CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-5245 for the Treatment of COVID-19 in Participants With High-Risk for Disease Progression
Short Title:	Study of GS-5245 in Participants With COVID-19 Who Have a High Risk of Developing Serious or Severe Illness
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EudraCT Number:** **ClinicalTrials.gov Identifier:**	This is a non-IND study 2022-002741-18 NCT05603143
Indication:	COVID-19
Protocol ID:	GS-US-611-6273
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 1: 29 March 2023
Amendment History:	Original: 01 August 2022 Admin Amendment 0.0.1: 22 August 2022 Amendment 0.1: 05 December 2022 Amendment 0.2: 20 January 2023 High-level summaries of the history of amendments are provided in Appendix 11.5.
Country-Specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 11.4.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AGM	African green monkey
ALT	alanine aminotransferase
ARA	acid-reducing agent
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{0-t}	partial area under the concentration versus time curve from time 0 to time t
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
BID	twice daily
CI	confidence interval
CL_{cr}	creatinine clearance
CL_r	renal clearance of unchanged drug in a specific interval (CL_r (interval)) or cumulatively over all collection intervals
C_{max}	maximum observed concentration of drug
COVID-19	coronavirus disease 2019
CP	conditional power
CSR	clinical study report
CYP	cytochrome P450 enzyme
DAIDS	Division of AIDS
DDI	drug-drug interaction
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EC_{50}	effective concentration
EDC	electronic data capture
FAM	famotidine
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GMR	geometric mean ratio
IB	investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	institutional ethics committee
IND	investigational new drug

IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LLOQ	lower limit of quantitation
MAV	medically attended visit
MDZ	midazolam
MMRM	mixed-effects model repeated measures
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptide
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PIT	pitavastatin
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PROMIS-29	Patient-Reported Outcomes Measurement Information System-29
QD	once daily dosing
RDV	remdesivir (Veklury®)
RNA	ribonucleic acid
RT-qPCR	reverse transcriptase-quantitative polymerase chain reaction
SAC	Safety Assessment Committee
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SSR	special situation report
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetic(s)
ULN	upper limit of normal
UK	United Kingdom
US	United States
WPAI + CIQ: COVID-19	Work Productivity and Activity Impairment + Classroom Impairment Questions: COVID-19 Infection

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-5245 for the Treatment of COVID-19 in Participants With High-Risk for Disease Progression

Short Title: Study of GS-5245 in Participants With COVID-19 Who Have a High Risk of Developing Serious or Severe Illness

IND Number: This is a non-IND study.
EudraCT Number: 2022-002741-18
ClinicalTrials.gov Identifier: NCT05603143

Study Centers Planned:

Approximately 300 centers globally

Objectives and Endpoints:

Primary Objective(s)	Primary Endpoint(s)
• To evaluate the efficacy of GS-5245 in reducing the rate of COVID-19–related hospitalization or all-cause death	• Proportion of COVID-19–related hospitalization or all-cause death by Day 29
Secondary Objective(s)	**Secondary Endpoint(s)**
• To evaluate the safety and tolerability of GS-5245 administered in nonhospitalized participants with COVID-19	• Incidence of treatment-emergent adverse events (AEs) and laboratory abnormalities • Incidence of serious AEs (SAEs) and AEs leading to study drug discontinuation
• To evaluate the efficacy of GS-5245 in reducing all-cause hospitalization	• Proportion of participants with all-cause hospitalization by Day 29
• To evaluate the efficacy of GS-5245 in reducing COVID-19–related medically attended visits (MAVs) or all-cause death	• Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29
• To evaluate the efficacy of GS-5245 in reducing COVID-19–related MAVs	• Proportion of participants with COVID-19–related MAVs by Day 29
• To evaluate the efficacy of GS-5245 in reducing all-cause death	• Proportion of participants with all-cause death by Day 29

• To evaluate the efficacy of GS-5245 in reducing the duration and severity of COVID-19 symptoms	• Time to COVID-19 symptom alleviation by Day 15
• To evaluate the antiviral activity of GS-5245 on SARS-CoV-2 nasal swab viral load at Day 5	• Change from baseline (Day 1) in SARS-CoV-2 nasal swab viral load at Day 5
• To evaluate the plasma pharmacokinetic(s) (PK) of GS-441524 (metabolite of GS-5245)	• Plasma concentrations and PK parameters AUC_{tau}, C_{tau}, and C_{max} of GS-441524, as available

Study Design: This Phase 3 study will be a randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral GS-5245 with placebo in nonhospitalized participants with COVID-19 who are at high risk of progression to hospitalization.

After screening procedures, eligible participants may be randomized in a 1:1 ratio to receive GS-5245 or placebo.

Randomization will be stratified by duration of symptoms at enrollment (≤ 3 days versus > 3 days), and vaccination status (ever versus never).

Number of Participants Planned:

Approximately 2300 participants will be randomized into this study. Up to 3150 participants may be enrolled depending on the sample size re-estimation result.

Target Population: Nonhospitalized participants with COVID-19 with at least 1 risk factor (if unvaccinated) and at least 2 risk factors (if vaccinated at any point) for disease progression.

Duration of Intervention: Participants will receive oral GS-5245 or placebo for 5 days.

Diagnosis and Main Eligibility Criteria:

Participants must meet all the following inclusion criteria to be eligible for participation in this study:

1) Aged ≥ 18 years at screening.

2) Willing and able to provide written informed consent, or with a legal representative who can provide informed consent (where locally and nationally approved).

3) SARS-CoV-2 infection confirmed by PCR or an approved alternative assay (eg, Rapid Antigen Test) ≤ 5 days before randomization. Serologic tests will not be accepted.

4) Initial onset of COVID-19 signs/symptoms ≤ 5 days before randomization with ≥ 1 of the following targeted signs/symptoms present at randomization:

    a) Stuffy or runny nose.

b) Sore throat.

c) Shortness of breath (difficulty breathing).

d) Cough.

e) Low energy or tiredness.

f) Muscle or body aches.

g) Headache.

h) Chills or shivering.

i) Feeling hot or feverish.

j) Nausea.

k) Vomiting.

l) Diarrhea.

5) Not currently hospitalized or requiring hospitalization.

6) Presence of ≥ 1 risk factor (if unvaccinated) or ≥ 2 risk factors (if vaccinated at any point) for progression to severe disease. Risk factors are the following:

a) Aged ≥ 50 years.

b) Current or recent (≤ 6 months prior to randomization) cancer (other than localized skin cancer).

c) Have human immunodeficiency virus infection.

d) Prior splenectomy.

e) Prior solid organ, stem cell, or bone marrow transplant.

f) Have systemic rheumatologic or dermatologic disorders.

g) Use of systemic immunosuppressive agents, eg, high-dose corticosteroids (ie, ≥ 20 mg of prednisone or equivalent per day administered for ≥ 2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor blockers, other biologic agents that are immunosuppressive or immunomodulatory.

h) Have cerebrovascular disease.

i) Have cardiovascular disease, including heart failure, coronary artery disease, cardiomyopathies, and hypertension.

j) Have chronic kidney disease (provided participant does not meet exclusion criterion 7).

k) Have chronic lung disease (interstitial lung disease, pulmonary embolism, pulmonary hypertension, bronchiectasis, or chronic obstructive pulmonary disease).

l) Have chronic liver disease.

m) Have cystic fibrosis.

n) Have diabetes mellitus, type 1 and/or type 2.

o) Have neurodevelopmental and/or neurodegenerative conditions.

p) Have a body mass index ≥ 25 kg/m^2.

q) Have sickle cell disease.

r) Have primary immunodeficiencies.

s) Have compensated cirrhosis.

t) Have asthma.

u) Have ≥ 20 pack-year smoking history and currently smoking or have quit within the past 15 years.

Exclusion criteria for participation include:

1) Anticipated access to and use of authorized or approved COVID-19 therapies during the current COVID-19 illness < 5 days after randomization (therapies include nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, intravenous remdesivir [RDV, Veklury®], monoclonal antibodies).

2) Received any approved, authorized, or investigational direct-acting antiviral drug against SARS-CoV-2 for the treatment of COVID-19 < 28 days or < 5 half-lives, whichever is longer, before randomization.

3) Anticipated need for hospitalization < 48 hours after randomization.

4) New oxygen requirement < 24 hours before randomization.

5) Known influenza or any other suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study drug.

6) Decompensated cirrhosis (Child-Pugh class B or class C) or acute liver injury/failure.

7) Undergoing dialysis, or known history of moderate or severe renal impairment, or known CL_{cr} < 60 mL/min (as calculated by Cockroft-Gault) or eGFR < 60 mL/min/1.73m^2 within the last 6 months. Potential participants meeting the laboratory criterion may be enrolled if test results available before dosing show that renal function no longer meets this criterion.

8) Known history of any of the following abnormal laboratory results (< 6 months before randomization) unless confirmed as resolved to not meet criteria at screening.

   a) Alanine aminotransferase (ALT) ≥ 5 × upper limit of normal (ULN).

   b) Bilirubin ≥ 2 × ULN (≥ 3 × ULN for participants with Gilbert's syndrome).

9) Positive urine pregnancy test at screening.

10) Breastfeeding (nursing).

11) Unwilling to use protocol-mandated birth control.

12) Known hypersensitivity to the study drug, its metabolites, or formulation excipient.

13) Requirement for ongoing therapy with or prior use of any prohibited medications.

14) Received an approved, authorized, or investigational COVID-19 vaccine (including booster dose) < 120 days before randomization.

15) Any inability to take study drug or comply with study procedures that, in the opinion of the investigator, would make the participant unsuitable for the study.

Study Procedures/Frequency:

- Screening: within 48 hours of the baseline visit (screening visit can be the same as day as the baseline visit).
- Study treatment period: Day 1 (baseline) to Day 5.
- Posttreatment follow-up: Up to 29 days (+ 5 days) after the first dose of study drug (in-person or virtual).

The schedule of study procedures is presented in Table 1.

Test Product, Dose, and Mode of Administration:

GS-5245 350 mg (1 × 350 mg tablet) administered orally **twice daily** without regard to food with approximately 240 mL of water for 5 days.

Reference Therapy, Dose, and Mode of Administration:

Placebo administered orally **twice daily** without regard to food with approximately 240 mL of water for 5 days.

Statistical Methods:

A total of 2300 participants provides > 90% power to detect a ratio of 0.25 (GS-5245 to placebo in the primary endpoint [proportion of COVID-19–related hospitalization or all-cause death by Day 29], which is equal to a hazard ratio of 0.25) using a 2-sided significance level of 0.05 assuming the event rate is 2% in the placebo group.

The primary endpoint will be analyzed using a Cox proportional hazards model with the stratification factors (duration of symptoms and vaccination status) as covariates. The hazard ratio and 95% CI will be provided.

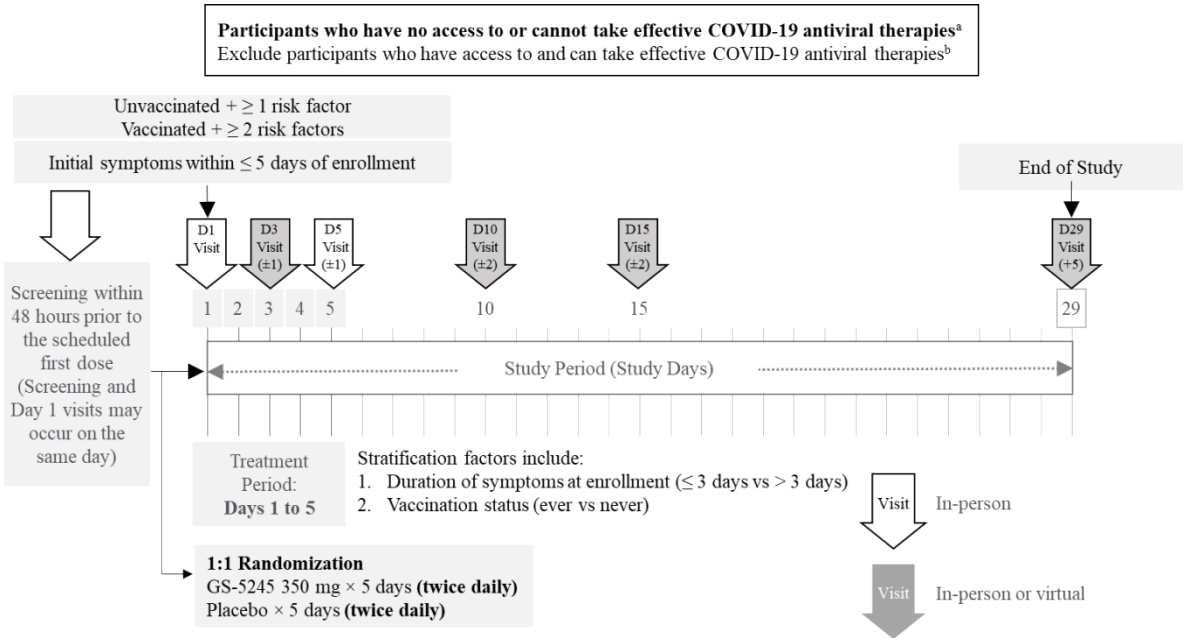
A gatekeeping approach will be used for testing the key secondary endpoints. The endpoints will be tested in the following sequential order:

- Proportion of participants with all-cause hospitalization by Day 29.
- Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29.
- Proportion of participants with COVID-19–related MAVs by Day 29.
- Proportion of participants with all-cause death by Day 29.

An unblinded interim analysis of efficacy and futility is planned after 50% of planned participants complete the Day 29 assessment or prematurely discontinue from the study, or 50% of expected primary endpoint events occur, whichever comes first. If the interim is triggered by 50% of enrollment, an additional unblinded interim analysis may be conducted after 50% of expected events have occurred. The unblinded interim analysis at 50% of expected events will include a sample size re-estimation.

