An Expanded/Phase II, Multi-Center, Randomized, Open-Label Study to Evaluate the Safety and Tolerability of Proxalutamide (GT0918) in Subjects with Metastatic Hormone Sensitive Prostate Cancer (mHSPC) and Metastatic Castrate Resistant Prostate Cancer (mCRPC) who Failed Either Abiraterone or Enzalutamide

Protocol Number: GT0918-US-1002 - expanded/phase II

Study Drug: Proxalutamide (GT0918)
IND Number: 124616
Study Sponsor: Suzhou Kintor Pharmaceutical, Inc.
Legal Registered Address:
1011 S. Hamilton Rd.
Chapel Hill. North Carolina.
United States. 27517.

Protocol Version: V 5.0

Confidential and Proprietary

Sponsor Signature Page

Protocol title: An Expanded/Phase II, Multi-Center, Randomized, Open-Label Study to Evaluate the Safety and Tolerability of Proxalutamide (GT0918) in Subjects with Metastatic Hormone Sensitive Prostate Cancer (mHSPC) and Metastatic Castrate Resistant Prostate Cancer (mCRPC) who Failed Either Abiraterone or Enzalutamide

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We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

Sponsor's Authorized Representative & Medical Expert:

_____ _____

(Signature) *Date (DD-MMM-YYYY)*

Xunwei Dong, M.D. Ph.D
Chief Medical Officer

Suzhou Kintor Pharmaceuticals, Inc.

Investigator Agreement

I confirm that I have read and understood this protocol and agree to conduct this study as outlined in the protocol and other information supplied to me. I agree to conduct this study in compliance with Good Clinical Practice (GCP) standards as defined by the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice, the ethical principles of the Declaration of Helsinki, all applicable national, state and local regulations, as well as the requirements of the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and any other institutional requirements.

Principal Investigator:

_____

Signature *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

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SUMMARY OF CHANGES

GT0918-US-1002 Protocol Version 5.0, changes below have been made to respond to questions and comments from investigational sites.

1. To add additional 6 cycles to current treatment duration to extend the treatment duration to 30 cycles, per subject's willing and investigators' discretion.

2. Disease Assessment scans (CT or MRI or bone scan) is added with Cycle 27 D28 and Cycle 30 D28.
3. Complete Physical Exam is added with Cycle 27 D28 and Cycle 30 D28
4. Abbreviated Physical Exam is added with Cycle 26 Day 1, Cycle 27 Day1, Cycle 29 Day 1, Cycle 30 Day 1.
5. 12-lead ECG is added with Cycle 25 Day 1 and Cycle 28 Day 1.
6. Exploratory markers test is added with Cycle 25 Day 1 and Cycle 28 Day 1.

7. Change Kintor Legal address is updated to 1011 S. Hamilton Rd. Chapel Hill. North Carolina, United States. 27517

1 SYNOPSIS (EXPANDED/PHASE II)

Name of Sponsor/Company: Suzhou Kintor Pharmaceutical, Inc.

Name of Investigational Product: Proxalutamide (GT0918)

Title of Study:

An Expanded/Phase II, Multi-Center, Randomized, Open-Label Study to Evaluate the Safety and Tolerability of Proxalutamide (GT0918) in Subjects with Metastatic Hormone Sensitive Prostate Cancer (mHSPC) or Metastatic Castrate Resistant Prostate Cancer (mCRPC) who Failed Either Abiraterone or Enzalutamide

Study period:

Date first subject enrolled: 2Q2019

Phase of development (2nd stage): Expanded/Phase II

Objectives (Expanded/Phase II):

Primary:

- Evaluate the safety and tolerability of GT0918 in subjects with mHSPC or mCRPC who failed either abiraterone or enzalutamide treatment and determine the Recommendation Phase II Dose (RP2D) for other Phase II or III studies.

Secondary:

- To evaluate radiographic progression-free survival (rPFS)
- To evaluate objective response rate
- To evaluate time to radiographic progression
- To evaluate Prostate Surface Antigen (PSA) 50% decline and maximum change at 12 weeks
- To evaluate PSA doubling time (PSA DT)
- To evaluate the time to PSA progression
- To identify exploratory biomarkers to characterize androgen receptor (AR) inhibition and/or down-regulation by GT0918

Study Design (Expanded/Phase II):

This study is an open-label, randomized, expanded/phase II study in subjects with mHSPC or mCRPC who progressed after either abiraterone or enzalutamide treatment. All subjects will be randomized to take 400 mg or 500 mg of GT0918 by oral administration once daily on an empty stomach (2-3 hours after a meal) for initial treatment of 6 months. Randomization of subjects will be stratified by prior therapy (abiraterone or enzalutamide).

Subjects will continue treatment with GT0918 for up to 24 additional cycles (total up to 30 cycles) at their assigned dose on an empty stomach until disease progression, intolerable toxicities/adverse events

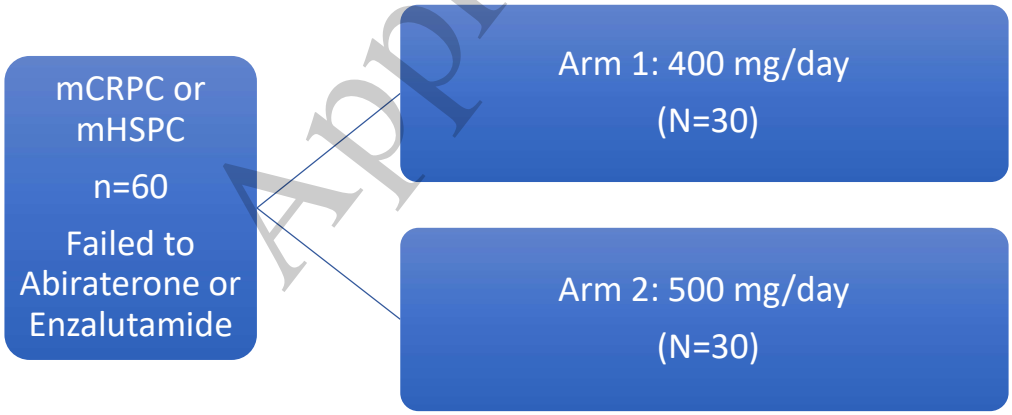
(AEs), or withdrawn consent. Subjects will end the study by completing the end of study (EOS) visit/assessment. The safety follow-up visit will occur 30 days after the last does. Any subject with drug related AE or SAE will be followed until resolution or the subject's condition stabilizes, which comes first. The safety follow-up visit can be performed via phone or in clinic as required.

Disease progression will be assessed by three methods as follow over the duration of the study.

1) Clinical assessment
2) Biochemical (PSA) progression measured every 4 weeks
3) Radiographic progression by CT scan and/or bone progression by radionuclide bone scan every 12 weeks

Progressive disease will be considered on the occurrence of the first assessed progression event. For subjects with PSA progression may continue on study drug until radiographic and/or clinical progression, at the discretion of the Investigator and with the Medical Monitor agreement. A treatment diagram for the study is provided below in **Figure 1**.

FIGURE 1



Biomarker Assessment:

Subjects will have blood drawn for circulating tumor cells (CTC), ct-DNA and ct-RNA obtained at baseline and every 12 weeks during the study, all subjects on study drug over 20 weeks (over 3 time points) will be analyzed for these tumor biomarkers.

Planned number of subjects: 60 (30 subjects per treatment arm) as displayed in **Figure 1**:

ARM1: 400mg /day of GT0918

Group 1: Post enzalutamide (N=15)

Group 2: Post abiraterone (N=15)

ARM 2: 500 mg/day of GT0918

Group 1: Post enzalutamide (N=15)

Group 2: Post abiraterone (N=15)

Study center(s):

10 study centers located in the United States.

Diagnosis and Inclusion/Exclusion criteria (expanded/phase II):

Inclusion criteria:

1. Signed informed consent obtained prior to any study-related procedure being performed.
2. Subjects at least 18 years of age or older at the time of consent.
3. Subjects with histologically confirmed mHSPC or mCRPC who received abiraterone or enzalutamide for the hormonal treatment of 6 month or longer.
4. Subjects with mHSPC are required to have no prior ADT (androgen deprivation therapy) or orchiectomy. For mCRPC, ongoing androgen deprivation therapy with a luteinizing hormone-releasing hormone (LHRH) "super-agonist" or antagonist, or bilateral orchiectomy. Serum testosterone level is < 50 ng/dL (< 0.5 ng/mL, < 1.7 nmol/L) at screening.
5. Metastatic disease documented by computed tomography (CT)/magnetic resonance imaging (MRI) or bone scan.
6. Progressive disease despite hormonal treatment with abiraterone or enzalutamide for over 6 months (but not both). However, if either abiraterone or enzalutamide were used less than 3 months before discontinuation due to toxicity, the subject is eligible. Progressive disease is defined by 1 or more of the following criteria:
    a. Subjects with a rising prostate specific antigen (PSA) value > 2 ng/mL in at least 2 measurements, at least 1 week apart. If the confirmatory PSA value is less than the screening PSA value, then an additional test for the rising PSA is required to document progression.
    b. Subjects with measurable disease, progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria
    c. Subjects with metastatic bone disease, progression defined by 2 or more new lesions in a radionuclide bone scan.
7. ECOG performance status of 0-1
8. Screening blood counts of the following:
    a. Absolute neutrophil count ≥ 1500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin > 9 g/dL (if asymptomatic).
9. Screening chemistry values of the following:

a. Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 2.5 × upper limit of the normal reference range (ULN)
b. Total bilirubin ≤ 2 × ULN
c. Creatinine ≤ 1.5 × ULN
d. Albumin > 2.8 g/dL.

10. At screening, life expectancy of at least 6 months.
11. Subjects whose partners are women of childbearing potential (WOCBP) must use an adequate method of birth control while on study drug and for at least 3 months after discontinuation of study drug.
12. Subject is willing and able to comply with all protocol required visits and assessments.

Exclusion criteria:

1. Discontinuation of enzalutamide or abiraterone less than 3 weeks prior to the start of study medication.
2. Prior chemotherapy and experimental therapy (Poly (ADP-ribose) polymerase (PARP) or checkpoint inhibitor)
3. Ongoing acute treatment-related toxicity associated with a previous therapy greater than grade 1 except for grade 2 alopecia or neuropathy.
4. History of impaired adrenal gland function (e.g., Addison's disease, Cushing's syndrome).
5. Known gastrointestinal disease or condition that affects the absorption of GT0918.
6. History of congestive heart failure New York Heart Association (NYHA) class III or IV or uncontrolled hypertension at screening.
7. History or family history of long QT syndrome, or ECG corrected QT interval equal to and over 500 ms (Common Terminology Criteria for Adverse Events (CTCAE) V 4.03 grade 2) at baseline.
8. History of other malignancy within the previous 3 years, except basal cell or squamous cell carcinoma, or non-muscle invasive bladder cancer.
9. Use of systemic glucocorticoid (e.g., prednisone, dexamethasone) within 14 days prior to the start of study medication. Inhaled or topical steroids are allowed.
10. Co-administration of CYP3A4 ligands that serve as substrates or induce or inhibit the enzyme (See Appendix 4 for the list of medications). If some medication needs to be used for the chronic illness, the medication shall be changed to another one that is not on the list or the dose should be reduced, at the discretion of the Investigator.
11. Prior use of any herbal products known to decrease PSA levels (e.g., PC-SPES or saw palmetto) within 30 days prior to the start of study medication.
12. Major surgery within 30 days prior to the start of study medication.
13. Blood transfusion (including blood products) within 1 week of screening.
14. Serious persistent infection within 14 days prior to the start of study medication.
15. Serious concurrent medical condition including CNS disorders.
16. Previous history of difficulty swallowing capsules or tablets.
17. Known hypersensitivity to GT0918 or its excipients (See Appendix 5 for drug details).

