Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

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

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Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

CONFIDENTIALITY STATEMENT

Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

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)
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (May 9, 1997)
- European Union (EU) Clinical Trial Directive 2001/20/EC
- Relevant regulations from all countries where the clinical study will be conducted

Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

PROTOCOL SIGNATURE PAGE

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Date: 5/27/15

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Signature: .....

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Title: Medical Monitor

Date: 28 MAY 2015

Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

INVESTIGATOR SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

Name
Title

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AI	Aromatase Inhibitor
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AR	Androgen Receptor
AST	Aspartate Aminotransferase
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BOR	Best Overall Response
CB	Clinical Benefit
CBR	Clinical Benefit Rate
CD-ROM	Compact Disk-Read Only Memory
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CT	Computerized Tomography
CTCs	Circulating Tumor Cells
CYP2C9	Cytochrome P450 2C9
CYP3A	Cytochrome P450, Family 3, Subfamily A
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End Of Treatment
ER	Estrogen Receptor
ER+/AR+	Estrogen Receptor Positive and Androgen Receptor Positive
EU	European Union
FAS	Full Analysis Set

FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HBV-DNA	Hepatitis B Virus-Deoxyribonucleic Acid
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High Power Field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IN	Investigator Notification
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
ISH	In situ hybridization
LBM	Lean Body Mass
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LH-RH	Luteinizing Hormone-Releasing Hormone
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association

ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PO	Per Os (oral)
PPS	Per Protocol Set
PR	Partial Response
PSA	Prostate Specific Antigen
QoL	Quality of Life
QT_CB	QT interval corrected for heart rate according to Bazett's formula
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
RNA-PCR	Ribonucleic Acid-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARM	Selective Androgen Receptor Modulator
SAS	Safety Analysis Set
SD	Stable Disease
SERM	Selective Estrogen Receptor Modulator
SHBG	Sex Hormone Binding Globulin
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNBC	Triple Negative Breast Cancer
TTP	Time To Progression
UGT2B7	UDP-Glucuronosyltransferase-2B7
ULN	Upper Limit of the Normal Range
US	United States
VAS	Visual Analog Scale
WBC	White Blood Cells
α	Alpha

Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

PROTOCOL SUMMARY

Title:	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
Sponsor:	GTx, Inc.
Indication:	Metastatic or locally advanced estrogen receptor positive and androgen receptor positive (ER+/AR+) BC
Study design:	This is an open label, multicenter, multinational, randomized, parallel design Phase 2 study to assess the efficacy and safety of GTx-024 in postmenopausal subjects with ER+/AR+ BC. Subjects will be randomized to receive either GTx-024 9 mg or 18 mg given orally (PO) daily for up to 24 months. Each dose arm will be treated independently and each assessed for efficacy using Simon's two-stage design[1]. Randomization will be 1:1 and stratified so as to balance subjects presenting with bone only metastases and all other subjects, and setting of immediately preceding therapy (adjuvant setting or metastatic setting). There is no intent to statistically compare the two dose arms, but to determine whether either or both doses result in an acceptable clinical benefit rate (CBR), defined as the proportion of evaluable subjects (i.e., subjects with centrally confirmed AR+ and who receive at least one dose of study drug) with either complete response (CR), partial response (PR), or stable disease (SD), by Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1[2], at week 24, consistent with 30% while maintaining an acceptable safety profile. Given such a result, future exploration of GTx-024 in ER+/AR+ BC would be warranted. Thirty-six to eighty-eight (36–88) subjects with centrally confirmed AR+ who receive at least one dose of study drug (evaluable subjects) will be needed for primary efficacy analysis purposes and will be a subset of the Full Analysis Set (FAS). Thirty-six to one hundred and eighteen (36–118) subjects, including replacement subjects, will be randomized in a 1:1 fashion to receive a daily PO dose of either GTx-024

	9 mg or 18 mg. Thirty of the aforementioned subjects may be considered replacement subjects to account for lack of centrally confirmed AR+ status, or for the rare subject who is randomized but does not receive study drug. The trial will test for an unacceptably low CBR of ≤ 10% versus a CBR more consistent with ≥ 30%. The first stage in each study arm will be assessed among the first 18 evaluable subjects. If at least 3/18 subjects achieve clinical benefit (CB) at week 24, then the trial arm will proceed to the second stage of recruitment of up to a total of 44 evaluable subjects in the FAS in that arm. Otherwise, the arm will be discontinued for lack of efficacy. Subjects who are not confirmed AR+ may remain on the trial, but will not be part of the primary efficacy analysis – these subjects will contribute to secondary and tertiary analyses as noted in Section 11 Statistical Considerations. Subjects on the 18 mg treatment arm who experience an adverse event (AE) with Grade ≥ 3 intensity (National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE], Version 4.0) and/or intolerance may have a dose reduction from 18 mg to 9 mg per day or a drug interruption based on the medical judgment of the Investigator and after confirmation by the study Medical Monitor. The drug interruption may last for a period of up to 5 days after which the subject must be rechallenged with study drug (18 mg or 9 mg) or discontinued from the study. In the case of a dose reduction, once the AE has resolved or reduced in intensity to Grade 1, the subject may be rechallenged with 18 mg or maintained at 9 mg at the discretion of the Investigator. Subjects on the 9 mg treatment arm who experience an AE with Grade ≥ 3 intensity (NCI-CTCAE 4.0) and/or intolerance may have a drug interruption based on the medical judgment of the Investigator and after confirmation by the study Medical Monitor. The drug interruption may last for a period of up to 5 days after which the subject must be rechallenged with study drug (9 mg) or discontinued from the study. In the event of hepatotoxicity, please also refer to Section 9.4 Halting Rules.

	The subjects who demonstrate CB from the treatment will be treated for up to 24 months from the date of randomization (as long as they continue to demonstrate CB from the treatment during these 24 months). Subjects who continue to demonstrate a CB from the study treatment at 24 months will be offered to continue in a safety extension study under a separate protocol. For safety purposes, all subjects will be followed-up for one month after the last dose of GTx-024 is received. In order to protect the safety of the subjects, a Safety Monitoring Committee (SMC) will be established for the study to review the safety data on an ongoing basis. The SMC will consist of, as a minimum, the Medical Monitor, a Safety Reviewer with an oncology background, a statistician, and two GTx, Inc. representatives, consistent with the SMC charter.
Objectives:	The **primary efficacy objective** of this trial is to estimate the CBR at 24 weeks (defined as CR, PR, or SD) (by RECIST 1.1) of GTx-024 9 mg and of GTx-024 18 mg given PO daily in subjects with ER+/AR+ BC who have centrally confirmed AR+ status. **Secondary efficacy objectives**: • Estimate the CBR at 24 weeks (by RECIST 1.1) of GTx-024 9 mg and 18 mg in all subjects randomized who receive at least one dose of study medication (the FAS) regardless of AR status as determined by the central laboratory The following secondary efficacy objectives apply to both centrally confirmed AR+ subjects (the evaluable subset of the FAS) as well as to all subjects in the FAS: • Estimate the objective response rate (ORR; defined as CR or PR) (by RECIST 1.1) of GTx-024 9 mg and 18 mg at 24 weeks • Estimate the best overall response rate (BOR) of GTx-024 9 mg and 18 mg

	• Estimate the progression free survival (PFS) of subjects receiving GTx-024 9 mg and 18 mg • Estimate the time to progression (TTP) of subjects receiving GTx-024 9 mg and 18 mg • Estimate duration of response (time from documentation of tumor response to disease progression or death) of subjects receiving GTx-024 9 mg and 18 mg **Tertiary objectives:** The following tertiary efficacy objectives apply to both centrally confirmed AR+ subjects (the evaluable subset of the FAS) as well as to all subjects in the FAS: • Assess the effect of GTx-024 9 mg and 18 mg on serum prostate specific antigen (PSA) • Assess the effect of GTx-024 9 mg and 18 mg on Quality of Life (QoL) as measured by EQ-5D-5L[3] • Assess the effect of GTx-024 9 mg and 18 mg on circulating tumor cells (CTCs) • Assess the impact of duration of prior CB on outcome • Assess the impact of time from diagnosis of metastases to randomization on outcome • Describe the effect of GTx-024 9 mg and 18 mg on tumor volumetrics • Assess the effect of plasma concentrations of GTx-024 and GTx-024 glucuronide on CBR at 24 weeks **Safety objective:** To describe the safety profile of GTx-024 9 mg and 18 mg PO daily in subjects with ER+/AR+ BC with centrally confirmed AR+ as well as in all subjects randomized and treated. **Pharmacokinetic objective:** To describe the plasma concentrations of GTx-024 *and* GTx-024 glucuronide at each of the assessed time points.
Target Population:	Adult postmenopausal women with metastatic or recurrent locally advanced ER+/AR+ BC. **Subject Inclusion criteria:** Subjects eligible for inclusion in this study must meet **all** of the following criteria: 1. Adult women (≥ 18 years of age) with metastatic or

	recurrent locally advanced BC, not amenable to curative treatment by surgery or radiotherapy, with objective evidence of disease progression. • Women must have received ≥ 1 prior hormonal treatment(s) in the metastatic or adjuvant setting ▪ If the most recent hormonal treatment was in the metastatic setting, duration of response (tumor regression or stabilization of disease) to this specific course of therapy must be ≥ 6 months ▪ If the most recent hormonal treatment was in the adjuvant setting, duration of response (disease free) to this specific course of therapy must be ≥ 3 years 2. Histological or cytological confirmation of ER+ BC as assessed by a local laboratory using slides, paraffin blocks, or paraffin sample or by medical history: ER+ (confirmed as ER expression more than or equal to 1% positive tumor nuclei) 3. Human epidermal growth factor receptor 2 (HER2)-negative tumor by local laboratory testing (immunohistochemistry [IHC] 0, 1+ regardless of fluorescence in situ hybridization [FISH] ratio; IHC 2+ with FISH ratio lower than 2.0 or HER2 gene copy less than 6.0; FISH ratio of 0, indicating gene deletion, when positive and negative in situ hybridization [ISH] controls are present) 4. Availability of paraffin embedded or formalin fixed tumor tissue; OR, a minimum of 10 and up to 20 slides of archived tumor tissue for central laboratory confirmation of AR status and molecular subtyping. Metastatic tumor tissue is preferred when possible 5. Postmenopausal women. Postmenopausal status is defined by the National Comprehensive Cancer Network as either: • Age ≥ 55 years and one year or more of amenorrhea • Age < 55 years and one year or more of amenorrhea, with an estradiol assay < 20 pg/mL

	• Age < 55 years and surgical menopause with bilateral oophorectomy a. *Note:* Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression 6. Radiological or clinical evidence (bone scan, computerized tomography [CT], and magnetic resonance Imaging [MRI]) of recurrence or progression within 30 days before randomization 7. Subject must have either measurable disease or bone-only non-measurable disease, evaluable according to RECIST 1.1 8. Adequate organ function as shown by: • Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3 • Platelet count ≥ 100,000 cells/mm^3 • Hemoglobin (Hgb) ≥ 9.0 g/dL • Serum aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 2.5 upper limit of the normal range (ULN) (or ≤ 5 if hepatic metastases are present) • Total serum bilirubin ≤ 2.0 × ULN (unless the subject has documented Gilbert Syndrome) • Alkaline phosphatase levels ≤ 2.5 × ULN (≤ 5 × ULN in subjects with liver metastasis) • Serum creatinine ≤ 2.0 mg/dL or 177 µmol/L • International normalized ratio (INR) or activated partial thromboplastin (aPTT) < 1.5 × ULN (unless on anticoagulant treatment at screening) 9. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status[4] 0 or 1 10. Subject is able to swallow capsules 11. Able and willing to give voluntary, written and signed informed consent before any screening procedure and according to local guidelines **Exclusion criteria:** Subjects eligible for this study must not meet **any** of the following criteria:

	1. Previously received > 1 course of chemotherapy (not including immunotherapies or targeted therapies) for the treatment of metastatic BC a. *Note*: Subjects may have received 1 course of chemotherapy prior to surgery for the treatment of locally advanced disease and 1 course of chemotherapy for the treatment of metastatic BC; however, if surgery could not be performed, this will count as the 1 chemotherapy course allowed prior to study 2. Known hypersensitivity to any of the GTx-024 components or subjects previously received treatment with Selective Androgen Receptor Modulator (SARM) 3. Subjects with radiographic evidence of central nervous system (CNS) metastases as assessed by CT or MRI that are not well-controlled (symptomatic or requiring control with continuous corticosteroid therapy [e.g., dexamethasone]) a. *Note*: Subjects with CNS metastases are permitted to participate in the study if the CNS metastases are medically well-controlled and stable for at least 28 days after receiving local therapy (irradiation, surgery, etc.) 4. Radiotherapy within 14 days prior to randomization except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture, which can then be completed within 7 days prior to randomization. Subjects must have recovered from radiotherapy toxicities prior to randomization 5. Currently receiving hormone replacement therapy, unless discontinued prior to screening 6. Subjects positive for Human Immunodeficiency Virus (HIV) 7. Subject has a concomitant medical condition that precludes adequate study treatment compliance or assessment, or increases subject risk, in the opinion of the Investigator, such as but not limited to:

	• Myocardial infarction or arterial thromboembolic events within 6 months prior to Baseline or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease, or a QT_CB (corrected according to Bazett's formula) interval > 470 msec • Serious uncontrolled cardiac arrhythmia grade II or higher according to NYHA • Uncontrolled hypertension (systolic > 150 and/or diastolic > 100 mm Hg) • Acute and chronic, active infectious disorders and non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy • Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome) • Another active cancer (excluding adequately treated basal cell carcinoma or cervical intraepithelial neoplasia [CIN]/cervical carcinoma in situ or melanoma in situ). Prior history of other cancer is allowed as long as there is no active disease within the prior 5 years 8. Major surgery within 28 days before randomization 9. Positive hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection at screening 10. History of non-compliance to medical regimens 11. Subjects unwilling to or unable to comply with the protocol 12. Subject is currently receiving treatment with any agent listed on the prohibited medication list (See Section 6.6 Concomitant Medications/Treatments for complete list) 13. Treatment with any investigational product within < 4 half-lives for each individual investigational product OR within 28 days prior to randomization
Phase:	2
Number of Sites:	The study will be conducted primarily in 20 sites in the United

	States (US) and Europe.
Study Duration:	The study duration is estimated at 3 years.
Subject Participation Duration:	It is expected the subjects will remain in the study for approximately two (2) years. There will be a screening period of up to 28 days and a follow-up period of 1 month.
Description of Agent or Intervention:	Three (3) GTx-024 3.0 mg softgels for a 9 mg daily dose or six (6) GTx-024 3.0 mg softgels for an 18 mg daily dose will be taken PO with water at approximately the same time each day, with or without food.
Estimated Time to Complete Enrolment:	It is anticipated the time to complete enrollment will be 12 months.
Statistical Considerations	This trial will employ a Simon's two-stage (optimal) design independently for each dose arm, 9 mg and 18 mg. The assumptions for the design are as follows: • H_0: CBR ≤ 0.10 • H_1: CBR ≥ 0.30 • Alpha (α) = 0.025 (one-sided) • Power = 90%. Based on the above assumptions, a sample size of N = 44 centrally confirmed AR+ subjects who have received at least one dose of study medication (evaluable subjects) are needed for each arm to proceed to completion of the second stage. An arm will proceed to the second stage if at least 3 subjects among the first 18 evaluable subjects randomized in stage 1 achieve CB, defined as CR, PR, or SD, as per RECIST 1.1 as determined by central review. Otherwise, the arm will be closed due to lack of efficacy. If an arm proceeds to the second stage, the efficacy criteria favoring further evaluation of the dose arm(s) in future trials will require at least 9/44 subjects to achieve CB; i.e., the null hypothesis of an unacceptably low rate of CB, ≤ 10.0%, can be rejected in favor of the alternative hypothesis that indicates the higher rate, ≥ 30%, is more likely.

	Over-enrollment: Subjects who are not centrally confirmed AR+ will be replaced by an over-enrollee in order to accrue the 44 subjects of the evaluable subset of the FAS. Subjects who are randomized but not centrally confirmed AR+ may, at the discretion of the Investigator, be maintained on the study, but these subjects will not be part of the evaluable subset of the FAS used for the primary analysis. However, these subjects are part of the FAS and will contribute to analysis as specified in Section 11 Statistical Considerations. Subjects who are randomized but do not receive treatment will also be replaced by an over-enrollee. Subjects who do not receive any study medication will not be included in any efficacy analyses. These two conditions may result in up to an additional 30 subjects being randomized (assumes 25% of enrolled subjects are not evaluable for the primary efficacy analysis).

Schedule of Events

Periods	**Screening** **Day –28 to –1**	**Randomization/ Baseline** **Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
Obtain ICF	X									
Demography	X									
Eligibility criteria check	X	X								
Medical history	X									
Prior anticancer treatment	X	X								
Concomitant medications	X	X	X	X	X	X		X	X	X
Diagnosis and extent of BC	X									

Periods	**Screening** **Day –28 to –1**	**Randomization/ Baseline** **Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
Hormonal receptor status (ER+) and HER2[3]	X									
AR status[3]	X									
Physical examination	X		X	X	X	X		X	X	X
Height	X									
Weight	X		X	X	X	X		X	X	X
Vital signs	X	X[4]	X	X	X	X		X	X	X
ECOG performance status	X	X[4]	X	X	X	X		X	X	X
Eye examination[5]	X	As clinically indicated							X	

Periods	**Screening** **Day –28 to –1**	**Randomization/ Baseline** **Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
Hematology	X	X[4]	X	X	X	X		X	X	X
Biochemistry	X	X[4]	X	X	X	X		X	X	X
HIV screening	X									
HBV screening[6]	X									
HCV screening	X									
Serum lipid profile		X	X	X	X	X		X	X	
Coagulation status	X		X	X	X	X		X	X	
Serum hormones		X	X	X	X	X		X	X	
PSA	X	X[4]	X	X	X	X		X	X	X

Periods	**Screening** **Day –28 to –1**	**Randomization/ Baseline** **Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
CTC enumeration		X		X		X		X	X	
CTC gene expression		X							X	
Urine analysis	X	As clinically indicated								
Radiological evaluation: CT/MRI[7]	X			X		X	X[8]	X	X	
Radiological evaluation: bone scan[9]	X			X		X	X[10]	X	X	
Pharmacokinetic samples[11]		X	X		X	X				
ECG	X									

Periods	**Screening** **Day –28 to –1**	**Randomization/ Baseline** **Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
AEs	X	X	X	X	X	X		X	X	To be followed up to 28 days post treatment
Serum Pregnancy Test	X									
GTx-024 9 mg or 18 mg dispensing/ administration		X[12]	X	X	X	X[13]		X[13]		
GTx-024 9 mg or 18 mg accountability			X	X	X	X		X	X	
QoL EQ-5D-5L		X	X	X	X	X		X	X	

[1] Subjects with clinical benefit at 24 weeks will continue on therapy for up to 24 months (as long as they still benefit from the treatment during these 24 months). If so, the subjects will be asked to come for a visit every 3 months and undergo the assessments for the treatment period.

[2] Visit 8 should occur at Week 36; i.e., 12 weeks after Visit 6 (Week 24).

[3] ER and HER2 as per medical record will be used to determine subject eligibility. ER status will be confirmed by a local laboratory if not available in the subject's medical history. AR status will be confirmed by a central laboratory.

[4] These medical procedures and assessments do not have to be repeated if done at screening within 7 days before randomization.

[5] Eye examination including best corrected distance visual acuity with refraction, intraocular pressure, slit lamp examination, and dilated fundus photography must be completed between Day –28 and Day –1, as clinically indicated during the treatment phase, and at EOT.

[6] HBV screening will be done as HBsAg.

[7] Imaging study (CT, MRI) is recommended to be performed within 7 days prior to randomization. The imaging studies will be assessed by both a local imaging facility and a blinded central reader. Subject eligibility will be based on local reading of the imaging studies. Medical decisions will be based on the local assessments.
At screening, week 12 (Visit 4), and week 24 (Visit 6), tumor volumetric assessments will be done for the subjects undergoing CT scanning.

[8] In compliance with RECIST 1.1 guidelines, subjects who have CR or PR at week 24 (Visit 6) require confirmation within a month as follows:

- For subjects with measureable lesions, subjects will undergo CT/MRI based on the Investigator's medical judgment

[9] Bone scans will be performed at screening and then every 12 weeks whilst subjects receive treatment (Visits 4, 6, and thereafter) in only those subjects with baseline bone metastases, or if clinically indicated.

[10] In compliance with RECIST 1.1 guidelines, subjects who have CR or PR at week 24 (Visit 6) require confirmation within a month as follows:

- For subjects with non-measurable lesions, subjects will undergo X-ray or bone-scanning based on the Investigator's medical judgment and location of disease.

[11] Blood sampling for pharmacokinetic assessment. The exact time (hh:mm) and date of the blood sample should be recorded on the eCRF. At the baseline visit, the blood sample should be collected before the subject is given their first dose of GTx-024. At visits 3 (week 6), 5 (week 18), and 6 (week 24), the date and approximate time of the last dose of GTx-024 prior to the blood sample should also be recorded; i.e., it should be documented whether the subject took the previous dose that morning or the evening before.

[12] First dose to be given at site during this visit.

[13] At Visits 6, 8, 9, 10, 11, 12, and 13, in order to accommodate the visit schedule of every 12 weeks (± 7 days), the subjects will receive two carton boxes of study drug (each containing 7 blisters) to cover study treatment for 14 weeks.

Abbreviations: AR = Androgen Receptor, BC = Breast Cancer, CR = Complete Response; CT = Computerized Tomography, CTCs = Circulating Tumor Cells, ECG = Electrocardiogram, ECOG = Eastern Cooperative Oncology Group, eCRF = electronic Case Report Form, EOT = End of Treatment, ER = Estrogen Receptor, FU = Follow-up, HBsAg = Hepatitis B surface Antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = Human Immunodeficiency Virus, ICF = Informed Consent Form, IHC = Immunohistochemistry, MRI = Magnetic Resonance Imaging, PR = Partial Response; QoL = Quality of Life, PSA = Prostate Specific Antigen, V = Visit.

1 ROLES AND RESPONSIBILITIES

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Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Breast cancer (BC) is the most commonly diagnosed cancer in women, and one in eight women will develop invasive BC in their lifetime. In 2012, 1.7 million women were diagnosed with BC, and there were 6.3 million women alive who had been diagnosed with BC in the previous five years. Since 2008, BC incidence has increased by more than 20%, while mortality has increased by 14%. BC is the most common cause of cancer death among women, representing 522,000 deaths in 2012 and the most frequently diagnosed cancer among women in 140 of 184 countries worldwide.

BC is a highly heterogeneous disease with diverse clinical (tumor size, histological subtype and grade, and lymph node status) and molecular characteristics. Clinical assessment of BC includes routine characterization of receptor status including the presence or absence of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) in the tumor tissue. Receptor status is used to assess metastatic potential as well as to guide treatment decisions. Hormonal manipulation with selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) is the standard treatment given to subjects with tumors that are positive for the ER (ER+). For those subjects with tumors overexpressing HER2, targeted therapy against HER2 is typically used with chemotherapy.

While ER, progesterone receptor, and HER2 are oncogenic in BC, another member of the steroid hormone receptor family, the androgen receptor (AR), has historically been considered anti-proliferative and beneficial, and expression of AR is prognostically favorable. Until the 1970s, BC was treated mostly with non-aromatizable androgens such as dihydrotestosterone or fluoxymesterone. AR is the most highly expressed receptor in BC with more than 75–95% of ER-positive and 10–35% of triple negative breast cancers (TNBC) expressing AR. Evidence also suggests that the AR target gene, prostate specific antigen (PSA), is a favorable prognostic marker in BC. A study

conducted with 156 BC samples to histologically determine AR and PSA expression showed that 72% of the samples expressed the two proteins with significant positive correlation between them.

Despite evidence of benefit, therapeutic efforts using androgens for the treatment of BC preceded knowledge regarding AR expression. Subsequently, the use of these agents fell from favor due to virilizing side effects, fears of aromatization to estrogen, and the advent of tamoxifen. Selective androgen receptor modulators (SARMs) are a new class of drugs under development for a variety of diseases due to their high specificity for AR, selective anabolic activity, lack of virilizing side effect, and ability to extend androgen therapy to women.

GTx-024 is an oral (PO) nonsteroidal SARM that is being developed for clinical use because of its selectivity for anabolic activity with minimal androgenic activity (i.e., tissue selectivity). GTx-024 binds to the AR with similar affinity as testosterone. However, GTx-024 is a nonsteroidal ligand that does not bind or activate ER or progesterone receptor and, unlike testosterone and other steroidal androgens, cannot be aromatized to estrogenic metabolites. The underlying hypothesis regarding the selectivity of GTx-024 is that this nonsteroidal molecule induces slight conformational changes in the AR upon binding. The altered conformational change in AR changes the interaction of AR with specific coactivator and corepressor proteins that exist in different tissues thereby resulting in a different mix of genes being turned on and off and conferring more selective anabolic activities. Differences in intracellular signaling pathways (i.e., non-genomic effects) and/or interactions with steroid biosynthetic enzymes (e.g., 5 alpha [α]-reductase) between GTx-024 and the steroids may also contribute to differences in selectivity. GTx-024 is an anabolic agonist in muscle and bone while acting neutral or antagonistic in androgenic tissues like the skin.

Various preclinical models have demonstrated that non-aromatizable AR agonists are anti-proliferative in BC cells. GTx-024 and its closely related analog, GTx-027, were tested in models of ER-positive BC. GTx-027 binds to and activates AR at comparable concentrations and, structurally, GTx-027 is comparable to GTx-024 with a difference of only one atom. The growth of MCF-7 ER-positive BC cells over-expressing AR (MCF-7-AR) and endogenously AR-expressing cells (ZR-75-1) were inhibited by AR

agonists, but not by antagonists or structurally similar non-binders. Furthermore, the growth of MCF-7-AR tumors in nude mice was completely inhibited by SARMs. Microarray analyses with tumors obtained from xenograft studies indicated that GTx-027 inhibited the expression of messenger ribonucleic acid (mRNA) for oncogenes and induced tumor suppressor genes. GTx-027 up- and down- regulated (725 vs. 641) a similar number of genes with BC pathway genes being the most regulated disease pathway. Several anti-proliferative genes increased (TIMP3, AHR, KLK3) and an equal number of proliferative genes (MTR, XRCC1, and progesterone receptor) decreased. GTx-027 not only increased most of the well-known AR-regulated genes, such as KLK3, SNAI2, and MUC1, but also inhibited several ER target genes such as progesterone receptor, ER, and pS2. Overall, these studies clearly establish the importance of androgens and the AR in the treatment of BCs.

