GTx-024 as a Treatment for Stress Urinary Incontinence in Women: A Proof of Concept Study

Protocol G201001
Version 1.0
Confidential

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CONFIDENTIALITY STATEMENT

STATEMENT OF COMPLIANCE

The 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) ICH E6; 62 Federal Register 25691 (May 9, 1997)

PROTOCOL SIGNATURE PAGE

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Protocol Date: 07 August 2015

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SIGNATURE:

Mayzie Johnston 08/07/15

Sponsor Date

Mayzie Johnston V.P Medical Affairs and Clinical Operations

Name and Title of Sponsor Representative

10/7/15

Principal Investigator: Date

Name of Principal Investigator *(Please Print)*

The signature of the Sponsor Representative constitutes approval of this protocol. The signature of the Principal Investigator constitutes approval of this protocol and an assurance that this study will be conducted according to all requirements of this protocol and according to Good Clinical Practices (GCP).

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LIST OF ABBREVIATIONS

AE	Adverse Event
AMDC	Adult Muscle Derived Cells
ALT	Alanine Transaminase
AR	Androgen Receptor
AR+/TNBC	AR Positive, Triple Negative Breast Cancer
AST	Aspartate Aminotransferase
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
°C	Degrees Celsius
CB	Clinical Benefit
CBC	Complete Blood Count
CD-ROM	Compact Disk Read Only Memory
CFR	Code Of Federal Regulations
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria For Adverse Events
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DSMB	Data And Safety Monitoring Board
DXA	Dual-Energy X-Ray Absorptiometry
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
CRF	Case Report Form
EMG	Electromyography
ER	Estrogen Receptor

ER+BC	Estrogen Receptor Positive Breast Cancer
ºF	Degrees Fahrenheit
FDA	Food And Drug Administration
FSFI	Female Sexual Function Index
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
GTx	GTx, Inc.
GTx-024	Enobosarm
HBsAg	Hepatitis B Surface Antigen
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQOL	Health Related Quality Of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference On Harmonization
IEC	Independent Ethics Committee
IIQ-7	Incontinence Impact Questionnaire
IMP	Investigational Medicinal Product
IN	Investigator Notification
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISD	Intrinsic Sphincter Deficiency
LBM	Lean Body Mass
LDL	Low-Density Lipoprotein
LUTS	Lower Urinary Tract Symptoms
MESA	Medical, Epidemiological And Social Aspects Of Aging
Mg	Milligram
MMRM	Mixed Model Repeat Measurement
MRI	Magnetic Resonance Imaging
MUCP	Maximum Urethral Closure Pressure

NA	Not Applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria For Adverse Events
NOAEL	No-Observable-Adverse-Effect-Levels
NSCLC	Non-Small Cell Lung Cancer
PCOS	Polycystic Ovarian Syndrome
Pgi-I	Patient Global Impression Of Improvement Scale
Pgi-S	Patient Global Impression Of Severity Scale
PFM	Pelvic Floor Muscle
PFS	Progression Free Survival
PI	Principal Investigator
PO	Per Os (Oral)
PrR	Progesterone Receptor
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Physical Therapy
PVR	Post Void Residual
QA	Quality Assurance
QOL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARM	Selective Androgen Receptor Modulator
SCP	Stair Climb Power
SD	Stable Disease
SHBG	Sex Hormone Binding Globulin
SUI	Stress Urinary Incontinence
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TNBC	Triple Negative Breast Cancer

UA	Urinalysis
UDI	Urinary Distress Inventory
UI	Urinary Incontinence
ULN	Upper Limit of Normal
UNK	Unknown
UPP	Urethral Pressure Profile
US	Ultrasound
UTI	Urinary Tract Infection

1 PROTOCOL SUMMARY

Title:	GTx-024 as a Treatment for Stress Urinary Incontinence in Women: A Proof of Concept Study
Sponsor:	GTx, Inc.
Indication:	Stress Urinary Incontinence (SUI)
Study Design:	This is a single site, single-arm, open-label proof of concept feasibility study.
Objectives:	**Primary Objective** Describe the effect of 12 weeks of treatment of GTx-024 on the number of stress incontinence episodes/day as assessed by the 3 day voiding diary. **Secondary Objectives** Describe the effect of 12 weeks of treatment of GTx-024 on the number of voids/day as assessed by the 3 day voiding diary. Describe the effect of 12 weeks of treatment of GTx-024 on urine volume per void as assessed by the 3 day voiding diary. Describe the effect of 12 weeks of treatment of GTx-024 on SUI as assessed by 24 hour pad weight test. Describe the effect of 12 weeks of treatment of GTx-024 on SUI as assessed by the Urethral Pressure Profile (UPP). Describe the effect of 12 weeks of treatment of GTx-024 on SUI as assessed by the Bladder Stress Test. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported stress urinary incontinence symptoms as assessed by the MESA Urinary Questionnaire. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported impression of stress urinary incontinence severity as assessed by the Patient Global Impression of Severity Scale (PGI-S) Describe the effect of 12 weeks of treatment of GTx-024 on patient reported impression of improvement as assessed by the Patient Global Impression of Improvement Scale (PGI-I). Describe the effect of 12 weeks of treatment of GTx-024 on patient reported urogenital distress as assessed by the Urinary Distress Inventory Questionnaire (UDI-6).

	Describe the effect of 12 weeks of treatment of GTx-024 on patient reported impact of urinary incontinence on daily life as assessed by the Incontinence Impact Questionnaire (IIQ-7). Describe the effect of 12 weeks of treatment of GTx-024 on patient reported sexual function as indicated on the completion of the Female Sexual Function Index Questionnaire (FSFI). Describe the effect of 12 weeks of treatment of GTx-024 on pelvic floor muscles as measured by MRI. **Safety objective:** To describe the safety profile of GTx-024 3 mg PO daily in subjects with SUI.
Target Population:	Adult postmenopausal women with SUI **Subject Inclusion Criteria**: Subjects eligible for inclusion in this study must meet **all** of the following criteria: 1. Give voluntary, written and signed, informed consent 2. Female 3. Age 18 to 80 years old 4. Clinically confirmed as postmenopausal. Subjects must have undergone the onset of spontaneous, medically induced or surgical menopause prior to the start of this study. Postmenopausal is defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy. 5. SUI symptoms for at least 6 months duration 6. Predominant SUI (MESA questionnaire) 7. 24 hour pad weight >3 gms at baseline 8. At least 4, but no more than 15, SUI episodes on each day of the 3 day baseline voiding diary 9. Serum AST and ALT within normal limits 10. Total bilirubin within normal limits 11. Positive Bladder Stress Test 12. Subject agrees to not start any new treatment (medication or otherwise) that is known to affect lower urinary tract function throughout the treatment and follow up periods. 13. Subject agrees to maintain on a stable dose of any medication known to affect lower urinary tract function, including but not limited to anticholinergics, tricyclic antidepressants, or alpha-adrenergic blockers, throughout the treatment and follow-up period.

	Subject Exclusion Criteria: Subjects eligible for this study must not meet **any** of the following criteria: 1. Pelvic floor physical therapy within the last 6 months 2. History of pelvic radiation treatment 3. History of urethral diverticula 4. History of urethral sling, anterior prolapse repair, ureteral bulking agents and/or other SUI procedure or surgery 5. Known vesicoureteral reflux, vaginal prolapse beyond the introitus, or other significant pelvic floor abnormalities 6. Patient has urinary incontinence of neurogenic etiology 7. Patient is morbidly obese (defined as 100 pounds over their ideal body weight, or body mass index 40 or greater) 8. Chronic hepatitis 9. Hepatic cirrhosis 10. HIV and/or hepatitis A, B, or C 11. Subjects taking systemic hormone products (excludes intravaginal application of estradiol topical/tablet agents and hormones delivered via vaginal rings) 12. Subjects with a history of breast or endometrial cancer. 13. Subjects with cerebrovascular disease, thromboembolic disorders, myocardial infarction, or angina. 14. Subject with an entry measurement of > 5 mm endometrial stripe thickness as measured by MRI. 15. Clinically confirmed urinary tract infection 16. Any other condition which per investigators' judgement may increase subject risk
Phase:	2
Number of Sites:	1
Study Duration:	12 weeks
Number of Subjects / Participation Duration:	Up to 35 subjects. Each subject may complete up to 5 months of study participation.
Estimated Time to Complete Enrollment:	6 months
Indication for Product Use:	GTx-024 has been tested as a treatment for muscle wasting associated with cancer cachexia, but is not currently marketed.
Instructions for Product Use:	Subjects will be instructed to take one 3 mg softgel capsule per day by mouth, without regard to food intake.

Statistical Considerations:	This is a proof of concept feasibility study, so no power calculation is needed. Therefore, up to 35 subjects meeting inclusion/exclusion criteria will be recruited until 30 subjects have completed treatment. Descriptive statistics will be performed to explore changes in primary and secondary outcomes measures between baseline and end of treatment. The primary efficacy measure will be a reduction in the number of stress incontinence episodes/day. Secondary efficacy measures will include reduction in number of voids per day, volume of voids, 24 hour pad weight, responses to validated questionnaires, changes in UPP measures, changes in sexual function, and changes in pelvic floor muscles as measured by MRI. Safety will be determined by the number and type of adverse events reported during treatment. Various imputation methods may be explored.
Study Intervention/Treatment:	Participation in this study includes 5 in person study visits and two telephone and/or mailed questionnaire visits. Additional in person and/or telephone visits may be added as needed. Study subjects will receive 3 mg of GTx-024 orally daily.

Table 1. Schedule of Measures.

