CLINICAL TRIAL PROTOCOL

IND NUMBER: 126605

Phase 2, Open-Label Extension Study to Assess Long-Term Safety and Tolerability of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number: G201004

Sponsor:	GTx, Inc. 175 Toyota Center Memphis, TN 38103
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Version of Protocol:	1.0
Date of Protocol:	21 May 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 Phase 2, Open-Label Extension Study to Assess Long-Term Safety and Tolerability of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number G201004

Protocol Date 21 May 2018

Protocol accepted and approved by:

Vice President, Clinical Development

Mayzie Johnston, PharmD
GTx, Inc.
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Signature

22 May 2018
Date

Protocol Approval – Lead Statistician

Study Title Phase 2, Open-Label Extension Study to Assess Long-Term Safety and Tolerability of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number G201004

Protocol Date 21 May 2018

Protocol accepted and approved by:

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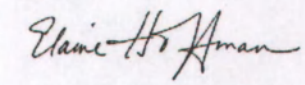

Signature Date

Protocol Approval – Principal Investigator

Study Title Phase 2, Open-Label Extension Study to Assess Long-Term Safety and Tolerability of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence

Protocol Number G201004

Protocol Date 21 May 2018

Protocol accepted and approved by:

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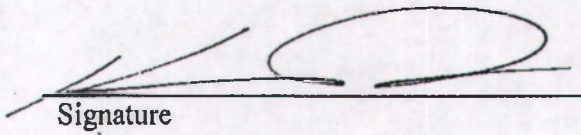

Signature

5/22/18

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "Phase 2, Open-Label Extension Study to Assess Long-Term Safety and Tolerability 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 1.0, dated 21 May 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 Harmonisation (ICH) E6; 62 Federal Register 25691 (May 9, 1997)

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PROTOCOL SYNOPSIS

Protocol Number:	G201004
Name of Investigational Product:	Enobosarm (GTx-024)
Title of Study:	Phase 2, Open-Label Extension Study to Assess Long-Term Safety and Tolerability of Enobosarm (GTx-024) in Postmenopausal Women With Stress Urinary Incontinence
Sponsor:	GTx, Inc.
Phase of Development:	Phase 2
Trial Site(s):	Approximately 65 (United States)
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. Relaxation of pelvic floor muscles 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 induced hypertrophy of the levator ani muscle to approximately 120% of that of a noncastrated 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 with the vehicle control. 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 who received doses of GTx-024 3 mg once daily for 12 weeks showed a mean reduction in stress incontinence episodes of 81%, with all 18 subjects seeing a clinically significant reduction (≥50% reduction in stress leaks) in the number of stress incontinence episodes by Week 12. A double-blind, placebo-controlled, parallel-design, randomized, multicenter, Phase 2 study (G201002) is currently ongoing to assess the clinical activity and safety of GTx-024 in postmenopausal women with SUI. The study consists of a screening period (4 weeks), treatment period (12 weeks), follow-up period (4 weeks), and durability period (16 weeks). The current 12-week, open-label extension study will enroll the following subjects from G201002: • From the first 225 subjects enrolled in G201002, only subjects randomly assigned to the placebo group and who have completed the 12-week treatment period and 16-week durability period of G201002 will be allowed to enroll in this study, once data from G201002 are unblinded. Placebo subjects who enrolled in the durability extension study (G201003) will be allowed to discontinue participation in G201003, once data from G201002 have been unblinded.

	• From Subject 226 onwards, any subject who was randomly assigned to any treatment group and who has completed the 12-week treatment period and the 4-week follow-up period in Study G201002 will be allowed to enroll. This open-label extension study will provide additional long-term safety and tolerability data for GTx-024.
Objectives:	**<u>Primary Objective - Safety</u>** The primary objective in this study is to assess long-term safety and tolerability of GTx-024 (3 mg administered once daily) in postmenopausal women with SUI. 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 and testosterone levels • Change from baseline in vital sign measurements • Change from baseline in endometrial stripe thickness as assessed with transvaginal ultrasound (only in subjects with an intact uterus) **<u>Secondary Objectives - Efficacy</u>** The secondary objectives of this study are to describe the efficacy of GTx-024 (3 mg administered once daily) as a treatment for SUI in postmenopausal women in relation to: • Change from baseline in the mean number of stress incontinence episodes per day as measured with the 3-day voiding diary • Change in subject-reported impression of SUI severity as measured with the Patient Global Impression of Severity scale (PGI-S) • Improvement relative to baseline in subject-reported impression of SUI improvement as measured with the Patient Global Impression of Improvement scale (PGI-I) • Change from baseline in the mean number of urge incontinence episodes per day as measured with the 3-day voiding diary • Change from baseline in the mean number of total incontinence episodes (stress + urge) as measured

