Protocol: A Phase 2 Open Label, Multi-Center, Multinational Study Investigating The Efficacy and Safety Of GTx-024 On Advanced, Androgen Receptor-Positive Triple Negative Breast Cancer (AR+ TNBC)	Compound No.: GTx-024 Author: Nancy Milligan

A Phase 2 Open Label, Multi-Center, Multinational Study Investigating The Efficacy and Safety Of GTx-024 On Advanced, Androgen Receptor-Positive Triple Negative Breast Cancer (AR+ TNBC)

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Protocol: A Phase 2 Open Label, Multi-Center, Multinational Study Investigating The Efficacy and Safety Of GTx-024 On Advanced, Androgen Receptor-Positive Triple Negative Breast Cancer (AR+ TNBC)	Compound No.: GTx-024 Author: Nancy Milligan

CONFIDENTIALITY STATEMENT

STATEMENT OF COMPLIANCE

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

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (May 9, 1997)
- EU Clinical Trial Directive 2001/20/EC
- Relevant regulations from all countries where the clinical study will be conducted

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PROTOCOL SIGNATURE PAGE

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Date: 5/31/2016

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Protocol: A Phase 2 Open Label, Multi-Center, Multinational Study Investigating The Efficacy and Safety Of GTx-024 On Advanced, Androgen Receptor-Positive Triple Negative Breast Cancer (AR+ TNBC)	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
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computerized Tomography
CTCs	Circulating Tumor Cells
CYP2C9	Cytochrome P450 2C9
CYP3A	Cytochrome P450, Family 3,Subfamily A
DHT	Dihydrotestosterone
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
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
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
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
INR	International Normalized Ratio
IRB	Institutional Review Board
ISH	In Situ Hybridization
LBM	Lean body mass
LDH	Lactate dehydrogenase
LDL	Low-Density Lipoprotein
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
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
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARM	Selective Androgen Receptor Modulator
SAS	Safety Analysis Set
SD	Stable Disease
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

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PROTOCOL SUMMARY

Title:	A Phase 2 Open Label, Multi-Center, Multinational Study Investigating The Efficacy and Safety Of GTx-024 On Advanced, Androgen Receptor-Positive Triple Negative Breast Cancer (AR+ TNBC)
Sponsor:	GTx, Inc.
Indication:	Advanced, AR+ TNBC
Study Design:	This is an open label, multicenter, multinational, Phase 2 study to assess the efficacy and safety of GTx-024 in female subjects with androgen receptor-positive, triple negative breast cancer (AR+ TNBC). Subjects will be administered GTx-024 18 mg orally (PO) daily for up to 12 months. Simon's two-stage (optimal) design[1] will be used to assess primary efficacy and will require up to 41 evaluable subjects; i.e., subjects with centrally confirmed AR+ who receive at least one dose of study drug. In order to obtain these numbers of evaluable subjects, 21 to 55 subjects, including over-enrollees (see below), will be enrolled to receive a daily PO dose of GTx-024 18 mg. Fourteen of the aforementioned subjects may be over-enrollees to allow for replacement of subjects to account for lack of centrally confirmed AR+ status, or for the rare subject who is enrolled but does not receive study drug. The trial will test for an unacceptably low clinical benefit rate (CBR) of ≤ 5% versus a CBR more consistent with ≥ 20%. The first stage will be assessed among the first 21 evaluable subjects. If at least 2/21 subjects achieve clinical benefit (CB) (defined as complete response [CR], partial response [PR], or stable disease [SD], per Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1[2]) at week 16, then the trial will proceed to the second stage of recruitment of up to a total of 41 subjects in the evaluable subset of the Full Analysis Set (FAS). Otherwise, the trial 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. With the exception of elevated liver function tests (LFTs) and hypercalcemia, both of which are further addressed below, subjects 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 7 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. For ≥ Grade 3 elevations in LFTs, study drug should be held. A recheck of LFTs should be done within 48 hours. Study drug may be restarted at the 18mg dose or reduced to a 9mg dose when LFTs have resolved to Grade 1 or better. In the event of hepatotoxicity, please also refer to Section 9.4 Halting Rules. In the event of ≥ Grade 2 hypercalcemia, study drug should be held until hypercalcemia resolves to Grade 1 or better. The subjects who demonstrate CB will be treated for up to 12 months from the date of the first dose of study treatment (as long as they continue to demonstrate CB from the treatment during these 12 months). Subjects who continue to demonstrate a beneficial response from the study treatment at 12 months will be offered to continue in a safety extension study under a separate protocol. All subjects will be followed-up at one month after the last dose of GTx-024 is received, for safety purposes, and for vital status every 60 days, thereafter, for up to 24 months. 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 16 weeks (defined as CR, PR, or SD) (by RECIST 1.1) of GTx-024 18 mg given PO daily in subjects with TNBC and centrally confirmed AR+ status. **Secondary efficacy objectives**: • Estimate the CBR at 16 weeks (by RECIST 1.1) of

	GTx-024 18 mg in all subjects enrolled who receive at least one dose of study medication (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 18 mg at 16 weeks • Estimate the CBR (by RECIST 1.1) of GTx-024 18 mg at 24 weeks • Estimate the ORR (defined as CR or PR) (by RECIST 1.1) of GTx-024 18 mg at 24 weeks • Estimate the best overall response rate (BOR) of GTx-024 18 mg • Estimate the progression free survival (PFS) of subjects receiving GTx-024 18 mg • Estimate the time-to-progression (TTP) of subjects receiving GTx-024 18 mg • Estimate duration of response (time from documentation of tumor response to disease progression or death) of subjects receiving GTx-024 18 mg • Estimate overall survival (OS) **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 18 mg on serum prostate specific antigen (PSA) • Assess the effect of GTx-024 18 mg on Quality of Life (QoL) as measured by EQ-5D-5L • Assess the effect of GTx-024 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 study enrollment on outcome • Describe the effect of GTx-024 18 mg on tumor volumetrics • Assess the effect of plasma concentrations of GTx-024 and GTx-024 glucuronide on CBR at 16 and 24 weeks **Safety objective:** To describe the safety profile of GTx-024 18 mg PO daily in subjects with TNBC and centrally confirmed AR+ as well as in

	all subjects enrolled 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 women with advanced TNBC with centrally confirmed AR+. **Subject Inclusion Criteria**: Subjects eligible for inclusion in this study must meet **all** of the following criteria: 1. Able and willing to give voluntary, written and signed, informed consent; 2. Women ≥ 18 years of age; 3. Women with TNBC who have received at least one but no more than two prior chemotherapy regimens for the treatment of advanced or metastatic TNBC; 4. Confirmation of AR+ (defined as ≥ 10% nuclear AR staining by immunohistochemistry [IHC]) TNBC in either the primary or metastatic lesion, assessed prior to the start of or during the screening period by a local laboratory or by medical history; 5. TNBC confirmed by medical history as: human epidermal growth factor receptor 2 [HER2]-negative (confirmed by 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); estrogen receptor (ER) negative (confirmed as ER expression less than or equal to 1% positive tumor nuclei); progesterone receptor negative (confirmed as progesterone receptor expression less than or equal to 1% positive tumor nuclei); 6. Availability of paraffin embedded or formalin fixed tumor tissue; OR, a minimum of 10 and up to 20 slides of archived tumor tissue or new biopsy, if archived tissue is unavailable, for central laboratory confirmation of AR status and molecular subtyping. Metastatic tumor tissue is preferred when possible; 7. Subjects must have either measurable disease or bone-only non-measurable disease according to RECIST 1.1; 8. Subjects with bone metastases should be treated with intravenous bisphosphonates or subcutaneous denosumab (or investigator preferred standard of care) prior to and during the trial, unless there is a contraindication or subject intolerance to these therapies;