	Screening Visit Days -21-0 ***Clinic Visit***	***Additional Screening Days -21-0*** ***Clinic Visit***	***Visit 1. Baseline[3] Week 0*** ***Clinic Visit***	***Visit 2. Week 1± 3 days*** ***Phone Call***	***Visit 3. Week 4 ± 3 days*** ***Clinic Visit***	***Visit 4. Week 8 ± 3 days*** ***Clinic Visit***	***Visit 5. Week 12 ± 3 days*** ***Clinic Visit***	***Visit 6. Week 16 ± 7 days*** ***Phone Call and Mail***
Consent	x							
Inclusion/Exclusion	x		x					
History			x					
Interview/Vital Signs	x		x		x	x	x	
Height/Weight	x				x	x	x	
24 hour Pad Weight	*Instruct*		x		x	x	x	
3 day Voiding Diary	*Instruct*		x		x	x	x	
Serum AST, ALT, Total Bilirubin	x				x	x	x	
Serum FSH[1] ,	x							
CBC			x				x	
UA Dipstick (with culture as needed)	x		x				x	
Lipid Panel			x				x	
Testosterone Levels			x				x	
SHBG			x				x	
UPP			x				x	
Pelvic MRI		x					x	
Bladder Stress Test	x						x	
Mammogram[2]		x						
Begin Daily[4] Treatment			x					
End Treatment							x	
Concomitant Meds	x		x	x	x	x	x	x
Adverse Events			x	x	x	x	x	x
HIV, Hep A, B, C Testing	x							
UDI-6; IIQ			x		x	x	x	x
PGI-S			x		x	x	x	x
MESA Questionnaire	x				x	x	x	x
PGI-I					x	x	x	x
FSFI Questionnaire			x		x	x	x	x
Bladder Scan PVR			x		x	x	x	
Ciprofloxacin 500 mg po (or equivalent)			x				x	
Focused Physical Exam			x				x	

[1] Age 18 to 80 years old is clinically confirmed as postmenopausal. Subjects must have undergone the onset of spontaneous, medically induced or surgical menopause prior to the start of this study. Postmenopausal is defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

[2] Mammogram within the last 6 months conducted outside the protocol may be utilized. Provided the data is available for assessment in this protocol, an additional mammogram will not be required.

[3] Visit 1, Baseline, may not be completed until all results of screening tests have been evaluated.

[4] After confirmation of meeting all eligibility criteria.

ROLES AND RESPONSIBILITIES

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2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND/RATIONALE

Stress urinary incontinence (SUI), the involuntary leakage of urine during activities that increase abdominal pressure (e.g. coughing, sneezing, physical exercise), affects up to 35% of adult women (Luber, 2004). Urinary incontinence and pelvic floor disorders are major health problems for women especially as they age.

There are a variety of treatments that may be used to treat SUI in women (Rovner, 2004). Behavioral modification and pelvic floor physical therapy are common initial treatment approaches even though surgical procedures (e.g. sling; bladder neck suspension) are often ultimately the most effective. Biological and other materials for injection into the urethra have also been marketed for treating intrinsic sphincter deficiency (ISD), a cause of SUI symptoms. In a study of autologous fat injected into the urethral sphincter only 22% of patients improved compared to 21% after placebo injection (Lee, 2001). However, the injection of muscle derived stem cells (AMDC) is a promising new therapy for SUI currently being tested in clinical trials. In a dose escalation study of AMDC, injected into the urethral sphincter, all dose groups had significantly fewer diary stress leaks at 12 months, but only patients who received the highest dose of AMDC had statistically significant reduction in mean pad weight (Peters, 2014). Pharmacologic therapies for SUI also have been tested with varying results. In a study of duloxetine (a selective serotonin reuptake inhibitor), the median incontinence episode frequency decreased 41% in the placebo group compared to 54% receiving duloxetine 20 mg/day, 59% for duloxetine 40 mg/day, and 64% for duloxetine 80 mg/day (Norton, 2002). Dmochowski and colleagues also demonstrated a statistically significant reduction in incontinence episode frequency with duloxetine therapy compared with placebo (50% vs 27%, respectively) (Dmochowski, 2003).

Pelvic floor muscle relaxation has been found to correlate with lower urinary tract symptoms (LUTS). 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 prolapse and urinary incontinence. As such, efforts have been made to improve pelvic floor muscle strength and function especially in post-reproductive and elderly women, to improve, if not cure, LUTS (specifically urinary incontinence, urinary frequency and nocturia). However, pelvic floor physical therapy (PT) is often less effective than more aggressive treatment such as surgery (Labrie, 2013). A prospective randomized trial of PT vs. surgery showed that 49% of women in the PT group crossed over to surgical treatment. Others have shown that after 3 to 15 years, 25 to 50% of women initially treated with physiotherapy have proceeded to surgery (Cammu, 2004; Lamers, 2007; B. K, Kvarstein, 2005). Yet, surgery is much more invasive and is associated with risk and complications (Brubaker

et al, 2011). Treatments with better outcomes than pelvic floor PT or those that augment the response to pelvic floor PT, are clearly needed. Androgen supplementation may be a novel treatment to augment pelvic floor muscle response and improve objective and subjective outcomes for SUI. Basic science literature indicates that smooth muscle cells in various female urogenital tissues have expressed androgen receptors (Berman, 2003) and that the levator ani and urethral sphincter, both containing large numbers of androgen receptors (Copas, 2001; Celayir, 2002), are sensitive to androgens (Nnodim, 1999; Nnodim, 2001).

In addition to the use of instruments to measure the efficacy of therapeutic approaches to SUI, MRI measurements of the pelvic floor have been utilized as tools to determine the impact on the supporting pelvic floor muscles (Tunn et al, 1999). Measurements of the levator hiatus, including the area, as well as, the anteroposterior and transverse diameters, have been demonstrated to be reproducibly measured and correlative with pelvic floor damage (Lammers et al., 2013). Similar measurements have been made to examine the recovery of levator ani muscle after vaginal delivery (Tunn et al, 1999). Therefore, MRI based measurements can provide for a non-invasive quantitative assessment of pelvic floor muscles and their potential response to therapeutic approaches with additional value to that provided by symptomatic assessments alone. MRI will also be used in this study to assess endometrial thickness at baseline. An endometrial stripe > 5 mm may exclude the subject from participating (Stanislavsky, Weerakkody, et al., 2015; Nakamura et al., 2014).

Androgen receptors in the pelvic floor/urethra

The para-urethral extracellular matrix is a target for sex steroid hormones, however the effects are not well known. Androgens stimulate collagen synthesis and inhibit degradation leading to increased collagen fibre compactness (Shin, 2005; Berger, 2005). Androgen receptors are densely expressed in both muscle and stromal cells of the levator ani muscle and fascia in women (Copas, 2001) and the levator ani muscle is considered to be one of the most androgen sensitive tissues in the body.

Impact of anabolic steroids

The effect of testoterone on urodynamic findings and histopathomorphology of the pelvic floor muscles has been studied in rat models of SUI. Testosterone was found to improve leak point pressures and significantly increase the size of myofibers in treated rats, suggesting that testosterone has both preventative and curative effects on rat models of SUI (Mammadov,2011). Since free testosterone levels were also higher in the treated group, there is potential for concerns regarding side effects of supplemental steroidal testosterone in women with SUI.

The anabolic effects of androgens in men have been widely studied, but less is known about the role and use of androgens in women. Prior studies have found that urinary levels of androgens were significantly higher in postmenopausal patients with SUI than in postmenopausal patients without incontinence (Jung, 2001). Furthermore, concentrations of androgen metabolites in urine of these patients were related positively

to the bladder neck descensus when measured by perineal ultrasound (a_Bai, 2003). Aizawa K et al. and others have published data demonstrating that increases in muscle mass due to resistance training or exercise is due, at least in part, to increases in local androgen concentrations and expression of androgen-synthesizing enzymes (Aizawa K, 2011). These findings support the notion that pelvic floor muscle strengthening exercise improves SUI symptoms by increasing androgen levels locally. These and other studies suggest that androgens may play a substantial role in SUI and that androgen metabolites might be involved in the relaxation of bladder muscle (b_Bai, 2003). This relaxation effect on the bladder may be related to the up regulation of nitric oxide synthase by androgens to produce more nitric oxide. The action of androgen on the lower urinary tract and pelvic floor is complex and may depend on anabolic effects, hormonal modulation, receptor expression, nitric oxide modulation, or combination of these factors (Ho MH, 2004).

Intriguing data come from studies conducted in women with polycystic ovarian syndrome (PCOS). PCOS is a hyper-androgenic disorder (>70 ng/dL compared to 15-50 ng/dL in normal pre-menopausal women) and clinical studies have demonstrated that PCOS can eliminate the increased risk for UI observed in obese women. Furthermore, obese women with PCOS have a similar prevalence of UI as those considered to have a normal body mass index (Montezuma T, 2011). In a separate study, none of the women with PCOS (18.6% with UI) suffered from UI compared to matched controls,even though pelvic floor muscle strength was not different (Antonio FI, 2013). These studies support the hypothesis that women with higher androgen levels, or potentially women treated with a selective androgen receptor modulator (SARM) will show improvements in UI symptoms.

Selective androgen receptor modulators

Although anabolic steroids may increase muscle mass and strength, lack of oral bioavailability and known potential risks have limited their use. Selective androgen receptor modulators (SARMS) have great potential to achieve similar benefits of anabolic steroid therapy (improved muscle mass, cholesterol/triglyceride levels, glucose metabolism, and bone density) with fewer adverse effects, such as hirsuitism and acne, in women.

SARMS may provide a new therapeutic option for pelvic floor and lower urinary tract disorders, as both testosterone and its more potent metabolite converted by 5-a reductase, dihydrotestosterone (DHT), have anabolic effects on muscle. The potential for SARMS as a treatment for SUI is strengthened by studies showing that urethral closure pressure is the factor most strongly associated with SUI (Delancey, 2007; Delancy, 2008). This finding is supported by both morphological and electromyographic (EMG) evidence. In imaging studies, the striated urethral sphincter has been found to be smaller in women with SUI compared to continent controls (Athanasiou, 1999; Morgan; 2009). In EMG studies, the striated urethral sphincters of women with SUI exhibit smaller EMG amplitudes and shorter motor-unit-potential durations, with more phases, than continent controls (Kenton, 2011; Takahashi, 2000), indicating primarily

myogenic changes. Furthermore, it is well accepted that pelvic floor muscle (PFM) rehabilitation is an effective treatment for SUI (Hay-Smith, 2009). PFM rehabilitation may be effective because it strengthens not only the pelvic floor but may also strengthen the striated urethral sphincter. This idea is supported by a recent publication that reported, based on ultrasound (US), a 12-week PFM exercise program produced a significant increase in the cross-sectional area of the urethra, at the level of the striated urethral sphincter, in middle-aged women (McLean, 2013). Because of limits in the resolution of US images, the authors were not able to determine which part of the urethra hypertrophied. The investigators suggested that PFM rehabilitation in older women with SUI could condition the striated urethral sphincter leading to measurable hypertrophy, observable on MRI.