Ongoing and Completed Clinical Trials with GTx-024

Twenty-one Phase 1, 2, and 3 clinical trials have been completed or are ongoing with GTx-024. These include:

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 (LBM) 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 LBM 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 PO 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 BC who have previously responded to hormone therapy.

2.2 Rationale

GTx-024 has been evaluated in 21 completed and ongoing clinical studies enrolling over 1,500 total subjects. GTx-024 has been generally well-tolerated, including single doses up to 100 mg and multiple doses up to 30 mg once daily for up to 14 days. In longer studies, GTx-024 has also been generally well-tolerated, including 1, 3, and 9 mg daily doses for up to 184 days.

Previous clinical studies demonstrated that daily doses up to 30 mg of GTx-024 were well-tolerated in healthy male volunteers. Both 10 mg and 30 mg daily doses were evaluated in Protocol G100402 for up to 14 days. Elevated alanine transaminase (ALT) (any elevation outside the upper limit of the normal range [ULN]) was the most common adverse event (AE) experienced. None of the subjects in the 10 mg dose

group were discontinued from the study due to ALT elevations. Six out of 71 subjects experienced ALT increases above two times the ULN.

GTx-024 3 mg given daily was evaluated in two completed Phase 3 trials, in over 600 subjects, for the prevention and treatment of muscle wasting (cachexia) in subjects with advanced non-small cell lung cancer receiving chemotherapy. GTx-024 3 mg increased LBM in both studies and was safe and well-tolerated. Subjects in the GTx-024 and placebo groups experienced similar AEs, and these AEs were consistent with the background chemotherapy regimen.

Although GTx-024 3 mg was chosen for its anabolic activity in muscle for the completed Phase 3 program, a dose of 9 mg once daily was selected for hormonal therapy in the ongoing Phase 2 trial in ER+/AR+ metastatic BC in order to achieve a higher exposure that is both safe and more likely to be efficacious in women with advanced BC. Seven out of twenty-two subjects with advanced, heavily pretreated (hormonal therapy, radiation, and chemotherapy) BC demonstrated clinical benefit (CB) (stable disease [SD]) at 6 months. In one subject with SD (by Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1[2]), tumor regression of 27% in a single target lesion was demonstrated. Consistent with the previous studies, GTx-024 remained safe and well-tolerated.

Reductions in sex hormone binding globulin (SHBG) have been identified as one of the most sensitive serum biomarkers for AR signaling in healthy volunteers and patients. SHBG was reduced by 15.1%, 15.6%, 18.2%, and 18.4% in young, healthy volunteers who received PO GTx-024 1 mg, 3 mg, 10 mg, and 30 mg daily for 14 days, respectively, in Protocol G100402, suggesting that doses of 10 mg and above maximally stimulate AR activity.

Dosing GTx-024 at 15–20 mg per day may provide therapeutic benefit in hormone receptor positive BC by two separate mechanisms: activating AR and inhibiting progesterone receptor, thereby increasing potential efficacy. Progesterone receptor expression in cancer stem cells has been shown to be involved in proliferation of cancer epithelial cells, and inhibiting progesterone receptor's activity is now considered a novel approach to treating BC. Hence, enobosarm at higher doses might

provide dual anti-proliferative effects in BC. Doses of 15–20 mg per day should provide saturation of the AR potentially providing better efficacy as opposed to a lower dose with partial occupancy of the AR and absence of any progesterone receptor inhibitory effect.

Based on the safety data collected to date in both preclinical and clinical settings, the company expects the 18 mg dose will be safe and generally well tolerated. However, in the event that a subject has a Grade 3 or greater toxicity, the 18 mg dose may be reduced to 9 mg until the AE resolves or for the remainder of treatment based on the Investigator's discretion. The 9 mg dose has been previously studied in postmenopausal women with metastatic BC and was safe and well tolerated.

Proof of concept was demonstrated in ER+ BC patients at a 9 mg dose with no serious adverse events (SAEs) and over 70% of AEs reported as Grade 1. The efficacy at 9 mg was modest with a 35% clinical benefit rate (CBR). The purpose of the 9 mg dose arm in the present investigation is to confirm the safety and efficacy findings of the prior proof of concept study in a larger population of ER+/AR+ BC patients, while the purpose of the 18 mg dose arm is to explore the safety and efficacy of this dosage in a similar patient population without compromising subject safety. By increasing the dose to 18 mg, there is potential for greater efficacy in ER+ patients due to the dual mechanism of action; AR agonist and progesterone receptor antagonist. In the event that safety and efficacy is demonstrated in both dosing arms, the data from this study will be informative in the design of any potential future trials comparing both doses of GTx-024 to an active comparator determining the most efficacious dose of GTx-024 with an acceptable safety profile in the treatment of ER+/AR+ BC patients.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

GTx-024 has generally been well-tolerated in clinical trials conducted to date. Certain AEs associated with GTx-024 may occur. The most commonly reported side effects for GTx-024 in the previous 21 clinical studies include:

- Headache
- Back pain
- Diarrhea
- Pain in arm or leg
- Upset stomach
- Constipation
- Fatigue (tiredness)
- Dizziness
- Increases in liver enzymes
- Flu-like symptoms
- Anemia (decrease in red blood cells)
- Reduction in high density lipoproteins (HDL)
- Visual disturbances

These side effects were based on information obtained from other clinical studies using GTx-024 in doses ranging from 0.1 mg to 3 mg. These studies suggest that side effects associated with the study drug resolve after GTx-024 is stopped.

In a Phase 2 clinical study using GTx-024 in cancer subjects, the following SAEs occurred in at least 2% but less than 10% of subjects. These SAEs are also consistent with the subject's cancer therapy and the severity of the illness, and, therefore, may have resulted from the GTx-024 or from the cancer progression and/or the cancer treatment:

- Febrile neutropenia
- Pneumonia

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 (GGT), alkaline phosphatase, or lactate dehydrogenase (LDH) have been observed in

subjects with elevated ALT levels. Consistent with the effects of other PO administered anabolic agents, GTx-024 causes a dose dependent reduction in 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[5,6,7,8,9].

There were no other consistent, clinically relevant, dose-related effects of GTx-024 on ECGs or vital signs measurements (blood pressure or heart rate).

Investigators should be aware that blood levels of the tumor marker, CA27.29, have been shown to be modulated by compounds with androgenic activity as a result of the marker binding to the androgen regulated protein MUC-1. As a result, administration of GTx-024 has the potential to result in increases in CA27.29 that are not necessarily reflective of disease progression[10,11].

The drug used in this research study may affect a fetus. Subjects should not become pregnant nor breastfeed a baby while participating in this research study. All subjects in this study are required to be confirmed as postmenopausal; however, a serum pregnancy test will be obtained at screening as a standard safety precaution.

2.3.2 Potential Benefits

GTx-024 9 mg once daily has been studied in 22 postmenopausal women with metastatic ER+ BC who have previously responded to hormonal therapy. The primary endpoint was assessed in 17 AR positive subjects. Six of these 17 subjects demonstrated CB (SD) at six months. In one subject with SD (RECIST 1.1), tumor regression of 27% in a single target lesion was demonstrated. Seven subjects in total (one subject with indeterminate AR status) achieved CB at six months. Among the seven subjects who achieved CB at six months, time to progression (TTP) was estimated as 10.2 months. The results also demonstrated that, after a median duration on study of 81 days, 41 percent of all subjects (9/22) achieved CB as best response and also had increased PSA, which appears to be an indicator of AR activity. As of the

finalization of this protocol, the study is still ongoing with one subject whose disease remains stable beyond 336 days.

Preclinical data with GTx-024 suggests that it is also anabolic in bone and decreases bone turn over markers. Treatment with GTx-024 may decrease bone turn over as compared with other hormonal therapies for the treatment of hormone receptor positive BC. Stronger bone microenvironment may decrease metastases to bone or delay time to skeletal related events.

3 OBJECTIVES

3.1 Study Objectives

The **primary efficacy objective** of this trial is to estimate the CBR at 24 weeks (defined as complete response [CR], partial response [PR], or SD) (by RECIST 1.1) of GTx-024 9 mg and of GTx-024 18 mg given PO daily in subjects with estrogen receptor positive and androgen receptor positive (ER+/AR+) BC who have centrally confirmed AR+ status.

Secondary efficacy objectives:

- Estimate the CBR at 24 weeks (by RECIST 1.1) of GTx-024 9 mg and 18 mg in all subjects randomized who receive at least one dose of study medication (the full analysis set [FAS]) regardless of AR status as determined by the central laboratory

The following secondary efficacy objectives apply to both centrally confirmed AR+ subjects (the evaluable subset of the FAS) as well as to all subjects in the FAS:

- Estimate the objective response rate (ORR; defined as CR or PR) (by RECIST 1.1) of GTx-024 9 mg and 18 mg at 24 weeks
- Estimate the best overall response rate (BOR) of GTx-024 9 mg and 18 mg
- Estimate the progression free survival (PFS) of subjects receiving GTx-024 9 mg and 18 mg
- Estimate the TTP of subjects receiving GTx-024 9 mg and 18 mg
- Estimate duration of response (time from documentation of tumor response to disease progression or death) of subjects receiving GTx-024 9 mg and 18 mg

Tertiary objectives:

The following tertiary efficacy objectives apply to both centrally confirmed AR+ subjects (the evaluable subset of the FAS) as well as to all subjects in the FAS:

- Assess the effect of GTx-024 9 mg and 18 mg on serum PSA

- Assess the effect of GTx-024 9 mg and 18 mg on Quality of Life (QoL) as measured by EQ-5D-5L[3]
- Assess the effect of GTx-024 9 mg and 18 mg on circulating tumor cells (CTCs)
- Assess the impact of duration of prior CB on outcome
- Assess the impact of time from diagnosis of metastases to randomization on outcome
- Describe the effect of GTx-024 9 mg and 18 mg on tumor volumetrics
- Assess the effect of plasma concentrations of GTx-024 and GTx-024 glucuronide on CBR at 24 weeks

Safety objective:

To describe the safety profile of GTx-024 9 mg and 18 mg PO daily in subjects with ER+/AR+ BC with centrally confirmed AR+ as well as in all subjects randomized and treated.

Pharmacokinetic objective:

To describe the plasma concentrations of GTx-024 *and* GTx-024 glucuronide at each of the assessed time points.

3.2 Study Outcome Measures

3.2.1 Primary Efficacy Outcome Measures

Response of CB at 24 weeks, in a subject with centrally confirmed AR+ status.

CB is defined as a CR, a PR, or SD as measured by RECIST 1.1 and confirmed by a central image-reading facility blinded to the GTx-024 dose received.

For subjects with non-measurable (non-target) disease only at baseline, SD is defined as those with non-CR/non-progressive disease (PD) combined response.

3.2.2 Secondary Efficacy Outcome Measures

- Response of CB in a subject at 24 weeks regardless of central confirmation of AR status (FAS)

The following secondary efficacy outcome measures apply to both the evaluable subset of the FAS as well as to the FAS:

- OR at week 24. OR is defined as attainment of a CR or PR at 24 weeks as measured by RECIST 1.1
- BOR as measured by RECIST 1.1 and defined as: the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. For a subject with non-measurable (non-target) disease only at baseline, SD will be defined as those with non-CR/non-PD combined response
- PFS defined as the time elapsed between randomization and tumor progression as measured by RECIST 1.1 or death due to any cause
- TTP defined as the time elapsed between randomization and tumor progression as measured by RECIST 1.1 or death due to disease progression
- Duration of response (time from documentation of tumor response to disease progression or death)

3.2.3 Tertiary Efficacy Outcome Measures

The following tertiary efficacy outcome measures apply to both the evaluable subset of the FAS as well as to the FAS:

- Serum PSA at each assessment, changes from baseline to each assessment, and percentage change from baseline of serum PSA at each assessment
- Subject reported QoL (EQ-5D-5L questionnaire) at each assessment and changes from baseline to each assessment
- CTCs at each assessment and changes from baseline to each assessment

- Impact of duration of prior CB on outcome (CB response at week 24, PFS, TTP, duration of response)
- Impact of time from diagnosis of metastases to randomization on outcome (CB response at week 24, PFS, TTP, duration of response)
- Tumor volume at each assessment and change from baseline to each assessment
- Plasma concentrations of GTx-024 and GTx-024 glucuronide on outcome (CB response at week 24)

3.2.4 Safety Outcome Measures

The following safety outcome measures apply to both the evaluable subset of the FAS as well as to all subjects enrolled and treated:

- AEs and concomitant medications
- Laboratory examinations (clinical chemistry, hematology, and urinalysis)
- Physical examinations
- Vital signs
- ECOG performance status
- Eye examinations

3.2.5 Pharmacokinetic outcome measures

- Plasma concentrations of GTx-024 and GTx-024 glucuronide at each of the assessed time points

4 STUDY DESIGN

This is an open label, multicenter, multinational, randomized, parallel design Phase 2 study to assess the efficacy and safety of GTx-024 in postmenopausal subjects with ER+/AR+ BC. Subjects will be randomized to receive either GTx-024 9 mg or 18 mg given PO daily for up to 24 months. Each dose arm will be treated independently and each assessed for efficacy using Simon's two-stage (optimal) design[1]. Subjects will be randomized in a 1:1 fashion to one of the two dose arms. Randomization will be stratified by subjects presenting with bone only metastases and all other subjects, and further by setting of immediately preceding therapy (adjuvant setting or metastatic setting) in order to balance the proportion of subjects with these presenting features in each dose arm. There is no intent to statistically compare the two dose arms, but to determine whether either or both doses result in an acceptable CBR, defined as the proportion of evaluable subjects (i.e., subjects with centrally confirmed AR+ and who receive at least one dose of study drug) with either CR, PR, or SD by RECIST 1.1 at week 24, consistent with 30% while maintaining an acceptable safety profile. Given such a result, future exploration of GTx-024 in ER+/AR+ BC would be warranted at that dose level.