	9. Eastern Cooperative Oncology Group (ECOG) performance status[3] 0 or 1 at the time of screening and enrollment; 10. Negative serum pregnancy test in women of childbearing potential (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization), no more than 7 days before the first dose of study treatment; 11. For women of childbearing potential who are sexually active, agreement to use a highly effective, non-hormonal form of contraception during and for at least 6 months after completion of study treatment; OR, a fertile male partner willing and able to use effective non-hormonal means of contraception (barrier method of contraception in conjunction with spermicidal jelly, or surgical sterilization) during and for at least 6 months after completion of study treatment; 12. Adequate organ function as shown by: • Absolute neutrophil count ≥ 1,000 cells/mm^3 • Platelet count ≥ 100,000 cells/mm^3 • Hemoglobin ≥ 9 g/dL • Serum aspartate aminotransferase (AST) and alanine aminotransferase (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 time (aPTT) < 1.5 × ULN (unless on anticoagulant treatment at screening); 13. Able to swallow capsules; 14. Any toxicity from prior chemotherapy has resolved or is Grade 1 (NCI-CTCAE, Version 4.0). **Subject Exclusion Criteria:** Subjects eligible for this study must not meet **any** of the following criteria: 1. Life expectancy < 4 months; 2. Subjects with radiographic evidence of central nervous system (CNS) metastases as assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) that are not well controlled (symptomatic or requiring control with continuous corticosteroid therapy [e.g., dexamethasone]). Note: Subjects with CNS metastases

	are permitted to participate in the study if the CNS metastases are medically well controlled prior to screening (as assessed by the Investigator) after receiving local therapy (irradiation, surgery, etc.); 3. Radiotherapy within 14 days prior to first dose of study treatment; 4. Have, in the judgment of the Investigator, a clinically significant concurrent illness or psychological, familial, sociological, geographical, or other concomitant condition that would not permit adequate follow-up and compliance with the study protocol; 5. Positive hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection at screening; 6. Positive human immunodeficiency virus (HIV) infection at screening; 7. Prior treatment with any anti-androgens, including but not limited to, enzalutamide and bicalutamide; 8. Major surgery within 28 days of the first dose of study treatment; 9. Be currently taking or have previously taken testosterone, methyltestosterone, oxandrolone (Oxandrin®), oxymetholone, danazol, fluoxymesterone (Halotestin®), testosterone-like agents (such as dehydroepiandrosterone, androstenedione, and other androgenic compounds, including herbals), or anti-androgens; 10. Treatment with any of the following hormone replacement therapies, unless discontinued at least 28 days prior to the first dose of study treatment: ● Estrogens ● Megesterol acetate; 11. Treatment with any investigational agent within 28 days before the first dose of study treatment; 12. 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; 13. 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); 14. Current treatment with intravenous bisphosphonate or denosumab with elevated serum calcium corrected for albumin or ionized calcium levels outside institutional normal limits at screening; 15. History of non-compliance to medical regimens; 16. Subjects unwilling to or unable to comply with the protocol procedures as assessed by the Investigator; 17. Concurrent participation in another therapeutic clinical trial.
Phase:	2
Study Duration:	The study duration is estimated at 2 years.
Subject Participation Duration:	The subjects will remain on treatment for up to 12 months (if they still benefit from the treatment). There will be a screening period of up to 28 days and a follow-up period of 1 month.
Description of Agent or Intervention:	Six (6) GTx-024 3.0 mg Softgels (capsules) 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 15 months.
Statistical considerations	This trial will employ a Simon's two-stage (optimal) design. The assumptions for the design are as follows: • H_0: CBR ≤ 0.05 • H_1: CBR ≥ 0.20 • Alpha (α) = 0.05 (one sided) • Power = 90% Based on the above assumptions, a sample size of N = 41 TNBC subjects with centrally confirmed AR+ who have received at least one dose of study medication (evaluable subjects) are needed to proceed to completion of the second stage. The trial will proceed to the second stage if at least

	2 subjects among the first 21 evaluable subjects enrolled in stage 1 achieve CB, defined as CR, PR, or SD, as per RECIST 1.1 as determined by central review. Otherwise, the trial will be closed due to lack of efficacy. If the trial proceeds to the second stage, the efficacy criteria favoring further evaluation of GTx-024 18 mg in future trials will require at least 5/41 subjects to achieve CB, i.e., the null hypothesis of an unacceptably low rate of CB, ≤ 5.0%, can be rejected in favor of the alternative hypothesis that indicates the higher rate, ≥ 20%, is more likely. Over-enrollment: Central laboratory confirmation of AR receptor status will not be available at the time of enrollment for most subjects. Subjects will be enrolled into the study based upon their medical history or locally confirmed TNBC AR+ hormonal status. Subjects who are later found after enrollment not to have centrally confirmed AR+ will be replaced by an over-enrolled subject in order to accrue the 41 subjects of the evaluable subset of the FAS. Subjects who are not centrally confirmed AR+ may, at the discretion of the Investigator, be maintained on the study based on medical history or a local finding of AR+, 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. Furthermore, subjects who are enrolled but do not receive treatment will also be replaced by an evaluable over-enrolled subject and will not be part of the FAS. This may result in up to an additional 14 subjects being enrolled.

Schedule of Events[1]

Periods	Screening Day –28 to –1	Baseline Day 1	Safety check	Treatment phase[1] (from Baseline to EOT)							As required if still on treatment	EOT/ Early termination	FU post treatment
Visit number Week/Day Procedure	V1	V2	Safety review Week 2 (± 3 days)	V3 Week 4 Day 28 (± 7 days)	V4 Week 8 Day 56 (± 7 days)	V5 Week 12 Day 84 (± 7 days)	V6 Week 16 Day 112 (± 7 days)	V7 Week 20 Day 140 (± 7 days)	V8 Week 24 Day 168 (± 7 days)	V9 Week 28 Day 196 (± 7 days)	V10–V12[2] Every 8 weeks (± 7 days)	VEOT 3 days after the last dose of GTx-024	VFU
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	X
Diagnosis and extent of BC	X												

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (± 3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
AR status[3]	X												
Physical examination	X			X	X	X	X		X		X	X	X
Height	X												
Weight	X			X	X	X	X		X		X	X	X
Vital signs	X	X[4]		X	X	X	X		X		X	X	X
ECOG performance status	X	X[4]		X	X	X	X		X		X	X	X
Hematology	X	X[4]		X	X	X	X		X		X	X	X
Biochemistry	X	X[4]	X	X	X	X	X		X		X	X	X
HIV screening	X												

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (± 3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
HBV screening[6]	X												
HCV screening	X												
Serum lipid profile		X		X	X	X	X		X		X	X	
Coagulation status	X			X	X	X	X		X		X	X	
Serum hormones		X		X	X	X	X		X		X	X	
PSA	X	X[4]		X	X	X	X		X		X	X	X
CTC enumeration		X			X		X		X			X	
CTC gene expression		X										X	

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (± 3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
Urine analysis	X	As clinically indicated											
Radiological evaluation: CT/MRI[7]	X				X		X	X[8]	X	X[8]	X	X	
Radiological evaluation: bone scan[9]	X				X		X	X[10]	X	X[10]			
Pharmacokinetic samples[11]		X		X		X	X		X				
ECG	X												

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (± 3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
AEs	X	X		X	X	X	X		X		X	X	To be followed up to 28 days post treatment
Serum pregnancy test	X												
Urine pregnancy test[12]		X		X	X	X	X		X		X	X	X
GTx-024 18 mg dispensing/ administration		X[13]			X		X		X		X		
GTx-024 18 mg accountability				X	X	X	X		X		X	X	
QoL EQ-5D-5L		X		X	X	X	X		X		X	X	

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (± 3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
28 (± 2 days) Follow-up after last dose													X
Vital Status Follow up (every 60 days after last dose)[5]													X

[1] Subjects with clinical benefit at 16 weeks will continue on therapy for up to 12 months (as long as they still benefit from the treatment during these 12 months). If so, the subjects will be asked to come for a visit every other month and undergo the assessments for the treatment period.
[2] Visit 10 should occur at Week 32; i.e., 8 weeks after Visit 8 (Week 24).
[3] AR status to be checked via nuclear AR staining by IHC, only if not available in the medical record of the subject. This assessment will be done in a local/regional laboratory. AR status assessed locally (or as per medical record) will be used to determine subject eligibility during. Prescreening or the study screening period. AR status will be confirmed by a central laboratory prior to Visit 2 (Day 1).
[4] These medical procedures and assessments do not have to be repeated if done at screening within 7 days before the first dose of study treatment.
[5]. Vital Status Follow up (every 60 days after last dose) for up to 24 months

[6] HBV screening will be done as HBsAg.

[7] Imaging study (CT, MRI) is recommended to be performed within 7 days prior to the first dose of study treatment. The imaging studies will be assessed by both a local imaging facility and a central reader. Subject eligibility will be based on local reading of the imaging studies. Medical decisions will be based on the local assessments.
At visits V1, V6, V8, and EOT, 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 16 and/or week 24 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 at weeks 8, 16, and 24 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 16 and/or week 24 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 4), 5 (week 12), 6 (week 16), and 8 (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] Urine pregnancy tests will be done at the site with a pregnancy stick test in premenopausal patients. Postmenopausal patients are exempt from monthly urine pregnancy test.

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

[14] A comprehensive metabolic panel (Chem 14), including serum calcium and liver function tests, will be performed at Week 2 (±3 days).

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, HER2 = Human Epidermal Growth Factor Receptor 2, 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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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Breast cancer is the most commonly diagnosed cancer in women and one in eight women will develop invasive breast cancer in their lifetime. In 2012, 1.7 million women were diagnosed with breast cancer and there were 6.3 million women alive who had been diagnosed with breast cancer in the previous five years. Since 2008, breast cancer incidence has increased by more than 20%, while mortality has increased by 14%. Breast cancer 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.

Clinical assessment of breast cancer 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 ER modulators or aromatase inhibitors (AIs) is the standard treatment given to subjects with tumors that are positive for the ER. For those subjects with tumors overexpressing HER2, targeted therapy against HER2 is typically used with chemotherapy.

Although the majority of breast cancers are considered hormone receptor positive (expressing ER, progesterone receptor, or HER2), 15–20% of women diagnosed with breast cancer will have Triple Negative Breast Cancer (TNBC) which is characterized by a lack of expression of ER, progesterone receptor, or HER2. TNBC occurs more frequently in younger patients (< 50 years of age) and generally shows a more aggressive behavior. For those patients with advanced TNBC, standard palliative treatment options are limited to cytotoxic chemotherapy. However, even after initial response to chemotherapy, the duration of the response may be short and there is a higher likelihood of visceral metastases, rapidly progressive disease, and inferior survival compared to hormone positive breast cancer. Therefore, research is focused on identifying therapeutic targets in TNBC. One such target is the androgen receptor (AR). The AR is the most highly expressed steroid receptor in breast cancer with up to 95% of ER+ breast cancers expressing AR. In TNBC, up to 30% of cancers may express AR. Historically, AR has been considered anti-proliferative and beneficial in hormone positive breast cancers. In TNBC, data demonstrates that the presence of AR and androgen synthesizing enzymes is associated with lower proliferation, lower tumor grade, better overall survival, and more favorable clinical outcomes as compared to those patients with TNBC not expressing AR. Evidence also suggests that the AR target gene prostate specific antigen (PSA) is a favorable prognostic marker in breast cancer. Based on these findings, research is focused on AR as a potential therapeutic target.

GTx-024 is an oral nonsteroidal selective androgen receptor modulator (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.

The effects of GTx-024 on *in vitro* proliferation of breast cancer cell lines were examined. MDA-MB-231 breast cancer cells and HCC-38 breast cancer cells stably transfected with the AR were treated with dihydrotestosterone (DHT), GTx-024, or the inactive R-isomer of GTx-024 in the presence and absence of bicalutamide, a known AR antagonist. DHT and GTx-024 inhibited the *in vitro* proliferation of the breast cancer cell lines with potencies ranging from approximately 1 to 100 nM. These effects were inhibited by co-treatment with bicalutamide and were not induced by the R-isomer of GTx-024, demonstrating dependence on the AR and the stereochemical configuration of the ligand. The ability of GTx-024 to stimulate AR action and inhibit progesterone receptor action may provide a dual mechanism to inhibit breast cancer cell growth. MDA-MB-231-AR cells were implanted subcutaneously in nude mice and were treated orally (PO) with vehicle or 30 mg/kg/day GTx-027, a close structural analog of GTx-024. Tumor growth was reduced significantly, with greater than 75% tumor growth inhibition observed, compared with vehicle-treated tumors. The intratumoral expression of genes and pathways that promote breast cancer development through its actions on the AR were also suppressed. Similar xenograft studies with GTx-024 are ongoing. These data, coupled with the early clinical success of androgens in breast cancer, support the clinical evaluation of GTx-024 and SARMs as a novel targeted therapy to treat AR-positive breast cancer.

Ongoing and Completed Clinical Trials with GTx-024

Twenty-three 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 lean body mass and physical function;

9. Protocol G100511, a Phase 1 study to assess the effect of severe renal impairment on the pharmacokinetics of GTx-024;

10. Protocol G100508, a Phase 1 study to assess the effect of mild and moderate hepatic impairment on the pharmacokinetics of GTx-024;

11. Protocol G100509, a Phase 1 mass balance study of GTx-024 in healthy volunteers;

12. Protocol G100507, a Phase 1 study to assess the pharmacokinetics and absolute oral bioavailability of GTx-024 in Caucasian and African American men and women;

13. Protocol G100510, a single-dose, randomized, double-blind, comparative, positive and placebo-controlled, four-period crossover Phase 1 study to define the electrocardiogram (ECG) effects of GTx-024, at therapeutic and supratherapeutic doses, in healthy male and female subjects: a thorough ECG trial;

14. Protocol G100512, a Phase 1 study to assess the effect of ketoconazole (Cytochrome P450, Family 3,Subfamily A [CYP3A4] inhibitor) on the pharmacokinetics of GTx-024;

15. Protocol G100513, a Phase 1 study to assess the effect of rifampin (CYP3A4 inducer) on the pharmacokinetics of GTx-024;

16. Protocol G100514, a Phase 1 study to assess the pharmacokinetic drug:drug interaction of GTx-024 and celecoxib (CYP2C9);

17. Protocol G100515, a Phase 1 study to assess the pharmacokinetic drug:drug interaction of GTx-024 and probenecid (UGT2B7);

18. Protocol G100516, a Phase 1 study to assess the pharmacokinetic drug:drug interaction of GTx-024 and rosuvastatin (breast cancer resistance protein [BCRP]);

19. Protocol G300504, a Phase 3 randomized, double-blind, placebo-controlled study of the effect of GTx-024 on muscle wasting in 321 subjects with non-small cell lung cancer receiving first line platinum plus a taxane chemotherapy;

20. Protocol G300505, a Phase 3 randomized, double-blind, placebo-controlled study of the effect of GTx-024 on muscle wasting in 320 subjects with non-small cell lung cancer receiving first line platinum plus a non-taxane chemotherapy;

21. Protocol G200801, a, Phase 2, open label study to examine AR status and the activity of GTx-024 hormonal therapy in 22 women with ER positive metastatic breast cancer who have previously responded to hormone therapy;

22. Protocol G200802, an ongoing Phase 2, open label, multinational, randomized, parallel design study investigating the efficacy and safety of GTx-024 on metastatic or locally advanced ER+/AR+ breast cancer in postmenopausal women;

23. Protocol G201001, an ongoing, Phase 2, proof of concept, open label study to examine GTx-024 as a treatment for stress urinary incontinence in women.

2.2 Rationale

GTx-024 has been evaluated in 23 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 upper limit of normal [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. In the 30 mg dose group, six 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 lean body mass in both studies and was safe and well tolerated when dosed for up to 168 days. 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+ and AR+ metastatic breast cancer in order to achieve a higher exposure that is both safe and more likely to be efficacious in women with advanced breast cancer. Seven out of twenty-two subjects with advanced, heavily pretreated (hormonal therapy, radiation, and chemotherapy) breast cancer 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% 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 breast cancer 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 breast cancer. Hence, enobosarm at higher doses might provide dual anti-proliferative effects in breast cancer. In TNBC, 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 breast cancer and was safe and well tolerated.

In TNBC patients, the 18 mg dose is preferred over a lower dose due to the aggressive phenotype of the disease and poor prognosis. Based on preclinical data, the 18 mg dose is more likely to saturate the AR and may lead to better clinical outcomes than a lower dose without receptor saturation or progesterone receptor inhibition.

The company believes that the 18 mg dose may provide greater efficacy in TNBC without compromising subject safety.

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
- Visual disturbances

These side effects were based on information obtained from 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 serious adverse events (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
- In an ongoing phase 2 study of GTx-024 in ER+/AR+ breast cancer, clinically significant hypercalcemia has been observed that was assessed by the investigators as possibly related to an 18 mg dose of GTx-024.

An AE that appears related to GTx-024 in clinical trials has been a dose-dependent, transient, asymptomatic increase in ALT. However, these increases were modest at doses up to 10 mg per day. Most of the subjects studied to date had ALT levels that remained within normal limits. One subject was discontinued for an ALT > 3 times the ULN. The ALT levels returned to normal with continued exposure to GTx-024 in most cases and, further, in instances when dosing was not continued, levels returned to normal. No significant increases in total bilirubin, gamma glutamyl transferase, alkaline phosphatase, or lactate dehydrogenase (LDH) have been

observed in subjects with elevated ALT levels. Consistent with the effects of other orally administered anabolic agents, GTx-024 causes a dose dependent reduction in high-density lipoprotein (HDL), the clinical significance of which is unknown at this time. The proposed mechanism for reduction in HDL is due to stimulation of reverse cholesterol transport and increased HDL catabolism by hepatic lipase. Reductions in HDL are temporary and typically return to baseline 12 months after treatment initiation[4,5,6,7,8].

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[9,10].

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. Counselling about preventing pregnancy will be provided, if necessary, to study participants.

2.3.2 Potential Benefits

GTx-024 9 mg once daily has been studied in 22 postmenopausal women with metastatic ER+ breast cancer 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% 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. The study is still ongoing with one subject whose disease remains stable beyond 336 days.

3 OBJECTIVES

3.1 Study Objectives

The **primary efficacy objective** of this trial is to estimate the clinical benefit rate (CBR) at 16 weeks (defined as complete response [CR], partial response [PR], or SD) (by RECIST 1.1) of GTx-024 18 mg given PO daily in subjects with TNBC and centrally confirmed AR+ status.

Secondary efficacy objectives:

- Estimate the CBR at 16 weeks (by RECIST 1.1) of GTx-024 18 mg in all subjects enrolled 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 18 mg at 16 weeks
- Estimate the CBR (by RECIST 1.1) of GTx-024 18 mg at 24 weeks
- Estimate the ORR (defined as CR or PR) (by RECIST 1.1) of GTx-024 18 mg at 24 weeks
- Estimate the best overall response rate (BOR) of GTx-024 18 mg
- Estimate the progression free survival (PFS) of subjects receiving GTx-024 18 mg
- Estimate the TTP of subjects receiving GTx-024 18 mg
- Estimate duration of response (time from documentation of tumor response to disease progression or death) of subjects receiving GTx-024 18 mg
- Estimate overall survival (OS)

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 18 mg on serum PSA
- Assess the effect of GTx-024 18 mg on Quality of Life (QoL) as measured by EQ-5D-5L
- Assess the effect of GTx-024 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 study enrollment on outcome
- Describe the effect of GTx-024 18 mg on tumor volumetrics
- Assess the effect of plasma concentrations of GTx-024 and GTx-024 glucuronide on CBR at 16 and 24 weeks

Safety objective:

To describe the safety profile of GTx-024 18 mg PO daily in subjects with TNBC and centrally confirmed AR+ as well as in all subjects enrolled 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 16 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.

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 16 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:

- CB response at 24 weeks
- OR at weeks 16 and 24. OR is defined as attainment of a CR or PR at 16 and 24 weeks, respectively, 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 treatment initiation and tumor progression as measured by RECIST 1.1 or death
- TTP defined as the time elapsed between treatment initiation 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)

- Duration of survival (time from date of first dose of study drug to death or last follow up date with a maximum of 24 months post first dose)

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 weeks 16 and/or 24, PFS, TTP, duration of response)
- Impact of time from diagnosis of metastases to study enrollment on outcome (CB response at weeks 16 and/or 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 weeks 16 and/or 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
- ECG parameters

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 Phase 2 study to assess the efficacy and safety of GTx-024 in female subjects with AR+ TNBC. Subjects will be administered GTx-024 18 mg given PO daily for up to 12 months. Simon's two-stage (optimal) design[1] will be used to assess primary efficacy and will require up to 41 evaluable subjects; i.e., subjects with centrally confirmed AR+ who receive at least one dose of study drug.

In order to obtain these numbers of evaluable subjects, 21 to 55 subjects including over-enrollees, will be enrolled to receive a daily PO dose of GTx-024 18 mg. Fourteen of the aforementioned subjects may be over-enrolled to allow for replacement of subjects to account for lack of centrally confirmed AR+ status, or for the rare subject who is enrolled but does not receive study drug. Forty-one TNBC subjects with centrally confirmed AR+ who receive at least one dose of study medication (evaluable subjects) will be needed for primary analysis purposes, and will be included in the FAS. The trial will test for an unacceptably low CBR of ≤ 5% versus a CBR more consistent with ≥ 20. The first stage will be assessed among the first 21 evaluable subjects. If at least 2/21 subjects achieve CB (defined as CR, PR, or SD) at week 16, the trial will proceed to the second stage of recruitment up to a total of 41 evaluable subjects. Otherwise the trial 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 below.

With the exception of elevated LFTs and hypercalcemia, both of which are further addressed below, subjects 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 7 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.

For ≥ Grade 3 elevations in liver function tests, study drug should be held. A recheck of LFTs should be done within 48 hours. At the discretion of the investigator, study drug may be restarted at the 18mg dose or reduced to a 9mg dose when the LFTs have resolved to Grade 1 or better.

In the event of ≥ Grade 2 hypercalcemia, study drug should be held until hypercalcemia resolves to Grade 1 or better.

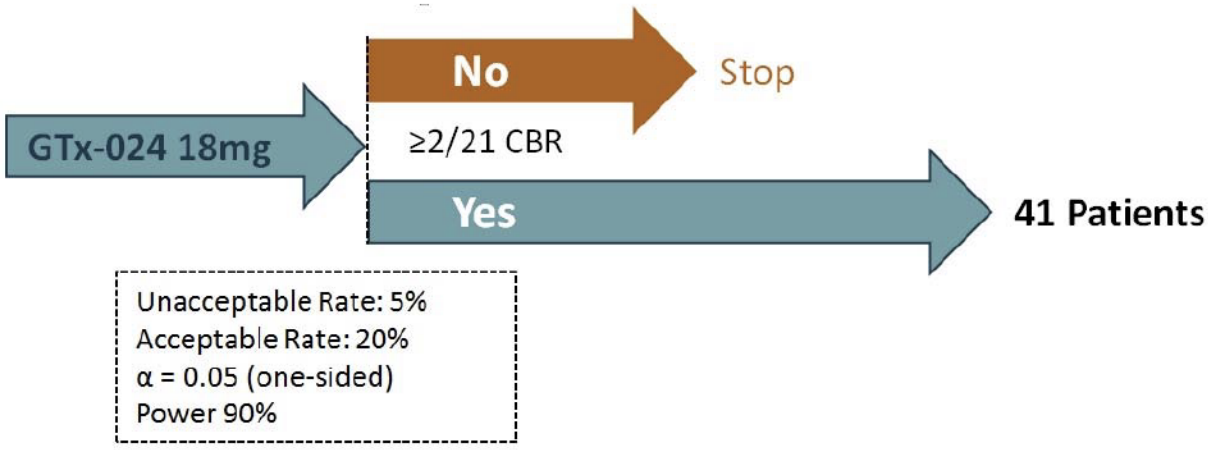
After randomization on Day 1, a safety check involving a comprehensive metabolic panel (Chem 14), including serum calcium and liver function tests, will be performed at Week 2 (±3 days). The week 2 safety check should include a clinic visit. The investigator may repeat these checks at Week 3 (±3 days) if clinically indicated.

