TITLE PAGE

Protocol Title:

A Randomized, Double-blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Proxalutamide (GT0918) in Outpatients with Mild to Moderate COVID-19 Illness

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SPONSOR SIGNATURE PAGE

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Protocol No.: GT0918-US-3001

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Sponsor: Suzhou Kintor Pharmaceuticals, Inc.

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:

Xunwei Dong 09 Jul 2021

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

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

Suzhou Kintor Pharmaceuticals, Inc.

INVESTIGATOR STATEMENT

Protocol title: A Randomized, Double-blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Proxalutamide (GT0918) in Outpatients with Mild to Moderate COVID-19 Illness

Protocol No.: GT0918-US-3001

Version: 2.0

The trial will be conducted in accordance with the ICH E6. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

- **I confirm agreement to conduct this study in compliance with the protocol.**
- **I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.**
- **I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.**

Principal Investigator: _____

Print/Type Name

Signed: _____

Signature Date: _____

(DD-MMM-YYYY)

ABBREVIATIONS

Term	Definition
AACR	American Association for Cancer Research
ACE2	Angiotensin Converting Enzyme 2
ACVPU	Alert, Consciousness, Verbal, Pain, Unresponsive Scale
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AR	Androgen Receptor
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
BID	Twice a Day
BP	Blood Pressure
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine kinase
CLIA	Clinical Laboratory Improvement Amendments
CMH	Cochran–Mantel–Haenszel
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services
CNS	Central Nervous System
Cr	Creatinine
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CROMS	Clinical Research Operations and Management Support
CRP	C-reactive Protein
CRPC	Castrate Resistant Prostate Cancer
COVID-19	Coronavirus Disease 2019
CQMP	Clinical Quality Management Plan
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Allergy and Infectious Diseases
DCR	Disease Control Rate

DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
DLT	Dose Limiting Toxicity
DMP	Data Management Plan
EC	Ethics Committee
ECOM	Extracorporeal Membrane Oxygenation
EOS	End of Study
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FiO2	Fraction of Inspired Oxygen in the Air
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
hEGR	Human Ether-a-go-go-related Gene
Hgb	Hemoglobin
HR	Heart Rate
IB	Investigator's Brochure
IC50	A quantitative measure that indicates how much of a particular inhibitory substance (e.g., drug) is needed to inhibit, in vitro, a given biological process or biological component by 50%
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IIT	Institute Initiated Trial
IND	Investigational New Drug Application
INR	International Normalized Ratio
iNOS	Inducible Nitric Oxide Synthase
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
IxRS	Interactive Web/Voice Response System
LLOQ	Lower Limit of Quantitation
LNCaP	Lymph Node Carcinoma of the Prostate
MCG	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MG	Milligram
MOP	Manual of Procedures
MTD	Maximum Tolerated Dose
N	Number (typically refers to subjects)

NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NP	Nasopharyngeal
NOAEL	No Observed Adverse Effect Level
NSAID	nonsteroidal anti-inflammatory drug
OHRP	Office for Human Research Protections
OP	Oropharyngeal
OTC	Over-the Counter
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PHI	Protected Health Information
PI	Principal Investigator
PLT	Platelet
PP	Per Protocol
PR	Partial Response
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
QD	Once A Day
QT Interval	Measured from the Beginning of the QRS Complex to the End of the T wave
QTc	Corrected Q-T Interval
RNA	Ribonucleic Acid
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Steering Committee
SD	Stable Disease
SDCC	Statistical and Data Coordinating Center
SDSP	Study Data Standardization Plan
SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO2	Saturation of Peripheral Oxygen
SUSAR	Suspected Unexpected Serious Adverse Reaction
T.Bili	Total Bilirubin

TEAE	Treatment Emergent Adverse Events
TMPRSS2	Transmembrane Protease Serine 2
TNF	Tumor Necrosis Factor
ULN	Upper Limited Number
UP	Unanticipated Problem
US	United States
WBC	White Blood Cell
WHO	World Health Organization

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PROTOCOL SUMMARY

Synopsis

Protocol Title:

A Randomized, Double-blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Proxalutamide (GT0918) in Outpatients with Mild to Moderate COVID-19 Illness.

Short Title: A Phase 3 Study to Evaluate the Efficacy and Safety of GT0918 in Outpatients with Mild to Moderate COVID-19 Illness

Protocol Number: GT0918-US-3001

Study Phase: 3

Sponsor: Suzhou Kintor Pharmaceuticals, Inc.

Rationale:

Coronavirus disease 2019 (COVID-19) emerged in late 2019 and spread rapidly, resulting in a global pandemic. New COVID-19 cases and deaths have been constantly rising. COVID-19 is caused by a novel coronavirus (SARS-CoV-2), and infected persons can have a wide range of disease severity, with many patients showing mild or moderate disease. Although many therapies have been and are being explored in various stages of COVID-19, for the large population with mild and moderate COVID-19, limited treatments are available. There is a huge unmet medical need for home-use, oral intake, treatments for mild to moderate COVID-19 patients to ameliorate symptoms and prevent hospitalization.

Much research has proven that SARS-CoV-2 cell entry and fusion depends on angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). In humans, androgens are the only known transcription promoters for the TMPRSS2 gene. Further, the ACE2 receptor, also critical for SARS-CoV-2 viral infectivity, is affected by male sex hormones with higher activity found in males. So, androgen receptor antagonists have the potential to reduce virus entry and viral infectivity.

Proxalutamide (GT0918), a new investigational androgen receptor (AR) antagonist with more specificity and activity in inhibiting androgen receptors, has shown to inhibit the expression of ACE2 and TMPRSS2 in lung epithelial cells. GT0918 can also down-regulate the protein expression level of inflammation-related factor inducible nitric oxide synthase (iNOS) and the mRNA expression level of iNOS and tumor necrosis factor (TNF). Recent research showed that GT0918 inhibited SARS-CoV-2 infection more effectively than Enzalutamide in LNCaP cells in a dose-dependent manner, with concentration that inhibits response by 50% (IC50) values of

97 nM. Furthermore, the preclinical results suggest that GT0918 should more effectively inhibit AR-dependent expression of ACE-2 and TMPRSS2 than Enzalutamide in a variety of SARS-Cov2 infected organs, including lung, Gastrointestinal (GI), heart, and kidney.

The clinical study of GT0918 treatment in Brazil for COVID-19 outpatients (NCT04446429) showed the hospitalization rate was significantly decreased in the GT0918 group compared with placebo group (0 vs. 27% in the male cohort and 3 vs.19% in the female cohort). No serious adverse event (SAE) occurred in the GT0918 group compared with 27% in the placebo group in the male cohort. In the female cohort, the percentage of subjects reported to have SAEs was 3% in the GT0918 group and 19% in the placebo group.

GT0918 will be administered to evaluate its effect in accelerating recovery following SARS-CoV-2 infection, limiting spread into lung cells, improving the clinical outcome and reducing hospitalization in COVID-19 infected outpatients with mild or moderate symptoms.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	**Primary**
To evaluate the efficacy in terms of clinical status following treatment with GT0918 compared to placebo	Percentage of subjects who do not experience any of the following events due to all causes by Day 28: • Hospitalization for ≥ 24 hours or • Supplemental oxygen for ≥24 hours in response to SpO2 ≤93% or • Death
Secondary	**Secondary**
	•

To evaluate the clinical efficacy of GT0918 compared to placebo using the NIAID 8- point scoring scale	Percentage of subjects achieving each clinical status by Days 7, 14 and 28 as defined below based on The National Institute of Allergy and Infectious Diseases (NIAID) 8- point scoring scale: 1 Death 2 Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) 3 Hospitalized, on non-invasive ventilation or high flow oxygen devices 4 Hospitalized, requiring supplemental oxygen 5 Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise) 6 Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care 7 Not hospitalized, limitation on activities and/or requiring home oxygen 8 Not hospitalized, no limitations on activities
To evaluate the clinical efficacy of GT0918 compared to placebo based on clinical status	• Proportion of subjects with all-cause hospitalization (defined as ≥24 hours) by Day 28 • Proportion of subjects hospitalized (defined as ≥24 hours) due to COVID-19 related events by Day 28 • Days of hospitalization due to all causes or COVID-19 • Proportion of subjects with all-cause mortality by Day 28 • Proportion of subjects with COVID-19 related mortality by Day 28 • Proportion of subjects admitted to an ICU due to COVID-19 by Day 28 • Days in intensive care unit (ICU) • Proportion of subjects requiring supplemental oxygen, high-flow oxygen, any ventilation or ECMO due to COVID-19 by Day 28 • Proportion of subjects requiring mechanical ventilation or ECMO due to COVID-19 by Day 28 • Days on supplemental oxygen/high flow oxygen devices/mechanical ventilation •
Characterize the effect of GT0918 compared to placebo on symptom improvement or resolution	Symptom Improvement: • Change in symptom score (total of ratings) from baseline to Days 3, 7, 14 and 28 • Time to symptom improvement • Proportion of subjects demonstrating symptom improvement via the symptom questionnaire (total of ratings) on Days 3, 7, 14 and 28 Symptom resolution:

	• Proportion of subjects demonstrating symptom resolution via the symptom questionnaire on Days 3, 7, 14 and 28 • Time to symptom resolution
Characterize the effect of GT0918 compared to placebo on SARS-CoV-2 viral load clearance	• Change from baseline to Days 3, 7, 14 and 28 in SARS-CoV-2 viral load • Proportion of subjects that achieve SARS-CoV-2 clearance (Days 3, 7, 14 and 28) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed to days 3, 7, 14 and 28
Characterize the effect of GT0918 compared to placebo on safety	Safety assessments such as AEs, SAEs and laboratory data
Exploratory	**Exploratory**
Characterize the pharmacokinetics of GT0918	• Mean trough concentration of GT0918 and GT0955 on Days 1, 3, 7 and 14 • To explore relationships between GT0918 and/or GT0955 exposure and selected efficacy and safety endpoints and/or biomarkers
Characterize emergence of viral resistance to GT0918	Screening for novel mutants in subjects who do not respond to GT0918 • Genotype of SARS-CoV-2 viral isolates
To explore biomarkers predictive of GT0918 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes	• The association between changes in disease related biomarkers with clinical endpoints

Study Design

Overall Design:

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of Proxalutamide (GT0918) in adult outpatients diagnosed with mild to moderate COVID-19.

The population of subjects with mild to moderate COVID-19 illness will be chosen to evaluate if anti-androgen therapy may effectively prevent progression to the severe form of COVID-19 illness by treating this population early in their disease course and prior to respiratory compromise and failure.

This study utilizes an adaptive design that maximizes efficiency in identifying a safe and efficacious therapeutic agent for COVID-19 during the current outbreak. The study is a multicenter trial that will be conducted in the United States (US) and other countries. Approximately 668 subjects will be randomized in a 1:1 ratio to either GT0918 or placebo. There will be one interim analysis. The interim analysis will be conducted when 334 subjects complete Day 28 after first dose. The blood samples for

population (pop) PK analysis need to be collected for at least 100 subjects, whom will also be randomized into the interventional treatment or placebo group with 1:1 ratio.

Randomization:

Subjects will be randomized into 1 of 2 arms with 1:1 ratio, each will receive an interventional treatment or placebo with standard of care.

Randomization will be stratified by:

- Sex: Male or Female
- Race and ethnicity (non-Hispanic White or other /Hispanic or Latino /non-Hispanic Black)
- Number of risk factors 0, 1-2, ≥3 (based on CDC defined conditions)

Study Duration

The subject will remain on study treatment up to 14 days. 14-day post treatment period with a post treatment visit on Day 28. The safety follow-up will be up to 28 days after last dose making the overall duration of monitoring 42 days for each subject.

End of Study

A subject is considered to have completed the study if he has completed all required phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last enrolled subject or last ongoing subject in the study, whichever comes later.

Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. The subject or legally authorized representative give signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Understand and agree to comply with planned study procedures.
3. Male and non-pregnant female subjects with age ≥18 years of age at the time of randomization.
4. Are currently not hospitalized.
5. Have one or more COVID-19-related symptoms within 5 days of onset of symptoms onset (FDA COVID-19-Related symptom guidance, See Appendix 2, available at: https://www.fda.gov/media/142143/download)

6. Must have first positive SARS-CoV-2 viral infection determination (has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen) ≤3 days prior to start of the first dose.
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception, as shown below, throughout the study and for 3 months after stopping GT0918 treatment. Highly effective contraception methods include:
    - Total Abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception, or
    - Use of one of the following combinations (a+b or a+c or b+c):
      a: Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
      b: Placement of an intrauterine device (IUD) or intrauterine system (IUS);
      c: Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository;
    - Female sterilization (have had prior surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment;
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject;

    In case of use of oral contraception women should have been stable for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, is she considered not of childbearing potential;

8. Regardless of their fertility status, male subjects must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective method of contraception (less than 1% failure rate) or effective method of contraception with nonpregnant women of childbearing potential partners for the duration of the study and until 90 days after the last dose.
9. Agree to the collection of nasopharyngeal swabs and venous blood.

Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Have $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA resource page, COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (fda.gov)).
2. Estimated glomerular filtration rate (eGFR) < 30 ml/min
3. Serum total bilirubin > 1.5 x ULN (upper limit of normal) and AST and ALT >3 x ULN
4. Subjects with significant cardiovascular disease as following:

   i. heart failure NYHA class ≥3
   ii. left ventricular ejection fraction <50%
   iii. those with a history of cardiac arrhythmias, including long QT syndrome.
5. Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19 or requires treatment with supplemental oxygen.
6. Have known allergies to any of the components used in the formulation of the interventions.
7. Have hemodynamic instability requiring use of vasopressors within 24 hours of randomization.
8. Suspected or proven serious, active bacterial, fungal, viral, or other infection (except COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention (i.e. known history of human immunodeficiency virus [HIV]).
9. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 30 days.
10. Have any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in this study.
11. Subjects with myopathy.

12. Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), where prior use is defined as the past 30 days or less than 5 half-lives of the investigational product (which is longer) from screening.
13. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
14. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
15. Subject taking an anti-androgen of any type including androgen depravation therapy, 5-alpha reductase inhibitors, etc. within 3 months before dosing.
16. Are investigator site personnel directly affiliated with this study.

Investigational and Reference therapy

For this study, investigational drug (study drug) refers to Kintor study drug Proxalutamide (GT0918). GT0918 will be supplied by Kintor or its designee as 100 mg tablets as individual patient supply packaged in blister.

- Arm 1: Subjects administered GT0918, 200 mg q.d. after regular conventional meal plus standard of care for 14 consecutive days
- Arm 2: Subjects administered GT0918, matched placebo q.d. after regular conventional meal plus standard of care for 14 consecutive days

The dose should be given the same time each day (+/- 2 hours for medication scheduling).

Any dose that is delayed may be given later that calendar day. Any dose that is missed (not given that calendar day) is not made up. The treatment course should continue as described above even if the subject becomes SARS-Cov-2 test negative or experiences complete resolution of symptoms.

All subjects may be treated according to standard of care simultaneously, and medications may be part of the treatment paradigm. The study treatment refers to the study drug/placebo plus standard of care. Dose escalation is not applicable in this study.

For the subjects who develop Grade 3 or 4 adverse events (AEs), suspected to be drug-related by the investigator, the study drug administration should be discontinued. This subject will enter post-treatment period with the safety follow-up up to 28 days after last lose. There is no dose interruption or reduction in this study.

Safety Assessment

- Safety assessments will include the incidence, and severity of AEs and laboratory abnormalities graded per Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).
- Safety evaluations will be performed per SoA during the study.
- The assessments, as described in Section 7.2.2, will occur at baseline, Days 3, 7, 14 and 28 or early withdrawal visit following randomizations (+/-2 days). The information will be recorded in the appropriate eCRF.
- Subjects will receive safety evaluation at regular visits as specified in the procedures, including physical examination, vital signs, laboratory tests. In addition, ECGs, chest X-ray, and CT-scan could be done per the investigator's discretion.
- In addition to scheduled visits in the protocol, unscheduled visits may be conducted as appropriate based on the subject`s AEs or clinical status.

Statistical considerations:

Sample size calculation

The primary endpoint event rate for the treatment arm is assumed at 97% and for the placebo arm is assumed at 91%.

The sample size was calculated using EAST v6.5 software for a group sequential test for 2 proportions. With a total of 668 subjects the study will have 90% power at a one-sided 0.025 significance level of the hospitalization or death rate using a Chi-square test with one interim analysis at 50% of the information (when 334 subjects have been observed for 28 days).