	with the 3-day voiding diary
Subject Population:	Inclusion Criteria Each subject must meet all of the following criteria to be enrolled in this study: 1. Be an eligible subject from G201002, where an eligible subject is defined as: a. one of the first 225 subjects who were randomly assigned to the placebo group in G201002 and who have completed the required treatment and durability periods of that study, or; b. any subject from 226 onwards, who was randomly assigned to any treatment group and who completed the required treatment and follow-up periods of that study 2. Be able to read, understand, and provide written, dated, informed consent prior to enrollment in the current study and be likely to comply with the study protocol and communicate with study personnel about AEs and other clinically important information 3. Provide written consent to participate in the study within the following timeframes: a. for G201002 Subjects 1-225, within 30 days after unblinding of G201002 (subjects who consent to participate in G201003 will be allowed to discontinue from that study and consent to this study upon unblinding of G201002) b. for G201002 Subjects 226-493, within 30 days of completing both the treatment and follow-up periods of G201002 4. Agree 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 agonists, or α-adrenergic blockers, throughout the duration of the study Exclusion Criteria A subject who meets any of the following criteria will be excluded from the study: 1. Starts any new treatment (medication, pelvic floor physical therapy, or other treatment known to impact the pelvic floor) after completing G201002

	that is known or suspected to affect lower urinary tract function, including vaginal rejuvenation 2. 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. 3. Has a current cancer diagnosis (with the exception of nonmelanoma skin cancer) or any history of breast or endometrial cancer 4. Has a known history or current episode of: a. New York Heart Association Stage ≥ 2 hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg) at screening and/or baseline. Subjects with hypertension that has been treated and controlled with medication for ≥ 2 weeks prior to screening are eligible for participation b. 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 c. Cardiac-related syncopal event within the past year d. Cardio or cerebral vascular disease requiring surgical intervention (e.g., bypass surgery, angioplasty). For subjects with previous stent placement, please contact the medical monitor e. Congestive heart failure of Stage > 2 according to New York Heart Association criteria f. Angina pectoris 5. Has a 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 interpretation of study

	results
Study Design	This is a multicenter, Phase 2, open-label extension study that will assess the long-term safety and tolerability of GTx-024. The current study will enroll the following subjects: • From the first 225 subjects enrolled in G201002, only subjects randomly assigned to the placebo group and who have completed the 12-week treatment period and 16-week durability period from G201002 will be allowed to enroll in this study, once data from G201002 are unblinded. Placebo subjects who enrolled in the durability extension study (G201003) will be allowed to discontinue participation in G201003, once data from G201002 have been unblinded • From Subject 226 onwards, any subject who was randomly assigned to any treatment group and who has completed the 12-week treatment period and the 4-week follow-up period in Study G201002 All subjects in this study will receive GTx-024 3 mg orally, once daily. **Baseline (Day 0)** Subjects will be evaluated, and an additional written informed consent for the open-label extension study will be obtained. Procedures will be performed at baseline as specified in the schedule of events for the study. **Long-term Open-label Extension Period** Subjects who continue to meet the eligibility criteria will attend clinic visits at 4-week intervals for the first 12 weeks of the open-label extension study (i.e., Weeks 4, 8, and 12). Following the first 12 weeks, subjects will attend clinic visits every 12 weeks (i.e., 12 weeks from Visit 3 onwards). At each clinic visit, study procedures will be performed as specified in the schedule of events. There is currently no planned end to this study; instead, subjects will be on treatment and followed until marketing approval is granted to GTx-024 or until the withdrawal of the Investigational New Drug application. If marketing approval is granted to GTx-024, a plan for the transition of subjects from study drug to commercial drug product or other therapy will be implemented. Data from this open-label extension study will be used to assess the long-term safety and tolerability of GTx-024.