STUDY SCHEMA

Figure 1. Study Schema



COVID-19 = coronavirus disease 2019; D = Day

a Access determined at the site level by the principal investigator and participant.

b Effective COVID-19 antiviral therapies such as nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, intravenous remdesivir, monoclonal antibodies, or any other locally authorized/approved direct-acting therapy against SARS-CoV-2.

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table

Study Visit	Screening[a]	Baseline/ Day 1[a, b]	Day 3[b]	Day 5[b]	Day 10	Day 15[b]	Day 29	Early Discontinuation Visit[b]
Visit Window			± 1 day[c]		± 2 days		+ 5 days	
Visit Type	In Person[d]		In Person[d] or Virtual[e]	In Person[d]	In Person[d] or Virtual[e]			In Person[d]
Written informed consent	X							
Medical history[f]	X							
Document SARS-CoV-2 infection	X							
Complete physical examination[g]	X	X		X				X
Symptom-directed physical examination			X			X		
Height and weight	X							
Vital signs[h]	X	X	X	X	X	X	X	X
Screening ALT, bilirubin, serum creatinine, and CL_{cr}/eGFR[i]	X							
Chemistry, coagulation, and hematology panels[j]		X	X	X		X		X
Urine or serum pregnancy tests[k]	X	X				X		X
Mid-turbinate nasal swab[l]		X	X	X	X	X		X
SARS-CoV-2 serology		X						
CCI								
CCI								
MAV information/oxygen supplementation requirement[o]		X	X	X	X	X	X	X

Study Visit	Screening[a]	Baseline/ Day 1[a, b]	Day 3[b]	Day 5[b]	Day 10	Day 15[b]	Day 29	Early Discontinuation Visit[b]
Visit Window			**± 1 day[c]**		**± 2 days**		**+ 5 days**	
Visit Type	**In Person[d]**		**In Person[d] or Virtual[e]**	**In Person[d]**	**In Person[d] or Virtual[e]**			**In Person[d]**
COVID-19 Symptom Questionnaire[p]		X	X	X	X	X	X	X
PROMIS-29		X				X	X	X
WPAI + CIQ: COVID19		X				X	X	X
Study drug dispensation		X						
Study drug dosing (GS-5245 or placebo)		X	X	X				
Study drug bottle return[q]				X	X	X	X	X
Adverse events and concomitant medications	X	X	X	X	X	X	X	X

ALT = alanine aminotransferase; CL_{cr} = creatinine clearance; COVID-19 = coronavirus disease 2019; ED = early discontinuation; eGFR = estimated glomerular filtration rate; MAV = medically attended visit; PCR = polymerase chain reaction; PK = pharmacokinetic(s); PROMIS-29 = Patient-Reported Outcomes Measurement Information System-29; RT-qPCR = reverse transcriptase-quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WPAI + CIQ:COVID19 = Work Productivity and Activity Impairment + Classroom Impairment Questions: COVID-19 Infection

a Screening window is within 48 hours of the Day 1 visit. Day 1 visit may occur on the same day as screening. If the Day 1 and screening visits are the same day, do not repeat physical exam and vital signs.
b Laboratory tests for safety will be performed on Days 1 and 5, on Days 3 and 15 when an in-person visit is conducted, and at early discontinuation.
c Day 3 and Day 5 visits should be conducted on separate calendar days.
d In-person is defined as a visit at a medical facility or elsewhere by a health care provider (where permitted).
e Virtual visit is defined as an interaction with a health care professional using telephone or online-based interaction (eg, telehealth, webcast, video conferencing).
f Medical history will include the date of first COVID-19 symptoms, overall COVID-19 symptoms, all COVID-19 vaccinations prior to screening, exposure source, demographics, baseline characteristics, allergies, and all other medical history.
g A complete physical examination must include source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. For participants with compensated cirrhosis, a complete physical exam must also include a clinical assessment of ascites (absent, slight, or moderate) and a clinical assessment of hepatic encephalopathy (Absent, Grade I, Grade II, Grade III, or Grade IV), as described in Section 6.3.2.1. Urogenital and reproductive examination should only be completed if clinically indicated.
h Vital signs include heart rate, respiratory rate, temperature, oxygen saturation, and blood pressure. Vital signs are collected at in-person visits only.
i **Screening:** Serum ALT, bilirubin, serum creatinine, and CL_{cr}/eGFR assessments at screening (prior to dosing) are not required unless deemed necessary by the investigator to confirm eligibility, using a local laboratory. See Appendix 11.4 for country-specific requirements.
j All required baseline laboratory assessments should be collected prior to first study drug dose.

k At screening, a urine pregnancy test will be performed at the local laboratory for participants assigned female at birth and of childbearing potential. On Day 1, Day 15, and ED visits, these participants will have a serum pregnancy test performed via the central laboratory for in-person visits or a urine pregnancy test for virtual visits. At screening, a follicle-stimulating hormone test is required to confirm the postmenopausal state in participants younger than 54 years, who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure, as described in Appendix 11.3

l A mid-turbinate nasal swab will be collected at in-person visits and used for SARS-CoV-2 RT-qPCR, potential multiplex viral PCR, potential infectious viral titer assessment, and potential resistance testing. The nasal swab must be collected by clinic/study personnel in person. For virtual visits on Days 3, 10, or 15 no samples will be collected.

[redacted]

o Medically attended visit information includes any interactions with health care professionals other than study staff or designees including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care professional. The nature and cause of the visit should be identified. Medically attended visit information and oxygen supplementation information should be collected through Day 29.

p The COVID-19 symptom questionnaire should be completed daily (at approximately the same time each day) from predose (prior to first dose on Day 1) through Day 15, and on Day 29. If a participant discontinues from the study early, the participant should complete this questionnaire during the early discontinuation visit.

q Study drug bottle should be returned by the participant on Day 5, if the participant has already completed both doses of study drug. If the participant has study drug at the end of the Day 5 visit, the participant may return the study drug bottle on Day 10. If the Day 10 visit is virtual, drug accountability should be performed virtually and the participant will be instructed on returning the study drug bottle.

1. INTRODUCTION

1.1. Background

Remdesivir (RDV; Veklury®) is approved for the treatment of COVID-19 in hospitalized and nonhospitalized patients in the United States (US), the European Union (EU), Japan, and other countries in pediatric and adult patients {VEKLURY 2022a, Veklury 2022b}. The broader utility of RDV for the nonhospitalized treatment of early infection with SARS-CoV-2 is limited due to the intravenous (IV) route of administration; therefore, availability of more convenient oral treatment options is crucial for early therapy. Molnupiravir (Lagevrio™) and nirmatrelvir/ritonavir (Paxlovid™) are the only 2 oral medications authorized for emergency use for the treatment of COVID-19 in the US. In the EU, nirmatrelvir/ritonavir is the only oral medication authorized for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progression to severe disease (Conditional approval). Molnupiravir is not authorized in the EU but the Committee for Medicinal Products for Human Use has issued advice on its use under Article 5(3) for the treatment of confirmed COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19 in the EU. Molnupiravir demonstrated limited efficacy in the MOVe-OUT study {Jayk Bernal 2022}. Nirmatrelvir/ritonavir demonstrated efficacy in nonhospitalized patients with COVID-19, but significant drug-drug interactions (DDIs) limit use particularly in participants aged 65 years and older or immunocompromised patients (Pfizer's EPIC-HR ["Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients"] [Study C4671005]) {Hammond 2022}. Furthermore, the pill burden of the recommended dosage of nirmatrelvir/ritonavir (a total of 30 tablets over 5 days), may be challenging from an adherence standpoint.

GS-5245 is a mono-5'-isobutyryl ester prodrug of GS-441524. Following oral administration, GS-5245 is extensively hydrolyzed presystemically to the parent nucleoside GS-441524, which can then enter cells where it is subsequently anabolized to the same active triphosphate metabolite (GS-443902) as RDV. GS-5245 has been developed with the intent to deliver consistent and high systemic exposures to GS-441524 following oral administration. At targeted therapeutic exposures with GS-5245, GS-441524 exposures are anticipated to be approximately 14-fold higher as compared to exposures with RDV.

Availability of a highly effective oral treatment with a high barrier to resistance, similar to that of RDV, with minimal DDIs and with fewer tablets to take (ie, the dose of GS-5245 selected for Phase 3 is one 350 mg tablet twice daily) has the potential to address a critical public health need in the ongoing COVID-19 pandemic.

GS-5245 represents a promising oral option for the treatment of COVID-19 in nonhospitalized patients who are at increased risk of progressing to severe COVID-19, that is anticipated to fulfill an unmet medical need.

1.2. Background on Study Interventions

1.2.1. GS-5245

1.2.1.1. General Information

GS-5245 is a mono-5'-isobutyryl ester prodrug of GS-441524, and following oral administration, is extensively hydrolyzed presystemically to yield the parent nucleoside of RDV, GS-441524. The prodrug GS-5245 was designed to specifically increase the oral bioavailability of GS-441524.

For further information on GS-5245, refer to the current investigator's brochure (IB) for GS-5245, including information on the following:

- Toxicology
- Nonclinical pharmacology
- Nonclinical pharmacokinetics (PK)

Additional relevant nonclinical toxicology and clinical data are provided in Section 1.2.1.1.1, Section 1.2.1.1.3, and Section 1.2.1.1.3.

1.2.1.1.1. Toxicology

1.2.1.1.1.1. Fertility Study

The objectives of the fertility study (Study TX-611-2011) were to determine the potential adverse effects/disturbances in the reproductive process resulting from oral administration of GS-5245 to male and female Wistar Han rats from premating to conception and from conception to implantation. These included identification of deficits in estrous cycling, tubal transport, implantation, development of the preimplantation stages of the embryo in the female, and functional reproductive effects (alterations in libido and epididymal sperm maturation) in the male. Four groups (25 main study and 6 toxicokinetic [TK] phases/groups) of male rats were administered GS-5245 by oral gavage doses once daily at 0 (vehicle control), 125, 250, or 500 mg/kg/day. Males were dosed for 14 days prior to mating and continuing through one day prior to euthanasia. Three groups (25 main and 6 TK/groups) of female rats were dosed at 0, 125, or 250 mg/kg/day. An additional 25 females were not dosed but used for breeding purposes only for the 500 mg/kg/day males. Females in the main study were dosed for 14 days prior to mating and continuing through Gestation Day 7.

There were no GS-5245–related effects on male survival, clinical and macroscopic observations, body weights, body weight gains, food consumption, and organ weights at ≤ 250 mg/kg/day. Male reproductive performance (mating, fertility, and pregnancy indices and precoital intervals) and spermatogenic parameters were unaffected by GS-5245 administration at ≤ 500 mg/kg/day. There were no GS-5245–related effects on female survival or clinical observations at 125 mg/kg/day or on premating and gestation body weights, body weight gains, food

consumption, estrous cycle length, reproductive performance, macroscopic findings, or organ weights at ≤ 250 mg/kg/day. Intrauterine survival was also not affected by GS-5245 administration at any dose level.

Based on the lack of effects on reproductive performance and spermatogenic parameters, a dose level of 500 mg/kg/day (the highest dose level tested in males) was considered to be the no observed adverse effect level (NOAEL) for male reproductive toxicity. Based on the lack of effects on female reproductive performance, estrous cyclicity, and intrauterine survival, the NOAEL for female reproductive toxicity and embryonic toxicity was considered to be 250 mg/kg/day (the highest dose level tested in females).

Based on mortality, clinical observations, body weight losses, and lower body weight gains and food consumption at 500 mg/kg/day in males, a dose level of 250 mg/kg/day was considered to be the NOAEL for male systemic toxicity. Based on mortality, clinical observations, body weight losses, and lower body weight gains and food consumption at 250 mg/kg/day in females, a dose level of 125 mg/kg/day was considered to be the NOAEL for female systemic toxicity.

At the NOAELs for male and female reproductive toxicity, systemic GS-441524 exposures were approximately 5.7- and 6.7-fold higher than projected therapeutic exposure with oral 350 mg twice daily GS-5245 administration.

The results and conclusions of the fertility study support the planned population in the Phase 3 study.

1.2.1.1.1.2. Phototoxicity

Results of a 3T3 neutral red uptake (NRU) test with GS-441524 using mouse fibroblasts showed that GS-441524 was not cytotoxic and did not display an half-maximal inhibitory concentration (IC_{50}) with or without ultraviolet radiation exposure, up to the highest soluble concentration tested (100 µg/mL) (Study TX-611-2026). Administration of GS-5245 is not considered to exhibit a photosafety risk.

1.2.1.1.2. Nonclinical Pharmacokinetics: Rat Absorption, Distribution, Metabolism, and Excretion Study

A single dose [^{14}C]GS-5245 radiolabeled study in rats following oral administration (Study AD-611-2021) showed rapid absorption, broad distribution to most tissues, and complete first-pass metabolism (Study AD-611-2022). No prodrug itself was detected in plasma, urine, bile, or feces. The plasma metabolite GS-441524 accounted for 98% of total plasma radioactivity exposure. Means of 33.1% and 51.7% of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours. Renal excretion was the major route of elimination of GS-441524 from the systemic circulation. Fecal excretion of GS-5245 as GS-441524 metabolite was the major route of elimination of unabsorbed drug and is concordant with moderate oral bioavailability in rats (Study AD-611-2009).

1.2.1.1.3. Clinical Studies of GS-5245

1.2.1.1.3.1. Study GS-US-611-6248

Study GS-US-611-6248 is an ongoing Phase 1 study in healthy volunteers to evaluate the safety, tolerability, and PK of GS-5245. This randomized, blinded, placebo-controlled study is evaluating single and multiple doses with staggered dose escalation and adaptive GS-5245 dose selection. The study will also evaluate the impact of food on bioavailability.