Statistical analysis:

The primary endpoint event rate will be compared between treatment and placebo arm using Cochran–Mantel–Haenszel (CMH) chi-square test using the stratification factors at time of randomization at the one-sided 0.025 level based on modified Intent-to-Treat (mITT).

An interim analysis will be conducted when 334 subjects complete Day 28 after first dose. An independent data monitoring committee (IDMC) will review the interim analysis report to conclude early efficacy, make recommendations about early study closure, change study population, or change to study sample size.

If the one-sided p-value is less than 0.0015, the stopping boundary for efficacy is met and the study could be stopped for efficacy.

Analysis Sets

The intent-to-treat analysis set (ITT) includes all randomized subjects.

The mITT set will include all randomized subjects who have received at least one dose of study medication.

The safety analysis set (SS) includes all subjects with at least one dose of study medication and will be analyzed as treated.

The Per-Protocol Analysis Set (PP) includes all mITT subjects without major protocol violations which will be defined under classification specification prior to unblinding of the study treatment code.

The Pharmacokinetic Analyses (PK) will be conducted on data from at least 100 subjects who receive intervention and have evaluable PK.

Schedule of Activities (SoA)

Assessments obtained previously as part of routine clinical care may be used as the screen assessment if they were done no more than one day before randomization. Visits may be conducted as a telephone call, outpatient clinic or home visit, if the protocol SoA is followed and in compliance with local regulatory.

Table 1 Schedule of Activities

-	Screen	Treatment Period				Early Withdrawal [19]	Post-treatment		Safety Follow Up [20]
Study Day (Visit Window ± days)	D-1	D1	D3	D7 (±1)	D14 (+1)	(+2)	D15	D28 (±2)	D42 Phone Call (±2)
Informed Consent	X								
Inclusion/Exclusion Review [1]	X								
Demographics [2]	X								
Preexisting Conditions and Medical History [3]	X								
NIAID Ordinal Scale[4]	X	Daily							
Prior Treatment [5]	X								
Tobacco Use	X								
Physical Examination [6]	X	Symptom Directed PE only if Clinical Indicated							

Vital Signs [7]	**X**		**X**	**X**	**X**	**X**		**X**	
Nasopharyngeal swabs [8]	**X**		**X**	**X**	**X**	**X**		**X**	
Randomization [9]	**X**	**X**							
Hematology [10]	**X**			**X**	**X**	**X**		**X**	
Chemistry [10]	**X**			**X**	**X**	**X**		**X**	
Biomarkers [10]	**X**		**X**		**X**	**X**		**X**	
Coagulation [10]	**X**				**X**	**X**		**X**	
Drugs and Diary Dispense [11]	**X**	**X**							
GT0918 or Placebo Administration [11]		**Daily from D1 to D14**							
Subject Diary [11]		**Daily from D1 to D14**							
Questionnaire (Symptoms; Overall Clinical Status;) [11]	**Daily**								
Chest X-ray or CT Scan [12]	**Clinically Indicated**								
12-ECG [12]	**Clinically Indicated**								
Hospitalization events [13]		**Daily**							

Clinical status and concomitant procedures if subject is hospitalized [14]		**Daily if hospitalized**							
Adverse Events [15]	**X**								
Concomitant Medications [16]	**X**								
Pharmacokinetics [17]		**X**	**X**	**X**	**X**				
Pregnancy test[18]	**X**							**X**	
COVID-19 vaccination status	**X**								

Annotation:

1. Inclusion/Exclusion review: every subject needs to meet all inclusion and exclusion criteria. The eligibility checklist needs to be signed by the investigator or sub-investigator.
2. Demographics: includes age, gender, race, and ethnicity.
3. Pre-existing conditions and medical history: obtained from interview or available information and including timing of exposure and onset of symptoms suggestive of SARS-CoV-2 infection.
4. NIAID ordinal scale to be completed daily through Day 28 or 14 days after last dose. This information can be collected from questionnaire; reported events; or directly from the patient.
5. Prior treatments within last 30 days.
6. Physical exam (PE): Full physical exam should be done at screening visit. For the subsequent visits, symptom directed PE can be done per investigator's discretion. If the result is clinically significant, the PE result should be recorded in eCRF.
7. Vital sign: documentation of hospital-based exam is acceptable. Vital signs include body temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate. For screening visit, SpO_2, and supplemental oxygen flow rate, FiO_2 if known and method of delivery if applicable, also need to be recorded. Record blood pressure and SpO_2 while subject is at rest.
8. Nasopharyngeal (NP) swabs: Only NP swab sample is acceptable. The method of taking samples should be consistent for each subject during the whole period of this study. This does not need to be the same before screening visit, when the subject is first time confirmed SARS-CoV-2 positive at local laboratory and/or Point of Care testing. Sample for first positive test must be collected within 3 days prior to start of dosing. Local laboratory and/or Point of Care testing are acceptable.
9. Randomization: randomization should be via the Interactive Voice/Web (IxRS) Response System. Randomization should be done after confirmation the subject meets all inclusion/exclusion criteria. Drugs and Diary Dispense should occur after randomization. It is allowed for the subject to take the drug on the

same day of the screening visit after confirmation of eligibility and randomization (the screening visit is counted as D1 too). The Subject Diary should start to be completed.

10. Laboratory tests: Hematology, Chemistry (including Creatinine Kinase), Biomarkers (including Procalcitonin, C-reactive protein, D-dimer, Ferritin, Troponin, Testosterone), Coagulation. For details refer to Section 7.2.2 and 7.2.4.
11. GT0918 or placebo administration: GT0918 or placebo will be given orally once daily on Days 1-14 during the study period after a meal (±2 hours for medication scheduling). The drug taken time should be recorded with subject diary. If the screening day is also D1, the subject does not need to follow the drug taken window on screening day/D1. For details refer to Section 6.1.

    Subject Diary should be completed every day since first dose until the last dose.

    Questionnaire should be completed every day since screening visit to the end of post-treatment by Day 28. For details refer to Section 7.2.6.
12. Chest X-ray or CT-Scan or 12-ECG can be done per investigator's discretion. If investigator deems the result is clinically significant, the result should be recorded with eCRF.
13. Hospitalization events: if the subject is hospitalized, the treatment may be continued to the 14 days per PI. Hospitalization is defined as ≥24 hours in hospital of care. For details refer to Section 7.1.2.

    Record if the following events occur:

    - Emergency room visits
    - Hospitalized
    - ICU admittance
    - Discharge
    - Extended care facility admittance(refers to long term care for chronic diseases or prolonged rehabilitation, which is not defined as hospitalization)
14. Documentation from hospital records is acceptable.

    Includes:

    - Limitation on activities due to COVID- 19
    - Ongoing hospital medical care
    - Supplemental oxygen
    - Non-invasive ventilation or high flow oxygen device
    - Mechanical ventilation
    - ECMO, or
15. Adverse events: any events that occur after signing the informed consent are considered AEs as defined in Section 10.3.
16. Concomitant medications: all medications administered within 30 days prior to the first dose of study treatment through 30 days after the last dose of study treatment will be recorded in the concomitant medications, for details refer to Section 6.4.
17. Pharmacokinetics (PK) samples only need to be taken for at least 100 subjects, who will be assigned according. For details refer to Section 7.2.3.
18. All women regardless of childbearing potential must complete a serum pregnancy test at screening visit, urinary pregnancy test on day 28 as per the schedule of assessment for women of childbearing potential. Local laboratories will be used for the analysis of serum and urinary pregnancy tests.
19. Early withdrawal (EW): if the subject is early withdrawn from this study for any reason (Section 7.1.4), the subject should complete the EW visit, and the visit should occur within 2 days of the EW day. The subject will go to the safety follow-up period for additional 28 days after his last dose.
20. D42 (or 28 days ±2 post last dose if subject is withdrawn early) safety follow-up visit is phone call visit.

1 BACKGROUND

Overview of Disease Pathogenesis, Epidemiology, and Current Treatment

Epidemiology

Coronavirus disease 2019 (Covid-19) emerged in late 2019 and spread rapidly, resulting in a global pandemic. New COVID-19 cases and deaths have been constantly rising. As of 20 December 2020, there have been over 75 million cases and over 1.6 million deaths since the start of the pandemic. In the US, the overall cumulative COVID-19-associated hospitalization rate through the week ending 05 December 2020, was 278.7 hospitalizations per 100,000 population. (CDC weekly summary).

Pathogenesis

COVID-19 is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and infected persons can have a wide range of disease severity, with many subjects showing asymptomatic, mild or moderate disease. In severe and critical cases, it results in progressive pulmonary infection, complicated by respiratory failure, with a high prevalence of acute respiratory distress syndrome. According to data from China, 81% of people with COVID-19 had mild or moderate disease, 14% had severe disease, and 5% had critical illness（3）.

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of SARS-CoV-2. Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage (NIH Therapeutic Management of Patients with COVID-19).

Available Therapeutic Options in COVID-19

Although many therapies have been and are being explored in various stages of COVID-19, for the large population with mild and moderate COVID-19, limited treatments are available. By December 2020, the FDA had issued an emergency use authorization (EUA) to only 2 treatments: Bamlanivimab given alone, as well as Casirivimab and Imedevimab given together for the treatment of mild to moderate COVID-19, which could work against the SARS-CoV-2 spike protein to reduce viral replication. However, both EUA-issued treatments are monoclonal antibodies and require IV injection. Therefore, there is a huge unmet medical need for home-use, oral intake, treatments for mild to moderate COVID-19 patients to ameliorate symptoms and prevent hospitalization.

Role of Androgen Receptor Antagonist in COVID-19

SARS-CoV-2 encodes nonstructural and structural proteins required for its viral life cycle. Among them, the spike glycoprotein plays a pivotal role in SARS-CoV-2 infection by recognizing and attaching to ACE2 transmembrane protein on host cells. The spike protein is also cleaved and activated by cell surface TMPRSS2 to facilitate membrane fusion and entry. It has been confirmed that targeting the expression or activity of ACE2 or TMPRSS2 plays a critical role in the pathogenicity of coronavirus infection. In mice models, inhibition of TMPRSS2 function can decrease the SARS-CoV-2 entry into lung cells and similar observation was shown in the inhibition of ACE2 function (5).

Furthermore, it has become clear that there is a gender disparity in severity of COVID-19 with males having higher hospitalization and mortality rates than females.

However, elevated testosterone level has also been observed in most female COVID-19 subjects (Maria Schroeder 2020), and there was a positive correlation between testosterone levels and pro-inflammatory cytokines in female COVID-19 subjects.

The data have shown that treatment with an antiandrogen reduces TMPRSS2 in human lung cells dramatically decreased TMPRSS2 levels in the lungs of mice (1). To determine therapeutic potential, the authors assessed uptake of live SARS-CoV-2 into human lung cells and saw a significant reduction in viral entry and infection upon treatment with an antiandrogen. Together with striking co-expression of AR and TMPRSS2 in specific lung cell types that are targeted by SARS-CoV-2., these data provide strong evidence to support clinical trials to assess the efficacy of antiandrogens as a treatment option for COVID-19.

Introduction to Investigational Treatment(s)

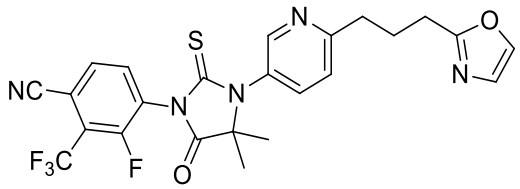
1.2.1 Overview of Proxalutamide (GT0918)

Compound Name: Proxalutamide Tablet (GT0918)

Chemical Name:

4-[4,4-dimethyl-3-[6-[3-(2-oxazolyl) propyl]-3-pyridinyl]-5-oxo-2-thioxo-1-imidazolidinyl]-3-fluoro-2-(trifluoromethyl)-benzonitrile

Chemical Structure



Molecular Formula: $C_{24}H_{19}F_4N_5O_2S$

Molecular Mass: 517.50 g/mol

Dosage Form: Tablet (100 mg)

GT0918 is a new investigational second-generation AR antagonist with more specificity and activity in inhibiting androgen receptors. GT0918 demonstrates a dual mechanism of action in cell assays: inhibiting the binding of androgen to AR as well as exhibiting pharmacological effects of inducing the downregulation of AR expression（2）.

1.2.2 Nonclinical Studies

1.2.2.1 Nonclinical Pharmacology

In vitro studies, GT0918 demonstrates a dual mechanism of action, i.e., highly effective in inhibiting the binding of androgen to AR as well as exhibiting pharmacological effects of inducing the downregulation of AR expression, while bicalutamide and enzalutamide did not affect AR level in the same study, GT0918 also down-regulated AR protein level in tumors in a dose-dependent manner (4).

1.2.2.2 Anti-tumor Activity in Xenograft Models

GT0918 is also effective in blocking AR signaling in breast cancer cells expressing AR. In an anti-proliferation assay, it selectively inhibited the growth of AR+ breast cancer cells such as MCF-7 and MDA-MB-453 while demonstrated no effects toward AR- breast cancer cells such as MDA-MB-231 and MDA-MB-468. Furthermore, GT0918 demonstrated excellent anti-tumor effectiveness in nude mice AR+ breast cancer xenograft tumor models including MCF-7 model and BT474 model. GT0918 did not significantly affect the body weight of animals. The optimal effective dose in nude mice was 10- 20 mg/kg (QD). The in vivo anti-tumor efficacy was better than that of enzalutamide at lower or equal dose.

GT0918 demonstrated the dose-dependent anti-tumor effectiveness in nude mice xenograft tumor models. GT0918 did not significantly affect the body weight of animals and effectively suppressed the elevation of PSA. The optimal effective dose in nude mice was 20 mg/kg (BID). The *in vivo* efficacy was similar to that of enzalutamide but required much lower drug exposure than enzalutamide.

GT0918 is also effective in blocking AR signaling in breast cancer cells expressing AR. In an anti-proliferation assay, it selectively inhibited the growth of AR+ breast cancer cells such as MCF-7 and MDA-MB-453 while demonstrated no effects toward AR- breast cancer cells such as MDA-MB-231 and MDA-MB-468. Furthermore, GT0918 demonstrated excellent anti-tumor effectiveness in nude mice AR+ breast cancer xenograft tumor models including MCF-7 model and BT474 model. GT0918 did not significantly affect the body weight of animals. The optimal effective dose in nude mice was 10- 20 mg/kg (QD). The *in vivo* anti-tumor efficacy was better than that of enzalutamide at lower or equal dose.

1.2.2.3 Safety Pharmacology and Toxicology

An in vitro cardiovascular safety pharmacology study for human ether-a-go-go-related gene (hERG) channel inhibition in CHO cells showed that GT0918 was a very weak hERG-mediated potassium channel blocker, with an IC50 much higher than 10 μM. This strongly suggests that the potential for QT prolongation at clinically relevant concentrations by 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.

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 Sprague Dawley 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.

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.

Altogether, these findings with high doses of GT0918 in animal were 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.

1.2.2.4 Drug Metabolism and Pharmacokinetic

In vitro studies to establish the metabolite profiles of GT0918 were performed in multiple animal species including mouse, rat, dog, monkey, and human. Drug metabolism and pharmacokinetic studies were also performed *in vivo* in rats and dogs.

Chemical inhibitor in human live microsomal incubation indicate CYP3A4 was the major cytochrome P450 enzyme responsible for the formation of major metabolites of GT0918 in human liver microsomes. LC-MS/MS results showed that GT0918 showed no significant inhibition on CYP1A2 and CYP2E1, weak inhibition on CYP2D6, CYP2C9, CYP2C19 and CYP3A (midazolam), but marked inhibition on CYP3A4 (testosterone). Therefore, the inhibitory effect of GT0918 on CYP3A4 *in vitro* and the corresponding *in vivo* drug interaction potential needs to be further investigated.

1.2.2.5 GT0918 Effect on TMPRSS2 and ACE2 Expression

The spike glycoprotein plays a pivotal role in SARS-CoV-2 infection by recognizing and attaching to ACE2 transmembrane protein on host cells. The spike protein is also cleaved and activated by cell surface TMPRSS2 to facilitate membrane fusion and entry. GT0918 has shown to inhibit protein expression of ACE2 and TMPRSS2 induced by androgen-AR activation in prostate and lung epithelial cells.

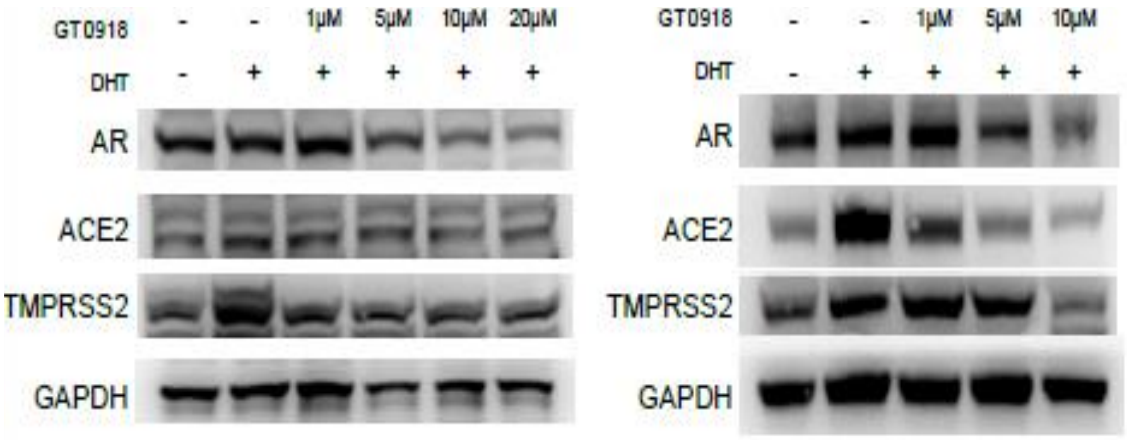


Figure 2. The protein levels of AR, ACE2 and TMPRSS2 in LNCaP (left) and A549 (right) cells with the indicated treatment were determined by western blotting.

GT0918 was also showed to inhibit macrophage activation markers iNOS and TNF-α expression induced by Lipopolysaccharide in macrophage cells. These results suggested that GT0918 could inhibit the pathogen-induced macrophage activation.

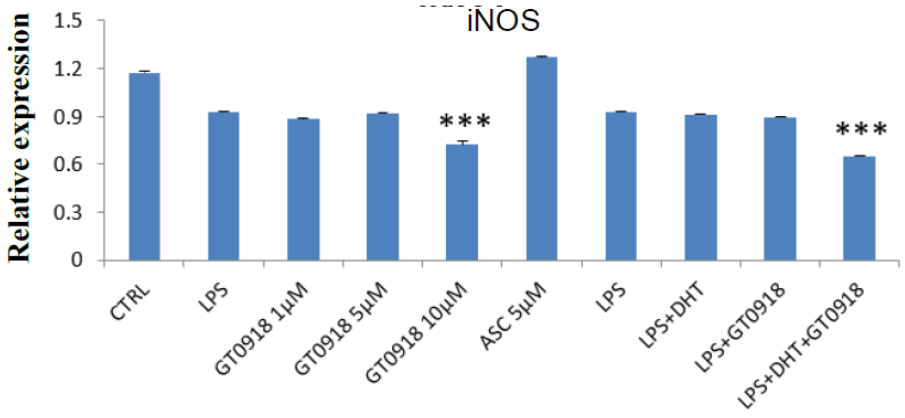


Figure 3 Relative expression of iNOS in RLE-6TN cells with the indicated treatment was determined by Quantitative PCR.

Recently, using this SARS-CoV-2 bioassay platform, we demonstrated that Proxalutamide more effectively inhibited SARS-CoV-2 infection than Enzalutamide in LNCaP cells in a dose-dependent manner, with concentration that inhibits response by 50% (IC50) values of 97 nM.

We have also compared the effect of Proxalutamide with Enzalutamide on the expression of androgen receptor (AR), ACE2 and TMPRSS2 in an AR overexpressing/androgen independent prostate cancer cell line C4-2B at the concentration of 12.5μM (data on file). The results showed that proxalutamide more effectively inhibited the expression of AR, ACE-2 and TMPRSS2 than

Enzalutamide in C4-2B cells. These results suggest that GT0918 should more effectively inhibit AR-dependent expression of ACE-2 and TMPRSS2 than Enzalutamide in a variety of SARS-Cov2 infected organs, including lung, GI, heart, and kidney.

1.2.3 Clinical Studies

1.2.3.1 Clinical Studies in Solid Tumors

Four clinical studies are ongoing in both China and the US and 3 studies conducted both in China and in US have been completed in prostate cancer and breast cancer.

1.2.3.1.1 Completed Clinical Studies in Solid Tumors

GT0918-US-1001

The US study is a Phase I/II open-label, non-randomized, dose escalation, 2-part, study in subjects with metastatic castrate resistant prostate cancer (mCRPC) who progressed after both hormonal therapy (abiraterone or enzalutamide) and chemotherapy (docetaxel), or who could not tolerate either or both therapies. The finished Phase 1 part (GT0918-US-1001) was a multiple dose-escalation evaluation to establish safety and tolerability of GT0918. Total of 40 subjects were enrolled into this study at 7 dose levels: 50 mg (n=3), 100 mg (n=6), 200 mg (n=6), 300 mg (n=7), 400 mg (n=7), 500 mg (n=6) and 600 mg (n=5). Of the 40 subjects in the GT0918-US-1001 study, 39 (98%) experienced at least 1 treatment-emergent adverse events (TEAE) during the study, with the most frequent AEs being fatigue, nausea, decreased appetite, anemia, weight decrease, diarrhea, constipation, back pain, and dizziness. Most of subjects reported TEAEs that were considered related to the study drug, with the most common drug-related AEs being fatigue (42.5%), decreased appetite (20%), nausea (15%), dizziness (12.5%), constipation (12.5%), anemia (10%), weight decrease (10%), dysgeusia (10%), and diarrhea (7.5%). Most TEAEs were Grade 1 or 2. Twenty subjects across all dose cohorts reported TEAEs of Grade 3 or higher. Each individual TEAE of Grade 3 or higher occurred sporadically in 1 or 2 subjects, except for the following: anemia (7/40), fatigue (5/40) and sepsis (3/40). The majority of Grade 3 or higher TEAEs were considered not related to the study drug. All serious adverse events (SAEs) and Grade 3 or higher AEs were reported across all dose cohorts. The majority of SAEs and Grade 3 or higher AEs, as well as 2 deaths, were due to disease progression and were not related to the study drug, except for one event of Grade 4 increased creatine phosphokinase (CK).

Overall, GT0918 was generally well tolerated in mCRPC subjects who had progressed after multi-lines of hormone therapies and chemotherapies. No DLT was reported and MTD was not established. No partial response (PR) or complete response (CR) was observed in the study. Clinical responses of stable disease (SD) were observed and used for decision on-treatment continuation. Dose levels of 400 and 500 mg/day were chosen for the Phase 2 study to further establish the safety and tolerability of GT0918.

GT0918-CN-1001

The GT0918-CN-1001 study was a Phase 1 study, conducted in China, to investigate safety, tolerability, and pharmacokinetics of GT0918 in subjects with advanced CRPC. Nineteen subjects were enrolled, and 16 subjects were treated with GT0918 at f5 dose levels: 50 mg (n

= 2), 100 mg (n = 4), 200 mg (n = 3), 300 mg (n = 3) and 400 mg (n = 4). GT0918 showed some preliminary anti-tumor activity. No DLT was observed. The MTD was not reached. All the GT0918-related adverse events (AEs) were Grade 1, including hypercholesterolemia, hyperglyceridemia, anemia, hot flush, fatigue, constipation, and loss of appetite. All subjects who received GT0918 showed some preliminary anti-tumor activity with SD (bone scans showed no change in target and non-target lesions comparing with baseline).

GT0918-CN-1003

The GT0918-CN-1003 was an open-label, randomized, Phase 2, multicenter study to evaluate the safety and efficacy in subjects with mCRPC. Total of 108 subjects were enrolled in the study and randomized in 1:1:1 ratio in to 100 mg, 200 mg and 300 mg cohorts: 100 mg (n=37), 200 mg (n=35) and 300 mg (n=36). Eighty-one subjects (75.0%) experienced ⩾grade 1 drug-related AEs. Fourteen subjects (13.0%) experienced ⩾ Grade 3 AEs based on CTCAE v4.03. Most common drug-related AEs experienced ⩾10% of subjects included aspartate aminotransferase increased (AST) (14.8%), alanine aminotransferase increased (ALT) (13.0%), white blood cell count decreased (12.0%), appetite decreased (13.0%), asthenia (17.6%), anemia (14.8%) and proteinuria (12.0%). Grade 3 asthenia, Grade 2 vomiting, Grade 2 hypokalemia, Grade 2 lung infection, Grade 3 anemia were the reported SAEs among all subjects. There were about 41.9% subjects who experienced Prostate-Specific Antigen (PSA) 50 reduction. Based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 evaluation, the Overall Response Rate (ORR) was 15.8% and Disease Control Rate (DCR) was 78.9%.

1.2.3.1.2 Ongoing Clinical Studies in Solid Tumors

GT0918-US-1002

The ongoing GT0918-US-1002 study was an open-label randomized, expanded/phase 2 study in subjects with metastatic hormone sensitive prostate cancer (mHSPC) or mCRPC who progressed after either Abiraterone or Enzalutamide treatment to further evaluate the safety, tolerability, and anti-tumor activity of once daily orally administered GT0918.

GT0918-CN-1004

A Phase 3, multicenter, randomized, double-blind, placebo-controlled study is being conducted to evaluate the efficacy and safety of GT0918 in subjects mCRPC who progressed after both Abiraterone and Docetaxel in China. Subjects in the GT0918 cohort or control cohort received GT0918/placebo tablets 200 mg QD until radiographic progression, unacceptable toxicity, or withdrawal from the study.

GT0918-CN-1005

A Phase 3, multicenter, randomized double-blind study to evaluate the efficacy and safety of GT0918 in combination with Abiraterone vs Placebo plus Abiraterone as first-line treatment in subjects with mCRPC in China. This two-stage study consisted of a dose-finding stage followed by a dose-expansion stage.

GT0918-CN-2001

A Phase 1/1b study is being conducted to assess the safety, tolerability, and pharmacokinetics of GT0918 in subjects with advanced breast cancer. This two-stage study consisted of a dose-escalation stage followed by a dose-expansion stage. All subjects received oral GT0918 once daily until disease progression, unacceptable toxicity, or withdrawal from the study.

1.2.3.2 Clinical Study in COVID-19

A randomized, double-blinded, clinical study of GT0918 was done in Brazil for both male and female subjects with mild or moderate COVID-19 illness (NCT04446429). Two hundred and sixty-two (262) men were included in the study. 134 men were assigned to the GT0918 group and 128 men were assigned to the control group. The mean age was 44.5±7.7 years old. Thirty-five subjects (27%) were hospitalized in the control group compared to 0 patients in the GT0918 group by Day 30. The proportion of COVID-19 subjects hospitalized was significantly different between the GT0918 and control arms; $p<0.0001$. No subject receiving GT0918 died compared to 2% in the control group. Additionally, it also showed a clinical meaningful SARS-Cov-2 viral load reduction and clearance in the GT0918 group compared to the placebo group (RT-PCR positive rate: 42.5% vs 93.8% on Day 7, 15.0% vs 56.2% on Day 14 and 10.0% vs 43.8% on Day 28, respectively).

Treatment-emergent adverse events were reported for 34% of subjects in the GT0918 group and for 61% of subjects in the placebo group. SAEs were only reported in the placebo group. There was no AE leading to discontinuation.

The most frequently reported TEAEs (occurring in ⩾10% of subjects) were diarrhea (21%), dehydration (15%), nausea (14%), abdominal pain (12%), dyspepsia (11%) and back pain (10%) in the GT0918 group. The most frequently reported TEAE were disease progression (54%), fatigue (45%), shortness of breath (36%), fever (20%), dehydration (14%), anosmia (13%), ageusia (12%), back pain (12%), and ear pain (10%) in the placebo group. Gastrointestinal TEAE were more frequent in the GT0918 group. General, respiratory, and nerve system TEAEs are more frequent in the placebo group. The TEAEs suspected to be related with study treatment (⩾10%) were diarrhea, nausea, abdominal pain and dyspepsia in the GT0918 group. No SAE was reported in the GT0918 group. Acute respiratory distress syndrome was reported as SAE in 27% of the subjects in the placebo group.

178 female subjects were randomized to the study with 76 in the GT0918 group and 102 in the control group. All subjects were also treated with the standard of care.

The mean age was 44.2 years old. Nineteen subjects (19%) were hospitalized in the control group compared to 2 patients (3%) in the GT0918 group by Day 30 . ($p<0.0001$). No subject receiving GT0918 died compared to one (1%) in the control group.

Treatment-emergent adverse events were reported with 36% of subjects in the GT0918 group and with 55% of subjects in the placebo group. TESAEs were reported with 3% and 19% of subjects in the GT0918 and placebo groups respectively.

Gastrointestinal TEAE were more frequent in the GT0918 group compared with the control group: Diarrhea (17% vs. 10%), Nausea (12% vs. 6%), Abdominal pain (12% vs 5%), Dyspepsia (12%

vs. 4%).Therefore, GT0918 may be an excellent treatment option to improve the clinical outcomes and reduce the hospitalization for COVID-19 infected patients.

Risks and Benefits

1.3.1 Overall Benefit-Risk

GT0918 dosed at 200 mg once daily has shown remarkable activity for accelerating SARS-Cov-2 clearance and decreasing the hospitalization rate significantly in subjects with mild to moderate COVID-19 illness. The clinically meaningful benefit combined with the clinically manageable safety profile of GT0918 strongly support a positive benefit-risk balance for treatment of COVID-19 subjects.

1.3.2 Potential Benefits to Clinical Study Subjects

All subjects with COVID-19 mild/moderate illness enrolled in this study will be randomized to receive GT0918 or placebo plus standard of care. The efficacy of GT0918 seen in the IIT study (NCT04446429) is highly encouraging in patients with mild or moderate COVID-19 illness. Based on preclinical and preliminary clinical data (Section 1.2.2 and 1.2.3), treatment with GT0918 is expected to be well tolerated and it is hypothesized that it will result in preventing disease progression by decreasing the expression of ACE2 and TMPRSS2 and preventing SARS-CoV-2 entry into lung cells.

1.3.3 Potential Risks to Clinical Trial Subjects

The safety profile of GT0918 is manageable. The adverse events identified with GT0918 treatment in COVID-19 were gastrointestinal AEs, including diarrhea, nausea, abdominal pain and dyspepsia.

In the study for subjects with COVID-19, there were no treatment related AEs or serious AEs during the course of the study.

Subjects in this study will be carefully monitored for key toxicities that have been observed with GT0918 with the following assessments: periodic laboratory, renal, and liver function, and coagulation. Risk will be further minimized by adherence to inclusion/exclusion criteria, avoidance of prohibited medication, close safety monitoring and dose modification guidelines. An independent data committee (IDMC) will be constituted and will monitor safety, efficacy as outlined in the protocol. A steering committee (SC) will be established comprising of investigators and Kintor personnel participating in the study to ensure transparent management of the study according to the protocol. A Kintor/delegated CRO safety management team will periodically review and evaluate all emerging data across the GT0918 program for potential safety signal assessment in a timely manner.

Furthermore, due to the short treatment duration (14 days) of 200 mg once a day, the risk of SAEs should be lower than completed and ongoing studies in oncology.

2 RATIONALE

2.1 Study Rationale and Purpose

The glycoprotein spikes on the surface of SARS-CoV-2 utilize membrane ACE2 receptors and TMPRSS2, to enter the host cells (6). Thus, targeting the expression or activity of ACE2 or TMPRSS2 plays a critical role in reducing the pathogenicity of coronavirus infection, GT0918 can down-regulate the ACE2 and TMRPSS2 expression in prostate, lung cancer cell lines and lung epithelial cell lines. Furthermore, the clinical study of GT0918 in Brazil for COVID-19 (NCT04446429) showed a clinically meaningful SARS-CoV-2 viral load reduction and clearance, decreased the hospitalization rate significantly in the GT0918 group compared to the placebo group. Therefore, GT0918 may be an efficient option to improve clinical outcome and reduce the rate of hospitalization in COVID-19 infected patients. Since SARS-CoV-2 replication is greatest just before or soon after symptom onset, GT0918 is likely to be most effective when used early. Therefore, in this study, GT0918 will be administered to evaluate the efficacy and safety in COVID-19 infected outpatients with mild or moderate symptoms.

2.2 Rationale for Study Design

This is a randomized, placebo-controlled two-arm study with the objective to evaluate the efficacy and safety of GT0918 in outpatients with mild or moderate COVID-19 illness. The study is designed per FDA guidance (COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (fda.gov)).

The randomized, double-blind, placebo-controlled, multicenter, parallel group design is the gold standard for a phase III study as it minimizes allocation bias, balancing both known and unknown prognostics factors in the assignment of treatments. The study is stratified by sex, race and ethnicity, the risk factors of COVID-19 severity (Section 4.1.1) The study will be conducted in outpatients including subjects with underlying medical conditions such as the elderly, underlying cardiovascular or respiratory disease, diabetes, chronic kidney disease, or other comorbidities. Both male and female subjects are being studied in line with the anti-androgenic mechanism of action, since elevated testosterone level has also been observed in most female COVID-19 subjects, and a positive correlation between testosterone levels and pro-inflammatory cytokines in female COVID-19 subjects (Maria Schroeder 2020).

The trial will ensure to include Hispanic, Latino non-Hispanic black, and others from United states and other countries.

The study drug GT0918 is evaluated in randomized, placebo-controlled, double-blind clinical studies using a superiority design. A futility analysis will be done for initial assessment of potential benefit before enrolling a large number of subjects.

IDMC will be used to ensure subject safety and study integrity.

The standard of care is accepted in both arms which is described in Section 6.4.

The primary endpoint is the percentage of subjects who do not experience all-cause hospitalization for at least 24 hours, do not require supplemental oxygen for at least 24 hours in response to SpO2 ⩽93% and are alive by Day 28.. Considering the incapability to hospitalize the subjects who meet the criteria of hospitalization, the supplemental oxygen requirement

provided outside for equal to or longer than 24 hours in response to SpO2 ⩽93% is also considered as the hospitalization. All-cause death by day 28 will also be included.

Proportion of patients alive, non-hospitalized and free of oxygen is generally considered an adequate composite study endpoint to measure clinical improving. Defining hospitalization as requiring greater than or equal 24 hours in patient care within 28 days of randomization eliminates the majority of patients who might attend hospital for reasons other than deterioration to severe disease or for necessary management of their condition.

According to FDA guidance, the 28-day time frame of endpoint is appropriate in the outpatient treatment trial.

The primary efficacy analysis will be conducted in the mITT population.

The secondary endpoints include the symptom improvement, symptom resolution, NIAID 8-point scoring scale, all-cause and COVID-19 related hospitalization, mechanical ventilation, viral load reduction and clearance at specific time points during the study and are designed to monitor response to GT0918 in terms of other important clinical and virological outcomes.

In addition, C_{trough} values will be monitored to establish exposure-response relationship of GT0918 in the treatment of SARS-CoV-2. The relevant biomarkers analysis will also be performed to evaluate their association with observed clinical responses to GT0918 and the disease state.

2.3 Rationale for GT0918 Dose and Regimen Selection

A dose of 200 mg was recommended based on a phase 2 study in prostate cancer with 28 days as a cycle, until disease progression. Fourteen days is used in this study to align with the standard time course of COVID-19. Based on available preliminary data from Brazil IIT study in subjects with COVID-19 mild/moderate illness, 200 mg, QD for 15 days has been demonstrated to be effective and displayed adequate safety in the treatment of COVID-19. Therefore, almost the same dose regimen is being used in this study with the same patient population as was used in the Brazilian study.

2.4 Rationale for Choice of Comparator Drugs

Subjects enrolled in this study will either be mild or moderate COVID-19 who are not hospitalized. There are no approved treatment options for this patient population except an EUA for the investigational monoclonal antibody therapy. Bamlanivimab alone or Casirivimab and Imedevimab given together_or Bamlanivimab and etesevimab given in combination for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Therefore, placebo comparator was selected, however, best supportive therapy/standard of care except those are prohibited in Section 6.4.2 can be administered in both treatment and control groups as required at the investigator's discretion.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary**
To evaluate the efficacy in terms of clinical status following treatment with GT0918 compared to placebo	Percentage of subjects who do not experience any of the following events due to all causes by Day 28: • Hospitalization for ≥ 24 hours • Supplemental oxygen for ≥24 hours in response to SpO2 ≤93% • Death
Secondary	**Secondary**
To evaluate the clinical efficacy of GT0918 compared to placebo using the NIAID 8- point scoring scale	Percentage of subjects achieving each clinical status on Days 7, 14 and 28 as defined below based on The National Institute of Allergy and Infectious Diseases (NIAID) 8- point scoring scale: 1 Death 2 Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) 3 Hospitalized, on non-invasive ventilation or high flow oxygen devices 4 Hospitalized, requiring supplemental oxygen 5 Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise) 6 Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care 7 Not hospitalized, limitation on activities and/or requiring home oxygen 8 Not hospitalized, no limitations on activities

To evaluate the clinical efficacy of GT0918 compared to placebo based on clinical status	• Proportion of subjects with all-cause hospitalization (defined as ≥24 hours) by Day 28 • Proportion of subjects hospitalized (defined as ≥24 hours) due to COVID-19 related events by Day 28 • Days of hospitalization due to all causes or COVID-19 • Proportion of subjects with all-cause mortality by Day 28 • Proportion of subjects with COVID-19 related mortality by Day 28 • Proportion of subjects admitted to an ICU due to COVID-19 by Day 28 • Days in intensive care unit (ICU) • Proportion of subjects requiring supplemental oxygen, high-flow oxygen, any ventilation or ECMO due to COVID-19 by Day 28 • Proportion of subjects requiring mechanical ventilation or ECMO due to COVID-19 by Day 28 • Days on supplemental oxygen/high flow oxygen devices/mechanical ventilation
Characterize the effect of GT0918 compared to placebo on symptom improvement or resolution	**Symptom Improvement:** • Change in symptom score (total of ratings) from baseline to Days 3, 7, 14 and 28 • Time to symptom improvement • Proportion of subjects demonstrating symptom improvement via the symptom questionnaire (total of ratings) on Days 3, 7, 14 and 28 **Symptom resolution:** • Proportion of subjects demonstrating symptom resolution via the symptom questionnaire on Days 3, 7, 14 and 28 • Time to symptom resolution
Characterize the effect of GT0918 compared to placebo on SARS-CoV-2 viral load clearance	• Change from baseline to Days 3, 7, 14 and 28 in SARS-CoV-2 viral load • Proportion of subjects that achieve SARS-CoV-2 clearance (Days 3, 7, 14 and 28) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed to days 3, 7, 14 and 28
Characterize the effect of GT0918 compared to placebo on safety	Safety assessments such as AEs, SAEs and laboratory data
Exploratory	**Exploratory**
Characterize the pharmacokinetics of GT0918	• Mean trough concentration of GT0918 and GT0955 on Days 1, 3, 7 and 14 • To explore relationships between GT0918 and/or GT0955 exposure and selected efficacy and safety endpoints and/or biomarkers

Characterize emergence of viral resistance to GT0918	Screening for novel mutants in patients who do not respond to GT0918 • Genotype of SARS-CoV-2 viral isolates
To explore biomarkers predictive of GT0918 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes	The association between changes in disease related biomarkers with clinical endpoints

4 STUDY DESIGN

4.1 Description of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of Proxalutamide (GT0918) in adult outpatients diagnosed with mild to moderate COVID-19. The study will be 2-arm comparison against matched placebo. The study will be conducted in around 100 sites in the USA and other countries.

This study utilizes an adaptive design that maximizes our efficiency in identifying a safe and efficacious therapeutic agent for COVID-19 during the current outbreak. There will be an interim analysis after 334 subjects complete Day 28 after the first dose to allow early stopping for futility, efficacy, or safety.

The study population will be subjects with mild to moderate COVID-19 illness chosen to evaluate if early intervention with anti-androgen therapy prior to respiratory compromise can effectively prevent progression to the severe form of COVID-19 illness.

Randomization is essential for establishing efficacy of these new therapeutic agents.

The blood samples for PK analysis need to be collected for at least 200 subjects, whom will also be randomized into the interventional treatment or placebo group with 1:1 ratio.

Schema

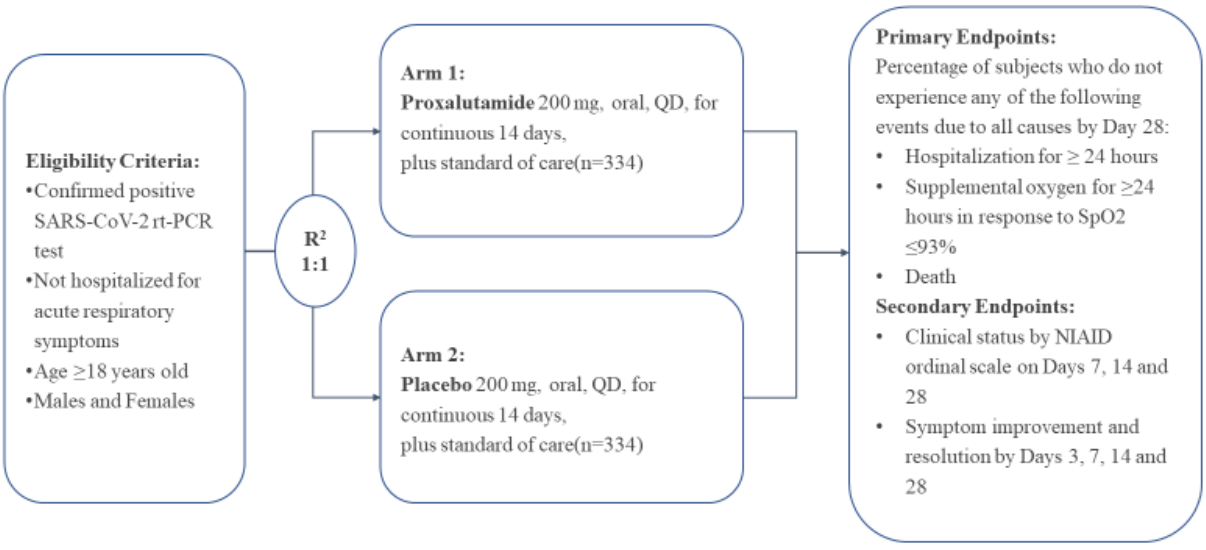


Figure 4: Study GT0918-US-3001 schema.

4.1.1 Screening and Randomization

After signing the study ICF, the screening assessments will be done within 1 day prior to randomization for selected assessments (See SoA) for the list of assessments to be performed).

The investigator will review symptoms, risk factors and other inclusion and exclusion criteria to confirm subject's eligibility.

Subjects will be randomized into 1 of 2 arms with 1:1 ratio, each will receive an interventional treatment/placebo.

Randomization will be stratified by the following factors:

- Sex: Male or Female
- Race and ethnicity (non-Hispanic White or others /Hispanic or Latino /non-Hispanic Black)
- Number of risk factors 0, 1-2, ≥3 (based on CDC defined conditions https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Adults with the following conditions are at increased risk of severe illness from the virus that causes COVID-19:
    - Age ≥ 65 years
    - Cancer
    - Chronic kidney disease
    - Chronic lung diseases, including COPD (chronic obstructive pulmonary disease) asthma (moderate to severe),interstitial lung disease, cystic fibrosis, and pulmonary hypertension
    - Dementia or other neurological conditions
    - Down Syndrome
    - Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies or hypertension
    - Immunocompromised state (weakened immune system) from solid organ transplant
    - Liver disease
    - Overweight and Obesity (body mass index [BMI] ≥25 kg/m^2)
    - Sickle cell disease or thalassemia
    - Smoking, current or former
    - Diabetes Type 1 or type 2)
    - HIV infection
    - Solid organ or blood stem cell transplant
    - Stroke or cerebrovascular disease, which affects blood flow to the brain

- Substance use disorders
- Others per most updated list from CDC website as above

4.1.2 Treatment Duration

Subject will receive treatment for 14 days, Day 1 to Day 14. From screening visit Day -1 to visit Day 28 ± 2 days post last treatment which corresponds to Day 42 Safety Follow-up visit. The scheduled procedure shown in the Schedule of activities (SoA)

4.2 Timing of Interim Analyses and Design Adaptations

The ongoing study may be modified based on planned interim analyses. Based on the observed data at the time of the interim analyses, the study may:

- suspend enrollment to GT0918 treatment arm demonstrating lack of efficacy, and/or
- initiate/expand enrollment to the existing GT0918 treatment arm

The modifications proposed are done so to ensure subjects are being exposed to treatment with an acceptable risk-benefit profile during the ongoing study. Additionally, the potential modifications will provide information to characterize the dose response profile more fully.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by IDMC members.

4.3 End of the study

A subject is considered to have completed the study if he has completed all required phases of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last enrolled subject or last ongoing subject in the study, whichever comes later.

4.4 Early Study Termination

The study can be terminated at any time for any reason by Kintor. Should this occur, the subject should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn subjects. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interest. The investigator will be responsible for informing IRBs and/or ECsof the early termination of the trial.

5 POPULATION

5.1 Patient Population

The target population of this study are those adult subjects with mild to moderate COVID-19 illness with first positive SARS-CoV-2 virus test within 3 days, to evaluate if anti-androgen therapy may effectively prevent progression to the severe form of COVID-19 illness by treating this population early in their disease course and prior to respiratory compromise and failure. This study plans to have around 668 subjects in the US or may expand to other countries/regions for GT0918 and the placebo groups, the randomization rate is 1:1.

5.2 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. The subject or legally authorized representative give signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Understand and agree to comply with planned study procedures.
3. Male and non-pregnant female subjects with age ≥18 years of age at the time of randomization.
4. Are currently not hospitalized.
5. Have one or more COVID-19-related symptoms within 5 days of symptoms onset ((FDA COVID-19-Related symptom guidance, See Appendix 2, available at: https://www.fda.gov/media/142143/download)
6. Must have first positive SARS-CoV-2 viral infection determination (has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen) ≤3 days prior to start of the first dose.
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception, as shown below, throughout the study and for 3 months after stopping GT0918 treatment. Highly effective contraception methods include:
    - Total Abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception, or
    - Use of one of the following combinations (a+b or a+c or b+c):

      a: Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

      b: Placement of an intrauterine device (IUD) or intrauterine system (IUS);

      c: Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository;

- Female sterilization (have had prior surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment;
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject;

In case of use of oral contraception women should have been stable for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, is she considered not of childbearing potential

8. Regardless of their fertility status, male subjects must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective method of contraception (less than 1% failure rate) or effective method of contraception with nonpregnant women of childbearing potential partners for the duration of the study and until 90 days after the last dose.
9. Agree to the collection of nasopharyngeal swabs and venous blood.

5.3 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Have $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA resource page, https://www.fda.gov/media/137926/download)
2. Estimated glomerular filtration rate (eGFR) < 30 ml/min
3. Serum total bilirubin > 1.5 x ULN (upper limit of normal) and AST and ALT >3 x ULN
4. Subjects with significant cardiovascular disease as following:
   i. heart failure NYHA class ⩾3
   ii. left ventricular ejection fraction <50%
   iii. those with a history of cardiac arrhythmias, including long QT syndrome.
5. Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19 or requires treatment with supplemental oxygen.
6. Have known allergies to any of the components used in the formulation of the interventions.
7. Have hemodynamic instability requiring use of vasopressors within 24 hours of randomization.
8. Suspected or proven serious, active bacterial, fungal, viral, or other infection (except COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention (i.e. known history of human immunodeficiency virus [HIV]).

9. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 30 days.
10. Have any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in this study.
11. Subjects with myopathy
12. Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), where prior use is defined as the past 30 days or less than 5 half-lives of the investigational product (which is longer) from screening.
13. Have participated, within the last 30 days before dosing, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
14. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
15. Subject taking or had taken an anti-androgen of any type including androgen depravation therapy, 5-alpha reductase inhibitors, etc. within 3 months before dosing.
16. Are investigator site personnel directly affiliated with this study.

6 TREATMENT

6.1 Study Treatment

For this study, study treatment in this study refers to GT0918 in the treatment arm and placebo in the placebo arm. GT0918 will be supplied by Kintor or its designee as 100 mg tablets as individual patient supply packaged in blister. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.1 Dosing Regimen

Eligible subjects will be randomized before or on Day 1 to receive either GT0918 or matched placebo. GT0918/placebo will be given 200mg orally once daily on Days 1-14 during the study period. Days 15-28 will be the post-treatment period without dosing with GT0918/placebo.

The study drug will be administered as a flat-fixed dose and not by body weight or body surface area. The dose should be given the same time each day (+/- 2 hours for medication scheduling) around 30 minutes after meal for consecutive 14 days. During screening visit (D-1) or D1, after confirmation of subject's eligibility, the drugs or placebo as well as Subject Diary with Questionnaire will be provided to subjects. The subject will document the dose date/time with the Diary and answer the Questionnaire daily.

The study treatment period is shown as below.

Timeline

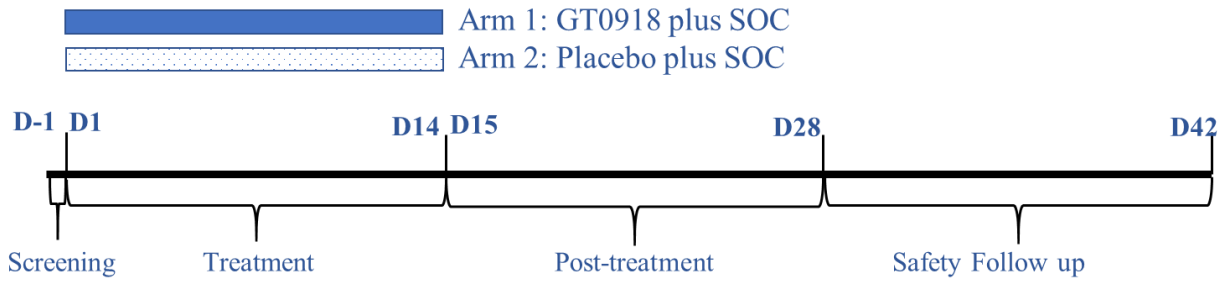


Figure 5. Overview of study period and group assignment

The investigator or responsible personnel will instruct the subject to take the study drugs as per-protocol. Subjects will be instructed to return unused study drugs (if applicable) to the sites at discontinuation or completion of treatment. The site personnel will ensure that appropriate dose of each study drug is administered, and that drug accountability is performed.

6.1.1.1 General Dosing Guidelines

The study treatments should be taken as follows:

- Subjects should be instructed to take the study treatment of GT0918/placebo two tablets together with a glass of water once a day at the same time each day.
- In general, study treatment may be taken after normal conventional meal (±2 hours for medication scheduling).
- Subjects will be instructed to swallow the tablets whole and not to chew or crush them.
- If vomiting occurs, during the course of treatment, no re-dosing of the drug is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during the treatment period must be noted in the AEs section of the eCRF. Missing dose should be documented at Subject Diary.
- Any doses that are missed should be skipped and should not be replaced or made up on a subsequent day.
- Subjects try to avoid consumption of grapefruit, grapefruit hybrids, pomelos, starfruit, Seville oranges or products containing their juice during the treatment period. These foods are known as CYP3A4 inhibitors and have a potential to increase exposure to GT0918. Orange juice is allowed.
- Multivitamins are permitted.

6.1.2 Guidelines for Continuation of Treatment

The treatment course continues as described above even if the subject becomes SARS-CoV-2 test negative.

6.1.3 Ancillary Treatments

This section is not applicable for this study.

6.1.4 Rescue Medication

This section is not applicable for this study.

6.1.5 Treatment Duration

The treatment period starts from Day 1 (first oral administration of drug or placebo) to D14, 14 consecutive days.

6.2 Dose Escalation

This section is not applicable for this study. No dose escalation or de-escalation is allowed through the whole study.

6.3 Dose Modifications

6.3.1 Dose Discontinuation

Any subject who develops ⩾ Grade 3 treatment emergent adverse events that are possibly, probably or definitely related to the study drug as assessed by the investigator will discontinue the treatment. There is no dose interruption or dose reduction in this study.

The treatment course should be continued if the subject becomes SARS-Cov-2 test negative or experiences complete resolution of symptoms.

For the subjects who are hospitalized during the study, the subject may continue the study treatment at the investigator's discretion based on individual benefit/risk assessment.

6.3.2 Follow-Up for Toxicities

Subjects, whose treatment is permanently discontinued due to an AE must be followed up at least twice a week if applicable (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks or until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (Section 7.1.6). Further information on follow-up procedures is provided in Section 8.1.

6.3.3 Anticipated Risks and Safety Concerns of the Study Treatment

Appropriate eligibility criteria and stopping rules are included in this protocol. Recommended guideline for supportive treatment for expected toxicities, including management of study drug induced AEs are provided in Section 6.3.2. More anticipated risks and safety concerns, reference of preclinical toxicity and clinical data are in the IB.

6.4 Concomitant Medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the subject is permitted, except when specifically prohibited.

The subject must be told to notify the investigational site about any new medication he takes after the start of study treatment. All medications, including herbal/natural medications (excluding study treatment), surgeries, and procedures (including physical therapy) administered within 30 days prior to the first dose of administration of study treatment through 28 days after the last dose of administration study treatment will be recorded in the concomitant medications or surgical and medical procedures eCRF, respectively.

6.4.1 Permitted Concomitant Therapy

Prior Treatment for Indication

Any prior therapy, such as antivirals, antibiotics, or antimalarials used as treatment prior to signing informed consent should be recorded.

Therapy prior to enrollment with antivirals including lopinavir/ritonavir, remdesivir, or other therapeutic agents (e.g., corticosteroids) are permitted.

Concomitant Therapy During the Study

Subjects should be treated according to standard of care, even as it evolves, and medications may be part of the treatment paradigm.

Therefore, remdesivir may be initiated as standard of care for subjects hospitalized with severe disease (if available through the FDA Emergency Use Authorizations) outside of local standard of care per written policies or guidelines.

If the local standard of care per written policies or guidelines (that is, not just an individual clinician decision) includes lopinavir/ritonavir, chloroquine, hydroxychloroquine or other investigational agents, then initiating these during the study is permitted, but may require additional safety monitoring by the site.

Acetaminophen and corticosteroid use are permitted during the study per investigator's discretion.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Sponsor if required.

Any medication, including not only physician prescribed medications, but also all over-the counter (OTC) medications, herbal medications, vitamin supplements, blood transfusion or others that the subject is receiving at the time of enrollment or during the study must be recorded along with:

- Reason for use including standard of care for COVID-19.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency for concomitant therapy.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

6.4.2 Prohibited Concomitant Therapy

Strong CYP3A enzyme inhibitors and inducers and P-gp transporter inhibitors and inducers are prohibited.

Any medicine or treatment may influence evaluation of efficacy of study drug is prohibited, Spironolactone, anti-androgen drug or treatment including but not limited to 5α-Reductase Inhibitors, androgen deprivation therapy, Enzalutamide, Bicalutamide, Abiraterone. Or Cycloprogesterone, Androgen, Estrogen or AR antagonists.

Convalescent COVID-19 plasma treatment is not allowed. The monoclonal antibody therapy Bamlanivimab alone, or Casirivimab and Imedevimab in combination under the EUA for the treatment of mild to moderate COVID-19 patients is prohibited in this study.

6.4.3 Concomitant Therapy to Be Used with Caution

Concomitant treatment of GT0918 with weak inhibitors or inducers of CYP3A4 is permitted. Caution is advised when GT0918 is co-administered with drugs that are moderate/strong inhibitors or inducers of CYP3A4. Duration of concomitant treatment should be kept as short as possible, or completely avoided whenever possible. Subjects receiving such medications must be monitored closely for any potential toxicity or decreased clinical benefit due to any individual concomitant medications.

Concomitant treatment of GT0918 with medications which have narrow therapeutic index/sensitive substrates for CYP3A4/2D6 is allowed with caution. Detailed lists of inhibitor, substrates and inducers of CYP3A or pertinent medicines are listed to Appendix 1.

Any narrow therapeutic index/sensitive CYP 3A, or 2D6, or both substrate drug(s) should be excluded from patient use if possible, then switch to a suitable alternative drug(s). If no suitable alternatives are available, it is recommended to reduce the dose of the narrow therapeutic index/sensitive CYP 3A, or 2D6, or the substrate drug(s).

Inducers or nutritional supplement of cytochrome P450 3A4, such as St. John's Wort Extract grapefruit, and immunosuppression medicine are needed to be used with caution.

6.5 Patient numbering, Treatment Assignment or Randomization

6.5.1 Patient numbering

Each subject will be assigned with unique number after signing off the inform consent form, which is the screening number, composite with site number 001 and subject number 001, 002…. After the screened subject is confirmed eligible to randomization, the screen number will service as the randomization number. Screen failure subject's number will not be assigned to other subjects. Re-screen may not be allowed, but retest with screening window or on D1 is allowed.

6.5.2 Treatment Assignment or Randomization

All subjects will be centrally randomized to study intervention using an interactive web response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. Subjects will be stratified by sex, race/ethnicity and risk factors of COVID-19 (Section 4.1.1).

All eligible subjects will be randomized initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made to achieve an equal allocation across the treatment arms at the end of enrollment.

6.5.3 Treatment Blinding

This is a double-blinded study. Neither subjects, nor investigators, nor the Sponsor study team will be aware of treatment assignments prior to the final data base lock at the conclusion of the study.

Unblinding procedures for this study

- Emergency unblinding for AEs may be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS.
- In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' intervention assignment is warranted.
- Subject safety must always be the first consideration in making such a determination. However, the investigator should make all attempts to contact the medical monitor in advance of unblinding.
- If a subject's intervention assignment is unblinded, the Sponsor must be notified immediately after breaking the blind even if consultation occurred in advance.
- The date and reason that the blind was broken must be recorded in the source documentation and case report form.

The investigator has the right to determine whether the subject is still ongoing with the treatment even unblinded based on the best interest of the subject. Investigator is encouraged to discuss with medical monitor or Sponsor.

6.6 Study Treatment Supply

First supply of study supplies plus the study drugs will be shipped to sites within 2 weeks before site initiation visit. Subsequent supplies will be provided upon sites request or automatically initiated via IWRS, which may be changed per local guidance and situation. The site needs to proactively inform Sponsor and CRO the numbers of potential subjects. Fourteen days dose of study drugs and placebo will be dispensed once by site staff during screening visit or D1 after eligibility is confirmed.

6.6.1 Study Treatment Preparation and Dispensation

The investigator or designee must confirm appropriate temperature conditions (if applicable) have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only subjects enrolled in the study may receive study drugs or matched placebo and only authorized site staff may supply and dispense them.

All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.6.2 Study Treatment Packaging and Labeling

GT0918 is an AR 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 yellowish. The drug product tablets are packaged in PTP aluminum and PVC blister foils. These packaging materials are in compliance with 21 Code of Federal Regulations (CFR) 174-186 – Indirect Food Additive Regulations. **Table 1: Summary of Study Drugs** provides a summary of the finished study drug products.

Table 1: Summary of Study Drugs

Study Drug Name	**GT0918**	**Matched Placebo**
Dosage Formulation	Tablet	Tablet
Identity of Formulation	100mg	placebo
Route of Administration	Oral	Oral
Dosing Instructions	Once Daily	Once Daily
Packaging and Labeling	The 100 mg tablet is circular in shape with 10 mm in diameter, color is light yellowish. Packaged in PTP aluminum and PVC blister foils. Each blister will contain 7 tablets and will be labeled as required per country requirement.	The matched placebo is circular in shape with 10 mm in diameter, color is light yellowish. Packaged in PTP aluminum and PVC blister foils. Each blister will contain 7 tablets and will be labeled as required per country requirement.

Number and Time of Drugs	Treatment period: 2 tablets daily	Treatment period: 2 tablets daily

6.6.3 Drug Supply and Storage

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 or CRO.

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

6.6.4 Study Treatment Compliance and Accountability

The investigation site will maintain records of study drug 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 if applicable. 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 drugs 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 subject diaries 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 drugs and will reconcile the products received from the drug dispensing center.

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

6.6.5 Disposal and Destruction

Study drugs will not be returned to the Sponsor or destroyed at the clinical site until accountability has been fully determined.

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed; used or unused tablets should be returned to the Sponsor or destroyed on-site following applicable site procedures or by the site's selected destruction vendor. Following the site's procedure for the destruction of hazardous material or study product destruction policy/standard operating procedure (SOP) when destroying used and unused items. A certificate of destruction should be provided to the Sponsor and retained in the Pharmacy Binder once completed.

7 VISIT SCHEDULE AND ASSESSMENTS

7.1 Study Flow and Visit Schedule

This study contains up to 1-day screening visit (D-1), 14 days treatment (D1-D14), additional 28 days safety follow-up period (D15-D42). See the SoA

7.1.1 Screening

After signing the study informed consent, the screening assessments will be done within 1 day prior to randomization (See SoA). Re-screening is not allowed in this study.

7.1.1.1 Eligibility Screening

In order to determine and conform the eligibility of the subject, once all screening procedures are completed, an eligibility checklist must be completed via IRT by the investigator or designee prior to randomization. Please refer and comply with detailed guidelines in the IRT manual.

7.1.1.2 Information to Be Collected on Screening Failures

A subject who signs the informed consent but fails to start on-treatment for any reason will be considered a screen failure. The reason for not starting on-treatment will be entered on the screening failure page or screening disposition page. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures unless the subject experienced a serious AE during the screening phase.

7.1.1.3 Subject Demographics and Other Baseline Characteristics

The data that will be collected at screening includes:

- Demography (date of birth and initials (where permitted), sex, race, ethnicity), BMI.
- Diagnosis (date and method of confirmation the positive SARS-CoV-2 test result).
- Days from onset of COVID-19 symptoms prior to first dosing.
- Medical History(including medication allergy history)/current medical conditions (e.g., all current medical conditions which are present at the time of signing informed consent). High-risk status for severe COVID-19 illness (such as hypertension, diabetes, coronary artery disease, obesity, chronic kidney disease, smoker, androgenic alopecia etc.). Ongoing medical conditions, symptoms and disease which are recorded on the medical history eCRF should include the toxicity grade.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered, they must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.
- Patient reported symptom questionnaires.
- Counsel subjects to use adequate birth control methods required during the study to avoid pregnancy.
- Obtain vital signs (including as below)

  - Height and weight are only needed at screening
  - Body temperature.
  - Systolic blood pressure (BP), diastolic BP.
  - Pulse rate.
  - Respiration rate.
  - Saturation of peripheral oxygen if applicable.
  - Supplemental oxygen flow rate, FiO_2 if known, and method of delivery, if applicable or clinical indicated.
  - Additional vital signs may be measured during the study if warranted, as determined by the investigator.
- Review recent radiographic imaging (X-ray or CT-scan) if applicable
- A complete physical examination will be performed at the screening visit.
  - This examination excludes pelvic, rectal, and breast examinations unless clinically indicated.
  - A symptom directed physical examination will be performed at other visits, as specified in the SoA and as clinically indicated.
  - Investigators should pay special attention to clinical signs related to COVID-19, to ongoing medical conditions and to previous serious illnesses.
- Obtain blood for screening laboratory evaluations.
- Serum pregnancy test (regardless of childbearing potential).

The first-time confirmed SARS-CoV-2 positive at local laboratory and/or Point of Care testing. Sample must be collected within 3 days prior to start of dosing. Clinical screening laboratory evaluations will be performed locally by the site. The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team. Study subjects who qualify will be immediately randomized. Tests or assessments can be redone once per investigator's discretion within the time window at screening visit. If a subject cannot meet inclusion and exclusion criteria during screening period, this subject is considered as screen failure, re-screening is not allowed.

7.1.2 Treatment Period

All subjects who are randomized to the study are considered as entering the treatment period. The subjects will be treated 14 consecutive days or less due to AE, lost to follow-up or consent withdrawal. During the treatment period, subjects will self-administrated GT0918 or matched placebo orally around 30 minutes after a meal, the dose should be given the same time each day (+/- 2 hours for medication scheduling). Subjects also need to record the time/date of dose with provided Subject Diary daily as well as completion of the questionnaire which allows subjects to self-evaluate their COVID-19 symptoms. Any dose that is delayed may be given later that calendar day. Any dose that is missed (not given that calendar day) is not made up, which should

be documented as dose missing on Subject Diary with a reason. The treatment course continues as described above even if the subject becomes SARS-COV-2 test negative.

On Days 3, 7, 14 and 28, nasopharyngeal swabs will be collected for viral load tests, meantime vital sign or other assessments will be performed and PK samples collection will be done per Schedule of Activities (SoA). On Day 14, safety laboratory tests are needed to evaluate clinical outcome and ensure safety. The above visits are preferred subjects in person to sites. However, infection control or other restrictions may limit the ability of the subject to return to sites. In this case, the visits may be conducted as outpatient clinic or home visits. The planned visit schedules and visit types/location should be discussed and confirmed during screening visit with every subject, any future changes will be coordinated according in advance.

Hospitalization should be closely monitored and documented with subject's source and eCRF as described in Section 7.2.1.1.

Meantime, the subjects' clinical status as detailed in Section 7.2.1.2 will be recorded in the eCRF.

7.1.3 End of Treatment

7.1.3.1 Study treatment discontinuation

Subjects may voluntarily discontinue from study treatment for any reason at any time. If a subject decides to discontinue from study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the subject's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

If oral administration of the study drugs is definitively discontinued, the subject will remain in the study for follow-up and any further evaluations that need to be completed as described in the SoA.

Subjects who completely discontinue study treatment should be scheduled for an End of Treatment visit within 2 days following the date study treatment is permanently discontinued, at which time all of the assessment listed for the EOT visit will be performed. For details of assessment, refer to SoA. If the decision to discontinue occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the subject return for an additional visit.

An End of treatment eCRF page should be completed, giving the date and reason for stopping the study treatment. If a withdrawal occurs, of if the subject fails to return for visits, the investigator must determine the primary reason for a subject's premature discontinuation and record the information on the EOT eCRF page. The EOT visit is considered as end of study.

At a minimum, all subjects who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for a safety evaluation during the 28 days following the last dose of study treatment. At this time the occurrence of any component of the primary efficacy endpoint will be assessed as well.

If a subject discontinues study treatment, but continues study assessments, the subject remains on study until he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the end of study eCRF page.

The investigator must contact the IRT to register the subject's discontinuation.

End of treatment/Premature withdrawal visit is not considered as the end of study.

A subject may be withdrawn from the study treatment earlier due to following reasons:

- AE
- Lost to follow-up
- Physician's decision
- Protocol deviation
- Death
- Subject/guardian decision
- Study terminated by the Sponsor
- Pregnancy
- Others

If the Sponsor or investigator identify a subject who did not meet enrollment criteria and was inadvertently enrolled, then the subject should be discontinued from study intervention unless there are extenuating circumstances that make it medically necessary for the subject to continue study intervention.

If the investigator and the Sponsor agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled subject to continue in the study with or without treatment with study drugs.

7.1.4 Withdrawal of Consent

Early withdrawal is expected to be uncommon.

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g., telephone, email, letter) to understand the primary reason for the subject's decision to withdraw his consent and record this information. Study treatment must be discontinued, and no further assessment conducted. Further

attempts to contact the subjects are not allowed unless safety findings require further communication or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation should be made at the time of the subject's study withdrawal.

At the time of early withdrawal from the study, if possible, an early withdrawal visit should be conducted, which can be referred to in the SoA and the subject will continue to follow-up. If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and inform Sponsor accordingly.

7.1.5 Follow-Up for Safety Evaluations

After the end of 14 days treatment period, subjects will enter a 14-day post-treatment (Day 15-Day 28 or 14 days after last dose) and another 14-day safety follow-up periods (Day 29-Day 42 or 14 days after post-treatment) during which information on the subject will be collected until Day 42 (±2). Information will be collected by clinic, sites or home visit or other means as appropriate on D28 (±2). Subject Questionnaire collected daily until Day 28. Day 42 (±2) is a phone call. All subjects are expected to complete follow-up visits except those lost to follow-up or consent withdrawal.

Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects that received study intervention. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the subject will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

The end of treatment eCRF page will be completed once a subject has discontinued study treatment, then the subject will complete post-treatment and safety follow-up periods.

On Day 28, nasopharyngeal swabs will be collected for viral load tests, meantime vital sign or other assessments will be performed per SoA. On Day 28, the safety laboratory tests are needed to evaluate clinical outcome and ensure the safety. The Day 28 visit is preferred for subjects to attend in person to sites. However, infection control or other restrictions may limit the ability of the subject to return to sites. In this case, the visit may be conducted as outpatient clinic or home visits. The planned visit schedules and visit types/location should be discussed and confirmed during screening visit with every subject, any future changes will be coordinated according in advance.

Subjects whose treatment is discontinued due to an AE, must be followed until resolution or stabilization of the event, whichever comes first. This could include all study assessments appropriate to monitor the event. Data collected should be added to AE CRF and the Concomitant Medications CRF.

7.1.6 Lost to Follow-Up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the

subject, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until due diligence has been completed. Subjects lost to follow-up should be recorded as such on the appropriate disposition CRF.

7.1.7 End of Safety Follow-Up

The end of post-treatment phase disposition eCRF page will be completed once a subject has discontinued study treatment, completed safety follow-up.

End of post-treatment follow-up may occur one of the following reasons:

- AE
- Lost to follow-up
- Physician's decision
- Progressive disease
- Subject/guardian decision
- Death
- Protocol deviation
- Pregnancy
- Study terminated by the Sponsor
- Others

7.2 Assessment

Planned time points for all safety assessments are provided in the SoA.

7.2.1 Efficacy Assessments

Non-Hospitalization events (7.2.1.1), NIAID ordinal scale (7.2.1.2) , symptom improvement and resolution(7.2.1.3) will be used to characterize the effect of GT0918 compared to placebo on clinical status from baseline to Days 14 and 28.

7.2.1.1 Composite Events for non-Hospitalization

The following events by Day 28 will be collected and recorded in the eCRF:

- Hospitalization (defined as ≥24 hours)
- Supplemental oxygen for ≥24 hours
- Death

The date of hospitalization events as above will be recorded in the eCRF. Additionally, the date for following events will also be recorded in the eCRF.

- Emergency room visit
- ICU admittance

- Discharge
- Extended care facility admittance (refers to long term care for chronic diseases or prolonged rehabilitation, which is not defined as hospitalization)

7.2.1.2 NIAID Ordinal Scale

The National Institute of Allergy and Infectious Diseases (NIAID) Ordinal Scale will be assessed by the site daily beginning on Day 1 through Day 28 using AE and Questionnaire data. NIAID Ordinal Scale outcomes will be analyzed on Day 7, Day 14 and Day 28.

NIAID Score Description

The NIAID scoring scale will be assessed daily and defined as the lowest score achieved for that day.

The scoring is based on the clinical status of the patient as described below.

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or other medical conditions preventing hospital discharge)
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized, limitation on activities and/or requiring home oxygen
8. Not hospitalized, no limitations on activities

The subjects' following conditions will be recorded in the CRF and include limitation on activities due to COVID-19:

- Ongoing hospital medical care
- Supplemental oxygen
- Non-invasive ventilation or a high flow oxygen device
- Mechanical ventilation
- ECMO

Subjects will also complete 3 questions about NAIDS as following in the patient questionnaire:

- Home oxygen
- Limited activities
- Hospitalization

7.2.1.3 Symptom improvement and resolution

Subjects will rate their overall clinical status and severity of symptoms associated with COVID-19 by a daily questionnaire. This questionnaire is for outpatients only.

Subjects will complete 3 questions about their overall clinical status daily, including

- Severity of symptoms
- General physical health, and
- Change in overall health including activity limitation, home oxygen, hospitalization, etc.

The questionnaire contains these symptoms

- Cough
- Shortness of breath
- Feeling feverish
- Fatigue
- Body aches and pain
- Sore throat
- Chills
- Headache
- Nausea
- Vomiting
- Diarrhea
- Changes in taste and smell.

Each symptom will be scored daily by the subject as experienced during the past 24 hours.

Detailed list of symptoms and rating score guideline is document per Appendix 5.

7.2.2 Safety and Tolerability Assessments

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For safety evaluations, baseline is defined as assessments done on Day 1 prior to the first dose of study treatment.

The investigator will report any vital signs considered clinically significant in the eCRF. For details on AE collection and reporting refer to AE Section 8.1.

7.2.2.1 Physical Examinations

A complete physical examination will be performed at the screening visit. This examination excludes pelvic, rectal, and breast examinations unless clinically indicated.

A symptom directed physical examination will be performed at other visits, as specified in the SoA and as clinically indicated.

Investigators should pay special attention to clinical signs related to COVID-19, to ongoing medical conditions and to previous serious illnesses.

7.2.2.2 Vital Signs

Vital signs will be measured as specified in the SoA and as clinically indicated. Vital sign measurements to be measured in the sitting position after 5 mins rest if applicable. Vital signs include:

- Height and weight are only needed at screening
- Body temperature
- Systolic BP, diastolic BP
- Pulse rate
- Respiration rate
- Saturation of peripheral oxygen
- Supplemental oxygen flow rate, FiO_2 if known, and method of delivery, if applicable or clinical indicated.

Additional vital signs may be measured during the study if warranted, 12-ECG assessment as determined by the investigator.

7.2.2.3 Clinical Laboratory Tests

Local clinical laboratory parameters will be used for the analysis of scheduled hematology, chemistry and other blood specimens collected as part of safety monitoring (as detailed in SoA) and the results will be collected in the eCRF, except for specific parameters which will be performed centrally by a Kintor designated laboratory (as detailed in Appendix 4).

Unscheduled assessments of these parameters can be performed more often as clinically indicated. It is preferable to use the same laboratory for all the assessments performed, especially for hematology.

Laboratory values obtained during the screening phase will be used to assess subject's eligibility.

The local laboratory must provide Kintor with a copy of the certification and a tabulation of normal ranges and units for all local laboratories used in the study.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

There are no specific notable range criteria for this study; however, the local and central laboratory will flag laboratory values falling outside of the normal range, on the local and central laboratory report (as applicable) (which the investigator should sign off) as per local practice, and the investigator will report any values considered clinically significant in the eCRF.

See Appendix 4 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

All protocol-required laboratory assessments, as defined in Appendix 4 must be conducted in accordance with the laboratory manual and the SoA.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Sponsor. If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

The investigator must review the laboratory report, document this review in timely manner, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

The laboratory reports must be filed with the source documents.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory requires a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), report in the AE section of the CRF and this test is recorded as unscheduled visit in eCRF.

7.2.2.4 Respiratory Support

Once enrolled in the study, subjects may be managed with high flow nasal cannula, non-invasive positive pressure ventilation or any other form respiratory support as needed per investigator discretion.

7.2.2.5 Pregnancy and assessment of fertility

All women of childbearing potential must complete a serum pregnancy test at screening visit, urinary pregnancy test at subsequent visits as per the schedule of assessment. Local laboratories will be used for the analysis of serum and urinary pregnancy tests.

Women who are determined not to be of childbearing potential before the study will only be tested at screening.

For postmenopausal women to be considered “of non-childbearing potential”, subjects should meet the criteria as outlined as following:

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural(spontaneous) amenorrhea with appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Please refer to Section 8.6 for information on reporting any pregnancies that occur while the subject is on study.

If pregnancy test is performed in between study visits by the subject and the result is positive, the subject must immediately notify the investigator.

7.2.3 Pharmacokinetics

The exposure-response relationship of GT0918 in the treatment of SARS-CoV-2 has not been established. Population PK analyses can be used to further inform dose selection in other populations and support concentration-response investigations with efficacy and safety outcomes. To accomplish this, sparse PK sampling techniques can be employed. Samples will be collected at pre-dose and 2h post first dose, and at pre-dose on Day 3, 7 and 14 from at least 100 subjects who receive intervention and have evaluable PK.

The PK data may be analyzed using validated LC-MS/MS methods with a LLOQ of approximately 5.00 ng/mL for GT0918.

7.2.4 Biomarkers

Blood samples will be collected from all subjects for exploratory biomarker research at the time specified in the SoA where local regulations allow.

The following will be monitored:

- C-reactive protein (CRP)
- Testosterone
- Ferritin
- D-dimer
- Procalcitonin
- Troponin

Samples will be stored and analysis may be performed on biomarkers thought to play a role in immune system related responses to viral infection including, but not limited to, immune pathways, cellular composition, serum analytes, or epigenetic biomarkers, to evaluate their association with observed clinical responses to GT0918 and the disease state.

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the intervention target (S protein), the COVID-19 disease state, pathways associated with disease, and/or the mechanism of action of the study intervention.

7.2.5 Polymerase Chain Reaction (PCR)

The second endpoint is the change from baseline to Day 3, 7, 14, 28 in SARS-CoV-2 viral load based on nasopharyngeal swab samples for reverse transcription-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 (if it is not able to get the samples at each time point, reason should be documented with subject source or eCRF, for example, due to lack of testing supplies, limited testing capacity, subject is able to go clinic or home visit is not able to schedule, etc.).

Quantitative RT-qPCR, which should be done in the central laboratory, is to determine the viral load change from different time points. Samples may additionally be used for exploratory viral RNA sequencing or viral culture. Additional details regarding sample collection and analysis can be found in the laboratory manual.

7.2.6 Patient Reported Outcomes

Subjects will be provided Subject's Diary which will contain the study drug administration information (date/time, with or without meal), and the Symptoms and Overall Clinical Status Subject Questionnaire for subjects to self-evaluate their health status from their own perspective. The questionnaire is required to be completed daily, should at the same time each day (+/- 2 hours for medication scheduling), from screening to end of follow-up at Day 28. Symptoms of COVID-19 are listed per FDA guidance (https://www.fda.gov/media/142143/download) and the questionnaire was modified based on this FDA guidance as well, referred to Appendix 5.

The Sponsor and investigators will make efforts to minimize the amount of missing data, include providing reminders (e.g., phone calls, text messages, email) to study subjects to complete Patient Reported Outcomes (PRO) instruments, monitoring compliance with PRO instrument completion throughout the assessment period, following up with study subjects who are not successfully completing PRO instruments (and, where permissible, close contacts if the study subject is not responding), and recording verbal responses for those who are unable to self-record because of illness or other circumstances. Sponsor and investigators/ sites will try to obtain contact information for close contacts of study subjects for use in case of nonresponse. This such close contacts include family member (s) or other close contact when subjects do not respond to follow-up, this process is described in the informed consent document, will be (is) approved by the institutional review board and agreed with subjects. The reasons for missing data should be documented with subject's CRF.

7.2.7 Virology

Characterize the effect of GT0918 compared to placebo on SARS-CoV-2 viral load clearance:

- Change from baseline to Days 3, 7, 14 and 28 in SARS-CoV-2 viral load.
- Proportion of subjects that achieve SARS-CoV-2 clearance (Days 3, 7, 14 and 28)
- Time to SARS-CoV-2 clearance.
- SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed to Days 3, 7, 14 and 28.

7.2.8 Development of resistance

Characterize emergence of virus resistance to GT0918

- Virus load assessment on Day -1/1(baseline prior to first dose), 3, 7, 14, 28.
- Exploratory endpoints will include:
    - Screening for novel mutants in patients who do not respond to GT0918:
        - Genotype of SARS-CoV-2 viral isolates.

For resistance analyses, include subjects who:

- Are not able to show two consecutive negative test results via RT-PCR testing by Day 28,

and/or

- Show a positive real-time RT-PCR test result after two consecutive negative RT-PCR test results,

and/or

- A confirmed rise in SARS-CoV-2 RNA of ≥1 log10 after achieving nadir on treatment.

Characterize emergence of host resistance to GT0918

- Testosterone levels on Day -1, 3, 7, 14, 28.

8. SAFETY MONITORING AND REPORTING

8.1 Adverse Events

8.1.1 Definitions and Reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after subject's signed informed consent has been obtained.

Adverse events that begin or worsen after informed consent should be recorded in the AEs CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF. Adverse event monitoring should be continued for 28 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The investigator (and/or designee) must document all AEs reported by the subject from the time subjects give consent through completion of the EOS visit. Any subject who is withdrawn from the study due to an AE shall be followed until the event has resolved or stabilized or 28 days after last dose and the investigator will document available follow-up information on the subject's source documentation and CRF.

Adverse events reported after consent but before the first dose of study treatment are still to be documented by the investigator but will be considered non-treatment-emergent AEs. Adverse events will be considered treatment emergent if the onset date is after the first dose of study drug.

All AEs and SAEs will be assessed for severity using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

For AEs not included in the Table, the following guidelines will be used to describe severity. In

addition, all deaths related to an AE are to be classified as grade 5 according to the DAIDS Table.

Mild: Mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated.

Moderate: Moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated.

Severe: Severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.

Potentially life-threatening: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

8.1.2 Events NOT Meeting the AE Definition:

- The following study-specific clinical events related to COVID-19 are exempt from AE reporting unless the investigator deems the event to be related to the administration of study drug:
    - Hypoxemia due to COVID-19 requiring supplemental oxygen;
    - Hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices;
    - Respiratory failure due to COVID-19 requiring invasive mechanical ventilation or ECMO.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Classification of AEs 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.

All AEs (regardless of seriousness or relationship to study drug) including those from the time of consent to the EOS visit are to be recorded in the subject's source documents and on the corresponding page(s) in the CRF. The investigator should specify the date of onset, intensity, action taken with respect to study drug, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug. All medications administered to treat an AE must be recorded in the subject's source documentation and reported in the CRF.

8.1.3 Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the AEs CRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an AE, should not be reported as AEs.

8.2 Adverse Events of Special Interest (AESI)

The Adverse events of special interest (AESI) search table will be used to map reported AEs to the notable AE groupings. AESI could be updated during the course of study based on accumulating safety data. Therefore the clinical study report includes the AE groupings (such as gastrointestinal disorders, cardiovascular disorders, increased liver transaminase, and neurological disorders, peripheral blood cytopenia and renal disorders). used and provide a listing of the corresponding AESI search table. AESI will be summarized regardless of study drug relationship, by grouping, PT and treatment arm.

8.3 Serious Adverse Events

8.3.1 Definitions

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as one of the following:

- Is fatal
- Is life-threatening
- Results inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Note that hospitalizations for the following reasons should not be reported as SAEs:
    a. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
    b. Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
    c. Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not an SAE.

8.3.2 SAE Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until at least 28 days after the patient has stopped study treatment must be reported to Kintor/delegated CRO within 24 hours of learning of its occurrence.

Any SAEs experienced after this 28-day period should only be reported to Kintor/delegated CRO if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English and submit the completed form within 24 hours to Kintor. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

The Investigator must also promptly notify the Institutional Review Board (IRB) /Independent Ethics Committee (IEC) of SAEs, including any follow-up information, in accordance with local institutional policy and applicable regulatory requirements. Regulatory authorities will be notified of any AE associated with the use of the study drug that is both serious and unexpected, in accordance with the appropriate local regulatory guidelines. Notification of the event will be made by written, expedited safety report by the Sponsor.

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Kintor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Follow-up information is submitted in the same way the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Kintor study treatment, the Kintor Drug Safety associate may urgently require further information from the investigator for Health Authority reporting. Kintor may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.

8.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent regulatory authorities and relevant IECs in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

If the SUSAR is fatal or life-threatening, associated with study treatment, and unexpected, regulatory authorities and IECs will be notified immediately as per national requirements once the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported as required.

If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study intervention, and unexpected, regulatory authorities and IECs will be notified as per national requirements once the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of subjects. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

8.5 Emergency Unblinding of Treatment Assignment

Emergency unblinding should only be undertaken for safety reasons when it is essential for effective treatment of the subject. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IWRS. When the investigator contacts the IWRS to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the drug treatment for the specified subject and a fax and/ or email (if allowed per local regulatory requirement) confirming this information. The system will automatically inform the Kintor monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IWRS in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, subject number and instructions for contacting Kintor (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the subject in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or backup can always be reached in case of emergency then the procedure above is not required.

Study treatment must be discontinued once emergency unblinding.

8.6 Pregnancies

To ensure subject safety, each pregnancy occurring after the start of study treatment and until 90 days after the last dose of study drugs must be reported to Kintor/delegated CRO immediately (within 24 hours) of learning of its occurrence. The subjects who become pregnant during the study must be withdrawn.
The pregnancy will be followed up from the estimated date of delivery plus 3 months to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported on a Clinical trial pregnancy form and reported by the investigator to Kintor/delegated CRO safety team. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE report form.

Details of all pregnancies in female partners of male subjects will be collected after the start of study treatment and until 90 days after the last dose of study drugs. A pregnancy outcome informed consent will be provided by Kintor. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 3 months after treatment has been stopped.

If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should inform IRB as well.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.7 Warnings and Precaution

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

8.8 Independent Data Monitoring Committee (IDMC)

An IDMC will be constituted and will be responsible for monitoring and reviewing the clinical study data for safety and efficacy during the study prior to the final data analysis. To minimize any bias introduced into the analysis of the study results, analysis plans will be finalized and approved prior to the interim analyses. The primary goal of the IDMC is to review the interim results regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

Responsibilities of the IDMC, communication flow between DMC, SC, and Kintor, and timing of data safety and efficacy reviews, will be included in the DMC charter document.

The IDMC will consist of at least 2 COVID-19 experts and one biostatistician and will be formed prior to the randomization of the first patient. Detailed recruitment status and interim analysis report will be provided to the IDMC. Recruitment will not be interrupted. Details will be provided in the IDMC charter.

It is envisioned that the DMC may make 4 types of recommendations, namely:

1. No safety or ethical issues, ethical to continue the study as planned
2. Serious safety concerns precluding further study treatment, regardless of efficacy
3. Ethical to continue the study but recommend an amendment to the protocol

4. Stop prematurely for lack of efficacy

8.9 Steering Committee

The SC will be established comprising investigators participating in the study, and Kintor representatives from the clinical study team.

The SC will be an advisory board for the study according to the protocol through recommending modifications as circumstances require. The SC will be consulted for the protocol amendments as appropriate. Together with the clinical study team, the SC will also develop recommendations for the publications of study results. The details of the role of the SC will be defined in a SC charter. The SC will not have access to unblinded study data.

9. DATA COLLECTION AND MANAGEMENT

9.1 Data Confidentiality

Prior to any testing under this protocol, including screening tests and assessments, subjects must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Suzhou Kintor Pharmaceuticals, Inc., its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Suzhou Kintor Pharmaceuticals, Inc. will protect individual subject information to the fullest extent possible during this study. At no time will a subject become identified in any publication or presentation.

However, the subject may have to become identified in the event of a regulatory authority auditor inspection in order to verify the accuracy of the data. Access to subject information is at the discretion of Suzhou Kintor Pharmaceuticals, Inc. and cannot occur prior to database lock or other specified events as determined solely by the discretion of Suzhou Kintor Pharmaceuticals, Inc.

9.2 Site Monitoring

At regular intervals during the study, the site will be contacted through monitoring visits or remote monitoring, letters, and telephone calls by a representative to review study progress, Investigator and subject compliance with study protocol requirements, and any emergent problems. During monitoring visits, the following points will be reviewed in accordance with all applicable regulatory requirements and SOPs: original medical records and other source documents, the Investigator site file, screening logs, subject informed consent, subject recruitment and follow-up, SAE documentation and reporting, documentation and reporting of endpoints, study drug allocation, subject compliance with the study drug regimen, study drug accountability, concomitant therapy use, and quality of data. In addition, other required regulatory documents will be reviewed, including but not limited to: IRB/IEC composition and correspondence, laboratory certification(s), delegation of authority, and Investigator and study personnel curricula vitae.

9.3 Data Collections

All data obtained for analysis in the clinical study described in this protocol will be reported in the CRF. Data reported in the CRFs should be consistent with and substantiated by the subject's medical record and original source documents. Any discrepancies must be explained. Unless explicitly allowed in the CRF instructions, blank data fields are not acceptable. If a field is blank because the item was not done, the field will be marked "Not Done." If the item is unknown, the field will be marked "Unknown."

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on CRFs.

9.4 Database Management

A designated CRO will be responsible for data management. Data Management will develop a Data Management Plan (DMP) document and provide it to Suzhou Kintor Pharmaceuticals, Inc. for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, dataflows, CRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Concurrent medications entered the database will be coded using a WHO Anatomical Therapeutic Chemical dictionary. Coexistent diseases and AEs will be coded using MedDRA.

9.5 Quality Control

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.

10. STATISTICAL METHODS AND DATA ANALYSIS

10.1 General Considerations

It is planned that the data from all centers participating in the study will be combined, so that an adequate number of patients are available for analysis. Kintor and/or a designated CRO will perform all analyses. And data analyses performed independently by any investigator should be submitted to Kintor before publication or presentation.

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. It 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.

Interim Analysis will be conducted based on the Data Monitoring Committee SAP.

10.2 Analysis Sets

10.2.1 Intent-to-Treat Analysis Set (ITT)

The intent-to-treat analysis set includes all randomized subjects.

10.2.2 Modified Intent-to-Treat Analysis Set (mITT)

The mITT analysis set includes all randomized subjects who have received at least one dose of the study treatment. The primary efficacy analysis will be conducted on the mITT Analysis Set.

10.2.3 Safety Analysis Set (SS)

The safety analysis set includes all subjects with at least one dose of study medication. The disposition, study summary, and safety analysis will be conducted on Safety Analysis Set.

10.2.4 Per-Protocol Analysis Set (PPS)

The per-protocol analysis set includes all ITT subjects without major protocol violations. The per-protocol analysis set will be defined under classification specification prior to unblinding of the study treatment code.

10.2.5 Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on data from at least 100 subjects who receive intervention and have evaluable PK.

10.3 Subject Demographics/Other Baseline Characteristics

Demographics and other baseline data including age, age group, race, ethnicity, BMI, baseline disease, underlying medical conditions 0, 1-2, ≥3 (as defined in Section 4.1.1.), and other disease characteristics will be summarized descriptively by treatment group using data from the ITT. Categorical data will be presented as frequencies and percentages and if appropriate their 95% confidence intervals. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.4 Treatments (Study Treatment, Concomitant Therapies, Compliance)

The safety set will be used for the analyses below.

The actual dose and duration of GT0918, as well as dose intensity (computed as the ratio of actual dose received to actual duration) and the relative dose intensity (computed as the ratio of the dose intensity to planned dose received/planned duration), will be listed and summarized using descriptive statistics. The total daily doses of GT0918 for each patient will be summarized using descriptive statistics (e.g., mean, median, and mode).

Concomitant medications and significant non-drug therapies will be listed by patient and summarized by ATC (Anatomical Therapeutic Chemical classification system) term for each treatment group. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

Compliance to the study drug will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver in the drug accountability form including dosages administered, dosing intervals, dose changes or interruptions with associated reasons.

10.5 Efficacy Analysis

10.5.1 Primary Efficacy Objective

The primary objective is to evaluate the efficacy of GT0918 in subjects with mild to moderate COVID-19 illness.

10.5.1.1 Primary Efficacy Variable

The primary efficacy endpoint is the proportion of subjects who do not experience any of the following events due to all causes by Day 28:

- Hospitalization for ⩾ 24 hours
- Supplemental oxygen for ⩾24 hours in response to SpO2 ⩽93%
- Death

10.5.1.2 Statistical Hypothesis, Model, and Method of Analysis

Primary Null Hypothesis H0: proportion of subjects who do not experience all-cause hospitalization (defined as ≥24 hours) and do not require supplemental oxygen for ≥24h in

response to $SpO_2 \leqslant 93\%$ and are alive by Day 28 in the GT0918 arm (p1) is equal to the proportion in the placebo arm (p2)

Primary Alternative Hypothesis Ha: the proportion of subjects who do not experience all-cause hospitalization (defined as ≥24 hours) and do not require supplemental oxygen for ≥24h in response to $SpO_2 \leqslant 93\%$ and are alive by Day 28 in GT0918 arm (p1) is less than the proportion in the placebo arm 2 (p2)

Mathematically written as:

H0: p1 - p2= 0

Ha: p1 - p2>0

The primary endpoint event rate will be compared between treatment and placebo arm using Cochran–Mantel–Haenszel (CMH) chi-square test using the stratification factors at time of randomization at the one-sided 0.025 level based on mITT. P-values and 95% exact confidence intervals for the treatment difference will be presented.

10.5.1.3 Handling of Dropouts, Missing Values/Censoring/Discontinuations

No dropouts will be replaced. Every effort will be made to avoid missing data. All subjects will be followed fully in the trial whenever possible. All patients who maintain consent to be followed for additional outcome information should remain in the study through the end of the double-blind period for all important safety and efficacy assessments. The only reasons for study withdrawal should be withdrawal of consent and loss to follow-up. To help prevent missing data, The following reinforcement will be taken: (1) the protocols and informed consent forms clearly differentiate treatment discontinuation from study withdrawal; (2) site investigators be trained about the importance of retention and steps to prevent missing data; (3) the consent forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early; and (4) continue following patients after discharge via telehealth visits or other approaches (e.g., telephone calls, texts, and emails to the patient and close contacts); and (5) steps will be taken to ascertain vital status in all randomized patients.

The extra effort to contact all subjects specifically those who discontinued treatment early to assess the occurrence of any component of the primary endpoint, hospitalization, need for oxygen, or death by day 28 will minimize missing data for the primary endpoint. For the primary analysis of the primary endpoint, patients with missing primary assessments will be included in the analysis and evaluated as treatment failures. Sensitivity analyses will be considered e.g. per protocol set analysis and complete case analysis (i.e. patients with non-missing primary assessments).

The SoA, outlined in the protocol, specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis but may not be reported as a protocol deviation.

Further details for handling missing data will be specified in the SAP and appropriate sensitivity analyses specified.

10.5.1.4 Subgroup Analyses

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

Subgroup analyses will be conducted for the primary endpoint and displayed graphically in forest plots. Subgroups may include:

- time from symptom onset to study randomization
- geographic region
- baseline severity of COVID-19
- age group
- sex
- race
- ethnicity
- baseline BMI
- concomitant medication of interest use (yes/no)
- strata used at time of randomization (number of risk factors)
- vaccination status

10.5.1.5 Sensitivity Analyses

Sensitivity analysis of the primary endpoint analysis will be conducted. Details will be specified in the SAP.

10.5.2 Secondary Objectives Variables

10.5.2.1 Hospitalization percentage

The percentage of subjects with all-cause and COVID-19 related hospitalization (defined as ≥24 hours) or requirement for supplemental oxygen for ≥24h in response to $SpO_2 \leq 93\%$ or death by Day 28 will be analyzed.

The proportion of subjects that experience hospitalization, supplemental oxygen, emergency room visit or death by Day 28 will be summarized by treatment in frequency tables and listed.

The total number of all-cause and COVID-19 related hospitalization and days of hospitalization due to all causes and COVID-19, will be summarized based on mITT.

10.5.2.2 COVID-19 Ordinal Outcomes Scale

The percentage of subjects at each clinical status using NIAID ordinal scale at Days 7, 14, and 28 will be analyzed.

1. Death

2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or other medical conditions preventing hospital discharge)
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized, limitation on activities and/or requiring home oxygen
8. Not hospitalized, no limitations on activities

Mean value by treatment group will be plotted over time.

Comparison of the mean worst daily NIAID ordinal scale values by Days 7, 14, and 28. The worst ordinal scale will be fitted by a proportional odds model with treatment, age, sex, baseline severity and number of risk factors as covariates.

In addition, proportion of subjects worsening from baseline will be presented, where worsening is defined as the proportion of subjects with any worsening on the NIAID ordinal scale from baseline to Days 7, 14, and 28.

The following events (observed at any time point during the study treatment period) will be summarized:

- Proportion of subjects hospitalized
- Duration of hospitalization (DOH; in days)
- Proportion (percentage) of subjects admitted to ICU

All hospitalization events will be listed.

10.5.2.3 Proportion of Symptom resolution

For each symptom resolution is defined as absent for at least 48 hours. The proportion of subjects with symptom resolution will be analyzed by symptom.

All symptom resolution is defined as all symptoms (those scored 0-3) on the symptom questionnaire scored as absent. The proportion of subjects with all symptom resolution will be analyzed.

These analyses will be performed at Days 7, 14, and 28 by treatment in frequency tables and listed.

In addition, the number of participants that achieve symptom resolution at Days 7, 14, and 28 will be analyzed using logistic regression to compare GT0918 versus placebo if there are sufficient data available.

10.5.2.4 Time to symptom resolution

Time to all symptom resolution is defined (in days) as:

First study day when symptom resolution status is changed to "Yes" – first dosing Date + 1.

If a patient has not experienced symptom resolution by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to symptom resolution will be evaluated up to Day 28 and will be summarized by treatment and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category.

Time to symptom resolution will be presented graphically.

10.5.2.5 Symptom Improvement

10.5.2.5.1 Proportion of subjects demonstrating symptom improvement via the symptom questionnaire on Days 3, 7, 14 and 28.

Symptom improvement is defined as a change in severity of total ratings from a higher score to a lower scorewhich is defined as following:

- symptoms scored as moderate or severe at baseline are scored as mild or absent,

OR

- symptoms scored as mild or absent at baseline are scored as absent.

The proportion of subjects that achieve symptom improvement at Days 7, 11, 14 and 28 will be summarized by treatment in frequency tables and listed.

10.5.2.6 Time to Symptom Improvement

Time to symptom improvement is defined (in days) as:

(Date when symptom improvement status is changed to "Yes" – first dosing Date + 1).

If a subject has not experienced symptom improvement by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to symptom improvement will be evaluated up to Day 28 and will be summarized by treatment and listed. In addition, a graphical presentation of the symptom improvement will be provided using a KM plot.

10.5.2.7 Virus Clearance

Proportion of subjects that achieve SARS-CoV-2 clearance at Days 3, 7, 14 and 28.

The proportion of subjects that achieve SARS-CoV-2 clearance at Days 3, 7, 14, and 28 will be summarized by treatment in frequency tables and listed.

10.5.2.8 Time to SARS-CoV-2 clearance

Time to SARS-CoV-2 clearance will be evaluated by day 28 and will be summarized by treatment and listed.

Time to SARS-CoV-2 clearance will be presented graphically.

10.5.2.9 Viral load reduction

SARS-CoV-2 viral load, including changes from baseline, will be summarized and plotted by treatment and listed. Baseline is defined as the Day 1 pre-dose assessment. Changes from baseline to Day 3, 7, 14 and 28 in SARS-CoV-2 viral load data in the log base 10 scale will be analyzed using a linear mixed-effect model.

The AUC from Day 1 pre-dose to Day 28 (AUC[0-D28]) will be calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification. No imputations of missing data will be conducted. No AUC(0-D28) values will be calculated when Day 1 pre-dose and/or Day 28 values are missing, or if there are more than 3 values missing in the profile.

The AUC (0-D28) will be summarized and plotted by treatment and listed.

10.6 Exploratory Objectives

10.6.1 Pharmacokinetics of GT0918

PK concentrations of GT0918 (and any relevant metabolites such as GT0955) will be summarized by time point using descriptive statistics by treatment only for GT0918 arm. All PK concentration data will be listed as appropriate

Data handling principles

Plasma samples may be assayed for GT0918 concentrations by Kintor or Kintor designated laboratory. The PK data may be analyzed using validated LC-MS/MS methods with a LLOQ of approximately 5.00 ng/mL for GT0918.

All concentrations below the LLOQ will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV. Any missing PK parameter data will not to be imputed.

10.6.2 Viral resistance to GT0918

If appropriate, the evaluation of viral resistance will be conducted as described in a separate bioanalytical analysis plan. Comparison from baseline to the last evaluable time point up to Day 28 on the emergence of viral resistance to GT0918.

10.7 Safety Analysis

10.7.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into 3 mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication

2. on-treatment period: from D 1 (the day of first dose of study drug) to D 14 (the day of last dose)

3. post-treatment period: from D 15 (the day after last dose) to D 28 (14 days after last dose)

4. safety follow up period: from D 28 (14 days after last dose) to D 42 (28 days after last dose)

10.7.2. Adverse events

Summary tables for AEs have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on DAIDS grades), type of AE, relation to study treatment by treatment group.

In an overview table, the number and percentage of subjects who experienced a TEAE, SAE, AE related to study drug, death due to an AE, discontinued from the study treatment, or discontinued from the study due to an AE will be summarized by treatment.

Treatment-emergent AEs may be reported separately for the treatment period and follow-up periods.

10.7.3 Laboratory abnormalities

For laboratory tests covered by DAIDS Version 2.1, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by DAIDS, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by treatment summaries will be generated separately for hematology, biochemistry, and coagulation laboratory tests:

- Frequency table for newly occurring on-treatment Grades 3 or 4.
- Shift tables using DAIDS grades to compare baseline to the worst on-treatment value.
- For laboratory tests where DAIDS grades are not defined, shift tables using the low/normal/high classification to compare baseline to the worst on-treatment value.

- Listing of all laboratory data with values flagged to show the corresponding DAIDS grades and the classifications relative to the laboratory normal ranges.

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

10.7.4 Other safety data

10.7.4.1 Vital signs

- Shift table from baseline to worst on-treatment result.
- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.7.4.2 Tolerability

Tolerability will be studied in terms of dose discontinuation due to AE.

Reasons for dose discontinuation will be listed and summarized by treatment.

10.8 Interim Analysis

An interim analysis will be conducted when 334 subjects completed Day 28 after first dose. The objective of the interim analysis to assess safety, futility, efficacy, sample size adjustment as well as potential enrichment of the population to enroll a population at higher risk for an infection requiring hospitalization or oxygen support in case the observed rates for the primary endpoint in the control arm are lower than expected. An independent data monitoring committee (IDMC) will review the unblinded interim analysis report to assess the objectives of the interim analysis and provide recommendations about early study closure, change study population, or change to study sample size. Rigorous steps will be taken (e.g., firewalls) where possible to minimize the information that can be inferred by observers.

The futility criterion for the study will be based on the conditional power of the study being <10%. The efficacy criterion will be based on the one-sided p-value of the primary endpoint analysis as <0.0015. In this case the stopping boundary for efficacy is met and the study could be stopped for efficacy.

The topline safety analysis will include treatment related SAE including death. The IDMC can recommend stopping the study.

The conditional power will be evaluated based on primary endpoint in the interim analysis. IDMC could recommend a change of the subject population to enroll more subjects if the event rate is lower than expected. The IDMC will review the interim efficacy results and in case of substantial treatment differences between subpopulations, e.g., <50 years compared to ≥50 years, provide recommendations for modifications of further enrollment. Criteria for those recommendations will be defined in the DMC charter. The consequences of those recommendations on the statistical analysis as well as the samples size adjustment will be summarized in a separate document and attached to the statistical analysis plan.
If the conditional power of the study at the time interim analysis is between 50% to 80% (promising zone approach), the sample size could be increased to a maximum of 1500 subjects based on the

efficacy in the interim analysis for overall population. If the conditional power of the study is above 80% power the sample size will not be changed. The detailed exact rule for sample size re-estimation will be pre-specified in the DMC charter.

Assuming there is no change in the study design regarding sample size modification, the p-value of 0.0245 will be used to conclude the efficacy of the treatment arm. O'Brien-Fleming Alpha Spending Function was used to calculate the efficacy boundary and the resulting alpha levels for the interim analysis and the final analysis.

10.9 Sample Size Calculation

The primary endpoint event rate for the treatment arm is assumed at 97 % and for the placebo arm is assumed at 91%.

The sample size was calculated using EAST v6.5 for a group sequential test for 2 proportions. With a total of 668 subjects the study will have 90% power at a one-sided 0.025 significance level of the hospitalization or death rate using a Chi-square test with one interim analysis at 50% of the information (when 334 subjects have been observed for 28 days).

11. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory and Ethical Compliance

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, and
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Investigator sites are compensated for participation in the study as detailed in the clinical study agreement.

11.2 Responsibilities of the Investigator and IRB/IEC/REB

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

11.3 Informed Consent Procedures

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 ICH guidelines. The investigator 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 investigator 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 ICF, 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.

11.4 Discontinuation of the Study

Discontinuation of specific sites or of the study as a whole are handled as part of regulatory, ethical, and study oversight considerations. In rare instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study intervention.

11.5 Publication of Study Protocol and Results

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.

11.6 Study Documentation, Record Keeping and Retention of Documents

The Investigator must maintain all study documentation as confidential and take measures to prevent accidental or premature destruction of these documents.

The Investigator must retain the study documents at least 2 years after the last approval of a marketing application/new drug application for the indication investigated or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (e.g., the Investigational New Drug application is withdrawn). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Suzhou Kintor Pharmaceuticals, Inc.

The Investigator must notify Suzhou Kintor Pharmaceuticals, Inc. prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform Suzhou Kintor Pharmaceuticals, Inc. The relevant records shall be transferred to a mutually agreed upon designee.

11.7 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.8 Confidentiality of Study Documents and Subject Records

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 investigator should keep a separate log of subjects, codes, names, and addresses. Documents which identify the subject by name (for example, the ICF) 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.

11.9 Audits and Inspections

Suzhou Kintor Pharmaceuticals, Inc.'s Quality Assurance Unit (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of CRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact Suzhou Kintor Pharmaceuticals, Inc. immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by Sponsor, its representatives, or any appropriate regulatory agencies.

11.10 Financial Disclosures

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.

12. PROTOCOL ADHERENCE

The Investigator will not make any changes to this protocol without prior written consent from the Sponsor Suzhou Kintor Pharmaceuticals, Inc. and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears necessary as the study progresses will be fully discussed by the Investigator(s) and Suzhou Kintor Pharmaceuticals, Inc. If agreement is reached regarding the need for an amendment, it will be written by Suzhou Kintor Pharmaceuticals, Inc. The written amendment must be submitted to the chairman of the IRB/IEC identified with this responsibility. Except for administrative amendments, Investigators must await IRB/IEC approval of protocol amendments before implementing the change(s).

Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the study. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB/IEC notified within 5 days. Suzhou Kintor Pharmaceuticals, Inc. will ensure submission of any protocol amendments to the appropriate regulatory agencies.

When, in the judgment of the chairman of the local IRB/IEC, the Investigators, and/or Suzhou Kintor Pharmaceuticals, Inc., the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject; the currently approved written ICF will require similar modification. In such cases, the Investigator will obtain repeat informed consent from subjects enrolled in the study before expecting continued participation.

13. REFERENCES

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14.APPENDICES

Appendix 1. Drugs that Should Be Used Cautiously with GT0918

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A4	boceprevir, cobicistat(h), danoprevir and ritonavir(j), elvitegravir and ritonavir(j), grapefruit juice(k), indinavir and ritonavir(j), itraconazole(h), ketoconazole, lopinavir and ritonavir(h,j), paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)(j), posaconazole, ritonavir(h,j), saquinavir and ritonavir(h,j), telaprevir(h), tipranavir and ritonavir(h,j), telithromycin, troleandomycin, voriconazole	aprepitant, ciprofloxacin, conivaptan(l), crizotinib, cyclosporine, diltiazem(m), dronedarone(h), erythromycin, fluconazole(f), fluvoxamine(a), imatinib, tofisopam, verapamil(h)	chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor(h), lomitapide, ranitidine, ranolazine(h), ticagrelor(h)
	clarithromycin(h), idelalisib, nefazodone, nelfinavir(h)	-	-
CYP2C8	gemfibrozil(e)	clopidogrel(b), deferasirox, teriflunomide	trimethoprim
	Strong Inducers	**Moderate Inducers**	**Weak Inducers**
CYP3A	apalutamide, carbamazepine(e), enzalutamide(g), mitotane, phenytoin(b), rifampin(a), St. John's wort(h)	bosentan, efavirenz(f), etravirine, phenobarbital, primidone	armodafinil, modafinil(i), rufinamide
CYP2C8	-	rifampin(a)	-

	Sensitive Substrates	Moderate Sensitive Substrates
CYP2D6	atomoxetine, desipramine, dextromethorphan, eliglustat(e), nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine	encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine, S-venlafaxine
CYP2C8	repaglinide(b)	montelukast, pioglitazone, rosiglitazone
CYP2C9	celecoxib(c)	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole(d), rabeprazole, voriconazole
CYP3A4	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir(f), ebastine, everolimus, ibrutinib, lomitapide, lovastatin(g), midazolam, naloxegol, nisoldipine, saquinavir(f), simvastatin(g), sirolimus, tacrolimus, tipranavir(f), triazolam, vardenafil	alprazolam, aprepitant, atorvastatin(c), colchicine, eliglustat(e), pimozide, rilpivirine, rivaroxaban, tadalafil
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir(f), lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Appendix 2. Common COVID-19-Related Symptoms

Example of an Assessment of 14 Common COVID-19-Related Symptoms: Items and Response Options

Example items For items 1–10, sample item wording could be: "What was the severity of your [insert symptom] at its worst over the last 24 hours?"	Example response options and scoring**
1. Stuffy or runny nose 2. Sore throat 3. Shortness of breath (difficulty breathing) 4. Cough 5. Low energy or tiredness 6. Muscle or body aches 7. Headache 8. Chills or shivering 9. Feeling hot or feverish 10. Nausea (feeling like you wanted to throw up)	None = 0 Mild = 1 Moderate = 2 Severe = 3
11. How many times did you vomit (throw up) in the last 24 hours? *	I did not vomit at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
12. How many times did you have diarrhea (loose or watery stools) in the last 24 hours? *	I did not have diarrhea at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
13. Rate your sense of smell in the last 24 hours	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2

14. Rate your sense of taste in the last 24 hours	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

*Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment
Guidance for Industry
** The response options shown for items 11 and 12 are intended only for use with a 24-hour recall period.

Reference to Appendix 5, each symptom will be scored daily by the subject as experienced during the past 24 hours. Also, subject will record the change of overall health and clinical outcomes as below.

- In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? Yes or No
- In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? Yes or No
- In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst? None, Mild, Moderate, or Severe
- In the past 24 hours, have you been hospitalized? Yes, No
- In the past 24 hours, have you required home oxygen? Yes, No
- In the past 24 hours, have you had any limitation on activities? Yes, No

Appendix 3 COVID-19: BASELINE SEVERITY CATEGORIZATION (Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry)

SARS-CoV-2 infection without symptoms

- Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test
- No symptoms

Mild COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute
- No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19

- Positive testing by standard RT-PCR assay or an equivalent test
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300
- No criteria for Critical Severity

Critical COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Evidence of critical illness, defined by at least one of the following:

- Respiratory failure defined based on resource utilization requiring at least one of the following:
  - Endotracheal intubation and mechanical ventilation, oxygen delivered by high- flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
- Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
- Multi-organ dysfunction/failure

NOTE: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection.

Appendix 4 Clinical Laboratory Parameters Collection Plan

Test category	Local/Central	Test Name
Hematology	Local	Hemoglobin Hematocrit Erythrocyte count (RBCs - Red Blood Cells) Leukocytes (WBCs - White Blood Cells) Differential Neutrophils, segmented Lymphocytes Monocytes Eosinophils Basophils Platelets
Clinical Chemistry	Local	Sodium Potassium Chloride Bicarbonate Total bilirubin Direct bilirubin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-glutamyl transferase (GGT) Blood urea nitrogen (BUN) Creatinine Creatine kinase (CK) Uric acid Total protein Albumin Calcium Phosphorus Glucose Amylase Lipase Lactate dehydrogenase (LDH)

Coagulation	Local	International normalized ratio (INR), activated partial thromboplastin time(aPTT)
Additional tests	Local/Central*	C-reactive protein (CRP); high-sensitivity Ferritin D-dimer Procalcitonin Troponin(preferably Troponin I)
Virology	Central	SARS-CoV-2 viral infection determination at screening-local SARS-CoV-2 viral load test (quantitative RT-PCR)—central
Pharmacokinetic Analyses	Central	Analyzed using validated LC-MS/MS methods with a LLOQ of approximately 5.00 ng/mL for GT0918
Hormones(Male &Female)	Central	Testosterone
Hormones(Female)	Local	Serum Pregnancy Urine Pregnancy

* Central laboratories will be used when it can't be tested on local laboratory.

Appendix 5. Subject Questionnaire

1. What was the severity of your stuffy or runny nose at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

2. What was the severity of your sore throat at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

3. What was the severity of your shortness of breath (difficulty breathing) at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

4. What was the severity of your cough at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

5. What was the severity of your Low energy or tiredness at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

6. What was the severity of your muscle or body aches at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

7. What was the severity of your headache at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

8. What was the severity of your chills or shivering at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

9. What was the severity of your feeling hot or feverish at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

10. What was the severity of your Nausea (feeling like you wanted to throw up) at its worst over the last 24 hours?

None =0	Mild =1	Moderate =2	Severe =3

11. How many times did you vomit (throw up) in the last 24 hours?

I did not vomit at all =0	1-2 times =1	3-4 times =2	5 or more times =3

12. How many times did you have diarrhea (loose or watery stools) in the last 24 hours?

I did not have diarrhea at all =0	1-2 times =1	3-4 times =2	5 or more times =3

13. Rate your sense of smell in the last 24 hours:

My sense of smell is THE SAME AS usual=0	My sense of smell is LESS THAN usual =1	I nave NO sense of smell =2

14. Rate your sense of taste in the last 24 hours:

My sense of taste is THE SAME AS usual=0	My sense of taste is LESS THAN usual =1	I have NO sense of taste =2

Overall Covid-19-related Symptoms

1. Overall, how bad are your symptoms TODAY (check one)?

No symptoms ☐	Mild ☐	Moderate ☐	Severe ☐

2. Overall, how is your general physical health today?

Poor ☐	Fair ☐	Good ☐	Excellent ☐

3. Have you returned to your usual physical health (before your COVID-19 illness) (check one)?

Yes ☐	No ☐

4. Have you returned to your usual activities (before your COVID-19 illness) (check one)?

Yes ☐	No ☐

NIAID Daily Questions

1. In the past 24 hours, have you been hospitalized?

Yes	No
☐	☐

2. In the past 24 hours, have you required home oxygen?

Yes	No
☐	☐

3. In the past 24 hours, have you had any limitation on your activities?

Yes	No
☐	☐