In a later study, Madill extended the findings of the McLean group (Madill, 2014). Using MRI, they were able to differentiate between smooth and striated sphincter muscle layers and determined that changes occurred primarily in the striated urethral sphincter of older women. These findings suggest that not only does the striated urethral sphincter contract synergistically with PFMs during voluntary and automatic contractions [Nnodim, 1999; Nnodim, 2001; Celayir, 2002], but also that PFM rehabilitation stresses the striated urethral sphincter sufficiently to produce a muscular hypertrophy training effect (Madill, 2014).

Selective androgen receptor modulators (SARMS) are currently in development for patients with muscle wasting secondary to cancer diagnosis. This class of drugs has been shown to stimulate the growth of skeletal muscle, similar to traditional anabolic steroids, but without undesirable side effects. SARMS, such as GTx-024, are orally bioavailable and tissue-selective, whereas testosterone and other anabolic steroids also have limited oral bioavailability and are only available in transdermal and intramuscular formulations potentially leading to skin reactions and fluctuations in serum concentrations of testosterone. SARMS may exhibit the beneficial effects of anabolic agents without the known associated risks (Mohler, Bohl, 2009).

Recently utilizing an ovariectomized rat model to miminc SUI by disrupting urethral continence, investigators demonstrated that the use of a SARM (GSK2849466A) was able to increase urethral baseline pressure (UBP) and the amplitude of urethral responses during sneezing (AURS) by 64% and 74%, respectively, as compared with the vehicle control. Further, all of the rats (8/8) in the vehicle treated group experience fluid leakage during sneezing whereas only one of the rats (1/8) in the SARM treated group experience 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 provides further support to the potential use of SARMs for the treatment of SUI. (Kadekawa et al, AUA Annual Meeting 2015, New Orleans, LA. PD27-11)

Summary of GTx-024

Preliminary studies related to stress urinary incontinence

Extensive clinical data related to the use of GTx-024 are described below; however, there are both pre-clinical and clinical data supporting the specific investigation of GTx-024 for the treatment of SUI. Among the preclinical findings are that GTx-024 has androgenic and anabolic activity in male and female rat models (Preclinical Reports n030105GTx024 and n112012.1). 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 (similar to what might be expected in females), GTx-024 has the ability to induce hypertophy of the levator ani muscle to approximately 120% of an intact male. These studies together provide an approximation of the expected effect of GTx-024, since currently there are no data in female models regarding levator ani hypertrophy or stress urinary inconcentince (Preclinical Report n112012.1). In two phase 3 studies (G300504 and G300505), 3 mg daily GTx-024 results in a mild increase (approximately 1.7%) in lean body mass with no differential effect in males and females. Based upon these preclinical and clinical analyses, we anticipate significant growth/bulking of the levator ani in females with SUI, which may also result in improvements in associated symptoms, and are therefore the focus of the study outlined herein.

Ongoing and Completed Clinical Trials with GTx-024

The following Phase 1, 2, and 3 clinical trials have been completed or are ongoing with GTx-024.

1. Protocol G100401, a Phase 1 single ascending dose study in 96 healthy, young, male volunteers;
2. Protocol G100402, a Phase 1 multiple ascending dose study in 50 healthy, young, male volunteers, and 23 elderly male volunteers with truncal obesity;
3. Protocol G100503, a Phase 1 single dose pharmacokinetic study to assess the effect of a dosage regimen that simulates a sustained release formulation to an immediate release formulation in 18 healthy, young male volunteers and 18 postmenopausal women;
4. Protocol G100506, a Phase 1 single dose pharmacokinetic study to assess the relative bioavailability of a 3 mg hard shell capsule formulation to be used during continued clinical development and to assess the effect of food on the pharmacokinetics of the 3 mg softgel formulation in 27 healthy, young, male volunteers;
5. Protocol 006, a Phase 1 single dose and multiple dose pharmacokinetic study in 24 postmenopausal, Japanese women;
6. Protocol G200501, a Phase 2 study in 60 postmenopausal women and 60 elderly men to assess lean body mass and physical function;
7. Protocol 003, a Phase 1b study in 44 postmenopausal women;
8. Protocol G200502, a Phase 2b study in 159 men and postmenopausal women

with cancer to assess lean body mass and physical function;
9. Protocol G100511, a Phase 1 study to assess the effect of severe renal impairment on the pharmacokinetics of GTx-024;
10. Protocol G100508, a Phase 1 study to assess the effect of mild and moderate hepatic impairment on the pharmacokinetics of GTx-024;
11. Protocol G100509, a Phase 1 mass balance study of GTx-024 in healthy volunteers;
12. Protocol G100507, a Phase 1 study to assess the pharmacokinetics and absolute oral bioavailability of GTx-024 in Caucasian and African American men and women;
13. Protocol G100510, a single-dose, randomized, double-blind, comparative, positive and placebo-controlled, four-period crossover Phase 1 study to define the electrocardiogram (ECG) effects of GTx-024, at therapeutic and supratherapeutic doses, in healthy male and female subjects: a thorough ECG trial;
14. Protocol G100512, a Phase 1 study to assess the effect of ketoconazole (Cytochrome P450, Family 3,Subfamily A [CYP3A4] inhibitor) on the pharmacokinetics of GTx-024;
15. Protocol G100513, a Phase 1 study to assess the effect of rifampin (CYP3A4 inducer) on the pharmacokinetics of GTx-024;
16. Protocol G100514, a Phase 1 study to assess the pharmacokinetic drug: drug interaction of GTx-024 and celecoxib (CYP2C9);
17. Protocol G100515, a Phase 1 study to assess the pharmacokinetic drug: drug interaction of GTx-024 and probenecid (UGT2B7);
18. Protocol G100516, a Phase 1 study to assess the pharmacokinetic drug: drug interaction of GTx-024 and rosuvastatin (breast cancer resistance protein [BCRP]);
19. Protocol G300504, a Phase 3 randomized, double-blind, placebo-controlled study of the effect of GTx-024 on muscle wasting in 321 subjects with non-small cell lung cancer receiving first line platinum plus a taxane chemotherapy;
20. Protocol G300505, a Phase 3 randomized, double-blind, placebo-controlled study of the effect of GTx-024 on muscle wasting in 320 subjects with non-small cell lung cancer receiving first line platinum plus a non-taxane chemotherapy;
21. Protocol G200801, an ongoing, Phase 2, open label study to examine AR status and the activity of GTx-024 hormonal therapy in 22 women with ER positive metastatic breast cancer who have previously responded to hormone therapy.
22. Protocol G200802, an ongoing, a Phase 2, open label, multi-center, multinational, randomized, parallel design study investigating the efficacy and safety of GTx-024 on metastatic or locally advanced ER+/AR+ Breast Cancer (BC) in Postmenopausal Women.
23. Protocol G200901, an ongoing, Phase 2, open label, multi-center, multinational study investigating the efficacy and safety of GTx-024 on advanced, Androgen Receptor-Positive Triple Negative Breast Cancer (AR+ TNBC)

2.2 RISKS ANALYSIS AND RISK ASSESSMENT

2.2.1 POTENTIAL ANTICIPATED ADVERSE EVENTS

An adverse event is any clinical event that impacts, or that has the potential to impact, the health or safety of a Clinical Study subject caused by or associated with the study device and/or testing. Assessment for potential adverse events will be ongoing throughout this trial.

The benefits of treatment may include improvement in the frequency, or severity of urine loss, and improvement in quality of life. Decreases in serum triglycerides, cholesterol, and body fat, and improvements in insulin resistance, lean body mass and physical endurance are also possible benefits.

Adverse event tables and serious adverse events discussed below and are presented separately by adverse events reported among healthy volunteers on a single trial of 86 days of GTx-024 3 mg versus placebo and those enrolled on cancer trials of at least 86 days exposure to GTx-024 3 mg or placebo.

Adverse events reported among > 5% of GTx-024 3mg treated healthy subjects
Percentage of subjects reporting a given adverse event at least once

Primary System Organ Class	Preferred Term	GTx-024 N=24	Placebo N=24
Gastrointestinal disorders	Diarrhea	8.3	12.5
	Dyspepsia	8.3	8.3
	Vomiting	8.3	0.0
General disorders and administration site conditions	Vessel puncture site bruise	12.5	4.2
	Fatigue	8.3	8.3
	Malaise	8.3	0.0
Infections and infestations	Herpes simplex	8.3	0.0
Injury, poisoning and procedural complications	Contusion	8.3	4.2
Investigations	Alanine aminotransferase increased	20.8	0.0
Musculoskeletal and connective tissue disorders	Back pain	12.5	16.7

Primary System Organ Class	Preferred Term	GTx-024 N=24	Placebo N=24
Nervous system disorders	Headache	20.8	20.8
	Dizziness	12.5	4.2
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	12.5	12.5

No serious adverse events (SAEs) were reported on this trial.

These side effects are based on information obtained from a clinical study (G200501) administering GTx- 024 3 mg for 86 days in healthy subjects– elderly males and postmenopausal females. Studies suggest that side effects associated with the study drug resolve after GTx-024 is stopped.

Adverse events reported among > 5% of GTx-024 3 mg treated cancer subjects
Percentage of subjects reporting a given adverse event at least once

Primary System Organ Class	Preferred Term	GTx-024 N=432	Placebo N=378
Blood and lymphatic system disorders	Anemia	34.7	34.7
	Neutropenia	18.3	23.3
	Thrombocytopenia	10.4	10.8
	Leukopenia	8.3	9.0
Gastrointestinal disorders	Nausea	34.7	34.9
	Vomiting	20.1	21.2
	Constipation	12.3	10.1
	Diarrhea	11.6	12.7
	Abdominal pain	5.1	3.7
General disorders and administration site conditions	Fatigue	15.7	16.7
	Asthenia	15.3	13.5
	Disease progression	11.8	16.7
	Pyrexia	10.2	9.8
Infections and infestations	Pneumonia	5.6	7.1
Investigations	Blood creatinine increased	8.1	5.0

Primary System Organ Class	Preferred Term	GTx-024 N=432	Placebo N=378
	Weight decreased	6.0	4.8
Metabolism and nutrition disorders	Decreased appetite	10.6	14.8
Musculoskeletal and connective tissue disorders	Arthralgia	8.1	7.9
	Pain in extremity	5.6	4.2
Nervous system disorders	Headache	7.4	6.1
	Peripheral sensory neuropathy	5.8	3.4
	Dizziness	5.6	6.3
Respiratory, thoracic and mediastinal disorders	Dyspnoea	12.3	7.4
	Cough	9.5	9.3
Skin and subcutaneous tissue disorders	Alopecia	17.8	18.5

Serious adverse events (SAEs) reported among > 2% of GTx-024 3 mg treated cancer subjects

Percentage of subjects reporting a given serious adverse event at least once

Primary System Organ Class	Preferred Term	GTx-024 N=432	Placebo N=378
Blood and lymphatic system disorders	Anemia	4.2	3.7
	Neutropenia	3.2	3.7
	Febrile neutropenia	2.3	1.6
Blood and lymphatic system disorders	Thrombocytopenia	2.3	1.6
General disorders and administration site conditions	Disease progression	7.9	11.9
Infections and infestations	Pneumonia	3.5	3.2
Neoplasms benign, malignant and unspecified (incl cysts and	Malignant neoplasm progression	2.8	2.1

An AE that appears related to GTx-024 in clinical trials has been a dose-dependent, transient, asymptomatic increase in ALT. However, these increases were modest at doses up to 10 mg per day. Most of the subjects studied to date had ALT levels that

remained within normal limits. One subject was discontinued for an ALT > 3 times the ULN. 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.