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

The subjects who demonstrate CB will be treated for up to 12 months from the date of the first dose of study treatment (as long as they continue to demonstrate CB from the treatment during these 12 months). Subjects who continue to demonstrate a beneficial response from the study treatment at 12 months will be offered to continue in a safety extension study under a separate protocol. All subjects will be followed-up for one month after the last dose of GTx-024 is received, for safety purposes. Additionally, all subjects will be followed for vital status every 60 days post the discontinuation of study treatment for up to 24 months.

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 (optimal) design could cause a pause in enrollment of the trial prior to proceeding to the second stage. For example, if the required 21 evaluable subjects in the first stage of the trial are enrolled and 19 have either terminated the trial or been assessed as not achieving CBR at 16 weeks, it will be necessary to pause enrollment until the remaining two evaluable subjects are fully assessed for CBR, i.e., either withdraw prior to week 16 or have the week 16 RECIST 1.1 assessment.

4.1 Substudies (if applicable)

Not applicable.

4.2 Safety Monitoring Committee (SMC)

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, 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

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

1. Able and willing to give voluntary, written and signed, informed consent;

2. Women ≥ 18 years of age;

3. Women with TNBC who have received at least one but no more than two prior chemotherapy regimens for the treatment of advanced or metastatic TNBC;

4. Confirmation of AR+ (defined as ≥ 10% nuclear AR staining by immunohistochemistry [IHC]) TNBC in either the primary or metastatic lesion, assessed prior to the start of or during the screening period by a local laboratory or by medical history;

5. TNBC confirmed by medical history as: HER2-negative (confirmed by 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); ER negative (confirmed as ER expression less than or equal to 1% positive tumor nuclei); progesterone receptor negative (confirmed as progesterone receptor expression less than or equal to 1% positive tumor nuclei);

6. Availability of paraffin embedded or formalin fixed tumor tissue; OR, a minimum of 10 and up to 20 slides of archived tumor tissue or new biopsy, if archived tissue is unavailable, for central laboratory confirmation of AR status and molecular subtyping. Metastatic tumor tissue is preferred when possible;

7. Subjects must have either measurable disease or bone-only non-measurable disease, according to RECIST 1.1;

8. Subjects with bone metastases should be treated with intravenous bisphosphonates or subcutaneous denosumab (or investigator preferred standard of care) prior to and/or during the trial, unless there is a contraindication or subject intolerance to these therapies. For subjects who are normocalcemic, therapy can be initiated at the time the subject initiates study drug;

9. Eastern Cooperative Oncology Group (ECOG) performance status[3] 0 or 1 at the time of screening and enrollment;

10. Negative serum pregnancy test in women of childbearing potential (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization), no more than 7 days before the first dose of study treatment;

11. For women of childbearing potential who are sexually active, agreement to use a highly effective, non-hormonal form of contraception during and for at least 6 months after completion of study treatment; OR, a fertile male partner willing and able to use effective non-hormonal means of contraception (barrier method of contraception in conjunction with spermicidal jelly, or surgical sterilization) during and for at least 6 months after completion of study treatment;

12. Adequate organ function as shown by:

    - Absolute neutrophil count ≥ 1,000 cells/mm^3
    - Platelet count ≥ 100,000 cells/mm^3
    - Hemoglobin ≥ 9 g/dL
    - Serum aspartate aminotransferase (AST) and ALT ≤ 2.5 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 time (aPTT) < 1.5 × ULN (unless on anticoagulant treatment at screening);

13. Able to swallow capsules;

14. Any toxicity from prior chemotherapy has resolved or is Grade 1 (NCI-CTCAE, Version 4.0).

5.2 Subject Exclusion Criteria

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

1. Life expectancy < 4 months;

2. Subjects with radiographic evidence of central nervous system (CNS) metastases as assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) that are not well controlled (symptomatic or requiring control with continuous corticosteroid therapy [e.g., dexamethasone]). Note: Subjects with CNS metastases are permitted to participate in the study if the CNS metastases are medically well controlled prior to screening (as assessed by the Investigator) after receiving local therapy (irradiation, surgery, etc.);

3. Radiotherapy within 14 days prior to the first dose of study treatment;

4. Have, in the judgment of the Investigator, a clinically significant concurrent illness or psychological, familial, sociological, geographical, or other concomitant condition that would not permit adequate follow-up and compliance with the study protocol;

5. Positive hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection at screening;

6. Positive human immunodeficiency virus (HIV) infection at screening;

7. Prior treatment with any anti-androgens, including but not limited to, enzalutamide and bicalutamide;

8. Major surgery within 28 days of the first dose of study treatment;

9. Be currently taking or have previously taken testosterone, methyltestosterone, oxandrolone (Oxandrin®), oxymetholone, danazol, fluoxymesterone (Halotestin®), testosterone-like agents (such as dehydroepiandrosterone, androstenedione, and other androgenic compounds, including herbals), or anti-androgens;

10. Treatment with any of the following hormone replacement therapies, unless discontinued at least 28 days prior to the first dose of study treatment:

    - Estrogens
    - Megesterol acetate;

11. Treatment with any investigational agent within 28 days before the first dose of study treatment;

12. 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;

13. 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);

14. Current treatment with intravenous bisphosphonate or denosumab with elevated serum calcium corrected for albumin or ionized calcium levels outside institutional normal limits at screening;

15. History of non-compliance to medical regimens;

16. Subjects unwilling to or unable to comply with the protocol procedures as assessed by the Investigator;

17. Concurrent participation in another therapeutic clinical trial.

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

Not applicable; all subjects will receive GTx-024 at 18 mg daily.

5.4.2 Masking Procedures

Treatment will be open label.

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 the Medical Monitor for the following reasons:

- Unable to tolerate study treatment (AE requiring permanent discontinuation of study treatment)
- AEs that require treatment with a prohibited medication or a procedure

- Development of any condition that may pose an additional risk to the subject or PI decision that this is in the best interest of the subject
- Pregnancy
- 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 and from the study 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 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 have TNBC and centrally confirmed AR+ status who are enrolled and receive study drug and go on to withdraw will not be replaced. Over-enrollment: Central laboratory confirmation of AR receptor status will not be available at the time of enrollment for most subjects. Subjects will be enrolled into the study based upon their medical history or locally confirmed TNBC AR+ hormonal status. Subjects who are later found after enrollment not to have centrally confirmed AR+ will be replaced by an over-enrolled subject in order for the correct number of eligible AR+ TNBC subjects to be included in the primary analysis. Subjects who are later found not to have centrally confirmed AR+ may, at the discretion of the Investigator, be maintained on the study based on a local finding of AR+, but these subjects will not be part of the evaluable subjects subset of the FAS. Furthermore, subjects who are enrolled but do not receive treatment will also be replaced by an evaluable over-enrolled subject and will not be part of the FAS. This may result in up to an additional 14 subjects being enrolled.

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 Softgels (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 Softgels 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 baseline, Visit 4 (week 8), Visit 6 (week 16), Visit 8 (if subject continues treatment after week 24), and thereafter (if subject continues treatment every 8 weeks), subjects will be provided with a carton of study drug containing 10 blister packs, equivalent to 10 weeks of dosing. 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 2 blister strips (for 18 mg treatment) 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–77°F), with excursions permitted to 30°C (86°F), protected from moisture.

6.2 Dosage, Preparation, and Administration of Study Intervention/Investigational Product

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.

In the event of a dose reduction, to 9 mg, three (3) GTx-024 3.0 mg Softgels will be taken daily, PO with water at approximately the same time each day, with or without food.

6.3 Modification of Study Investigational Product Dosing for a Subject

With the exception of elevated LFTs and hypercalcemia, both of which are further addressed below, subjects who experience an AE with Grade ≥ 3 intensity (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 7 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.

