sample Size Calculation

The sample size calculation was performed using PASS v12.0.1 for binary outcomes. The sample size calculation was performed for a binary response (i.e., a responder is defined as having a ≥ 50% reduction at the end of treatment compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary). The assumptions were a 60% active treatment response and 40% placebo response. The overall discontinuation rate was anticipated to be approximately 25%.

Given these assumptions, a randomized sample size of approximately 400 subjects (randomized in a 1:1:1 ratio for placebo, 1 mg GTx-024, and 3 mg GTx-024, respectively) will have 80% power to detect a treatment difference of 20%. A 2-sided hypothesis test with 5% significance is assumed for each pairwise comparison between GTx-024 and placebo (i.e., alternatively using a 1-sided significance level of 2.5%).

7.5 Analysis Sets

Data analysis will be performed on a full analysis set (FAS), a per protocol set (PPS), an intent-to-treat (ITT) set, a durability set (DS), and a safety analysis (SA) set.

The FAS is used for the primary analysis. The FAS consists of all randomized subjects who receive at least 1 dose of study drug and have at least 1 post baseline primary efficacy assessment (3-day voiding diary). All analyses using the FAS will group participants according to randomized treatment.

The PPS is used for a supportive analysis and will be defined as all subjects included in the FAS who do not have any significant protocol deviations. All analyses using the PPS will group subjects according to treatment actually received.

The ITT set consists of all randomized subjects who receive at least 1 dose of study drug. All analyses using the ITT set will group subjects according to randomized treatment. Subjects who do not have any postbaseline assessments will be treated as non-responders for ITT analyses.

The DS is used for exploratory analyses to assess the durability of the effect of treatment and will be defined as all subjects who complete a Week 12 final visit and a Week 16, Week 20, or Week 28 assessment.

The SA set contains all subjects randomized in the study who receive at least 1 dose of study drug. All analyses using the SA set will group subjects according to treatment actually received.

All efficacy analyses performed on the FAS will be repeated on the PPS and the ITT set. Further details will be provided in the SAP.

7.6 Description of Subgroups to be Analyzed

No subgroup analyses are planned.

7.7 Statistical Analysis Methodology

Before unblinding, a separate SAP will be finalized, providing detailed methods for all endpoints. In general, summary statistics (n, mean, standard deviation, median, minimum and maximum values for continuous variables, and number [%] of subjects in each category for categorical variable) will be provided by treatment group and visit. Source data for summary tables and statistical analyses will be presented as subject data listings.

All statistical analyses will be performed using SAS (v9.4 or higher). Unless stated otherwise, all statistical tests will be 2-sided using a 5% significance level, leading to 95% (2-sided) confidence intervals. No adjustment will be made for multiplicity due to 2 dose levels of GTx-024 being compared with placebo. The trial is not powered to show a statistical difference between the 2 dose arms of GTx-024.

The primary efficacy period is defined as baseline (Day 0) through Week 12. Change from baseline and determination of responder rate status will be between baseline and visits through Week 12. The durability period is defined as Week 12 to Week 16, Week 20, and/or Week 28.

7.7.1 Analysis of the Primary Efficacy Endpoint

The primary analysis will be conducted on the primary endpoint using the FAS.

The primary efficacy endpoint (i.e., a binary response indicator where a responder is defined as having a ≥ 50% reduction at the end of treatment compared to baseline in the mean number of stress incontinence episodes per day as assessed by the 3-day voiding diary) will be evaluated using a logistic regression model. The logistic regression model will include treatment group as a covariate. The odds ratio of response between each dose level of GTx-024 and placebo (together with the corresponding 95% confidence interval) will be reported. The null hypothesis is that there is no treatment effect for either dose level of GTx-024. This will be tested against the alternative hypothesis that there is a treatment effect for at least 1 of the dose levels of GTx-024.

The corresponding *P*-value for the comparison between each dose level of GTx-024 and placebo will be derived using the standard normal distribution. Subjects who have missing diary data for the screening period or the Week 12 visit will be counted as non-responders for this analysis.

Sensitivity analyses will be specified in the SAP.

7.7.2 Analysis of Secondary Efficacy Endpoints

For binary secondary endpoints (responders), the treatment effect will be estimated using a logistic regression model with treatment as a covariate.