Thirty-six to 88 (36–88) subjects with centrally confirmed AR+ who receive at least one dose of study drug (evaluable subjects) will be needed for primary efficacy analysis purposes and will be a subset of the FAS. Thirty-six to one hundred and eighteen (36–118) subjects, including replacement subjects, will be randomized in a 1:1 fashion to receive a daily PO dose of either GTx-024 9 mg or 18 mg. Thirty of the aforementioned subjects may be considered replacement subjects to account for lack of centrally confirmed AR+ status or for the rare subject who is randomized but does not receive study drug (assumes 25% of enrolled subjects are not evaluable for the primary efficacy analysis). Other statistical parameters that are part of the sample size calculation are $\alpha = 0.025$ (one-sided) and power = 90%. The first stage in each study arm will be assessed among the first 18 evaluable subjects. If at least 3/18 subjects achieve CB (defined as CR, PR, or SD) at week 24, the arm will proceed to the second stage of recruitment up to a total of 44 evaluable subjects per arm. Otherwise, the arm will be discontinued for lack of efficacy. Statistical significance, i.e., rejection of

the null hypothesis of an unacceptably low CBR of ≤ 10% in favor of the alternative hypothesis that indicates the higher rate, ≥ 30%, is more likely, will be declared if at least 9/44 subjects achieve CB at week 24 in that arm.

Subjects who are not centrally confirmed AR+ may remain on the trial, but will not be part of the primary efficacy analysis – these subjects will contribute to secondary and tertiary analyses as noted in Section 11 Statistical Considerations.

Subjects on the 18 mg treatment arm who experience an AE with Grade ≥ 3 intensity (National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE], Version 4.0) and/or intolerance may have a dose reduction from 18 mg to 9 mg per day or a drug interruption based on the medical judgment of the Investigator and after confirmation by the study Medical Monitor. The drug interruption may last for a period of up to 5 days after which the subject must be rechallenged with study drug (18 mg or 9 mg) or discontinued from the study. In the case of a dose reduction, once the AE has resolved or reduced in intensity to Grade 1, the subject may be rechallenged with 18 mg or maintained at 9 mg at the discretion of the Investigator.

Subjects on the 9 mg treatment arm who experience an AE with Grade ≥ 3 intensity (NCI-CTCAE 4.0) and/or intolerance may have a drug interruption based on the medical judgment of the Investigator and after confirmation by the study Medical Monitor. The drug interruption may last for a period of up to 5 days after which the subject must be rechallenged with study drug (9 mg) or discontinued from the study.

In the event of hepatotoxicity, please also refer to Section 9.4 Halting Rules.

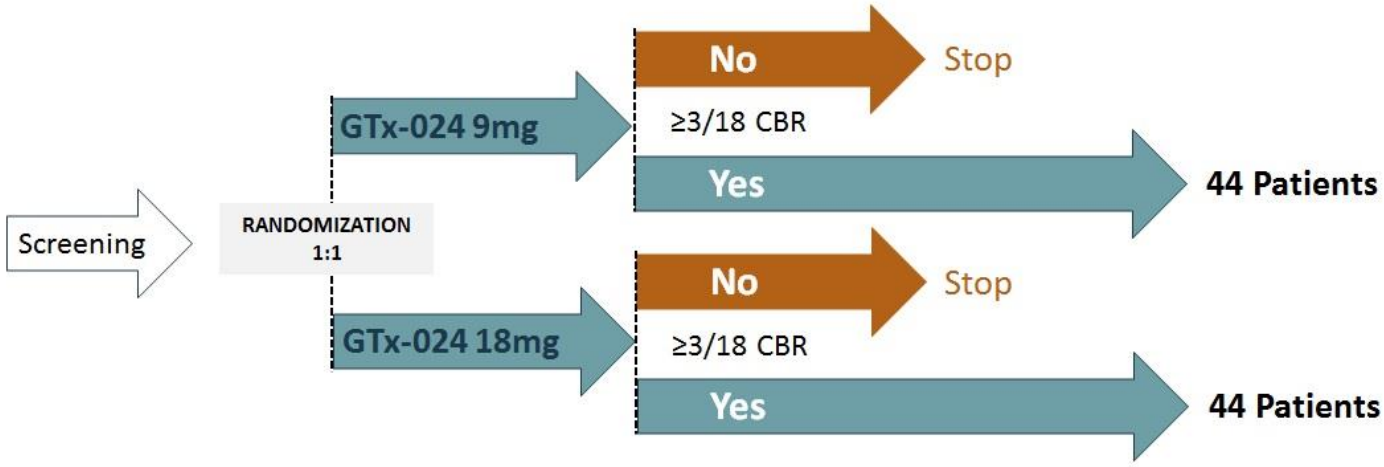
For safety analysis, subjects will be analyzed in the treatment arm in which they are initially dosed. For efficacy analysis, subjects will be analyzed according to the treatment arm to which they were randomized.

The subjects who demonstrate CB will be treated for up to 24 months from the date of randomization (as long as they continue to demonstrate CB from the treatment during

these 24 months). Subjects who continue to demonstrate a CB from the study treatment at 24 months will be offered to continue in a safety extension study under a separate protocol. For safety purposes, all subjects will be followed-up for one month after the last dose of GTx-024 is received.

A flow chart of the study is shown in Figure 1 below.

Figure 1: Flow chart of Study Plan



Possible pause in enrollment: The implementation of Simon's two-Stage design could cause a pause in enrollment of the trial prior to proceeding to the second stage. For example, if the required 18 evaluable subjects in the first stage of an arm are enrolled and 15 have either terminated the trial or been assessed as not achieving CBR at 24 weeks, it will be necessary to pause enrollment in that arm until the remaining three evaluable subjects are fully assessed for CBR, i.e., either withdraw prior to week 24 or have the week 24 RECIST 1.1 assessment.

4.1 Substudies (if applicable)

Not applicable.

4.2 Safety Monitoring Committee

In order to protect the safety of the subjects, a Safety Monitoring Committee (SMC) will be established for the study to review the safety data on an ongoing basis. The SMC will consist of, as a minimum, the Medical Monitor, a Safety Reviewer with an oncology background, a statistician, and two GTx, Inc. representatives, consistent with the SMC charter.

The first safety review meeting will occur approximately one to two weeks following the enrollment of first 5 subjects in the study. Additionally, the SMC chairman or GTx, Inc. may call an unscheduled review of the study by the SMC if there is a concern for subject safety. Following the meetings, the SMC chairperson is responsible for communicating one of the following recommendations to GTx, Inc.:

- Continue the study without modification
- Continue the study with modifications (to be specified); or
- Stop the study due to safety (specific safety concern[s] to be specified)

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

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

1. Adult women (≥ 18 years of age) with metastatic or recurrent locally advanced BC, not amenable to curative treatment by surgery or radiotherapy, with objective evidence of disease progression.
   - Women must have received ≥ 1 prior hormonal treatment(s) in the metastatic or adjuvant setting
     - If the most recent hormonal treatment was in the metastatic setting, duration of response (tumor regression or stabilization of disease) to this specific course of therapy must be ≥ 6 months
     - If the most recent hormonal treatment was in the adjuvant setting, duration of response (disease free) to this specific course of therapy must be ≥ 3 years
2. Histological or cytological confirmation of ER+ BC as assessed by a local laboratory using slides, paraffin blocks, or paraffin sample or by medical history: ER+ (confirmed as ER expression more than or equal to 1% positive tumor nuclei)
3. Human epidermal growth factor receptor 2 (HER2)-negative tumor by local laboratory testing (immunohistochemistry [IHC] 0, 1+ regardless of fluorescence in situ hybridization [FISH] ratio; IHC 2+ with FISH ratio lower than 2.0 or HER2 gene copy less than 6.0; FISH ratio of 0, indicating gene deletion, when positive and negative in situ hybridization [ISH] controls are present)
4. Availability of paraffin embedded or formalin fixed tumor tissue; OR, a minimum of 10 and up to 20 slides of archived tumor tissue for central laboratory confirmation of AR status and molecular subtyping. Metastatic tumor tissue is preferred when possible
5. Postmenopausal women. Postmenopausal status is defined by the National Comprehensive Cancer Network as either:

- Age ≥ 55 years and one year or more of amenorrhea
- Age < 55 years and one year or more of amenorrhea, with an estradiol assay < 20 pg/mL
- Age < 55 years and surgical menopause with bilateral oophorectomy
  a. *Note:* Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression

6. Radiological or clinical evidence (bone scan, computerized tomography [CT], and magnetic resonance Imaging [MRI]) of recurrence or progression within 30 days before randomization
7. Subject must have either measurable disease or bone-only non-measurable disease, evaluable according to RECIST 1.1
8. Adequate organ function as shown by:
   - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
   - Platelet count ≥ 100,000 cells/mm^3
   - Hemoglobin (Hgb) ≥ 9.0 g/dL
   - Serum aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 2.5 upper limit of the normal range (ULN) (or ≤ 5 if hepatic metastases are present)
   - Total serum bilirubin ≤ 2.0 × ULN (unless the subject has documented Gilbert Syndrome)
   - Alkaline phosphatase levels ≤ 2.5 × ULN (≤ 5 × ULN in subjects with liver metastasis)
   - Serum creatinine ≤ 2.0 mg/dL or 177 µmol/L
   - International normalized ratio (INR) or activated partial thromboplastin (aPTT) < 1.5 × ULN (unless on anticoagulant treatment at screening)
9. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status[4] 0 or 1
10. Subject is able to swallow capsules
11. Able and willing to give voluntary, written and signed informed consent before any screening procedure and according to local guidelines

5.2 Subject Exclusion Criteria

Subjects eligible for this study must not meet **any** of the following criteria:

1. Previously received > 1 course of chemotherapy (not including immunotherapies or targeted therapies) for the treatment of metastatic BC
    a. *Note*: Subjects may have received 1 course of chemotherapy prior to surgery for the treatment of locally advanced disease and 1 course of chemotherapy for the treatment of metastatic BC; however, if surgery could not be performed, this will count as the 1 chemotherapy course allowed prior to study
2. Known hypersensitivity to any of the GTx-024 components or subjects previously received treatment with SARM
3. Subjects with radiographic evidence of central nervous system (CNS) metastases as assessed by CT or MRI that are not well-controlled (symptomatic or requiring control with continuous corticosteroid therapy [e.g., dexamethasone])
    a. *Note*: Subjects with CNS metastases are permitted to participate in the study if the CNS metastases are medically well-controlled and stable for at least 28 days after receiving local therapy (irradiation, surgery, etc.)
4. Radiotherapy within 14 days prior to randomization except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture, which can then be completed within 7 days prior to randomization. Subjects must have recovered from radiotherapy toxicities prior to randomization
5. Currently receiving hormone replacement therapy, unless discontinued prior to screening
6. Subjects positive for Human Immunodeficiency Virus (HIV)
7. Subject has a concomitant medical condition that precludes adequate study treatment compliance or assessment, or increases subject risk, in the opinion of the Investigator, such as but not limited to:
    - Myocardial infarction or arterial thromboembolic events within 6 months prior to Baseline or severe or unstable angina, New York Heart Association (NYHA)

Class III or IV disease, or a QT_CB (corrected according to Bazett's formula) interval > 470 msec
- Serious uncontrolled cardiac arrhythmia grade II or higher according to NYHA
- Uncontrolled hypertension (systolic > 150 and/or diastolic > 100 mm Hg)
- Acute and chronic, active infectious disorders and non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
- Another active cancer (excluding adequately treated basal cell carcinoma or cervical intraepithelial neoplasia [CIN]/cervical carcinoma in situ or melanoma in situ). Prior history of other cancer is allowed as long as there is no active disease within the prior 5 years

8. Major surgery within 28 days before randomization
9. Positive hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection at screening
10. History of non-compliance to medical regimens
11. Subject unwilling to or unable to comply with the protocol
12. Subject is currently receiving treatment with any agent listed on the prohibited medication list (See Section 6.6 Concomitant Medications/Treatments for complete list)
13. Treatment with any investigational product within < 4 half-lives for each individual investigational product OR within 28 days prior to randomization

5.3 Strategies for Recruitment, Retention, and to Improve Adherence to Intervention Protocols

No special strategies or activities will be employed for recruitment and retention.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

Eligible subjects will be randomized in a 1:1 ratio to GTx-024 9 mg daily or GTx-024 18 mg daily. If based on halting rules (Section 9.4 Halting Rules) or for any other reason the 18 mg arm is terminated, randomization will end and all future enrollees will be enrolled on the 9 mg arm.

5.4.2 Masking Procedures

Treatment periods will be open label.

Tumor lesions will be assessed using RECIST 1.1 at the site based on the local reading facility; however, scans will also be sent to the central imaging facility, blinded to the GTx-024 dose, for final efficacy outcomes analysis.

5.4.3 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 the following reasons:

- AEs that require treatment with a forbidden medication or 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
- Sponsor's decision
- Subject unable to follow Investigators' instructions and comply with the study procedures
- Protocol deviation
- Disease progression

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

5.4.4 Handling of Withdrawals

Every effort will be made to ensure that subjects who withdraw (for whatever reason) from the study will still be asked to continue scheduled evaluations and participate in the follow-up evaluation. Subjects who withdraw due to an AE or SAE will be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

Subjects who are randomized but do not go on to receive study drug will be replaced; otherwise, subjects who receive at least one dose of study drug and who withdraw from the study will not be replaced.