18. Any condition that, in the opinion of the investigator, would impair the subject's ability to comply with study procedures.

Investigational product, dosage and mode of administration:

GT0918 will be provided as 100 mg tablet for oral administration daily. The dose consumption is either 400 or 500 mg, once a day (QD), dependent on randomization.

Reference product, dosage and mode of administration

No reference product will be used.

Duration of study (expanded/phase II):

The part II study will have 3 periods, screening, treatment and post-treatment safety follow up. The screening period is up to 3 weeks. The treatment period includes first 6-cycle treatment and potential additional cycles for eligible subjects up to 24 cycles. After the first 6 cycles of treatment, subjects without progressive disease (PD) may continue GT0918 treatment with the approval of the investigator and sponsor; treatment can continue until a subject experience an intolerable adverse event (AE) or bone or radiographic disease progression, withdraws consent or termination of the study by the sponsor. This approval is required for entering the next 6 cycle treatments (for starting on C7D1, C13D1, C19D1, C25D1). All subjects will have End-of-study visit over 30 days after last dose. A post-treatment safety window of 30 days is allowed for record of any possible delayed study drug-related AEs and SAEs after the last dose of study medication.

Criteria for evaluation (expanded/phase II):

Safety monitoring:

Toxicity reported during the study will be graded according to the CTCAE v4.03. Laboratory Assessments will include PSA, blood chemistry, hematology, lipid profiles, ECGs, and urinalysis.

Safety and tolerability data will be reviewed on an ongoing basis in order to make decisions for dose selection and safety management. The following will be promptly reported to the assigned Medical Monitor from Sponsor:

a. SAEs, within 24 hours
b. AEs resulting in permanent discontinuation from study, regardless of seriousness or relationship to study drug.
c. Treatment **modifications** (i.e., dose discontinuation, temporary interruption, or dose reduction).

Dose modification is allowed for this trial. Subjects may skip or discontinue treatment if they experience at least one of the following adverse events that are considered by the Investigator to be **"possibly", "probably" or "definitely"** related to study drug. Treatment modifications will be made based on the specified criteria:

1) For any subjects experiencing grade 3 or 4 hematologic or biochemical toxicity, study drug will be temporarily interrupted until toxicity resolves to grade 1 or better

2) For any subjects experiencing grade 2 non-hematologic toxicity with significant impact on subject's daily active life, such as asthenic condition (including asthenia and fatigue), hepatoxicity mental impairment and anxiety, study drug will be temporally interrupted until toxicity resolves to grade 1 or better
3) If the Investigator considers that continuing study drug is clinically beneficial for the subjects, the treatment and dose can be resumed. For some subjects if dose reduction is safe and clinically appropriate, a dose range of 25-50% dose reduction from original starting dose can be considered. The dose modification and schedule must be discussed with the medical monitor prior to implementation. Possible dose reductions are proposed as follow.
    i. For dose cohort of 400mg: starting dose can be 200mg or 300mg
    ii. For dose cohort of 500mg: starting dose can be 300mg or 400mg
4) Dose restoration: If any subjects on reduced dose for 2 cycles or more, the subject will have an option for the dose modification, for example, either to remain on the same dose or increase one dose level up or resume initial dose. The dose modification shall be considered based on investigator's clinical judgement for the best interest and care of subject and it must be discussed with medical monitor before implemented and document CRF timely and properly.

d. The Investigator will make critical laboratory safety data available in a timely manner.

Availability of these data will also enable the Sponsor to notify other participating study centers, as well as regulatory authorities, of events occurring during the trial.

Assessment of safety:

Safety will be assessed by AEs, vital signs, 12-lead ECG, pain score, and laboratory tests.

Assessment of efficacy variables:

a. Assessment of PSA: Blood samples will be collected to determine the serum total PSA concentration.
b. Change of PSA from baseline: The proportion of subjects achieving a ≥50% reduction in PSA at 3 months (12 weeks) as compared to baseline (study entry) will be determined.
a. Assessment of soft tissue and bone (RECIST and Prostate Cancer Working Group (PCWG)-2 criteria):
    1) Soft tissue: Chest, abdomen, and pelvic CT or MRI will be performed. Changes in the size of target lesions will be evaluated. The timepoint overall response will be reported.
    2) Bone scan: Radionuclide bone scan will be performed. Number of Bone Lesion, and changes in the number of lesions will be reported.
    3) Skeletal-related events: Severity of skeletal-related event (bone pain, analgesia intake) will be assessed monthly per PCWG2.
b. Performance status: ECOG performance status will be assessed. Changes from baseline will be evaluated

Assessment of exploratory markers: • Circulating tumor cells • ct-DNA/ct-RNA
Statistical methods: **Analysis Populations:** The Safety Analysis Set (SAF) will include all subjects who take at least 1 dose of study medication. Safety analyses will be conducted using the safety population. The Full Analysis Set (FAS) will include all evaluable subjects used as the supportive analysis population for efficacy. The FAS population will be used as the primary analysis population for efficacy. The Per Protocol (PP) Analysis Set will include all FAS subjects with the Week 12 PSA assessment and without major protocol violations.

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotrophic hormone
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate transaminase
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last sample with a quantifiable concentration
BAP	bone alkaline phosphatase
C	clearance
C_{max}	peak plasma concentration
CNS	central nervous system
CR	complete response
CRPC	castration resistant prostate cancer
CRU	clinical research unit
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYPC19	cytochrome P450 C19

Abbreviation	Definition
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EoS	end of study
ET	early termination
FDG-PET	fluorodeoxyglucose positron emission tomography
FDHT-PET	fluorodihydrotestosterone positron emission tomography
FSH	follicle stimulation hormone
GnRH	gonadotropin releasing hormone
ITT	intent-to-treat
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
MED	minimal effective dose
MedDRA	Medical Dictionary for Regulatory Activities
Min	minutes
mRNA	messenger RNA
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

NOAEL	no observed adverse effect level
NYHA	New York Heart Association
PCWG2	Prostate Cancer Working Group 2
PD	progressive disease
PK	pharmacokinetics
PP	per protocol
PR	partial response
PSA	prostate specific antigen
PAP	prostatic acid phosphatase
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
RP2D	recommended Phase II dose
SAE	serious adverse event
SAS	Statistical Analysis Software
SD	stable disease
$t_{½}$	terminal elimination half-life
T_{max}	the time to reach the peak plasma concentration
TSH	thyroid stimulating hormone
TURP	transurethral resection of prostate
λz	terminal elimination rate constant
UA	urine analysis
ULN	upper limit of normal
V_z	volume of distribution
WOCBP	women of childbearing potential

3 INTRODUCTIONS

3.1 Background on Prostate Cancer

Prostate cancer is the most common malignant tumor in men and is the second leading cause of cancer-related deaths in men, second only to lung cancer. Prostate cancer does not have remarkable symptoms at its early stage. Once symptoms are observed, the disease will be often at an advanced stage. Then the cancer progresses rapidly. If it is not treated in a timely manner, the average survival time will be only 3 to 5 years from the date when the symptoms are discovered. Metastasis is very common in subjects with prostate cancer. Approximately 1/3 to 2/3 of subjects have lymph node metastases at their first medical visit, and hematologic metastases are often seen in bone. This disease depends on dihydrotestosterone (DHT) which activates androgen receptor (AR) signaling. Endocrine therapy (including surgery, chemotherapy or anti-androgen deprivation therapy or combined androgen blockade therapy) is a preferred treatment for prostate cancer. This treatment is very effective for the majority of subjects at the initial stage but after a median period of treatment of 14 to 30 months, almost all subjects will gradually develop castration resistant prostate cancer (CRPC) with a median survival of less than 20 months, and urgently need a further treatment.

As for the specific treatment for prostate cancer, surgical castration (radical prostatectomy, transurethral resection of prostate [TURP], and bilateral orchiectomy) and medical castration (luteinizing hormone releasing hormone [LHRH] antagonist and gonadotropin-releasing hormone [GnRH] antagonist) are the preferred means for early treatment, and they can be performed in combination with treatments such as endocrine, immune, differentiation, gene and radiation therapies. Most androgens are from the testes and a lesser amount originate from the adrenal glands; surgical castration can only remove the androgens originating from the testes, and the adrenal glands still secrete a significant amount of steroids, producing androgens and precursors of testosterone that enter prostatic tissues and are then released into the blood. Prostate cancer is highly sensitive to androgen. To achieve the purpose of treatment of prostate cancer, synthesis of androgen must be suppressed to prevent its interaction with AR on the cell surface, thereby blocking the physiological effects of androgen. The usual androgen deprivation therapy (ADT) is mainly focused on the hypothalamic-pituitary-testicular gonadal axis generated by androgen. The drug treatments are: 1) endocrine axis blocking therapy; 2) direct inhibition of androgen synthesis, and 3) androgen receptor inhibitor. For example, estrogen (Diethylstilbestrol, Transdermal estradiol and Conjugated estrogens [Premarin® tablets]) can be used to regulate the hypothalamic-pituitary-gonadal axis to reduce testosterone production; inhibitors produced by adrenal androgen (corticosteroids, ketoconazole and CYPC19 inhibitor abiraterone) reduce testosterone synthesis by inhibiting the relevant enzymes. Androgen receptor (AR) antagonists in combination with anti-androgen drugs are currently the most effective drug

treatment to manage the prostate cancer where castration failed. Nilutamide, flutamide, bicalutamide (trade name Casodex®) and enzalutamide (trade name XTANDI®) all belong to this class of androgen receptor antagonists.

Enzalutamide (Xtandi) has a higher antagonistic activity than bicalutamide in CRPC cells and effectively suppresses the activation, preventing AR transfer from then cytoplasm to the nucleus and from binding to DNA, ultimately achieving significant clinical efficacy for advanced castration-resistant prostate cancer. Enzalutamide has shown long half-life in subjects (3-13 days). When administered once a day, it will lead to serious drug accumulation, resulting in significant side effects, fatigue 34%, headache12%, and some serious neurotoxicity, such as induced epilepsy of 1-2 %.