Estimated Study Duration:	There is no scheduled end to the study, and duration will depend on the commercial availability of GTx-024.
Safety Assessments:	Safety assessments will include the following: • AEs • Clinical laboratory analyses • Levels of sex hormone–binding globulin and testosterone • Endometrial stripe thickness as assessed with transvaginal ultrasound (only for subjects with an intact uterus) Other standard safety assessments will include vital signs, height and weight measurements, concomitant medications, medical history, and brief physical examination findings.
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. • 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.
Study Drug:	Study drug will be provided as softgel capsules in bottle packaging. All subjects will receive GTx-024 3 mg once daily.
Sample Size Calculation:	No power calculations were carried out, as no formal statistical analysis will be performed.
Analysis Sets:	The safety analysis set (SAS) contains all subjects in the study who receive ≥ 1 dose of study drug. All safety

	analyses will use the SAS. The full analysis set (FAS) contains all randomized subjects who receive ≥ 1 dose of study drug and have ≥ 1 postbaseline primary efficacy assessment (3-day voiding diary). All efficacy analyses will use the FAS.
Methods of Analysis:	A separate statistical analysis plan (SAP) will be finalized, providing detailed methods for all endpoints. In general, descriptive or 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 visit. Source data for summary tables and statistical analyses will be presented as subject data listings. No imputation for missing values will be done. All statistical analyses will be performed using SAS (version 9.3 or higher). No formal statistical analysis will be performed as the open-label extension study is not powered for inferential statistics. Two-sided 95% confidence intervals will be provided where appropriate. Change from baseline will be between baseline (Day 0) and scheduled visits. The SAP will specify up to which visit summaries will be produced, as not all subjects will have been in the study for the same length of time. Further details on the analysis of the efficacy endpoints will be provided in the SAP. **Safety Analyses** All safety parameters (including AEs) will be summarized using the SAS. All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. All treatment-emergent AEs will be summarized and presented in the listings according to the number of subjects who report 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 treatment during the open-label extension study. **Efficacy Analyses** The primary analysis will be conducted on the primary endpoints at scheduled visits using the FAS. For continuous and ordinal endpoints, the treatment effect will be summarized descriptively by visit.

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBC	complete blood count
CFR	Code of Federal Regulations
CMP	comprehensive metabolic panel
EDC	electronic data capture
eCRF	electronic case report form
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HDL	high-density lipoprotein
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute–Common Terminology Criteria for Adverse Events
OTC	over-the-counter
PGI-I	Patient Global Impression of Improvement scale
PGI-S	Patient Global Impression of Severity scale
SAE	serious adverse event
SAP	statistical analysis plan
SARM	selective androgen receptor modulator
SAS	safety analysis set
SHBG	sex hormone–binding globulin
SUI	stress urinary incontinence
ULN	upper limit of normal
US	United States

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). Relaxation of pelvic floor muscles 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 induced hypertrophy of the levator ani muscle to approximately 120% of that of a noncastrated 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 with the vehicle control (GTx, Inc. 2017; Herzog and Fultz 1990; 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 that was 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 who received doses of GTx-024 3 mg once daily for 12 weeks showed a mean reduction in stress incontinence episodes of 81%, with all 18 subjects experiencing clinically significant reduction (≥50% reduction in stress leaks) in the number of stress incontinence episodes by Week 12.

A double-blind, placebo-controlled, parallel-design, randomized, multicenter, Phase 2 study (G201002) is currently ongoing to assess the clinical activity and safety of GTx-024 in postmenopausal women with SUI. The study consists of a screening period (4 weeks), treatment period (12 weeks), follow-up period (4 weeks), and durability period (16 weeks).