For continuous secondary endpoints, treatment effects will be estimated using a mixed model repeated measures analysis (MMRM). The MMRM model will specify an unstructured variance/covariance matrix and include treatment group, visit, and baseline as covariates.

For ordinal endpoints, treatment effects will be estimated using a proportional odds model.

Further details on the analysis of secondary efficacy endpoints will be provided in the SAP.

7.7.3 Analysis of Exploratory Efficacy Endpoints

Durability of treatment effect will be examined in the DS for the exploratory efficacy endpoints. Additional sensitivity analyses of exploratory and secondary efficacy endpoints may also be conducted as exploratory analyses, including sensitivity analyses with regard to missing data. Further details of the exploratory analyses will be provided in the SAP.

7.7.4 Safety Analyses

All safety parameters (including AEs, vital signs, laboratory evaluations, SHBG, testosterone, and endometrial stripe thickness) will be summarized using the SA set. No formal hypothesis testing will be performed.

All AEs will be coded using the latest version of MedDRA. All TEAEs will be summarized and presented in the listings by the number of subjects reporting an event, the percentage of subjects with that event, the number of events, and the grade, duration, and relationship to treatment. Percentages will be based on the number of subjects who received each treatment during the study.

Clinical laboratory safety tests will be performed, and normal ranges will be provided for each laboratory test. Values outside the normal range will be assessed for clinical significance by the investigator. Shift tables (change from baseline value to on-treatment values) will be presented for each laboratory measurement and assessment time. Each parameter outside the normal range will be designated as high (H) or low (L) in the individual data listings.

7.8 Data Quality Assurance

Standard operating procedures are available for all activities relevant to the quality of this study. Designated personnel will be responsible for implementing and maintaining quality assurance and quality control systems to ensure that the study is conducted and that data are generated, documented, and reported in compliance with the study protocol, Good Clinical Practice (GCP), and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules, and regulations relating to the conduct of the clinical trial.

An authorized quality assurance auditor will audit the study data and procedures at periodic intervals as indicated. Domestic or foreign regulatory authorities, the IRB, and a Sponsor-authorized auditor may request access to all study documentation for an on-site inspection or audit. The Investigator must notify GTx, Inc. of any regulatory authority inspections and forward copies of the inspection report to GTx, Inc.

Electronic data systems will be in accordance with applicable aspects of 21 Code of Federal Regulations (CFR) Part 11, ICH Guidelines, GCP, local laws and legislation, and the Health Insurance Portability and Accountability Act.

7.8.1 On-Site Audits

At any time, quality assurance representatives of the Sponsor and/or regulatory bodies may visit the unit to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to study records, documentation, and regulatory files. At all times, subject privacy will be of utmost importance and respected. Typically, sufficient notice will be given to the Investigator to prepare for the visit.

7.8.2 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. Source documents may include, but are not restricted to, such documents as laboratory reports, ECG strips, and 3-day voiding diaries.

Investigative site personnel will enter subject data into InForm® (the eCRF program). The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable GTx standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the MedDRA, an internal validated medication dictionary.

After database lock, each study site will receive a CDROM containing all of their site-specific eCRF data as entered into Oracle Clinical Remote Data Capture for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the study site's data from the study will be created and sent to the Sponsor for storage. PPD will maintain a duplicate CDROM copy for their records. In all cases, subject initials will not be collected or transmitted to the Sponsor.

8 Ethics

8.1 Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the Sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Subject Information and Consent

A written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB for review and approval before the start of the study. If

the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor PPD is financially responsible for further treatment of the subject's disease.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the Sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the investigator/institution as to when these events stated in 21 CFR 312.62(c) have occurred. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

10 Study Management

10.1 Monitoring

10.1.1 Monitoring the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the Sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, representatives of the Sponsor, FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator’s IRB for approval before subjects can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior Sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although GTx has every intention of completing the study, GTx reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

10.4 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the Sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical study registers.

