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 Nonhospitalized Participants
Short Title:	Study of GS-5245 in Nonhospitalized Participants With COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EU CT Number:** **ClinicalTrials.gov Identifier:**	158222 2023-503277-38 NCT05715528
Indication:	COVID-19
Protocol ID:	GS-US-611-6549
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 4: 12 December 2023
Amendment History:	Original: 14 September 2022 Amendment 1: 05 December 2022 Amendment 2: 20 January 2023 Amendment 3: 21 March 2023 High-level summaries of the histories of amendments are provided in Appendix 11.8.
Country-specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 11.7.

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

1-OH-MDZ	1-hydroxymidazolam
AE	adverse event
AGM	African green monkey
ALT	alanine aminotransferase
ARA	acid-reducing agent
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
$AUC_{x\text{-}xx}$	partial area under the concentration versus time curve from time "x" to time "xx"
C_{24}	concentration at 24 hours post-dose
CFR	Code of Federal Regulations
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
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval
CYP	cytochrome P450 enzyme
DAB	dabigatran
DAIDS	Division of AIDS
DDI	drug-drug interaction
DMC	data monitoring committee
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EU	European Union
FAM	famotidine
FAPS	Full Analysis Positive Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GD	gestation day

Gilead	Gilead Sciences
GMR	geometric mean ratio
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard 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	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LLOQ	lower limit of quantitation
LPLV	last participant's last visit
MAV	medically attended visit
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MET	metformin
NOAEL	no observed-adverse-effect level
NRU	neutral red uptake
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PIT	pitavastatin
PK	pharmacokinetic(s)
PROMIS-29	Patient-Reported Outcomes Measurement Information System-29
PRO	patient-reported outcome
RDV	remdesivir
RNA	ribonucleic acid
RT-qPCR	reverse transcriptase-quantitative polymerase chain reaction
RWD	real-world data
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SSR	special situation report
$t_{1/2}$	elimination half-life

TK	toxicokinetic(s)
ULN	upper limit of normal
US	United States
WPAI + CIQ: COVID19	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 Nonhospitalized Participants

Short Title: Study of GS-5245 in Nonhospitalized Participants With COVID-19

IND Number: 158222
EU CT Number: 2023-503277-38
ClinicalTrials.gov Identifier: NCT05715528

Study Centers Planned: Approximately 300 centers globally

Objectives and Endpoints:

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of GS-5245 in reducing the duration of COVID-19 symptoms • To evaluate the safety and tolerability of GS-5245 administered in nonhospitalized participants with COVID-19	• Time to COVID-19 symptom alleviation by Day 29 • Incidence of treatment-emergent adverse events (AEs) and laboratory abnormalities • Incidence of serious AEs (SAEs) and AEs leading to study drug discontinuation
Secondary Objectives	**Secondary Endpoints**
• To assess the impact of GS-5245 on time to resolution of COVID-19 symptoms • To evaluate the impact of GS-5245 on moderate relapse of COVID-19 symptoms • To evaluate the efficacy of GS-5245 in reducing COVID-19–related medically attended visits (MAVs) or all-cause death • To evaluate the efficacy of GS-5245 in reducing COVID-19–related hospitalizations or all-cause death • To evaluate the antiviral activity of GS-5245 on SARS-CoV-2 nasal swab viral load at Day 5 • To evaluate the effect of GS-5245 on duration of viral shedding	• Time to COVID-19 symptom resolution by Day 29 • Proportion of participants with moderate relapse of COVID-19 symptoms 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 hospitalization or all-cause death by Day 29 • Change from baseline in SARS-CoV-2 nasal swab viral load at Day 5 • Time to antigen negativity

• To evaluate the effect of GS-5245 on viral rebound • To evaluate the plasma PK of GS-441524 (metabolite of GS-5245) • To evaluate the impact of GS-5245 on relapse of COVID-19 symptoms	• Proportion of participants with viral antigen rebound • Plasma concentrations and PK parameters AUC_{tau}, C_{tau}, and C_{max} of GS-441524, as available • Proportion of participants with relapse of COVID-19 symptoms by Day 29

Study Design: This Phase 3 study will be a global randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral GS-5245 with placebo in nonhospitalized participants with COVID-19, without risk factors for progression to severe disease regardless of vaccination status.

Randomization will be stratified by vaccination status (completed primary vaccination series: Yes or No).

Number of Participants Planned: Approximately 1900 participants may be enrolled.

Target Population: Nonhospitalized participants ≥ 18 to < 65 years of age (at all sites), or aged ≥ 12 to < 18 years weighing ≥ 40 kg (US sites only after the first data monitoring committee [DMC] meeting has occurred), with COVID-19, without risk factors for progression to severe disease regardless of vaccination status.

Duration of Intervention: Participants will receive oral GS-5245 or placebo, twice daily, 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 to < 65 years (at all sites), or aged ≥ 12 to < 18 years weighing ≥ 40 kg (US sites only, after the first DMC meeting has occurred) at screening.
2) Willing and able to provide written informed consent (and assent as applicable). For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures.
3) SARS-CoV-2 infection confirmed, ≤ 3 days before randomization, by polymerase chain reaction, rapid antigen test, or an approved alternative assay. Serologic tests will not be accepted.
4) Willing and able to complete the COVID-19 Symptom Questionnaire prior to first dose and daily throughout study period.
5) Initial onset of COVID-19 signs/symptoms ≤ 3 days before randomization with ≥ 2 of the following targeted symptoms, at moderate or higher severity, 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.

6) Not currently hospitalized or requiring hospitalization.