The current 12-week, open-label extension study will enroll the following subjects from G201002:

- From the first 225 subjects enrolled in G201002, only subjects randomly assigned to the placebo group and who have completed the 12-week treatment period and 16-week durability period from G201002 will be allowed to enroll in this study, once data from G201002 are unblinded. Placebo subjects who enrolled in the durability extension study (G201003) will be allowed to discontinue participation in G201003, once data from G201002 have been unblinded
- From Subject 226 onwards, any subject who was randomly assigned to any treatment group and who has completed the 12-week treatment period and the 4-week follow-up period in Study G201002 will be allowed to enroll

This open-label extension study will provide additional long-term safety and tolerability data for GTx-024. All subjects in this study will receive GTx-024 3 mg orally, once daily.

2 Study Objectives

2.1 Primary Objective

The primary objective in this study is to assess long-term safety and tolerability of GTx-024 (3 mg administered once daily) in postmenopausal women with SUI.

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 levels
- Change from baseline in vital sign measurements
- Change from baseline in endometrial stripe thickness as assessed with transvaginal ultrasound (only in subjects with an intact uterus)

2.2 Secondary Objectives

The secondary objectives of this study are to describe the efficacy of GTx-024 (3 mg administered once daily) as a treatment for SUI in postmenopausal women in relation to:

- Change from baseline in the mean number of stress incontinence episodes per day as measured with the 3-day voiding diary
- Change in subject-reported impression of SUI severity as measured with the Patient Global Impression of Severity scale (PGI-S)
- Improvement relative to baseline in subject-reported impression of SUI improvement as measured with the Patient Global Impression of Improvement scale (PGI-I)
- Change from baseline in the mean number of urge incontinence episodes per day as measured with the 3-day voiding diary
- Change from baseline in the mean number of total incontinence episodes (stress + urge) as measured with the 3-day voiding diary

3 Investigational Plan

3.1 Study Design

This is a multicenter, Phase 2, open-label extension study that will assess the long-term safety and tolerability of GTx-024.

The current study will enroll the following subjects from G201002:

- From the first 225 subjects enrolled in G201002, only subjects randomly assigned to the placebo group and who have completed the 12-week treatment period and 16-week durability period will be allowed to enroll in this study, once data from G201002 are unblinded. Placebo subjects who enrolled in the durability extension study (G201003) will be allowed to discontinue participation in G201003, once data from G201002 have been unblinded
- From Subject 226 onwards, any subject who was randomly assigned to any treatment group and who has completed the 12-week treatment period and the 4-week follow-up period in Study G201002

All subjects in this study will receive GTx-024 3 mg orally, once daily.

The study consists of the following visits:

Baseline (Day 0)

Subjects will be evaluated, and an additional written informed consent for the open-label extension study will be obtained. Procedures will be performed at baseline as specified in the schedule of events (Table 12–1) for the study.

Long-term Open-label Extension Period

Subjects who continue to meet the eligibility criteria will attend clinic visits at 4-week intervals for the first 12 weeks of the open-label extension study (i.e., Weeks, 4, 8, and 12). Following the first 12 weeks, subjects will attend clinic visits every 12 weeks (i.e., 12 weeks from Visit 3 onwards). At each clinic visit, study procedures will be performed as specified in the schedule of events (Table 12–1).

There is currently no planned end to this study; instead, subjects will be on treatment and followed until marketing approval is granted to GTx-024 or until the withdrawal of the Investigational New Drug application. If marketing approval is granted to GTx-024, a plan

for the transition of subjects from study drug to commercial drug product or other therapy will be implemented.

Data from this open-label extension study will be used to assess the long-term safety and tolerability of GTx-024.

3.1.1 Rationale of Study Design

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 open-label extension study will provide additional long-term safety and tolerability data for GTx-024.

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. Dose-dependent increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed. A higher incidence of transient, asymptomatic increases in ALT levels reported as AEs occurred in the group receiving GTx-024 3 mg (20.8%) compared with the placebo group (0%). One subject who received 3 mg/day of GTx-024 was discontinued due to an ALT level >3 times the upper limit of normal (ULN). The ALT levels returned to normal with continued exposure to GTx-024 in most cases and, furthermore, in instances when dosing was not continued, levels returned to normal. No significant increases in levels of 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 levels are temporary and typically return to baseline levels 12 months after treatment initiation.