5.4.5 Termination of Study

The Sponsor can stop this study at any time, for any reason. This study may be prematurely terminated if, in the opinion of the Investigator or the Sponsor, there is sufficient reasonable cause to stop the study at the clinical site. Written notification, documenting the reason for study termination, will be provided to the Investigator or Sponsor by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient adherence to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Plans to modify, suspend, or discontinue the development of the study drug

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will also be informed

promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

GTx-024 3.0 mg softgel capsules will be supplied by GTx, Inc.

6.1.2 Formulation, Packaging, and Labelling

GTx-024 3.0 mg Softgels will be supplied as opaque, white to off-white, size 5, oval Softgel capsules with “GTx” imprinted in black ink on the outer shell containing 3.0 mg of GTx-024. The liquid Softgel fill is composed of GTx-024 dissolved in polyethylene glycol 400. GTx-024 3.0 mg Softgels will be packaged in blister packs. Each blister pack will contain sufficient study drug for one (1) week of dosing. At randomization (Visit 2) and at Visits 3, 4, and 5), subjects will be provided with a carton of study drug containing 7 blister packs, equivalent to 7 weeks of dosing. At Visits 6, 8, 9, 10, 11, 12, and 13, in order to accommodate the visit schedule of every 12 weeks (± 7 days), the subjects will receive two carton boxes of study drug (each containing 7 blisters) to cover study treatment for 14 weeks. Subjects will be requested to bring with them the carton box with all blister packs at every visit.

Each blister pack will be comprised of an appropriate number of blister strips (1 blister for the 9 mg treatment arm and 2 blisters for the 18 mg treatment arm) encased in a child-resistant heat-sealed card. The blister strips are composed of a PVC/ACLAR base and an aluminum foil/PVC/PVAC copolymer and polymethacrylate (product contact) lidding. Perforations on the back of the heat-seal card overlay the foil lidding. To remove the study drug, subjects will release the appropriate perforation by depressing a release button on the inside of the card. Once released, the perforation can be removed and the study drug pushed through the foil.

Dosing instructions will be provided on the study drug label and in the subject information sheet.

6.1.3 Product Storage and Stability

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

6.2 Dosage, Preparation, and Administration of Study Investigational Product

Three (3) GTx-024 3.0 mg softgels for a 9 mg daily dose or six (6) GTx-024 3.0 mg softgels for an 18 mg daily dose will be taken PO with water at approximately the same time each day, with or without food.

6.3 Modification of Study Investigational Product for a Subject

Subjects on the 9 mg treatment arm who experience an AE with Grade ≥ 3 intensity (NCI-CTCAE 4.0) and/or intolerance may have a drug interruption based on the medical judgment of the Investigator and after confirmation by the study Medical Monitor. The drug interruption may last for a period of up to 5 days after which the subject must be rechallenged with study drug (9 mg) or, as appropriate, subjects should be discontinued from study.

Subjects in the 18 mg treatment group who experience an AE with Grade ≥ 3 intensity (NCI-CTCAE 4.0) and/or intolerance may have a dose reduction from 18 mg to 9 mg per day or a drug interruption based on the medical judgment of the Investigator and after confirmation by the study Medical Monitor. The drug interruption may last for a period of up to 5 days after which the subject must be rechallenged with study drug (18 mg or 9 mg) or discontinued from the study. In the case of a dose reduction, once the AE has resolved or reduced in intensity to Grade 1, the subject may be rechallenged with 18 mg or maintained at 9 mg at the discretion of the Investigator.

In the event of hepatotoxicity, please also refer to Section 9.4 Halting Rules.

6.4 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 person 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 electronic case report form (eCRF) will document any treatment interruptions or discontinuations.

6.5 Assessment of Subject Compliance with Study Investigational Product

Subjects should be instructed to return all unused study medication and containers at clinic Visits 3, 4, 5, and 6; Visits 8–13 if still on treatment after week 24; and end of treatment (EOT) 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 eCRF.

All study medication returned by subjects must be accounted for and verified by the GTx, Inc., study monitor. After verification of all study medication, return of used packages and unused study medication must be authorized by the study monitor before being returned to GTx, Inc., or authorized representative.

6.6 Concomitant Medications/Treatments

Forbidden medications and treatments during the study include:

- Major surgery within 28 days before randomization
- Testosterone, methyltestosterone, oxandrolone (Oxandrin®), oxymetholone, danazol, fluoxymesterone (Halotestin®), testosterone-like agents (such as dehydroepiandrosterone, androstenedione, and other androgenic compounds, including herbals), or antiandrogens. Previous therapy with testosterone and testosterone-like agents is acceptable with a 28-day washout (if previous testosterone therapy was long-term depot within the past 6 months, the site should contact the Medical Monitor)
- Treatment with any of the following hormone replacement therapies, unless discontinued at least 28 days prior to randomization
    - Estrogens
    - Megesterol acetate
- Treatment with any investigational agent within < 4 half-lives for each individual investigational product OR within 28 days prior to randomization
- Local palliative radiation within 7 days before randomization
- Radiotherapy within 14 days prior to randomization, except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture which can then be completed within 7 days prior to randomization. Subjects must have recovered from radiotherapy toxicities prior to randomization
- All other anticancer treatments (including, but not limited to, all SERMs, AIs, and fulvestrant)

- Caution should be exercised when administering potent CYP3A4 inducers, UDP inhibitors, and substrates of BCRP with GTx-024. Drug-drug interaction studies conducted with GTx-024 3 mg have demonstrated that concomitant use of CYP3A4 inducers may decrease the rate and extent of exposure of GTx-024 and its glucuronide metabolite. UDP inhibitors may increase GTx-024 and glucuronide exposure. Concomitant administration of GTx-024 with BCRP substrates may lead to increased exposure of the BCRP substrate.

7 STUDY SCHEDULE

Subjects with CB at 24 weeks (Visit 6) will continue on therapy as long as they are still benefitting from the treatment. Treatment may continue for up to 24 months from the date of randomization (as long as they continue to demonstrate CB from the treatment during these 24 months).

Subjects who continue to demonstrate a CB from the study treatment at 24 months will be offered to continue in a safety extension study under a separate protocol.

All visits may be scheduled within a time window of ± 7 days.

7.1 Screening

Screening assessments must occur within 28 days prior to randomization for determination of subject's overall eligibility. Informed consent will be obtained from the subjects before any other study procedure or test. AEs will be collected from the signing of the informed consent form (ICF). The following tests and procedures will be performed during the screening visit (Visit 1):

- Eligibility criteria check
- Subject medical history (current and past)
- Demography (age, gender, race)
- Diagnosis and extent of cancer
- Review of prior/concomitant medications, including previous and current anticancer treatment
- Physical examination, including height, weight, and vital signs (heart rate, respiratory rate, body temperature, blood pressure in a sitting position)
- ECOG performance status
- ECG

- Blood sampling for: screening for HIV, HBV, and HCV
- Blood sampling for: hematology, biochemistry, coagulation status, and serum pregnancy test
- Blood sampling for specific blood tests: PSA
- Urine analysis
- AE collection (from the moment of ICF signing)
- Radiological evaluation of the BC (as applicable CT/MRI/bone scan). Imaging results will be confirmed by a central imaging facility blinded to the dose of GTx-024 to be received, although a subject will be enrolled based on the local imaging and Investigator's assessment. The central imaging facility will also perform tumor volumetric assessment for the subjects undergoing CT scanning. It is recommended these procedures are done as close to the randomization visit (Visit 2) as possible (if possible within 7 days prior to randomization)
- Review of medical history to confirm the hormonal receptor status of the tumor (ER, HER2). ER status will be confirmed by a local laboratory if not available in the subject's medical history. AR status will be confirmed at a central laboratory
- Eye examination including best corrected distance visual acuity with refraction, intraocular pressure, slit lamp examination, and dilated fundus photography (must be completed between Day –28 and Day –1)

7.2 Randomization/Baseline

The following tests and procedures will be performed during the randomization/baseline visit (Visit 2), or results checked and confirmed:

- Eligibility criteria checked; prior to randomization
- Review of prior/concomitant medications, including previous and current anticancer treatment
- Vital signs (heart rate, respiratory rate, body temperature, blood pressure in a sitting position), if not done within the last 7 days

- ECOG performance status, if not done within the last 7 days
- Blood sampling for: hematology, biochemistry, and PSA, if not done within the last 7 days; and serum lipid profile, serum hormones, and CTCs (enumeration and gene expression)
- Urine analysis, if clinically indicated
- AE collection
- Subjects will be asked to complete a QoL questionnaire (EQ-5D-5L; before initiation of treatment)
- Randomization
- The first dose of study drug will be administered at this visit. Subjects will be given a carton box of 7 blister packs containing GTx-024
- Blood sample for pharmacokinetic assessment. The baseline blood sample should be collected before the subject is given their first dose of GTx-024. The exact time (hh:mm) and date of the blood sample will be recorded on the eCRF.

7.3 Treatment Phase

The first dose of study drug will be administered on the day of randomization (Visit 2). GTx-024 will be administered daily for up to 24 months from randomization or until disease progression (whichever is sooner), subject's withdrawal of consent, or intolerability.

During the study treatment phase, the subjects will be scheduled for a visit every 6 weeks. Visit 7 at week 28 will only take place in subjects who have CR or PR at Visit 6 (week 24; see below).

The following tests and procedures will be performed during Visits 3, 4, 5, and 6 (weeks 6, 12, 18, and 24) in the treatment phase:

- Review concomitant medications

- Physical examination, including weight and vital signs (heart rate, respiratory rate, body temperature, blood pressure in a sitting position)
- ECOG performance status
- Blood sampling for: hematology, biochemistry, serum lipid profile, coagulation status, serum hormones, and PSA
- Urine analysis, if clinically indicated
- AE collection
- Subjects will be asked to complete a QoL questionnaire (EQ-5D-5L)
- GTx-024 drug accountability/dispensation

Radiologic assessments for anti-tumor effect will be done every 12 weeks whilst subjects receive treatment (Visits 4, 6, and thereafter). The same imaging technique must be used throughout the study in a given subject. Bone scans will be performed at screening and then every 12 weeks whilst subjects receive treatment (Visits 4, 6, and thereafter) in only those subjects with baseline bone metastases, or if clinically indicated. In addition, if any subject has CR or PR at Visit 6 (week 24), in compliance with RECIST 1.1 guidelines, a confirmation of the CR or PR (CT/MRI/bone scan) should be done 4 weeks later (Visit 7; week 28). The central imaging facility will also perform tumor volumetric assessment for the subjects undergoing CT scanning during Visits 4 and 6 (weeks 12 and 24). Blood sampling for CTC enumeration will be done at the same visits as the radiological assessments during the treatment phase; i.e., every 12 weeks whilst subjects receive treatment (Visits 4 and 6), but not at the confirmation of the CR or PR visit (Visit 7; week 28) or at Visits 8–13.

Dispensing of GTx-024 will be done at all study visits (except Visit 7) during the treatment phase (every 6 weeks at Visits 3, 4, and 5). At Visits 6, 8, 9, 10, 11, 12, and 13, in order to accommodate the visit schedule of every 12 weeks (± 7 days), the subjects will receive two carton boxes of study drug (each containing 7 blisters) to cover study treatment for 14 weeks.

At any time point during the treatment period, if clinically indicated, an eye examination including any or all of the following procedures will be performed based on medical judgment: best corrected distance visual acuity with refraction, intraocular pressure, slit lamp examination, and dilated fundus photography.

Blood samples for pharmacokinetic assessment will be collected at Visit 3 (week 6), Visit 5 (week 18), and Visit 6 (week 24). The exact time (hh:mm) and date of each blood sample will be recorded on the eCRF. The date and approximate time of the last dose of GTx-024 prior to the blood sample should also be recorded; i.e., it should be documented whether the subject took the previous dose that morning or the evening before.

7.4 End of Treatment (EOT) Visit

For all subjects the EOT visit should happen as soon as possible after the last dose of GTx-024 has been taken and no later than 3 days after that. The following tests and procedures will be performed during the EOT visit:

- Review of concomitant medications
- Physical examination, including weight and vital signs (heart rate, respiratory rate, body temperature, blood pressure in a sitting position)
- ECOG performance status
- Blood sampling for: hematology, biochemistry, serum lipid profile, coagulation status, and serum hormones
- Blood sampling for specific blood tests: PSA and CTCs (enumeration and gene expression)
- Urine analysis, if clinically indicated
- AE collection
- Radiological evaluation of the BC (as applicable CT/MRI/bone scan). Imaging results will be confirmed by a central imaging facility blinded to the GTx-024 dose.

The same imaging technique must be used throughout the study in a given subject.

- Subjects will be asked to complete a QoL questionnaire (EQ-5D-5L)
- GTx-024 drug accountability
- Eye examination including best corrected distance visual acuity with refraction, intraocular pressure, slit lamp examination, and dilated fundus photography

7.5 Post-treatment Follow-up

Subjects will be followed up for 1 month after the last dose of GTx-024. They will undergo the following procedures:

- Review of concomitant medications
- Physical examination, including weight and vital signs (heart rate, respiratory rate, body temperature, blood pressure in a sitting position)
- ECOG performance status
- Blood sampling for: hematology and biochemistry
- Blood sampling for PSA
- Urine analysis, if clinically indicated
- AE collection

7.6 Early Termination Visit

An early termination visit will happen in case of:

- A subject withdrawing from the study at their discretion
- GTx, Inc. terminating the study in the interest of subject welfare
- Investigator withdrawing the subject from the study

Subjects will be asked to attend a final visit so that the procedures for the EOT (see above) may be performed.