As of 02 May 2022, 48 participants have been administered GS-5245 at single doses of 100 mg (Cohort 1), 300 mg (Cohort 2), 900 mg (Cohort 3) and 1600 mg (Cohort 4) and multiple doses for 5 days at doses of 500 mg twice daily (Cohort 5) and 900 mg once daily (Cohort 6). Each cohort enrolled 8 participants who were randomized in a 3:1 ratio to receive oral GS-5245 or placebo. Preliminary PK and blinded safety data are available for all participants dosed in these 6 cohorts.

Additionally, preliminary topline PK data are available from 22 participants (11 in each cohort) administered GS-5245 at a single dose of 500 mg under fasted (Cohort 8) and fed (Cohort 9) conditions. The formulation of GS-5245 evaluated in these cohorts is the same as that for administration in the current Phase 3 study. Administration in the fasted state was defined as at least 10 hours of overnight fasting. Administration in the fed state was defined as within 5 minutes of completion of a high-fat/high-calorie meal (800 to 1000 kcal, 50% fat). Additionally, participants in both cohorts were restricted from food (4 hours after dose) and water consumption (1 hour before and 2 hours after dose) except for 240 mL water given at the time of dosing. Topline safety data from Cohorts 8 and 9 are not yet available.

Disposition and Baseline Characteristics

Overall, for Cohorts 1 to 6, most participants were male (56.3%) and not Hispanic or Latino (87.5%). Approximately even proportions were White (45.8%) or Black or African American (41.7%). The median age was 31 years. Demographics were generally balanced between the groups.

Participant characteristics data for Cohorts 8 and 9 are not yet available.

Safety Results

Overall, for Cohorts 1 to 6, administration of GS-5245 or placebo was generally safe and well tolerated.

Treatment-emergent adverse events (AEs) were reported for 10 of 48 (20.8%) participants. Most AEs were Grade 1. There was 1 Grade 2 AE (vertigo not attributed to study drug), and no Grade 3 or higher AEs. There were no serious AEs (SAEs), AEs leading to premature discontinuation of study drug or deaths. The only AEs reported in more than 1 participants were headache (3 of 48 participants [6.3%]), and contact dermatitis (2 of 48 participants [4.2%]). The only AEs attributed to study drug was Grade 1 headache, which was reported for 2 of 8 (25%) of participants in Cohort 5 (500 mg twice daily for 5 days).

Overall, 25 of 48 participants (52.1%) had graded laboratory abnormalities. For each laboratory parameter, most abnormalities were reported for 1 or fewer participants in each cohort. The most frequently reported graded laboratory abnormality was decreased creatinine clearance (CL_{cr}) which was reported for 13 of 48 participants (27.1%) overall and for 6 of 8 participants (75%) in Cohort 4 (1600 mg single dose). Creatinine clearance decreases were generally transient and returned to baseline levels. There was only 1 Grade 3 or higher laboratory abnormality: 1 participant in Cohort 2 whose lipase was within normal limits on Days 2 and 5 (300 mg single dose) experienced a lipase elevation at Day 3.

There were no clinically relevant changes in vital signs, electrocardiograms (ECGs), or ophthalmologic examinations.

The safety profiles for Cohorts 8 and 9 are not yet available. In these cohorts, no SAEs, deaths, pregnancies, or study drug–related discontinuations were reported.

Pharmacokinetic Results

Plasma:

Overall, GS-5245 PK was characterized by fast absorption, linear PK, and similar terminal phases across 100 mg to 900 mg single doses tested. Less than dose-proportional increases in PK exposures were observed between 900 mg to 1600 mg (Table 2). Plasma exposures were exclusive to the GS-441524 metabolite; no detectable levels of GS-5245 prodrug were observed in the plasma at the 100 mg to 900 mg doses and transient exposure was observed at the 1600 mg dose. Multiple-dose PK was consistent with what was expected based on single-dose PK. Accumulation of GS-441524 after 5 days of dosing was consistent with plasma $t_{1/2}$ (approximately 35% and 13% after twice daily and once daily dosing, respectively) (Table 3).

Administration of GS-5245 with a high-fat meal had no effect on the overall plasma exposures of GS-441524; both C_{max} and AUC_{inf} were within the predefined no-effect bounds (0.60-1.67 for C_{max} and 0.70-1.43 for AUC_{inf}). The geometric least squares mean ratio (90% CI) of fed versus fasted for GS-441524 C_{max} and AUC_{inf} were 0.94 (0.73-1.22) and 1.13 (0.99-1.29), respectively. A high-fat meal slowed the rate of GS-5245 absorption, increasing GS-441524 T_{max} from 0.75 to 3.0 hours; this increase in T_{max} is consistent with the anticipated delay in gastric emptying following a meal. The PK in Cohort 8 was consistent with data from previous cohorts, which received GS-5245 in fasted state.

Urine:

GS-441524 metabolite renal excretion rate (CL_r) was 150 to 180 mL/min, which is above the typical glomerular filtration rate (120 mL/min) and consistent with historical data with IV RDV. No GS-5245 prodrug was detected in urine. The majority of the dose excreted in urine as GS-441524 was recovered over the first 6 to 12 hours after dosing with small incremental increases over the subsequent intervals (up to 96 hours). Approximately 40% to 45% of GS-5245 dose was recovered as GS-441524 in urine over first 24 hours postdose.

Peripheral Blood Mononuclear Cells (PBMCs):

Robust intracellular activation of GS-441524 to active triphosphate metabolite (GS-443902) was observed. Dose-proportional increases in the intracellular concentrations of GS-443902 were observed in PBMCs. Substantial accumulation of intracellular GS-443902 levels was observed after repeat dosing for 5 days (6-fold for twice daily and 3-fold for once daily; $AUC_{0\text{-}24h}$), which was consistent with the long half-life of this metabolite (Table 4).

Table 2. GS-US-611-6248: Plasma Pharmacokinetic Parameters of GS-441524 in Single Ascending Dose Cohorts 1 Through 4

PK Parameter[a]	GS-5245 100 mg (N = 6)	GS-5245 300 mg (N = 6)	GS-5245 900 mg (N = 6)	GS-5245 1600 mg (N = 6)
GS-441524				
C_{max} (ng/mL)	570 (30.5)	1830 (32.6)	5980 (45.1)	7060 (24.7)
T_{max} (h)	0.75 (0.56, 0.75)	0.75 (0.56, 1.5)	0.75 (0.75, 0.75)	1.50 (0.75, 1.88)
$t_{1/2}$ (h)	6.3 (6.0, 6.7)	6.1 (5.0, 6.9)	6.5 (6.3, 6.9)	12.5 (7.1, 19.2)
AUC_{inf} (h•ng/mL)	3820 (35.0)	10,900 (23.1)	37,200 (34.9)	48,100 (18.8)

%CV = percentage coefficient of variation; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
a Data presented as mean (%CV), except for T_{max} and $t_{1/2}$ [median (Q1, Q3)].

Table 3. GS-US-611-6248: Plasma Pharmacokinetic Parameters of GS-441524 in Multiple Ascending Dose Cohorts 5 and 6

PK Parameter[a]	Multiple Dose Day 1 (GS-5245 500 mg BID) (N = 6)	Multiple Dose Day 5 (GS-5245 500 mg BID) (N = 6)	Multiple Dose Day 1 (GS-5245 900 mg QD) (N = 6)	Multiple Dose Day 5 (GS-5245 900 mg QD) (N = 6)
GS-441524				
C_{max} (ng/mL)	3820 (32.7)	4620 (18.2)	6230 (14.5)	5180 (19.6)
T_{max} (h)	0.75 (0.69-1.5)	0.75 (0.50-1.5)	0.75 (0.75-1.88)	1.5 (0.75-3.0)
C_{24} (ng/mL)	—	533 (17.0)	—	158 (29.5)
$t_{1/2}$ (h)	—	—	—	10.3 (9.1, 19.0)
$AUC_{0\text{-}24h}$ (h•ng/mL)[b]	~31,800[b]	~43,000[b]	32,000 (11.5)	35,500 (12.3)

%CV = percentage coefficient of variation; BID = twice daily; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; QD = once daily
a Data are presented as mean (%CV), except for T_{max} as median (Q1, Q3).
b For BID dosing $AUC_{0\text{-}24h} = 2 \times AUC_{0\text{-}12h}$ and does not account for the expected additional accumulation; Day 1 $AUC_{0\text{-}12h}$ = 15,900 (18.4); Day 5 $AUC_{0\text{-}12h}$ = 21,500 (19.3).

Table 4. GS-US-611-6248: PBMC Pharmacokinetic Parameters of GS-443902 in Multiple Ascending Dose Cohorts 5 and 6

PK Parameter[a]	Multiple Dose Day 1 (GS-5245 500 mg BID) (N = 6)	Multiple Dose Day 5 (GS-5245 500 mg BID) (N = 6)	Multiple Dose Day 1 (GS-5245 900 mg QD) (N = 6)	Multiple Dose Day 5 (GS-5245 900 mg QD) (N = 6)
GS-443902				
C_{max} (μM)	8.67 (41.4)	46.8 (50.0)	7.15 (56.5)	27.5 (44.1)
T_{max} (h)	9.0 (6.0, 12.0)	12.0 (4.5, 12.0)	24.0 (6.0, 24.0)	—
C_{24} (μM)	—	46.0 (33.4)	—	23.2 (65.6)
$t_{1/2}$ (h)	—	—	—	34.8 (28.9, 44.3)[c]
$AUC_{0\text{-}24h}$ (h•μM)[b]	~132[b]	~852[b]	104 (45.7)	348 (6.0)

%CV = percentage coefficient of variation; BID = twice daily; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; QD = once daily

a Data are presented as mean (%CV), except for T_{max} and $t_{1/2}$ as median (Q1, Q3).

b For BID dosing $AUC_{0\text{-}24h} = 2 \times AUC_{0\text{-}12h}$ and does not account for the expected additional accumulation; Day 1 $AUC_{0\text{-}12h}$ = 65.9 (39.8); Day 5 $AUC_{0\text{-}12h}$ = 426 (48.4).

c n = 3.

Conclusion

Overall, GS-5245 at single doses of 100 mg to 1600 mg and multiple doses of 500 mg twice daily or 900 mg once daily has been generally safe and well tolerated. Transient Grade 2 CL_{cr} changes were predominantly observed in participants who received 1600 mg or placebo (6 of 8 participants [75%]). There were no AEs associated with the laboratory findings. The only treatment-related AE reported in more than 1 participant was Grade 1 headache (n = 2).

Oral administration of GS-5245 resulted in high plasma exposures of the GS-441524 metabolite, with no detectable levels of prodrug itself. GS-5245 exhibited linear PK and similar terminal phases across 100 mg to 900 mg single doses tested. Less than proportional increases in AUC and C_{max} were observed between the 900 mg and 1600 mg single doses tested. Terminal plasma $t_{1/2}$ of GS-441524 following oral administration of GS-5245 was 6 to 6.5 hours. Robust activation of GS-441524 to intracellular active triphosphate metabolite was observed and significant accumulation following twice daily dosing. Administration of GS-5245 with a high-fat meal decreased the rate but not the extent of GS-5245 absorption; thus, GS-5245 may be administered without regard to food.

1.2.1.1.3.2. Study GS-US-611-6409

Study GS-US-611-6409 is an ongoing Phase 1 study to evaluate transporter and cytochrome P450 enzyme (CYP)-mediated DDIs between GS-5245 and probe drugs. This is an open-label, multicenter, fixed- (Cohorts 1, 2, 3, 5, and 7) or randomized-sequence (Cohorts 4 and 6) crossover study in healthy participants. The following interactions are planned to be evaluated in each cohort:

- Cohorts 1 and 2: GS-5245 as a victim of strong P-glycoprotein (P-gp) inhibition using ritonavir and nirmatrelvir/ritonavir, respectively.
- Cohort 3: GS-5245 perpetrator effect on a probe CYP3A substrate midazolam (MDZ).
- Cohort 4: GS-5245 perpetrator effect on a probe P-gp substrate, dabigatran (DAB).
- Cohort 5: GS-5245 perpetrator effect on a probe organic anion transporting polypeptide (OATP) 1B1/1B3 substrate, pitavastatin (PIT).
- Cohort 6: GS-5245 perpetrator effect on a probe organic cation transporter (OCT) 1 substrate metformin (MET).
- Cohort 7: GS-5245 as a victim of gastric acid suppression using famotidine (FAM).

As of February 22, 2023, preliminary PK results are available in Cohorts 1 (n = 15), 3 (n = 19), 5 (n = 23), and 7 (n = 14). For Cohort 1, participants received a single dose of GS-5245 350 mg on Day 1, followed by ritonavir 100 mg twice daily on Days 4 to 8 with a single dose of GS-5245 350 mg coadministered on Day 6. For Cohort 3, participants received a single dose of MDZ 2.5 mg on Day 1 and a single dose of GS-5245 500 mg coadministered with a single dose of MDZ 2.5 mg on Day 3. For Cohort 5, participants received a single dose of PIT 2 mg and a single dose of GS-5245 500 mg coadministered with a single dose of PIT 2 mg on Day 4. For Cohort 7, participants received a single dose of GS-5245 350 mg on Day 1 and a single dose of FAM 40 mg followed by a single dose of GS-5245 350 mg 2 hours after FAM on Day 4. All doses were oral and administered under fasting conditions. Cohort 2 was not enrolled based on emerging results from Cohort 1.

The safety profiles for Cohorts 1, 3, 5, and 7 are not yet available. In these cohorts, no SAEs, deaths, pregnancies, or study drug–related discontinuations were reported.

Pharmacokinetic Results

GS-5245 as a Perpetrator

Cohort 3: Midazolam was used as a sensitive CYP3A substrate. Coadministration of MDZ with GS-5245 did not result in changes to plasma exposures of MDZ or its metabolite, 1-hydroxymidazolam (1-OH-MDZ), as the geometric mean ratio (GMR) and 90% CI for C_{max}, AUC_{last}, and AUC_{inf} were mostly within the predefined no-effect bounds of 80.0% to 125% (Table 5).

Table 5. GS-US-611-6409: Plasma Pharmacokinetic Parameters of Midazolam in Cohort 3

PK Parameter[a]	MDZ 2.5 mg (Reference, N = 19)	MDZ 2.5 mg + GS-5245 500 mg (Test, N = 19)	%GMR (90% CI) Test/Reference
MDZ			
C_{max} (ng/mL)	10.0 (39.6)	11.5 (39.3)	114 (105, 124)
AUC_{last} (h•ng/mL)	29.3 (50.5)	32.4 (51.2)	109 (103, 115)
AUC_{inf} (h•ng/mL)	30.7 (50.7)	33.5 (50.6)	108 (102, 114)
1-OH-MDZ			
C_{max} (ng/mL)	3.75 (47.4)	4.27 (33.8)	117 (104, 132)
AUC_{last} (h•ng/mL)	9.59 (44.5)	10.4 (27)	112 (103, 122)
AUC_{inf} (h•ng/mL)	10.0 (30.8)[b]	11.4 (25.9)[c]	116 (107, 126)

%CV = percentage coefficient of variation; CI = confidence interval; GMR = geometric mean ratio; MDZ = midazolam; PK = pharmacokinetic(s); 1-OH-MDZ = 1-hydroxymidazolam
a Data are presented as mean (%CV), unless otherwise specified.
b N = 13, terminal elimination slope was not reliably estimated for some profiles, ie, adjusted $R^2 < 0.8$.
c N = 18, terminal elimination slope was not reliably estimated for some profiles, ie, adjusted $R^2 < 0.8$.

Cohort 5: Pitavastatin was used as a sensitive OATP1B1/1B3 substrate. Coadministration of PIT with GS-5245 did not result in clinically significant changes to plasma exposures of PIT, as the GMR for C_{max}, AUC_{last}, and AUC_{inf} were increased by 28% to 31% (Table 6).

Table 6. GS-US-611-6409: Plasma Pharmacokinetic Parameters of Pitavastatin in Cohort 5

PK Parameter[a]	PIT 2.0 mg (Reference, N = 23)	PIT 2.0 mg + GS-5245 500 mg (Test, N = 20)	%GMR (90% CI) Test/Reference
PIT			
C_{max} (ng/mL)	24.7 (43.1)	31.1 (61.1)	130 (112, 151)
AUC_{last} (h•ng/mL)	56.5 (47.7)	77.90 (68.1)[b]	131 (121, 142)
AUC_{inf} (h•ng/mL)	61.70 (45.5)	83.11 (66.2)[b]	128 (118, 138)

%CV = percentage coefficient of variation; CI = confidence interval; GMR = geometric mean ratio; PIT = pitavastatin; PK = pharmacokinetic(s)
a Data are presented as mean (%CV), unless otherwise specified.
b N = 18, terminal elimination slope was not reliably estimated for some profiles, ie, adjusted $R^2 < 0.8$.

GS-5245 as a Victim

Cohort 1: Ritonavir was used as a strong P-gp inhibitor. Coadministration of GS-5245 with ritonavir did not result in changes to plasma exposures of GS-441524, as the GMR and 90% CI for C_{max}, AUC_{last}, and AUC_{inf} were within the predefined no-effect bounds of 70.0% to 143% (Table 7).

Table 7. GS-US-611-6409: Plasma Pharmacokinetic Parameters of GS-441524 in Cohort 1

PK Parameter[a]	GS-5245 350 mg (Reference, N = 15)	RTV 100 mg BID + GS-5245 350 mg (Test, N = 15)	%GMR (90% CI) Test/Reference
GS-441524			
C_{max} (ng/mL)	2,700 (52.2)	2,700 (36.3)	104 (93.3, 117)
AUC_{last} (h•ng/mL)	13,700 (27.5)	15,700 (20.6)	116 (108, 124)
AUC_{inf} (h•ng/mL)	14,000 (26.8)	15,800 (20.4)	114 (106, 122)

%CV = percentage coefficient of variation; BID = twice daily; CI = confidence interval; GMR = geometric mean ratio; PK = pharmacokinetic(s); RTV = ritonavir

a Data are presented as mean (%CV), unless otherwise specified.

Cohort 7: Famotidine was used as a representative acid-reducing agent (ARA). The overall effect of increased gastric pH by FAM on the absorption of GS-5245 was small. There was a 32.5% decrease in the C_{max} of GS-441524 with FAM, while the GMR and 90% CI for AUC_{last} and AUC_{inf} of GS-441524 were within the predefined no-effect bounds of 70.0% to 143% (Table 8).

Table 8. GS-US-611-6409: Plasma Pharmacokinetic Parameters of GS-441524 in Cohort 7

PK Parameter[a]	GS-5245 350 mg (Reference, N = 14)	GS-5245 350 mg + FAM 40 mg (Test, N = 13)[b]	%GMR (90% CI) Test/Reference
GS-441524			
C_{max} (ng/mL)	2670 (31.6)	1800 (29.5)	67.5 (55.3, 82.3)
AUC_{last} (h•ng/mL)	13,900 (19.6)	10,500 (18.8)	76.6 (71.4, 82.3)
AUC_{inf} (h•ng/mL)	14,000 (19.4)	10,700 (17.9)	77.0 (71.9, 82.5)

%CV = percentage coefficient of variation; CI = confidence interval; FAM = famotidine; GMR = geometric mean ratio

a Data are presented as mean (%CV), unless otherwise specified.

b Data were not provided for 1 participant on Day 4.

Conclusion

GS-5245 as a perpetrator: GS-5245 is not an inhibitor of CYP3A (as observed with MDZ) or a clinically relevant inhibitor of OATP1B1/1B3 (as observed with PIT).

GS-5245 as a victim: There was no effect of P-gp inhibition (as observed with coadministration of GS-5245 with ritonavir) on plasma exposures of GS-441524. There was no clinically significant effect of increased gastric pH (as observed with FAM) on the plasma exposures of GS-441524; thus, GS-5245 may be coadministered with ARAs including antacids, other histamine H2-receptor antagonists, as well as proton-pump inhibitors.

1.3. Rationale for This Study

COVID-19 is a cause of an ongoing global pandemic with IV RDV being the first antiviral treatment approved by regulatory agencies in the US {VEKLURY 2022a, Veklury 2022b}, Europe {VEKLURY 2022a, Veklury 2022b} and multiple countries. More convenient options are needed for early intervention in the nonhospitalized COVID-19 population.

The oral bioavailability of RDV is low based on nonclinical studies (< 1% in cynomolgus monkey) and unlikely to generate adequate human systemic exposure of RDV to drive antiviral activity against SARS-CoV-2 in the lung {Mackman 2021}. GS-5245 is an ester prodrug of the parent nucleoside of RDV, GS-441524. Following oral administration, GS-5245 is projected to deliver high systemic levels of GS-441524 and adequate formation of the active nucleoside triphosphate metabolite, GS-443902, in tissues where SARS-CoV-2 replicates. Administration of oral GS-5245 therefore represents a promising approach for the treatment of COVID-19.

This Phase 3 superiority study will evaluate GS-5245 compared with placebo in participants who are at high risk for disease progression but who:

- Cannot take existing therapies that are authorized or approved (ie, nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, IV RDV, monoclonal antibodies, or any other locally authorized or approved direct-acting therapy against SARS-CoV-2) because of medical contraindications or clinical concerns from the investigator.

- Continue to lack access to existing therapies that are authorized or approved after exhausting all locally available means in attempts to make these therapies accessible for participants.

Participants who do not have medical or clinical contraindications to authorized or approved therapies, and also have concurrent access to and ability to easily receive nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, IV RDV, monoclonal antibodies, or any other locally authorized or approved direct-acting therapy against SARS-CoV-2, are excluded from enrollment and should be treated with these agents outside this clinical study.

1.4. Rationale for Dose Selection of GS-5245

The proposed dose for evaluation in this Phase 3 study is GS-5245 350 mg **twice daily** for 5 days. This dose was selected based on the totality of available clinical and nonclinical data and with careful consideration of the overall risk-benefit profile.

GS-5245 safety and PK were evaluated in a Phase 1 single and multiple ascending dose study (GS-US-611-6248) in healthy participants. Single GS-5245 doses up to 1600 mg and multiple doses of GS-5245 500 mg twice daily and GS-5245 900 mg once daily for 5 days were generally safe and well tolerated (most AEs were Grade 1 in severity). A graded laboratory abnormality of decreased CL_{cr} was observed across all cohorts, although there was a disproportionately higher number of participants with decreased CL_{cr} at the highest dose evaluated (single GS-5245 1600 mg dose).

Following oral administration of GS-5245, the GS-441524 metabolite was the only circulating species. The plasma half-life of this metabolite was approximately 6 hours, supporting twice daily dosing. The twice daily dosing regimen also provided higher daily exposure (AUC_{0-24h}), higher C_{tau} concentrations, and lower C_{max} as compared with once daily dosing (Section 1.2.1.1.2).

GS-5245 builds on the already proven mechanism of action of RDV that is inhibition of SARS-CoV-2 RNA polymerase by the active triphosphate metabolite, GS-443902. The major metabolic pathways leading to formation of the GS-443902 metabolite are different between RDV and GS-5245. For GS-5245, the major metabolic pathway is through phosphorylation of the GS-441524 metabolite by cellular kinases, a pathway that is believed to play a minor role in activation of RDV to GS-443902 metabolite. In order to overcome the less efficient conversion to GS-443902, the levels of GS-441524 need to be approximately 14-fold higher, as compared with what is observed after RDV, in order to result in the similar levels of intracellular active metabolite. Robust intracellular formation of active metabolite was observed in the GS-US-611-6248 clinical study in PBMCs (eg, GS-5245 500 mg administered twice daily achieved GS-443902 levels comparable with IV RDV on Day 1 and exceeded those on later days by approximately 4-fold). The intracellular formation of GS-443902 was dose-proportional and significant accumulation was observed following twice daily dosing (approximately 6-fold accumulation by Day 5).

GS-5245 showed therapeutic efficacy in multiple SARS-CoV-2 animal models (ie, mouse, ferret and African green monkeys [AGMs]). Administration of GS-5245 to SARS-CoV-2-infected mice (10 mg/kg twice daily; AUC_{0-24h} = 10,500 h•ng/mL), ferrets (20 mg/kg once daily; AUC_{0-24h} = 28,500 h•ng/mL) and AGM (60 mg/kg once daily; AUC_{0-24h} = 25,700 h•ng/mL) for 5 days resulted in a significant reduction of clinical signs of respiratory disease, infectious virus titers in lungs, and genomic RNA compared with vehicle-treated animals. Similarly, in the AGM model, IV delivery of parent nucleoside (20 mg/kg once daily; AUC_{0-24h} = 42,800 h•ng/mL) and oral administration of GS-621763, a tri-isobutyryl ester tool prodrug of GS-441524 (60 mg/kg once daily; AUC_{0-24h} = 18,200 h•ng/mL); (120 mg/kg once daily; AUC_{0-24h} = 36,400 h•ng/mL) significantly reduced SARS-CoV-2 levels in the lower airways, as early as 1 to 2 days after infusion {Cox 2021, Pitts 2022}.

GS-5245 350 mg twice daily dose was selected for evaluation in this Phase 3 study for the treatment of COVID-19 in participants at high risk for disease progression; this dosing regimen should provide systemic exposures of GS-441524 (predicted AUC_{0-24h} = 30,100 h•ng/mL) associated with efficacy in the SARS-CoV-2 animal models. Moreover, this dosing regimen allows for GS-441524 concentrations over the dosing interval to be predominantly maintained above the effective concentration (EC_{50}) needed for SARS-CoV-2 viral inhibition in normal human bronchial epithelia cells (EC_{50} = 713 ng/mL). This dosing regimen also provides a substantial exposure (C_{max}) margin relative to the 1600 mg dose (approximately 2- to 3-fold) where potential drug-related effects on CL_{cr} were observed. Additionally, plasma exposures of GS-441524 in participants with mild renal impairment are expected to be within the range of those observed in the GS-5245 500 mg twice daily cohort in Study GS-US-611-6248. This is supported by the RDV renal impairment study (GS-US-540-9015), where mild renal impairment

resulted in approximately 19% increase in AUC_{inf} and approximately 6.7% increase in C_{max} of this metabolite.

1.4.1. Participants with Compensated Cirrhosis

Hepatic metabolism and/or excretion is expected to be minimal (< 20%) in the elimination of GS-5245 or the plasma metabolite GS-441524, and thus, hepatic impairment is unlikely to alter the PK sufficiently to warrant dose adjustment of GS-5245. In the first-in-human study (GS-US-611-6248), GS-5245 was shown to be extensively hydrolyzed to GS-441524 metabolite presystemically with no detectable concentrations of the prodrug itself in plasma. Most of the absorbed dose (assuming 40% to 60% absorption) was excreted in urine over 24 hours postdose as GS-441524 metabolite (see Section 1.2.1.1.3.1).

The proposed biotransformation and elimination pathways of GS-5245 and GS-441524 are also supported by nonclinical data, including the radiolabeled absorption, distribution, metabolism, and excretion study in rats (Study AD-611-2021; Study AD-611-2022). Renal excretion was the major route of elimination of GS-441524 from the systemic circulation in these studies. Additional data from portal vein-cannulated dog and cynomolgus monkey (Study AD-611-2016; AD-611-2017) suggest GS-5245 metabolism occurs primarily in the gut. Only transient and low levels of intact GS-5245 were observed in the portal vein. This is consistent with the in vitro intestinal instability of GS-5245 (Study AD-611-2024).