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

2.2.2 STUDY RISKS

Study Procedures

Urethral catheterization

Less Frequent (occurring more than 1%, but less than 10% of the time)
- Discomfort
- Mild cramping
- Infection

Rare (occurring less than 1% of the time)
- Bleeding
- Urinary tract infection
- Inability to pass urine
- Puncture of the bladder
- Burning with urination

Antibiotic (a medicine to prevent infection)

Less Frequent (occurring more than 1% but less than 10% of the time)
- Diarrhea
- Nausea and vomiting
- Cramping

Rare (occurring less than 1% of the time)
- Headache
- Itching
- Rash
- Allergic reaction

Blood Drawing

Most Frequent (occurring more than 10% of the time):
- Pain
- Bleeding

Bruising at the needle puncture site
Rare (occurring less than 1% of the time):
Blood clot
Infection
Feeling lightheaded
Fainting

Mammogram
Most Frequent (occurring more than 10% of the time):
Discomfort

Gynecological Exam
Rare (occurring less than 1% of the time):
Discomfort

Pelvic MRI
Rare (occurring less than 1% of the time):
Discomfort

2.2.3 METHODS TO MINIMIZE RISK

Subjects will be monitored at each visit for changes since last visit and adverse effects of treatment. Since elevations in ALT are possible, serum liver function tests will be monitored during treatment. (Refer to Section 9.4 Halting Rules)

Subjects will receive a prophylactic antibiotic at visits where catheterization/UPP occur to decrease risk of urinary tract infection (UTI). Any infection will be appropriately treated.

3. OBJECTIVES

3.1 PRIMARY OBJECTIVE

1. Describe the effect of 12 weeks of treatment of GTx-024 on the number of stress incontinence episodes/day as assessed by the 3 day voiding diary.

3.2 SECONDARY OBJECTIVES

1. Describe the effect of 12 weeks of treatment of GTx-024 on the frequency of voids/day as assessed by the 3 day voiding diary.

2. Describe the effect of 12 weeks of treatment of GTx-024 on urine volume per void as assessed by the 3 day voiding diary.

3. Describe the effect of 12 weeks of treatment of GTx-024 on SUI as assessed by 24 hour pad weight test.

4. Describe the effect of 12 weeks of treatment of GTx-024 on SUI as assessed by the Urethral Pressure Profile (UPP).

5. Describe the effect of 12 weeks of treatment of GTx-024 on SUI as assessed by the Bladder Stress Test.

6. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported stress urinary incontinence symptoms as assessed by the MESA Urinary Questionnaire.

7. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported impression of symptom severity as assessed by the Patient Global Impression of Severity Scale (PGI-S).

8. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported impression of improvement as assessed by the Patient Global Impression of Improvement Scale (PGI-I).

9. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported urogenital distress as assessed by the Urinary Distress Inventory Questionnaire (UDI-6).

10. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported impact of urinary incontinence on daily life as assessed by the Incontinence Impact Questionnaire (IIQ-7).

11. Describe the effect of 12 weeks of treatment of GTx-024 on patient reported sexual function as assessed by the Female Sexual Function Index Questionnaire (FSFI).

12. Describe the effect of 12 weeks of treatment of GTx-024 on pelvic floor muscles as measured by MRI.

3.3 STUDY END POINTS

Primary end point

1. Change in frequency of daily stress urinary incontinence episodes from Baseline to Week 12.

Secondary end points

1. Change in frequency of daily voids from Baseline to Week 12.
2. Change in urine volume per void from Baseline to Week 12.
3. Change in 24 hour pad weight from Baseline to Week 12.
4. Change in maximum urethral closure pressure measurements from Baseline to Week 12.
5. Change in urine leakage (yes/no) on the Bladder Stress Test from Baseline to Week 12 as assessed while (a) coughing, and/or (b) performing a Valsalva maneuver.
6. Change in total score on the stress incontinence section of the MESA Urinary Questionnaire from Baseline to Week 12.
7. Change in Patient Global Impression of Severity (PGI-S) Scale from Baseline to Week 12.
8. Patient Global Impression of Improvement (PGI-I) Scale at Week 12.
9. Change in total score on the Urinary Distress Inventory (UDI-6) from Baseline to Week 12.
10. Change in total score on the Incontinence Impact Questionnaire (IIQ-7) from Baseline to Week 12.
11. Change in total score on the Female Sexual Function Index (FSFI) from Baseline to Week 12 as well as the change in subdomain scores: libido, arousal, lubrication, orgasm, satisfaction, and pain.
12. Change in pelvic floor muscles from Baseline to Week 12 as measured by MRI. Quantitative assessments may include the area of the levator hiatus, the anteroposterior and transverse diameters, and other relevant parameters.

4. METHODOLOGY

4.1 STUDY DESIGN

This is a single site, proof of concept feasibility study to describe the effect of GTx-024 3 mg in postmenopausal female subjects with SUI. Postmenopausal will be defined as clinically confirmed female subjects who have undergone the onset of spontaneous, medical or surgical menopause prior to the start of this study. Durability of treatment will also be explored by evaluating validated measures at 4 weeks after last dose. Up to 35 subjects will be enrolled in this study.

Institutional Review Board (IRB) approval from Beaumont's Human Investigations Committee will be obtained prior to beginning any study activity. Once IRB approval is obtained, potential participants will be identified from existing medical records, or physician or other referrals.

Potential subjects may be prescreened by telephone prior to the first in person study visit (initial screening visit). At the first in person study visit, subjects will be seen in the Urology Clinical Research space and informed consent will be obtained prior to any study activity. At Study Visit, 2, inclusion/exclusion criteria will be verified, study data will be collected, and consented participants may begin treatment.

Enrolled subjects will agree to maintain on a stable dose of any medication known to affect lower urinary tract function, including but not limited to anticholinergics, tricyclic antidepressants, or alpha-adrenergic blockers, throughout the treatment and follow-up period. Subjects enrolled in the study will agree to not start any new treatment (medication or otherwise) that is known to affect lower urinary tract function throughout the treatment and follow up periods. Subjects will also agree to refrain from performing any Kegal exercises and maintain current dietary habits throughout the treatment and follow up periods.

4.2 MEDICAL MONITORING

A Medical Monitor will be responsible for monitoring the safety and data of this trial. The data that will be monitored include adverse events related to the study drug and procedures.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1 SUBJECT INCLUSION CRITERIA

Subject Inclusion Criteria: Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Give voluntary, written and signed, informed consent
2. Female
3. Age 18 to 80 years old
4. Clinically confirmed as postmenopausal. Subjects must have undergone the onset of spontaneous, medically induced or surgical menopause prior to the start of this study. Postmenopausal is defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
5. SUI symptoms for at least 6 months duration
6. Predominant SUI (MESA questionnaire)
7. 24 hour pad weight >3 gms at baseline
8. At least 4, but no more than 15, SUI episodes on each day of the 3 day baseline voiding diary.
9. Serum AST and ALT within normal limits
10. Total bilirubin within normal limits
11. Positive Bladder Stress Test
12. Subject agrees to not start any new treatment (medication or otherwise) that is known to affect lower urinary tract function throughout the treatment and follow up periods.
13. Subject agrees to maintain on a stable dose of any medication known to affect lower urinary tract function, including but not limited to anticholinergics, tricyclic antidepressants, or alpha-adrenergic blockers, throughout the treatment and follow-up period.

5.2 SUBJECT EXCLUSION CRITERIA

Subject Exclusion Criteria: Subjects eligible for this study must not meet any of the following criteria:

1. Pelvic floor physical therapy within the last 6 months
2. History of pelvic radiation treatment
3. History of urethral diverticula
4. History of urethral sling, anterior prolapse repair, ureteral bulking agents and/or other SUI procedure or surgery
5. Known vesicoureteral reflux, vaginal prolapse beyond the introitus, or other significant pelvic floor abnormalities
6. Patient has urinary incontinence of neurogenic etiology
7. Patient is morbidly obese (defined as 100 pounds over their ideal body weight, or body mass index 40 or greater)
8. Chronic hepatitis
9. Hepatic cirrhosis
10. HIV and/or hepatitis A, B, or C

11. Subjects taking systemic hormone products (excludes intravaginal application of estradiol topical/tablet agents and hormones delivered via vaginal rings)
12. Subjects with a history of breast or endometrial cancer.
13. Subjects with cerebrovascular disease, thromboembolic disorders, myocardial infarction, or angina.
14. Subject with an entry measurement of > 5 mm endometrial stripe thickness as measured by MRI.
15. Any other condition which per investigators' judgement may increase subject risk
16. Clinically confirmed urinary tract infection

5.3 STRATEGIES FOR RECRUITMENT, RETENTION, AND TO IMPROVE ADHERENCE TO INTERVENTION PROTOCOLS

Potential subjects will be identified from existing medical records, physician referrals, or recruited via advertisement or word of mouth. During initial telephone contact, patients' history will be reviewed for inclusion/exclusion criteria. Those subjects who initially qualify will be invited to an in person study visit (study visit 1).

5.4 TREATMENT ASSIGNMENT PROCEDURES

All subjects enrolled in this study will receive a daily oral dose of GTx-024, 3 mg.

5.4.1 REASONS FOR WITHDRAWAL

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 reasons potentially including:

- Unable to tolerate study treatment (AE requiring permanent discontinuation of study treatment)
- AEs that require treatment with a prohibited medication or a procedure
- Development of any condition that may pose an additional risk to the subject or PI decision that this is in the best interest of the subject
- Study terminated by sponsor
- Subject unable to follow Investigators' instructions and comply with the study procedures
- Major protocol violation

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

5.4.2 EARLY TERMINATION OR SUSPENSION OF THE STUDY

Any decision to suspend enrollment or terminate the study will be made by the Sponsor, PI and, if appropriate, the local IRB. If a decision is made to terminate the study, subjects who have received treatment will be followed for up to 28 days.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 STUDY PRODUCT DESCRIPTION

GTx-024 (enobosarm); United States Adopted Names Council official generic name) is an orally bioavailable nonsteroidal SARM with tissue-selective anabolic and androgenic pharmacologic activity (Dalton, 2011).

6.2 ACQUISITION

GTx-024 3 mg Softgels (capsules) will be supplied by GTx, Inc.

6.3 FORMULATION, PACKAGING, AND LABELLING

The drug product will be supplied as opaque, white to off-white, size 5, oval Softgel capsules containing 3 mg GTx-024. “GTx” will be imprinted in black ink on the outer shell of the capsule. The liquid Softgel fill is composed of GTx-024 dissolved in polyethylene glycol 400 (PEG400).

GTx-024 3 mg Softgels will be packaged in high density polyethylene (HDPE) 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. Each bottle of study drug will be labeled with dosing and storage instructions.

6.4 PRODUCT STORAGE AND STABILITY

Recommended storage will be at controlled room temperature 15°C–25°C (59°F–77^{o}F), with excursions permitted to 30°C (86°F), protected from moisture.

6.5 DOSAGE, PREPARATION, AND ADMINISTRATION OF STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

One (1) GTx-024 3 mg Softgel capsule will be taken PO with water at approximately the same time each day, with or without food.

6.6 ACCOUNTABILITY PROCEDURES FOR THE STUDY INVESTIGATIONAL PRODUCT(S)

The Investigator is responsible for the correct storage of study medication according to GTx, Inc. recommendations. The study medication made available for this clinical trial must be used in accordance with the protocol and dispensed only under the supervision of the Investigator and documented sub-Investigators. The Investigator must maintain complete and accurate records, showing the receipt and disposition of all supplies of the study medication delivered by the GTx, Inc. authorized representative. These records must include a master record which lists the date of receipt of all study medication shipments, batch numbers, expiration date, and quantities received. In addition, a dispensing record which includes all quantities dispensed, identification of the subject to whom study medication was dispensed, the date of each dispensing, and the identification of the dispenser will also be maintained. The master dispensing records are separate from records kept for individual trial subjects.

It is the Investigator's responsibility to ensure that study medication used by trial subjects plus unused study medication equal the total amount received from the GTx, Inc. authorized representative. Damaged and/or contaminated packets must also be accounted for in the dispensing records. All discrepancies must be explained in writing. The study personnel responsible for study medication administration to the subject will record the date and time the initial treatment is given to the subject. In addition, the Drug Accountability case report form (CRF) will document any treatment interruptions or discontinuation.

6.7 ASSESSMENT OF SUBJECT COMPLIANCE WITH STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

Subjects should be instructed to return all unused study medication and containers at each clinic visit during the clinical trial period so that drug accountability can be performed. The dispensing pharmacy is required to count all returned study capsules and record this on the proper CRF.

All study medication returned by subjects must be accounted for and verified by the study research nurse clinician and research pharmacist. After verification of all study medication, used packages and unused study medication will be returned to GTx, Inc., or authorized representative.

Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with taking study drug. The investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug at each in person visit after baseline. When study drug is administered at the research facility, it will be administered under the supervision of study personnel. Compliance with taking study drug will be monitored by the accounting of 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 steps are taken to improve compliance. Subjects who are less than 80% or more than 120% compliant with the dosage regimen for any two consecutive visit periods during the study may be withdrawn from the study.

6.8 CONCOMITANT MEDICATIONS/TREATMENTS

Forbidden medications and treatments during the study duration include:

- Systemic hormonal products including but not limited to estrogens, progestins, testosterone, methyltestosterone, oxandrolone (Oxandrin®), oxymetholone, danazol, fluoxymesterone (Halotestin®), other androgenic compounds, including herbals. Intravaginal application of estradiol topical/tablet agents and hormones delivered via vaginal ring are allowed.
- Treatment with any investigational agent within 6 months before the first dose of study treatment;

Previous and Concomitant Medication (Drugs and Therapies)
The Investigator or designee must record the use of previous (all medication taken within 30 days prior to Screening (Visit 1) and current concomitant treatment, both drug and non-drug therapies, prescribed and over-the-counter and all alternative medicines, in the CRFs. This also includes drugs used on a chronic and as-needed basis. Subjects must be instructed not to start any new medication, both prescribed and over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use. Subjects must be instructed to notify the Investigator immediately if medications were required for emergency use.

7. STUDY SCHEDULE

7.1 STUDY VISITS

Each subject may complete up to 5 months of study participation.

Screening Visit, Days -21-0
The study will be explained in detail and adequate time will be allowed for answering potential subjects questions prior to signing the IRB approved informed consent document. Informed consent will be obtained from those volunteers meeting initial inclusion/exclusion criteria and expressing willingness to participate prior to conducting any further study tests or measures.

Once informed consent is obtained, a detailed interview with vital signs will be conducted to further review for inclusion/exclusion criteria. A subject number will be assigned. Height and weight will be measured. Subjects will complete the MESA questionnaire to assess incontinence type (stress, urge, or mixed). If urinary incontinence type is stress predominant, then the subject will be instructed to complete a 24 hour pad weight and 3 day voiding diary prior to the next study visit. A bladder

stress test will be done to confirm SUI. Lab tests will also be drawn at this visit as outlined in Table I. A baseline urinalysis will be obtained. Concomitant medications will also be assessed and recorded.

Additional Screening, Days -21-0
If the subject has qualified for the study during the Screening visit, the following procedures will be performed between Screening Visit and Visit 1. Mammogram, if not done within the last 6 months, will be performed. Pelvic MRI will be performed

Study Visit 1: Week 0, Clinic Visit
Subjects still meeting inclusion/exclusion criteria after all Screening study measures have been completed and reviewed will return for Visit 1 where the 24 hour pad weight and 3 day voiding diary will be collected and reviewed. An interview with vital signs will be conducted. A detailed medical history will be taken, including past gynecological and obstetric history (gravida, para, prior abortions and deliveries) and a focused physical exam, including standard gynecological pelvic exam and skin assessment, will be done. Urine dipstick will be done and PVR will be measured. If subject still meets inclusion/exclusion criteria, UPP will be performed. A dose of Ciprofloxacin or equivalent will be given prophylactically to prevent bladder infection. Serum lab tests consisting of a CBC, lipid panel and testosterone level will be drawn.Questionnaires (UDI-6, IIQ, FSFI, and PGI-S) will also be completed at this visit. Concomitant medications and adverse events, will be assessed and recorded. A baseline MRI measurement will be scheduled and/or completed prior to receiving study drug.

Subjects who meet all the inclusion and none of the exclusion criteria will receive study drug. Study drug will be packaged in bottles. Each study drug bottle will be preprinted with a Medication ID number. The Medication ID number assigned to the subject will be noted in the case report form (CRF) for study drug.

The first dose of study drug will be taken during this visit if the subject meets all criteria for enrollment. A one month supply of study drug (35 count bottles) will be dispensed with administration instructions.

Study Visit 2: Week 1, Phone Call
Approximately 1 week after beginning treatment, subjects will be contacted by phone to assess for concomitant meds and adverse events. Subjects will also be instructed to complete a 24 hour pad weight and 3 day voiding diary within the week preceding their next study visit.

Study Visit 3: Week 4, Clinic Visit
Approximately 4 weeks after beginning treatment, subjects will return to the clinical research office for an in person visit. An interview with vital signs will be conducted. Height and weight and PVR will be measured. Pad weights will be measured, and the 3 day voiding diary will be collected and reviewed. Blood will also be drawn to measure serum AST, ALT, and total bilirubin. Questionnaires will also be completed, and

concomitant meds and adverse events, including any vaginal bleeding, discharge, infections and/or spotting, will be assessed and recorded. Subjects will also be instructed to complete a 24 hour pad weight and 3 day voiding diary in the week preceding their next study visit. A 30 day supply of study drug will be dispensed with administration instructions.

Study Visit 4: Week 8, Clinic Visit
Approximately 8 weeks after beginning treatment, subjects will return to the clinical research office for an in person visit. An interview and vital signs will be conducted. Height and weight and PVR will be measured. Pad weights will be measured, and the 3 day voiding diary will be collected and reviewed. Blood will also be drawn to measure serum AST, ALT, and total bilirubin. Questionnaires will also be completed and concomitant meds and adverse events including any vaginal bleeding, discharge, infections and/or spotting,will be assessed and recorded. Subjects will also be instructed to complete a 24 hour pad weight and 3 day voiding diary in the week preceding their next study visit. A 30 day supply of study drug will be dispensed with administration instructions.

Study Visit 5: Week 12, Clinic Visit
Approximately 12 weeks after beginning treatment, subjects will return to the clinical research office for an in person visit. An interview with vital signs will be conducted. A focused physical exam will be done. Gynecological pelvic exam will only be done at this visit if clinically indicated. Urine dipstick will be done and PVR will be measured Height and weight will be measured. 24 hour pad weights and 3 day voiding diaries will be collected/reviewed. Blood will also be drawn to measure laboratory values as outlined in Table 1. UPP,Bladder Stress Test, and MRI will be performed at end of treatment, questionnaires will be administered, and concomitant medications/adverse events will be assessed and recorded. All study medication will be collected and accounted for.

Study Visit 6: Week 16, Telephone/mailed questionnaire visit
Approximately 4 weeks after study drug treatment has ended, subjects will be contacted by phone to assess for concomitant meds and adverse events. Subjects will also be instructed to complete and return mailed questionnaires.

7.2 EARLY TERMINATION

Subjects may withdraw from the study voluntarily. In addition, if the PI determines that continued participation might present a safety risk for the subject then the PI may withdraw the subject from the study. Those subjects who receive study drug will be followed for 28 days after stopping study participation. Every effort will be made to obtain all end of treatment measures as outlined in (Table 1.Visit 6) in the event that a subject withdraws, or is withdrawn, from the study before completing treatment.

8. STUDY PROCEDURES/EVALUATIONS

Please see Table1 Schedule of Measures for an outline of the timing of the study procedures. Please see Appendix A, B, C, D, E for outcomes measures.

Interview with Vital Signs
All potential subjects will be interviewed/assessed to confirm inclusion/absence of exclusion criteria. A review of systems will be completed, concomitant medications will be assessed, and vital signs (temperature, blood pressure, pulse and respirations) will be assessed. Laboratory results will also be reviewed at specified time points as outlined in Table 1.

History
A detailed history will include review of gravida, prior abortions,, parity, deliveries, and history of gynecological conditions and/or cancer.

Focused Physical Exam
A standard brief physical exam will be done. This will include a gynecological pelvic exam and visual skin exam with specific attention to androgenic changes.

Urinalysis
A clean catch midstream voided urine specimen will be obtained, and evaluated by urine dipstick. If results or clinical symptoms indicate, the specimen will be sent for culture and the patient will receive appropriate treatment for UTI per standard of care.

24 Hour Pad Weight Test
The 24-hour pad test should be completed during 1 day of each scheduled 3-day 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 should be given one type of incontinence pad at the clinic. They may choose from a “light” pad or a “heavy” pad, but the pads dispensed **MUST** be used for the 24- hour test. Subjects should receive 8 incontinence pads for use during each 24-hour test period.

Urethral Pressure Profile (UPP) and Bladder Stress Test
To conduct the UPP and Bladder Stress Test, a urodynamic catheter will be placed and the bladder will be filled with 300 ml of fluid, such as saline. UPP will be performed. Subjects will be instructed to perform a provocative maneuver to increase abdominal pressure (cough, Valsalva, or similar event). Urine loss during this even indicates a positive stress test.

Ultrasound Bladder Scan
Subjects will be asked to void, and the volume of urine remaining in the bladder after voiding (post void residual) will be measured via bladder ultrasound scan.

Mammogram
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.

Magnetic Resonance Imaging(MRI)
MRI will be done at baseline and end of treatment to observe changes in pelvic floor muscles along with the thickness of the endometrium (mm). Quantiative assessments may include the area of the levator, the anteroposterior and transverse diameters, and/or other relevant parameters. Endometrial thickness can accurately be assessed by MRI (Stanislavsky, Weerakkody, et al., 2015; Nakamura et al., 2014); therefore, it is being used as a safety assessment in this study.

Medical, Epidemiological and Social Aspects of Aging (MESA) Questionnaire
The MESA questionnaire measures severity of specific types (stress, urgency, mixed) of urinary incontinence (UI). Two subscales, the urgency UI (6 items) and the stress UI (9 items). Test-retest reliability on “any incontinence” is high (agreement coefficient = .89). Validity (agreement between self-report on the MESA and clinician’s assessment) = 87% in women. The MESA questionnaire has demonstrated agreement on incontinence = 79% and 69% and 72% accuracy in predicting urodynamic diagnosis of stress UI and uninhibited detrusor contraction (Herzog, 1990a; Herzog, 1990b).

3 Day Voiding Diary
Subjects will record each episode of urinary leakage and record its severity. Subjects will also be asked to record urinary frequency, and urgency. Urine volume will also be recorded. 3 day bladder diaries are reliable measures of mean number of UI episodes/day, UI type, mean voids/24 hours, and mean voids during sleeping hours. 2-week test-retest results correlate with diurnal micturition ($r=.89$, $p<0.001$) and UI episodes ($r=.91$, $p<0.001$). Compared to participant recall of the previous week, Spearman rank correlation = .57 for voiding frequency and .70 for UI episodes (Brown, 2003: Locher, 2001; Wyman, 1988). For this study, any episode of vaginal discharge or spotting will also be recorded on the diary.

Patient Global Impression of Improvement (PGI-I)
PGI-I is a global rating of improvement using 7-point scale. Construct validity was established in two randomized controlled studies (n=1,133 subjects) of drug treatment for predominant stress incontinence (Wagner, 1996; Yalcin, 2003).

Patient Global Impression of Severity (PGI-S)
PGI-S is a global rating of symptoms severity using a 7 point scale (Yalcin, 2003).

UDI-6 and IIQ-7
The Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) assess symptom distress and the impact of urinary incontinence on daily life. The

urogenital distress inventory (UDI) and incontinence impact questionnaire (IIQ) were both developed to assess the impact of UI on HRQoL (Shumaker, 1994; Wyman, 1987). Short versions of the UDI and IIQ, UDI- 6, and IIQ-7, were developed to reduce the respondents' burden. The UDI-6 and IIQ-7 are both ''A grade'' recommended by the Fourth International Consultation on Incontinence (Shumaker, 1994; Wyman, 1987; Uebersax, 1995; Staskin, 2008).

Female Sexual Function Index (FSFI)
The FSFI is a 19-question validated tool evaluating sexual function in several domains: libido, arousal, lubrication, orgasm, satisfaction and pain (Rosen et al, 2000). Each subdomain is scored separately and the total score is calculated.

9. ASSESSMENT OF SAFETY

9.1 METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

9.1.1 ADVERSE EVENTS

ICH E6 defines an AE as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

The period of observation for which AEs are to be collected begins after the subject has signed the ICF, throughout the study intervention period, and for 28 days post treatment.

All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and captured on the appropriate CRF.

Information to be collected includes event description, time of onset, Investigator's assessment of severity, Investigator's assessment of relationship to study drug, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship to study drug. All AEs will be followed to adequate resolution as per Section 9.3 TYPE AND DURATION OF FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the condition deteriorates at any time during the study, it will be recorded as an AE.
All AEs must be graded for intensity and relationship to study drug.

9.1.2 INTENSITY OF EVENT

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 from

Table 1 should be used:

Table 1: Description of Grades According to the CTCAE

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
5	Death related to AE

If the intensity changes within a day, the maximum intensity should be recorded. If the intensity changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each change in intensity). Changes in the intensity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

9.1.3 DRUG – ADVERSE EVENT RELATIONSHIP

Classification of Relationship/Causality of Adverse Events (AE/SAE) to study drug: The investigator will determine the relationship between the study drug administration and the occurrence of an AE/SAE as defined below:

Not Related: The temporal relationship of the adverse event is determined to be Not Related to study drug administration.

Possibly Related: The temporal relationship of the adverse event to study drug administration makes a causal relationship possible. Other medications, therapeutic interventions, or underlying conditions provide a probable explanation for the observed event.

Probably Related: The temporal relationship of the adverse event to study drug administration makes a causal relationship.

Probable: Other medications, therapeutic interventions or underlying conditions provide a possible explanation for the observed event.

Related: The temporal relationship of the adverse event is determined to be Related to study drug administration.

Unable to Determine: The temporal relationship of the adverse event to study drug administration makes a causal relationship unable to determine or unknown.

9.1.4 SERIOUS ADVERSE EVENTS

An SAE is defined as an AE that meets 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
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

All SAEs will be:

- Recorded on the appropriate CRF
- Reported to the designated Safety department/pharmacovigilance contractor using a SAE Report Form within 24 hours of awareness
- Followed through to resolution by a study Investigator
- Reviewed and evaluated by a study Investigator

9.2 REPORTING PROCEDURES

9.2.1 SERIOUS ADVERSE EVENTS

All SAEs, including death due to any cause, which occur after the subject signs the ICF and within 28 days following the last administration of study drug, whether or not related to the study drug, must be reported immediately to the designated Safety Department/pharmacovigilance contractor within **24 hours** by e-fax, e-mail, or telephone (see contact information below). At the very least, the following information must be reported:

- Date and time of report
- Reporter's name and phone number
- Investigator's name and site number
- Subject number
- SAE information: event term, onset date, causal relationship
- Study drug: start date of study drug and whether or not study drug has been withheld or discontinued

SAE Reporting Contact Information:
US Safety Toll-Free E-Fax Line: **1 866 966 2970**
US Safety Toll-Free Unmanned Hotline: **1 866 966 8429**
Safety E-mail: **sae@cmedresearch.com**

Information about all SAEs is collected and recorded on the SAE Report Form. The Investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form, and send the completed, signed form by e-fax or e-mail within 24 hours to the assigned drug safety group. As a back-up, the site may report SAEs using the unmanned safety hotline, with a completed SAE Report Form forwarded to the assigned drug safety group within 24 hours following notification on the hotline. The original copy of the SAE Report Form and the e-fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information must also be sent to the same assigned drug safety group by e-fax or e-mail using either a new SAE Report Form stating that this is a follow-up to the previously reported SAE (giving the date of the original report), or by using a follow-up query form.

If an SAE is not previously documented (new occurrence) in the Investigator's Brochure (IB) and is thought to be related to the relevant Investigational Medicinal Product (IMP), the assigned drug safety group may urgently require further information from the Investigator for Regulatory Authority reporting. The drug safety group may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the regulatory/competent

authorities and relevant IRBs/IECs in accordance with Food and Drug Administration (FDA) regulations 21 CFR 312.32, International Conference on Harmonization (ICH) guidelines, and European Clinical Trials Directive 2001/20/EC, or as per national regulatory requirements in participating countries. Adequate documentation must be maintained showing that Regulatory Authorities and IRBs/IECs have been properly notified.

SAEs must be reported within 24 hours*, regardless of relationship, on a SAE Report Form* to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event.

The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably. The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

The SAE Report Form must be signed by the PI or assigned designee.

Other supporting documentation of the event may be requested by the safety department/pharmacovigilance contractor and should be provided as soon as possible.

All SAEs will be followed until satisfactory resolution as per Section 9.3 TYPE AND DURATION OF FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS.

9.2.2 REGULATORY REPORTING

Suspected (considered related to the study drug) and unexpected (not previously described in the reference safety document) serious adverse reactions (SUSARs) will be reported in an expedited manner by GTx, Inc. to applicable Regulatory Authorities, EudraVigilance, IECs and IRBs, and Investigators in compliance with FDA regulations 21 CFR 312.32, ICH guidelines, the European Clinical Trials Directive 2001/20/EC, the European Commission's "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" (CT-3, June 2011), and other applicable local regulations and guidelines, as required. The timelines stipulated by applicable national regulations and guidelines shall be adhered to, typically death and life-threatening SUSARs shall be reported within 7 days and all other SUSARs shall be reported within 15 days.

Additionally, events may occur during a clinical trial which do not fall within the definition of a SUSAR and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. Examples are new events

related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects such as:

- A SAE which could be associated with the trial procedures and which could modify the conduct of the trial
- A significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- A major safety finding from a newly completed animal study (such as carcinogenicity)

These events/observations are not to be reported as SUSARs, but they might require other action, such as urgent safety measures and their notification, substantial amendments, or early termination of the trial, and shall be reported in accordance with applicable local regulations and guidelines.

All serious events designated as expected and/or “not related” to study drug(s), will be reported to the applicable Regulatory Authorities and IECs/IRBs at least annually in a summary format”.

9.3 TYPE AND DURATION OF FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

AEs will be collected up until 28 days after the last dose of study treatment, and will continue to be followed up until one of the following occurs:

Resolved or improved to baseline
Death
Investigator confirms that no further improvement can be expected

9.4 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 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 (> 5%)

All subjects discontinued from the study should be followed until abnormal values return to normal.

ALL DISCONTINUATIONS SHOULD BE DISCUSSED WITH THE MEDICAL MONITOR PRIOR TO DISCONTINUATION.

10. STATISTICAL CONSIDERATIONS

Since this is a proof of concept feasibility study, no power calculation is needed. Based on Dalton, 2011, 10-20% of patients may withdraw from the study before completing treatment. Therefore, we will recruit up to 35 patients meeting inclusion/exclusion criteria until 30 subjects have completed treatment. Descriptive statistics will be used to explore changes in primary and secondary outcomes measures between baseline and end of treatment. Although the primary efficacy measure will be a change in frequency of daily stress leaks between Baseline and Week 14 weeks, response to treatment will also consider secondary efficacy measures (change in frequency of voids per day, urine volume per void , change in 24 hour pad weight , responses to validated questionnaires, changes in UPP measures, changes in sexual function), and change in pelvic floor muscles as measured by MRI. Safety will be reported by the number and type of adverse events reported during treatment. No imputations for missing data will be conducted. There will be no adjustment for multiple testing.

10.1 STATISTICAL METHODS

Primary end point

- The average number of episodes per day of leaking (SUI) will be calculated by summing the number of episodes over the 3 day period and dividing by 3, the change from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

Secondary end points

- The average number of voids per day will be calculated by summing the number of voids over the 3 day period and dividing by 3, the change from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- The average volume per void will be calculated by summing the total urine amount over the 3 day period and dividing by the total number of voids recorded over 3 days, the change from Baseline to Week 1[2 will be computed and this

change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Change in maximum urethral closure pressure measurements from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Change in 24 hour pad weight from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Change in total score on the stress incontinence section of the MESA Urinary Questionnaire from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Change in Patient Global Impression of Severity (PGI-S) Scale from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test

- Patient Global Impression of Improvement (PGI-I) Scale at Week 12. Descriptive statistics, (min, max, median, mean, standard deviation) will summarize these scores.

- Change in total score on the Urinary Distress Inventory (UDI-6) from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Change in total score on the Incontinence Impact Questionnaire (IIQ-7) from Baseline to Week 12 will be computed and this change will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Change in total score on the Female Sexual Function Index (FSFI) as well as the change in subdomain scores: libido, arousal, lubrication, orgasm, satisfaction, and pain from Baseline to Week 12 will be computed and these changes will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Changes in pelvic floor muscles from Baseline to Week 12 will be summarized with descriptive statistics (min, max, median, mean, standard deviation) and analyzed for a significant change from Baseline using the Exact Wilcoxon sign rank test.

- Qualitative changes in pelvic muscles will be described as decreased, increased or no change at Week 12 relative to Baseline.

Exploratory Analyses

Changes from baseline to each of the assessment times prior to Week 12 for the above endpoints will be explored, described and tested for significance using the same analytical methods noted for the primary and secondary objectives above. Durability treatment will be assessed by evaluating changes in study measures between week 12 and 16 (end of study). There will be no adjustment for multiple testing, nor will any data be imputed.

Repeated measures (mixed models) will be used to examine the change over time by incorporating all available assessment times to test for a significant non-zero slope over time and estimate that slope and its standard error.

Various imputation methods may be explored if any of the above analyses indicate promise for the compound in the treatment of SUI. These imputation methods may allow for better estimation of effect size and consequently sample size estimation in future trials.

11. QUALITY CONTROL AND 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, 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 study.

An authorized Quality Assurance auditor will audit the study data and procedures at periodic intervals as indicated. Domestic or foreign regulatory authorities, the IRB/IEC, 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 CFR Part 11, ICH Guidelines, GCP, local laws and legislation, and the Health Insurance Portability and Accountability Act.

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.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL CONSIDERATIONS

This clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with global regulations including 21 CFR 312.

The investigator is responsible for obtaining approval for this clinical study from the relevant IRB at the associated institution. The study will not begin until a favorable opinion of the IRB has been obtained. The investigator is responsible for complying with requirements imposed by the IRB and/or regulatory authority. Furthermore, the investigator will ensure that local regulations concerning data protection are followed. For ethical considerations, all patients will be required to sign a consent indicating their willingness to participate and that they have been fully informed of the risks and benefits of participation.

12.2 INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE

The protocol and the proposed ICF will be reviewed and approved by a properly constituted IRB/IEC before the study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC will be given to GTx, Inc. or designee before study initiation. The signed IRB/IEC approval letter must identify the documents approved (i.e., list the Investigator's name, the protocol number and title, the date of the protocol, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit subjects must also be reviewed by the IRB/IEC. Clinical supplies will not be shipped to a site until a signed approval letter from the IRB/IEC has been received and a contractual agreement has been signed by both parties.

Prior to study start, the Investigator will be required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GTx, Inc. monitors, auditors, GTx, Inc. Clinical Quality Assurance representatives, designated agents of GTx, Inc., IRBs/IECs/Research Ethics Boards (REBs), and regulatory authorities as required.

12.3 PRE-STUDY DOCUMENTATION

The Investigator must provide GTx or its designee with the following documents prior to the enrollment of any subjects:

- Copy of the signed Investigator Agreement page
- Copy of the IRB/IEC approval letter for protocol and informed consent
- Completed, signed, and dated Form FDA 1572
- Current curricula vitae, licenses, and financial disclosures for the Investigator(s) and sub Investigators listed on the 1572
- Where applicable, list of IRB/IEC committee members and a statement of adherence to GCP
- Copy of approved informed consent document
- Executed clinical trial agreement
- Name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. GTx or its designee must be notified if the central laboratory is changed or if any additional laboratory is to be used
- List of normal laboratory values (i.e., reference ranges and units of measure) for each central laboratory to be used during the study. GTx or its designee must be notified if normal values change

12.4 INFORMED CONSENT PROCESS

Eligible subjects will only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

The informed consent documents must be reviewed and approved by GTx or its designee and the investigative site IRB/IEC prior to the initiation of the study.

Each subject will receive an IRB/IEC approved informed consent document with study information. Subjects should be given ample time to read the information and the opportunity to ask questions. Informed consent must be obtained from each subject prior to performing any protocol-specific evaluations. The signed ICF will be retained with the study records and the subject will receive a copy of the signed informed consent for his/her records. The process of obtaining informed consent will be documented in the subject source documents.

The date when a subject's informed consent was actually obtained will be captured in their CRFs.

The Investigator (or designated staff) will explain the nature of the study as well as its risks and benefits to the subject (or the subject's legal representative).

12.5 SUBJECT CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests (if applicable) in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

12.6 PROTOCOL ADHERENCE

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

12.7 PERMISSION TO REVIEW SUBJECTS' SOURCE RECORDS

The Investigator agrees to allow the FDA and other regulatory agencies, individuals delegated by the IRB/IEC and Competent Authorities, and the Sponsor or its designee to have access to all the original documentation of the study, including the ICFs signed by the subjects enrolled into the study and the relevant subject medical files. The individuals who are given access to the documentation must take every reasonable precaution to keep the identity of the subjects and the proprietary information of the Sponsor as confidential information in accordance with relevant applicable legislation.

12.8 PROTOCOL AMENDMENTS

All amendments to the study protocol must be submitted to the IRB/IEC for written approval. The approval letter, signed by the IRB/IEC Chairperson, must refer specifically to the Investigator, the protocol number and protocol title, the protocol

amendment number, and the date of the protocol amendment. A copy of the approval letter and revised informed consent document (if applicable) must be sent to GTx or its designee. A protocol amendment may be implemented only after it has been approved by the IRB/IEC and has been approved by the appropriate regulatory authority. In the case of a protocol change intended to eliminate an apparent immediate hazard to subjects, the change may be implemented immediately, but the change must then be documented in a protocol amendment and approved as described above.

12.9 CHANGE IN INVESTIGATOR

If any Investigator retires, relocates, or withdraws from an investigation during the conduct of the study the responsibility for conduct of the study may be transferred to another appropriately qualified Investigator at the investigative site. GTx or its designee must be notified. An updated Form FDA 1572 must be submitted to GTx or its designee.

12.10 STUDY DISCONTINUATION

GTx, Inc. reserves the right to discontinue this study under the conditions specified in the clinical study agreement.

12.11 INDEMNITY

The Sponsor certifies that it has taken out a liability insurance policy that is consistent with the requirements for which the study is being conducted. This insurance policy is in accordance with local laws and requirements. An insurance certificate will be provided to the PI requiring this document. The insurance of the Sponsor does not relieve the PI and the collaborators of any obligation to maintain their own liability insurance policy as required by applicable law.

13. DATA HANDLING AND RECORD KEEPING

The Investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the source data. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the CRF will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Study records will be maintained in locked offices with access limited to authorized individuals. Each participant will be given an identification number that will be used to enter the data into a password protected database and for the analysis.

13.1 DATA CAPTURE METHODS

13.1.1 DATA COLLECTION

Study specific data will be collected on paper case report forms (CRFs). Completed questionnaires and voiding diaries will be used as source documents, and these documents will be kept in the study files. Blank data fields should be noted as unknown (UNK) or not applicable (NA) if source information is not available or data not collected. While completing the questionnaire, if a subject leaves a question blank, it will be deemed permanently missing. All CRFs will be maintained at the study site for the length of time as determined by the IRB and federal regulations and as provided in the site's clinical study agreement. Data will be entered into a password protected electronic database that does not contain subject identifiers. Identifiers linked to unique Study ID will be kept separately from the study data. Data entry will be reviewed for accuracy.