GT0918 is a new investigational second-generation androgen receptor antagonist with more specificity and activity in inhibiting androgen receptors; in particular, it can maintain a pure role of an antagonist because it does not activate the AR of CRPC cells compared to bicalutamide. As compared to enzalutamide, GT0918 has improvement in target potency as well as drug disposition properties. It is expected to reduce drug accumulation, which may reduce drug exposure in the CNS, therefore avoiding the CNS side effect such as seizure.

In addition, GT0918 demonstrates a dual mechanism of action in cell assays, i.e., highly effective in inhibiting AR as well as exhibiting pharmacological effects of inducing the down-regulation of AR expression; the mechanism that is not seen in bicalutamide and enzalutamide. Considering that over-expression of AR is one of the major mechanisms for generating resistance in castration therapy for prostate cancer, GT0918 could alleviate the resistance of castration therapy for prostate cancer because of the dual mechanism of action thus is expected to be a more effective and less toxic second-generation CRPC drug therapy. GT0918 may provide clinical benefits to some of the CRPC subjects who have developed resistance to enzalutamide or abiraterone treatments.

3.2 Background on GT0918

3.2.1 Nonclinical Studies

Safety pharmacology, single dose and repeated dose toxicity studies, as well as genotoxicity study in pre-clinical *in vitro* and *in vivo* animal models suggests that GT0918 has an acceptable safety profile when projected for human use. The starting dose of 50 mg of GT0918 is selected for the treatment of subjects with metastatic castrate resistant prostate cancer (mCRPC) in the proposed dose ascending MTD study.

The maximum tolerated dose (MTD) was 500 mg/kg in the acute animal study, and the no observed adverse effect level (NOAEL) was 60 mg/kg after GT0918 orally administered to SD rats for 28 days. In Beagle dogs, the MTD and NOAEL were 2000 mg/kg and 50 mg/kg, respectively, in the acute and the 28-day study. The adverse effect noted in rat and dog studies were reversible during the 4-week recovery period. No seizure or convulsion was observed in animals throughout the general toxicology studies including high doses in acute studies as well as repeat dosing studies.

In the 13-week oral gavage toxicity and toxicokinetics study in Sprague Dawley rats with a 4-week recovery, male and female Sprague Dawley rats were given the vehicle control article or GT0918 at a dose level of 20, 45, or 90 mg/kg/day via oral gavage once daily for 13 weeks. No test article-related mortality, clinical observations, ophthalmic findings, food consumption, or hematology, coagulation, and urinalysis changes were noted. Low body weight was observed during the dosing phase in animals given ≥45 mg/kg/day, and recovered during the recovery phase. Minor clinical chemistry changes (e.g., increased cholesterol, phosphorus, and globulin and decreased albumin and chloride) were observed during the dosing phase and recovered in the recovery phase. Large adrenal glands (females ≥45 mg/kg/day) and small prostates (males 90 mg/kg/day) were observed during the dosing phase and recovered in the recovery phase. Microscopic findings, including those in the adrenal cortex (≥20 mg/kg/day), liver (≥45 mg/kg/day), seminal vesicles and prostate (atrophy, noted males ≥45 mg/kg/day), and mammary gland (males ≥20 mg/kg/day), were observed in the dosing phase. These microscopic findings had partially to completely resolved after the 4-week recovery phase. Since the findings were not severe, they were not considered as adverse. Based on these findings, the no observed adverse effect level (NOAEL) and the highest none-severely toxic dose (HNSTD) were 90 mg/kg/day. The corresponded GT0918 AUC_{0-t} values in males and females on Day 91 were 159,000 and 495,000 h*ng/mL, respectively.

In the 13-week oral gavage toxicity and toxicokinetics study in Beagle dogs with a 4-week recovery, male and female dogs were given GT0918 at a dose level of 5, 15, and 50/30 mg/kg/day via oral capsule once daily for up to 13-weeks, which resulted in overt toxicity at the dose level of 50/30 mg/kg/day. GT0918 related findings included clinical observations (hypoactivity, thin appearance, hunched posture, and et al.) and decreased body weight and food consumption in animals given >15 mg/kg/day. These findings were generally mild in animals given 15 mg/kg/day and showed evidence of reversibility during the recovery phase. Clinical chemistry and hematology changes were minor and reversible. GT0918 related increased liver weights and correlated hepatocellular hypertrophies were considered toxicologically significant. GT0918 related organ weight decreases and microscopic findings in male reproductive organs were consistent with the expected pharmacologic effects, and they were reversible, although the finding in prostate was considered adverse at 15 mg/kg/day. Due to the severe clinical

observations and marked decreases in body weight and food consumption in animals given 50/30 mg/kg/day, effects at this dose were considered adverse; animals generally tolerated a dose of 30 mg/kg/day up to 8 weeks when they were supplemented with canned dog food. Despite marked atrophy in the prostate of one male given 15 mg/kg/day, the no observed adverse effect level (NOAEL) was 15 mg/kg/day. The highest none-severely toxic dose (HNSTD) was 15 mg/kg/day for both males and females, which corresponds to mean C_{max} and AUC values for GT0918 of 11,600 ng/mL and 156,000 ng*hr/mL, respectively, in males and 16,300 ng/mL and 218,000 ng*hr/mL, respectively, in females on Day 90 of the dosing phase; mean C_{max} and AUC values for GT0955 were 5250 ng/mL and 94,200 ng*hr/mL, respectively, in males and 8320 ng/mL and 135,000 ng*hr/mL, respectively, in females on Day 90 of the dosing phase.

A battery of safety pharmacology studies under the U.S. GLP guidelines including behavioral effects in Sprague Dawley rats using the functional observational battery and a cardiovascular and respiratory safety pharmacology study in conscious Beagle dogs were conducted. GT0918 inhibited hERG-mediated potassium current in CHO cells with an IC_{50} much higher than 10 μM. This strongly suggests that the potential for QT prolongation at clinically relevant concentrations of GT0918 is low. In addition, no evidence of QTc prolongation was observed in the cardiovascular and respiratory safety pharmacology study in conscious Beagle dogs after oral administration at doses up to 50 mg/kg.

No significant changes in CNS function were observed with GT0918 in rats at doses up to 180 mg/kg. GT0918 did not produce adverse effects on cardiovascular functions, respiratory functions and the body temperature in conscious beagle dogs after oral administration at doses up to 50 mg/kg.

In addition, no evidence for activity of GT0918 was identified using *in vitro* Ames test, chromosomal aberration assay in Chinese hamster lung fibroblast with or without S9 metabolic activation system and *in vivo* micronucleus study using bone marrow in ICR mice.

The above-mentioned 13-week subchronic toxicity studies in SD rats and Beagle dogs, safety pharmacology studies as well as genotoxicity studies conducted under the U.S. GLP regulations will support the IND opening of GT0918 in U.S.

Altogether, these findings with high doses of GT0918 in animal were fairly benign. When choosing a dose for start of clinical studies in humans, algorithms were used to choose a lower dose at which these findings would be absent or minimized. Based upon the preclinical findings, same class drugs, the following common adverse events may be encountered during clinical trial: hot flush, headache, nausea, vomiting, dizziness, loss of appetite, diarrhea, and fatigue. Other reported adverse events from same class drugs will be monitored including not limited to back pain, constipation, hypertension, pain in extremities, arthralgia, and some rare cases of seizures.

3.2.2 Clinical Studies

In the Phase I/II trial of GT0918 US 1001, part 1 study of dose escalation, 40 subjects have been treated with GT0918 at seven dose levels: daily 50 mg (n = 3), 100 mg (n = 6), 200 mg (n=6), 300 mg (n=7), 400 mg (n=7), 500 mg (n=6), 600 mg (n=5). All subjects progressed on multiple lines of therapies including, but not limited to, bicalutamide, abiraterone, enzalutamide, docetaxel, cabazitaxel, radium 223, sipuleucel T and pembrolizumab. No DLT has been identified in the planned dose escalation cohorts thus MTD is not defined. GT0918 has been shown generally well tolerated and it has some CTCAE grade 1 and 2 AEs reported, such as fatigue, lethargy, nausea, loss of appetite, anemia, hypercholesterolemia, hyperglycemia, hyperglyceridemia, hot flush, constipation, etc. Three events of 2 grade 3 fatigue, 1 grade 3 anemia, and one event of grade 4 elevated creatine kinase (CK) were reported. Stable disease by imaging scans at 20 weeks by dose group were; 1/50 mg, 1/100mg, 3/400mg, 1/500mg. PSA decreases were also seen among subjects with increasing dosing for a period of time. This is the part II study to further evaluate the safety and tolerability of 2 dosages: 400 and 500 mg in selected subjects with mCRPC progressed on prior treatment either abiraterone or enzalutamide. Early phase 1 study performed in China included 19 subjects who were treated with GT0918 in various doses 50 mg, 100 mg, 200 mg, 300 mg and 400 mg over 3 months. Mild to moderated drug-related AEs were reported, such as hypercholesterolemia, hyperglycemia, hyperglyceridemia, peripheral edema, hot flash, fatigue, nausea, constipation.

Therefore three more clinical trials (China Phase 1 Bioavailability Study, GT0918-CN-1001, GT0918-CN-1002) regarding to GT0918 bioavailability in healthy subject and as a monotherapy drug in mCRPC subjects have finished in China and five on-going GT0918 clinical trials in mCRPC and breast cancer subjects. More information regarding to these trials can be found in investigator brochure.

3.2.3 Anticipated Clinical Risks/Benefits

GT0918, a new investigational second generation of androgen receptor antagonist, has been orally administrated daily to over one hundred subjects with mCRPC or metastatic triple negative breast cancer (mTNBC) with androgen receptor (AR) positive. It has been shown that GT0918 was generally well-tolerated with some CTCAE grade 1 and 2 AEs, such as fatigue, lethargy, nausea, loss of appetite, anemia, hypercholesterolemia, hyperglycemia, hyperglyceridemia, hot flush, constipation, hepatoxicity etc. Two events of grade 3 fatigue and one event of grade 4 elevated creatine kinase (CK) were reported. All the participating subjects who had progressed disease after the prior standard and experimental therapies, including abiraterone and enzalutamide, showed promising clinical responses and disease control rate with the study drug GT0918. The ratio of risks versus benefits supports further clinical evaluations of

selected 2 doses of 400 mg and 500 mg in mCRPC and mHSPC subjects whose disease progressed after abiraterone or enzalutamide.

For hepatoxicity of GT0918 monotherapy in mCRPC subjects, increased ALT and increased AST are the most common AEs in both China and the US. The severity is mostly grade 1-2. Among 2.0% (19/958) of the subjects reported grade 3 and 4 hepatoxicity AEs that believed to be study drug related. 9 subjects developed drug induced liver injury and 2 subjects experienced hepatic failure (as of 11/18/2020).

3.3 Rationale

Suzhou Kintor Pharmaceutical, Inc. is developing GT0918, a new investigational androgen receptor (AR) antagonist for the treatment of castration resistant prostate cancer (CRPC) and metastatic hormone sensitive cancer (mHSPC). The anticipated dosing regimen is once daily for oral administration. The proposed dosage form for clinical research is 100 mg per tablet.

GT0918 is a new investigational second generation of androgen receptor antagonist with more specificity and activities in inhibiting androgen receptors; in particular, it can maintain a pure role of an antagonist because it does not activate AR of CRPC cells compared to bicalutamide. As compared to enzalutamide, GT0918 has improvement in target potency as well as drug disposition properties. It is expected to reduce drug accumulation, which may reduce drug exposure in the CNS, therefore avoiding the CNS side effects of enzalutamide such as seizure, thus improving the safety profile.

In addition, GT0918 demonstrates a dual mechanism of action in cell assays, i.e., highly effective in inhibiting AR as well as other pharmacological effects such as down-regulation of AR expression; a mechanism that is not seen in bicalutamide or enzalutamide. Considering that over-expression of AR is one of the major mechanisms for generating resistance in castration therapy for prostate cancer, GT0918 could alleviate resistance of castration therapy for prostate cancer as result from the dual mechanism of action thus is expected to be a more effective and less toxic second-generation CRPC drug therapy. GT0918 may provide clinical benefits to some of the subjects who have developed resistance to enzalutamide or abiraterone treatments. These properties make GT0918 an ideal candidate suitable for testing in subjects with metastatic hormonal sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).

In the Phase I/II study, GT0918−US−1001, part I study of dose escalation, 40 subjects have been treated with GT0918 at seven dose levels (detail see above 3.2.2), who progressed on multiple lines of therapies including abiraterone and enzalutamide. GT0918 has been generally well-tolerated. Early phase I study performed in China included 19 subjects who were treated with

GT0918 in various doses 50 mg, 100 mg, 200 mg, 300 mg and 400 mg over 3 months. Mild to moderated drug-related AEs were reported, such as hypercholesterolemia, hyperglycemia, hyperglyceridemia, peripheral edema, hot flush, fatigue, nausea, constipation, hepatoxicity. Based on clinical outcomes from both phase I studies, this expanded/phase II is recommended to further evaluate the safety and tolerability of GT0918 at 2 dosages: 400 mg and 500 mg in eligible subjects with mCRPC and mHSPC.

4 STUDY OBJECTIVES (EXPANDED/PHASE II)

4.1 Primary Objective

- To evaluate the safety and tolerability of GT0918 in subjects with mHSPC or mCRPC who failed either abiraterone or enzalutamide treatment, and to determine the RP2D for Ph III and/or other confirming studies

4.2 Secondary Objectives

- To evaluate radiographic progression-free survival (rPFS)
- To evaluate objective response rate
- To evaluate time to radiographic progression
- To evaluate PSA 50% decline and maximum change at 12 weeks
- To evaluate PSA doubling time (PSA DT)
- To evaluate the time to PSA progression
- To identify exploratory biomarkers to characterize androgen receptor (AR) inhibition and/or down-regulation by GT0918

5 STUDY ENDPOINTS

5.1 Primary Endpoint

- To select the recommended Phase II dose (RP2D) for future clinical trials and/or other confirmatory studies based on safety, tolerability and dose exposure

5.2 Secondary Endpoints

- To evaluate safety and tolerability of GT0918 assessed by AEs, SAEs, vital signs, ECG, physical exam, and laboratory safety assessments of 400 mg daily vs. 500 mg daily over 6 months or longer treatment.
- To evaluate proportion of subjects with a $\geq$ 50% PSA suppression or increased PSA doubling time at 12 weeks and 24 weeks
- CT/MRI and bone scans will be done at 12-week intervals to determine time to progression, and percentage of radiographic disease progression at 6 and 12 months
- Exploratory markers include circulating tumor cells, cell free circulating tumor DNA (ct-DNA)/RNA (ct-RNA), etc.

6 INVESTIGATIONAL PLANS (EXPANDED/PHASE II)

6.1 Description of Overall Study Design and Plan

This expanded/Phase II, open-label, randomized, and multi-center clinical study is designed to evaluate the safety, tolerability and efficacy of GT0918, an orally administered AR antagonist, in mHSPC or mCRPC subjects who failed prior treatment of either abiraterone or enzalutamide. All subjects will be randomized to either take 400 mg or 500 mg for daily administration as recommended by the phase I clinical data. Each arm will be 30 subjects. Subjects will have initial treatment up to 6 cycles with an option to continue up to additional 24 cycles as long as there is no progressive disease, no intolerable adverse event, no radiographic disease progression, no consent withdrawn by the subject or no termination of the study by the sponsor.

6.2 Discussion of Study Design

GT0918 is an oral androgen receptor antagonist with superior characteristics compared to currently marketed AR antagonists based on both preclinical and clinical data.

Based on clinical experience and outcomes from phase 1 (part I) dose escalation of GT0918, it is recommended for 400 mg or 500 mg oral administration daily for the first initial treatment up to 6 cycles. Dose reduction is allowed for subjects (see Section 8.6.3) who experiences any study drug related intolerable toxicities. Study drug GT0918 is suggested to be taken on an empty stomach. If dosing before meal time, it is recommended to wait 1 hour before eating. If dosing after meals, it is recommended to wait 2 hours before taking the study drug.

By the end of 6 cycles of initial treatment, subjects will have an end-of-6-cycles assessment to be determined for further treatment (Section 9.2.2.) Eligible subjects (without PD) have the option to be treated for additional up to 24 cycles at their assigned dose level until PD, intolerable toxicity or as investigator's discretion (Section 9.2.3). At the end of 12, 18 and 24 cycles, assessments will be performed to determine if the subjects will move into the next 6 cycle treatment.

All subjects on study drug of GT0918 are required to perform End-of-Study (EoS) assessment before termination (Section 9.2.4). A post-treatment safety window of 30 days is allowed for any possible delayed study drug-related AEs and SAEs after the last dose of study medication or end-of-study visit which ever occur later. See schedule of assessments (Appendix 1)

Duration of Study (expanded/phase II)

This Phase II study is an open-label, randomized, multi-center study in mHSPC or mCRPC subjects who progressed on prior treatment with either abiraterone or enzalutamide.

The study has 2 periods, a 3-week Screening Period, a up to 6 cycles Treatment Period (+ option of continued treatment, see above). The study will be conducted at 10 centers in the United States.

7 SELECTION AND WITHDRAWAL OF SUBJECTS (Expanded/Phase II)

7.1 Inclusion Criteria

1. Signed informed consent obtained prior to any study-related procedure being performed.
2. Subjects at least 18 years of age or older at the time of consent.
3. Subjects with histologically confirmed mHSPC or mCRPC who received abiraterone or enzalutamide for the hormonal treatment of 6 months or longer.
4. Subjects with mHSPC are required to have no prior ADT or orchiectomy. For mCRPC, ongoing androgen deprivation therapy with a luteinizing hormone-releasing hormone (LHRH) "super-agonist" or antagonist, or bilateral orchiectomy. Serum testosterone level is < 50 ng/dL (< 0.5 ng/mL, < 1.7 nmol/L) at screening.
5. Metastatic disease documented by computed tomography (CT)/magnetic resonance imaging (MRI) or bone scan.
6. Progressive disease despite hormonal treatment with abiraterone or enzalutamide, but <u>not</u> both. However, if either of these 2 drugs was used less than 3 months before discontinuation due to toxicity, the subject is eligible. Progressive disease is defined by 1 or more of the following criteria:

a. Subjects with a rising prostate specific antigen (PSA) value > 2 ng/mL in at least 2 measurements, at least 1 week apart. If the confirmatory PSA value is less than the screening PSA value, then an additional test for the rising PSA is required to document progression.
b. Subjects with measurable disease, progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria
c. Subjects with metastatic bone disease, progression defined by 2 or more new lesions in a radionuclide bone scan.

7. ECOG performance status of 0-1
8. Screening blood counts of the following:
    a. Absolute neutrophil count ≥ 1500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin > 9 g/dL (if asymptomatic).
9. Screening chemistry values of the following:
    a. Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 2.5 × upper limit of the normal reference range (ULN)
    b. Total bilirubin ≤ 2 × ULN
    c. Creatinine ≤ 1.5 × ULN
    d. Albumin > 2.8 g/dL.
10. At screening, life expectancy of at least 6 months.
11. Subjects whose partners are women of childbearing potential (WOCBP) must use an adequate method of birth control while on study drug and for at least 3 months after discontinuation of study drug.
12. Subject is willing and able to comply with all protocol required visits and assessments

7.2 Exclusion Criteria

1. Discontinuation of enzalutamide or abiraterone less than 3 weeks prior to the start of study medication.
2. Prior chemotherapy and experimental therapy (PARP or checkpoint inhibitor).
3. Ongoing acute treatment-related toxicity associated with a previous therapy greater than grade 1 except for grade 2 alopecia or neuropathy.
4. History of impaired adrenal gland function (e.g., Addison's disease, Cushing's syndrome).
5. Known gastrointestinal disease or condition that affects the absorption of GT0918.
6. History of congestive heart failure New York Heart Association (NYHA) class III or IV or uncontrolled hypertension at screening.

7. History or family history of long QT syndrome, or ECG corrected QT interval equal to and over 500 ms (CTCAE grade 2) at baseline.
8. History of other malignancy within the previous 3 years, except basal cell or squamous cell carcinoma, or non-muscle invasive bladder cancer.
9. Use of systemic glucocorticoid (e.g., prednisone, dexamethasone) within 14 days prior to the start of study medication. Inhaled or topical steroids are allowed.
10. Co-administration of CYP3A4 ligands that serve as substrates or induce or inhibit the enzyme. (See Appendix 4 of list of medications) If such medication needs to be used for the chronic illness, the medication shall be changed to another one that is not on the list or the dose should be reduced, at the discretion of the Investigator.
11. Prior use of any herbal products known to decrease PSA levels (e.g., PC-SPES or saw palmetto) within 30 days prior to the start of study medication.
12. Major surgery within 30 days prior to the start of study medication.
13. Blood transfusion (including blood products) within 1 week of screening.
14. Serious persistent infection within 14 days prior to the start of study medication.
15. Serious concurrent medical condition including CNS disorders.
16. Previous history of difficulty swallowing capsules.
17. Known hypersensitivity to GT0918 or its excipients (See Appendix 5 for drug details).
18. Any condition that, in the opinion of the investigator, would impair the subject's ability to comply with study procedures

7.3 Withdrawal, Removal, and Replacement of Subjects

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following reasons. All sites are required to inform project team, Medical Monitor or/and sponsor and discuss possible alternatives in order to keep high quality of study data. No replacement of subjects in Phase II study.

1) Progressive disease

2) Unacceptable toxicity or AE

3) Subject withdrawal of consent: At any time, a subject's participation in the study may terminate at his request or on the basis of the Investigator's clinical judgment. The reason for subject withdrawal will be noted on the case report form (eCRF).

4) Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study.

5) General or specific changes in the subject's condition that renders him ineligible for further treatment according to the inclusion/exclusion criteria.

6) Protocol deviation: The subject's findings or conduct failed to meet the protocol entry criteria or the subject failed to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). The deviation necessitated premature termination from the study.

7) Lost to follow-up: The subject stopped coming for visits, and study personnel were unable to contact the subject after at least 3 documented attempts (including certified letter) to contact the subject.

8) This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her site for any reason including safety or low enrollment.

9) There is no subject replacement in this phase II study.

7.4 Follow-Up for Drug Discontinuation/Subject Withdrawal from Study

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the project team and sponsor and discuss possible alternatives in order to keep high quality of study data. The date and the reason for study discontinuation must be recorded on the eCRF. In the event where a subject discontinues prematurely from the study due to a study drug-related AE or SAE, the AE or SAE will be followed until it is resolved (returns to normal or baseline values) or stabilizes. Office visits are recommended for these subjects until it is judged by the investigator to be no longer necessitated.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

8 TREATMENTS

8.1 Details of Study Medication

GT0918 is an androgen receptor antagonist (MW 517.5 g/mol). The dosage form for clinical research is a 100 mg tablet weighing 320 mg per tablet. The 100 mg tablet is circular in shape with 10 mm in diameter. The color is light pinky with PRO print on pills. The drug product tablets are packaged in PTP aluminum and PVC blister foils. These packaging materials are in compliance with 21CFR 174-186 – Indirect Food Additive Regulations.

The recommended storage conditions for GT0918 tablets are room temperature, with a shelf-life of 2 years. All drug supplies will be provided by the Sponsor.

8.2 Dosing Schedule (expanded/phase II)

In expanded/Phase II, all subjects will be randomized into 2 groups to take either 400 or 500mg oral GT0918 once a day for 28 days each cycle for initial treatment of 6 cycles. At the end of 6/12/18/24 cycles of GT0918 treatment, subjects without progressive disease (PD) may continue study drug GT0918 treatment with the approval of the investigator, medical monitor and sponsor; treatment can continue until a subject experience an intolerable adverse event (AE) or experiences disease progression, withdraws consent or until termination of the study by the sponsor. All subject's disease condition will be re-evaluated every 3 cycles (84 days $\pm$ 7) in order to qualify for additional treatment. If any subject shows mix response (for example, only PSA raising or mix response on imaging scan, or lesion increasing in size without PSA raising, or no clinical progression), treatment can be continued for additional 4-6 weeks and then another PSA or tumor assessment can be scheduled to confirm if disease progression is determined. In case PD is confirmed that will conclude with an end-of-study visit.

All subjects will have safety review at the end of every cycle conducted by participating principal investigators (PIs) and medical monitor. In addition, the medical monitor can prompt a safety review at any time.

Toxicity reported during the study will be graded according to the CTCAE (Common Terminology Criteria for Adverse Events) v4.03. Laboratory Assessments will include blood chemistry, hematology, ECGs, and urinalysis.

8.3 Study Treatment Assignment

Subjects will be randomized between the 2 treatment arms.

8.4 Blinding

NOT APPLICABLE

8.5 Treatment Accountability and Compliance

The investigation site will maintain records of study drug (investigational product) delivered to the study site; the inventory at the site; the distribution to and use by each subject; and the return of study drug to the Sponsor for storage and/or disposal. These records should include dates, quantities, batch/blister card/pouch/serial numbers, expiration dates, in-clinic temperature log(s), and unique code numbers assigned to the study drug and study subjects.

At each visit after initiation of treatment, site staff will record compliance of subjects with their assigned regimen. Subjects will be instructed to bring their study drug pouches containing unused/partially used/empty blister cards back for inspection at each study visit. Subjects are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug on schedule and maintaining the prescribed interval between doses.

Investigators will maintain records that document adequately that the subjects were provided with the correct study drug kits and will reconcile the products received from the drug dispensing center. Study drug will not be returned to the Sponsor or destroyed at the clinical site until accountability has been fully determined.

Medication containers must be returned at each visit, as compliance will be assessed by tablet counts. Noncompliance is defined as taking less than 80% or more than 120% of study drug during any outpatient evaluation period (visit to visit). Discontinuation for noncompliance is at the investigator's discretion and is to be noted on the eCRF.

8.6 Prior and Concomitant Illnesses and Medications

Investigators should document all prior significant illnesses that the subject has experienced within 5 years prior to screening. Medical histories with ongoing or worsening condition before 5 years prior to screening may be documented per investigator's discretion. Additional illnesses present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF.

8.6.1 Permitted Treatment

- Full supportive care is to be administered per normal or routine practice at the study center. Concomitant anti-cancer therapy is not permitted. Palliative and supportive care for disease-related symptoms will be allowed to subjects in this study (e.g. bisphosphonates). However, subjects requiring palliative radiation anti-cancer therapy will be removed from the study.

- Subjects are required to continue the LHRH super-agonists/antagonists (if currently receiving this therapy prior to Cycle 1, Day 1) therapy unless having undergone bilateral orchiectomy.
- Standard therapies for concurrent medical conditions, such as if the subject is taking a regimen for pain control under physician supervision.
- Treatment for nausea, vomiting, and diarrhea, should they occur is allowed, using standard agents per institute's standard of practice. Tylenol and over the counter NSAIDs are also allowed.
- Subjects may receive antibiotics for infections that might occur

8.6.2 Prohibited Treatment

- Glucocorticoids and herbs known to alter PSA levels (saw palmetto or PC-SPES)
- Any concurrent chemotherapy, radiotherapy, hormonal therapy (AR antagonists.), or immunotherapy
- Inducers or inhibitors of CYP3A4, or sensitive CYP3A substrates (detail see appendix 4)
- Other investigational agents

8.6.3 Dose modification and missing dose

Treatment modifications will be made based on specified safety criteria. Subjects may skip or discontinue treatment with GT0918 if they experience at least one adverse event, (noted below), following their dose of GT0918, and are considered by the Investigator to be **"possibly", "probably" or "definitely" related to study drug.** Treatment modifications must be reported to the project team and discussed with the assigned medical monitor.

1) For any subjects experiencing grade 3 or 4 hematologic and/or biochemical toxicity, study drug will be temporarily interrupted until toxicity resolves to grade 1 or better
2) For any subjects experiencing grade 2 non-hematologic toxicity with significant impact on subject's daily active life, such as asthenic condition (including asthenia and fatigue), hepatoxicity, mental impairment and anxiety, study drug will be temporarily interrupted until toxicity resolves to grade 1 or better
3) If the Investigator considers that continuing study drug is clinically beneficial for the subjects, the treatment and dose can be resumed. For some subjects if dose reduction is safe and clinically appropriate, a dose range of 25-50% dose reduction from original starting dose can be considered. The dose modification and schedule must be

discussed prior to implementation with the assigned medical monitor. Possible dose reductions are proposed as follow.

i. For dose cohort of 400mg: starting dose can be 200mg or 300mg
ii. For dose cohort of 500mg: starting dose can be 300mg or 400mg

Dose restoration: If any subjects on reduced dose for 2 cycles or more, the subject will have an option for the dose modification, for example, either to remain on the same dose or increase one dose level up or resume initial dose. The dose modification shall be considered based on investigator's clinical judgement for the best interest and care of subject and it must be discussed with medical monitor before implemented and document CRF timely and properly.

The subject may discontinue study drug for up to 5 consecutive days without being discontinued for noncompliance, which is at the investigator's discretion and is to be noted on the eCRF.

Study drug GT0918 is administrated orally once per day on empty stomach at least one hour before or 2 hours after a meal. Subjects are recommended to take GT0918 on the same time of the day during entire treatment. In case there is accidentally a missing dose of study drug on usual dosing time, the subject may take the drug as soon as possible within 8 hours. If the drug cannot be taken within 8 hours of the scheduled dosing time, the subject should omit the dosing on that day and report missing dose in CRF. However, a subject is not allowed to have "missing doses" in consecutive days unless he has intolerable toxicities and is requested by investigator for study drug interruption.

9 STUDY PROCEDURES

The Schedule of Assessments (Appendix 1) outlines the timing of procedures, and assessments to be performed throughout the study.

9.1 Subject Informed Consent

Prior to performing any study-related procedures, the Investigator (or his/her designated staff member) will obtain signed written informed consent from the subject.

9.2 Expanded/Phase II Study Visits

9.2.1 Screening Visit

Screening Visit (days -21 to -1) will occur within 3 weeks prior to Day 1. Re-screening is allowed for some special cases where clinical reassessments are required and approved by medical monitor. Assessments performed as part of standard of care and obtained prior to

informed consent but within 28-days of enrollment may be used in some cases to satisfy the screening criteria. The following assessments and tests will be performed:

- Informed consent
- Inclusion/Exclusion Criteria
- Demographics, Medical and Surgical History
- Schedule CT or MRI, or/and bone scan preferably within -7 days of Day 1 of treatment

  OR

  Document/Assess Disease Status (Obtain CT or MRI or/and bone scan that may be performed as part of standard care within 6 weeks prior to Day 1 to confirm screening requirements)
- Vital Signs, including Height and Body Surface Area (BSA) (Screening only)
- Complete Physical Exam
- ECOG performance status
- Laboratory Tests (fasting where applicable): hematology, PT/PTT/INR, chemistry including electrolytes, urinalysis, lipid profile and blood glucose, PSA, LDH, and testosterone
- 12 lead ECG
- Assess Prior/Concomitant medication usage. If pain medications are taken, list name, dosage, frequency, etc.

9.2.2 On-Treatment Visits

Cycle 1, Day 1 (Week 1) before dosing for ALL subjects

- Admit to Clinical Research Unit (CRU)
- Confirm screening eligibility test results are acceptable for study participation
- Review and record Interim Medical and Surgical History (prior to first dose)
- Vital signs (prior to first dose)

- Abbreviated Physical Exam
- ECOG (prior to first dose)
- Laboratory Tests (fasting where applicable): hematology, chemistry & electrolytes, urinalysis, lipid profile and blood glucose, PSA, and LDH
- 12 lead ECG
- Assess AEs
- Assess Concomitant Medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Study drug disposition
- Exploratory markers: circulating tumor cells (CTC), ct-DNA and ct-RNA

Cycle 1 Day 15

- Subject returns to CRU
- Vital Signs
- Abbreviated Physical exam
- ECOG
- Assess for AEs
- Assess compliance by pill count
- Assess concomitant meds usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Study drug disposition

Cycle 2 Day 1 (Study day 29)

- Subject returns to CRU
- Vital signs
- Abbreviated Physical Exam

- ECOG performance status
- Laboratory Tests: hematology, chemistry & electrolytes, lipid profile and glucose, PSA, LDH, testosterone, and urinalysis
- 12-lead ECG
- Assess AEs
- Assess Concomitant Medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Assess compliance by pill count
- Study drug disposition

Cycle 3 Day 1 (Study day 57)

- Subject returns to CRU
- Vital signs
- Abbreviated Physical Exam
- ECOG performance status
- Laboratory Tests: hematology, chemistry & electrolytes, lipid profile and glucose, PSA, LDH, testosterone, and urinalysis
- Assess AEs
- Assess Concomitant Medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Assess compliance by pill count
- Study drug disposition

Cycle 4 Day 1 Study day 85

- Subject returns to office/CRU
- Vital signs
- Complete Physical Exam

- ECOG performance status
- Laboratory Tests: hematology, chemistry & electrolytes, lipid profile and glucose, PSA, PT/PTT/INR, LDH, testosterone, urinalysis
- Assessment of exploratory markers: circulating tumor cells (CTC), ct-DNA and ct-RNA, and androgen receptor (AR) related gene profiles
- 12-lead ECG
- CT/MRI, Bone Scan
- Assess AEs
- Assess Concomitant Medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Assess compliance by pill count
- Study drug disposition
- Exploratory Markers

<u>Cycle 5 Day 1 Study day 113</u>

- Subject returns to office/CRU
- Vital signs
- Abbreviated Physical Exam
- ECOG performance status
- Laboratory Tests: hematology, chemistry & electrolytes, lipid profile and glucose, PSA, LDH, testosterone, and urinalysis
- Assess AEs
- Assess Concomitant Medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Assess compliance by pill count
- Study Drug disposition

Cycle 6 Day 1 Study day 141

- Subject returns to office/CRU
- Vital signs
- Abbreviated Physical Exam
- ECOG performance status
- Laboratory Tests: hematology, chemistry & electrolytes, lipid profile and glucose, PSA, LDH, testosterone, and urinalysis
- Assess AEs
- Assess Concomitant Medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Assess compliance by pill count
- Study drug disposition

Study day 169 (if eligible for continuous treatment, this will be Cycle 7 Day 1)

- Subject returns to CRU
- Disease Assessment scans (CT or MRI or bone scan).
- Vital signs
- Complete Physical Exam
- ECOG performance status
- Laboratory Tests: hematology, chemistry & electrolytes, lipid profile and glucose, PSA, PT/PTT/INR, LDH, testosterone, urinalysis,
- 12-lead ECG
- Exploratory markers: circulating tumor cells (CTC), ct-DNA and ct-RNA
- Assess AEs
- Assess Concomitant Medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.

- Assess compliance by pill count
- Study drug disposition (if on Cycle 7 Day 1)

9.2.3 Expansion Study (Additional Cycles after Cycle 6 Day 28 (Cycle 7 Day 1, to Cycle 30 Day 28)

Eligible subjects (no disease progression) have the option to continue additional cycles (up to 18 more cycles) on their assigned dose level until they exhibit PD and/or investigator discretion. Visits will occur every cycle/month, i.e. every 28 days (+/- 3 days). Every 3 cycles, the subjects will be given a disease assessment scan (CT and/or MRI or bone scan). Every 6 cycles, the subjects will be assessed by Investigator and discussed with Medical Monitor or/and Sponsor to determine whether to proceed into the next 6 cycles.

- Subject returns to office
- Disease Assessment scans (CT or MRI or bone scan) are to be performed every 3 cycles (84 +/- 14 days, Cycle 7 Day 1, Cycle 10 Day 1, Cycle 13 Day 1, Cycle 16 Day 1, Cycle 19 Day 1, Cycle 22 Day 1, Cycle 24 Day 28, Cycle 27 D28 and Cycle 30 D28).
- Vital signs
- Complete Physical Exam (Every 3 cycles on Cycle 7 Day 1, Cycle 10 Day 1 Cycle 13 Day 1, Cycle 16 Day 1, Cycle 19 Day 1, Cycle 22 Day 1, Cycle 24 Day 28, Cycle 27 D28 and Cycle 30 D28)
- Abbreviated Physical Exam (Cycle 8 Day 1, Cycle 9 Day 1, Cycle 11 Day 1, Cycle 12 Day 1, Cycle 14 Day 1, Cycle 15 Day 1, Cycle 17 Day 1, Cycle 18 Day 1, Cycle 20 Day 1, Cycle 21 Day 1, Cycle 23 Day 1, Cycle 24 Day 1, Cycle 26 Day 1, Cycle 27 Day1, Cycle 29 Day 1, Cycle 30 Day 1)
- ECOG status
- Laboratory Tests: hematology, chemistry & electrolytes, testosterone, PSA, and urinalysis, lipid profile/blood glucose performed every 3 months (For subjects with abnormal lipid profiles monthly testing is required.)
- 12-lead ECG (every 3 cycles on Cycle 7 Day 1, Cycle 10 Day 1 Cycle 13 Day 1, Cycle 16 Day 1, Cycle 19 Day 1, Cycle 22 Day 1, Cycle 25 Day 1 and Cycle 28 Day 1)

- Exploratory markers (every 3 cycles on Cycle 7 Day 1, Cycle 10 Day 1, Cycle 13 Day 1, Cycle 16 Day 1, Cycle 19 Day 1, Cycle 22 Day 1, Cycle 25 Day 1 and Cycle 28 Day 1)
- Administer study drug from subject supply in the office
- Study drug disposition (unless this is the last visit of the extension study)
- Assess AEs
- Assess Concomitant medication usage/confirmation. If pain medications are taken, list name, dosage, frequency, etc.
- Assess compliance by pill count

9.2.4 End-of-Study (EOS)

All subject will have End-of-study visit before discontinued. If the EoS is equal to or less than 14 days from previous scheduled visit, the EoS visit can be omitted and the assessment will be the previous visit.

- Subject (if qualified) returns to office/CRU
- Vital signs
- Abbreviated Physical Exam
- ECOG status
- Laboratory Tests: hematology, chemistry & electrolytes, and urinalysis
- Assess AEs
- Assess Concomitant medication usage/confirmation
- Assess compliance by pill count
- Exploratory markers

9.2.5 Unscheduled Visits

The Investigator may at his/her discretion arrange for a subject to have an unscheduled assessment, especially in the case of adverse events (AEs) that require follow-up or an AE

considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

9.2.6 30-day safety follow-up "window"

GT0918 is a new 2nd generation of androgen receptor antagonist. The phase I data shows that the average elimination half-life between 400 mg and 500 mg is approximately 7 days (189 to 267 hours). Thus the safety follow-up "window" is set for 30 days after last dose of study drug GT0918 for any possible drug-related AE or SAE. Drug-related AE should be followed up until complete resolution or equal to the level of baseline. The safety follow-up visit can also be done over the phone or in the office if there is SAE and clinically indicated. If subject starts with different treatment or therapy, the window of safety follow-up will be closed. Any AE and/or SAE unrelated to the study drug is not required to report.

- Safety assessment on the AEs.

10 EFFICACY ASSESSMENTS

Efficacy measures, timing, and required tests are detailed in Section 14 ("Statistical Analysis").

11 EXPLORATORY MARKERS

- CTCs, ct-DNA and ct-RNA

12 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, electrocardiogram (ECG) recording, AEs, clinical laboratory results (routine hematology and chemistry) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments.

12.1 Vital Signs

Vital signs (body temperature, respiration rate, heart rate, systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments. All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same non-dominate arm for the duration of the study. Body weight (without shoes) will be recorded whenever vital signs are recorded. Height (without shoes) and BSA will be recorded at screening only.

Vital sign measurements will be repeated manually if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

12.2 Physical Examination

Complete physical examinations (general appearance, skin, HEENT including thyroid, heart, lungs, abdomen, cervical and axillary lymph nodes, extremities, neurological, and musculoskeletal systems) will be performed at Screening (Day -21 to Day -1) and at continued treatment Cycles 2-24. In addition, medical history will be recorded at screening and prior to first dose at Cycle 1, Day 1; including smoking history, if applicable. 30 days after last dose, a physical exam will be performed.

An abbreviated physical examination to verify continued subject eligibility and to follow up any change in medical history will be performed at the visits indicated in the Schedule of Assessments. Symptom-driven limited physical examinations will be performed as clinically indicated at any study visit. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

12.3 Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in the Schedule of Assessments. ECGs will be performed during Screening. At Screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. Additional ECGs will be done on Cycle 1 Day 1, Cycle 1 Day 29, Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 Cycle 13 Day 1, Cycle 16 Day 1, Cycle 19 Day 1, Cycle 22 Day 1, Cycle 24 Day 28 and at the end of the study (or earlier if clinically indicated). An assessment of normal or abnormal will be recorded. If the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present. ECGs will be archived for further evaluation as necessary. If technical issues impede the interpretation, all available ECGs at each time point will be used to interpret the result.

ECGs, including the heart rate, PR, QRS, and the QTc intervals will be calculated automatically by the ECG equipment and will be assessed by the investigator or their designee. The designated physician will review the ECGs to detect a prolongation of the QTc compared to the Baseline tracing. QTc intervals automatically determined by the ECG equipment will be acceptable for detection of prolongation, provided that it is confirmed by a qualified physician later. The mean of the QTc intervals collected at each time point will be compared to the Baseline tracing. For individual subjects, prolongation of the QTc will be defined as (a) an increase in the QTc to > 500 ms for a subject without pre-existing bundle-branch block; (b) an increase in the QTc to >

550 ms for a subject with a pre-existing bundle-branch block; or (c) an increase in the QTc by > 60 ms at any single time point or by >30 ms at 2 successive time points. In any case of QT prolongation detected by the investigative site, the tracing will be promptly forwarded to the medical monitor for confirmation.

If QT interval prolongation is confirmed, the next dose of study medication will be held until normalization of the QT interval has been observed by 2 sets of triplicate ECGs taken with a minimum of 1 hour apart. A grade 3 QTc interval prolongation (QTc >500 ms on 2 consecutive ECGs) will be considered a DLT and reported to sponsor immediately. In the case of any dysrhythmias that are believed by the investigator to be drug-induced, they will be treated with appropriate measures such as magnesium administration, anti-arrhythmics, temporary pacing, etc., until the arrhythmia resolves.

12.4 Laboratory Assessments

Laboratory assessment samples are to be obtained at designated visits as detailed in the Schedule of Assessments.

Table 1: Laboratory Assessments

Hematology	Serum chemistry	Urine analysis (dipstick)

Full and differential blood count Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential	Albumin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Blood Urea Nitrogen (BUN) or Urea Carbon dioxide (CO_2) Creatinine Electrolytes (Na, K, Cl, Ca, P) Glucose Lactate dehydrogenase (LDH) Total bilirubin Direct bilirubin Total cholesterol Triglycerides Testosterone every 28 days PSA every 28 days	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen
Coagulation		
PT/PTT/INR		

Blood samples will be analyzed at a local laboratory facility. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated by a local laboratory. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the subject's source documents and medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant should be

considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.5 Adverse Events

12.5.1 Adverse Event Description and Reporting

An adverse event (AE) is any symptom, physical sign, syndrome, or disease that either emerges or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening and up until the first dose of study medication will be documented in the medical history eCRF. Worsening of these conditions and newly emerged symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the study.

Progressed disease (PD) and death caused by PD are not AE/SAE and should not be reported on the AE page of the eCRF.

Laboratory test results will be recorded on the laboratory results pages of the eCRF. Laboratory test value abnormalities, if not clinically significant, should not be reported on the AE page of the eCRF as AEs. Clinically significant laboratory abnormalities should be recorded as AEs. Conditions that result from a pre-planned surgical procedure arranged before the subject enrollment, are not considered AE or SAEs if the expected conditions were known before study inclusion. Such medical condition should be reported in the subject's medical history.

Additionally, anticipated AEs for this study population, listed below, must be reported by Investigators to the Medical Monitor but will not be expedited on an individual basis. Instead these AEs will be reviewed in aggregate every 3 months by the Sponsor. This aggregate review may result in an expedited safety report.

List of Anticipated AEs for this Study

diarrhea	loss of appetite	pain in extremities
dizziness	nausea	Arthralgia/myalgia
fatigue/lethargy	vomiting	back pain
headache	constipation	hot flush
hypercholesterolemia	hyperglycemia	hyperglyceridemia

peripheral edema	anemia	fever/chills/flu-like symptoms
blurred vision	dry eyes	taste changes/sensitivity to salt
gastro-esophageal reflux	increased CK levels	onychoschizia
Spinal cord compression	Elevated transaminase	Liver injury
Hepatic failure	Hepatic cirrhosis	

List of adverse events (potential AR antagonist class effects and AEs reported from enzalutamide and abiraterone in clinical trials):

Enzalutamide: seizures, posterior reversible encephalopathy syndrome (PRES), hypersensitivity, embryo-fetal toxicity, hypertension

Abiraterone: hypertension, hypokalemia, fluid retention (from increased mineralocorticoid levels), hepatotoxicity (post-marketing experience)

Subjects will be asked about and instructed to report AEs at each study visit. All drug-related AEs are to be followed until resolution or until a stable clinical endpoint is reached.

All AEs are to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event (if any), and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

The purposes of this phase II trial is to study safety and tolerability of GT0918, the period of collection of AEs is from the time of first dose to the last dose of study drug or EoS visit. The 30-day safety follow up "window" is set to capture possibly drug-related AE and/or SAE. Regardless if subject has discontinued from study drug, any drug-related AE or SAE is required to follow until the event is resolved or stabilized at a level of baseline.

When subject starts with new therapy, the safety window of AE collection is closed simultaneously. All drug-unrelated or irrelevant AEs/SAEs such as disease progression and/or from new treatment should NOT be reported.

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in **Table 2** and **Table 3**.

Table 2: Classification of Adverse Events by Intensity

Grade 1: MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Grade 2: MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
Grade 3: SEVERE: An event that prevents normal everyday activities.
Grade 4: LIFE THREATENING: An event that requires urgent intervention.
Grade 5: DEATH: An event that is related to death.

Table 3: Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence

from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.

DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAE V4.03) (Grades 1 to 5).

12.5.2 Serious Adverse Events

An AE is considered "serious" if it is judged by the Investigator or Sponsor to meet 1 or more of the following criteria:

- Is fatal
- Is life-threatening
- Results in subject hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

- Other important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes listed above.

Since SAEs are critically important for identification of significant safety problems, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting. Hospital admission or death caused by progressive disease will not be considered an SAE and do not require expedited reporting. For such cases, initial SAE report of signs or symptoms can be made, but once final diagnosis of PD is made for the underlying cause of sign or symptom, update of SAE report is required and likely to be retracted as result.

The Investigator must notify the Ethics Review Committee/IRB of such an event in writing as soon as is practical and in accordance with international and local laws and regulations

12.5.3 Serious Adverse Event Reporting

All SAEs occurring during the period between the first dose and the last dose of GT0918 or EOS must be reported to the INC Pharmacovigilance Group and will be evaluated by the medical monitor and the Sponsor. The 30-day safety follow-up "window" is set to capture possible drug-related AEs and SAE whereas unrelated SAEs should not be reported. When subject starts new therapy, the window of SAE report is closed simultaneously. All SAEs must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event unless the SAE is determined not related to study drug. Notification can be made using the dedicated fax line and/or telephone line for the CRO Pharmacovigilance Group:

INC Pharmacovigilance Fax:	+1 877 464 7787
INC Pharmacovigilance Contact:	INCDrugSafety@INCResearch.com
CRO, Inc.:	Syneos Health (INC)
Address:	1030 Sync Street, Morrisville, NC 27560
Telephone:	+1 919 745 3026

If the Investigator contacts the INC Pharmacovigilance Group by telephone, then a written report must follow within 1 business day and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE electronic CRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other applicable

documents. SAE reports must be made irrespective to whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the CRO Pharmacovigilance Group within 10 calendar days. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.5.4 Overdose

The Investigator must immediately notify the Sponsor and CRO Medical Monitor of any occurrence of overdose with study drug.

12.5.5 Pregnancy

Pregnancy occurring in the female partner of a subject participating in the study should be reported to the Investigator and the Sponsor. The reporting timeframe is from start of study drug up to 90 days after the last dose of study drug. Pregnancy is not an SAE; however, the outcome of a pregnancy must be reported to detect a potential SAE (congenital anomaly, premature birth, or birth defect). Procedures and policies at the site and at the Sponsor, regarding pregnancies, will be followed to ensure that the safety and well-being of the fetus are appropriately followed through the pregnancy to birth. In the event that a pregnancy occurs, the Investigator will then (and only then) obtain the partner's consent so that the Sponsor can hold her data on file. If the female partner is unwilling to sign the consent her data may not be held in the safety database. However, this will not affect the ability of the male subject to continue in the study.

12.5.6 Safety Review and Teleconferences

Safety review of AEs, laboratory data, concomitant medication, etc. will be performed by the study Medical Monitor on regular basis. Safety call and teleconferences will be held between the investigators/sites and medical monitor and Sponsor to discuss some important drug-related AEs and management of AEs/SAEs during the trial. The frequency may vary based on accrual and study activities.

13 STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and percentages of subjects for each category by treatment group. No interim analyses are planned for the Phase II dose expansion study.

13.1 Determination of Sample size

Phase II dose expansion stage consists of 2 arms of 30 subjects/arm, for a total of 60 subjects for Phase II. Altogether, up to 60 subjects will be estimated for the randomization and stratified by prior medication (abiraterone or enzalutamide).

Of note, the study does not allow disease progression on both abiraterone or enzalutamide. If prior treatment of one of these 2 drugs (i.e. abiraterone) only lasted less than 3 months due to toxicity, the subject (i.e. progressed on enzalutamide) is eligible and prior therapy of enzalutamide will be considered.

13.2 Analysis Populations

The Safety Analysis Set (SAF) will include all subjects who take at least 1 dose of study medication. Safety analyses will be conducted using the safety population.

The Full Analysis Set (FAS) will include all evaluable subjects used as the supportive analysis population for efficacy. The FAS population will be used as the primary analysis population for efficacy.

The Per Protocol (PP) Analysis Set will include all FAS subjects with the Week 12 PSA assessment and without major protocol violations.

13.3 Demographic and Baseline Characteristics

Data will be tabulated by #subjects (%) or Median (range) for the following variables:

- # Subjects
  - ◊ Age in years - median (range)
- Treatment of Primary Tumor, # (%)
  - ◊ Surgery
  - ◊ Radiation
  - ◊ No primary therapy
- Prior hormonal therapy # (%)
  - ◊ 1 line
  - ◊ 2 lines
  - ◊ 3 lines
  - ◊ >/= 4 lines
- Prior chemotherapy # (%)
  - ◊ None
  - ◊ 1 line (2 or more are excluded)

Clinical State of Disease

- PSA in ng/mL - median (range)
- Sites of disease # (%)
  - ◊ Bone only
  - ◊ Bone and soft tissue
  - ◊ Soft tissue only
- Soft tissue disease
  - ◊ Lymph node (LN) only
  - ◊ Visceral lesion only

- ◊ Lymph node + visceral lesion
- ◊ Other (pelvis/bladder) alone

- Prior required hormonal treatment
  - abiraterone,
  - enzalutamide

13.4 Efficacy Analysis

Assessment of Efficacy Variables:

1. Assessment of PSA: Blood samples will be collected to determine the serum total PSA concentration.
2. Change of PSA from baseline:
   a. The percentage of change of PSA from baseline Week 12 will be calculated. Maximum percentage change of PSA from baseline at any time will be calculated.
   b. The proportion of subjects achieving a ≥50% reduction in PSA at 3 months (12 weeks) as compared to baseline (study entry) will be determined.
3. Assessment of soft tissue and bone:
   c. Soft tissue: Chest, abdomen, and pelvic CT, or MRI (if CT not possible), will be performed. Changes in the size of target lesions will be evaluated.
   d. Bone scan: Radionuclide bone scan will be performed. Changes in the number of lesions will be reported.
   e. Skeletal-related events: Severity of skeletal-related event (bone pain, analgesia intake) will be assessed monthly per PCWG2.
4. Symptomatic progression will be evaluated by type. Symptomatic progression is defined as evidence of unequivocal symptomatic or clinical progression defined by at least 1 of the following:
   - A marked escalation in cancer-related pain that is assessed by the Investigator to indicate the need for other systemic therapy or palliative radiotherapy. Ignore early changes (≤ 12 weeks) in pain or health-related quality of life in absence of compelling evidence of disease progression. Confirm progression of pain or health-related quality of life ≥ 3 weeks later,

- An immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression,
- A marked deterioration in ECOG performance status to Grade 3 or higher, or
- Performance status: ECOG performance status will be assessed. Changes from baseline will be evaluated.

13.5 Exploratory Analyses

Assessment of Exploratory Variables:

Exploratory markers will be taken at baseline and every 3 months during the study.

The exploratory variables will be summarized using descriptive statistics. The descriptive statistics will include the actual values and the changes from baseline for the exploratory variables.

13.6 Safety Analysis

Assessment of safety will be based on the incidence of AEs, AEs resulting in discontinuation, and serious adverse events (SAEs) in each dose level. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will be provided showing the number and percentage of subjects who experienced at least 1 AE. These summaries will be presented by dose level, system organ class, and the preferred term. The occurrence of AEs will also be tabulated by severity and relationship to study medication. SAEs and AEs resulting in discontinuation will be summarized separately. All vital sign measurements, clinical laboratory results, pain score, and ECG findings will be summarized by dose level and time point using descriptive statistics or frequency distributions.

All safety summaries will be performed by dose levels and by all subjects.

13.7 Interim Analysis

Not applicable

13.8 Data Monitoring Committee

Not applicable

14 STUDY MANAGEMENT

14.1 Approval and Consent

14.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with GCP guidelines.

14.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, informed consent forms (ICFs), and subject information sheets.

14.1.3 Informed Consent

For each study subject, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Principal Investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and International Conference on Harmonization (ICH) guidelines. The PI will provide the Sponsor or its representative with a copy of the IRB/IEC-approved ICF prior to the start of the study.

Should changes to the Informed Consent form become necessary during the study, the PI will ensure that the changes are approved by the sponsor or its representative prior to submission to the IRB. All revisions of the protocol must be reflected in the IC form, if applicable, and reviewed by the IRB. Subjects must be made aware of those applicable changes in the protocol and must consent to participate in the revised protocol.

14.1.4 Subject Confidentiality

All communications, reports, and subject samples will be identified by site number, and a code number and/or initials to maintain subject confidentiality. All records will be kept confidential to the extent permitted by law. If a waiver or authorization separate from the statement in the Informed Consent is required for permitting access to a subject's medical records (e.g. HIPAA), the Investigator will obtain such authorization prior to enrolling a subject in the study. The PI should keep a separate log of subjects, codes, names, and addresses. Documents which identify the subject by name (for example, the Informed Consent form) should be kept in strict confidence.

The sponsor and its business associates agree to keep all subject information confidential. Data resulting from analyses will be entered into a database that is not accessible to the public. Subject data will be identified only by the subject screen number, randomization number and initials, and not by any other annotation or identifying information.

The sponsor and its business associates will take every possible step to reduce the risk of releasing information to the public that would enable subjects to be personally identified.

14.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by the Sponsor. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access. The eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

14.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source documents are filed and kept secure by the Investigator at each research site and can be obtained by contacting the Investigator to arrange access.

14.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the

Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

14.5 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

14.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

14.7 Protocol Amendment and Protocol Deviation

14.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of subjects or the conduct of the study will be classified as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

14.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor, medical monitor and/or the CRO study manager must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

14.8 Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IRBs/IECs will review and approve this protocol and the ICF. All subjects are required to give written informed consent prior to participation in the study.

14.9 Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

14.10 Publication Policy / Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

15 REFERENCES

General references for prostate cancer:

1. NCCN 2015 Prostate Cancer Guidelines
2. Merck Manual Professional Version online at http://www.merckmanuals.com/professional/genitourinary-disorders/genitourinary-cancer/prostate-cancer
3. PDQ General Information about Prostate Cancer at http://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq
4. XTANDI package insert 9/2014 and 10/2015
5. MHE Tan et al., Androgen receptor: structure, role in prostate cancer and drug discovery. Acta Pharmacologica Sinica (2015) 36: 3-23.
6. Oken MM, et al 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655
7. Eisenhauer et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Can 45 (2009) 228-247.

16 APPENDICES

16.1 Schedule of Assessments [1]

	Screening	Cycle 1-6								Additional Cycles 7-30 [12]	EOS [14]	Safety F/U[15]
Study Day	Day -21 to Day -1	Day 1 C1D1	Day 15 C1D15	Day 29 C2D1	Day 57 C3D1	Day 85 C4D1	Day 113 C5D1	Day 141 C6D1	Day 169/C7D1 End-of-6 month	From Day 169 (every 4 wks.)	Over 30 days after last dose	30 days after last dose
Assessments	**Weeks**	w1	w3	w5	w9	w13	w17	w21	w25			
Informed Consent	X											
Inclusion/Exclusion	X	X										
Medical History [2]	X	X										
CT/MRI/Bone Scan [3]	X					X			X	X [13]		
Vital Signs [4]	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam [5]	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status [6]	X	X	X	X	X	X	X	X	X	X		
Clinical Chemistry & electrolytes [7]	X	X		X	X	X	X	X	X	X	X	
Hematology [7]	X	X		X	X	X	X	X	X	X	X	
Lipid Profile & blood glucose [8]	X	X		X	X	X	X	X	X	X [13]		
Urinalysis	X	X		X	X	X	X	X	X	X	X	
PSA [9]	X	X		X	X	X	X	X	X	X		
Testosterone	X			X	X	X	X	X	X	X		
12-lead ECG [10]	X	X		X		X			X	X [13]	x	
PT/PTT/INR	X					X			X			
Exploratory markers [11]		X				X			X	X [13]	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X

Concomitant Meds[16]	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Disposition		X	X	X	X	X	X	X		X		
Study Drug Treatment		X	X	X	X	X	X	X	X	X		
Compliance Assessment			X	X	X	X	X	X	X	X	X	

Abbreviations: ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; PT/PTT/INR=Prothrombin Time/ Partial Prothrombin Time/International Normalized Ratio; CT=Computed tomography; MRI=Magnetic resonance imaging; PSA=prostate surface antigen; EOS=End-of-Study.

Note: For days not specifically designated on the schedule of assessments, the standard of care for the individual institution will be followed, any AEs and concomitant medications will be recorded on the CRF.

1. This schedule applies to Phase II study of GT0918 including screening, treatment of first 6 cycles and additional cycles for eligible subjects. One cycle constitutes 4 weeks of treatment. See Section 9.2 Expanded/Phase II Study Visits.
2. Full medical and surgical history will be recorded at Screening. At Cycle 1, Day 1; an interim history prior to first dose of study drug is to be recorded as concomitant illness.
3. Imaging that is performed during standard care within 6 weeks of Cycle 1 Day 1 prior to informed consent may be used to confirm screening requirements. Disease status will be measured by radiologic methods (CT or MRI or bone scan) at screening, and every 3 cycles, i.e. 84 days (+/- 14 days) after Day 1. No subject is permitted to have additional cycles until it is confirmed that disease progression has not occurred.
4. Vital signs will include weight, height (Screening only), BSA (Screening only), body temperature, respiratory rate, radial pulse rates, and systolic/diastolic blood pressures.
5. Complete physical examinations will be conducted at Screening (Day -28 to Day -1), on Days 85 (C4D1) and 169 (C7D1), on every 3 months during the extension study. All other physical examinations will be abbreviated. Complete physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, muscular skeletal and nervous system. Abbreviated physical examinations will focus on new symptoms and will include examinations identified as relevant by the investigator. PE record if subject complains bone pain, compromised urinary or bowel movements. For bone pain, location and severity are needed in CRF. If pain killers are taken, names, dosage, and frequency use are noted under concomitant medication in CRF.
6. After Cycle 1, ECOG performance status will be assessed every cycle (4 weeks) during Cycles 2-6 and extension cycles, and at EOS/ET Visits.
7. Hematology and chemistry assessments will be done as defined with a window of (±3 days) every cycle (4 weeks).
8. Fasting lipid and glucose will be done at Screening, and on Days 1, 29, 57, 85, 113, 141, and 169 (±3 days) in Cycle 1-6. For extension cycles, lipid profile and blood glucose are to be assessed every 3 cycles (12 weeks). For subjects with abnormal lipid profiles, monthly testing is required in extension cycles.
9. PSA will be processed in local lab.
10. ECGs will be performed in triplicate at Screening, on Cycle 1 Day 1 and Cycle 2 Day 1 (Day 29). Single ECGs are to be conducted on Day 85, 169, and quarterly (every 3 month) during additional cycles. For any subject with abnormal or questionable ECG, monthly monitoring ECG is required. If there is reading error, artifacts or suspicious readings, triplicate readings with at least 15 min between each reading are recommended. The final test result will take the average of 3 readouts.

11. Exploratory markers of circulating tumor cells, ct-DNA and ct-RNA will be assessed every 3 cycles and at EOS/ET.
12. Subjects are eligible for additional cycles in a 6-month Extension Study if they complete 6 cycles of treatment and have "no disease progression". The same dose levels will be kept for the additional cycles. Subjects will be assessed by Investigator/Medical Monitor or/and Sponsor at the end every 6 cycles (end-of-6/12/18/24 cycles) to be determined if to proceed into the next 6 cycle treatments. Subjects are required to have office visits monthly (every 4 weeks +/- 3days) and all assessments marked with "X" will be performed every 4 weeks unless specified otherwise.
13. CT/MRI/bone scan, ECG, and exploratory markers will be assessed every 12 weeks. TSH/T3/T4 and PT/PTT/INR will be assessed every 12 weeks only in the first 6 cycles.
14. EoS is used for subjects on study drug GT0918. If EoS is equal to or less than 30 days from previous scheduled visit or to next planned visit, the EoS visit can be either omitted or combined.
15. Safety follow-up is recommended 30 days after last dose of study drug GT0918 or/and EoS whichever occurs later for any possibly delayed drug-related SAE. For drug-related AE/SAE should be followed up until complete resolution or equal to level of baseline.
16. In concomitant medication, specify if pain medications are taken or not. If so, list name, dosage, frequency, etc.

16.2 APPENDIX 1: ECOG Performance Status

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655.

16.3 APPENDIX 2: RECIST Guidelines v1.1

EA Eisenhauer et al. New response evaluation criteria in solid tumors:

Revised RECIST guideline (version 1.1). Eur J Can 45 (2009) 228-247.

Key sections of the article are included here as a guideline. It is strongly recommended; however, to read the entire article, since it highlights the changes from v1.0 and gives many useful examples.

Measurability of tumor at baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no less than 5 mm for spirals).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Malignant lymph nodes:

- To be considered pathologically enlarged and measurable, a lymph node must be >/= 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with >/= 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal

masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

- Clinical lesions will only be considered measurable when they are superficial and >/= 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT, MRI:

- CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. If there is concern about radiation exposure or dye with CT, MRI may be used instead of CT in selected instances.

Ultrasound:

- Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy:

- The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies

are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers:

- Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology:

- These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above). In studies where the primary endpoint is tumor progression (either time to progression or prostage with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether subjects having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of >/= 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis </= 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be

used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented stages should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of nontarget disease

The concept of progression of non-target disease requires additional explanation as follows:

When the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial

worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease. This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is

the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

16.4 APPENDIX 3: New York Heart Association Classifications

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest[a]	Physical Ability to Work[b]
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

[a] To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
[b] At accustomed occupation or usual tasks.

Source: Bruce RA. 1956. Evaluation of functional capacity and exercise tolerance of cardiac patients. Mod Concepts Cardiovasc Dis 25(4):321-326. (Modified from New York Heart Association, 1953).

16.5 APPENDIX 4: Drugs with Potential Interactions with Metabolism

GT0918 is CYP 3A4 inhibitor and it has potential of drug interactions. For all study subjects on any drug on this table, an alternative treatment shall be considered. If there is no alternative for the drug or the drug must be used as part of standard of care during the trial, for the sake of safety for study subject, the dose of drug must be adjusted or reduced,

CYP 3A inhibitors

Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

CYP 2D6 inhibitors

Bupropion, fluoxetine, paroxetine, quinidine

CYP 3A inducers

Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort

CYP 3A4 substrates

Amlodipine/felodipine/nifedipine, Amiodarone, Apixaban/dabigatran/rivaroxaban, Atorvastatin/lovastatin/simvastatin, Diltiazem/verapamil, Edoxaban, Isosorbide dinitrate/mononitrate, Ivabradine, Ticagrelor, Warfarin

16.6 APPENDIX 5: Ingredients of GT0918 Drug Product

Ingredients	Dosage (mg)	Proportion (%)
ProxalutamideGT0918 (API)	100.0	30.49%
Corn Starch	192.8	58.78%
Hyposubstituted Hydroxypropyl Cellulose	12.8	3.90%
Hydroxypropyl Methylcellulose E6	9.6	2.93%
Magnesium Stearate	4.8	1.46%
Film Coating Premix (gastric soluble) ®85G640066	8.0	2.44%