In an ongoing, Phase 2 study of GTx-024 in estrogen receptor–positive/androgen receptor-positive breast cancer that is examining daily doses of GTx-024 at 9 and 18 mg, several cases of clinically significant hypercalcemia have been observed that were assessed by the investigators as possibly related to GTx-024. Subjects with hypercalcemia had

estrogen receptor–positive breast cancer with bone metastases. Hypercalcemia has not been observed in previous studies of healthy individuals or at doses <9 mg.

Subjects will be monitored at each visit for health changes since the previous visit and adverse effects of treatment. Since elevations in ALT levels 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 liver function tests or other signs of hepatotoxicity (Section 6.3.2). Subjects 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

Up to 500 subjects will be enrolled at around 65 sites in the United States (US). Subjects will be enrolled in the current study 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. Be an eligible subject from G201002, where an eligible subject is defined as:
    a. one of the first 225 subjects who were randomly assigned to the placebo group in G201002 and who have completed the required treatment and durability periods of that study, or;
    b. any subject from 226 onwards, who was randomly assigned to any treatment group and who completed the required treatment and follow-up periods of that study
2. Be able to read, understand, and provide written, dated informed consent prior to enrollment in the current study and be likely to comply with the study protocol and communicate with study personnel about AEs and other clinically important information
3. Provide written consent to participate in the study within the following timeframes:
    a. for G201002 Subjects 1-225, within 30 days after the unblinding of G201002 (subjects who consent to participate in G201003 will be allowed to discontinue from that study and consent to this study upon unblinding of G201002)
    b. for G201002 Subjects 226-493, within 30 days of completing both the treatment and follow-up period of G201002

4. Agree 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 agonists, or α-adrenergic blockers, throughout the duration of the study

4.1.2 Exclusion Criteria

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

1. Starts any new treatment (medication, pelvic floor physical therapy, or other treatment known to impact the pelvic floor) after completing G201002 that is known or suspected to affect lower urinary tract function, including vaginal rejuvenation
2. 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.
3. Has a current cancer diagnosis (with the exception of nonmelanoma skin cancer) or any history of breast or endometrial cancer
4. Has a known history or current episode of:
    a. New York Heart Association Stage ≥ 2 hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg) at screening and/or baseline. Subjects with hypertension that has been treated and controlled with medication for ≥ 2 weeks prior to screening are eligible for participation
    b. 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
    c. Cardiac-related syncopal event within the past year

d. Cardio or cerebral vascular disease requiring surgical intervention (e.g., bypass surgery, angioplasty). For subjects with previous stent placement, please contact the medical monitor

e. Congestive heart failure of Stage > 2 according to New York Heart Association criteria

f. Angina pectoris

5. Has a current or past history of any physical condition that, in the investigator's opinion, might put the subject at risk, impact absorption of the study drug, or interfere with interpretation of study results

4.2 Withdrawal of Subjects from the Study

The duration of the study is not fixed and is defined for each subject as the date signed, written informed consent is provided through the last follow-up visit depending on the commercial availability of GTx-024.

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 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 if the principal investigator decides it 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 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). Subjects who discontinue from study drug will be monitored for AEs for 30 days after they stop treatment with study drug. Every effort will be made to obtain all end-of-treatment measures as outlined in Table 12–1, in the event that a subject withdraws, or is withdrawn, from the study before transitioning to commercial product or other therapy. 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 discontinue prematurely from the study will not be replaced.

5 Study Treatments

Refer to Section 3.1 for a full description of the study design. All subjects will receive GTx-024 3 mg administered orally, once daily. Study drug will be supplied as opaque, white to off-white, size 5, oval softgel capsules.

5.1 Method of Assigning Subjects to Treatment Groups

Subjects who meet all eligibility criteria will continue the current open-label extension study with randomization code as assigned by an interactive web response system.

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 required to take one 3 mg Softgel capsule per day. In the event of a missed dose, subjects will be instructed to skip the missed dose and continue dosing as per label instructions from the next day.