13.2 STUDY SITE RESPONSIBILITIES

All data requested on the CRF must be recorded. Data will be transcribed by authorized personnel at the study site from the source documents into the CRF for enrolled subjects. All information on the CRF must be traceable to these source documents. All electronic entries (including any changes or updates) will be traceable through the system. Only the PI or authorized staff may enter or modify data in the database using their unique password. The Investigator must certify that the data entered in the CRFs are complete and accurate by electronically signing the CRF.

13.3 CRF TIMING/REPORTS

A final report for the study will be completed upon completion of the study and the analysis of data. Please see information concerning publication policy (Section 14).

13.4 STUDY RECORDS RETENTION

Study documents must be retained for a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of GTx, Inc., if applicable. It is the responsibility of GTx, Inc. to inform the PI when these documents no longer need to be retained.

13.5 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol that affects a subject's safety and primary efficacy, GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the PI, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1 Quality Assurance and Quality Control, section 5.1.1
5.20 Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation.
All deviations from the protocol must be addressed in study subject source documents. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations will be sent to the local IRB/IEC per their guidelines. The PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

14. PUBLICATION POLICY

Following completion of the study, it is expected some Investigators may wish to publish the results of this research in scientific journal(s). Publication rights are governed by the investigatory site's clinical trial agreement with GTx, Inc. The Investigator may request to publish this study in a scientific journal, but must have written authorization of GTx, Inc.

The data generated by this study are confidential information and the property of GTx, Inc. This confidential information may be published only in collaboration with participating personnel from GTx, Inc. or upon GTx's written consent, or otherwise under terms of the investigatory site's clinical trial agreement with GTx, Inc. All unpublished information shall not be disclosed to any third parties without the prior written consent of GTx, Inc.

The International Committee of Medical Journal Editors member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the U.S. National Library of Medicine. It is GTx's responsibility to register this trial in an acceptable registry.

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1. APPENDIX A: MESA URINARY QUESTIONNAIRE

MESA Urinary Questionnaire				
NAME (printed): _____				
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	Sometimes	Rarely	Never
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	Sometimes	Rarely	Never
3.	Do you lose urine when you suddenly have the feeling that your bladder is full?			
	Often	Sometimes	Rarely	Never
4.	Does washing your hands cause you to urinate?			
	Often	Sometimes	Rarely	Never
5.	Does cold weather cause you to lose urine?			
	Often	Sometimes	Rarely	Never
6.	Does drinking cold beverages cause you to lose urine?			
	Often	Sometimes	Rarely	Never
	Stress Incontinence			
1.	Does coughing gently cause you to lose urine?			
	Often	Sometimes	Rarely	Never
2.	Does coughing hard cause you to lose urine?			
	Often	Sometimes	Rarely	Never

3.	Does sneezing cause you to lose urine?			
	Often	Sometimes	Rarely	Never
4.	Does lifting things cause you to lose urine?			
	Often	Sometimes	Rarely	Never
5.	Does bending over cause you to lose urine?			
	Often	Sometimes	Rarely	Never
6.	Does laughing cause you to lose urine?			
	Often	Sometimes	Rarely	Never
7.	Does walking briskly cause you to lose urine?			
	Often	Sometimes	Rarely	Never
8.	Does straining, if you are constipated, cause you to lose urine?			
	Often	Sometimes	Rarely	Never
9.	Does getting up from a sitting to a standing position cause you to lose urine?			
	Often	Sometimes	Rarely	Never

Total Calculator:

URGE SYMTOM INDEX LOOK-UP TABLE				
1/18 = 6%	5/18 = 28%	9/18 = 50%	13/18 = 72%	17/18 = 94%
2/18 = 11%	6/18 = 33%	10/18 = 56%	14/18 = 78%	18/18 = 100%
3/18 = 17%	7/18 = 39%	11/18 = 61%	15/18 = 83%	
4/18 = 22%	8/18 = 44%	12/18 = 67%	16/18 = 89%	

Total Score _____/18

STRESS SYMPTOM INDEX LOOK-UP TABLE						
1/27 = 4%	5/27 = 19%	9/27 = 33%	13/27 = 48%	17/27 = 63%	21/27 = 78%	25/27 = 93%
2/27 = 7%	6/27 = 22%	10/27 = 37%	14/27 = 52%	18/27 = 67%	22/27 = 81%	26/27 = 96%
3/27 = 11%	7/27 = 26%	11/27 = 41%	15/27 = 56%	19/27 = 70%	23/27 = 85%	27/27 = 100%
4/27 = 15%	8/27 = 30%	12/27 = 44%	16/27 = 59%	20/27 = 74%	24/27 = 89%	

Total Score _____/27

2. APPENDIX B: PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S) SCALE AND PATIENT GLOBAL IMPRESSION OF IMPROVEMENT (PGI-I) SCALE

Patient Global Impression of Severity (PGI-S) Scale
Check the one number that best describes how your urinary tract condition is now.
1. Normal
2. Mild
3. Moderate
4. Severe

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

3. APPENDIX C: URINARY DISTRESS INVENTORY (UDI-6) AND INCONTINENCE IMPACT QUESTIONNAIRE (IIQ-7)

Urinary Distress Inventory (UDI-6)

1. Do you experience, and, if so, how much are you bothered by frequent urination?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

2. Do you experience, and, if so, how much are you bothered by urine leakage related to the feeling of urgency?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

3. Do you experience, and, if so, how much are you bothered by urine leakage related to physical activity, coughing, or sneezing?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

4. Do you experience, and, if so, how much are you bothered by small amounts of urine leakage
(drops)?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

5. Do you experience, and, if so, how much are you bothered by difficulty emptying your bladder?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

6. Do you experience, and, if so, how much are you bothered by pain or discomfort in the lower
abdominal or genital area?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

Incontinence Impact Questionnaire (IIQ-7)

7. Has urine leakage affected your ability to do household chores (cooking, cleaning, laundry, etc)?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

8. Has urine leakage affected your physical recreation such as walking, swimming, or other exercise?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

9. Has urine leakage affected your entertainment activities (movies, concerts, etc.)?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

10. Has urine leakage affected your ability to travel by car or bus more than 30 minutes from home?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

11. Has urine leakage affected your participation in social activities outside your house?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

12. Has urine leakage affected your emotional health (nervousness, depression, etc.)?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

13. Has urine leakage affected your feeling frustrated?
Not at all **0** *Slightly* **1** *Moderately* **3** *Greatly***4**

14. Total Score for UDI-6=_____

15. Total Score for IIQ-7=_____

4. APPENDIX D: FEMALE SEXUAL FUNCTION INDEX (FSFI)

Female Sexual Function Index (FSFI)

Name _____ Date _____

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
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?
   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low

☐Very low or none at all

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

☐Almost always or always

☐Most times (more than half the time)

☐Sometimes (about half the time)

☐A few times (less than half the time)

☐Almost never or never

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

☐Very high

☐High

☐Moderate

☐Low

☐Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

☐No sexual activity

☐Very high confidence

☐High confidence

☐Moderate confidence

☐Low confidence

☐Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

☐No sexual activity

☐Almost always or always

☐Most times (more than half the time)

☐Sometimes (about half the time)

☐A few times (less than half the time)

☐Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

☐No sexual activity

☐Almost always or always

☐Most times (more than half the time)

☐Sometimes (about half the time)

☐A few times (less than half the time)

☐Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

☐No sexual activity

☐Extremely difficult or impossible

☐Very difficult

☐Difficult

☐Slightly difficult

☐Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

☐No sexual activity

☐Almost always or always

☐Most times (more than half the time)

☐Sometimes (about half the time)

☐A few times (less than half the time)

☐Almost never or never

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

☐Extremely difficult or impossible

☐Very difficult

☐Difficult

☐Slightly difficult

☐Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

☐No sexual activity

☐Almost always or always

☐Most times (more than half the time)

☐Sometimes (about half the time)

☐A few times (less than half the time)

☐Almost never or never

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

☐Extremely difficult or impossible

☐Very difficult

☐Difficult

☐Slightly difficult

☐Not difficult

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

☐Very satisfied

☐Moderately satisfied

☐About equally satisfied and dissatisfied

☐Moderately dissatisfied

☐Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

☐No sexual activity

☐Very satisfied

☐Moderately satisfied

☐About equally satisfied and dissatisfied

☐Moderately dissatisfied

☐Very dissatisfied

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

☐Very satisfied

☐Moderately satisfied

☐About equally satisfied and dissatisfied

☐Moderately dissatisfied

☐Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

☐Very satisfied

☐Moderately satisfied

☐About equally satisfied and dissatisfied

☐Moderately dissatisfied

☐Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

☐Did not attempt intercourse

☐Almost always or always

☐Most times (more than half the time)

☐Sometimes (about half the time)

☐A few times (less than half the time)

☐Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

☐Did not attempt intercourse

☐Almost always or always

☐Most times (more than half the time)

☐Sometimes (about half the time)

☐A few times (less than half the time)

☐Almost never or never

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

☐Very high

☐High

☐Moderate

☐Low

☐Very low or none at all

Thank you for completing this questionnaire

5. APPENDIX E: VOIDING DIARY

VOIDING DIARY

Wake Time: _____ **Study ID: _____**

Bed Time: _____ **Date (m/d/y): _____**

Time	Fluid Intake (ounces)	Urine Amount cc's/ml's or ounces (oz)	Leaking (if you leak, first give the episode a "score" in the first column then circle if you think it is stress or urge incontinence, or both in the second column)		Urgency	Pad Replaced	Bowel Movement	Pelvic and/or Bladder/Urinary Related Pain	Vaginal discharge color	Vaginal discharge amount
A: a.m. **P**: p.m.		Amount Voided	**0:** None **1:** Mild **5:** Mod. **10:** Severe	**S:** Stress **U:** Urge	**0:** None **1:** Mild **5:** Mod. **10:** Severe	**1:** Tissue **2:** Pantiliner **3:** Thick Pad **4:** Diaper	**N:** Normal **C:** Constipated **D:** Diarrhea **L:** Leaking stool	**0:** None **1:** Mild 5: Mod **10:** Severe .	**0: no discharge** **1: red** **2: brown** **3: white** **4: yellow**	**1: Spotting** **2: dime size** **3: quarter size** **5: more than quarter size**
5:00 AM				S U						
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