7.7 Unscheduled Visit

A page will be included in the eCRF that asks about whether any unscheduled visits have taken place and provides space for the recording of any collected data, including unscheduled vital signs, ECGs, and laboratory results on the unscheduled visit eCRF page. Early/late planned visits will not be considered to be unscheduled visits.

8 STUDY PROCEDURES/EVALUATIONS

Please see the APPENDIX A: SCHEDULE OF EVENTS for an outline of the timing of the study procedures/evaluations.

8.1 Clinical Evaluations

All treatment decisions will be based on Investigator assessments, including determination of PD.

Imaging Assessments:
CT with contrast of the chest, abdomen, and pelvis including the liver and the adrenals will be performed to assess tumor status. If contrast is contraindicated, CT without contrast for chest and pelvis and MRI of the abdomen should be performed. Whichever imaging method is selected should be used for all study assessments in a given subject.

Bone scintigraphy (bone scans) will be performed to assess bone metastases. Bone scans will be performed at screening and then every 12 weeks whilst subjects receive treatment (Visits 4, 6, and thereafter) in only those subjects with baseline bone metastases, or if clinically indicated.

Tumor lesions will be assessed using RECIST 1.1 at the site based on the local reading facility. Scans will be sent to the central imaging facility, blinded to the GTx-024 dose, for final efficacy outcomes analysis.

In compliance with RECIST 1.1, if any subject has CR or PR at Visit 6 (week 24), a confirmation of the CR or PR (CT/MRI/bone scan) should be done 4 weeks later (Visit 7; week 28).

Tumor volumetrics will be performed by the assigned central vendor only for subjects who have CT scans at screening and then at weeks 12 and 24 (Visits 4 and 6). Tumor volumetrics will be performed by an independent 3rd party vendor who is masked to individual subject treatment and outcomes.

Medical History and Medication History:

The medical history of the subject will be obtained by the PI from the subject's medical record. The medical history will include a review of the hormonal status of the BC (ER, HER2).

Medication history will include all medications currently being taken (rather than the lifelong medication history) and will include both prescription and over-the-counter medicines (also including nutritional supplements or herbal treatments). This will include prior cancer treatments taken.

Demographics:

The following demographic data will be collected: age, gender, and race.

Physical Examination:

Physical examination will include organ palpation, lymph nodes palpation, skin turgor, and muscle weakness measurement.

Height and weight will also be measured as outlined in the schedule of events.

AEs will be followed-up to resolution, and while further physical examinations may take place, they will not be mandatory.

Vital Signs:

Vital signs at scheduled visits will include body temperature, respiratory rate, blood pressure, and heart rate. Vital signs may be taken at any other times. Blood pressure and heart rate measurements will be performed with subjects in a seated position.

ECOG Performance Status:

ECOG performance status will also be measured (see APPENDIX B: ECOG PERFORMANCE STATUS).

ECG:

A standard 12-lead ECG will be performed at screening. Tracings must be dated and signed by the Investigator (or his/her designee) and filed with the subject's source documentation. Results from 12-lead ECG should be captured on the ECG Evaluation eCRF. Significant findings must be recorded as Relevant Medical History/Current Medical Conditions (if present before treatment). ECG may be repeated at the discretion of the Investigator at any time during the study and as clinically indicated; any clinically relevant findings should be added to the AE eCRF.

Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), subject number, and date, and kept in the source documents at the study site. Clinically significant abnormalities present when the subject signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Medical Monitor prior to randomizing the subject in the study. The PI will take the final decision if any observed deviations in the ECG are sufficient to require that the subject be excluded from the study.

Eye examination:

An eye examination will be performed at screening, as clinically indicated during the treatment phase, and at EOT. The eye examination should include best corrected distance visual acuity with refraction, intraocular pressure, slit lamp examination, and dilated fundus photography.

QoL (EQ-5D-5L):

Subjects will complete the EQ-5D-5L at the time points as per the schedule of events.

The EQ-5D-5L is a standardized instrument to measure health outcome. It is applicable to a wide range of health conditions and treatments, and provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L takes only a few minutes to complete. Instructions to respondents are included in the

questionnaire. An EQ-5D-5L self-complete version was designed to increase sensitivity and reduce ceiling effects. This is available in paper format.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

All tests listed below (Table 1) will be performed by a central laboratory as per APPENDIX A: SCHEDULE OF EVENTS. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI. Hematological and biochemistry tests will be performed at screening, at baseline (only if screening was done longer than 7 days before start of the treatment), at each visit during the treatment phase (except Visit 7), or as medically necessary, and at the discontinuation from study treatment (within 3 days after discontinuation).

A serum lipid profile includes: total cholesterol, low-density lipoprotein (LDL), HDL, and triglycerides. This assessment will be performed at baseline; at Visits 3, 4, 5, and 6 (weeks 6, 12, 18, and 24) and Visits 8–13 (every 12 weeks ± 7 days if still on treatment after week 24) during the treatment phase; and at EOT.

INR and aPTT are examined as coagulation assessments. They will be performed at screening (and checked at the baseline visit only if screening was done longer than 7 days before start of the treatment); at Visits 3, 4, 5, and 6 (weeks 6, 12, 18, and 24) and Visits 8–13 (every 12 weeks ± 7 days if still on treatment after week 24) during the treatment phase; and at EOT.

Serum hormones include: testosterone, estradiol, and SHBG. This assessment will be performed at baseline; at Visits 3, 4, 5, and 6 (weeks 6, 12, 18, and 24) and Visits 8–13 (every 12 weeks ± 7 days if still on treatment after week 24) during the treatment phase; and at EOT.

Any particular clinical findings seen before taking study treatments must be documented in the Relevant Medical History/Current Medical Conditions eCRF.

Findings compatible with AEs after taking study treatment must be documented in the AE eCRF.

Urinalysis includes macroscopic and microscopic examinations. Macroscopic examination includes: specific gravity, pH, protein, glucose, bilirubin, ketones, blood cells, and leukocytes. Microscopic examination includes: white blood cells (WBC)/high power field (HPF), red blood cells (RBC)/HPF and any additional findings. Urinalysis will be performed only at screening and if medically indicated.

Significant findings must be recorded as Relevant Medical History/Current Medical Conditions (if present before treatment). Urinalysis may be repeated at the discretion of the Investigator at any time during the study and as clinically indicated; any clinically relevant findings should be added to the AE eCRF.

The categories of subjects listed in Section 5 Study Enrollment and Withdrawal should be tested for hepatitis B serologic markers and viral load at screening: HBV-DNA, HBsAg, HBcAb, and HBsAb. Subjects with hepatitis C risk factors and additional subjects at the discretion of the Investigator should be tested for HCV ribonucleic acid-polymerase chain reaction (RNA-PCR) test at screening. For a list of hepatitis C risk factors, refer to Section 5.

HIV, HBV, and HCV screening will be performed at screening for all subjects. If a subject test is positive for HIV, HBV, or HCV, she will be considered ineligible for the study according to the Exclusion Criteria. Please note that subjects whose test is negative for HBV-DNA, HBsAg, and HBcAb but positive for HBsAb with prior history of vaccination against Hepatitis B will be eligible. The fact that the subject had been vaccinated should be entered into the subject's Medical History eCRF. Results will not be reported in the eCRF.

Protocol: 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	Compound No.: GTx-024 Author: Nancy Milligan

Table 1: Clinical Laboratory Tests

Hematology	**Serum Chemistry**
• Hemoglobin • Hematocrit • Total and differential leukocyte count • RBC count • Platelet count	• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • AST • ALT • Albumin • Sodium • Potassium • Creatinine
Urinalysis	**Additional Tests**
• pH • Specific gravity • Protein* • Glucose • Ketones • Bilirubin • Blood* • Nitrite* • Urobilinogen • Leukocyte esterase*	• HIV test • HBV-DNA • HBsAg • HBcAb • HBsAb • HCV • Serum lipid panel (total cholesterol, LDL, HDL, triglycerides) • Coagulation tests (INR, aPTT) • Serum pregnancy test • PSA • Hormonal status of the tumor (AR) • CTCs • Blood hormone levels, including testosterone, estradiol, SHBG
* If urinalysis is positive for protein, blood, nitrite, and/or leukocyte esterase, a microscopic examination (for RBC, WBC, bacteria, casts, and epithelial cells) will be performed.	

8.2.2 Special Assays or Procedures

Pharmacokinetic assessment:

Blood samples for pharmacokinetic assessment will be collected at baseline (pre-dose), Visit 3 (week 6), Visit 5 (week 18), and Visit 6 (week 24). One blood sample will be collected in a 6 mL K2-ethylenediaminetetraacetic acid (EDTA) blood collection tube on each of these days. The exact time (hh:mm) and date that each blood sample is collected will be recorded on the eCRF. At the baseline visit, the blood sample should be collected before the subject is given their first dose of GTx-024. At visits 3 (week 6), 5 (week 18), and 6 (week 24), the date and approximate time of the last dose of GTx-024 prior to the blood sample should be recorded; i.e., it should be documented whether the subject took the previous dose that morning or the evening before. Immediately after collection, the tubes will be gently inverted several times to mix the anticoagulant with the blood sample.

Blood samples will be kept on wet ice (ice packs in a water bath is also acceptable) for up to 20 minutes until processed. The plasma fraction will be separated by placing the collection tube into a centrifuge for 10 minutes at 1,500 x g. The plasma fraction will be withdrawn by pipette and divided into two 2 mL polypropylene transfer vials (with each tube receiving approximately equal aliquots).

All sample collection and freezing tubes will be clearly labeled in a fashion which identifies the subject, the study number, the visit number, and freezing tube aliquot letter. Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing. Samples will be stored in a freezer at –20°C or lower. Samples will be shipped in a thermal insulated container with sufficient dry ice to assure they remain frozen.

Any remaining plasma samples after completion of the protocol outlined pharmacokinetic analysis may be used to identify and quantify the metabolites of GTx-024.

Circulating Tumor Cells (CTCs):

Blood samples will be collected for CTC enumeration at Visits 2, 4, 6, 8, and EOT and for gene expression at Visit 2 and EOT.

The enumeration sample will be collected in a 10 mL CellSave tube.

The gene expression sample will be collected in a 10 mL EDTA blood collection tube.

All CTC samples are to be stored under ambient conditions and shipped on the same day of collection. CTC enumeration testing is to be completed within 96 hours of collection and gene expression within 36 hours of collection.

8.2.3 Specimen Preparation, Handling, and Shipping

As a central laboratory will be used for specimen analysis, the PI and all members of the investigational team will be instructed to follow the instructions of the central laboratory manual provided by the central laboratory concerning specimen preparation, handling, storage, and shipment.

9 ASSESSMENT OF SAFETY

9.1 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.1.1 Adverse Events

ICH E6 guidelines define 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 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 eCRF.

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 4.0. For any AE that is not specifically covered in NCI-CTCAE 4.0, the criteria from Table 2 should be used:

Table 2: Description of Grades According to the NCI-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

The causal relationship of the study drug to the AE will be assessed by the Investigator.

If there is a reasonable suspected causal relationship to the study treatment, i.e., there are facts (evidence) or arguments to suggest a causal relationship, the drug-event relationship should be assessed as related.

The following criteria should be considered by the Investigator to assess the relationship (or association) of each AE to the study drug:

- **Related** - There is a reasonable causal relationship to the study treatment, i.e., there is evidence or arguments to suggest a causal relationship. The following criteria should be considered in order to assess the relationship as related:
  - Reasonable temporal association with drug administration
  - It may or may not have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
  - Known response pattern to suspected drug
  - Disappears or decreases on cessation or reduction in dose
  - Reappears on rechallenge
- **Not related** - This category applies to any AE that does not appear to have a reasonable relationship to the use of study drug (see above guidelines)

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

9.1.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Clinical laboratory values will be listed with abnormal values flagged. Clinically significant laboratory values will be reported as an AE. The AE will be followed to resolution as per Section 9.3 Type and Duration of Follow-up of Subjects after Adverse Events.

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:

UK Safety E-Fax Line: **0044 (0)1403 330459**

UK Safety Unmanned Hotline: **0044 (0)1403 758462**

US Safety Toll-Free E-Fax Line: **001 866 966 2970**

US Safety Toll-Free Unmanned Hotline: **001 866 966 8429**

Cmed 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 in English, 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 a either 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 Code of Federal Regulations (CFR) 312.32, 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 regulatory authorities, EudraVigilance, IECs, 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. 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:

- An 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)
- A temporary halt of a trial for safety reasons if the trial is conducted with the same IMP in another country by the same Sponsor, recommendations of the SMC, if any, where relevant for the safety of subjects

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.

9.2.3 Other Adverse Events

Progression of Underlying Malignancy

If progression of underlying malignancy is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST 1.1, or other criteria as determined by the protocol, it should not be reported as an AE. Similarly, hospitalization due exclusively to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as solely due to the progression of the

underlying malignancy, or does not meet the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

Liver Toxicity Management

Elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report the occurrence of either of the following as an SAE:

- Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

For subjects with liver metastasis and elevated ALT or AST of > 3 × ULN at baseline, the values will not be reported as an SAE if ≤ 5 × ULN.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the eCRF and reported to the Sponsor within 24 hours after learning of the event, as per Section 9.2 Reporting Procedures.