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

1) Any risk factors for progression to severe disease.
2) Planning to receive a direct acting antiviral or monoclonal antibody against SARS-CoV-2 for the treatment of COVID-19.
3) Received any approved, authorized, or investigational direct acting antiviral drug or monoclonal antibody against SARS-CoV-2 for the treatment of COVID-19 < 28 days or < 5 half-lives, whichever is longer, before randomization.
4) Received any convalescent COVID-19 plasma or other antibody-based anti-SARS-CoV-2 prophylaxis at any time prior to study entry.
5) Received an approved, authorized, or investigational COVID-19 vaccine (including booster dose) < 120 days before randomization.
6) Self-reported COVID-19 diagnosis < 120 days before randomization.
7) Anticipated need for hospitalization < 48 hours after randomization.
8) New oxygen requirement < 24 hours before randomization.
9) 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.
10) Known history of chronic liver disease, limited to cirrhosis, nonalcoholic steatohepatitis, alcoholic liver disease, and autoimmune hepatitis.
11) Undergoing dialysis, or known history of chronic kidney disease.
12) Known history of any of the following abnormal laboratory results < 6 months before randomization, unless confirmed as not meeting the exclusion criteria below, at screening:
    a) ALT ≥ 5 × upper limit of normal (ULN).
    b) Bilirubin ≥ 2 × ULN (≥ 3 × ULN for participants with Gilbert's syndrome).
    c) CL_{cr} < 60 mL/min or eGFR < 60 mL/min/1.73 m^2.

13) Persistent symptoms from previous COVID-19 illness that may interfere with the evaluation of response to the study drug.

14) Positive urine pregnancy test at screening.

15) Breastfeeding (nursing).

16) Unwilling to use protocol-mandated contraception.

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

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

19) Any other factor, including inability to complete the patient-reported outcome (PRO) questionnaire for the primary endpoint, making the participant, in the opinion of the investigator, unsuitable to participate in the study.

20) Concurrent participation/enrollment in a separate therapeutic clinical study.

Study Procedures/Frequency:

- Screening: within 24 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 90 days after the first dose of study drug

The schedule of study procedures is presented in Table 1.

Test Product, Dose, and Mode of Administration: GS-5245 350 mg (1 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 sample size of approximately 1900 participants (assuming 90% are CoV-2 positive at baseline as confirmed by the central laboratory) provides approximately 87% power to detect a median difference of 2 days in time to symptom alleviation, which is equal to a hazard ratio (HR) of 1.18 using a 2-sided significance level of 0.05, assuming the placebo group median time to symptom alleviation is 13 days.

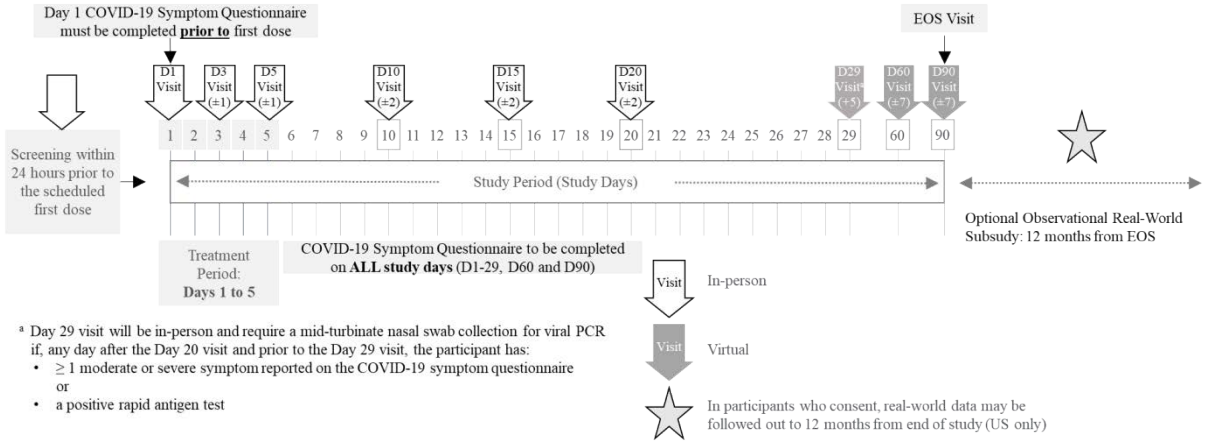
The median time to symptom alleviation and its 95% CI will be estimated by treatment group using the Kaplan-Meier method. A stratified log-rank test with stratification factor included will be used to compare the treatment difference in time to COVID-19 symptom alleviation.

In addition, a Cox proportional hazards regression model will be used to estimate the HR and its 2-sided 95% CI. Stratification factor will be included as a covariate in the Cox proportional hazards model.

An interim analysis of efficacy and futility is planned after approximately 50% of planned participants complete the Day 29 assessment, or prematurely discontinue from the study. The DMC will conduct a review of safety and formal evaluation of futility and efficacy based on the unblinded interim analysis results.

STUDY SCHEMA

Figure 1. Study Schema



COVID-19 = coronavirus disease 2019; D = Day; EOS = end of study; PCR = polymerase chain reaction

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table

Study Visit	Screening[a, b]	Baseline Day 1[a]	Day 3	Day 5	Day 10	Day 15	Day 20	Day 29	Day 60	EOS Day 90	Early Discontinuation Visit
Visit Window			± 1 day[c]		± 2 days			+ 5 days	± 7 days		
Visit Type	In Person[d]							In Person[e] or Virtual[f]	Virtual[f]		In Person[d]
Written informed consent (and assent as applicable)	X										
CCI											
Medical history[h]	X										
Document SARS-CoV-2 infection	X										
Complete physical examination[i]	X	X		X							X
Symptom-directed physical examination			X			X					
Height and weight	X										
Vital signs[j]	X	X	X	X	X	X					X
COVID-19 Symptom Questionnaire[k]		X	X	X	X	X	X	X	X	X	X
WPAI + CIQ:COVID19		X			X			X	X	X	X
PROMIS-29		X						X	X	X	X
Household contacts[l]						X					
Chemistry, coagulation, and hematology panels[m]		X	X	X	X	X					X
Urine or serum pregnancy tests[n]	X	X				X					X
SARS-CoV-2 rapid antigen test[o]		X	X	X	X	X		X			X
Mid-turbinate nasal swab[p]		X	X	X	X	X	X	X			X
SARS-CoV-2 serology		X									

Study Visit	Screening[a, b]	Baseline Day 1[a]	Day 3	Day 5	Day 10	Day 15	Day 20	Day 29	Day 60	EOS Day 90	Early Discontinuation Visit
Visit Window			± 1 day[c]		± 2 days			+ 5 days	± 7 days		
Visit Type	In Person[d]							In Person[e] or Virtual[f]	Virtual[f]		In Person[d]
Sparse PK[q]		X	X	X							
CCI											
MAV information/oxygen supplementation requirement[s]		X	X	X	X	X	X	X	X	X	X
Study drug dispensation		X									
Study drug dosing (GS-5245 or placebo)[t]		X	X	X							
Study drug bottle return[u]				X	X						X
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X

COVID-19 = coronavirus disease 2019; EOS = end of study; MAV = medically attended visit; PK = pharmacokinetic(s); PROMIS-29 = Patient-Reported Outcomes Measurement Information System-29; 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 24 hours of the Day 1 visit. The Day 1 visit may occur on the same day as screening. If screening and the Day 1 visit are the same day, do not repeat physical examination and vital signs.

b Local screening laboratory tests including serum creatinine, creatinine clearance/estimated glomerular filtration rate, alanine aminotransferase, and bilirubin assessments at screening (prior to randomization) are not required unless deemed necessary by the investigator to confirm eligibility. Testing for influenza is also not required at screening.

c Day 3 and Day 5 visits should be conducted on separate calendar days.

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

e Day 29 visit will be an in-person visit and require a nasal swab collection, only if any day after the Day 20 visit and prior to the Day 29 visit the participant has ≥ 1 moderate or severe symptom reported on the COVID-19 symptom questionnaire or has a positive rapid antigen test.

f Virtual visit is defined as an interaction with a health care professional using telephone or online-based interaction (eg, telehealth, webcast, video conferencing).

g Long COVID-19 sequelae will be assessed using linked data between clinical study participant and real-world data (RWD).

h Medical history will include the date of first COVID-19 symptoms, overall COVID-19 symptoms, all COVID-19 vaccinations prior to screening, prior COVID-19 illness (including positive test type, month, and year), demographics, baseline characteristics, allergies, and all other relevant medical history.

i 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. Urogenital and reproductive examination should only be completed if clinically indicated.

j Vital signs include heart rate, respiratory rate, temperature, oxygen saturation, and blood pressure.

k The COVID-19 Symptom Questionnaire will be completed daily (at approximately the same time each day) from predose to Day 29 visit, then at Day 60 and Day 90 visits.

l The number of contacts in the household and how many tested positive for COVID-19 to be recorded.

m Baseline laboratory assessments should be collected prior to first study drug dose.

n 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 early discontinuation/unscheduled visits, these participants will have a serum pregnancy test via central laboratory. 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 11.4.

o Rapid antigen tests will be self-collected daily on all visit and non-visit days, up to Day 15, thereafter, on Days 17, 19, 21, 23, 25, 27, and 29.

p The samples will be used for SARS-CoV-2 reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR), potential infectious viral titer assessment, and potential resistance testing. Multiplex viral PCR will only be performed at Baseline/Day 1 visit.

q Sparse PK samples will be collected at Day 1 visit (0.75 hours postdose and 2 hours postdose), Day 3 visit (predose [within 1 hour before dosing] and 0.75 hours postdose), and Day 5 visit (predose [within 1 hour before dosing] and 0.75 hours postdose); ± 20% time window will be applied for all postdose time points. On Days 1, 3, and 5, one of the 2 doses must be administered during the in-person visit. If a visit occurs on Day 6, PK samples should not be collected.

r CCI [redacted]

s 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 EOS/Day 90 visit.

t Study drug dosing is twice daily for 5 days.

u Study drug bottle should be returned by the participant on Day 5, if the participant has already completed all doses of study drug. If the participant has study drug remaining by the conclusion of the Day 5 visit, the participant must return the study drug bottle on the Day 10 visit.

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}. There are currently no approved therapies for people with a standard risk of progression to severe disease but who may benefit from a shorter duration of illness as assessed by symptoms, ability to return to usual health and activities, or duration of infectiousness.

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 drug-drug interactions and with few 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 standard 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 and Section 1.2.1.1.2.

1.2.1.1.1. Toxicology

1.2.1.1.1.1. Fertility Study

The objectives of the fertility study (Gilead Study Number 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] phase/group) 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/group) 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 (GD) 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 GS-5245 administration.

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) (TX-611-2026). Administration of GS-5245 is not considered to exhibit a photosafety risk.

1.2.1.1.2. Clinical Studies of GS-5245

1.2.1.1.2.1. 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 or placebo 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 participants (25%) 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, electrocardiogram (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:

The GS-441524 metabolite renal clearance (CL_r) was 150 to 180 mL/min, which is above the typical estimated glomerular filtration rate (eGFR, 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 the 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_{0-24h}), 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 $t_{1/2}$ as 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]	~31,800b	~43,000b	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} and $t_{1/2}$ as median (Q1, Q3).
b For BID dosing, $AUC_{0\text{-}24h} = 2 \prime AUC_{0\text{-}12h}$ 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, $AUC_{0\text{-}24h} = 2 \prime AUC_{0\text{-}12h}$ 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 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 high-fat meal decreased the rate but not the extent of GS-5245 absorption; thus, GS-5245 may be administered without regard to food.

1.2.1.1.2.2. 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 drug-drug interactions (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 BID 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 and 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; 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
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			
Cmax (ng/mL)	2700 (52.2)	2700 (36.3)	104 (93.3, 117)
AUClast (h•ng/mL)	13,700 (27.5)	15,700 (20.6)	116 (108, 124)
AUCinf (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; 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 was 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 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}, EU {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 study will evaluate GS-5245 compared with placebo in participants with a standard risk of disease progression for whom there are no existing therapies that are authorized or approved. While this standard risk population may have a low composite rate of COVID-19-related hospitalization or death, participants may benefit from effective antiviral therapy resulting in a shorter duration of illness as assessed by symptoms, a quicker ability to return to usual health and activities, and a shortened duration of infectiousness.

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 $t_{1/2}$ of this metabolite was approximately 6 hours, supporting twice-daily dosing. The twice-daily dosing regimen also provided higher daily exposure ($AUC_{0\text{-}24h}$), higher C_{tau} concentrations, and lower C_{max} as compared with once-daily dosing (Section 1.2.1.1.2.1).

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; $AUC_{0\text{-}24h}$ = 10,500 h•ng/mL), ferrets (20 mg/kg once daily; $AUC_{0\text{-}24h}$ = 28,500 h•ng/mL), and AGM (60 mg/kg once daily; $AUC_{0\text{-}24h}$ = 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 the parent nucleoside (20 mg/kg once daily; $AUC_{0\text{-}24h}$ = 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; $AUC_{0\text{-}24h}$ = 18,200 h•ng/mL; (120 mg/kg once daily; $AUC_{0\text{-}24h}$ = 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 was selected for evaluation in this Phase 3 study for the treatment of COVID-19 in participants at standard risk for disease progression; this dosing regimen should provide systemic exposures of GS-441524 (predicted $AUC_{0\text{-}24h}$ = 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 half-maximal 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.

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 150 participants have reached Day 29 or prematurely discontinued

from the study and when approximately 50% of planned participants have completed the Day 29 assessment, or prematurely discontinued from the study.

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 11.3 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 Objectives	Primary Endpoints
• To evaluate the efficacy of GS-5245 in reducing the duration of COVID-19 symptoms	• Time to COVID-19 symptom alleviation by Day 29
• 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
Secondary Objectives	**Secondary Endpoints**
• To assess the impact of GS-5245 on time to resolution of COVID-19 symptoms	• Time to COVID-19 symptom resolution by Day 29
• To evaluate the impact of GS-5245 on moderate relapse of COVID-19 symptoms	• Proportion of participants with moderate relapse of COVID-19 symptoms 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 hospitalizations or all-cause death	• Proportion of participants with COVID-19–related hospitalization or all-cause death by Day 29
• To evaluate the antiviral activity of GS-5245 on SARS-CoV-2 nasal swab viral load at Day 5	• Change from baseline in SARS-CoV-2 nasal swab viral load at Day 5
• To evaluate the effect of GS-5245 on duration of viral shedding	• Time to antigen negativity
• To evaluate the effect of GS-5245 on viral rebound	• Proportion of participants with viral antigen rebound
• To evaluate the plasma 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
• To evaluate the impact of GS-5245 on relapse of COVID-19 symptoms	• Proportion of participants with relapse of COVID-19 symptoms by Day 29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3. STUDY DESIGN

3.1. Study Design Overview

This Phase 3 study will be a global, randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral GS-5245 with placebo in nonhospitalized participants with COVID-19, without risk factors for progression to severe disease, regardless of vaccination status. Participants aged ≥ 12 and < 18 (weighing ≥ 40 kg) will be enrolled only in participating US sites, and after conclusion of the first planned DMC meeting.

Randomization will be stratified by vaccination status (completed primary vaccination series: Yes or No).

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

3.2. Duration of Intervention

Participants will receive oral GS-5245 or placebo for 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:

- Any SAE suspected to be related to study drug.
- Any ≥ Grade 3 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.
- Baseline or on-treatment CL_{cr} < 50 mL/min using the Cockcroft-Gault equation (for participants aged ≥ 18 to < 65 years of age) or eGFR < 50 mL/min/1.73 m^2 using the Bedside Schwartz formula (for participants aged ≥ 12 to < 18 years of age). No confirmation repeat testing is required to meet this criterion.
- Baseline or on-treatment alanine aminotransferase (ALT) ≥ 5 × upper limit of normal (ULN).

- Baseline or on-treatment bilirubin ≥ 2 × ULN (≥ 3 × ULN for participants with Gilbert's syndrome).
- 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.
- Participant request to discontinue for any reason.
- Participant noncompliance.
- Pregnancy (refer to Appendix 11.4).
- Discontinuation of the study by sponsor.

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, institutional review board (IRB), or independent ethics committee (IEC).

3.3.3. Lost 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) (LPLV).

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), patient-reported outcomes (PROs), and interactive response technology (IRT).

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 1900 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 to < 65 years (at all sites), or aged ≥ 12 to < 18 years weighing ≥ 40 kg (US sites only, after the first DMC meeting has occurred) at screening.

2) Willing and able to provide written informed consent (and assent as applicable). For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures.

3) SARS-CoV-2 infection confirmed, ≤ 3 days before randomization, by polymerase chain reaction (PCR), rapid antigen test, or an approved alternative assay. Serologic tests will not be accepted.

4) Willing and able to complete the COVID-19 symptom questionnaire prior to first dose and daily throughout the study period.

5) Initial onset of COVID-19 signs/symptoms ≤ 3 days before randomization with ≥ 2 of the following targeted symptoms, at moderate or higher severity, 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.

6) Not currently hospitalized or requiring hospitalization.

4.3. Exclusion Criteria

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

1) Any risk factors for progression to severe disease (Appendix 11.5).

2) Planning to receive a direct acting antiviral or monoclonal antibody against SARS-CoV-2 for the treatment of COVID-19.

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

4) Received any convalescent COVID-19 plasma or other antibody-based anti-SARS-CoV-2 prophylaxis at any time prior to study entry.

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

6) Self-reported COVID-19 diagnosis < 120 days before randomization.

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

8) New oxygen requirement < 24 hours before randomization.

9) 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.

10) Known history of chronic liver disease, limited to cirrhosis, nonalcoholic steatohepatitis, alcoholic liver disease, and autoimmune hepatitis.

11) Undergoing dialysis, or known history of chronic kidney disease

12) Known history of any of the following abnormal laboratory results < 6 months before randomization, unless confirmed as not meeting the exclusion criteria below, at screening:

a) ALT ≥ 5 × ULN.

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

c) CL_{cr} < 60 mL/min or eGFR < 60 mL/min/1.73 m^2.

13) Persistent symptoms from previous COVID-19 illness that may interfere with the evaluation of response to the study drug.

14) Positive urine pregnancy test at screening.

15) Breastfeeding (nursing).

16) Unwilling to use protocol-mandated contraception.

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

18) Requirement for ongoing therapy with or prior use of any prohibited medications (Table 9).

19) Any other factor, including inability to complete the PRO questionnaire for the primary endpoint, making the participant, in the opinion of the investigator, unsuitable to participate in the study.

20) Concurrent participation/enrollment in a separate therapeutic clinical 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 vaccination status (completed primary vaccination series: Yes or No).

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 PK 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 Patient Safety who are responsible for safety signal detection, investigational new drug (IND) 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 datasets 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 participate 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 contains 10 tablets and polyester packing material. Each bottle 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 randomized to the GS-5245 group will receive GS-5245 350 mg (1 tablet) administered orally twice daily without regard to food for 5 days.

Participants randomized to the placebo group will receive placebo administered orally twice daily without regard to food for 5 days.

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

5.4. Prior and Concomitant Medications

5.4.1. Prior and Concomitant Medications That Are Prohibited

Medications in Table 9 are prohibited while participants are taking study drug. 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).

There are no restrictions on the symptomatic treatment of COVID-19 other than those indicated in Table 9. There are no restrictions on concomitant medications based on the potential for PK DDI with GS-5245.

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

COVID-19 = coronavirus disease 2019; IV = intravenous; RDV = remdesivir
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 to capture the following information:

- The date received, quantity, and condition of study drug bottles.
- The date, participant number, and the quantity of study drug bottles dispensed.
- 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 (and Assent as Applicable)

Written informed consent (and assent as applicable) must be obtained from each participant, or with a parent or legal guardian who can provide informed consent, before initiation of any screening procedure. After a participant has provided informed consent (and assent as applicable), the investigator and other study personnel will determine if the participant is eligible for participation in the study (Section 4.2). The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (and assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

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6.2. Screening, Participant Enrollment, and Treatment Assignment

Participants will be screened within 24 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 24 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.

Laboratory tests including serum creatinine, CL_{cr}/eGFR, ALT, and bilirubin are not required at screening unless deemed necessary by the investigator to confirm eligibility. Testing for influenza is also not required at screening. Pregnancy testing is required at screening for participants assigned female at birth and of childbearing potential as described in Table 1.

Once written informed consent has been obtained, all screening and admission tests and assessments have been completed (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, screening, randomization, and Day 1 dosing should occur on the same day.

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). Virtual visit is defined as an online-based interaction (eg, telehealth, webcast, video conferencing).

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 study procedures.

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.

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 (See Appendix 11.5).

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 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.

- Chemistry

  eGFR according to:

  Participants aged ≥ 18 to < 65 years: 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: $$\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}\ (\text{mL/min})$$

  Participants aged ≥ 12 and < 18 years: Bedside Schwartz formula. Height at screening will be used for all calculations using the Schwartz formula:

  Adolescents: $$\frac{(0.413 \times \text{height in cm})}{(\text{serum creatinine in mg/dL})} = \text{eGFR}\ (\text{mL/min/1.73 m}^2)$$

- 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 in-person 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 professional.

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 11.4.

6.3.2.9 Household Contacts

Information regarding number of household contacts and number of contacts diagnosed with COVID-19 will be collected at the times shown in Table 1.

6.3.3. Pharmacokinetics

Pharmacokinetic assessments will be conducted in all participants during an in-person visit as per Table 1.

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6.3.4. SARS-CoV-2 Rapid Antigen Test

Rapid antigen tests will be performed by participants on self-collected nasal swabs (anterior nares) to assess antigen positivity at the time points specified in Table 1. Results will be self-reported, with investigator confirmation by review of photographic documentation encouraged, but not required.

6.3.5. 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).

6.3.6. Clinical Virology

6.3.6.1. Virology Testing

6.3.6.1.1. 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 PCR (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, and the emergence of viral resistance (by SARS-CoV-2 sequencing and/or phenotypic testing).

6.3.6.1.2. 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.

6.3.7. Patient-Reported Outcomes

The COVID-19 symptom questionnaire is required for the primary, secondary, and exploratory endpoints of the study. The ability to complete the COVID-19 symptom questionnaire is required for enrollment. The Work Productivity and Activity Impairment + Classroom Impairment Questions: COVID-19 Infection Specific (WPAI + CIQ: COVID19), and Patient-Reported Outcomes Measurement Information System (PROMIS-29) are required for this study. All PRO data will be collected electronically on a device. The participant should read and answer the questionnaire individually without external assistance. Patient-reported outcomes are outlined in Appendix 11.6.

Patient-reported outcomes will be required at the time points shown in Table 1. The following PROs will be utilized for this study:

6.3.7.1. COVID-19 Symptom Questionnaire

The COVID-19 symptom questionnaire, 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.

6.3.7.1.1. Procedures to Minimize Missing COVID-19 Symptom Data

For the purposes of this study, it is important to minimize missing symptom data to ensure interpretable analyses for efficacy endpoints based on the symptom questionnaire. Therefore, the following steps are put in place to help participants remain compliant with questionnaire completion per protocol required time points:

- Participants will receive reminders/notifications at regular intervals every day to complete questionnaire.
- Site staff and the study monitor will review symptom questionnaire data completion reports to monitor compliance.
- Site staff will contact participants with missing data (or their close contact in case of nonresponse, where feasible).
- Participants will be provided with a Value Sheet (if available) to highlight the significance of symptom questionnaire data and importance of participant compliance for the purposes of this study.

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

The WPAI + CIQ: COVID-19 Infection Specific 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 problem during the past 7 days. It has been validated to quantify work or education impairments for numerous diseases {Reilly 1993}.

6.3.7.3. 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 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}.

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[redacted].

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). 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 90 visit or early discontinuation visit, as applicable) for assessments and procedures specified in Table 1.

6.6. Poststudy Care

The long-term care of the participants will remain the responsibility of their primary treating physicians. 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.

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.

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 ICF 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, 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 90 days after first 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 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).

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 Situation 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 SSR 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 Section 7.4.2.2 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 start of the study to 30 days after the last study drug 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 Section 7.4.1. 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 11.4 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 CFR, the EU Regulation 536/2014 and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies the 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 Regulation 536/2014, 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.

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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.

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 (for participants ≥ 18 to < 65 years of age) or eGFR < 50 mL/min/1.73 m^2 by Bedside Schwartz formula (for participants ≥ 12 and < 18 years of age) will be discontinued from study drug whether considered related to the study drug or not (refer to Section 3.3.1.1). No confirmation repeat testing is required to meet this criterion.

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.

8.1.1. Primary Endpoint

The primary endpoint is the time (days) to COVID-19 symptom alleviation by Day 29 on the targeted symptoms measured via the COVID-19 symptom questionnaire. Symptom alleviation is defined as follows: all targeted symptoms scored moderate or severe at baseline are scored as mild or none for at least 48 consecutive hours and all targeted symptoms scored mild or none at baseline are scored as none for at least 48 consecutive hours; the first day of the 48 consecutive hours will be considered the symptom alleviation date.

Targeted symptoms are those listed below:

- Stuffy or runny nose.
- Sore throat.
- Shortness of breath (difficulty breathing).
- Cough.
- Low energy or tiredness.
- Muscle or body aches.
- Headache.
- Chills or shivering.
- Feeling hot or feverish.

8.1.2. Secondary Efficacy Endpoints

8.1.2.1. Key Secondary Efficacy Endpoints

The alpha-controlled secondary endpoints include the following:

- Time to COVID-19 symptom resolution by Day 29.

COVID-19 symptom resolution is defined as all targeted symptoms scored as none for at least 48 consecutive hours. The first day of the 48 consecutive hours will be considered the date of symptom resolution. The time to COVID-19 symptom resolution is the time (days) from the first dose date to the date of symptom resolution.

- Proportion of participants with moderate relapse of COVID-19 symptoms by Day 29.

COVID-19 symptom relapse is defined as the first day of at least 2 consecutive diary entries (regardless of missing entries in between) where there is any symptom (regardless of severity) after achieving short symptom recovery, or if a participant is hospitalized for COVID-19 after achieving short symptom recovery.

Short symptom recovery is defined as the first day of at least 2 consecutive diary entries (regardless of missing entries in between) where all targeted symptoms are absent. If a hospitalization for COVID-19 event occurs prior to the short recovery day, this participant is considered not having short symptom recovery for 28 days.

COVID-19 moderate symptom relapse is defined as having at least 1 symptom being moderate or severe OR at least 2 mild symptoms OR a hospitalization for COVID-19, observed on a day during COVID-19 symptom relapse (first day of symptom relapse to Day 28).

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

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.

- Proportion of participants with 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 trial 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.

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

A planned interim analysis of safety and efficacy is planned after approximately 50% of the planned participants reach Day 29 or prematurely discontinue from the study (see Section 8.10).

8.2.2. Primary Analysis

The unblinded primary analysis will be conducted after all participants have completed the Day 29 assessments or discontinued from the study prematurely, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis will serve as the final analysis of the primary efficacy endpoint and key secondary efficacy endpoints. If the study is stopped based on interim efficacy analysis recommendations from the DMC, the interim analysis will be considered the primary analysis.

8.2.3. 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.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The Full Analysis Set (FAS) 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.

The Full Analysis Positive Set (FAPS) includes all participants who are (1) randomized into the study, (2) have received at least 1 dose of study drug, and (3) are SARS-CoV-2 positive at baseline as confirmed by the central laboratory. 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 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 treatment, and (3) have a baseline SARS-CoV-2 viral

load greater than or equal to the lower limit of quantification (LLOQ). 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.

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8.3.1.6. Biomarkers

The Biomarker Analysis Set will include all randomized participants who received at least 1 dose of study drug and have a sample collected for biomarker evaluation.

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 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, and 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 Efficacy Analysis

The time to COVID-19 symptom alleviation is defined as follows:

- For participants with symptom alleviation by Day 29 (event), time to COVID-19 symptom alleviation is calculated as symptom alleviation date minus the first dose date plus 1.
- For participants who complete Day 29 of the study or discontinue from the study before Day 29 without symptom alleviation (censored), the time will be calculated as the last date on which the symptom alleviation is assessed by Day 29 minus the first dose date plus 1 or Day 28 whichever occurs first.

Handling of intercurrent events is defined in Section 8.5.3.

The median time to symptom alleviation and its 95% CI will be estimated by treatment group using the Kaplan-Meier method. A stratified log-rank test with stratification factor included will be used to compare the treatment difference in time to COVID-19 symptom alleviation.

The proportion of participants with symptom alleviation using Kaplan-Meier estimates will be provided in tables and plots by treatment.

In addition, a Cox proportional hazards regression model will be used to estimate the hazard ratio (HR) and its 2-sided 95% CI. Stratification factor will be included as a covariate in the Cox proportional hazards model.

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

Sensitivity analysis associated with the primary endpoint may be performed:

- A sensitivity analysis using a competing risk analysis approach will be provided, with intercurrent events (death or COVID-19–related hospitalization) as the competing risk.
- Missing symptom alleviation status will be imputed using multiple imputation assuming missing at random.
- Depending on the percentage of participants with other concomitant respiratory viral coinfection(s) at baseline, a sensitivity analysis may be conducted using the respiratory viral coinfection status (yes/no) at baseline as an additional stratification factor in the stratified log-rank test and as an additional covariate in the Cox proportional hazards model.

8.5.2. Secondary Efficacy Analyses

8.5.2.1. Key Secondary Efficacy Endpoints

Four alpha-controlled secondary efficacy endpoints are considered as the key secondary endpoints and will be tested in the following sequential order using a gatekeeping approach:

- Time to COVID-19 symptom resolution by Day 29.
- Proportion of participants with moderate relapse of COVID-19 symptoms by Day 29.
- The proportion of participants with COVID-19–related MAVs or all-cause death by Day 29.
- Proportion of participants with COVID-19–related hospitalization or all-cause death by Day 29.

The time to COVID-19 symptom resolution will be analyzed in a similar manner to the primary endpoint using the FAPS.

Proportion of participants with moderate relapse of COVID-19 symptoms will be estimated with 95% CIs including participants in the FAPS who have achieved short symptom recovery.

The proportion of participants with MAVs or all-cause death by Day 29 in the FAPS will be summarized using Kaplan-Meier estimates and compared between treatment groups using the log-rank test. Similar analysis methods will be used for the proportion of participants with COVID-19–related hospitalization or all-cause death by Day 29.

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 symptom duration and main clinical outcome measures (eg, hospitalization/death) are shown in Table 11.

Table 11. Handling of Intercurrent Events

Endpoint	Intercurrent event	Strategy	Description
Time to COVID-19 symptom alleviation by Day 29 Time to COVID-19 symptom resolution by Day 29	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/resolution (censored at Day 28)
	Discontinue randomized treatment prior to symptom alleviation/resolution (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/resolution (censor at Day 28)
Proportion of participants with moderate relapse of COVID-19 symptoms by Day 29 Proportion of participants with relapse of COVID-19 symptoms by Day 29	Hospitalization for the treatment of COVID-19 or all-cause death after short symptom recovery	Composite policy	Hospitalization for the treatment of COVID-19 or all-cause death means moderate relapse/relapse
	Discontinue randomized treatment after short symptom recovery (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 after short symptom recovery	Composite policy	Use of rescue medication means moderate relapse/relapse
Proportion of COVID-19–related hospitalization or all-cause death by Day 29 Proportion of participants with COVID-19-related MAVs or all-cause death 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)
	Use of rescue medication	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)

AE = adverse event; COVID-19 = coronavirus disease 2019

8.6. Safety Analysis

Descriptive summaries will be provided for the primary safety endpoints of treatment-emergent AEs and laboratory abnormalities and incidence of SAEs and AEs leading to study drug discontinuation. No formal statistical comparison of safety endpoints between treatment groups is planned. All safety data collected on or after the first dose date of study drug 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 MedDRA. 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). The DAIDS scale is available at:

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

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline up to 30 days after the date of the last dose of study drug 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 2-sided type I error rate of 0.05 for the primary efficacy endpoint 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 in a sequential manner only if the primary efficacy endpoint is met).

An example O'Brien-Fleming stopping boundary at 50% of planned participants reaching Day 29 or prematurely discontinuing from the study is: reject the null hypothesis with 1-sided *P* value ≤ 0.0015 or reject the alternative hypothesis with 1-sided *P* value > 0.3495. The actual stopping boundaries will depend on the exact timing of the interim analysis. If the efficacy stopping boundary is crossed at the interim analysis, the primary endpoint will not be tested again at the primary analysis.

8.8. Pharmacokinetic Analysis

Plasma concentrations and PK parameters AUC_{tau}, C_{tau}, and C_{max} (and others, as available) for GS-441524 (metabolite of GS-5245) will be listed and summarized using descriptive statistics by treatment. Exposure-response analysis for safety and/or efficacy may be conducted, if needed and sufficient data are available.

8.9. Sample Size

A total sample size of approximately 1900 participants (assuming 90% are CoV-2 positive at baseline as confirmed by the central laboratory) provides approximately 87% power to detect a median difference of 2 days in time to alleviation of targeted symptoms, which is equal to an HR of 1.18 using a 2-sided significance level of 0.05 assuming the placebo group median time to symptom alleviation is 13 days. The estimate of median time to COVID-19 symptom alleviation is based on the EPIC-SR study.

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 interim analysis using the Lan-DeMets approach with O'Brien-Fleming type spending function).

8.10. Data Monitoring Committee

A multidisciplinary DMC consisting of non-Gilead personnel will review the progress of the study, perform interim reviews of safety data, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination 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.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of

the study. If the DMC recommends stopping the study for futility or efficacy, a Gilead Oversight Committee will be unblinded to review the DMC recommendation.

- The first DMC meeting will be based on data collected after the first 150 participants have reached Day 29 or prematurely discontinued from the study, and will include safety data.

- Enrollment of adolescent participants (aged ≥ 12 to < 18 years), at US sites only, may commence after conclusion of the first DMC meeting.

The second DMC meeting will occur when approximately 50% of planned participants complete the Day 29 assessment, or prematurely discontinue from the study. The DMC meeting will include review of safety and formal evaluation of futility and efficacy.

The significance level for futility and efficacy will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level is set at 5% (2 sided).

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 Gilead 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, the EU, 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 Gilead. 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 Nonhospitalized Participants

GS-US-611-6549, Amendment 4 Protocol, 12 December 2023

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

PPD

Sr Assoc Clinical Development Director

[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. Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in at Least 1 Country Following EU Regulation No. 536/2014	Authorized in at Least 1 ICH Country	Authorized by Swissmedic
GS-5245	Study drug	No	No	No

EU = European Union; ICH = International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)

11.3. 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 Gilead or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. Gilead 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 patient-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, 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.

11.4. 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 Day 1 and 15 visits.

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.

11.5. Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19

- Obesity (body mass index [BMI] ≥ 30 kg/m^2 for those ≥ 18 years or > 95th percentile in those ≥ 12 but < 18 years of age).
- Diabetes mellitus, type 1 and type 2.
- Heart failure, coronary artery disease, or cardiomyopathies.
- Chronic kidney disease, or undergoing dialysis.
- Chronic liver disease, limited to cirrhosis, nonalcoholic steatohepatitis (NASH), alcoholic liver disease, and autoimmune hepatitis.
- Chronic lung diseases limited to:
  - Chronic obstructive pulmonary disease.
  - Interstitial lung disease.
  - Cystic fibrosis.
  - Pulmonary hypertension.
  - Bronchiectasis.
- Current pulmonary embolism.
- Moderate to severe asthma (or asthma of any severity participants ≥ 12 and < 18 years of age).
- Active pulmonary tuberculosis.
- Cerebrovascular disease.
- Down syndrome.
- Pregnancy.
- One or more of the following immunocompromising conditions or immunosuppressive treatments:
  - Receiving chemotherapy or other therapies for cancer.
  - Hematologic malignancy (active or in remission).

- History of a hematopoietic stem cell or a solid organ transplant.
- Human immunodeficiency virus infection: not on antiretroviral therapy or with cluster of differentiation 4+ cell count < 200 cells per cubic millimeter.
- Primary immunodeficiencies.
- Taking systemic immunosuppressive agents (eg, high-dose corticosteroids [ie, ≥ 20 mg of prednisone or equivalent per day when administered for 2 or more weeks], alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory).

11.6. Patient Reported Outcomes

11.7. Country-Specific Requirements

Additional Country-Specific Requirements for the United States

Country-Specific Requirements	Protocol Section
CCI [redacted]	Sections 6.1.1, 6.3.8, and 7.5.1
To achieve broad access and for generalizability of study results, included adolescents (age ≥12 to < 18 years) in the US only at participating sites. Enrolment may commence after the first DMC meeting.	Table 1, Sections 3.3.1.1, 4.2, 4.3, 6.1, 6.1.1, 6.3.2.5, and 8.10

11.8. 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 protocol amendment 3 to this amendment will be made available upon the publication of this protocol.

11.8.1. Amendment 4 (12 December 2023)

Rationale for Key Changes Included in Amendment 4	Affected Sections
Key secondary endpoints were reordered to reflect the current clinical outcomes of COVID-19.	Synopsis, Sections 2, 8.1.2.1, and 8.5.2.1
The definition of the primary efficacy analysis set was clarified.	Sections 8.3.1.1, 8.5.1, and 8.5.2.1
The definition of the virology analysis set was clarified.	Section 8.3.1.3
The futility stopping boundary and study power were revised to align with primary efficacy analysis set clarification.	Synopsis, Sections 8.7 and 8.9
Minor changes included to provide clarification.	Throughout, as needed

11.8.2. Amendment 3 (21 March 2023)

Rationale for Key Changes Included in Amendment 3	Affected Sections
Revision of exclusion criteria and the list of underlying medical conditions associated with higher risk for severe COVID-19 to align with current clinical practice and COVID-19 epidemiology per FDA communication.	Synopsis, Section 4.3, and Appendix 11.5
Provided clarification on pregnancy reporting period for both participant pregnancies and partner pregnancies to ensure alignment throughout the protocol.	Section 7.4.2.3 and Appendix 11.4
Given recently available phototoxicity results demonstrating that GS-5245 is not considered a photosafety risk, text previously included regarding UV protection measure recommendations have been removed. Recently available PK data have also been included.	Sections 1.2.1.1.1.2, 1.2.1.1.2.2, and 5.3
Addition of visit windows for Study Days 3 and 5 to allow participants greater scheduling flexibility, moved serum pregnancy test from screening visit to Day 1 visit, as urine pregnancy test at screening is already being performed, and clarification of study drug bottle return on Day 10.	Table 1
Addition of definitions for medically attended visits and COVID-19–related hospitalization.	Section 8.1.2.1
Prior and concomitant medications that are prohibited was expanded to include ensitrelvir.	Section 5.4.1
A list of study interventions and their authorization status is provided as per template update.	Appendix 11.2
Minor changes included to correct typographic errors.	Throughout, as needed

11.8.3. Amendment 2 (20 January 2023)

Rationale for Key Changes Included in Amendment 2	Affected Sections
Patient-reported outcome (PRO) tools were updated to minimize participant noncompliance with data reporting and interference of missing data with endpoint interpretability, per Food and Drug Administration (FDA) advice. Procedures to minimize missing PRO data were added.	Appendix 11.5 and Section 6.3.7.1.1
Secondary and CCI [redacted] were updated to reflect revised objectives incorporating FDA feedback. Symptom relapse and symptom alleviation definitions, addition of evaluation of impact of SARS-CoV-2 lineage on key endpoints, and sensitivity analysis using the respiratory viral coinfection status (yes/no) at baseline was added for the primary efficacy analysis were added.	Synopsis, Sections 2, 8.1.1, 8.1.2.1, 8.5.1, and 8.5.3
Inclusion criterion "5" was updated to indicate the severity of disease symptoms as per FDA guidance. Additionally, exclusion criterion "12" was updated to exclude participants with prior or current elevated bilirubin level (≥ 2 × ULN; ≥ 3 × ULN for participants with Gilbert's syndrome).	Synopsis, Section 4.2
Data of Phase 1 drug-drug interaction (DDI) were added and the restrictions on coadministration of acid-reducing agents removed, and hormonal contraceptive measures amended, to reflect DDI study conclusions.	Sections 1.2.1.1.2.2, and 5.4.1, and Appendix 11.3
Clarification was added noting a Gilead internal unblinded team will be involved in planned interim unblinding only upon DMC recommendation.	Synopsis and Section 5.1.3
PK parameters were specified for the PK analysis of GS-441524 (metabolite of GS-5245).	Synopsis, Sections 2 and 8.8
Clarification was added regarding the PK samples collections for the participants in the CCI [redacted]	Table 1 (footnote "p") and Section 6.3.3.1
Additional text was included regarding UV protection measure recommendation (pending phototoxicity evaluation of GS-5425).	Section 5.3
Clarification regarding discontinuation of participants from the study drug in case of Grade 4 clinically significant laboratory abnormality or clinical event, and was similarly updated for Grade 3.	Sections 7.7.1.4 and 7.7.1.3
A clarification was added regarding the type of nasal swab samples to be collected per FDA feedback.	Study schema, Table 1, Sections 6.3.4 and 6.3.6.1.1
Minor changes included to correct typographic errors.	Throughout, as needed

11.8.4. Amendment 1 (05 December 2022)

Rationale for Key Changes Included in Amendment 1	Affected Sections
Expansion in scope of study from Phase 2 to Phase 3.	Throughout, as needed
Change in primary, secondary, and CCI endpoints to reflect Phase 3 objectives.	Synopsis, Tables 1 and 8, Sections 2, 6, and 8
Changes to the visit schedule to optimize characterization of viral kinetics and detection of any potential resistance-associated mutations.	Table 1 and Section 6
Inclusion and exclusion criteria were revised to incorporate FDA feedback on the study population.	Synopsis, Sections 4.2, 4.3, and Appendix 11.4
An optional observational long COVID-19 assessment using observational data (obtain, store, and use existing health records data to assess long COVID-19 symptoms and conditions) to evaluate the potential effect of GS-5245 on the incidence and persistence of long COVD-19 sequelae is only applicable to participants in the Unites States (US) at participating sites.	Sections 6.1.1, 6.3.8, and 7.5.1
To achieve broad access and for generalizability of study results, included adolescents (age ≥ 12 to < 18 years) in the US only at participating sites. Enrolment may commence after the first DMC meeting.	Table 1, Sections 3.3.1.1, 4.2, 4.3, 6.1, 6.1.1, 6.3.2.5, and 8.10
Minor changes to correct typographic errors.	Throughout, as needed

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	13-Dec-2023 00:17:30