5.3 Identity of Study Drug

The GTx-024 study drug is an opaque, white to off-white, size 5, oval softgel capsule that contains the active ingredient GTx-024 (3 mg) dissolved in the inactive excipient polyethylene glycol 400. 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 high-density polyethylene bottles with induction seal and child-resistant closure. Each bottle will contain sufficient study drug for 35 days of dosing according to the study protocol. Three bottles (a total of 105 dosing days) will be packaged together in one subject kit. For the first 3 visits, sites will collect the study drug previously dispensed, perform accountability, and re-dispense the same kit.

Each subject kit, and the bottles contained in the kit, will be labeled with a unique medication identification number. A clinical label with the medication identification number will be affixed to the outside of each bottle and subject kit. The label will also 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 of 15°C to 25°C (59°F-77°F), with excursions permitted to 30°C (86°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.

5.5 Overdose Management

In Phase 1 studies, subjects have safely received single doses of up to GTx-024 100 mg. 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 the 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

This is an open-label study, and all subjects will receive study drug (GTx-024 3 mg).

5.6.1 Breaking the Blind

Not applicable, as this is an open-label study.

5.7 Treatment Compliance

Individual subject compliance in taking study drug will be monitored by counting the unused medication that is returned by the subject at visits. Compliance will be documented. If compliance is < 80% or > 120%, the investigator or designee is to counsel the subject and ensure that steps are taken to improve compliance. Subjects who are < 80% or > 120% compliant with the dose 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 baseline, Day 0) 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, and 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 other investigational agent
- New pelvic floor exercises (including Kegel) throughout the follow-up period

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an additional informed consent form (ICF) for this open-label extension study. Subjects will have the opportunity to have any questions answered before they sign 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 Baseline (Day 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 who meet initial inclusion/exclusion criteria and express willingness to participate before study site personnel conduct any study assessments of such subjects.

Once informed consent is obtained, the subjects will be assigned a subject number and a detailed interview will be conducted with the subject about her concomitant medications, and recent medical history will be evaluated. Height and weight will be measured, and vital signs will be assessed as presented in Table 12–1.

The subject's eligibility criteria will be reviewed. During the visit, the subject will complete the PGI-S. Blood will be drawn for a comprehensive metabolic panel (CMP), complete blood count (CBC), lipid panel, hormone panel, and SHBG tests. A baseline transvaginal ultrasound examination will also be performed in subjects with an intact uterus.

The subject will be provided with a 3-day voiding diary and instructed to complete the 3-day voiding diary within the week preceding her next study visit.

Study drug will be dispensed with administration instructions. The medication identification number assigned to the subject will be noted in the eCRF for study drug accountability. The subject will take the first dose of study drug during the baseline visit. The subject will be reminded to bring all unused study drug (in its original packaging) to her next clinic visit. Any subject who prematurely discontinues the study or study drug will be asked to return to the study site and complete end-of-study assessments.

6.1.2 Study Visits 1 to 3: Weeks 4 to 12, Clinic Visit

The subject will return to the study site for a clinic visit as per the schedule of events described in Table 12–1. Concomitant medications and AEs will be reviewed. Weight and vital signs will be measured.

The 3-day voiding diary provided to the subject at her previous visit will be collected and completion verified. The subject will be provided with a new 3-day voiding diary and instructed to complete it within the week preceding her next study visit. The subject will also complete the PGI-S and PGI-I during each site visit. Blood will be drawn for a CMP, CBC, lipid panel, hormone panel, and SHBG tests.

Study drug will be dispensed with administration instructions. The medication identification number assigned to the subject will be noted in the eCRF for study drug accountability. The subject will be reminded to bring all unused study drug (in its original packaging) to her next clinic visit.

A transvaginal ultrasound examination will be performed in subjects with an intact uterus only at Visit 3.

6.1.3 Study Visit 4 Onwards: Week 24 Onwards, Clinic Visit

During the long-term safety period (after Visit 3), the subject will return to the study site for clinic visits. Concomitant medications and AEs will be reviewed. Weight and vital signs will be measured. Blood will be drawn for a CMP, CBC, and lipid panel. Completion of a 3-day voiding diary will be verified.

The hormone panel and SHBG tests will be assessed every 24 weeks only (i.e., every other clinic visit).

A transvaginal ultrasound examination will be performed every 24 weeks (i.e., every other clinic visit) in subjects with an intact uterus. Study drug will be dispensed, with administration instructions, at each clinic visit. The medication identification number assigned to the subject will be noted in the eCRF for study drug accountability. The subject will be reminded to bring all unused study drug (in its original packaging) to her next clinic visit.

The subject will be provided with a new 3-day voiding diary and instructed to complete it within the week preceding her next study visit.

Any subject who prematurely discontinues study or study drug will be asked to return to the study site and complete the end-of-study assessments.

6.1.4 End-of-Study Visit

Approximately 30 days after the last dose of GTx-024, the subject will return to the study site for an end-of-study clinic visit. Unused study drug will be collected. Concomitant medications and AEs will be reviewed. Weight and vital signs will be measured. Blood will be drawn for a CMP, CBC, lipid panel, hormone panel, and SHBG test. Completion of a 3-day voiding diary will be verified.

The subject will complete the PGI-S and PGI-I questionnaires.

The subject will be instructed on the transition to commercial drug or other therapy by the physician.

6.2 Efficacy Assessments

Efficacy assessments will include a 3-day voiding diary, PGI-S, and PGI-I.

6.2.1 Three-Day Voiding Diary

Subjects will record all urinary voids, specifying each episode of urinary leakage, including type (stress or urge). 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.

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

6.2.2 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 12.2). Validity of the PGI-S has been established for application in SUI.

6.2.3 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 12.3). Validity of the PGI-I has been established for application in SUI.

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 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 that requires 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 that requires 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 end of the study.

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) 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 National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. For any AE that is not specifically covered in NCI-CTCAE version 4.0, the criteria that should be used are as follows:

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 noninvasive 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 × 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 blood pressure, 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 baseline only and weight will be measured as indicated in Table 12–1.

6.3.3.3 Prior and Concomitant Medications

At the baseline 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 Transvaginal Ultrasound

Only for subjects with an intact uterus, transvaginal ultrasound will be performed at the baseline visit, Week 12 and every 24 weeks only (i.e., every other clinic visit) to observe changes in the endometrial stripe thickness (mm). Transvaginal ultrasound examinations will be evaluated locally.

6.4 Other Assessments

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 or other safety assessments, 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:

- Complete blood count, including red blood cells, white blood cells, mean corpuscular volume, hemoglobin, hematocrit, platelets, and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)

- Comprehensive metabolic panel (Chem 16), including 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)
- Fasting lipid panel, including total cholesterol, low-density lipoprotein, HDL, and triglycerides
- Hormone panel, including testosterone, free testosterone, and estradiol
- SHBG

7 Statistical and Analytical Plan

7.1 Primary Safety Endpoint

The primary objective in this study is to assess the safety and tolerability of GTx-024 3 mg administered once daily in relation to the following:

- Incidence of AEs
- Change from baseline in clinical laboratory evaluations
- Change from baseline in SHBG and testosterone levels
- Change from baseline in vital sign measurements
- Change from baseline in endometrial stripe thickness as assessed with transvaginal ultrasound (only in subjects with an intact uterus)

7.2 Secondary Efficacy Endpoints

The secondary objective in this study is to assess the efficacy of GTx-024 3 mg administered once daily at each scheduled visit in relation to the following:

- Change from baseline in the mean number of stress incontinence episodes per day as measured with the 3-day voiding diary
- Change from baseline in subject-reported impression of SUI severity as measured with the PGI-S
- Improvement relative to baseline in subject-reported impression of SUI improvement as measured with the PGI-I
- Change from baseline in the mean number of urge incontinence episodes per day as measured with the 3-day voiding diary
- Change from baseline in the mean number of total incontinence episodes (stress + urge) as measured with the 3-day voiding diary

These analyses will be described in further detail in the statistical analysis plan (SAP).

7.3 Sample Size Calculation

No power calculations were carried out, as no formal statistical analysis will be performed.

7.4 Analysis Sets

Data analysis will be performed on a safety analysis set (SAS) and a full analysis set (FAS).

The SAS set contains all subjects in the study who receive ≥ 1 dose of study drug. All safety analyses will use the SAS.

The FAS is used for efficacy analysis. The FAS consists of all randomized subjects who receive ≥ 1 dose of study drug and have ≥ 1 postbaseline primary efficacy assessment (3-day voiding diary). Further details will be provided in the SAP.

7.5 Description of Subgroups to be Analyzed

No subgroup analyses are planned.

7.6 Statistical Analysis Methodology

A separate SAP will be finalized, providing detailed methods for all endpoints. In general, descriptive or 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 visit. Source data for summary tables and statistical analyses will be presented as subject data listings.

All statistical analyses will be performed using SAS (version 9.3 or higher). No formal statistical analysis will be performed, as the open-label extension study is not powered for inferential statistics. Two-sided 95% confidence intervals will be provided where appropriate. No imputation will be done for missing data. The SAP will specify up to which visit summaries will be produced, as not all subjects will have been in the study for the same length of time. Further details on the analysis of efficacy endpoints will be provided in the SAP.

The study period is defined as baseline (Day 0) through end of study. Change from baseline will be between baseline (Day 0) and scheduled visits.

7.6.1 Analysis of Safety Endpoints

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

All AEs will be coded using the latest version of MedDRA. All treatment-emergent AEs will be summarized and presented in the listings by the number of subjects who report 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.

7.6.2 Analysis of Secondary Efficacy Endpoints

For continuous primary endpoints, treatment effects will be summarized descriptively according to visit.

For ordinal primary endpoints, treatment effects will be summarized descriptively according to visit.

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

7.7 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, International Council for Harmonisation (ICH) Guidelines, GCP, local laws and legislation, and the Health Insurance Portability and Accountability Act.

7.7.1 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.

7.7.2 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 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 CD-ROM 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 CD-ROM 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 CD-ROM 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 US Food and Drug Administration (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 the 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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Luber KM. The definition, prevalence, and risk factors for stress urinary incontinence. Rev Urol. 2004;6 Suppl 3:S3-9.

Mohler ML, Bohl CE, Jones A, et al. Nonsteroidal selective androgen receptor modulators (SARMs): dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. J Med Chem. 2009;52(12):3597-617.

12 Appendices

12.1 Appendix: Schedule of Events

Table 12–1 Schedule of Events for Protocol G201004

Procedure	Baseline Day 0	V1	V2	V3	Long-term Safety	End of Study
Day or Week	Week 0	Week 4	Week 8	Week 12	Every 12 weeks following V3	30 days after last dose of GTx-024
Visit Window (days)	–	±7	±7	±7	±7	±7
Informed consent	X					
Eligibility criteria review	X					
Medical history	X					
Concomitant medications	X	X	X	X	X	X
Height[a] and weight	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
3-Day voiding diary	X	X	X	X	X	X
PGI-S	X	X	X	X	X	X
PGI-I		X	X	X	X	X
Adverse event reviews	X	X	X	X	X	X
CMP (Chem 16 panel)	X	X	X	X	X	X
CBC	X	X	X	X	X	X
Lipid panel	X	X	X	X	X	X
Hormone panel[b]	X	X	X	X	X	X
SHBG[b]	X	X	X	X	X	X
Transvaginal ultrasound[c]	X			X	X	
Dispense study drug	X	X	X	X	X	
Collect unused study drug		X	X	X	X	X

Abbreviations: CBC, complete blood count; CMP, comprehensive metabolic panel; PGI-I, Patient Global Impression of Improvement scale; PGI-S, Patient Global Impression of Severity scale; SHBG, sex hormone–binding globulin; V, visit.

[a] Height is measured at baseline only.

[b] During the long-term safety period, the hormone panel and SHBG will be assessed every 24 weeks only (i.e., every other clinic visit).

[c] During the long-term safety period, the transvaginal ultrasound will be assessed every 24 weeks only (i.e., every other clinic visit)

12.2 Appendix: Patient Global Impression of Severity Scale

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

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12.3 Appendix: Patient Global Impression of Improvement Scale

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

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