For ≥ Grade 3 elevations in LFTs, study drug should be held. A recheck of LFTs should be done within 48 hours. At the discretion of the investigator, study drug may be restarted at the 18mg dose or reduced to a 9mg dose when the LFTs have resolved to Grade 1 or better.

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

In the event of ≥ Grade 2 hypercalcemia, study drug should be held until hypercalcemia resolves to Grade 1 or better.

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 each clinic visit during the clinical trial period so that drug accountability can be performed. The dispensing pharmacy is required to count all returned study capsules and record this on the proper eCRF.

All study medication returned by subjects must be accounted for and verified by the 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 duration include:

- Major surgery within 28 days before the first dose of study treatment;
- Testosterone, methyltestosterone, oxandrolone (Oxandrin®), oxymetholone, danazol, fluoxymesterone (Halotestin®), testosterone-like agents (such as dehydroepiandrosterone, androstenedione, and other androgenic compounds, including herbals), 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)
- Any prior or current use of anti-androgens including enzalutamide and bicalutamide;
- Treatment with any of the following hormone replacement therapies within 28 days before the first dose of study treatment:
    - Estrogens
    - Megesterol acetate;
- Treatment with any investigational agent within 28 days before the first dose of study treatment;
- Local palliative radiotherapy or localized radiotherapy for lytic lesions at risk of fracture within 7 days prior to the first dose of study treatment;
- Radiotherapy within 14 days prior to the first dose of study treatment.. Subjects must have recovered from radiotherapy toxicities prior to the first dose of study treatment;
- Any antineoplastic treatment (including, but not limited to chemotherapy);.

- 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 16 weeks will continue on therapy as long as they are still benefitting from the treatment. Treatment may continue for up to 12 months from the date of the first dose of study treatment (as long as they continue to demonstrate CB from the treatment during these 12 months).

Subjects who continue to demonstrate a beneficial response from the study treatment at 12 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

For potential subjects without documented evidence of AR+ status, a Prescreening period is allowed any time prior to the Screening assessment (Visit 1), in order to determine AR status through a local laboratory. Should your institution require consent from the potential subject for prescreening tests, a separate prescreening consent should be obtained. Subjects will not be assigned a study number during the Prescreening period. Once AR status is determined to be positive, the potential subject must sign the full study consent form and may proceed to the Screening Visit (Visit 1).

Screening assessments must occur within 28 days prior to the first dose of study treatment for determination of subject's overall eligibility. Informed consent will be obtained from the subjects before performing 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, 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 (if applicable)
- Blood sampling for specific blood tests: PSA
- Urine analysis
- AE collection (from the moment of ICF signing)
- Radiological evaluation of the breast cancer (as applicable CT/MRI/bone scan). Imaging results will be confirmed by a central imaging facility, 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 baseline visit as possible (if possible within 7 days prior to baseline)
- Review of medical history to confirm the hormonal receptor status of the tumor (HER2, ER, PR)
- AR status will be locally assessed via nuclear AR staining by IHC, only if it is not available in the medical record of the subject. This assessment will be done in a local/regional laboratory and confirmed at a central laboratory

7.2 Baseline

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

- Eligibility criteria checked
- Review of prior/concomitant medications, including previous and current anticancer treatment
- Vital signs (heart rate, respiratory rate, 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
- Urine pregnancy test for premenopausal subjects (will be done at the site with a pregnancy stick test)
- First dose to subject at this visit. Subject will be given a carton box of 10 blister cards 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 at baseline (Visit 2). GTx-024 will be administered for up to 12 months from the first dose of treatment or until disease progression (whichever is sooner), subject's withdrawal of consent, or intolerability. Subjects who benefit from the treatment at week 16 and still benefit from the treatment at week 24 may continue to receive GTx-024 for a total of 12 months from the date of the first dose of study treatment (as long as they still benefit from the treatment during these 12 months). Subjects who continue to demonstrate a beneficial response at 12 months will be offered to continue in a safety extension study under a separate protocol.

After randomization on Day 1, a safety check involving a comprehensive metabolic panel (Chem 14), including serum calcium and liver function tests, will be performed at Week 2 (±3 days). The Week 2 safety check should include a clinic visit. The investigator may repeat these checks at Week 3 (±3 days) if clinically indicated.

During the first 4 months of the treatment phase, the subjects will be asked to come for a visit every 4 weeks (Visits 3, 4, 5, and 6), and then every 8 weeks (Visit 8 and Visits 10–12 as required if still on treatment). Visits 7 and 9 at weeks 20 and 28 will only take place in subjects who have CR or PR at Visit 6 (week 16) or Visit 8 (week 24), respectively (see below).

The following tests and procedures will be performed during Visits 3, 4, 5, 6, and 8 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, only if clinically indicated
- Urine pregnancy test for premenopausal subjects (at the site)
- AE collection
- Subjects will be asked to complete a QoL questionnaire
- GTx-024 drug accountability/dispensation

Radiologic assessments for anti-tumor effect will be done every 8 weeks whilst subjects receive treatment (Visit 4, Visit 6, Visit 8, and thereafter). In addition, if a subject has CR or PR at Visit 6 (week 16) or Visit 8 (Week 24), in compliance with RECIST 1.1 guidelines, a confirmation of the CR or PR should be done 4 weeks later (i.e., Visit 7 and/or Visit 9, as

applicable). The same imaging technique must be used throughout the study in a given subject. Bone scans will be performed at screening and then at weeks 8, 16, and 24 in only those subjects with baseline bone metastases, or if clinically indicated. The central imaging facility will also perform tumor volumetric assessment for the subjects undergoing CT scanning during Visit 6 and Visit 8. Blood sampling for CTC enumeration will be done at the same visits as the radiological assessments during the treatment phase; i.e., every 8 weeks whilst subjects receive treatment (Visits 4, 6, and 8), but not at the confirmation of the CR or PR visits (Visits 7 and 9) or at Visits 10–12.

Dispensing of GTx-024 will be done every 8 weeks: at Visit 4 (week 8), Visit 6 (week 16), Visit 8 (if subject continues treatment after week 24), and thereafter if a subject continues treatment every 8 weeks.

Blood samples for pharmacokinetic assessment will be collected at Visit 3 (week 4), Visit 5 (week 12), Visit 6 (week 16), and Visit 8 (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

The following tests and procedures will be performed during the 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:

- Review of concomitant medications
- Physical examination, including weight and vital signs (heart rate, respiratory rate, 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
- Urine pregnancy test for premenopausal subjects (at the site)
- AE collection
- Radiological evaluation of the breast cancer (as applicable CT/MRI/bone scan). Imaging results will be confirmed by a central imaging facility. The same imaging technique must be used throughout the study in a given subject. The central imaging facility will also perform tumor volumetric assessment for the subjects undergoing CT scanning
- Subjects will be asked to complete a QoL questionnaire

- GTx-024 drug accountability

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, vital signs (heart rate, respiratory rate, temperature, blood pressure in a sitting position)
- ECOG performance status
- Blood sampling for: hematology, biochemistry
- Blood sampling for PSA
- Urine analysis, if clinically indicated
- Urine pregnancy test for premenopausal subjects (at the site)
- AE collection

Subjects who continue to demonstrate a beneficial response from the study treatment at 12 months will be offered to continue in a safety extension study under a separate protocol.

Long Term Follow-Up

All subjects will be followed for vital status. For those subjects that discontinue prior to twelve (12) months of study treatment, vital status will be obtained by chart review or by telephone every 60 days from the date study treatment was discontinued. For subjects that die during the Long Term Follow Up period, the date of death will be collected. Vital status will be followed on all patients for up to 24 months post the discontinuation of study treatment.

7.6 Early Termination Visit

An early termination visit will happen in case of:

- A subject withdrawing from the study at their decision
- 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 Safety Checks and Unscheduled Visits

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

The laboratory results from the safety checks in Weeks 2 and 3 will be recorded on the unscheduled visit eCRF page.