11 Reference List

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12 Appendices

12.1 Appendix: Schedule of Events

Table 12–1 Schedule of Events for Protocol G201002

Procedure	Screening Visit	Additional Screening Procedures	Baseline V1	V2[a]	V3	V4	V5	V6	V7 and V8
Day or Week	**Days –28 to 0**	**Days –28 to 0**	**Week 0**	**Week 1**	**Week 4**	**Week 8**	**Week 12 or Early Withdrawal**	**Week 16 or 30 days after last dose of study drug**	**Weeks 20 and 28**
Visit Window (days)	–	–	–	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X								
Eligibility criteria review	X		X						
Medical history	X								
Concomitant medications	X		X	X	X	X	X	X	X
MESA incontinence questionnaire	X						X		
Bladder stress test	X						X		
Height[b] and weight	X				X	X	X	X	
Vital signs	X		X		X	X	X	X	
Pelvic examination	X						X		
Physical examination	X				X	X	X	X	
UA dipstick (with culture as needed)	X		X		X	X	X		
CMP (Chem 14 panel)[c]	X				X	X	X	X	
Viral serology[d]	X								
Serum FSH	X								
CBC	X						X	X	
Lipid panel	X						X	X	X
C-reactive protein (CRP)	X						X	X	
Hormone panel	X						X	X	X

Procedure	Screening Visit	Additional Screening Procedures	Baseline V1	V2[a]	V3	V4	V5	V6	V7 and V8
Day or Week	**Days –28 to 0**	**Days –28 to 0**	**Week 0**	**Week 1**	**Week 4**	**Week 8**	**Week 12 or Early Withdrawal**	**Week 16 or 30 days after last dose of study drug**	**Weeks 20 and 28**
Visit Window (days)	–	–	–	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
SHBG	X						X	X	X
Mammography[e]		X							
Transvaginal ultrasound[f]		X					X		
Electrocardiography		X							
24-Hour pad weight test		X			X	X	X	X	X
3-Day voiding diary		X			X	X	X	X	X
Randomization			X						
Adverse event reviews			X	X	X	X	X	X	X
UDI-6			X		X	X	X	X	X
IIQ-7 Short Form			X		X	X	X	X	X
I-QOL			X		X	X	X	X	X
FSFI			X		X	X	X	X	X
PGI-S			X		X	X	X	X	X
PGI-I					X	X	X	X	X
Vaizey Incontinence Severity Score			X		X	X	X	X	X
Dispense study drug			X		X	X			
Collect unused study drug					X	X	X		

Abbreviations: CBC, complete blood count; CMP, comprehensive metabolic panel; FSFI, Female Sexual Function Index; FSH, follicular-stimulating hormone; IIQ-7, Incontinence Impact Questionnaire; I-QOL, Incontinence Quality of Life questionnaire; MESA, Medical, Epidemiological, and Social Aspects of Aging; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Severity; SHBG, sex hormone-binding globulin; UA, urinalysis; UDI-6, Urogenital Distress Inventory; V, visit.

[a] This visit is a telephone call.

[b] Height will be measured at screening only.

[c] Comprehensive metabolic panel (Chem 14) including serum calcium and liver function tests (can be repeated once at the Investigator's discretion); the results of all tests/re-tests must be available within the screening window and prior to randomization.

[d] The viral serology panel includes testing for active hepatitis B and active hepatitis C.

[e] Evidence of mammography conducted within the 6 months prior to screening is acceptable and will remove the need for a mammography during screening.

[f] The transvaginal ultrasound should be administered at the end-of-treatment visit if earlier than Week 12.

12.2 Appendix: Medical, Epidemiological, and Social Aspects of Aging Questionnaire

MESA INCONTINENCE QUESTIONNAIRE – page 1 of 2
1. Over the past three months, have you had urine loss beyond your control? ☐ Yes ☐ No
2. How long ago did your urine loss start? ☐ Years ☐ Months ☐ Days
Urge Incontinence
1. Some people receive very little warning and suddenly find that they are losing, or about to lose, urine beyond their control. How often does this happen to you? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
2. If you can't find a toilet or find a toilet that is occupied and you have an urge to urinate, how often do you end up losing urine and wetting yourself? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
3. Do you lose urine when you suddenly have the feeling that your bladder is full? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
4. Does washing your hands cause you to urinate? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
5. Does cold weather cause you to lose urine? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
6. Does drinking cold beverages cause you to lose urine? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
Stress Incontinence
1. Does coughing gently cause you to lose urine? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
2. Does coughing hard cause you to lose urine? ☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)