9.2.4 Reporting of Pregnancy

If a subject becomes pregnant during the study, she must be instructed to stop taking the study drug and immediately inform the Investigator. The Investigator must report all pregnancies within **24 hours** to the Sponsor as per Section 9.2 Reporting Procedures, regardless of seriousness. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. The clinical outcome of the pregnancy should be documented. Specifically, the estimated date of conception, expected date of delivery, actual date of delivery, date of last

menstrual period, and details of contraceptives should be documented. The pregnancy course should be described in full. If the subject gives birth, the weight and length of the child, Apgar scores (with explanation of score < 10), and congenital abnormalities should be documented. Concomitant drugs and medical history of the mother should be documented. Smoking status and alcohol intake during pregnancy and illicit drug use prior to and during pregnancy should be recorded. Pregnancy will be followed until completion. If the new-born is healthy, additional follow-up is not necessary.

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
- Start of new anticancer regimen
- 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 a determination made regarding dose reduction, interruption, or withdrawal of the subject from the study.

Dose reduction, interruption, or withdrawal of the subject from the study 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%)

For subjects with known liver metastasis and elevated ALT or AST of ≤ 5 × ULN at baseline, discontinuation of treatment should be considered if:

- ALT or AST > 5 × ULN and total bilirubin > 2 × ULN

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

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

If any 2 out of the first 10 subjects enrolled in the 18 mg arm meet the above hepatotoxicity criteria, or if a total of 5 subjects ever meet these criteria in the 18 mg arm, the 18 mg dose will be reduced to 9 mg for all subjects; the 18 mg arm will be permanently halted and all subjects will be enrolled into the 9 mg arm.

If a total of 5 subjects in the 9 mg arm ever meet the above hepatotoxicity criteria, the study will be halted.

9.5 Safety Oversight

In order to protect the safety of the subjects, an SMC will be established for the study to review the safety data on an ongoing basis. The SMC will consist of, as a minimum, the Medical Monitor, a Safety Reviewer with an oncology background, a statistician, and two GTx, Inc. representatives, consistent with the SMC charter.

The Medical Monitor will be a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion through review of AEs, immediately after they occur or are reported, with follow-up through to resolution. The Medical Monitor will evaluate individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

The Medical Monitor will be selected based on relevant study-related or therapeutic expertise and participation is for the duration of the study. The Medical Monitor will be able to readily access participant records in real time.

10 CLINICAL MONITORING

The purpose of the site monitoring visit is to ensure that the study is being conducted in accordance with the protocol (and any subsequent amendments), current ICH Guideline on Good Clinical Practice (GCP) requirements, and applicable IRB/IEC and regulatory requirements.

An authorized study monitor (clinical research associate [CRA]) will visit the site prior to initiation and at periodic intervals to review the study records (including ICFs, inventory of study drug, and eCRFs), and assess compliance with the study protocol. The monitor(s) will also visit at conclusion of the study to help resolve any remaining data queries and close out all record keeping.

It is the responsibility of the Investigator to make sure all necessary source documentation and records are available to the CRA during his/her visit and to provide a suitable space for the CRA to review these documents. Additionally, the Investigator must also be available as needed during the monitoring visit. It is the CRA's responsibility to arrange the visits with the unit in advance and to notify the unit of the documentation that he/she will need during the visit.

All findings resulting from monitoring visits will be documented and shared with the Investigator and Sponsor via follow-up letters and monitoring reports. As much as possible, issues/discrepancies should be resolved during the monitoring visits, but those remaining at the end of the visit will be followed through until resolution.

11 STATISTICAL CONSIDERATIONS

This section is an overview of the statistical design and its rationale. A separate Statistical Analysis Plan (SAP) will provide further detail of statistical tests, handling of missing data, and various methods for imputing time-to-event to account for the difference between the last known event free time and the subsequent first event date, as well as specifications of tables, figures, and listings.

11.1 Study Hypotheses

This trial will employ a Simon's two-stage (optimal) design independently for each dose arm, 9 mg and 18 mg. The assumptions for the design are as follows:

- H_0: CBR ≤ 0.10
- H_1: CBR ≥ 0.30
- α = 0.025 (one-sided)
- Power = 90%

11.2 Sample Size Considerations

Based on the above assumptions, a sample size of N = 44 ER+/AR+ BC subjects with centrally confirmed AR+ status who receive at least one dose of study treatment (evaluable subjects) are needed for each arm that proceeds to the second stage. An arm will proceed to the second stage if at least 3 subjects among the first 18 evaluable subjects randomized achieve CB, defined as CR, PR, or SD as per RECIST 1.1, as determined by central review. If an arm proceeds to the second stage, a statistical success that favors further evaluation of the dose arm(s) in future trials will require at least 9/44 subjects to achieve CB at week 24, i.e., the null hypothesis of an unacceptably low rate of CB, ≤ 10.0%, can be rejected in favor of the alternative hypothesis that indicates the higher rate, ≥ 30.0%, is more likely. The lower limit of the exact 95% confidence interval at exactly 9 CBs, 11.0%, exceeds 10.0%[12].

At any time during the first stage, if 3 evaluable subjects in any one arm achieve CB at week 24, that arm will proceed to the second stage; otherwise, it will be halted for lack of efficacy. If at any time, 9 evaluable subjects in an arm achieve CB at week 24, the efficacy criteria for that arm has been met; however, the arm should proceed to full accrual of 44 evaluable subjects in the successful arm(s) in order to better characterize the CB rate, evaluate secondary endpoints, and describe the safety profile of the dose level(s). To reiterate, the intent of the trial is not to statistically compare the CB rate between the two dose arms and the trial is not powered to do so.

Subjects whose AR+ status is not centrally confirmed will be replaced in order to accrue the necessary number of evaluable AR+ subjects to be included in the primary analysis. Subjects who are not confirmed AR+ may remain on the trial, but will not be part of the primary efficacy analysis – these subjects will contribute to secondary and tertiary analyses as noted below. Subjects who are randomized but never receive study drug will be replaced as well. Assuming that 25% of subjects enrolled are not evaluable for the primary efficacy analysis for the reasons noted above, up to 30 additional subjects may need to be randomized.

11.3 Planned Interim Analyses (if applicable)

No interim analysis is planned.

11.4 Final Analysis Plan

11.4.1 Analysis sets

Full Analysis set (FAS): All subjects who are randomized and receive at least one dose of study drug.

Evaluable subjects: Subjects in the FAS who have centrally confirmed AR+ status; these subjects are the subjects in the primary efficacy analysis.

Per protocol set (PPS): All subjects with centrally confirmed AR+ who have baseline scans, receive at least 80% of the anticipated doses, and complete the week 24 RECIST 1.1 evaluation, and have no major protocol deviations.

Safety analysis set (SAS): All subjects who are randomized and receive at least one dose of study drug.

Safety analysis subjects will be analyzed in the treatment arm in which they are initially dosed. Efficacy analysis subjects will be analyzed according to the treatment arm to which they were randomized.

11.4.2 Definition of analysis endpoints; primary, secondary, tertiary, exploratory, safety

Primary efficacy endpoint

Tumor response in terms of clinical benefit will be assessed by RECIST 1.1 criteria from centrally read CT scans obtained at the 24 week assessment. Tumor response is judged relative to baseline tumor assessments. An evaluable subject will be considered to have a response of CB if the assessment indicates CR, PR, or SD. The primary assessment is among evaluable subjects in the FAS at 24 weeks in each of the 9 mg and 18 mg arms. An evaluable subject who does not have a week 24 assessment for any reason remains in the evaluable subset of the FAS and is considered a failure to achieve CB (CR, PR, or SD).

Secondary efficacy endpoints

- CBR in the FAS and PPS at 24 weeks in each of the 9 mg and 18 mg arms

The following secondary efficacy endpoints will be assessed among subjects in each of the 9 mg and 18 mg arms among the evaluable subjects, the FAS, and the PPS:

- ORR (CR or PR assessed by RECIST 1.1 criteria) at 24 weeks

- Best (confirmed) overall response rate (BOR). BOR is defined as the best observed response for each subject up to and including the EOT. Reponses of CR or PR should be confirmed by a repeat assessment at least 4 weeks later.
- PFS: PFS is defined as the time from randomization until objective tumor progression or death due to any cause. Subjects who have no PFS events will be censored at the date of the last adequate tumor assessment. If the subject has no post-baseline tumor assessments, they will be censored at the time of randomization
- TTP: TTP is defined as the time from randomization until objective tumor progression or death due to disease progression. Subjects who have not progressed will be censored at the date of the last adequate tumor assessment. If the subject has no post-baseline tumor assessments but is known to be alive, they will be censored at the time of randomization
- Duration of response: Duration of response, in responders, is defined as the period from the date of initial CR or PR until the date of disease progression or death from any cause. Only subjects with BOR of CR or PR (i.e., responders) will be included in the analysis of duration of response. Subjects with no documented progression or death after CR or PR will be censored at the last date at which they are known to have had the CR or PR

Tertiary efficacy endpoints

The following tertiary efficacy endpoints will be assessed among subjects in each of the 9 mg and 18 mg arms among the evaluable set of subjects and among the FAS:

- PSA: PSA will be obtained during routine laboratory assessments and results at each scheduled assessment will be compared with baseline along with percentage change from baseline
- QoL: QoL will be obtained using the EQ-5D-5L, with each scheduled assessment compared with baseline
- CTCs: The number of CTCs will be obtained at each scheduled assessment and compared with baseline

- Duration of prior CB: The impact of duration of prior CB on outcome (CB response at week 24, PFS, TTP, duration of response)
- Time from diagnosis of metastases to randomization: The impact of time from diagnosis of metastases to randomization on outcome (CB response at week 24, PFS, TTP, duration of response)
- Tumor volume and change from baseline in tumor volume
- Pharmacokinetics: GTx-024 and GTx-024 glucuronide plasma concentrations and outcome (CBR at weeks 16 and/or 24)

Safety endpoints

The following safety endpoints will be assessed among evaluable subjects as well as all subjects enrolled and treated:

- AEs and concomitant medications
- Laboratory examinations (clinical chemistry, hematology, and urinalysis)
- Physical examinations
- Vital signs
- ECOG performance status
- Eye examinations

Pharmacokinetic endpoints

- Plasma concentrations of GTx-024 18 mg and GTx-024 glucuronide at each assessment

11.4.3 Statistical methodology

11.4.3.1 Demographic data

Continuous demographic data (i.e., age, weight, height, and body mass index [BMI]) will be summarized by descriptive statistics (arithmetic mean, standard deviations, median, minimum, maximum, and total number of subjects). Categorical demographic

data (i.e., gender, race, ethnicity, and ECOG performance status) will also be listed and tabulated in frequency counts and percentage.

11.4.3.2 Primary efficacy analysis

The primary efficacy analysis is based on rules as set forth in Simon's two stage (optimal) design as previously described, and is based on the proportion of evaluable subjects in the FAS who achieve CB at 24 weeks. At least 3/18 evaluable subjects must achieve CB in order for the arm to proceed to the second stage. If an arm proceeds to the second stage, ≥ 9/44 subjects must have CB at 24 weeks to deem the efficacy criteria to have been met in that arm. This is the minimum number of successes needed to rule out an unacceptably low, 10%, CB rate (lower limit of the 95% confidence interval). The exact 95% confidence intervals about the CBR at week 24 will be constructed.

11.4.3.3 Second efficacy analysis

- The exact 95% confidence intervals about the CBR at week 24 among subjects in the FAS and PPS in each of the 9 mg and 18 mg arms will be constructed

The following secondary efficacy analyses will be performed in subjects in each of the 9 mg and 18 mg arms among the evaluable subjects, the FAS, and the PPS:

- The exact 95% confidence interval about the ORR (CR or PR) will be constructed at week 24
- The exact 95% confidence interval about the BOR will be constructed at week 24
- PFS: Median PFS and 95% confidence intervals will be estimated by the Kaplan-Meier method and the survival function and associated 95% confidence intervals will be constructed at key time points
- TTP: Median TTP and 95% confidence intervals will be estimated by the Kaplan-Meier method and the survival function and associated 95% confidence intervals will be constructed at key time points
- Duration of response: Median duration of response and 95% confidence intervals will be estimated by the Kaplan-Meier method and the survival function and

associated 95% confidence intervals will be constructed at key time points for responders

11.4.3.4 Tertiary efficacy analysis

The following tertiary efficacy analyses will be performed in subjects in each of the 9 mg and 18 mg arms among the evaluable subjects and among the FAS:

- PSA changes from baseline to each scheduled assessment will be described and tested for a significant change from baseline. Percentage change from baseline will be summarized and analyzed as well
- QoL: The EQ visual analog scale (VAS) will be summarized by descriptive statistics at baseline and each assessment. Mean changes from baseline will also be summarized using descriptive statistics and 95% confidence intervals. EQ-5D-5L single item scale scores (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be summarized by means of frequency counts at baseline and at each assessment
- CTCs: Changes in the number of CTCs from baseline to each scheduled assessment will be described and tested for a significant change from baseline
- Duration of prior CB: The impact of duration of prior CB on the current CB response will be explored in an exploratory way using logistic regression models with and without other covariates. The impact of duration of prior CB on PFS, TTP, and duration of response outcomes will be assessed in a Cox proportional hazards model with and without other covariates
- Time from diagnosis of metastases to randomization: The impact of time from diagnosis of metastases to randomization on the current CB outcome will be explored in an exploratory way using logistic regression models with and without other covariates. The impact of time from diagnosis of metastases to randomization on PFS, TTP, and duration of response outcomes will be assessed in a Cox proportional hazards model with and without other covariates
- Tumor volumetrics: The effect of GTx-024 9 mg and 18 mg on tumor volume will be described visually using waterfall plots

- GTx-024 and GTx-024 glucuronide plasma concentrations will be assessed for their association with CBR at week 24 using logistic regression by creating binary variables for the concentrations by dichotomizing at the median concentration at week 24

11.4.3.5 Safety; AEs/labs/study drug exposure/vitals/other

Routine safety assessments for AEs, laboratory variables (clinical chemistry, hematology, and urinalysis), physical examinations, vital signs, ECOG performance status, and eye examinations will be done.