8 STUDY PROCEDURES/EVALUATIONS

Please see 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 (and/or MRI) imaging scans of the brain, chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. For the purposes of this trial, CT scans with intravenous contrast enhancement are the preferred anatomic imaging modality. MRI scans with contrast of the brain, abdomen and pelvis may be used in lieu of CT scans for patients who are unable to receive an intravenous iodine contrast agent; however, MRI exams of the chest are not recommended. In these cases, a non-contrast CT of the chest is recommended to evaluate the lung parenchyma. 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 at weeks 8, 16, and 24 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 for final efficacy outcomes analysis.

Tumor volumetrics will be performed by the assigned central vendor only for subjects who have CT scans at Visits 1, 6, 8, and EOT. Tumor volumetrics will be performed by an independent 3rd party vendor who is masked to individual subject outcomes.

Medical History and Medication History:

The medical history of the subject will be obtained by the PI from the subject's medical record. 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.

Physical Examination:

Physical examination will include measurement of height, weight, 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. AEs will be followed-up to resolution, and while further physical examinations may take place, they will not be mandatory.

The physical examination will include also 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 the 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 enrolling 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.

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 and tablet 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, 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, 6, and 8 during the treatment phase, and at EOT.

INR and aPTT are examined as coagulation assessments. They will be performed at screening, at Visits 3, 4, 5, 6, and 8 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, 6, and 8 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 treatments 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.

HIV, HBV, and HCV screening will be performed at screening for all subjects. If a subject test is positive for HIV, HBV, or HCV, the subject will be considered ineligible for the study according to the Exclusion Criteria. The fact that the subject has been vaccinated should be entered into the subject's Medical History eCRF. Results will not be reported in the eCRF.

Table 1: Clinical Laboratory Tests

Hematology	Serum Chemistry (Chem 14)
• 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 • Calcium • Total globulin • Total protein • Glucose • Chloride • Total Carbon dioxide
Urinalysis	**Additional Tests**
• pH • Specific gravity • Protein* • Glucose • Ketones • Bilirubin • Blood* • Nitrite* • Urobilinogen • Leukocyte esterase*	• HIV test • HBsAg • HCV • Serum lipid panel • Coagulation tests (INR, aPTT) • Serum pregnancy test • Urine pregnancy test (premenopausal subjects) • PSA • AR status of the tumor • 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 4), Visit 5 (week 12), Visit 6 (week 16), and Visit 8 (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 4), 5 (week 12), 6 (week 16), and 8 (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.

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

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

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

All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and captured on the appropriate 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, Version 4.0. For any AE that is not specifically covered in NCI-CTCAE, Version 4.0, the criteria from Table 2 should be used:

Table 2: Description of Grades According to the CTCAE

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

If the intensity changes within a day, the maximum intensity should be recorded. If the intensity changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each change in intensity).

Changes in the intensity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

9.1.3 Drug – Adverse Event Relationship

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 re-challenge

- **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 to 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**

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 either a new SAE Report Form stating that this is a follow-up to the previously reported SAE (giving the date of the original report), or by using a follow-up query form.

If an SAE is not previously documented (new occurrence) in the Investigator's Brochure (IB) and is thought to be related to the relevant Investigational Medicinal Product (IMP), the assigned drug safety group may urgently require further information from the Investigator for Regulatory Authority reporting. The drug safety group may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the regulatory/competent authorities and relevant IRBs/IECs in accordance with Food and Drug Administration (FDA) regulations 21 CFR 312.32, International Conference on Harmonization (ICH) guidelines, and European Clinical Trials Directive 2001/20/EC, or as per national regulatory requirements in participating countries. Adequate documentation must be maintained showing that Regulatory Authorities and IRBs/IECs have been properly notified.

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

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

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

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

All SAEs will be followed until satisfactory resolution as per Section 9.3 Type and Duration of Follow-up of Subjects after Adverse Events.

9.2.2 Regulatory Reporting

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

Additionally, events may occur during a clinical trial which do not fall within the definition of a SUSAR and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. Examples are new events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects such as:

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

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 the study 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 study meet the above hepatotoxicity criteria, or if a total of 5 subjects ever meet these criteria and hepatotoxicity is not attributable to an underlying condition (i.e. liver progression), then the 18 mg dose will be reduced to 9 mg for all subjects; i.e., all subjects that are receiving 18 mg will be reduced to 9 mg and all newly enrolled subjects will receive a 9 mg dose. If any of these criteria are met in a total of 5 subjects following the study wide reduction to the 9 mg dose, the study will be halted (i.e., there will be no dose reduction, only study drug discontinuation).

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 Guidelines 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 details 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. The assumptions for the design are as follows:

- H_0: CBR ≤ 0.05
- H_1: CBR ≥ 0.20
- α = 0.05 (one sided)
- Power = 90%

11.2 Sample Size Considerations

Based on the above assumptions, a sample size of N = 41 TNBC subjects with centrally confirmed AR+ status who received at least one dose of study treatment (evaluable subjects) are needed if the trial continues to completion of the second stage. The trial will proceed to the second stage if at least 2 subjects among the first 21 evaluable subjects achieve CB, defined as SD, PR, or CR as per RECIST 1.1. If the trial proceeds to the second stage, a statistical success that favors further evaluation of GTx-024 18 mg in future trials will require at least 5/41 subjects to achieve CB at week 16, i.e., the null hypothesis of an unacceptably low rate of CB, ≤ 5.0%, can be rejected in favor of the alternative hypothesis that indicates the higher rate, 20%, is more likely. The lower limit of the exact 90% confidence interval at exactly five CBs, 6.1%, exceeds 5.0%[11]. At any time during the first stage, if two subjects achieve CB at week 16, the trial will proceed to the second stage; otherwise, it will be halted for lack of efficacy. If at any time, 5 subjects achieve CB at week 16, the efficacy criteria has been met; however, the trial should proceed to full accrual of 41 evaluable subjects in order to better characterize the CB rate, evaluate secondary endpoints, and describe the safety profile of the drug.

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. This may result in up to 14 additional subjects enrolled (a total of 55 subjects) to account for discordant local/central AR status results and for the rare subject who is enrolled but never received study drug.

11.3 Planned Interim Analyses (if applicable)

The number of clinical benefit responses during Stage I of this Simon's Two-Stage design will determine whether the trial moves forward to Stage II. No interim analyses beyond this determination will be performed, thus no database lock will be necessary.

11.4 Final Analysis Plan

11.4.1 Analysis sets

Full Analysis Set (FAS): All subjects who are enrolled 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 and complete the week 16 RECIST 1.1 evaluation, receive at least 80% of the anticipated 18 mg dose, and have no major protocol deviations.

Safety Analysis Set (SAS): All subjects who are enrolled and receive at least one dose of study drug.

11.4.2 Definition of analysis endpoints; primary, secondary, tertiary, exploratory, and 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 16 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 SD, PR, or CR. The primary assessment is among the evaluable subjects in the FAS at 16 weeks. An evaluable subject who does not have a week 16 assessment for any reason remains in the evaluable subset of the FAS and is considered a failure to achieve CB (SD, PR, or CR).

Secondary efficacy endpoints

- CBR in the FAS at 16 weeks.

The following secondary efficacy endpoints will be assessed among evaluable subjects (if not already listed above), the FAS (if not already listed above), and the PPS:

- CBR at weeks 16 and 24
- ORR (PR or CR assessed by RECIST 1.1 criteria) at weeks 16 and 24.
- 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 PR or CR should be confirmed by a repeat assessment at least 4 weeks later.
- PFS: PFS is defined as the time from treatment initiation until objective tumor progression or death. 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 enrollment.
- TTP: TTP is defined as the time from treatment initiation until objective tumor progression or death due to PD. 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 was known to be alive, they will be censored at the time of enrollment.
- Duration of response: Duration of response, in responders, is defined as the period from the date of initial PR or CR until the date of PD 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.
- Overall Survival: OS is defined as the time from treatment initiation until death or date of last follow up to a maximum of 24 months post treatment initiation. Subjects known to be alive at their last follow up will be censored at that time.

Tertiary efficacy endpoints

The following tertiary efficacy endpoints will be assessed among evaluable subjects and the FAS:

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

- Duration of prior CB: the impact of duration of prior CB on outcome (CB response at weeks 16 and/or 24, PFS, TTP, duration of response).
- Time from diagnosis of metastases to enrollment: the impact of time from diagnosis of metastases to study enrollment on outcome (CB response at weeks 16 and/or 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.
- ECG parameters.

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 16 weeks. At least 2/21 subjects must achieve CB in order for the trial to proceed to the second stage. If the trial proceeds to the second stage, ≥ 5/41 subjects must have CB at 16 weeks to deem the efficacy criteria to have been met. This is the minimum number of successes needed to rule out an unacceptably low, 5%, CB rate (lower limit of the 90% confidence interval). The exact 90% and 95% confidence intervals about the CBR at week 16 will be constructed.

11.4.3.3 Secondary efficacy analysis

- The exact 90% and 95% confidence intervals about the CBR at week 16 among subjects in the FAS will be constructed.

The following secondary efficacy analyses will be performed, if not already done so above, among the evaluable subjects, the FAS, and the PPS:

- The exact 90% and 95% confidence intervals about the CBR at 16 and 24 weeks will be constructed.
- The exact 95% confidence interval about the ORR (PR or CR) will be constructed at weeks 16 and 24.
- The exact 95% confidence interval about the BOR will be constructed at weeks 16 and 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.

- Overall Survival: Median OS 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. Follow up will be up to 24 months post treatment initiation for each subject and subjects alive at that time will be censored.

11.4.3.4 Tertiary efficacy analysis

The following tertiary efficacy analyses apply to the evaluable subjects and 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 enrollment: the impact of time from diagnosis of metastases to study enrollment 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 study enrollment 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 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 weeks 16 and 24 using logistic regression by creating binary

variables for the concentrations by dichotomizing at the median concentration at weeks 16 and 24.

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

Routine safety assessments of AEs, laboratory variables (clinical chemistry, hematology, and urinalysis), physical examinations, vital signs, ECOG performance status, and ECGs 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, Version 4.0.

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 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 (CRO's) standard.

No evaluable subject will have missing data for the primary efficacy analysis because subjects who have the week 16 assessment will be classified as having CB or not, and those who do not have a week 16 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 analyses 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:

- Subject 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
- Investigational product accountability records and drug-related correspondence.

In addition, all regional 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 designee before study initiation. The signed IRB/IEC approval letter must identify the documents approved (i.e., list the Investigator's name, the protocol number and title, the date of the protocol, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit subjects must also be reviewed by the IRB/IEC. Clinical supplies will not be shipped to a site until a signed approval letter from the IRB/IEC has been received and a contractual agreement has been signed by both parties.

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

14.3 Pre-study Documentation

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

- Copy of the signed Investigator Agreement page
- Copy of the IRB/IEC approval letter for protocol and informed consent
- Completed, signed, and dated Form FDA 1572
- Current curricula vitae, licenses, and financial disclosures for the Investigator(s) and sub Investigators listed on the 1572
- Where applicable, list of IRB/IEC committee members and a statement of adherence to GCP

- Copy of approved informed consent document
- Executed clinical trial agreement
- Name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. GTx or its designee must be notified if the central laboratory is changed or if any additional laboratory is to be used
- List of normal laboratory values (i.e., reference ranges and units of measure) for each central laboratory to be used during the study. GTx or its designee must be notified if normal values change

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 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 (or the subject's legal representative).

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.

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

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 or its designee must be notified. An updated Form FDA 1572 must be submitted to GTx 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 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 a 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 no longer need to be retained.

15.6 Protocol Deviations

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

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the CRA 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**	**Baseline**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1** **Day –28 to –1**	**V2** **Day 1**	**Safety review Week 2 (±3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
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	X
Diagnosis and extent of BC	X												
AR status[3]	X												

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (±3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
Physical examination	X			X	X	X	X		X		X	X	X
Height	X												
Weight	X			X	X	X	X		X		X	X	X
Vital signs	X	X[4]		X	X	X	X		X		X	X	X
ECOG performance status	X	X[4]		X	X	X	X		X		X	X	X
Hematology	X	X[4]		X	X	X	X		X		X	X	X
Biochemistry	X	X[4]		X	X	X	X		X		X	X	X
HIV screening	X												
HBV screening[6]	X												
HCV screening	X												

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (±3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
Serum lipid profile		X		X	X	X	X		X		X	X	
Coagulation status	X			X	X	X	X		X		X	X	
Serum hormones		X		X	X	X	X		X		X	X	
PSA	X	X[4]		X	X	X	X		X		X	X	X
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[8]	X	X	

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (±3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
Radiological evaluation: bone scan[9]	X				X		X	X[10]	X	X[10]			
Pharmacokinetic samples[11]		X		X		X	X		X				
ECG	X												
AEs	X	X		X	X	X	X		X		X	X	To be followed up to 28 days post treatment
Serum pregnancy test	X												
Urine pregnancy test[12]		X		X	X	X	X		X		X	X	X

Periods	**Screening** **Day –28 to –1**	**Baseline** **Day 1**	**Safety check**	**Treatment phase[1] (from Baseline to EOT)**								**EOT/ Early termination**	**FU post treatment**
											As required if still on treatment		
Visit number **Week/Day** **Procedure**	**V1**	**V2**	**Safety review Week 2 (±3 days)**	**V3** **Week 4** **Day 28 (± 7 days)**	**V4** **Week 8** **Day 56 (± 7 days)**	**V5** **Week 12** **Day 84 (± 7 days)**	**V6** **Week 16** **Day 112 (± 7 days)**	**V7** **Week 20** **Day 140 (± 7 days)**	**V8** **Week 24** **Day 168 (± 7 days)**	**V9** **Week 28** **Day 196 (± 7 days)**	**V10–V12[2]** **Every 8 weeks (± 7 days)**	**VEOT** **3 days after the last dose of GTx-024**	**VFU**
GTx-024 18 mg dispensing/ administration		X[13]			X		X		X		X		
GTx-024 18 mg accountability				X	X	X	X		X		X	X	
QoL EQ-5D-5L		X		X	X	X	X		X		X	X	
28 (± 2 days) Follow-up after last dose													X
Vital Status Follow- up (every 60 days after last dose)[5]													

[1] Subjects with clinical benefit at 16 weeks will continue on therapy for up to 12 months (as long as they still benefit from the treatment during these 12 months). If so, the subjects will be asked to come for a visit every other month and undergo the assessments for the treatment period.
[2] Visit 10 should occur at Week 32; i.e., 8 weeks after Visit 8 (Week 24).
[3] AR status to be checked via nuclear AR staining by IHC, only if not available in the medical record of the subject. This assessment will be done in a local/regional laboratory. AR status assessed locally (or as per medical record) will be used to determine subject eligibility during a Prescreening or the study screening period. AR status will be confirmed by a central laboratory prior to Visit 2 (Day 1).
[4] These medical procedures and assessments do not have to be repeated if done at screening within 7 days before the first dose of study treatment.
[5] Vital Status Follow-up (every 60 days after last dose) for up to 24 months
[6] HBV screening will be done as HBsAg.
[7] Imaging study (CT, MRI) is recommended to be performed within 7 days prior to the first dose of study treatment. The imaging studies will be assessed by both a local imaging facility and a central reader. Subject eligibility will be based on local reading of the imaging studies. Medical decisions will be based on the local assessments.
At visits V1, V6, V8, and EOT, 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 16 and/or week 24 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 at weeks 8, 16, and 24 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 16 and/or week 24 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 4), 5 (week 12), 6 (week 16), and 8 (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] Urine pregnancy tests will be done at the site with a pregnancy stick test in premenopausal patients. Postmenopausal patients are exempt from monthly urine pregnancy test.
[13] First dose to be given at site during this visit.

[14] A comprehensive metabolic panel (Chem 14), including serum calcium and liver function tests, will be performed at Week 2 (±3 days).

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, HER2 = Human Epidermal Growth Factor Receptor 2, 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[3]	
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