MESA INCONTINENCE QUESTIONNAIRE – page 2 of 2			
3. Does sneezing cause you to lose urine?			
☐ Often (3)	☐ Sometimes (2)	☐ Rarely (1)	☐ Never (0)
4. Does lifting things cause you to lose urine?			
☐ Often (3)	☐ Sometimes (2)	☐ Rarely (1)	☐ Never (0)
5. Does bending over cause you to lose urine?			
☐ Often (3)	☐ Sometimes (2)	☐ Rarely (1)	☐ Never (0)
6. Does laughing cause you to lose urine?			
☐ Often (3)	☐ Sometimes (2)	☐ Rarely (1)	☐ Never (0)
7. Does walking briskly cause you to lose urine?			
☐ Often (3)	☐ Sometimes (2)	☐ Rarely (1)	☐ Never (0)
8. Does straining, if you are constipated, cause you to lose urine?			
☐ Often (3)	☐ Sometimes (2)	☐ Rarely (1)	☐ Never (0)
9. Does getting up from a sitting to a standing position cause you to lose urine?			
☐ Often (3)	☐ Sometimes (2)	☐ Rarely (1)	☐ Never (0)

12.3 Appendix: Patient Global Impression of Severity

PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S) SCALE

Check the one number below that best describes how your urinary tract condition is now.

☐ 1 Normal

☐ 2 Mild

☐ 3 Moderate

☐ 4 Severe

12.4 Appendix: Patient Global Impression of Improvement

PATIENT GLOBAL IMPRESSION OF IMPROVEMENT (PGI-I) SCALE

Check the one number that best describes how your urinary tract condition is now, compared with how it was before you began taking medication in this study.

- ☐ 1 Very much better
- ☐ 2 Much better
- ☐ 3 A little better
- ☐ 4 No change
- ☐ 5 A little worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

12.5 Appendix: Urogenital Distress Inventory

UROGENITAL DISTRESS INVENTORY SHORT FORM: UDI-6

1. Do you usually experience frequent urination? ☐ 1 Yes ☐ 0 No

If Yes, how much does this bother you? ☐ 1 Not at all ☐ 2 Somewhat ☐ 3 Moderately ☐ 4 Quite a bit

2. Do you usually experience urine leakage associated with a feeling of urgency; that is, a strong sensation of needing to go to the bathroom? ☐ 1 Yes ☐ 0 No

If Yes, how much does this bother you? ☐ 1 Not at all ☐ 2 Somewhat ☐ 3 Moderately ☐ 4 Quite a bit

3. Do you usually experience urine leakage related to coughing, sneezing or laughing? ☐ 1 Yes ☐ 0 No

If Yes, how much does this bother you? ☐ 1 Not at all ☐ 2 Somewhat ☐ 3 Moderately ☐ 4 Quite a bit

4. Do you experience small amounts of urine leakage (that is, drops)? ☐ 1 Yes ☐ 0 No

If Yes, how much does this bother you? ☐ 1 Not at all ☐ 2 Somewhat ☐ 3 Moderately ☐ 4 Quite a bit

5. Do you experience difficulty emptying your bladder? ☐ 1 Yes ☐ 0 No

If Yes, how much does this bother you? ☐ 1 Not at all ☐ 2 Somewhat ☐ 3 Moderately ☐ 4 Quite a bit

6. Do you usually experience pain or discomfort in the lower abdomen or genital region? ☐ 1 Yes ☐ 0 No

If Yes, how much does this bother you? ☐ 1 Not at all ☐ 2 Somewhat ☐ 3 Moderately ☐ 4 Quite a bit

If Yes, then is your pain relieved after emptying your bladder? ☐ 1 Yes ☐ 0 No

12.6 Appendix: Incontinence Impact Questionnaire Short Form

Incontinence Impact Questionnaire – Short Form IIQ-7

Some people find that accidental urine loss may affect their activities, relationships, and feelings. The questions below refer to areas in your life that may have been influenced or changed by your problem. For each question, check the response that best describes how much your activities, relationships, and feelings are being affected by urine leakage.

Has urine leakage affected your....

	Not at All	Slightly	Moderately	Greatly
1. Ability to do household chores (cooking, housecleaning, laundry)?	☐0	☐1	☐2	☐3
2. Physical recreation such as walking, swimming, or other exercise?	☐0	☐1	☐2	☐3
3. Entertainment activities (movies, concerts, etc.)?	☐0	☐1	☐2	☐3
4. Ability to travel by car or bus more than 30 minutes from home?	☐0	☐1	☐2	☐3
5. Participation in social activities outside your home?	☐0	☐1	☐2	☐3
6. Emotional health (nervousness, depression, etc.)?	☐0	☐1	☐2	☐3
7. Feeling frustrated?	☐0	☐1	☐2	☐3

12.7 Appendix: Incontinence Quality of Life

PLEASE WRITE IN TODAY'S DATE:
Day Month Year

PARTICIPANT ID:

PLEASE READ THIS CAREFULLY

ON THE FOLLOWING PAGES YOU WILL FIND SOME STATEMENTS THAT HAVE BEEN MADE BY PEOPLE WHO HAVE URINARY INCONTINENCE (LEAKING URINE WHEN YOU DON'T WANT TO).

PLEASE CHOOSE THE RESPONSE THAT APPLIES BEST TO YOU RIGHT NOW AND CIRCLE THE NUMBER OF YOUR ANSWER.

IF YOU ARE UNSURE ABOUT HOW TO ANSWER A QUESTION, PLEASE GIVE THE BEST ANSWER YOU CAN. **THERE ARE NO RIGHT OR WRONG ANSWERS.**

IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT:

English (US) version

INCONTINENCE – QUALITY OF LIFE

Your Feelings

(Please circle the number of your answer)

1. I worry about not being able to get to the toilet on time

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

2. I worry about coughing or sneezing because of my urinary problems or incontinence.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

3. I have to be careful standing up after I've been sitting down because of my urinary problems or incontinence.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

4. I worry about where toilets are in new places.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

5. I feel depressed because of my urinary problems or incontinence.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

INCONTINENCE – QUALITY OF LIFE

(Please circle the number of your answer)

6. Because of my urinary problems or incontinence, I don't feel free to leave my home for long periods of time.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

7. I feel frustrated because my urinary problems or incontinence prevents me from doing what I want.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

8. I worry about others smelling urine on me.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

9. My urinary problems or incontinence is always on my mind.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

10. It's important for me to make frequent trips to the toilet.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

INCONTINENCE – QUALITY OF LIFE
(Please circle the number of your answer)

11. Because of my urinary problems or incontinence, it's important to plan every detail in advance.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

12. I worry about my urinary problems or incontinence getting worse as I grow older.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

13. I have a hard time getting a good night of sleep because of my urinary problems or incontinence.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

14. I worry about being embarrassed or humiliated because of my urinary problems or incontinence.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

15. My urinary problems or incontinence makes me feel like I'm not a healthy person.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

INCONTINENCE – QUALITY OF LIFE
(Please circle the number of your answer)

16. My urinary problems or incontinence makes me feel helpless.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

17. I get less enjoyment out of life because of my urinary problems or incontinence.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

18. I worry about wetting myself.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

19. I feel like I have no control over my bladder.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

20. I have to watch what or how much I drink because of my urinary problems or incontinence.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

INCONTINENCE – QUALITY OF LIFE

About You

A-1 How long have you had urinary problems or incontinence? *(Please write the number below)*

_____ _____
YEARS **MONTHS**

A-2 How many medical appointments have you made in the past year to treat your urinary problems or incontinence? *(Please write the number on the line provided)*

_____ **NUMBER OF APPOINTMENTS IN THE LAST YEAR**

A-3 How would you describe the severity of your urinary problems or incontinence? *(Please circle the number of your answer)*

1 **MILD**

2 **MODERATE**

3 **SEVERE**

A-4 Do you lose urine when you cough, sneeze, run, walk, jump or when you do some other specific activity?

0 **NO**

1 **YES**

A-5 Do you lose control of your bladder before you can get to the bathroom?

0 **NO**

1 **YES**

INCONTINENCE – QUALITY OF LIFE

A-6 Do you lose urine at times not associated with any specific activity or the need to go to the bathroom?

0 NO

1 YES

A-7 In the last month, how many times did you lose urine, even a small amount, when you didn't want to? *(Please write the number on the line provided)*

_____ NUMBER OF TIMES IN THE LAST MONTH

A-8 In the last month, how many times did you lose urine, even a small amount, when you didn't want to?

0 NOT AT ALL IN THE LAST MONTH

1 1 TO 2 TIMES IN THE LAST MONTH

2 4 TIMES (ABOUT ONCE A WEEK)

3 2 TO 3 TIMES PER WEEK

4 ABOUT 1 TIME A DAY

5 ONE OR TWO TIMES A DAY

6 THREE OR FOUR TIMES A DAY

7 FIVE OR MORE TIMES A DAY

12.8 Appendix: Female Sexual Function Index

FEMALE SEXUAL FUNCTION INDEX (FSFI) – page 1 of 4

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

* Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

* Sexual intercourse is defined as penile penetration (entry) of the vagina.

* Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.					
1. Over the past 4 weeks, how often did you feel sexual desire or interest?	Almost always or always ☐5	Most times (more than half the time) ☐4	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐2	Almost never or never ☐1
2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?	Very high ☐5	High ☐4	Moderate ☐3	Low ☐2	Very low or none at all ☐1

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.						
3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?	No sexual activity ☐0	Almost always or always ☐5	Most times (more than half the time) ☐4	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐2	Almost never or never ☐1
4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?	No sexual activity ☐0	Very high ☐5	High ☐4	Moderate ☐3	Low ☐2	Very low or none at all ☐1

FEMALE SEXUAL FUNCTION INDEX (FSFI) – page 2 of 4						
5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?	No sexual activity ☐0	Very high confidence ☐5	High confidence ☐4	Moderate confidence ☐3	Low confidence ☐2	Very low or no confidence ☐1
6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?	No sexual activity ☐0	Almost always or always ☐5	Most times (more than half the time) ☐4	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐2	Almost never or never ☐1
7. Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?	No sexual activity ☐0	Almost always or always ☐5	Most times (more than half the time) ☐4	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐2	Almost never or never ☐1
8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?	No sexual activity ☐0	Extremely difficult or impossible ☐1	Very difficult ☐2	Difficult ☐3	Slightly difficult ☐4	Not difficult ☐5
9. Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	No sexual activity ☐0	Almost always or always ☐5	Most times (more than half the time) ☐4	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐2	Almost never or never ☐1
10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	No sexual activity ☐0	Extremely difficult or impossible ☐1	Very difficult ☐2	Difficult ☐3	Slightly difficult ☐4	Not difficult ☐5
11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?	No sexual activity ☐0	Almost always or always ☐5	Most times (more than half the time) ☐4	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐2	Almost never or never ☐1

FEMALE SEXUAL FUNCTION INDEX (FSFI) – page 3 of 4						
12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?	No sexual activity ☐0	Extremely difficult or impossible ☐1	Very difficult ☐2	Difficult ☐3	Slightly difficult ☐4	Not difficult ☐5
13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?	No sexual activity ☐0	Very satisfied ☐5	Moderately satisfied ☐4	About equally satisfied and dissatisfied ☐3	Moderately dissatisfied ☐2	Very dissatisfied ☐1
14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?	No sexual activity ☐0	Very satisfied ☐5	Moderately satisfied ☐4	About equally satisfied and dissatisfied ☐3	Moderately dissatisfied ☐2	Very dissatisfied ☐1
15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?		Very satisfied ☐5	Moderately satisfied ☐4	About equally satisfied and dissatisfied ☐3	Moderately dissatisfied ☐2	Very dissatisfied ☐1
16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?		Very satisfied ☐5	Moderately satisfied ☐4	About equally satisfied and dissatisfied ☐3	Moderately dissatisfied ☐2	Very dissatisfied ☐1
17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?	Did not attempt intercourse ☐0	Almost always or always ☐1	Most times (more than half the time) ☐2	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐4	Almost never or never ☐5

FEMALE SEXUAL FUNCTION INDEX (FSFI) – page 4 of 4						
18. Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?	Did not attempt intercourse ☐0	Almost always or always ☐1	Most times (more than half the time) ☐2	Sometimes (about half the time) ☐3	A few times (less than half the time) ☐4	Almost never or never ☐5
19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?	Did not attempt intercourse ☐0	Very high ☐1	High ☐2	Moderate ☐3	Low ☐4	Very low or none at all ☐5

Thank you for answering these questions.

12.9 Appendix: Vaizey Incontinence Score

Vaizey Incontinence Score

Please answer the following questions by placing a mark in the box that best applies to you.

	Never	Rarely	Sometimes	Weekly	Daily
How often do you have incontinence (accidents) with solid stool?					
How often do you have incontinence (accidents) with liquid stool?					
How often do you lose control of gas/wind?					
How often do your bowel symptoms affect your lifestyle?					
				No	Yes
Do you use a Pad or anal plug?					
Do you medications to make that make you constipated?					
Do you have to rush to the toilet as soon as you have an urge to go?					