Parexel International

Suzhou Kintor Pharmaceuticals, Inc.

GT0918-US-3001

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

Statistical Analysis Plan

Version: 2.0

Parexel Project Number: 261488

SPONSOR SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Approver	Xunwei Dong Project Role: Chief Medical Officer, Suzhou Kintor Pharmaceuticals, Inc.
Approver	Ran He Project Role: Vice President Biostatistics, Suzhou Kintor Pharmaceuticals, Inc.

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	Signatory
Author	Cralen Davis Project Role: Biostatistics Lead

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REVISION HISTORY

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<tr><th>Version No.</th><th>Effective Date</th><th>Summary of Change(s)</th></tr>
<tr><td>1.0</td><td>23 Sep 2021</td><td>New document</td></tr>
<tr><td>1.9</td><td>11 Mar 2022</td><td>

Correction of typographic errors.
Decimal places for p-value.
Lab DAIDS toxicity grade for aPTT.
Added more details for SARS-CoV-2 viral load.
Subjects with missing primary assessments will be treated as meeting the primary endpoint.
Removed sensitivity analysis of the primary endpoint using multiple imputation.
Removed sensitivity analysis of primary endpoint using generalized linear mixed effects model.
Added the following sensitivity analysis of primary endpoints:

Among subjects with doing days >7 days;
Removing the constraint of ⩾24 hours in hospitalization and supplemental oxygen use;
By treating missing primary assessments as hospitalization;
By treating missing primary assessments as hospitalization and among subjects with dosing days > 7 days.

Added sensitivity analysis for hospitalization percentage (defined in protocol section 10.5.2.1) among subset of mITT subjects:

With dosing days > 7 days;
With hospitalization or usage of supplemental oxygen irrespective of 24 hours;
With one or two major risk factors:

Single risk factor: age (≥ 50 years; ≥ 60 years), major underlying medical conditions (overweight, obesity, hypertension, diabetes, smoking)
Combination of age factor in column 1 and other major risk factors in column 2 in the table below (e.g., age ≥ 50 years and/or obesity at randomization; aged ≥ 60 years and/or obesity at randomization);

<table>
<tr><th>Age</th><th>Major underlying medical conditions</th></tr>
<tr><td>≥ 50 years
≥ 60 years</td><td>Overweight
Obesity
Hypertension
Diabetes
Smoking</td></tr>
</table>
</td></tr>
</table>

		○ With age ≥50 years and days from symptom onset to study randomization ≤5 days and/or days from the positive SARS-CoV-2 prior to first dosing ≤3 days With age ≥50 years and higher than normal biomarkers (CRP, Ferritin, D-dimer) • Regarding statistical analysis of viral load, more analyses were added, including two sample t-tests between treatment groups at Days 3, 7, 14, and 28; ANCOVA analysis of change in viral load from baseline at days 3 and 28; and MMRM modeling of change in viral load at day 3, 7, 14, and 28 from baseline. • Added sustained 100% viral reduction and associated statistical analyses of GEE, KM plots, log rank test and Cox regression models. • Added subgroup analysis of primary endpoints based on (1) Days from the Positive SARS-CoV-2 Prior to First Dosing; (2) Biomarker status at baseline; and (3) Common types of viral variants. • More details were added to the time-to-event analysis. • Updated statistical model for viral resistance. • Removed the following analyses ○ Proportion of subjects admitted to an intensive care unit (ICU) due to COVID-19 by Day 28 ○ Days in ICU due to all causes or COVID-19 by Day 28 ○ Time to ICU by Day 28 ○ Proportion of subjects requiring invasive mechanical ventilation or ECMO due to COVID-19 by Day 28 ○ Days on supplemental oxygen/high flow oxygen devices/ invasive mechanical ventilation due to COVID-19 by Day 28 ○ Proportion of subjects with all-cause mortality by Day 28 and Day 42 ○ Proportion of subjects with COVID-19 related mortality by Day 28 and Day 42 • Corrected “RT-PCR” as “ddPCR”. • Removed subgroup analysis of primary endpoint based on Concomitant medication of interest used. • Section 4.10.1.1.3 was added to justify the change in the SAP from the protocol.
2.0	14 Mar 2022	Finalized

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
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

Abbreviation / Acronym	Definition / Expansion
CSR	Clinical Study Report
DAIDS	Division of Allergy and Infectious Diseases
DCR	Disease Control Rate
ddPCR	Droplet Digital Polymerase Chain Reaction
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

Abbreviation / Acronym	Definition / Expansion
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
PTT	Partial Thromboplastin 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
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

Abbreviation / Acronym	Definition / Expansion
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

1 INTRODUCTION

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.

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.

This Statistical Analysis Plan (SAP) provides a detailed description of the statistical methods and analyses to be carried out for the Clinical Study Report (CSR) in support for study GT0918-US-3001.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol Amendment, Version 2.0 (Jul 08, 2021)
- electronic Case Report Form (eCRF), Version 2.0 (Aug 13, 2021)

2 STUDY OBJECTIVES

2.1 Primary

- 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

2.2 Secondary

- To evaluate the efficacy of GT0918 compared to placebo in terms of hospitalization percentage
- Characterize the effect of GT0918 compared to placebo on SARS-CoV-2 viral load
- To evaluate the clinical efficacy of GT0918 compared to placebo using the NIAID 8- point scoring scale
- Characterize the effect of GT0918 compared to placebo on symptom improvement or resolution
- Characterize the effect of GT0918 compared to placebo on safety

2.3 Exploratory

- Characterize the pharmacokinetics of GT0918 and its metabolite GT0955
- Characterize emergence of viral resistance to GT0918
- Explore biomarkers predictive of GT0918 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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 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.

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 an interim analysis after 334 subjects completing Day 28 after the first dose to allow early stopping for futility, efficacy, or safety. 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.

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 of any age 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/m2)
  - Sickle cell disease or thalassemia
  - Smoking, current or former
  - Diabetes Type 1 or 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

GT0918 will be supplied as 100 mg tablets as individual patient supply packaged in blister. GT0918/placebo will be given 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 safety follow-up will be up to 28 days after last dose making the overall duration of monitoring 42 days for each patient.

The study treatment period is shown as below.

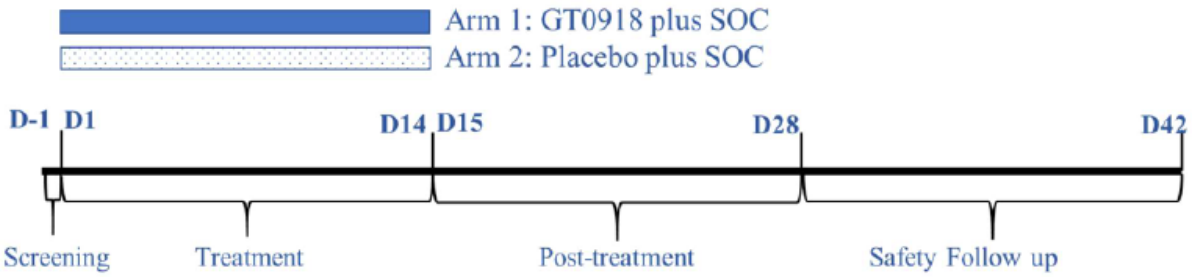

Figure 1: Overview of Study Period and Group Assignment

3.2 Planned Interim Analysis

An interim analysis will be conducted when 334 subjects complete 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 study sample size.

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. The boundary is estimated based on O'Brien and Fleming type alpha spending method. In this case the stopping boundary for efficacy is met and the study could be stopped for efficacy. Assuming there is no change in the study design regarding sample size modification, the one-sided p-value of <0.024 will be used for the final analysis to conclude the efficacy of the treatment group.

The conditional power will be evaluated based on primary endpoint in the interim analysis. 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 and the stopping boundary for efficacy is not met, the sample size will not be changed.

Rigorous steps will be taken (e.g., firewalls) where possible to minimize the information that can be inferred by observers.

3.3 Endpoints

3.3.1 Primary

- 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

3.3.2 Secondary

Hospitalization Percentage

- Percentage of subjects who 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

Virologic Response

- Change from baseline to Days 3, 7, 14 and 28 in SARS CoV-2 viral load
- Proportions of subjects that achieve sustained 100% SARS-CoV-2 viral reduction at Days 3, 7, 14 and 28
- Time to sustained 100% SARS-CoV-2 viral reduction
- 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

NIAID Ordinal Scale

- Percentage of subjects achieving each clinical status at Days 3, 7, 14 and 28 as defined below based on The National Institute of Allergy and Infectious Diseases (NIAID) 8- point ordinal 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 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

- Proportion of subjects with all-cause hospitalization (defined as ≥ 24 hours) by Day 28
- Proportion of subjects with COVID-19 related hospitalization (defined as ≥ 24 hours) by Day 28
- Days of hospitalization due to all causes or COVID-19 by Day 28
- Time to hospitalization due to all causes or COVID-19 by Day 28

- Proportion of subjects requiring supplemental oxygen, high-flow oxygen, any ventilation or ECMO due to COVID-19 by Day 28

Symptom Questionnaire

- 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

Safety

- Safety assessments such as AEs, SAEs and laboratory data

3.3.3 Exploratory

- Mean trough concentration of GT0918 and its relevant metabolite 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
- Screening for novel mutants in subjects who do not respond to GT0918
  - Genotype of SARS-CoV-2 viral isolates
- The association between changes in disease related biomarkers with clinical endpoints

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

Baseline: the last available pre-treatment assessment, unless otherwise specified.

For subjects who are screened, randomized, and undertake the first treatment on the same date, the self-reported symptom questionnaire and ordinal scale at Day 1 visit will be flagged as baseline if baseline assessment is missing.

End of Study (EOS): all required phases of the study including the last scheduled procedure shown in the SoA have been completed.

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.

Study Day will be calculated relative to the date of dose administration i.e. Study Day = Assessment Date - First Dose Date + 1, if Assessment Date is on or after First Dose Date. Assessment Date - First Dose Date, if Assessment Date is before First Dose Date.

If more than one laboratory value is available for a given study day, the last valid observation will be used in summaries, unless otherwise stated. If it is not possible to determine which is the last measurement due to missing times, then the average of all measurements for that study day will be used as the value for that study day. All observations will be presented in listings.

For subjects with duplicate self-reported symptom questionnaire or ordinal scale on the same day for the same visit, the record with the worst total score for questions 1 through 14 will be used for summary purpose. All records will be listed.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.0001, in general, will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999".

Confidence intervals will be presented to one more decimal place than the raw data.

Analysis Visit Window:

For unscheduled visits, analysis visit windows will be applied as in Table below. Analysis visit windows are only used for by visit summaries, not for time to event calculation which will based on actual date of data collected.

Table 1 Analysis Visit Window for Unscheduled Visits of blood samples

Mapped to	**Visit Window**
Screening	[Day -1, Day 1]
Day 3	[Day 2, Day 4]
Day 7	[Day 6, Day 8]
Day 14	[Day 13, Day 15]
Day 28	[Day 26, Day 30]
Day 42	[Day 40, Day 44]

4.3 Software

All report outputs will be produced using SAS® version 9.4 [1] or a later version in a secure and validated environment.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. The disposition summary will include:

- number of patients screened
- number of patients screened failure
- number of patients in each analysis sets
- number of patients completed treatment
- number and reason of patients withdrew early from the treatment
- number of patients completed post-treatment
- number of patients withdrew early from the post-treatment
- number of patients completed study
- number and reason of patients withdrew early from the study

By-subject listings of eligibility details, randomization details, visit dates and withdrawal/study completion details (including reason for discontinuation and duration of treatment prior to discontinuation) will be provided. Disposition data will be listed and summarized for all enrolled population.

4.4.2 Protocol Deviations

Protocol deviations will be identified and classified into major or minor. Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification. The final determination of major protocol deviations and the exclusion of patients from any of the analysis populations will be made prior to database lock.

A summary of the number and percentage of subjects with a major protocol deviation will be provided by treatment group and type of deviations using ITT set. A by-subject listing will be provided for all reported protocol deviations.

4.5 Analysis Sets

The Intent-to-Treat Analysis Set (ITT) includes all randomized subjects.

The Modified Intent-to-Treat Analysis Set (mITT) includes all randomized subjects who have received at least one dose of study medication. The primary efficacy analysis will be conducted on the mITT Analysis Set.

The Safety Analysis Set (SS) includes all subjects with at least one dose of study medication and will be analyzed as treated. The disposition, study summary, and safety analysis will be conducted on Safety Analysis Set.

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 200 subjects who receive intervention and have evaluable PK.

4.6 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group using the ITT set. The summaries provided will include the following:

- Demography
  - Age in years, age group (<50 years; ≥ 50 years), age group (<60 years; ≥ 60 years), and age group (<65 years; ≥ 65 years)
  - Sex
  - Race
  - Ethnicity
  - Baseline height
  - Baseline weight
  - Baseline BMI
  - Baseline BMI categories as below
    - Underweight (<18.5)
    - Normal (≥18.5 and <25.0)
    - Overweight (≥25.0 and <30.0)
    - Obesity (≥30.0)
      - Obesity Class 1 (≥30.0 and < 35.0)
      - Obesity Class 2 (≥35.0 and < 40.0)
      - Obesity Class 3 (≥40.0)
- Other Baseline Characteristics
  - Days from the positive SARS-CoV-2 prior to first dosing and test type
  - Days from onset of COVID-19 symptoms prior to first dosing
  - Prior COVID-19 therapy
  - Number of high-risk medical factors (0; 1-2; ≥3)
  - High-risk medical status by below categories
    - Age ≥ 65 years
    - Cancer
    - Chronic kidney disease
    - Chronic lung diseases
      - Chronic obstructive pulmonary disease
      - Asthma
      - Interstitial lung disease
      - Cystic fibrosis
      - Pulmonary hypertension
    - Dementia or other neurological conditions
      - Dementia

  - Other
- Down syndrome
- Heart conditions
  - Heart failure
  - Coronary Artery Disease
  - Cardiomyopathies
  - Hypertension
- Immunocompromised state (weakened immune system) from solid organ transplant
- Liver disease
- Overweight and Obesity (BMI ≥25 kg/m^2)
  - Overweight (BMI ≥25.0 kg/m^2 and <30.0 kg/ m^2)
  - Obesity (BMI ≥30.0 kg/ m^2 and <40.0 kg/ m^2)
  - Sever Obesity (BMI ≥40.0 kg/ m^2)
- Sickle cell disease or Thalassemia
  - Sickle cell
  - Thalassemia
- Smoking (current or former)
  - Current
  - Former
- Diabetes (type 1 or type 2)
  - Type 1
  - Type 2
- HIV infection
- Solid organ or blood stem cell transplant
  - Solid organ transplant
  - Blood stem cell transplant
- Stroke or cerebrovascular disease, which affects blood flow to the brain
  - Stroke
  - Cerebrovascular disease
- Substance use disorders
- Other

- Medical history will be reported by system organ class (SOC) and preferred term (PT) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher.
- Medication allergy history will also be reported by SOC and PT separately.

- Baseline patient reported COVID-19 symptom questionnaires will be summarized.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. By-subject listings of demographic data, other baseline characteristics (as summarized above), high-risk medical status, medical history and patient reported COVID-19 symptom questionnaires at baseline will be provided.

4.7 Concomitant Medication

All medications administered within 30 days prior to the first dose of study treatment through 28 days after the last dose of study treatment will be recorded in the concomitant medications. Medications will be coded using Anatomical Therapeutic Chemical (ATC) Classification codes by World Health Organization Drug Dictionary (WHO-DD-March 2021) or latest version. Prior and concomitant medications will be summarized by ATC class level II, and Preferred Term.

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior only. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

In the summary of prior and concomitant medications, each subject will be counted once within each unique term. For example, if a subject takes amoxycillin on 2 separate occasions, the subject is counted only once under the corresponding ATC class.

Summaries and by-subject listings will be given for Safety set. The summary will group the medication by Prior only, Prior and Concomitant and Concomitant only.

Standard of Care

Subjects should be treated according to standard of care.

Remdesivir may be initiated as standard of care for subjects hospitalized with severe disease.

All medications administered as the local standard of care per written policies or guidelines (that is, not just an individual clinician decision) such as lopinavir/ritonavir, chloroquine, hydroxychloroquine or other investigational agents. will be summarized separately.

4.8 Prior and Concomitant Procedures

Prior and concomitant non-drug therapies will be summarized by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher ATC class level II, and Preferred Term for each treatment group and listed using Safety set.

4.9 Treatment Compliance

The compliance rate will be assessed as: Compliance Rate (%) = (cumulative dose [mg] / planned dose [mg]) * 100.

Non-compliance is defined as taking less than 80% or more than 120% of study drug during any outpatient evaluation period (visit to visit).

A summary of treatment compliance, including the number and percentage of compliant, and non-compliant subjects, will be provided using Safety set. A by-subject listing of treatment compliance data will also be provided.

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

Primary Null Hypothesis H0: proportion of subjects who do not experience all-cause hospitalization (defined as ≥24 hours), do not require supplemental oxygen for ≥24h in response to SpO2≤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), do not require supplemental oxygen for ≥24h in response to SpO2≤93% and are alive by Day 28 in GT0918 arm (p1) is greater 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 age and the stratification factors at time of randomization at the one-sided 0.025 level based on mITT set. P-values and 95% exact confidence intervals for the treatment difference will be presented. The actual alpha level used for the final analysis will take into account the adjustment required for the interim analysis.

4.10.1.1 Handling of Dropouts or Missing Data

4.10.1.1.1 Handling for Primary Endpoints

No dropouts will be replaced. Every effort will be made to avoid missing data. 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. Subjects with missing primary assessments by day 28 will be treated as meeting the primary endpoint (i.e., not experiencing hospitalization (≥ 24 hours) or using supplemental oxygen in response to SpO2 ≤93% (≥ 24 hours), or alive). Justification for missing primary endpoint handling is provided in Section 4.10.1.1.3.

4.10.1.1.2 Imputation of Partial Dates

Imputed dates will be used only to assign reported AEs and Medications to the different study periods: Screening Period, Treatment Period, Post-Treatment Period and Safety-Follow Up Period; for

determining the category for reported Medication as 'PRIOR ONLY', 'PRIOR and CONCOMITANT' or 'CONCOMITANT ONLY' and to determine if an AE is treatment emergent.

Both observed and imputed dates will be included into the analysis datasets. Dates will be displayed in listings with only the information available in the database.

Partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y' with

blank: indicates that no imputation was done,
D = 'Day': indicates that the day portion of the date is imputed,
M = 'Month': indicates that the month and day portions of the date are imputed,
Y = 'Year': indicates that the entire date (year, month, and day) is imputed.

Table 2 Partial Date Imputation Rules for AEs and Medications

Date	Missing Element	Rule
Start Date	day, month, and year	Set to the first dose date
	day, month only	If the year matches the first dose date, then impute to the month and day of the first dose date. Otherwise, assign January 1st.
	day only	If the year and month match the first dose date, then impute to the day of the first dose date. Otherwise, assign the first day of the month.
End Date	day, month, and year	No imputation and assign a missing value
	day, month only	Set to December 31st or last study visit, whichever occurs first.
	day only	Set to the last day of the month or last study visit, whichever occurs first.

Thus, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to treatment.

4.10.1.1.3 Changes in missing data handling from the protocol

A change was made in handling of dropout and missing data as presented in the protocol amendment version 2.0 of Section 10.5.1.3: *For the primary analysis of the primary endpoint, patients with missing primary assessments will be included in the analysis and evaluated as treatment failure (*i.e., hospitalization, supplemental oxygen use, or death*).*

In the current SAP, handling of subjects with missing primary assessments by day 28 are updated to treat as meeting the primary endpoint (i.e., not experiencing hospitalization ($\geqslant$ 24 hours) or using supplemental oxygen in response to SpO2 $\leqslant$93% ($\geqslant$ 24 hours), or alive) for the following reasons. Firstly, in the latest version of Informed Consent Form (ICF), a clear statement was made to inform subjects that medical care related with hospitalization would be reimbursed by the sponsor to ensure all hospitalization events would be captured. Secondly, site-contacted subjects who were initially lost to follow-up as well as the majority of subjects in this study did not experience any hospitalization nor oxygen use through day 28. Additionally, known reasons for subjects who discontinued early from the study were related to reasons like "patient felt better" or "subject left out of town" rather than reasons related to worsening in the clinical status or treatment related adverse events. Moreover,

only less than two percent of hospitalization was observed in this study. Given the low hospitalization percentage, imputation of relatively high proportion of missing primary assessments as hospitalization could substantially bias or even lead to misleading conclusion of the treatment efficacy.

4.10.1.2 Multiple Comparisons/Multiplicity

One interim analysis is planned. The method of adjusting the Type I error rate used in this study is O'Brien and Fleming type alpha spending. The actual alpha spending will be calculated based on the actual information used for the interim analysis.

4.10.1.3 Examination of Subgroups

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

Summaries of the primary efficacy variable by treatment group and subgroup will be produced. No formal statistical analysis will be performed within subgroup. Forest plot will be used to evaluate the subgroup effects.

Subgroups may include:

- Sex (Male; Female)
- Geographic region (USA vs non-USA)
- Baseline severity of COVID-19 (Mild; Moderate)
- Age group (<50 years vs. ≥ 50 years, <60 years vs. ≥ 60 years)
- Race and ethnicity (Non-Hispanic White or others; Hispanic or Latino; Non-Hispanic Black)
- Baseline BMI (BMI category: Underweight; Normal; Overweight; Obesity)
- Days from symptom onset to study randomization (≤5 days; >5 days)
- Number of risk factors at time of randomization (0; 1-2; ≥3)
- Vaccination status (Non; Partial Vaccinated; Fully Vaccinated)
- Days from the Positive SARS-CoV-2 Prior to First Dosing (≤3 days; >3 days)
- Biomarkers like C-reactive protein (CRP), ferritin, D-dimer at baseline (Low; Normal; High)
- Most common baseline viral variants (i.e., Gamma, Delta, Mu)

4.10.2 Primary Efficacy Variables

Clinical question of interest: Does the study drug Proxalutamide (GT0918) increase the proportion of subjects who do not experience all-cause hospitalization for at least 24 hours, do not require supplemental oxygen for at least 24h in response to SpO2≤93% and are alive by Day 28, in comparison to placebo?

Intercurrent events (may occur between randomization and Day 28), not mutually exclusive:

- IE1: subject's withdrawal from the study prior to Day 28
- IE2: subject lost to follow-up prior to Day 28
- IE3: subject did not receive any dose of study treatment

Attributes of Estimand (following a treatment policy strategy) [ICH E9 (R1) Addendum 2019]

- Population: all subjects in the mITT population
- Treatment Conditions:
  - condition of interest: randomized to GT0918 + standard of care and treated
  - alternative/control condition: randomized to placebo + standard of care and treated
- Endpoint: the proportion of subjects who do not experience all-cause hospitalization (defined as ≥24 hours), do not require supplemental oxygen for ≥24h in response to SpO2≤93% and are alive by Day 28
  Note: All-Cause Hospitalization includes: Hospitalization, Emergency room and ICU. Extended Care Facility Admittance is excluded.
- Population-level Summary: estimated incidence probability for subjects not experiencing all-cause hospitalization (defined as ≥24 hours), not requiring supplemental oxygen for ≥24h in response to SpO2≤93% and alive by Day 28 (in each treatment group separately)

Main Estimator for Estimand: Odds ratio by Day 28 with adjusting stratification factors defined by baseline clinical status used in the stratified randomization

- Intercurrent events IE1 and IE2 will be disregarded for the inclusion of subjects in the statistical analysis, IE3 restricts the inclusion of subjects to those who received at least one dose of study treatment. Hence, the main estimator for Estimand will be based on the mITT analysis set.
- Subjects with missing primary assessments by day 28 will be treated as meeting primary endpoint. The primary endpoint event rate will be compared between treatment and placebo arm using CMH Chi-square test with adjusting age and the stratification factors (sex, race and ethnicity, and number of risk factors) at time of randomization. The hypothesis test will be performed at the one-sided 0.025 level based on mITT. Odd ratio with 95% exact confidence interval and p-value will be presented.
- The number and proportion of subjects that do not experience any of the 3 components (all-cause hospitalization, requirement of supplemental oxygen and death) of the primary endpoint by Day 28 will be summarized by treatment for the mITT population in frequency tables and listed.
- The individual components of the primary endpoint will be summarized as well.

The following sensitivity analysis will be performed for the primary endpoint:

- Among subjects with dosing days > 7 days;
- Per protocol analysis set;
- Complete case analysis set (subjects without any missing primary endpoint assessments);
- Removing the constraint of ⩾24 hours in hospitalization and supplemental oxygen use;
- By treating missing primary assessments as hospitalization;
- By treating missing primary assessments as hospitalization and among subjects with dosing days > 7 days.

All sensitivity analyses will be performed using mITT sets except the per protocol analysis. Also, all sensitivity analyses will be conducted using the same one-sided CMH chi-square tests introduced for the primary endpoint analysis.

Interim analysis

An interim analysis will be conducted when 334 subjects complete Day 28 after first dose 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 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.

The one-sided Type I error rate (0.025) for the primary efficacy endpoint will be adjusted following O'Brien and Fleming type alpha spending method. The actual alpha spending will be calculated based on the actual information used for the interim analysis and used as the efficacy boundary, as shown below. The efficacy criterion will be based on the one-sided p-value of the primary endpoint analysis as less than the actual alpha spending. In this case the stopping boundary for efficacy is met and the study could be stopped for efficacy.

$$\text{O'Brien and Fleming: } \alpha_{IA}(t^*) = 2 - 2\Phi(Z_{1-\alpha/2}/\sqrt{t^*}),$$

where IA means interim analysis, Φ denotes the standard normal cumulative distribution function and t* denotes the fraction of information that has been observed at Interim Analysis timepoint.

The futility of a study that is underway can be determined by calculating its conditional power, which is the probability of statistical significance at the completion of the study given the data obtained so far. The futility criterion for the study will be based on the conditional power of the study being <10%. The conditional power will be evaluated based on primary endpoint in the interim analysis. If the conditional power of the study at the time interim analysis performed 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 and the stopping boundary for efficacy is not met, the sample size will not be changed. The general lower one-sided conditional power is computed as

$$CP_{IA}(\theta) = \Phi\left(\frac{-Z_{IA}\sqrt{I_{IA}} - z_{1-\alpha}\sqrt{I_{FA}} - \theta(I_{FA} - I_{IA})}{\sqrt{I_{FA} - I_{IA}}}\right),$$

where

IA representing interim analysis and FA representing final analysis,

$\theta = P_2 - P_1$ (the expected difference under the alternative hypothesis),

$Z_{IA} = (p_{2IA} - p_{1IA})\sqrt{\hat{I}_{IA}}$ (the z-statistic computed from the observed data),

$I_{IA} = \frac{1}{\sigma^2}\left(\frac{1}{n_{1IA}} + \frac{1}{n_{2IA}}\right)^{-1}$ (the interim information level),

$I_{FA} = \frac{1}{\sigma^2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{-1}$ (the final information level),

where

p_{jIA} is the sample proportion for group j, estimating p_j at IA,
$\hat{I}_{IA}$ is the estimated information from the sample at IA,
n_{jIA} is the sample size in group j at IA,
n_j is the final sample size in group j,
$\sigma^2 = \bar{p}(1 - \bar{p})$ with $\bar{p} = (P_1 + P_2)/2$

The conditional power calculated based on different software may be slightly different.

4.10.3 Secondary Efficacy Variables

Hospitalization Percentage

Hospitalization percentage is defined as the percentage of subjects who 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

The same process used for the primary endpoint analysis will be used to compare the difference between treatment groups.

The following sensitivity analysis for hospitalization percentage will be performed among subset of mITT subjects:

- With dosing days > 7 days;
- With one or several major risk factors below:
  - Single risk factor: age (≥ 50 years; ≥ 60 years), major underlying medical conditions (overweight, obesity, hypertension, diabetes, smoking);
  - Combination of age factor in column 1 and other major underlying medical conditions in column 2 in the table below (e.g., age ≥ 50 years and/or obesity at randomization; age ≥ 60 years and/or obesity at randomization);

Age	Major underlying medical conditions
≥ 50 years ≥ 60 years	Overweight Obesity Hypertension Diabetes Smoking

- With aged ≥50 years and days from symptom onset to study randomization ≤5 days and days from the positive SARS-CoV-2 Prior to first dosing ≤3 days;
- With aged ≥50 years and higher than normal biomarkers (CRP, Ferritin, D-dimer).

All sensitivity analyses will be conducted using one-sided CMH chi-square tests used for the primary endpoint analysis. Forest plots for the sensitivity analysis will be presented.

Change from Baseline to Days 3, 7, 14 and 28 in SARS CoV-2 Viral Load

Change of SARS-CoV-2 viral load from baseline, which will be evaluated in 1og base 10 scale, will be summarized, and plotted by treatment group and listed. Two sample t-tests will be used to compare differences in the change of SARS-CoV-2 viral load between treatment groups at Day 3, 7, 14 and 28, respectively.

Also, an analysis of covariance (ANCOVA) model will be used to compare the change from baseline in SARS-CoV-2 viral load at Day 3 with fixed effects for treatment group, age and stratification factors (sex, race and ethnicity, and number of risk factors), and baseline viral load as a covariate. If systematic pattern is identified from the residual of predicted values, a transformation of the baseline viral load will be employed to improve the performance of the model. Estimated treatment differences

in comparison to placebo along with corresponding two-sided 95% confidence intervals (CIs) and p-values will also be presented.

Additionally, change from baseline in SARS-CoV-2 viral load at Day 3, 7, 14 and 28 will be compared using a mixed model repeated measures (MMRM). The model will include treatment group, visit, treatment-by-visit interaction, age and stratification factors (sex, race and ethnicity, and number of risk factors) as fixed effects, baseline viral load as a covariate, and subject as a random effect. If the unstructured covariance matrix fails to converge, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. If systematic pattern is found in the residual of predicted values, a transformation of the baseline viral load will be employed to improve the performance of the model. Comparisons of GT0918 to placebo for change from baseline in viral load and the corresponding two-sided 95% CIs along with p-values will be calculated and plotted based on the MMRM model at each visit.

Sustained 100% SARS CoV-2 Viral Reduction

SARS-CoV-2 viral reduction (%) is calculated as

(viral load after baseline – viral load at baseline) / (viral load at baseline) * 100%.

If the value of SARS-CoV-2 viral reduction is greater than or equal to 100 the result of 100% SARS CoV-2 viral reduction will be set as "Yes". Otherwise, a negative result of "No" will be obtained.

Sustained 100% SARS CoV-2 viral reduction (Yes/No) is defined when at least two consecutive negative ("No") tests (≥24 hours apart) are obtained. The date of sustained 100% SARS CoV-2 viral reduction is defined as the earlier date of the consecutive negative tests.

The proportion of subjects that achieve sustained 100% SARS CoV-2 viral reduction at Days 3, 7, 14, and 28 will be summarized by treatment in frequency tables, plotted and listed. Generalized estimating equation (GEE) model will be used to model the proportions of achieving SARS-CoV-2 clearance at different visits. The model will consider treatment group, visit, treatment-by-visit interaction, age and stratification factors (sex, race and ethnicity, and number of risk factors) as fixed effects, and subject as a random effect. Comparisons of GT0918 to placebo for odds ratios (ORs), corresponding 95% CIs and p-values will be calculated at each visit.

Time to Sustained 100% SARS CoV-2 Viral Reduction

Time to sustained 100% SARS-CoV-2 viral reduction (in days) is defined as:

Date when sustained 100% SARS CoV-2 viral reduction is changed to 'Yes' - first dosing date + 1.

If a patient has not experienced SARS-CoV-2 clearance by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the post-treatment period.

Time to sustained 100% SARS CoV-2 viral reduction and will be summarized and plotted by treatment group with mITT set using the Kaplan-Meier (KM) method. The 2-sided 95% CIs for the 25th, 50th and 75th percentiles, as well as at days 3, 7, 14 and 28 using the Brookmeyer and Crowley method will be reported when estimable. P-value will be obtained from the log-rank test stratified by age, and sex, race and ethnicity, and number of risk factors at randomization. Hazard ratios and corresponding 95% confidence intervals will be obtained from a Cox proportional hazard model which treated treatment group as a unique covariate, and age, and sex, race and ethnicity, and number

of risk factors as stratas. The Cox proportional hazard model will be also performed by subgroup of duration since symptom onset to randomization category (≤3 days; >3 days).

SARS CoV-2 Viral Clearance

SARS-CoV-2 Viral clearance (Yes/No) is defined when at least two consecutive negative tests proceed a positive test with all tests ≥24 hours apart. The date of viral clearance is defined as the earliest date between the consecutive negative tests.

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, plotted and listed. Viral clearance can only be achieved (Yes) at days with a negative result. Generalized estimating equation (GEE) model will be used to model the proportions of achieving SARS-CoV-2 clearance at different visits. The model will consider treatment group, visit, treatment-by-visit interaction, age and stratification factors (sex, race and ethnicity, and number of risk factors) as fixed effects, and subject as a random effect. Comparisons of GT0918 to placebo for odds ratios (ORs), corresponding 95% CIs and p-values will be calculated at each visit.

Time to SARS-CoV-2 Clearance

Time to SARS-CoV-2 clearance (in days) is defined as:

Date when SARS-CoV-2 clearance status is changed to 'Yes' - first dosing date + 1.

If a patient has not experienced SARS-CoV-2 clearance by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the post-treatment period.

Time to SARS-CoV-2 clearance will be applying the same KM methods and Cox proportional hazard models introduced for the time to sustained 100% SARS CoV-2 viral reduction analysis.

Viral Load AUC

SARS-CoV-2 viral load area under the concentration-time curve (AUC) 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 (LoQ) at Days 3, 7, 14 and 28. Per ICON central lab, LoQ is 59.9 copies/mL. 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 group and listed.

Viral Resistance by Day 28

The proportion of viral resistance at day 28 will be summarized by treatment group and listed. The CMH chi-square test introduced for the primary endpoint analysis will be used to compare the difference of proportion of viral resistance between treatment groups by day 28.

Viral resistance is defined as when subjects:

- Are not able to show two consecutive negative test results via ddPCR testing by Day 28 without any missing scheduled tests, and/or

- Show a positive real-time ddPCR test result after two consecutive negative ddPCR test results, and/or
- A confirmed rise in SARS-CoV-2 RNA of ≥1 log10 after achieving nadir on treatment.

COVID-19 Ordinal Outcomes Scale

Below summaries will be provided using mITT set:

- The percentage of subjects at each clinical status using NIAID 8-point ordinal scale at Days 3, 7, 14, and 28
- Comparison of the proportion of NIAID ordinal scale by Days 3, 7, 14, and 28: ordinal generalized estimating equation (GEE) with treatment, age, stratification factors (sex, race and ethnicity, and number of risk factors), visit, and interaction of visit and treatment will included in the model as fixed effects, and subject will be included as a random effect. Odds ratios with 95% confidence intervals and p-values will be presented. If data are too sparse for one level of the above factors, the factor will not be included in the statistical model/test to avoid convergence issue. Inferential analysis will only be performed if data warrants.
- Proportion of subjects worsening from baseline (worsening is defined as any worsening on the NIAID ordinal scale from baseline to Days 3, 7, 14, and 28)

Stacked bar plot by treatment group and visits at Day 1, 3, 7, 14 and 28 will be produced for NIAID ordinal scale. Also, mean value by treatment group will be plotted over time.

All NIAID ordinal scales through the study period will be listed in listing.

Other Analysis for Clinical Status

Below summaries for other analysis for clinical status will be provided as well:

- Summary of Hospitalization and Extended Care Facility Admissions by Day 28 (COVID-19 related will be summarized separately)
  Note: Hospitalization (≥24 hours) includes: Hospitalization, Emergency room and ICU. Extended Care Facility Admittance is excluded.
  - Number and proportion of subjects hospitalized
  - Duration of Hospitalization
  - Number and proportion of subjects hospitalized by admission type: Hospitalization, Emergency Room, Intensive Care Unit (ICU) and Extended Care Facility
  - Duration by admission type
  - Comparisons of proportion of hospitalization between treatment group will be made using FIRTH logistic regression. with adjusting age and the stratification factors (sex, race and ethnicity, and number of risk factors). Odds ratios with 95% confidence intervals and p-values will be present. If data are too sparse for one level of the above factors, the factor will not be included in the statistical model/test to avoid convergence issue. Inferential analysis will only be performed if data warrants.
- Summary of New Oxygen Use by Day 28 (COVID-19 related will be summarized separately)
  - Number and proportion of subjects requiring any oxygen use
- Summary of COVID-19 Related Medical Attended Visits by Day 28
  - Proportion of subjects with COVID-19 related medical attended visits

All hospitalization events and COVID-19 related medical attended visits will be listed.

Time to Hospitalization

Time to Hospitalization (in days) is defined as:

First hospital admission date - first dosing date + 1.

Note: Hospitalization (≥24 hours) includes Hospitalization, Emergency room and ICU. Extended Care Facility Admittance is excluded.

The following two summaries will be generated separately:

- All-Cause Hospitalization
- COVID-19 Related Hospitalization

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

Time to hospitalization will be evaluated up to Day 28 and will be summarized and plotted by treatment group with mITT set using the Kaplan-Meier (KM) method. The 2-sided 95% CIs for the 25th, 50th and 75th percentiles, as well as at days 3, 7, 14 and 28 using the Brookmeyer and Crowley method will be reported when estimable. P-value will be obtained from the log-rank test stratified by age, and sex, race and ethnicity, and number of risk factors at randomization. Hazard ratios and corresponding 95% confidence intervals will be obtained from a Cox proportional hazard model which treated treatment group as a unique covariate, and age, and sex, race and ethnicity, and number of risk factors as stratas. The Cox proportional hazard model will be also performed by subgroup of duration since symptom onset to randomization category (≤3 days; >3 days).

If cases of hospitalization are too sparse (e.g., <1 case in one treatment group), no time to hospitalization analyses will be performed.

Proportion of Symptom Resolution

All symptom resolution is defined as

all symptoms (those scored 0-3*) on the symptom questionnaire scored as absent (scored 0), with each symptom resolution absent for at least 48 hours.

Note: * Seven individual questions from COVID-19-Related Symptom Questionnaire are included here: questions 3, 4, 5, 6, 7, 8 and 9.

Additionally, all symptom resolution will be defined differently to include all individual questions scored 0-3 and related outputs will be noted as sensitivity analysis. It is defined as

all symptoms (those scored 0-3*) on the symptom questionnaire scored as absent (scored 0), with each symptom resolution absent for at least 48 hours.

Note: * Nine individual questions from COVID-19-Related Symptom Questionnaire are included here: questions 1 through 9.

The proportion of subjects with all symptom resolution will be performed at Days 3, 7, 14, and 28 by treatment in frequency tables and listed using mITT set. Generalized estimating equation (GEE) model will be fitted with the response of symptom resolution mapped to categories of Yes or No and with treatment, age, stratification factors (sex, race and ethnicity, and number of risk factors), time

effect and time*treatment interaction terms included in the model as covariates. Odds ratios with 95% confidence intervals and p-values will be present.

Total symptom score (seven individual questions from COVID-19-Related Symptom Questionnaire included here are questions 3, 4, 5, 6, 7, 8 and 9) and change from baseline in total symptom score to Days 3, 7, 11, 14 and 28 will be summarized by treatment group. Change from baseline will be compared using mixed model repeated measures (MMRM) with the fixed effects of baseline total symptom score, age and stratification factors (sex, race and ethnicity, and number of risk factors) and the random effect of subjects and with time effect and time*treatment interaction terms included in the model. Change from baseline in total symptom score will also be graphically displayed.

Additionally, total symptom score will be calculated differently to include nine individual questions (1 through 9) and related outputs will be noted as sensitivity analysis.

A summary of overall COVID-19 related symptoms, including overall symptoms severity, overall general physical health and returned to usual physical health, at Days 3, 7, 11, 14 and 28 will be provided in frequency table and listed.

Additionally, the proportion of subjects with at least 2 points decrease in symptom score (total of ratings) from baseline to Days 3, 7, 14 and 28 will be summarized and listed as well. Generalized estimating equation (GEE) model will be fitted with the response of at least 2 points decrease mapped to categories of Yes or No and with treatment, age, stratification factors (sex, race and ethnicity, and number of risk factors), time effect and time*treatment interaction terms included in the model as covariates. Odds ratios with 95% confidence intervals and p-values will be present.

Time to All Symptom Resolution

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

> First date when all 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 post-treatment period.

Time to all symptom resolution will be applying the same KM methods and Cox proportional hazard models introduced in the time to hospitalization section.

Symptom Improvement

Symptom improvement is defined as a change in severity of overall symptoms * from a higher score to a lower score, which 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.
>
> Note: * The overall symptoms question (overall question 1) under overall COVID-19 related symptoms from COVID-19-Related Symptom Questionnaire is included here.

Additionally, symptom improvement will be defined by individual symptom questions from symptom questionnaire as below and related outputs will be noted as sensitivity analysis. It is defined as a patient experiencing both:

symptoms * scored as moderate or severe at baseline are subsequently scored as mild or absent,
AND
symptoms * scored as mild or absent at baseline are subsequently scored as absent.

Note: * Seven individual questions from COVID-19-Related Symptom Questionnaire are included here: questions 3, 4, 5, 6, 7, 8 and 9.

The proportion of subjects with symptom improvement at Days 3, 7, 11, 14 and 28 will be summarized by treatment in frequency tables and listed using mITT set. Generalized estimating equation (GEE) model is fitted with the response of symptom improvement mapped to categories of Yes or No and with treatment, age, stratification factors (sex, race and ethnicity, and number of risk factors), time effect and time*treatment interaction terms included in the model as covariates. Odds ratios with 95% confidence intervals and p-values will be present.

Time to Symptom Improvement

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

Date when symptom improvement status is changed to 'Yes' - first dosing date + 1.

If a patient 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 post-treatment period.

Time to symptom improvement will be applying the same KM methods and Cox proportional hazard models introduced in the time to hospitalization section.

4.11 Safety Evaluation

All safety analyses will be based upon the Safety set. All listings and tables will be presented by treatment group.

The overall observation period will be divided into 5 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 the day of first dose of study drug (D1) to the day of last dose (up to D14).
3. post-treatment period: from the day after last dose (up to D15) to D28.
4. treatment and post-treatment period: from D1 to D28.
5. safety follow up period: from D29 to D42.

4.11.1 Extent of Exposure

Duration of study treatment exposure, the actual cumulative dose (mg), dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment.

Duration of treatment exposure is defined as the time from initial dose to last non-zero dose. Duration of treatment is calculated as: (Last Dose Date - First Dose Date) + 1.

Dose intensity is computed as the ratio of actual dose received to actual duration.

Relative dose intensity is computed as the ratio of the dose intensity to planned dose received/planned duration.

In addition, the duration of exposure to study treatment will be categorized into time intervals (0-4 days, 0-7 days and 0-14 days); frequency counts and percentages will be presented for the number of patients in each interval. The number of patients, who have dose reductions or interruptions, and the reasons, will be summarized by treatment.

Listings of all doses of the study treatment along with dose change reasons will be produced.

The safety population will be used for all summaries and listings of study treatment.

The actual dose and duration of GT0918, as well as dose intensity and the relative dose intensity, 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).

4.11.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher.

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.

Treatment-emergent AEs (TEAE) are defined as AEs that either start or worsen in severity on or after the date/time of study drug administration and through the end of study.

Overview of AEs

An overall summary table of AEs will be provided with the number and percentage of subjects (incidence) reporting an event for the following categories:

- All AEs
- All TEAEs
  - TEAEs Related to Study Drug
  - TEAEs with Toxicity Grade 3 and Higher
  - TEAEs Related to Study Drug with Toxicity Grade 3 and Higher
    Note: Related is defined as "Definitely", "Probably", "Possibly" related, or missing relationship to study treatment.
  - TEAEs Leading to Study Drug Discontinuation
  - TEAEs of Special Interest
- TEAEs by Maximum Toxicity Grade (based on the Division of AIDS (DAIDS) [2])
  - Grade 1
  - Grade 2
  - Grade 3
  - Grade 4
  - Grade 5
  - Not Gradable
- TEAEs by Maximum Severity
  - Mild
  - Moderate

  - Severe or Medically Significant
  - Life Threatening
  - Died
- All Serious AEs (SAEs)
  - SAEs Related to Study Drug
  - SAEs with Outcome Fatal

TEAE Summaries by System Organ Class and Preferred Term

The incidence for the following will be summarized by SOC and PT, unless otherwise specify:

- All TEAEs
- TEAEs Related to Study Drug
- TEAEs with Toxicity Grade 3 and Higher
- TEAEs Related to Study Drug with Toxicity Grade 3 and Higher
- TEAEs by Maximum Toxicity Grade
- TEAEs Related to Study Drug by Maximum Toxicity Grade
- TEAEs by Maximum Severity

Adverse event summaries will be ordered by decreasing incidence for SOC, and PT within SOC, in the GT0918 treatment group. In case of equal number of subjects sorting will be done alphabetically.

For each subject and each adverse event, the worst toxicity recorded will be attributed and used in the by-maximum-toxicity summaries.

Separate tables for on-treatment period and safety follow up period will be provided, and below by-subject listings will be provided:

- All AEs
- All AEs Related to Study Drug
- All AEs with Toxicity Grade 3 and Higher

4.11.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

SAE

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:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - 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.

- 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.

AE Summaries by System Organ Class and Preferred Term

The incidence for the following will be summarized by SOC and PT, unless otherwise specify:

- SAEs
- SAEs Related to Study Drug
- SAEs with Outcome Fatal
- TEAEs Leading to Study Drug Discontinuation

Separate tables for on-treatment period and safety follow up period will be provided, and below by-subject listings will be provided:

- All SAEs
- All Fatal SAEs
- All AEs leading to Study Drug Discontinuation

Adverse Events of Special Interest (AESI)

Adverse events of special interest to be monitored include gastrointestinal, cardiovascular, hepatic, and neurological adverse events (dizziness, headache), hematological (anemia, leukopenia, neutropenia) and elevated creatinine kinase. (Appendix 6.5)

TEAEs of special interest will be summarized by SOC and PT.

Time to TEAEs of Special Interest

Time to TEAEs of special interest (in days) is defined as:

First date when TEAEs of special interest onset - first dosing date + 1.

If a patient has not experienced TEAEs of special interest by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit.

Time to TEAEs of special interest will be summarized for Safety set using the Kaplan-Meier (KM) method. Log-rank test will be used. P-values and hazard ratios with 95% confidence intervals based on Cox proportional hazard model stratified by duration since symptom onset to randomization category (≤3 days; >3 days) will be present.

4.11.4 Clinical Laboratory Evaluation

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), except for specific parameters which will be performed centrally. For a list of the parameters to be evaluated, see Table Clinical Laboratory Parameters in appendices.

For parameters where a DAIDS Version 2.1 scale exists, laboratory results will be graded according to DAIDS Version 2.1 toxicity grade. 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.

A single measure for partial thromboplastin time (PTT) will be collected and both non-activated and activated PTT (aPTT) can be captured in the measure. DAIDS toxicity grading scale for partial thromboplastin time (PTT) will be used for the PTT/aPTT measure.

Laboratory values obtained during the screening phase will be used to assess subject's eligibility, and therefore it will be listed only, but not summarized in tables.

Laboratory values reported as a character value, such as <40, will be transformed into numerical values for summary reasons.

4.11.4.1 Hematology, Clinical Chemistry, and Coagulation

The following by treatment summaries will be generated separately for hematology, clinical chemistry, 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.

4.11.4.2 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

The by visit biomarker data will be summarized by treatment group for the Safety set. Biomarker data over time will also be plotted for each biomarker type.

4.11.4.3 Pharmacokinetics

PK analysis will be performed on the PK set.

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 200 subjects who receive intervention and have evaluable PK.

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

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.

4.11.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Vital signs include:

- Height and weight at screening only
- Body temperature
- Systolic blood pressure (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 if applicable or clinical indicated

The observed Vital Signs value and change from baseline to each post-baseline time point will be summarized using descriptive statistics.

A by-subject listing of vital sign parameters will be provided.

Physical Findings

Full physical exam should be done at screening visit. For the subsequent visits, symptom directed physical exam can be done per investigator's discretion.

A by-subject listings of physical examination results will be provided.

ECG

A 12-lead ECG can be done per investigator's discretion. All ECG findings including interpretation and clinically significant status will be listed by subject.

Chest X-ray and CT-scan

Chest X-ray or CT-Scan can be done per investigator's discretion. The results will be listed by subject if any.

Pregnancy Test

Pregnancy test results at Day 28 visit will be listed by subject.

4.11.6 Independent Data Monitoring Committee (IDMC)

An IDMC will be responsible for monitoring and reviewing the clinical study data for safety and efficacy during the study prior to the final data analysis. 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. An 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. More details please refer to section 4.11.2.1. Rigorous steps will be taken (e.g., firewalls) where possible to minimize the information that can be inferred by observers.

4.12 Determination of Sample Size

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 about 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).

5 REFERENCES

[1] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[2] Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric DAIDS Adverse Event Grading Tables | DAIDS Regulatory Support Center (RSC) (nih.gov)

6 APPENDICES

6.1 Schedule of Assessments (SoA)

Table 4 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]	**X**	**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 screening visit until D14 or the last dose.

    Questionnaire should be completed every day since screening visit to the end of post-treatment. 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
    - Extended care facility admittance
    - Discharge
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 200 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.

6.2 NIAID 8-Point Ordinal 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 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

6.3 Clinical Laboratory Parameters

Table 5 Clinical Laboratory Parameters

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), partial thromboplastin time: non-activated (PTT) or activated (aPTT)
Additional tests	Local/Central*	C-reactive protein (CRP); high-sensitivity Ferritin D-dimer Procalcitonin Troponin (preferably Troponin I)

Test category	Local/Central	Test Name
Virology	Central	SARS-CoV-2 viral infection determination at screening - local SARS-CoV-2 viral load test (quantitative ddPCR) - 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.

6.4 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 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

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 ☐

6.5 Adverse Events of Special Interest (AESI)

SMQ	Preferred Term
Liver related investigations, signs and symptoms	Alanine aminotransferase abnormal
Liver related investigations, signs and symptoms	Alanine aminotransferase increased
Liver related investigations, signs and symptoms	Ammonia abnormal
Liver related investigations, signs and symptoms	Ammonia increased
Liver related investigations, signs and symptoms	Ascites
Liver related investigations, signs and symptoms	Aspartate aminotransferase abnormal
Liver related investigations, signs and symptoms	Aspartate aminotransferase increased
Liver related investigations, signs and symptoms	AST/ALT ratio abnormal
Liver related investigations, signs and symptoms	Bacterascites
Liver related investigations, signs and symptoms	Bile output abnormal
Liver related investigations, signs and symptoms	Bile output decreased
Liver related investigations, signs and symptoms	Biliary ascites
Liver related investigations, signs and symptoms	Bilirubin conjugated abnormal
Liver related investigations, signs and symptoms	Bilirubin conjugated increased
Liver related investigations, signs and symptoms	Bilirubin urine present
Liver related investigations, signs and symptoms	Biopsy liver abnormal
Liver related investigations, signs and symptoms	Blood bilirubin abnormal
Liver related investigations, signs and symptoms	Blood bilirubin increased
Liver related investigations, signs and symptoms	Blood bilirubin unconjugated increased
Liver related investigations, signs and symptoms	Bromosulphthalein test abnormal
Liver related investigations, signs and symptoms	Child-Pugh-Turcotte score abnormal
Liver related investigations, signs and symptoms	Child-Pugh-Turcotte score increased
Liver related investigations, signs and symptoms	Computerised tomogram liver abnormal
Liver related investigations, signs and symptoms	Congestive hepatopathy
Liver related investigations, signs and symptoms	Foetor hepaticus
Liver related investigations, signs and symptoms	Galactose elimination capacity test abnormal
Liver related investigations, signs and symptoms	Galactose elimination capacity test decreased
Liver related investigations, signs and symptoms	Gamma-glutamyltransferase abnormal
Liver related investigations, signs and symptoms	Gamma-glutamyltransferase increased
Liver related investigations, signs and symptoms	Guanase increased
Liver related investigations, signs and symptoms	Hepaplastin abnormal
Liver related investigations, signs and symptoms	Hepaplastin decreased
Liver related investigations, signs and symptoms	Hepatic artery flow decreased
Liver related investigations, signs and symptoms	Hepatic enzyme abnormal
Liver related investigations, signs and symptoms	Hepatic enzyme decreased
Liver related investigations, signs and symptoms	Hepatic enzyme increased
Liver related investigations, signs and symptoms	Hepatic function abnormal

Liver related investigations, signs and symptoms	Hepatic hydrothorax
Liver related investigations, signs and symptoms	Hepatic hypertrophy
Liver related investigations, signs and symptoms	Hepatic hypoperfusion
Liver related investigations, signs and symptoms	Hepatic mass
Liver related investigations, signs and symptoms	Hepatic pain
Liver related investigations, signs and symptoms	Hepatic sequestration
Liver related investigations, signs and symptoms	Hepatic vascular resistance increased
Liver related investigations, signs and symptoms	Hepatic venous pressure gradient abnormal
Liver related investigations, signs and symptoms	Hepatic venous pressure gradient increased
Liver related investigations, signs and symptoms	Hepatobiliary scan abnormal
Liver related investigations, signs and symptoms	Hepatomegaly
Liver related investigations, signs and symptoms	Hepatosplenomegaly
Liver related investigations, signs and symptoms	Hyperammonaemia
Liver related investigations, signs and symptoms	Hyperbilirubinaemia
Liver related investigations, signs and symptoms	Hypercholia
Liver related investigations, signs and symptoms	Hypertransaminasaemia
Liver related investigations, signs and symptoms	Kayser-Fleischer ring
Liver related investigations, signs and symptoms	Liver function test abnormal
Liver related investigations, signs and symptoms	Liver function test decreased
Liver related investigations, signs and symptoms	Liver function test increased
Liver related investigations, signs and symptoms	Liver induration
Liver related investigations, signs and symptoms	Liver palpable
Liver related investigations, signs and symptoms	Liver scan abnormal
Liver related investigations, signs and symptoms	Liver tenderness
Liver related investigations, signs and symptoms	Magnetic resonance imaging hepatobiliary abnormal
Liver related investigations, signs and symptoms	Magnetic resonance proton density fat fraction measurement
Liver related investigations, signs and symptoms	Mitochondrial aspartate aminotransferase increased
Liver related investigations, signs and symptoms	Molar ratio of total branched-chain amino acid to tyrosine
Liver related investigations, signs and symptoms	Oedema due to hepatic disease
Liver related investigations, signs and symptoms	Perihepatic discomfort
Liver related investigations, signs and symptoms	Retrograde portal vein flow
Liver related investigations, signs and symptoms	Total bile acids increased
Liver related investigations, signs and symptoms	Transaminases abnormal
Liver related investigations, signs and symptoms	Transaminases increased
Liver related investigations, signs and symptoms	Ultrasound liver abnormal
Liver related investigations, signs and symptoms	Urine bilirubin increased
Liver related investigations, signs and symptoms	White nipple sign
Liver related investigations, signs and symptoms	X-ray hepatobiliary abnormal

Haematopoietic erythropenia	Anaemia macrocytic
Haematopoietic erythropenia	Aplasia pure red cell
Haematopoietic erythropenia	Aplastic anaemia
Haematopoietic erythropenia	Erythroblast count decreased
Haematopoietic erythropenia	Erythroid maturation arrest
Haematopoietic erythropenia	Erythropenia
Haematopoietic erythropenia	Hypoplastic anaemia
Haematopoietic erythropenia	Microcytic anaemia
Haematopoietic erythropenia	Proerythroblast count decreased
Haematopoietic erythropenia	Red blood cell count decreased
Haematopoietic erythropenia	Reticulocyte count decreased
Haematopoietic erythropenia	Reticulocytopenia
Haematopoietic leukopenia	Agranulocytosis
Haematopoietic leukopenia	Band neutrophil count decreased
Haematopoietic leukopenia	Band neutrophil percentage decreased
Haematopoietic leukopenia	Basophil count decreased
Haematopoietic leukopenia	Basophilopenia
Haematopoietic leukopenia	B-lymphocyte count decreased
Haematopoietic leukopenia	Cyclic neutropenia
Haematopoietic leukopenia	Eosinopenia
Haematopoietic leukopenia	Eosinophil count decreased
Haematopoietic leukopenia	Febrile neutropenia
Haematopoietic leukopenia	Granulocyte count decreased
Haematopoietic leukopenia	Granulocytes maturation arrest
Haematopoietic leukopenia	Granulocytopenia
Haematopoietic leukopenia	Idiopathic neutropenia
Haematopoietic leukopenia	Leukopenia
Haematopoietic leukopenia	Lymphocyte count decreased
Haematopoietic leukopenia	Lymphopenia
Haematopoietic leukopenia	Metamyelocyte count decreased
Haematopoietic leukopenia	Monoblast count decreased
Haematopoietic leukopenia	Monocyte count decreased
Haematopoietic leukopenia	Monocytopenia
Haematopoietic leukopenia	Myeloblast count decreased
Haematopoietic leukopenia	Myelocyte count decreased
Haematopoietic leukopenia	Neutropenia
Haematopoietic leukopenia	Neutropenic infection
Haematopoietic leukopenia	Neutropenic sepsis
Haematopoietic leukopenia	Neutrophil count decreased
Haematopoietic leukopenia	Promyelocyte count decreased
Haematopoietic leukopenia	Pure white cell aplasia

Haematopoietic leukopenia	Radiation leukopenia
Haematopoietic leukopenia	T-lymphocyte count decreased
Haematopoietic leukopenia	White blood cell count decreased
Haematopoietic thrombocytopenia	Acquired amegakaryocytic thrombocytopenia
Haematopoietic thrombocytopenia	Megakaryocytes decreased
Haematopoietic thrombocytopenia	Platelet count decreased
Haematopoietic thrombocytopenia	Platelet maturation arrest
Haematopoietic thrombocytopenia	Platelet production decreased
Haematopoietic thrombocytopenia	Platelet toxicity
Haematopoietic thrombocytopenia	Thrombocytopenia
Haematopoietic cytopenias affecting more than one type of blood cell	Aplastic anaemia
Haematopoietic cytopenias affecting more than one type of blood cell	Autoimmune aplastic anaemia
Haematopoietic cytopenias affecting more than one type of blood cell	Bicytopenia
Haematopoietic cytopenias affecting more than one type of blood cell	Bone marrow failure
Haematopoietic cytopenias affecting more than one type of blood cell	Cytopenia
Haematopoietic cytopenias affecting more than one type of blood cell	Febrile bone marrow aplasia
Haematopoietic cytopenias affecting more than one type of blood cell	Full blood count decreased
Haematopoietic cytopenias affecting more than one type of blood cell	Gelatinous transformation of the bone marrow
Haematopoietic cytopenias affecting more than one type of blood cell	Immune-mediated cytopenia
Haematopoietic cytopenias affecting more than one type of blood cell	Myelosuppression
Haematopoietic cytopenias affecting more than one type of blood cell	Pancytopenia
Haematopoietic cytopenias affecting more than one type of blood cell	Panmyelopathy
Agranulocytosis	Agranulocytosis
Agranulocytosis	Aplastic anaemia
Agranulocytosis	Autoimmune aplastic anaemia
Agranulocytosis	Bone marrow failure
Agranulocytosis	Cytopenia
Agranulocytosis	Febrile bone marrow aplasia
Agranulocytosis	Febrile neutropenia
Agranulocytosis	Immune-mediated cytopenia
Agranulocytosis	Myelosuppression

Agranulocytosis	Neutropenic colitis
Agranulocytosis	Neutropenic infection
Agranulocytosis	Neutropenic sepsis
Agranulocytosis	Pancytopenia
Agranulocytosis	Panmyelopathy
Agranulocytosis	Pure white cell aplasia
Agranulocytosis	Granulocyte count decreased
Agranulocytosis	Granulocytopenia
Agranulocytosis	Granulocytopenia neonatal
Agranulocytosis	Laryngopharyngitis
Agranulocytosis	Mucosal ulceration
Agranulocytosis	Neutropenia
Agranulocytosis	Neutrophil count decreased
Agranulocytosis	Neutrophil percentage decreased
Agranulocytosis	Parapharyngeal space infection
Agranulocytosis	Peritonsillar abscess
Agranulocytosis	Peritonsillitis
Agranulocytosis	Pharyngeal abscess
Agranulocytosis	Pharyngeal ulceration
Agranulocytosis	Pharyngitis
Agranulocytosis	Pharyngitis bacterial
Agranulocytosis	Pharyngitis mycoplasmal
Agranulocytosis	Pharyngitis streptococcal
Agranulocytosis	Pharyngotonsillitis
Agranulocytosis	Stomatitis necrotising
Agranulocytosis	Thrombophlebitis septic
Agranulocytosis	Tonsillar ulcer
Agranulocytosis	Tonsillitis
Agranulocytosis	Tonsillitis bacterial
Gastrointestinal nonspecific inflammation	Acute oesophageal mucosal lesion
Gastrointestinal nonspecific inflammation	Chronic gastritis
Gastrointestinal nonspecific inflammation	Colitis
Gastrointestinal nonspecific inflammation	Cryptitis
Gastrointestinal nonspecific inflammation	Duodenitis
Gastrointestinal nonspecific inflammation	Enteritis
Gastrointestinal nonspecific inflammation	Erosive duodenitis
Gastrointestinal nonspecific inflammation	Erosive oesophagitis
Gastrointestinal nonspecific inflammation	Feline oesophagus
Gastrointestinal nonspecific inflammation	Functional gastrointestinal disorder
Gastrointestinal nonspecific inflammation	Gastric mucosa erythema
Gastrointestinal nonspecific inflammation	Gastritis

Gastrointestinal nonspecific inflammation	Gastritis erosive
Gastrointestinal nonspecific inflammation	Gastrointestinal erosion
Gastrointestinal nonspecific inflammation	Gastrointestinal mucosa hyperaemia
Gastrointestinal nonspecific inflammation	Gastrointestinal mucosal exfoliation
Gastrointestinal nonspecific inflammation	Haemorrhagic erosive gastritis
Gastrointestinal nonspecific inflammation	Intestinal angioedema
Gastrointestinal nonspecific inflammation	Oesophageal mucosa erythema
Gastrointestinal nonspecific inflammation	Oesophagitis
Gastrointestinal nonspecific inflammation	Reactive gastropathy
Gastrointestinal nonspecific inflammation	Reflux gastritis
Gastrointestinal nonspecific inflammation	Remnant gastritis
Gastrointestinal nonspecific inflammation	Ulcerative duodenitis
Gastrointestinal nonspecific inflammation	Ulcerative gastritis
Gastrointestinal nonspecific dysfunction	Acid peptic disease
Gastrointestinal nonspecific dysfunction	Duodenogastric reflux
Gastrointestinal nonspecific dysfunction	Dyspepsia
Gastrointestinal nonspecific dysfunction	Gastrooesophageal reflux disease
Gastrointestinal nonspecific dysfunction	Gastrooesophageal sphincter insufficiency
Gastrointestinal nonspecific dysfunction	Rebound acid hypersecretion
Arrhythmia related investigations, signs and symptoms	Chronotropic incompetence
Arrhythmia related investigations, signs and symptoms	Electrocardiogram repolarisation abnormality
Arrhythmia related investigations, signs and symptoms	Electrocardiogram RR interval prolonged
Arrhythmia related investigations, signs and symptoms	Electrocardiogram U wave inversion
Arrhythmia related investigations, signs and symptoms	Electrocardiogram U wave present
Arrhythmia related investigations, signs and symptoms	Electrocardiogram U-wave abnormality
Arrhythmia related investigations, signs and symptoms	Sudden cardiac death
Torsade de pointes/QT prolongation	Electrocardiogram QT interval abnormal
Torsade de pointes/QT prolongation	Electrocardiogram QT prolonged
Torsade de pointes/QT prolongation	Long QT syndrome
Torsade de pointes/QT prolongation	Long QT syndrome congenital
Torsade de pointes/QT prolongation	Torsade de pointes
Torsade de pointes/QT prolongation	Ventricular tachycardia
Torsade de pointes/QT prolongation	Cardiac arrest
Torsade de pointes/QT prolongation	Cardiac death
Torsade de pointes/QT prolongation	Cardiac fibrillation
Torsade de pointes/QT prolongation	Cardio-respiratory arrest

Torsade de pointes/QT prolongation	Electrocardiogram repolarisation abnormality
Torsade de pointes/QT prolongation	Electrocardiogram U wave inversion
Torsade de pointes/QT prolongation	Electrocardiogram U wave present
Torsade de pointes/QT prolongation	Electrocardiogram U-wave abnormality
Torsade de pointes/QT prolongation	Loss of consciousness
Torsade de pointes/QT prolongation	Sudden cardiac death
Torsade de pointes/QT prolongation	Sudden death
Torsade de pointes/QT prolongation	Syncope
Torsade de pointes/QT prolongation	Ventricular arrhythmia
Torsade de pointes/QT prolongation	Ventricular fibrillation
Torsade de pointes/QT prolongation	Ventricular flutter
Torsade de pointes/QT prolongation	Ventricular tachyarrhythmia
	Dizziness
	Headache
	Creatine Kinase increase
	Proteinuria

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Reason for signing: Approved	Name: Cralen Davis Role: Biostatistics Date of signature: 14-Mar-2022 19:51:25 GMT+0000

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