Together, clinical and nonclinical data indicate minimal liver involvement in metabolism of GS-5245 following oral administration and support the use of the full clinical dose in participants with compensated cirrhosis in this Phase 3 study.

1.5. Risk/Benefit Assessment for the Study

Potential risks of a participant's study involvement include unknown AEs, general risks associated with laboratory blood draws, and the associated pain and discomfort of phlebotomy.

Strategies to mitigate these risks include close monitoring of participants' clinical statuses, laboratory values, and AEs. Parameters for discontinuation of the study drug due to AEs will be clearly defined and closely followed.

Participants in this study will receive either GS-5245 or placebo. Conducting a fully powered Phase 3 safety and efficacy study allows for the most rapid assessment of the potential of GS-5245 to provide a treatment option for participants with COVID-19. Participant safety will be further protected by the oversight of the data monitoring committee (DMC) that will evaluate safety data when the first 200 participants reach Day 29 or prematurely discontinue from the study and when 50% of planned participants complete the Day 29 assessment or prematurely discontinue from the study, or 50% of expected primary endpoint events occur, whichever happens earlier.

Participants who are willing and able to take an authorized or approved therapy for COVID-19 will be excluded from the study. Before approving the study, institutional review boards (IRBs)/institutional ethics committees (IECs) will evaluate whether in accordance with local authorizations, approvals, treatment guidelines, and availability, there are potentially eligible participants who cannot or will not be able to access alternative care.

An infectious disease pandemic may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.2 for further details on the risks and risk mitigation strategy.

Considering the above, the benefit -risk balance for this study is considered positive.

1.6. Compliance

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objective(s)	Primary Endpoint(s)
• To evaluate the efficacy of GS-5245 in reducing the rate of COVID-19–related hospitalization or all-cause death	• Proportion of COVID-19–related hospitalization or all-cause death by Day 29
Secondary Objective(s)	**Secondary Endpoint(s)**
• To evaluate the safety and tolerability of GS-5245 administered in nonhospitalized participants with COVID-19	• Incidence of treatment-emergent AEs and laboratory abnormalities • Incidence of SAEs and AEs leading to study drug discontinuation
• To evaluate the efficacy of GS-5245 in reducing all-cause hospitalization	• Proportion of participants with all-cause hospitalization by Day 29
• To evaluate the efficacy of GS-5245 in reducing COVID-19–related medically attended visits (MAVs) or all-cause death	• Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29
• To evaluate the efficacy of GS-5245 in reducing COVID-19–related MAVs	• Proportion of participants with COVID-19–related MAVs by Day 29
• To evaluate the efficacy of GS-5245 in reducing all-cause death	• Proportion of participants with all-cause death by Day 29
• To evaluate the efficacy of GS-5245 in reducing the duration and severity of COVID-19 symptoms	• Time to COVID-19 symptom alleviation by Day 15
• To evaluate the antiviral activity of GS-5245 on SARS-CoV-2 nasal swab viral load at Day 5	• Change from baseline (Day 1) in SARS-CoV-2 nasal swab viral load at Day 5
• To evaluate the plasma PK of GS-441524 (metabolite of GS-5245)	• Plasma concentrations and PK parameters AUCtau, Ctau, and Cmax of GS-441524, as available
CCI [redacted]	[redacted]

CCI [redacted]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3. STUDY DESIGN

3.1. Study Design Overview

This Phase 3 study will be a randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral GS-5245 with placebo in nonhospitalized participants with COVID-19 who are at high risk of progression to hospitalization.

After screening procedures, eligible participants may be randomized in a 1:1 ratio to receive treatment with GS-5245 or placebo.

Randomization will be stratified by duration of symptoms at enrollment (≤ 3 days versus > 3 days) and vaccination status (ever versus never).

An overview of the study design is shown in Figure 1.

3.2. Duration of Intervention

Duration of dosing is 5 days.

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participants

3.3.1.1. Criteria for Early Discontinuation for the Individual Participants From Study Intervention

Study drug will be discontinued in the following instances:

- An SAE suspected to be related to study drug.
- Any ≥ Grade 3 clinically significant AE suspected to be related to study drug.
- An AE, or worsening of clinical condition requiring clinical intervention, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Any ≥ Grade 3 clinically significant laboratory abnormality (if confirmed by repeat testing) suspected to be related to study drug.
  Except if baseline or on-treatment CL_{cr} < 50 mL/min or eGFR < 50 mL/min/1.73m^2, then study drug is to be discontinued without confirmation by repeat testing and irrespective of relatedness.
- Unacceptable toxicity, as defined in Section 7.7, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the participant's best interest.
- Baseline or on-treatment alanine aminotransferase (ALT) ≥ 5 × ULN.

- Baseline or on-treatment bilirubin ≥ 2 × ULN (≥ 3 × ULN for participants with Gilbert's syndrome).
- Participant request to discontinue for any reason.
- Participant noncompliance.
- Pregnancy (refer to Appendix 11.3).
- Discontinuation of the study by sponsor.

If a participant discontinues study drug, every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures.

3.3.1.2. Criteria for Early Discontinuation for the Individual Participant From the Study

The participant will be discontinued from the study regardless of whether treatment is ongoing in the following instances:

- Withdrawal of consent.
- Death.

3.3.2. Criteria for Early Discontinuation of the Study

The study will be discontinued in the following instances:

- Discontinuation of the study at the request of Gilead Sciences (Gilead) or a regulatory agency, IRB, or IEC.

3.3.3. Loss to Follow-up

Should the participant fail to attend a scheduled protocol-specific visit, sites will need to make at least 3 attempts by a combination of telephone, email, or mail to contact the participant. Sites must document all attempts to contact the participant. If a participant does not respond within 5 days after the third contact, the participant will be considered lost to follow-up and no additional contact will be required.

3.4. Definitions for Time of Primary Endpoint and End of Study

3.4.1. Primary Endpoint

The date for the last participant visit for the primary endpoint is the date of the last visit to perform assessments for the primary analysis.

3.4.2. End of Study

The end of this study will be the last participant's last observation (or visit).

3.5. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, participant charts), central laboratory, local laboratory, and specialty laboratory (for PK data), participant-reported outcomes, and interactive response technology (IRT).

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 2300 participants will be randomized into the study.

4.1.1. Participant Replacement

Participants who discontinue before the end of the study will not be replaced.

4.2. Inclusion Criteria

Participants must meet all the following inclusion criteria to be eligible for participation in this study:

1) Aged ≥ 18 years at screening.

2) Willing and able to provide written informed consent, or with a legal representative who can provide informed consent (where locally and nationally approved).

3) SARS-CoV-2 infection confirmed by PCR or an approved alternative assay (eg, Rapid Antigen Test) ≤ 5 days before randomization. Serologic tests will not be accepted.

4) Initial onset of COVID-19 signs/symptoms ≤ 5 days before randomization with ≥ 1 of the following targeted signs/symptoms present at randomization.

    a) Stuffy or runny nose.

    b) Sore throat.

    c) Shortness of breath (difficulty breathing).

    d) Cough.

    e) Low energy or tiredness.

    f) Muscle or body aches.

    g) Headache.

    h) Chills or shivering.

    i) Feeling hot or feverish.

    j) Nausea.

    k) Vomiting.

l) Diarrhea.

5) Not currently hospitalized or requiring hospitalization.

6) Presence of ≥ 1 risk factor (if unvaccinated) or ≥ 2 risk factors (if vaccinated at any point) for progression to severe disease. Risk factors are the following:

   a) Aged ≥ 50 years.

   b) Current or recent (≤ 6 months prior to randomization) cancer (other than localized skin cancer).

   c) Have human immunodeficiency virus infection.

   d) Prior splenectomy.

   e) Prior solid organ, stem cell, or bone marrow transplant.

   f) Have systemic rheumatologic or dermatologic disorders.

   g) Use of systemic immunosuppressive agents, eg, high-dose corticosteroids (ie, ≥ 20 mg of prednisone or equivalent per day administered for ≥ 2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor blockers, other biologic agents that are immunosuppressive or immunomodulatory.

   h) Have cerebrovascular disease.

   i) Have cardiovascular disease, including heart failure, coronary artery disease, cardiomyopathies, and hypertension.

   j) Have chronic kidney disease (provided participant does not meet exclusion criterion 7).

   k) Have chronic lung disease (interstitial lung disease, pulmonary embolism, pulmonary hypertension, bronchiectasis, or chronic obstructive pulmonary disease)

   l) Have chronic liver disease.

   m) Have cystic fibrosis.

   n) Have diabetes mellitus, type 1 and/or type 2.

   o) Have neurodevelopmental and/or neurodegenerative conditions.

   p) Have a body mass index ≥ 25 kg/m^2.

   q) Have sickle cell disease.

r) Have primary immunodeficiencies.

s) Have compensated cirrhosis.

t) Have asthma.

u) Have ≥ 20 pack-year smoking history and currently smoking or have quit within the past 15 years.

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) Anticipated access to and use of authorized or approved COVID-19 therapies during the current COVID-19 illness < 5 days after randomization (therapies include nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, IV RDV, monoclonal antibodies).

2) Received any approved, authorized, or investigational direct-acting antiviral drug against SARS-CoV-2 for the treatment of COVID-19 < 28 days or < 5 half-lives, whichever is longer, before randomization.

3) Anticipated need for hospitalization < 48 hours after randomization.

4) New oxygen requirement < 24 hours before randomization.

5) Known influenza or any other suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study drug.

6) Decompensated cirrhosis (Child-Pugh class B or class C) or acute liver injury/failure.

7) Undergoing dialysis, or known history of moderate or severe renal impairment, or known CL_{cr} < 60 mL/min (as calculated by Cockroft-Gault) or eGFR < 60 mL/min/1.73m^2 within the last 6 months. Potential participants meeting the laboratory criterion may be enrolled if test results available before dosing show that renal function no longer meets this criterion. See Appendix 11.4 for country-specific requirements.

8) Known history of any of the following abnormal laboratory results (< 6 months before randomization) unless confirmed as resolved to not meet criteria at screening. See Appendix 11.4 for country-specific requirements regarding these laboratory exclusions.

   a) ALT ≥ 5 × ULN.

   b) Bilirubin ≥ 2 × ULN (≥ 3 × ULN for participants with Gilbert's syndrome).

9) Positive urine pregnancy test at screening.

10) Breastfeeding (nursing).

11) Unwilling to use protocol-mandated birth control.

12) Known hypersensitivity to the study drug, its metabolites, or formulation excipient.

13) Requirement for ongoing therapy with or prior use of any prohibited medications. Prohibited medications are identified in Section 5.4.1.

14) Received an approved, authorized, or investigational COVID-19 vaccine (including booster dose) < 120 days before randomization.

15) Any inability to take study drug or comply with study procedures that, in the opinion of the investigator, would make the participant unsuitable for the study.

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Randomization, Blinding, and Treatment Code Access

5.1.1. Randomization

Participants who meet randomization eligibility criteria will be randomized in a 1:1 ratio to GS-5245 or placebo starting on Day 1 and assigned a participant number. Randomization will be stratified by duration of symptoms at enrollment (≤ 3 days versus > 3 days) and vaccination status (ever versus never).

5.1.2. Blinding

The study is a double-blinded study where participants, personnel directly involved in the conduct of study, and sponsor will not know the treatment participants received.

During the study, participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the participants. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management who facilitates the data transfer of pharmacokinetic files between Gilead and vendors will remain unblinded. Individuals in Clinical Virology and Biomarker and Bioanalytical Operations performing sample selection for resistance analysis may be unblinded. Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in an IRT for purposes of study drug inventory management will remain unblinded. Individuals in Gilead Patient Safety who are responsible for safety signal detection, investigational new drug safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions may be unblinded to individual case data and/or group-level summaries. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or regulatory agency inspections. Biostatisticians and programmers employed by contract research organizations may be unblinded for dataset creation and analyses (eg, outputs for DMC review, PK merge with clinical data).

5.1.3. Planned Interim Internal Unblinding

Additionally, if the DMC recommends early study discontinuation due to efficacy/futility after reviewing the unblinded interim analysis results, a Gilead internal unblinded team independent of the blinded study team may be assembled, to assess the safety, any available PK, and/or efficacy of GS-5245 for planning and development of this compound. This group will consist of at least 1 representative from Clinical Development, Biostatistics, and Patient Safety, and may include other personnel as necessary. The Gilead medical monitor, other Clinical Development, Biostatistics, or Patient Safety personnel directly interacting with the study sites or data processing or analysis will not be participating in the internal monitoring committee and will not be unblinded to the participant treatment assignment.

The membership, conduct, and meeting schedule of the internal unblinded team will be documented as specified in Gilead procedural documents.

5.1.4. Procedures for Breaking the Blind on Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain the participant's treatment assignment directly from the IRT for that participant. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in any case of treatment unblinding.

Blinding of study drug is critical to the integrity of this clinical study. Therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study drug discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

5.2. Description and Handling

5.2.1. Formulation

The GS-5245 350-mg strength tablets are oval shaped, debossed with "GSI" on one side and "5245" on the other side, and film-coated light yellow. In addition to the active ingredient, each film-coated tablet contains the following inactive ingredients: microcrystalline cellulose, crospovidone, magnesium stearate, macrogol polyvinyl alcohol graft copolymer, talc, titanium dioxide, glyceryl mono and dicaprylocaprate (glyceryl monocaprylocaprate type I), polyvinyl alcohol, and yellow iron oxide.

Placebo tablets are identical in size, shape, color, and appearance to the corresponding active strength GS-5245 tablets. The placebo tablets contain commonly used excipients, including lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, macrogol polyvinyl alcohol graft copolymer, talc, titanium dioxide, glyceryl mono and dicaprylocaprate (glyceryl monocaprylocaprate type I), polyvinyl alcohol, and yellow iron oxide.

5.2.2. Packaging and Labeling

The GS-5245 350 mg tablets and corresponding placebo tablets are packaged in white, high-density polyethylene bottles. Each bottle also contains polyester packing material and is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to participating centers shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), the EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), the Japan-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs), as applicable, and/or other local regulations, as applicable.

5.2.3. Storage and Handling

GS-5245 and placebo tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label. Until dispensed to the participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration

Participants will receive study drug with dosing frequency, as follows:

- GS-5245 350 mg (1 × 350 mg tablet) or placebo administered orally **twice daily** without regard to food for 5 days.

Study drug will be administered with approximately 240 mL of water.

5.4. Prior and Concomitant Medications

5.4.1. Prior and Concomitant Medications That Are Prohibited

There are no restrictions on concomitant medications based on the potential for PK DDI with GS-5245. Medications in Table 9 are prohibited while participants are taking study drug.

For all participants, medical care, including hospitalization, if required, is not restricted. Additionally, medications used for supportive and symptomatic treatment of COVID-19 are allowed and there are no restrictions other than those indicated in Table 9. Permissible medications may include anti-inflammatories (eg, ibuprofen, naproxen), COVID-19 specific immunomodulator therapies (eg, dexamethasone, tocilizumab, baricitinib, anakinra), antipyretics (eg, paracetamol/acetaminophen), bronchodilators and inhaled corticosteroids (eg, albuterol, fluticasone), decongestants (eg, phenylephrine, pseudoephedrine) and any other locally prescribed or over-the-counter treatments for COVID-19 symptoms.

In instances where a prohibited medication is initiated before discussion with the Gilead medical monitor, the investigator must notify Gilead as soon as the investigator is aware of the use of the prohibited medication. In such instances, study drug must be discontinued, but the participant should continue in the study (See Section 6.4).

Table 9. Prior and Concomitant Medications That Are Prohibited

Medication Class	Prohibited Medications[a]
COVID-19 medications	Nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, IV RDV, monoclonal antibodies against COVID-19, or any other locally authorized/approved direct-acting therapy against SARS-CoV-2

COVID-19 = coronavirus disease 2019; IV = intravenous; RDV = remdesivir; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
a Concomitantly with GS-5245.

5.5. Accountability for Study Drug(s)

The investigator is responsible for ensuring adequate accountability of all used and unused study drug bottles. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug bottles dispensed to participants must be returned to the site.

Each investigational site must keep accountability records that capture:

- The date received, quantity, and condition of study drug bottles.
- The date, participant number, and the quantity of study drug bottles.
- The date, quantity of used, unused study drug bottles returned, and number of tablets within returned bottles along with the initials of the person recording the information.

5.5.1. Study Drug Return or Disposal

Gilead recommends that used and unused study drugs, which includes bottles, be destroyed at the site. If the site has an appropriate standard operating procedure for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug bottles in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If the study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drugs. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be provided to Gilead.

If the site does not have an appropriate standard operating procedure for study drug destruction, used and unused study drugs are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant screened or enrolled in the study are presented in tabular form in Table 1 and described in the sections below.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Informed Consent

Written informed consent must be obtained from each participant before initiation of any screening procedure. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study (Section 4.2).

CCI [redacted]

6.2. Screening, Participant Enrollment, and Treatment Assignment

Participants will be screened within 48 hours before enrollment in the study. Each participant will be assigned a unique screening number using an IRT. Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 48 hours for randomization into the study.

Entry into screening does not guarantee enrollment into the study. Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

It is the responsibility of the investigator to ensure that participants are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study.

Once written informed consent has been obtained, all screening and admission tests and assessments have been assessed (including recording the dates of COVID-19 vaccinations), and study eligibility has been confirmed, participants will be randomized to receive GS-5245 or placebo on Day 1. Whenever possible, Day 1 dosing should occur on the same day as randomization.

This Phase 3 superiority study will evaluate GS-5245 compared with placebo in participants who do not have access to or cannot take existing therapies that are authorized or approved (ie, nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, IV RDV, monoclonal antibodies, or any other locally authorized/approved direct-acting therapy against SARS-CoV-2).

Participants who have access to and intend to take aforementioned existing therapies are excluded from enrollment and must be treated with these agents outside this clinical study.

Participants will receive GS-5245 or placebo as described in Section 5.3.

6.3. Instructions for Study Procedures

An in-person visit is defined as a visit at a medical facility or elsewhere by a health care provider (where permitted).

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-required procedures, on the AE electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After study drug administration, report all AEs and SAEs. See Section 7 for additional details.

6.3.2. Safety Assessments

Safety will be evaluated throughout the study. Refer to Table 1 for a schedule of assessments.

6.3.2.1. Physical Examination

Physical examinations conducted throughout the study during in-person visits will be a complete physical examination or a symptom-driven physical examination, as outlined in Table 1.

For participants with compensated cirrhosis, when a complete physical exam is conducted, the exam should also include:

- Clinical assessment of ascites (absent, slight, or moderate).
- Clinical assessment of hepatic encephalopathy, as follows:
  - Absent: no clinical manifestations of hepatic encephalopathy.
  - Grade I: changes in behavior, mild confusion, slurred speech, disordered sleep.
  - Grade II: lethargy, moderate confusion.
  - Grade III: marked confusion (stupor), incoherent speech, sleeping but arousable.
  - Grade IV: coma, unresponsive to pain.

6.3.2.2. Medical History

Review medical history, including the date of first COVID-19 symptoms, overall COVID-19 symptoms, exposure source, vaccination history, demographics, baseline characteristics, allergies, and all other medical history.

6.3.2.3. Vital Signs

Vital sign measurements include heart rate, respiratory rate, temperature, oxygen saturation, and blood pressure. Refer to Table 1 for vital signs collection time points.

6.3.2.4. Body Mass Index

Height and weight will be collected at screening for calculation of body mass index for inclusion criteria.

6.3.2.5. Clinical Laboratory Assessments

Blood sample collection for the following laboratory analyses (Table 10) will be performed at the specified time points, where visits are conducted in person (Table 1). If screening laboratory analyses are deemed necessary by the investigator prior to randomization, these analyses should be performed using a local laboratory for expedited results. If a ≥ Grade 3 clinically significant laboratory abnormality needs to be repeated for confirmation, a local laboratory may be used if urgent results are needed for participant safety. However, a concurrent second set of blood samples should be drawn and sent to the central laboratory for proper documentation and data integrity. All other laboratory analyses performed on blood samples after screening should be collected and sent to the central laboratory. See Appendix 11.4 for country-specific requirements.

- Chemistry

  eGFR according to Cockcroft-Gault equation for CL_{cr} {Cockcroft 1976}. Weight at screening will be used for all CL_{cr} calculations.

  Men: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}\ (\text{mL/min})$

  Women: $\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}\ (\text{mL/min})$

- Hematology
- Coagulation

Table 10. Laboratory Analytes

Safety Laboratory Measurements			
Chemistry (Serum or Plasma)	**Hematology**	**Coagulation**	**Other Laboratory Measurements**
alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, lactate dehydrogenase, creatine phosphokinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, uric acid, creatinine clearance	hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count with differential (absolute and percentage) including neutrophils, monocytes, eosinophils, basophils, lymphocytes	prothrombin time, partial thromboplastin time, international normalized ratio	serum and urine pregnancy tests and serum follicle-stimulating hormone in amenorrhoeic participants < 54 years of age pharmacokinetics anti-SARS-CoV-2 antibodies

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Refer to Table 1 for collection time points.

6.3.2.6. Concomitant Medications

Review of concomitant medications and protocol restrictions will occur at the times shown in Table 1. See Section 5.4 for more information about concomitant medications.

6.3.2.7. Medically Attended Visits

Review of MAV information will occur at the times shown in Table 1. Medically attended visits are any interaction with health care professionals other than study staff or designees including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care profession.

6.3.2.8. Pregnancy Tests

Urine and/or serum pregnancy tests will be performed for participants assigned female at birth and of childbearing potential at the times shown in Table 1. At screening, a follicle-stimulating hormone test is required to confirm the postmenopausal state in participants younger than 54 years, who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure, as described in Appendix 11.3.

6.3.3. Pharmacokinetics

Sparse PK assessments will be conducted in all participants during an in-person visit as per Table 1. CCI [redacted] .CCI [redacted]

6.3.4. SARS-CoV-2 Serology

Blood samples will be collected to assess anti-SARS-CoV-2 antibodies at the time point specified in Table 1. Any remaining specimens from blood samples collected during the study will be stored and retained for possible future biomarker-related testing. These stored samples may be used by Gilead or its research partners for retesting anti-SARS-CoV-2 antibodies, for testing to learn more about how the study drug has worked, or for clinical laboratory testing to provide additional safety data. At the conclusion of this study, these samples may be retained in storage by Gilead for a period of up to 15 years.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of the study or per country requirements (Section 9.1.4).

6.3.5. Clinical Virology

6.3.5.1. Virology Testing

6.3.5.1.1. Virology Samples to Address the Study Objectives

Mid-turbinate nasal swab samples will be used to assess SARS-CoV-2 viral load by reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR). Once viral load testing is complete, the remnant samples may be used to evaluate respiratory viral coinfection, SARS-CoV-2 infectious viral titer, CCI [redacted]

6.3.5.1.2. Virology Sample Storage

Any remaining specimens from nasal swab samples collected during the study will be stored and retained for possible future virology-related testing. These stored samples may be used by Gilead or its research partners for viral genotyping/phenotyping assays or their development, for retesting the amount of virus present in the sample, or for testing to learn more about how the study drug has worked or clinical laboratory testing to provide additional safety data. At the conclusion of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements.

6.3.6. Patient-Reported Outcomes

The COVID-19 symptom questionnaire is required for a secondary endpoint of this study. CCI [redacted]. Patient-reported outcomes, if available, will be required at the time points shown in Table 1.

6.3.6.1. COVID-19 Symptom Questionnaire

The COVID-19 symptom questionnaire, if available, to be completed daily at approximately the same time each day, was adapted from published FDA guidance on Assessing COVID-19–Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and

Biological Products for COVID-19 Prevention or Treatment Guidance for Industry {U. S. Department of Health & Human Services (DHHS) 2020}. It aims to capture the most clinically relevant symptoms of COVID-19 using an easily interpretable verbal response scale.

6.3.6.2. Work Productivity and Activity Impairment Questionnaire + Classroom Impairment Questions: COVID-19 Infection

The WPAI + CIQ: COVID-19 Infection Specific questionnaire, if available, is a questionnaire to measure impairments in both paid work and unpaid work, as well as educational impact. It measures absenteeism and presenteeism, as well as the impairments in unpaid activity because of health problems during the past 7 days. It has been validated to quantify work or education impairments for numerous diseases {Reilly 1993}.

6.3.6.3. Patient-Reported Outcomes Measurement Information System-29

Up to 30% of people infected with SARS-CoV-2 have at least 1 symptom persisting longer than 4 weeks {Azzolini 2022}. PROMIS-29, if available, is a set of person-centered measures assessing physical, mental, and social health {HealthMeasures 2022}. The tool has been used to determine the prevalence and characteristics of impairment after recovery from acute COVID-19 {Romano 2022}.

6.4. Assessments for Early Discontinuation From the Study

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (see Section 3.3.1.1, Criteria for Early Discontinuation for the Individual Participant). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.5. Assessments for End of Study

A participant who completes or discontinues from the study early will have an end of study visit (either Day 29 visit or early discontinuation, as applicable) for assessments and procedures specified in Table 1.

6.6. Poststudy Care

The long-term care of the participant will remain the responsibility of their primary treating physician. There is no provision for poststudy availability.

6.7. Sample Storage

The stored biological samples may be used by Gilead or its research partner for additional testing to provide supplemental data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, or transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (Section 7.1.3).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death.
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- In-patient hospitalization or prolongation of existing hospitalization.

- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.3. Study Drugs and Gilead Concomitant Medications Special Situation Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, participant, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one’s professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/alcohol, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship for each study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Toxicity Grading Scale, Version 2.1 (corrected, July 2017) available at https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (Section 8.6.3). For each episode, the highest grade attained should be reported as defined in the grading scale.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Before Study Drug Initiation

After informed consent, but before initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs that are related to protocol-required procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug and report the AEs on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the informed consent form [ICF]) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to Gilead Patient Safety as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead Patient Safety.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situation Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead Patient Safety (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Medications Reports

7.3.5.1. Gilead Concomitant Medications Special Situation Report

Special situation reports involving a Gilead concomitant medication (not considered study drug), that occur after the participant first consents to participate in the study (ie, signing of the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead Patient Safety utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Medications Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs because of a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE eCRF. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead Patient Safety within 24 hours of the investigator's knowledge of the event from the time of the ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours to:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead Patient Safety.

7.4.2. Special Situation Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information within 24 hours of the investigator's knowledge to Gilead Patient Safety from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SSR information electronically, record the SSR on the paper special situations reporting form and transmit within 24 hours to:

Gilead Patient Safety
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead Patient Safety.

See Section7.4.2.2 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead Patient Safety utilizing the paper SSR form and transmitted to:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs because of a non-Gilead concomitant medication, must be reported on the AE eCRF.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies identified at any time from the start of the study to 30 days after last study dose in participants and/or pregnancies in partners resulting from exposure to sperm from a participant in the study period in which contraceptive measures are needed. Pregnancies should be reported to Gilead Patient Safety within 24 hours of becoming aware of the pregnancy using the pregnancy report form. Contact details for transmitting the pregnancy report form are as follows:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion because of complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after the study must be reported to the Gilead Patient Safety. However, if a pregnancy-related SAE occurs in a partner, it should not be captured in the eCRF, but reported via the paper pregnancy outcome report form.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead Patient Safety using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

Refer to Appendix 11.3 for Pregnancy Precautions, Definition for Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable suspected unexpected serious adverse reactions as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant suspected unexpected serious adverse reaction reports associated with any study drug. The investigator should notify the IRB/IEC of suspected unexpected serious adverse reaction reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (corrected, July 2017). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The DAIDS scale is available at:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

7.7. Toxicity Management

7.7.1. GS-5245

All clinical and clinically significant laboratory toxicities will be managed according to the guidelines described below.

The Gilead medical monitor should be consulted prior to study drug discontinuation when medically feasible. Before discontinuation of study drug for AEs or laboratory abnormalities, an assessment of the participant's medical situation should be made by the investigator.

For Grade 3 and Grade 4 clinically significant laboratory abnormalities that need to be confirmed by repeat testing, a local laboratory may be used if urgent results are needed for participant safety. However, a concurrent second set of blood samples should be drawn and sent to the central laboratory for proper documentation and data integrity.

7.7.1.1. Laboratory Events Meeting Discontinuation Criteria

Laboratory events meeting discontinuation criteria are discussed in Section 3.3.1.1.

7.7.1.2. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.7.1.3. Grade 3 Laboratory Abnormality or Clinical Event

For a Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.

For a Grade 3 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to study drug, **the participant will be discontinued from study drug**. The participant should be managed according to local practice.

Additionally, participants who have a $CL_{cr} < 50$ mL/min (by Cockcroft-Gault equation) will be discontinued from study drug whether considered related to the study drug or not (refer to Section 3.3.1.1).

Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation but requires discussion with the Gilead medical monitor.

7.7.1.4. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to study drug, **the participant will be discontinued from study drug**. The participant should be managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically nonsignificant Grade 4 laboratory abnormality (eg, Grade 4 creatine kinase elevation after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to study drug.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment-related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

8. STATISTICAL CONSIDERATIONS

Details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

Before the final analysis, interim analyses will be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

8.2.1.1. Data Monitoring Committee Analysis

The first DMC meeting will be based on data collected after the first 200 participants have reached Day 29 or prematurely discontinued from the study and will include safety data.

The second DMC meeting will be based on data collected after 50% of planned participants complete the Day 29 assessment or prematurely discontinue from the study, or 50% of expected primary endpoint events occur, whichever happens earlier. The DMC meeting will include review of safety and formal evaluation of futility and efficacy. The DMC may provide recommendation on stopping enrollment to the study if the prespecified boundaries for efficacy (outlined in Section 8.7) or futility are crossed. If the second DMC meeting is triggered by 50% planned enrollment, a third DMC meeting may be conducted after 50% of expected primary endpoint events as appropriate. If the second DMC meeting is triggered by 50% of expected primary endpoint events, a third DMC meeting is not planned. An interim analysis communication plan will be created.

Further details are provided in the DMC charter.

8.2.2. Final Analysis

The unblinded final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. Unless efficacy or futility boundaries are crossed at the interim analysis, the analysis of the primary endpoint of COVID-19–related hospitalization or all-cause death by Day 29 and key α-controlled secondary endpoints will be conducted at the time of the final analysis. The overall type I error rate will be controlled at the two-sided 0.05 significance level using the Lan-DeMets approach with O'Brien-Fleming type spending function.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analyses is defined as the Full Analysis Set (FAS), which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of study drug. Participants will be grouped according to the treatment to which they were randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of study drug. Participants will be grouped according to the treatment which they received.

All data collected during treatment plus 30 days will be included in the safety summaries.

8.3.1.3. Virology

The Virology Analysis Set will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have positive SARS-CoV-2 viral load at baseline. Participants will be grouped according to the treatment they received.

8.3.1.4. Pharmacokinetics

The PK Analysis Set will include all randomized participants who received at least 1 dose of GS-5245 and had at least 1 nonmissing PK concentration datum reported by the PK laboratory for each respective analyte.

CCI [redacted]

[redacted]

8.3.2. Data Handling Conventions

Natural logarithm transformation for PK parameters will be applied for PK analysis.

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation, will be imputed to the value of the lower or upper limit plus or minus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Missing data can have an impact upon the interpretation of the study data. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

All available data for participants that do not complete the study will be included in data listings.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, randomization stratification group, age. For categorical demographic and baseline characteristics, a Cochran-Mantel-Haenszel test will be used to compare treatment groups. For continuous demographic and baseline characteristics, a Wilcoxon rank sum test will be used to compare treatment groups.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint is the proportion of COVID-19–related hospitalization or all-cause death by Day 29. COVID-19–related hospitalization is defined as ≥ 24 hours of acute care for a reason related to COVID-19, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with COVID-19. This includes specialized acute medical care units within an assisted living facility or nursing home. This does not include hospitalization for the purposes of public health and/or clinical study execution. The date and duration of hospital admission, and primary reason for hospitalization (including if the hospitalization is related to COVID-19) will be recorded.

The primary endpoint will be analyzed using a Cox proportional hazards model with the stratification factors (duration of symptoms and vaccination status) as covariates. The hazard ratio and 95% CI will be provided. Handling of intercurrent events is defined in Section 8.5.3.

The number and percentage of participants with COVID-19–related hospitalization or all-cause death by Day 29, and reasons for missing data will be summarized.

The FAS will be used for the primary efficacy endpoint analysis.

Sensitivity analyses may be conducted using the following alternative approaches for the primary endpoint.

- Missing hospitalization status will be imputed using multiple imputation assuming missing at random.

- A participant with missing hospitalization status will be imputed as the participant was hospitalized.

8.5.2. Secondary Analyses

The secondary endpoints of COVID-19–related MAVs or all-cause death by Day 29 and all-cause death will be analyzed similarly as in the primary analysis. The secondary endpoints of all-cause hospitalization by Day 29 and COVID-19–related MAVs will be analyzed using a competing risk analysis approach, with death as the competing risk.

Medically attended visits are defined as any interactions with health care professionals other than study staff or designees including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care professional. The nature and cause of the visit should be identified.

All-cause hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with COVID-19. This includes specialized acute medical care units within an assisted living facility or nursing home. This does not include hospitalization for the purposes of public health and/or clinical study execution. The date and duration of hospital admission, and primary reason for hospitalization (including if the hospitalization is related to COVID-19) will be recorded.

A gatekeeping approach will be used for testing the key secondary endpoints. The endpoints will be tested in the following sequential order:

- Proportion of participants with all-cause hospitalization by Day 29.

- Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29.

- Proportion of participants with COVID-19–related MAVs by Day 29.

Change from baseline in SARS-CoV-2 nasal swab viral load to Day 5 will be summarized by treatment groups and compared between treatment groups using a mixed-effects model repeated measures (MMRM) approach.

The Kaplan-Meier product limit method will be used to estimate, and log-rank test will be used to compare treatment groups for the time to symptom alleviation of targeted COVID-19 symptoms.

Handling of intercurrent events for key secondary efficacy endpoints is defined in Section 8.5.3.

8.5.3. Intercurrent Events

Handling of intercurrent events for the primary endpoint and secondary efficacy endpoints relevant to hospitalization/death and symptom duration are shown in Table 11.

Table 11. Handling of Intercurrent Events

Endpoint	Intercurrent event	Strategy	Description
Proportion of COVID-19–related hospitalization or all-cause death by Day 29 Proportion of participants with all-cause hospitalization by Day 29	Discontinue randomized treatment prior to endpoint (due to AE, lack of efficacy, investigator's discretion, noncompliance with study drug, protocol violation, participant decision, lost to follow-up)	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29 Proportion of participants with COVID-19–related MAVs by Day 29 Proportion of participants with all-cause death by Day 29	Use of rescue medication	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
Time to COVID-19 symptom alleviation by Day 15	Hospitalization for the treatment of COVID-19 or all-cause death	Composite policy	Hospitalization for the treatment of COVID-19 or all-cause death means never achieve symptom alleviation (censored at Day 14)
	Discontinue randomized treatment prior to symptom alleviation (due to AE, lack of efficacy, investigator's discretion, noncompliance with study drug, protocol violation, participant decision, lost to follow-up)	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
	Use of rescue medication	Composite policy	Use of rescue medication means never achieve symptom alleviation (censor at Day 14)

AE = adverse event; COVID-19 = coronavirus disease 2019; MAV = medically attended visit

8.6. Safety Analysis

All safety data collected on or after the randomization date through 30 days after the date of the last dose of study drug will be summarized by treatment group (according to the study drug received). Data for the pretreatment period and after the date of last dose of study drug plus 30 days will be included in data listings.

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days.

Summaries (number and percentage of participants) of treatment-emergent AEs (by system organ class, and preferred term) will be provided by treatment group.

8.6.3. Laboratory Evaluations

Selected laboratory test data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (corrected, July 2017).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline up to the date of last dose of study drug plus 30 days will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the participant has been discontinued from treatment for at least 30 days will be included in a data listing.

8.7. Adjustments for Multiplicity

The overall two-sided type I error rate of 0.05 for the primary and key α-controlled secondary endpoints will be controlled using the Lan-DeMets approach with O'Brien-Fleming type spending function accompanying a gatekeeping testing strategy (ie, the primary efficacy endpoint will be tested first, and the key α-controlled secondary endpoints will be tested only if the primary efficacy endpoint is met).

The O'Brien-Fleming approach will be used for decision making. The information fraction and the actual stopping boundaries will depend on the exact timing of the interim analysis. Example decision boundaries are shown in Table 12.

Table 12. Boundaries for Interim and Final Analysis

DMC Scenario Example	Interim Efficacy Boundary (One-Sided *P* Value)	Interim Futility Boundary (One-Sided *P* Value)	Final Two-Sided *P* Value
Second DMC occurs at 50% of primary endpoint events (0.5 information fraction)	≤ 0.0015	> 0.5055	≤ 0.0490
Second DMC occurs at 50% of enrollment (0.35 information fraction) and the third DMC at 50% of primary endpoint events (0.5 information fraction)	2nd DMC: ≤ 0.0002 3rd DMC: ≤ 0.0015	2nd DMC: > 0.8342 3rd DMC: > 0.5128	≤ 0.0490

DMC = data monitoring committee

8.8. Pharmacokinetic Analysis

Plasma concentrations and pharmacokinetic parameters for GS-5245 metabolite, GS-441524, will be listed and summarized using descriptive statistics by treatment. Exposure-safety and efficacy may be conducted as needed, if sufficient data are available.

8.9. Sample Size

A total of 2300 participants provides > 90% power to detect a ratio of 0.25 (GS-5245 to placebo) in the primary endpoint (proportion of COVID-19–related hospitalization or all-cause death by Day 29), which is equal to a hazard ratio of 0.25 using a 2-sided significance level of 0.05 assuming the placebo event rate is 2% in the placebo group. The estimate of 2% in the placebo group is based on the placebo event rate for COVID-19 in the EPIC-SR study {Pfizer Inc 2022} and vaccine efficacy data from the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report {Ferdinands 2022, Thompson 2022}.

The sample size may be increased based on the unblinded sample size re-estimation. The sample size calculation was performed using software EAST (Version 6.5, module for log-rank test given accrual duration and study duration and 1 or 2 interim analyses using the Lan-DeMets approach with O'Brien-Fleming type spending function, with sample size re-estimation).

8.9.1. Sample Size Re-estimation

A sample size re-estimation is planned at the interim analysis when approximately 50% of expected primary endpoint events occur, due to the uncertainty in hospitalization or death rate in the placebo arm. All possible interim results will be partitioned into 3 zones–Favorable, Promising, and Unfavorable–depending on the size of observed conditional power (CP) under the current trend at the interim. If the CP falls into the Favorable zone, the study will continue

with the originally planned sample size of 2300 patients. If the CP falls into the Promising zone, the total sample size may be increased. If the CP falls into the Unfavorable zone but the interim result has not met the futility boundary, the study will also continue with the originally planned sample size of 2300 patients.

The DMC will review the unblinded data at the interim analysis and communicate the decision on sample size to the study team. The overall type I error is controlled at 0.05 using the method proposed by Cui-Hung-Wang approach {Cui 2019, Muller 2004}. Further details will be included in the DMC charter and an adaptation plan.

8.10. Data Monitoring Committee

A multidisciplinary DMC consisting of non-Gilead personnel will review the progress of the study, perform interim review of safety data after the first 200 participants have reached Day 29 or prematurely discontinued from the study, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study drug warrant the early discontinuation of the study in the best interests of the participant, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design. The DMC will have 2 or 3 formal (unblinded data review) meetings. The first formal meeting will review safety data after the first 200 participants complete the Day 29 assessment or prematurely discontinue from the study. The second formal meeting will review safety, efficacy, and futility data after 50% of participants complete the Day 29 assessment or prematurely discontinue from the study or 50% of expected primary endpoint events have occurred, whichever happens earlier. If the second DMC meeting is triggered by 50% of planned participants completing the Day 29 visit or prematurely discontinuing, a third DMC meeting may be conducted after 50% of expected primary endpoint events, as appropriate. The DMC may make a recommendation of stopping enrollment to the study if the prespecified efficacy or futility stopping criteria are met.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study discontinuation, Gilead retains final decision-making authority on all aspects of the study. If the DMC recommends stopping the study for lack of efficacy, a Gilead Oversight Committee will be unblinded to confirm the DMC recommendation.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the study drug. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC for any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements).

The ICF will inform participants about planned sample retention. In addition to the study-specific ICF to be signed by each participant participating in the study, participants will be required to document additional consent to provide additional samples in accordance with applicable regulations. The results of the tests performed on the samples will not be given to the participant or the investigator. The stored biological samples will be destroyed no later than 15 years after the end of study or per country requirements, but participants may at any time request that their stored samples be destroyed.

9.1.5. Confidentiality

The investigator must ensure that participants anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions or in accordance with local regulations. Note: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remains the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IRB/IEC, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification.

- Documentation that participant meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria]).
- Documentation of the reason(s) a consented participant is not enrolled.
- Participation in study (including study number).
- Study discussed and date of informed consent.
- Dates of all visits.
- Documentation that protocol-specific procedures were performed.
- Results of efficacy parameters, as required by the protocol.
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return.
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE.
- Concomitant medication (start and end date; dose if relevant; dose changes).
- Date of study completion and reason for early discontinuation if it occurs.

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, the US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Electronic Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a non-EDC vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the eCRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB/IEC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.4.2)

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study personnel may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and the accuracy of the data recorded in the eCRF. The study monitor is responsible for routine review of the eCRF form at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, or on-site monitoring) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at his or her site. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority(ies) and IRB/IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

11.1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-5245 for the Treatment of COVID-19 in Participants With High-Risk for Disease Progression

GS-US-611-6273, Amendment 1 Protocol, 29 March 2023

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Director, Clinical Development

[See appended electronic signature]

Date

[See appended electronic signature]

Signature

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

11.2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

    a) Participants may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any participant visits. Without study drugs, the participant would not be able to continue receiving the study drug as planned per protocol.

        Mitigation plan: Study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on study drug as determined by the principal investigator. A remote study visit, via phone or video conferencing, must be performed before remote study drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study participants if permitted by the local ethics committee/institutional review board/regulatory authority as applicable and with sponsor's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug, the participant would not be able to continue receiving the study drug as planned per protocol.

        Mitigation plan: The site's study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow-up:

    a) Participants may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

        Mitigation plan: For participants who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the participant within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

i) Confirm if participant has experienced any AEs/SAEs/special situations (including pregnancy) and follow up on any unresolved AEs/SAEs.

ii) Review the current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm electronic diary questionnaires and participant-reported outcomes have been completed and transmitted.

iv) If applicable, confirm the participant's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in (1).

v) If applicable, remind the participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study because of the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with the local ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if has been approved by the local ethics committee/institutional review board. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur in case scheduled visits cannot be conducted as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol because of the pandemic must be reported in the eCRF and described in the clinical study report (CSR). Any remote study visits that are conducted in lieu of clinic visits because of the pandemic will be documented as a protocol deviation related to the pandemic.

b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

   Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   There may be an increased amount of missing data because of participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

   Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the CSR will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of GS-5245 in study participants remains unchanged.

11.3. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2, Tanner staging only required if the participant is believed to be prepubescent) until becoming postmenopausal, or unless the participant is permanently sterile or has medically documented ovarian failure. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

b. Definition of Fertility in a Participant Assigned Male at Birth

For the purposes of this study, a participant assigned male at birth is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or with medical documentation.

2) Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-5245 is contraindicated in pregnancy as a malformative effect is noted in early pregnancy based on nonclinical data. An increased rate of adverse fetal effects, including postimplantation loss and fetal visceral malformations related to the development of the heart, blood vessels, and liver, were noted in rabbits administered GS-5245 250 mg/kg/day. Data from clinical pharmacokinetic interaction studies of GS-5245 have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential

The inclusion of participants assigned female at birth and of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of less than 1% per year. They must have a negative pregnancy test at the screening visit before randomization. A pregnancy test will also be performed at the Day 15 visit.

Duration of required contraception for participants assigned female at birth and of childbearing potential in this clinical study should start from the screening visit until 14 days after the last study dose.

Participants assigned female at birth and of childbearing potential must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Hormonal or nonhormonal intrauterine device (IUD).
- Subdermal contraceptive implant.
- Bilateral tubal occlusion (upon medical assessment of surgical success).
- Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success).

Or

Participants assigned female at birth and of childbearing potential who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)

- Diaphragm with spermicide
- Cervical cap with spermicide
- Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

The above requirements apply only as specified, and not to sexual encounters in which pregnancy is not a possible outcome.

3) Contraception Requirements for Participants Assigned Male at Birth

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a partner assigned female at birth from exposure to the participant's seminal fluid and pose a potential risk to an embryo/fetus. A participant assigned male at birth with a partner assigned female at birth and of childbearing potential must use highly effective contraceptive measures with a failure rate of less than 1% per year through at least 14 days after last dose of study drug. Please refer to the contraceptive requirements listed above for female participants.

Participants assigned male at birth must also refrain from sperm donation or cryopreservation of germ cells during treatment and until the end of contraception requirement.

The above requirements apply only as specified, and not to sexual encounters in which pregnancy is not a possible outcome.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to Be Followed in the Event of Pregnancy

Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 30 days after the last study drug dose. Study drug must be discontinued immediately, and medical monitor should be notified.

Participants assigned male at birth whose partner has become pregnant or suspects they are pregnant from start of study to 30 days after the last study drug dose must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

11.4. Country-Specific Requirements

11.4.1. Additional Country-Specific Requirements for South Africa

A summary of changes specific to sites in South Africa is provided below. These changes are not reflected in the body of the protocol but should be considered a part of the protocol requirements for South Africa.

Country-specific Requirements	Protocol Sections
As per a request for Supplementary Information on 11 November 2022 from South Africa, study procedures were updated to clarify that the screening serum creatinine, creatinine clearance (CL_{cr})/estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), bilirubin, and aspartate aminotransferase (AST) assessments are mandatory to detect laboratory abnormalities prior to the first study drug dose.	Section 6.3.2.5, and Table 1 footnote i

Study Visit	Screening[a]	Baseline/ Day 1[a,b]	Day 3[b]	Day 5[b]	Day 10	Day 15[b]	Day 29	Early Discontinuation Visit[b]
Study Window			± 1 day[c]		± 2 days		+ 5 days	
Visit Type	In Person[d]		In Person[d] or Virtual[e]	In Person[d]	In Person[d] or Virtual[e]			In Person[d]
Screening ALT, AST, bilirubin, serum creatinine, and CL_{cr} /eGFR[i]	X							

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CL_{cr} = creatinine clearance; eGFR = estimated glomerular filtration rate

11.4.2. Additional Country-Specific Requirements for the United Kingdom

A summary of changes specific to sites in the United Kingdom (UK) is provided below. These changes are not reflected in the body of the protocol but should be considered a part of the protocol requirements for the UK.

Country-specific Requirements	Protocol Sections
Screening serum creatinine, CL_{cr}/eGFR, ALT, AST, and bilirubin assessments are mandatory to detect laboratory abnormalities prior to dosing of study drug to ensure that kidney and liver function are not exclusionary prior to administering the first dose of study drug. Study procedures Table 1, footnote i has been updated.	Section 6.3.2.5 and Table 1 footnote i
Exclusion Criteria 7 and for any/all reference to historical eGFR or CL_{cr} laboratory values, will have the word "known" removed in all such instances. The phrase "within the last 6 months" has been removed as this is not applicable for the UK. Exclusion Criteria 7 now reads as "Undergoing dialysis, or history of moderate or severe renal impairment, or CL_{cr} < 60 mL/min (as calculated by Cockroft-Gault) or eGFR < 60 mL/min/1.73m^2. Potential participants meeting the laboratory criterion may be enrolled if test results available before dosing show that renal function no longer meets this criterion."	Section 4.3
Exclusion Criteria 8 and any/all reference to ALT or bilirubin, will have the word "known," and "history", "< 6 months before randomization", and "unless confirmed as resolved to not meet criteria at screening" removed in all such instances and specific range of ULN amended. Exclusion Criteria 8 now reads as: "Any of the following abnormal laboratory results at screening: a. ALT ≥ 5 × ULN. b. Bilirubin > ULN."	Section 4.3

11.5. Amendment History

High-level summaries of the history of this study's amendments are provided in tabular form in the subsections below (from most recent amendment to oldest), with changes listed in each table in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing the original protocol to this amendment will be made available upon the publication of this protocol.

11.5.1. Amendment 1 (29 March 2023)

Rationale for Key Changes Included in Amendment 1	Affected Sections
Addition/modification of risk factors and targeted signs/symptoms of COVID-19 to inclusion criteria to align with Center for Disease Control and Prevention.	Synopsis and Section 4.2
Overall clarifications and updates to inclusion/exclusion criteria resulting from queries received from sites and/or regulatory agencies.	Synopsis, Sections 4.2 and 4.3
Additional relevant nonclinical toxicology, pharmacology, and PK language included based on Phase 1 drug-drug interactions and radiolabeled ADME. Consequently, restrictions on coadministration of acid-reducing agents were removed, hormonal contraceptive measures amended, and phototoxicity results demonstrating that GS-5245 is not considered a photosafety risk have been incorporated.	Sections 1.2.1.1.1, 1.2.1.1.1.1, 1.2.1.1.1.2, 1.2.1.1.2, 5.4.1, and Appendix 11.3
Text updated regarding the clinical studies of GS-5245 to include latest available data including food effect data from Study GS-US-611-6248. Consequently, restrictions on administration of GS-5245 around food intake were removed.	Synopsis, Sections 1.2.1.1.3.1, 1.2.1.1.3.2, and 5.3
Language updated regarding participants with compensated cirrhosis.	Sections 1.4.1 and 6.3.2.1
Prior and concomitant medications that are prohibited was expanded to include ensitrelvir.	Section 5.4.1
CCI [redacted]	Sections 6.3.6, 6.3.6.1, 6.3.6.2, and 6.3.6.3
Updates to secondary CCI [redacted] objectives and endpoints to capture omissions (PK) and reflect additional analyses (PROs, viral titer, and coinfections).	Synopsis, Section 2
Study drug discontinuation criteria clarifications and updated language (with corresponding inclusion criteria and toxicity management) for exclusion of participants with prior or current elevated bilirubin level.	Synopsis, Table 1, Sections 3.3.1.1, 4.3, 7.7.1.3, and 7.7.1.4
Addition/clarification of efficacy analysis to include handling of intercurrent events.	Sections 8.5.1, 8.5.2, and 8.5.3
Addition of definitions for medically attended visits and COVID-19–related hospitalization.	Section 8.5
Minor changes to include clarifications or correct omissions/errors.	Throughout, as needed

11.5.2. Amendment 0.2 (20 January 2023)

Rationale for Key Changes Included in Amendment 0.2	Affected Sections
Cohort numbers are corrected to include 1600 mg dose in the information presented for Phase 1 Study GS-US-611-6248 in healthy volunteers to evaluate the safety, tolerability, and PK of GS-5245.	Sections 1.2.1.2.1 and 1.4
Screening serum creatinine, CL_{cr}/eGFR, ALT, AST, and bilirubin assessments are mandatory to detect laboratory abnormalities prior to dosing of drug to ensure that kidney and liver function are not exclusionary prior to administering the first dose of study drug. Study procedures Table 1, footnote h was updated.	Section 6.3.2.4 and Table 1 footnote h
Exclusion Criteria 7 and for any/all reference to historical eGFR or CL_{cr} laboratory values, will have the word "known" removed in all such instances. The phrase "within the last 6 months" has been removed as this is not applicable for the UK.	Section 4.3
Exclusion Criteria 8 and any/all reference to ALT or bilirubin, will have the word "known," and "history" " and "< 6 months before randomization" removed in all such instances as this is not applicable for the UK.	Section 4.3
Exclusion Criteria 8b, the phrase "bilirubin ≥ 5 × ULN" has been changed to "bilirubin > ULN." This has been changed at the request of the Medicine and Healthcare Products Regulatory Agency.	Section 7.4.3
In Exclusion Criterion 13 after the requirement for ongoing therapy with or prior use of any prohibited medications, reference added "Prohibited medications are identified in Section 5.4.1."	Section 4.3
For instances of study drug administration "participants should take measures to minimize exposure to ultraviolet (UV) light for the duration of the study and for 1 week after the last dose of study drug. Possible examples of UV protection measures include using sunscreen with broad spectrum sun protection factor of 30 or above, wearing hats and long-sleeved clothing with UV protection factor of 50 or above, and avoiding UV exposure between the hours of 10am and 4pm." This has been added at the request of the Medicines and Healthcare Products Regulatory Agency as there is no currently available data on the phototoxicity of study drug.	Section 5.3
Minor changes to correct typographic errors.	Throughout, as needed

11.5.3. Amendment 0.1 (05 December 2022)

Rationale for Key Changes Included in Amendment 0.1	Affected Sections
As per a request for Supplementary Information (RSI) on 11 November 2022 from South Africa, study procedures were updated to clarify that the screening blood tests are mandatory to detect laboratory abnormalities prior to the first study drug dose for sites in South Africa due to the high risk of disease progression in the intended population group.	Section 6.3.2.4, and Table 1 footnote h
Changes introduced in Administrative Amendment 1 dated 22 August 2022 are integrated in this amendment but are not summarized here as the changes were administrative in nature. However, these changes will be reflected in the red-lined document comparing the original protocol to this amendment.	Section 7.4.2.2 (old section #), Section 7.3.5.1, Section 7.4.2.1, and Appendix 11.3
Minor changes to correct typographic errors.	Throughout, as needed

11.5.4. Administrative Amendment 0.0.1 (22 August 2022)

Rationale for Key Changes Included in Amendment 0.0.1	Affected Sections
As defined in Section 7.4.2.1, this study will use an Electronic Special Situations Reporting Process for Study Drug. Deleted old Section 7.4.2.2 as it previously specified a Paper Special Situation Reporting Process for Study Drug which was not intended to be used in this section. This section was included in error.	Section 7.4.2.2 (old section)
Fixed broken link so it now links to newly numbered Section 7.4.2.2 (Reporting Process for Gilead Concomitant Medications)	Section 7.3.5.1
Fixed broken link so it now links to newly numbered Section 7.4.2.2 (Reporting Process for Gilead Concomitant Medications)	Section 7.4.2.1
Updated section link so it now links to newly numbered Section 7.4.2.3 (Pregnancy Reporting Process)	Appendix 11.3

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	30-Mar-2023 16:34:06