Safety analyses will be conducted among the SAS. AEs will be coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA®). AEs, laboratory outcomes, and results from physical examinations will be graded according to NCI-CTCAE 4.0.

The results of the eye examinations will be summarized.

Summaries of safety data will be presented for subjects in the FAS with centrally confirmed AR+ status as well as in all subjects enrolled and treated (SAS and FAS).

11.4.3.6 Pharmacokinetic analyses

- Descriptive statistics will be used to summarize the plasma concentrations of GTx-024 9 mg and 18 mg and GTx-024 glucuronide at each assessment

11.4.3.7 Missing data/Outliers/Dropout considerations

No imputation for missing data will be carried out other than to complete partial dates using standard imputation techniques as per the Contract Research Organization's standard.

No evaluable subject will have missing data for the primary efficacy analysis because subjects who have the week 24 assessment will be classified as having CB or not, and those who do not have a week 24 assessment will classified as not having CB.

With regards to missing start and stop dates for AEs and medications, imputation rules will be provided in the SAP. In addition, rules to determine in which period each AE belongs for the summary tables will also be provided in the SAP.

11.4.3.8 Other statistical analysis considerations

Additionally, sensitivity analysis and exploratory analysis of the data may be performed and will be described in the SAP.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Access to study-specific eCRFs will be provided to all sites. Source documents are all documents, data, and reports from which the subject's eCRF data is obtained. This includes, but is not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, laboratory reports, microfiches, radiographs, and correspondence. The Investigator and the study staff are responsible for maintaining a comprehensive and centralized filing system of study related documentation, available for inspection at any time by representatives from GTx, Inc. or their designee, all applicable regulatory authorities, and all applicable ethics committees. Elements should include:

- Study files containing signed ICFs and subject identification lists
- Study files containing the protocol, all amendments, IB, copies of pre-study documentation (if applicable), and all correspondence to and from the IEC, competent authorities, and GTx, Inc.
- Investigational product accountability records and drug-related correspondence

In addition, all source documents supporting entries in the eCRFs and the safety database must be maintained and be readily available for at least 15 years after the completion or the discontinuation of the study. After that period of time, the documents may be destroyed subject to local regulations.

Should the Investigator wish to assign the study records to another party or another location, GTx, Inc. must be notified.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and GTx, Inc. to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit.

Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

Each eCRF will be reviewed and electronically signed by the PI.

ICH GCP guidelines require that the eCRF will in no case be considered source data.

13 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.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC and US CFR Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

14.2 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 their 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, and regulatory authorities as required.

14.3 Pre-study Documentation

The Investigator must provide GTx, Inc. 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 site-specific 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, Inc. 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, Inc. or its designee must be notified if normal values change

14.4 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, Inc. 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 eCRFs.

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

14.4.1 Informed Consent/Assent Process (in Case of a Minor)

Not applicable.

14.5 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 as provided under each subject's ICF.

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.

14.6 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.

14.7 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.

14.8 Protocol Amendments

All amendments to the study protocol must be submitted to the IRB/IEC and competent authorities/regulatory agencies for written approval. The approval letter 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, Inc. 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.

14.9 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, Inc. or its designee must be notified. An updated Form FDA 1572 must be submitted to GTx, Inc. or its designee.

14.10 Study Discontinuation

GTx, Inc. reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 5.4.5 Termination of Study.

14.11 Future Use of Stored Specimens

Left over biospecimens (for example, blood and tissue samples) after analyses may be stored for future research uses from subjects who have consented and provided it is not prohibited by local laws and Ethics Committees. No additional samples will be collected except for those listed above. The samples will be stored for up to 10 years and destroyed after that. The samples may undergo genetic tests, tests for biomarkers, and other uses as described in the informed consent, including tests specific for the indication. It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable under local regulations), to obtain written informed consent from each individual who has consented to have their biospecimens stored for future research. Subjects must receive an explanation that they are completely free to refuse long-term storage of their samples for future research and may withdraw their sample at any time and for any reason during the 10 year storage period of the specimen(s) unless their sample has been retained in an anonymized manner (in which case it can no longer be identified as relating to the subject).

The informed consent for optional specimen donation will be incorporated as a specific section into the main clinical trial ICF or provided as a separate document based on the local legislation requirements.

14.12 Indemnity

The Sponsor certifies that it has taken out a liability insurance policy that is consistent with the requirements within the countries in 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 in countries 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.

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

GTx, Inc. and/or its designee will provide guidance to Investigators on making corrections to the source documents and eCRFs.

Cmed will serve as the Statistical and Data Coordinating Center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

15.1 Data Capture Methods

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by Data Management. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Cmed personnel will be responsible for the training of Investigator designated site staff on the correct use of the Electronic Data Capture (EDC) system. Authorized study staff will only be given access once they have received training.

15.2 Study Site Responsibilities

All data requested on the eCRF must be recorded. Data will be transcribed by authorized personnel at the study site from the source documents into the eCRF for enrolled subjects. All information on the eCRF 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 eCRFs are complete and accurate by electronically signing the eCRF.

15.3 Data Management Responsibilities

The Cmed Biometrics department will serve as the Statistical and Data Management center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

Data management staff at Cmed will review the data in the eCRFs according to their internal standard operating procedures and systematically validate the data using appropriate electronic checks in addition to relevant manual checks. For any errors identified in the data, Cmed will generate a formal query to be addressed by the investigational site staff within the EDC system.

For classification purposes, concomitant medications, AEs, and medical history entered into the eCRF will be coded using relevant medication and medical term dictionaries. These will be specified in the study-specific Data Management Plan.

15.4 Timing/Reports

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

15.5 Study Records Retention

After the trial is completed, the Investigator will receive a Compact Disk-Read Only Memory (CD-ROM) with the eCRFs of the subject data for the site for archiving at the

investigational study site. Study documents, including the CD-ROM, 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 are no longer need to be retained.

15.6 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol that affects a subject's safety and primary efficacy, GCP, or Manual of Procedures requirements. The non-compliance 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 Non-compliance, 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, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the appropriate project manager responsible for the conduct of the study.

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 are responsible for knowing and adhering to their IRB/IEC requirements.

16 PUBLICATION POLICY

Following completion of the study, it is expected some Investigators will publish the results of this research in scientific journal(s). Publication rights are governed by each 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 provided by GTx, Inc. to vendors and investigatory teams shall not be published or 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.

17 LITERATURE REFERENCES

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APPENDIX A: SCHEDULE OF EVENTS

Periods	**Screening**	**Randomization /**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1** **Day –28 to –1**	**V2** **Day 1**	**V3** **Week 6 Day 42 (± 7 days)**	**V4** **Week 12 Day 84 (± 7 days)**	**V5** **Week 18 Day 126 (± 7 days)**	**V6** **Week 24 Day 168 (± 7 days)**	**V7** **Week 28 Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
Obtain ICF	X									
Demography	X									
Eligibility criteria check	X	X								
Medical history	X									
Prior anticancer treatment	X	X								
Concomitant medications	X	X	X	X	X	X		X	X	X
Diagnosis and extent of BC	X									

Periods	**Screening** **Day –28 to –1**	**Randomization / Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
Hormonal receptor status (ER+) and HER2[3]	X									
AR status[3]	X									
Physical examination	X		X	X	X	X		X	X	X
Height	X									
Weight	X		X	X	X	X		X	X	X
Vital signs	X	X[4]	X	X	X	X		X	X	X
ECOG performance status	X	X[4]	X	X	X	X		X	X	X
Eye examination[5]	X	As clinically indicated							X	

Periods	**Screening** **Day –28 to –1**	**Randomization / Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
Hematology	X	X[4]	X	X	X	X		X	X	X
Biochemistry	X	X[4]	X	X	X	X		X	X	X
HIV screening	X									
HBV screening[6]	X									
HCV screening	X									
Serum lipid profile		X	X	X	X	X		X	X	
Coagulation status	X		X	X	X	X		X	X	
Serum hormones		X	X	X	X	X		X	X	
PSA	X	X[4]	X	X	X	X		X	X	X

Periods	**Screening** **Day –28 to –1**	**Randomization / Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
CTC enumeration		X		X		X		X	X	
CTC gene expression		X							X	
Urine analysis	X	As clinically indicated								
Radiological evaluation: CT/MRI[7]	X			X		X	X[8]	X	X	
Radiological evaluation: bone scan[9]	X			X		X	X[10]	X	X	
Pharmacokinetic samples[11]		X	X		X	X				
ECG	X									

Periods	**Screening** **Day –28 to –1**	**Randomization /** **Day 1**	**Treatment phase[1] (from randomization to EOT)**						**EOT/ Early termination**	**FU post treatment**
							Confirmation of CR or PR	**As required if still on treatment**		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**V3** **Week 6** **Day 42 (± 7 days)**	**V4** **Week 12** **Day 84 (± 7 days)**	**V5** **Week 18** **Day 126 (± 7 days)**	**V6** **Week 24** **Day 168 (± 7 days)**	**V7** **Week 28** **Day 196 (± 7 days)**	**V8[2]– V13** **Every 12 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU** **28 days (± 2 days) after the last dose of GTx-024**
AEs	X	X	X	X	X	X		X	X	To be followed up to 28 days post treatment
Serum Pregnancy Test	X									
GTx-024 9 mg or 18 mg dispensing/ administration		X[12]	X	X	X	X[13]		X[13]		
GTx-024 9 mg or 18 mg accountability			X	X	X	X		X	X	
QoL EQ-5D-5L		X	X	X	X	X		X	X	

[1] Subjects with clinical benefit at 24 weeks will continue on therapy for up to 24 months (as long as they still benefit from the treatment during these 24 months). If so, the subjects will be asked to come for a visit every 3 months and undergo the assessments for the treatment period.

[2] Visit 8 should occur at Week 36; i.e., 12 weeks after Visit 6 (Week 24).

[3] ER and HER2 as per medical record will be used to determine subject eligibility. ER status will be confirmed by a local laboratory if not available in the subject's medical history. AR status will be confirmed by a central laboratory.

[4] These medical procedures and assessments do not have to be repeated if done at screening within 7 days before randomization.

[5] Eye examination including best corrected distance visual acuity with refraction, intraocular pressure, slit lamp examination, and dilated fundus photography must be completed between Day –28 and Day –1, as clinically indicated during the treatment phase, and at EOT.

[6] HBV screening will be done as HBsAg.

[7] Imaging study (CT, MRI) is recommended to be performed within 7 days prior to randomization. The imaging studies will be assessed by both a local imaging facility and a blinded central reader. Subject eligibility will be based on local reading of the imaging studies. Medical decisions will be based on the local assessments. At screening, week 12 (Visit 4), and week 24 (Visit 6), tumor volumetric assessments will be done for the subjects undergoing CT scanning.

[8] In compliance with RECIST 1.1 guidelines, subjects who have CR or PR at week 24 (Visit 6) require confirmation within a month as follows:

- For subjects with measureable lesions, subjects will undergo CT/MRI based on the Investigator's medical judgment

[9] Bone scans will be performed at screening and then every 12 weeks whilst subjects receive treatment (Visits 4, 6, and thereafter) in only those subjects with baseline bone metastases, or if clinically indicated.

[10] In compliance with RECIST 1.1 guidelines, subjects who have CR or PR at week 24 (Visit 6) require confirmation within a month as follows:

- For subjects with non-measurable lesions, subjects will undergo X-ray or bone-scanning based on the Investigator's medical judgment and location of disease.

[11] Blood sampling for pharmacokinetic assessment. The exact time (hh:mm) and date of the blood sample should be recorded on the eCRF. At the baseline visit, the blood sample should be collected before the subject is given their first dose of GTx-024. At visits 3 (week 6), 5 (week 18), and 6 (week 24), the date and approximate time of the last dose of GTx-024 prior to the blood sample should also be recorded; i.e., it should be documented whether the subject took the previous dose that morning or the evening before.

[12] First dose to be given at site during this visit.

[13] At Visits 6, 8, 9, 10, 11, 12, and 13, in order to accommodate the visit schedule of every 12 weeks (± 7 days), the subjects will receive two carton boxes of study drug (each containing 7 blisters) to cover study treatment for 14 weeks.

Abbreviations: AR = Androgen Receptor, BC = Breast Cancer, CR = Complete Response; CT = Computerized Tomography, CTCs = Circulating Tumor Cells, ECG = Electrocardiogram, ECOG = Eastern Cooperative Oncology Group, eCRF = electronic Case Report Form, EOT = End of Treatment, ER = Estrogen Receptor, FU = Follow-up, HBsAg = Hepatitis B surface Antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = Human Immunodeficiency Virus, ICF = Informed Consent Form, IHC = Immunohistochemistry, MRI = Magnetic Resonance Imaging, PR = Partial Response; QoL = Quality of Life, PSA = Prostate Specific Antigen, V = Visit.

APPENDIX B: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[4]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead