CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Placebo-controlled Study of the Safety and Efficacy of Obeldesivir to Treat Nonhospitalized Adults With Acute Respiratory Syncytial Virus (RSV) Infection
Plain Language Short Title:	Study of Obeldesivir to Treat Nonhospitalized Adults With Acute Respiratory Syncytial Virus (RSV) Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	166945
EU CT Number:	Not Applicable
ClinicalTrials.gov Identifier:	~~Not Available~~ NCT06585150
Diagnosis or Condition:	RSV Infection
Protocol ID:	GS-US-685-6819
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List
Protocol Version/Date:	Amendment 2: 21 October 2024
Amendment History	Original: 31 May 2024 Amendment 1: 06 August 2024 Amendment 2: 21 October 2024 A high-level summary of the changes in each amendment is provided in Appendix 11.6
Country-Specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 11.5.

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are not considered to be investigational new drug application sites.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ADME	absorption, distribution, metabolism, and excretion
AGM	African green monkey
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AUC	area under the concentration versus time curve
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”
BAL	bronchoalveolar lavage
CD4	clusters of differentiation 4
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C_{trough}	concentration at the end of the dosing interval
DAIDS	Division of AIDS
DDI	drug-drug interaction
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQoL (5 dimensions)
EQ-5D-5L	EuroQol (5-dimensions, 5-levels)
ET	early termination
EU	European Union
FAPS	Full Analysis Positive Set
FDA	Food and Drug Administration
G	General
GDRC	Gilead Data Review Committee
Gilead	Gilead Sciences
HCPGI-S	Health Care Professional Global Impression of Severity
HIV	human immunodeficiency virus
HR	hazard ratio
HRQOL	health-related quality of life
IB	investigator’s brochure

ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ICU	intensive care unit
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
LA	Laboratory Assessment
LLOQ	lower limit of quantitation
LRTI	lower respiratory tract infection
MAV	medically attended visit
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History/Physical Characteristics
NIPPV	noninvasive positive pressure ventilation
OEC	Other Exclusion Criteria
OIC	Other Inclusion Criteria
ODV	obeldesivir (GS-5245)
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PopPK	population pharmacokinetic
PK	pharmacokinetic(s)
PS	Patient Safety
PT	prior/concurrent therapy
RDV	remdesivir (Veklury®)
RiiQ™	Respiratory Infection Intensity and Impact Questionnaire™
RSV	respiratory syncytial virus
RT-qPCR	reverse transcriptase-quantitative polymerase chain reaction
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TELA	treatment-emergent laboratory abnormality
ULN	upper limit of normal
US, USA	United States, United States of America

PROTOCOL SYNOPSIS

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

Study Title: A Phase 2 Randomized, Placebo-controlled Study of the Safety and Efficacy of Obeldesivir to Treat Nonhospitalized Adults With Acute Respiratory Syncytial Virus (RSV) Infection

Plain Language Short Title: Study of Obeldesivir to Treat Nonhospitalized Adults With Acute Respiratory Syncytial Virus (RSV) Infection

Regulatory Agency Identifier Number(s):

IND Number: 166945
EU CT Number: Not Applicable
ClinicalTrials.gov Identifier: Not Available

Study Sites Planned: Approximately 110 to 130 study sites planned in up to 2 countries.

Objectives and Endpoints:

Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of obeldesivir (ODV; GS-5245) in reducing the duration of symptoms in nonhospitalized adult participants with acute RSV infection • To evaluate the safety and tolerability of ODV administered to nonhospitalized adult participants with acute RSV infection	• Time to alleviation of targeted RSV symptoms as measured by Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) through Day 15 • Incidence of treatment-emergent adverse events (AEs) and laboratory abnormalities through Day 29 • Incidence of serious adverse events and AEs leading to study drug discontinuation
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of ODV in durably alleviating symptoms of RSV	• Time to sustained alleviation of targeted RSV symptoms as measured by RiiQ through Day 15
• To evaluate the efficacy of ODV in preventing progression of RSV infection to the lower respiratory tract	• Time to RSV-related lower respiratory tract infection through Day 29
• To evaluate the efficacy of ODV in preventing hospitalization or death from any cause	• Time to RSV-related hospitalization or all-cause death through Day 29
• To evaluate the efficacy of ODV in preventing medically attended visits (MAVs) or death from any cause	• Time to RSV-related MAVs or all-cause death through Day 29
• To evaluate the antiviral activity of ODV on RSV nasal swab viral load at Days 3, 5, 7, 10, and 15	• Change from baseline in RSV viral load through Days 3, 5, 7, 10, and 15
• To evaluate the plasma pharmacokinetics (PK) of GS-441524 (metabolite of ODV)	• PK parameters AUC_{tau}, C_{trough}, and C_{max} of GS-441524, as available

Study Design: This is a Phase 2, randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral ODV with placebo for the treatment of acute RSV infection in nonhospitalized adult participants with ≥ 1 risk factors for severe RSV disease (Figure 1).

A total of approximately 240 participants is planned for this study. Up to approximately 25% of total enrollment may consist of participants who qualify for inclusion by the age criterion (ie, MH1 risk factor a) alone and with no other risk factors for severe RSV disease. Up to approximately 50% of total enrollment may consist of participants who qualify for inclusion by the presence of chronic cardiovascular disease (ie, MH1 risk factor e) without additional medical comorbidity risk factors (ie, MH1 risk factors b, c, or d). Note that the 50% cap applies to both those participants with MH1 risk factor e alone or those participants with MH1 risk factors a and e. No caps are present for participants with medical history of chronic obstructive pulmonary disease (COPD), asthma or specified chronic lung disease. All the enrolled participants will be randomized 1:1 to receive ODV or placebo-to-match for 5 days. Randomization will be stratified by vaccination status (ever vs never).

Number of Participants Planned: Approximately 240

Study Population: Nonhospitalized participants 18 years of age or older with acute RSV infection and at least 1 risk factor for severe RSV disease.

Main Eligibility Criteria:

Main Inclusion Criteria:

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

General (G)

G1. Participants ≥ 18 years of age willing and able to provide written informed consent.

Medical History (MH)/Physical Characteristics

MH1. Exhibits at least 1 of the following risk factors for severe RSV disease:

a) Age ≥ 60 years.

b) Moderate or severe COPD with a history of ≥ 1 exacerbation during the preceding 12 months.

c) Asthma with a history of ≥ 1 exacerbation during the preceding 12 months.

d) One or more of the following chronic lung diseases:

   i) Bronchiectasis

   ii) Interstitial lung disease (eg, idiopathic pulmonary fibrosis)

   iii) Pulmonary hypertension

e) Chronic cardiovascular disease exclusive of treated or untreated hypertension:

   i) Congestive heart failure

   ii) Past or present history of coronary artery disease (including stable angina) AND receiving 1 or more medications for its treatment (eg, nitrates, beta-blockers, and angiotensin converting enzyme inhibitors)

MH2. RSV infection confirmed ≤ 3 days before randomization by a locally available approved or authorized polymerase chain reaction assay or alternative nucleic acid-based detection, including a respiratory viral panel, or respiratory pathogen panel. Serologic tests will not be accepted.

MH3. New onset or increased from baseline of ≥ 2 of the following signs and/or symptoms, and at least one sign/symptom of moderate severity at screening, and onset ≤ 3 days before randomization:

a) Nasal congestion.

b) Sore throat.

c) Cough.

d) Wheezing.

e) Shortness of breath (ie, dyspnea).

f) Expectoration (ie, sputum production).

MH4. RSV vaccine status:

a) Participants whose only risk factor is age ≥ 60 years (ie, risk factor a) must not have received, at any time, any doses of investigational or licensed vaccine for RSV.

b) For all other participants, receipt of ≥ 1 dose(s) of investigational or licensed RSV vaccine, at any time prior to randomization, is allowed.

Main Exclusion Criteria:

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

Medical History/Physical Characteristics

MH1. Currently requiring or expected to require hospitalization within 48 hours after randomization.

MH2. Documented previous infection and/or hospitalization for RSV during the current respiratory virus season.

MH4. Documented to be positive for influenza A or B virus, and/or SARS-CoV-2 ≤ 7 days prior to randomization.

MH5. Concurrent infections requiring treatment with any systemic antibacterial, antifungal, or antimycobacterial therapy ≤ 7 days prior to randomization.

MH7. Participants with a history of cystic fibrosis.

Laboratory Assessments (LA)

LA1. Undergoing dialysis, known history of moderate or severe renal impairment, known CL_{cr} < 60 mL/min (as calculated by Cockroft-Gault), or estimated glomerular filtration rate < 60 mL/min/1.73 m^2 within the preceding 6 months prior to randomization.

a) Potential participants meeting laboratory criterion LA1 may be enrolled if test results available before dosing show that renal function no longer meets this criterion.

LA2. Known history of any of the following abnormal laboratory results (< 6 months prior to randomization) unless confirmed as resolved at screening.

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

b) Positive urine or serum pregnancy test or pregnant at screening.

Prior/Concurrent Therapy (PT) or Clinical Study Experience

PT1. Received any approved or authorized, direct-acting antiviral drug or monoclonal antibody against RSV < 28 days or < 5 half-lives, whichever is longer, before randomization.

PT2. Received an investigational product < 28 days or < 5 half-lives, whichever is longer, before randomization.

Test Product, Dose, and Mode of Administration: Oral ODV 700 mg twice daily on Day 1 (ie, 2 tablets each for 2 administrations) followed by 350 mg twice daily on Days 2 to 5 (ie, 1 tablet each for 8 administrations) for a total of 5 days of drug dosing.

Reference Therapy, Dose, and Mode of Administration: Placebo-to-match for ODV with a dosing schedule same as above.

Duration of Intervention: Participants will receive oral ODV or placebo-to-match for 5 days.

Study Procedures/Frequency: The study procedures and frequency of assessments are provided in Table 1.

Statistical Methods:

Efficacy: 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 alleviation of RSV symptoms. 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.

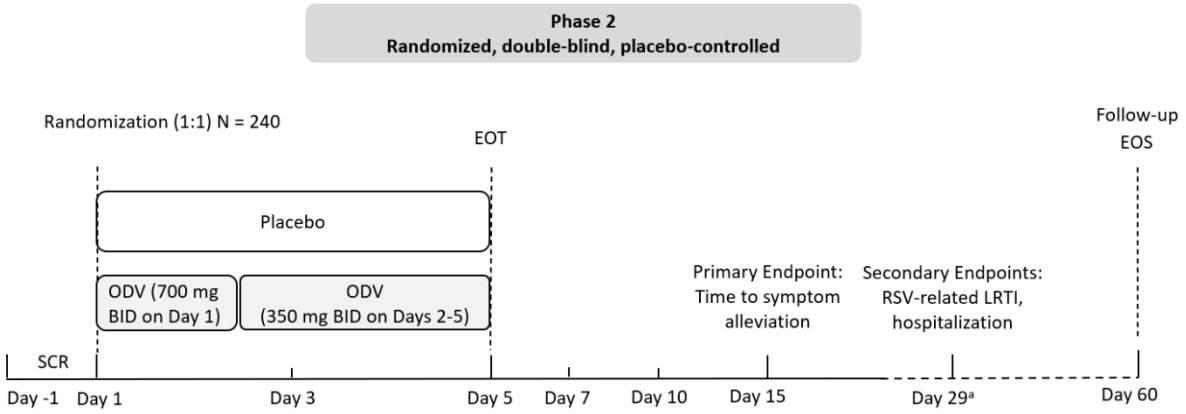
Safety: Safety data collected during the period from the first dose of study drug up to the date of last dose of study drug plus 30 days will be summarized by treatment group (according to the study drug received).

Pharmacokinetics: PK parameters of interest will be listed and summarized for GS-441524 using descriptive statistics by treatment.

Sample Size: A total sample size of approximately 240 participants provides at least 80% power to detect a difference of 36 hours (placebo to ODV HR 0.7) between ODV over placebo, assuming a median time to symptom alleviation in the placebo group of 5 days (120 hours), and a reduction in median time to symptom alleviation in the ODV group to 3.5 days (84 hours) using a 2-sided significance level of 0.1.

STUDY SCHEMA

Figure 1. Study Schema



BID = twice daily; EOS = end of study; EOT = end of treatment; LRTI = lower respiratory tract infection; N = number of participants; ODV = obeldesivir (GS-5245); RSV = respiratory syncytial virus; SCR = screening

a At Day 29, an unblinded primary analysis will be conducted and site and participants will remain blinded.

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table

Study Day	Screening[a, b]	Baseline Day 1[a, c, d]	Day 3[d]	Day 5[c, d]	Day 7	Day 10	Day 15[c]	Day 29	Day 60 Follow-up Visit	ET Visit[c]
Visit Window			**± 1 Day[e]**			**± 2 Days**		**+ 5 Days**	**+ 5 Days**	
Type of Visit	**In Person[f]**	**In Person[f]**	**In Person[f]**	**In Person[f]**	**In Person[f] or Virtual[g]**	**In Person[f] or Virtual[g]**	**In Person[f]**	**In Person[f] or Virtual[g]**	**Virtual[g]**	**In Person[f]**
Written informed consent	X									
Medical history[h] and demography	X									
Documented RSV infection[i]	X									
Vital signs[j]	X	X		X			X			X
Height and weight	X	X (weight only)								
Complete physical examination[k]	X	X								X
Symptom-directed physical examination[l]			X	X	X	X	X	X		
Serum ALT, bilirubin, creatinine, and CL_{cr}/eGFR[m]	X									
Chemistry and hematology panels		X		X			X	X[n]		X
Urine or serum pregnancy test[o]	X	X					X			X
Midturbinate nasal swab[p]		X	X	X	X	X	X			X
Provide nasal self-swab collection kits[p]		X	X (as needed)	X (as needed)	X (as needed)					
Perform nasal self-swab collection training[p]		X	X (as needed)	X (as needed)	X (as needed)	X (as needed)				
Anti-RSV antibody assessment		X								
Sparse PK[q]		X	X	X						X
Intensive PK substudy venous and capillary blood (optional)[r]		X		X						X
Cytokine profiling		X								
MAVs and hospitalization information[s]		X	X	X	X	X	X	X	X	X
Pre-Existing Symptom Questionnaire		X (predose)								
RiiQ[t]		X	X	X	X	X	X	X		X

Study Day	Screening[a, b]	Baseline Day 1[a, c, d]	Day 3[d]	Day 5[c, d]	Day 7	Day 10	Day 15[c]	Day 29	Day 60 Follow-up Visit	ET Visit[c]
Visit Window			**± 1 Day[e]**			**± 2 Days**		**+ 5 Days**	**+ 5 Days**	
Type of Visit	**In Person[f]**	**In Person[f]**	**In Person[f]**	**In Person[f]**	**In Person[f] or Virtual[g]**	**In Person[f] or Virtual[g]**	**In Person[f]**	**In Person[f] or Virtual[g]**	**Virtual[g]**	**In Person[f]**
PGIS		X	X				X	X		
PGIC[u]				X						X
HCPGIS		X	X	X			X	X		X
EQ-5D-5L		X		X			X	X		X
Study drug dispensation		X								
Study drug dosing (ODV or placebo)[v]		X	X	X						
Study drug bottle return[w]				X	X	X	X	X		X
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X		X
Vital status (alive/dead) and exacerbation history[x]									X	

ALT = alanine aminotransferase; BID = twice daily; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol (5-dimensions, 5-levels); ET = early termination; HCPGIS = Health Care Professional Global Impression of Severity; MAV = medically attended visit; NIPPV = noninvasive positive pressure ventilation; ODV = obeldesivir; PCR = polymerase chain reaction; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); RiiQ = Respiratory Infection Intensity and Impact Questionnaire; RSV = respiratory syncytial virus; RT-qPCR = reverse transcriptase-quantitative polymerase chain reaction

a Screening window is within 24 hours of the Day 1 visit. Day 1 visit may occur on the same day as screening. If the Day 1 and screening visits are the same day, do not repeat assessments.

b Patients anticipated to be eligible for the study and without documented RSV infection will be consented for RSV testing. Patients who are RSV positive will be approached to consent for the screening and treatment phase of the study.

c Laboratory tests for safety will be performed on Days 1, 5, and 15, and at the ET visit.

d All Day 1 assessments excluding PK assessments must occur before administration of the first dose of study drug. Day 3 and 5 assessments should occur prior to the withheld morning or afternoon dose (see footnote v).

e Day 3, Day 5, and Day 7 visits should be conducted on separate calendar days.

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

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

h Medical history will include the date of first RSV symptoms, overall RSV symptoms, all RSV vaccinations prior to screening, baseline characteristics, allergies, and medications taken within 30 days of the screening visit.

i RSV infection documented by PCR or alternative nucleic acid-based detection.

j Vital signs include heart rate, body temperature, and blood pressure. Vital signs are collected at in-person visits only.

k 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, and nails; musculoskeletal; and neurological. Genitourinary and reproductive examination should only be conducted if clinically indicated.

l Symptom-directed physical examinations will be performed on Days 3, 5, 7, 10, 15, and 29 and only during in-person visits.

m Serum ALT, bilirubin, serum creatinine, and CL_{cr}/eGFR assessments at screening are not required unless deemed necessary by the investigator to confirm eligibility.

n Chemistry and hematology laboratory testing on Day 29 is only required if any Day 15 laboratory values were Grades 3 or 4 laboratory abnormalities.

o At screening, a urine pregnancy test will be performed at the local laboratory for participants assigned female at birth and of childbearing potential. On Days 1 and 15, and ET/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 11.3.

p A midturbinate nasal swab will be collected at in-person visits. If the visits on Days 7 or 10 occur virtually, participants will perform a self-swab. Details regarding self-swab collection and analysis are provided in Section 6.3.9.1.

q Sparse PK samples will be collected relative to the in-clinic dose on Day 1 at 0.25, 0.75, and 1.5 hours postdose, on Day 3 at predose (< 5 minutes before dose), and on Day 5 at predose (< 5 minutes before dose), 0.75, and 2 hours postdose.; ± 20% time window will be applied for postdose collection time points. A single PK sample will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose or at the ET visit for all participants who discontinue the study earlier than Day 10

r Participants who consent to the optional intensive PK samples and have them collected will not provide samples for sparse PK. In the optional intensive PK substudy: approximately 30 participants at participating study sites will have intensive venous and capillary blood PK samples collected simultaneously relative to the in-clinic dose on Day 1 at 0.25, 0.5, 0.75, 1.5, 3, 4 hours, and on Day 5 at predose (< 5 minutes before dose), 0.25, 0.5, 0.75, 1.5, 3, 4 hours after morning or evening dose at the clinic.; ± 20% time window will be applied for all postdose collection time points. Single venous and capillary PK samples will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose or at the ET visit, for all participants who discontinue the study earlier than Day 10.

s For the purposes of efficacy analysis, 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 and hospitalization information should be collected at all visits except Screening.

t The RiiQ must be completed prior to dosing on Day 1 and preferably prior to dosing on Days 2-5, at approximately the same time each day, through Day 29. If a participant discontinues from the study early, the participant should complete this questionnaire during the ET visit.

u The PGIC will be collected only once on Day 5 (or Day 6) visit after the final dose, or on ET visit if the last dose occurs prior to Day 5 visit.

v Study drug will be administered, without regard to food, orally at doses of 700 mg twice daily on Day 1 (ie, 2 tablets each for 2 administrations) followed by 350 mg twice daily on Days 2 to 5 (ie, 1 tablet each for 8 administrations) for a total of 5 days of drug dosing. On Day 1, 3, and 5, participants will be coming into the clinic in the morning or afternoon and should withhold either their morning or afternoon dose until they arrive in clinic. All assessments on Days 3 and 5 excluding PK assessments should occur prior to the withheld morning or afternoon dose.

w Study drug bottle should be returned by the participant on Day 5, if the participant has already completed both doses of study drug on that day. If the participant has study drug at the end of the Day 5 visit, the participant may return the study drug bottle on Days 7, 10, or 15. If the Days 7 or 10 visit are virtual, drug accountability should be performed virtually, and the participant will be instructed on returning the study drug bottle on Days 15 or 29.

x Document history of any chronic disease exacerbations that occurred after Day 29.

1. INTRODUCTION

1.1. Background

Respiratory syncytial virus (RSV) is a well-recognized cause of respiratory tract infection worldwide, with severe illness occurring more often in patients at high risk such as infants, older adults, and those with chronic medical conditions{World Health Organization (WHO) 2024}. In older adults or those with coexisting conditions, RSV-related lower respiratory tract infection (LRTI) may lead to exacerbation of underlying diseases, hospitalization, and death {Belongia 2018, Branche 2022, Falsey 2005}. Though there are monoclonal antibodies for the prevention of RSV infection in children, and recently approved vaccines for RSV for expectant mothers and older adults, there are currently no approved oral agents for the treatment of RSV infection. There remains a significant unmet need for safe and effective treatments for both children and adults.

Obeldesivir (ODV; GS-5245) is a mono-5'-isobutyryl ester prodrug of GS-441524, which has potent antiviral activity against RSV demonstrated both in vitro and in vivo. Following oral administration, ODV 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 remdesivir (RDV; Veklury®). Obeldesivir has been developed with the intent to deliver consistent and high systemic exposures to GS-441524 following oral administration.

Availability of a highly effective oral treatment with a high barrier to resistance, minimal drug-drug interactions (DDIs), and few tablets to take has the potential to address a critical unmet medical need for RSV therapy. Obeldesivir represents a promising oral option for the treatment of RSV in nonhospitalized patients who are at high risk of progression to severe RSV disease.

1.2. Background on Study Intervention(s)

1.2.1. Obeldesivir

1.2.1.1. General Information

Obeldesivir 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 ODV was designed to specifically increase the oral bioavailability of GS-441524.

For further information on ODV, refer to the current investigator's brochure (IB).

1.3. Rationale for This Study

Respiratory syncytial virus is a well-recognized cause of respiratory tract illness worldwide {World Health Organization (WHO) 2024}. There are currently no approved oral agents for the treatment of RSV infection, and there remains a significant unmet need for safe and effective treatments for both children and adults.

Obeldesivir is an ester prodrug of the parent nucleoside of RDV, GS-441524. It has potent in vitro antiviral activity against RSV and exhibits therapeutic efficacy against RSV in an African green monkey animal model. Following oral administration, ODV delivers high systemic exposures of GS-441524 and adequate formation of the active triphosphate metabolite, GS-443902, in tissues where RSV replicates. Administration of oral ODV therefore represents a promising approach for the treatment of RSV.

This study will evaluate ODV compared with placebo in adult participants at higher risk of RSV disease progression due to age or underlying chronic medical conditions for whom there are no existing oral therapies that are authorized or approved. Patients at high risk of severe RSV disease may benefit from effective antiviral therapy that could result in a shorter duration of illness, reduced progression of disease to the lower respiratory tract, and reduced incidence of medically attended visits (MAVs), hospitalizations, and/or death.

1.4. Rationale for Dose Selection of Study Drug

The proposed ODV dosing regimen for evaluation in this Phase 2 study is 700 mg twice daily on Day 1 followed by 350 mg twice daily on Days 2 to 5. This dosing regimen was selected based on the totality of available clinical and nonclinical data and with careful consideration of the overall benefit-risk profile.

Pharmacokinetic and safety of ODV were evaluated in a comprehensive clinical program with 6 Phase 1 studies in healthy adult participants (first-in-human Study GS-US-611-6248, absorption, distribution, metabolism, and excretion [ADME] Study GS-US-611-6408, DDI studies GS-US-611-6409 and GS-US-611-6469, Japanese bridging study GS-US-611-6586, and renal impairment study GS-US-611-6472 [interim data]) and 2 pivotal Phase 3 studies in adult and adolescent participants with COVID-19 (Studies GS-US-611-6549 and GS-US-611-6273). Obeldesivir was generally safe and well tolerated (most adverse events (AEs) were Grade 1 in severity) following single dose up to 1600 mg and multiple doses of 350 mg twice daily, 500 mg twice daily, and 900 mg once daily for 5 days in healthy participants and ODV 350 mg twice-daily doses for 5 days in COVID-19 participants.

A GS-441524 population PK (PopPK) model incorporating weight-based allometric scaling on clearance and volume parameters was developed using nonlinear mixed effects modeling and data obtained from the above listed studies (except the ADME study GS-US-611-6408). The developed PopPK model was used to evaluate intrinsic and extrinsic factors impacting the ODV PK. Body weight, estimated glomerular filtration rate (eGFR), and presence of COVID-19 disease were found to have a significant impact on the PK of GS-441524.

Utilizing the PopPK estimated plasma exposures, a logistic regression PK/pharmacodynamics (PD) analysis was conducted to characterize the exposure-safety relationship with Grade 3 or higher CL_{cr} treatment-emergent laboratory abnormalities (TELA; Division of AIDS [DAIDS] grading). The established relationship was used to predict the rate of Grade 3 or higher CL_{cr} TELAs associated with exposures following various dosing regimens.

The clinical PK efficacy target for RSV infection is based on nonclinical data obtained from PK and efficacy studies in African green monkeys (AGMs). In an AGM efficacy study, once-daily oral administration of ODV at 30 mg/kg and 90 mg/kg reduced RNA viral loads of RSV A2 in bronchoalveolar lavage (BAL) fluid and throat swabs. In BAL fluid, a > 2 $\log_{10}$ mean reduction in RNA viral load of ODV-treated animals receiving doses of both 30 mg/kg and 90 mg/kg was observed on Day 5, the time of peak viral load in vehicle-treated control animals. Since the planned clinical RSV dosing regimens are twice-daily treatments, plasma exposures of GS-441524 obtained from AGM PK studies were estimated for 30 mg/kg in AGM twice daily for 5 days using the nonparametric superposition function in Phoenix® WinNonlin®. The estimated exposure (C_{max} or AUC) for 30 mg/kg in AGM twice daily was selected as the PK efficacy target when evaluating different clinical ODV dosing regimens for the treatment of RSV.

Pharmacokinetic simulations were performed to evaluate different dosing regimens in adult patients (> 18 years) with normal kidney function and those with mild renal impairment. The simulated population was based on the latest National Health and Nutrition Examination Survey (NHANES) database, with 1000 participants included in each dosing regimen evaluated. Based on the performed simulations, following a dosing regimen of 700 mg twice daily on Day 1 and 350 mg twice daily on Days 2 to 5, Day 1 predicted mean C_{max} and AUC_{0-12} are 4.76 µg/mL and 20.41 h•µg/mL, respectively, and Day 5 predicted mean C_{max} and AUC_{0-12} are 2.54 µg/mL and 13.68 h•µg/mL, respectively. Note that the predicted mean C_{max} is the highest C_{max} on Days 1 and 5 and predicted mean AUC_{0-12} corresponds to a morning dose on Days 1 and 5. Days 1 and 5 predicted C_{max} values are below those observed in Study GS-US-611-6248 (first-in-human) in participants who received 900 mg once daily for 5 days (6.23 µg/mL and 5.18 µg/mL, respectively) and Days 1 and 5 predicted AUC_{0-12} values are below the observed AUC_{0-12} in Study GS-US-611-6248 (first-in-human) in participants who received 500 mg twice daily for 5 days (Day 5 AUC_{0-12}: 21.48 h•µg/mL). Both these regimens were generally safe and well tolerated and thus the above proposed dosing regimen is anticipated to be safe and well tolerated.

The outlined approach allowed an informed dose selection to ensure clinical exposures of GS-441524 will be above the AGM efficacy target and below the exposure predicted to have an acceptable rate of Grade 3 or higher CL_{cr} TELA in participants with normal kidney function or mild renal impairment.

Obeldesivir and RDV generate the same active triphosphate metabolite (GS-443902) through different metabolic pathways. Following ODV administration, GS-443902 PK was dose-proportional and accumulation was observed following twice-daily dosing. The proposed RSV dosing regimen (700 mg twice daily on Day 1, 350 mg twice daily on Days 2 to 5) is expected to provide plasma concentrations of GS-441524 sufficient to support higher intracellular exposures of the active metabolite (GS-443902) in peripheral blood mononuclear cell than RDV on Days 1 through 5.

1.5. Benefit-Risk 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 ODV or placebo. Conducting a Phase 2 proof-of-concept study to investigate the safety and efficacy of ODV for the treatment of RSV is a measured approach that will provide data in the development of ODV as an oral treatment option for patients with RSV.

Moreover, ODV has been studied in 2 Phase 3 studies for COVID-19, OAKTREE (GS-US-611-6549), and BIRCH (GS-US-611-6273), with over 1200 participants exposed to ODV. In these studies, ODV 350 mg twice daily for 5 days was found to be safe and well tolerated further ensuring the protection of participant safety. The overall safety profile of ODV 700 mg twice daily on Day 1, followed by 350 mg twice daily for Days 2 to 5 is expected to be favorable.

An unanticipated event such as a disaster or public health emergency may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.2 for further details on the risks and risk mitigation strategy.

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

2. OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of ODV in reducing the duration of symptoms in nonhospitalized adult participants with acute RSV infection • To evaluate the safety and tolerability of ODV administered to nonhospitalized adult participants with acute RSV infection	• Time to alleviation of targeted RSV symptoms as measured by Respiratory Infection Intensity and Impact Questionnaire (RiiQ TM) through Day 15 • Incidence of treatment-emergent AEs and laboratory abnormalities through Day 29 • Incidence of serious AEs (SAEs) and AEs leading to study drug discontinuation
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of ODV in durably alleviating symptoms of RSV • To evaluate the efficacy of ODV in preventing progression of RSV infection to the lower respiratory tract • To evaluate the efficacy of ODV in preventing hospitalization or death from any cause • To evaluate the efficacy of ODV in preventing MAVs or death from any cause • To evaluate the antiviral activity of ODV on RSV nasal swab viral load at Days 3, 5, 7, 10, and 15 • To evaluate the plasma PK of GS-441524 (metabolite of ODV)	• Time to sustained alleviation of targeted RSV symptoms as measured by RiiQ through Day 15 • Time to RSV-related LRTI through Day 29 • Time to RSV-related hospitalization or all-cause death through Day 29 • Time to RSV-related MAVs or all-cause death through Day 29 • Change from baseline in RSV viral load through Days 3, 5, 7, 10, and 15 • PK parameters AUC_{tau}, C_{trough}, and Cmax of GS-441524, as available
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the efficacy of ODV in alleviating respiratory and systemic symptoms of RSV • To evaluate the efficacy of ODV in alleviating lower respiratory tract symptoms of RSV • To evaluate the emergence of viral resistance to ODV • To evaluate the efficacy of ODV in improving time to negative RSV nasal swab viral load • To determine the antiviral activity of ODV on RSV nasal swab infectious viral titer • To evaluate the efficacy of ODV in reducing long-term impact of RSV on medical visits, hospitalizations, chronic disease exacerbations, and death from any cause • To evaluate the impact of ODV on prevention of intensive care unit (ICU) admission • To evaluate the impact of ODV on need for noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation	• Time to alleviation of all RSV symptoms as measured by RiiQ through Day 15 • Time to sustained alleviation of all RSV symptoms as measured by RiiQ through Day 15 • Time to alleviation of lower respiratory tract symptoms of RSV as measured by RiiQ through Day 15 • Emergence of viral resistance to ODV • Proportion of participants with negative RSV nasal swab viral load through Days 3, 5, 7, 10, and 15 • Change from baseline in RSV nasal swab infectious viral titer through Days 3, 5, 7, 10, 15, as applicable • Proportion of participants with negative RSV nasal swab infectious viral titer at Days 3, 5, 7, 10, 15, as applicable

• To evaluate the impact of ODV on duration of hospitalization • To evaluate the impact of ODV on health-related quality of life (HRQOL) • To evaluate the impact of ODV on the prevalence of persistent symptoms • To evaluate the efficacy of ODV in treating RSV in participants with respiratory viral coinfection • To evaluate anti-RSV antibodies • To evaluate immune responses secondary to RSV infection and treatment	• Proportion of participants with all-cause MAVs, hospitalizations, exacerbations of chronic disease (eg, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF]), and all-cause death through Day 60 • Proportion of participants admitted to the ICU through Day 29 • Proportion of participants requiring NIPPV or mechanical ventilation through Day 29 • Hospital length of stay (days) • Change from baseline in EuroQol (5 dimensions, 5 levels) (EQ-5D-5L) at Days 5 and 14 • Duration of persistent symptoms (eg, wheezing or cough) • Symptom duration and virologic response in participants with viral coinfections • Characterization and titer of baseline anti-RSV antibodies • Characterization of cytokine profiles at baseline

3. STUDY DESIGN

3.1. Study Design Overview

This is a Phase 2, randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral ODV with placebo for the treatment of acute RSV infection in nonhospitalized adult participants with ≥ 1 risk factors for severe RSV disease.

A total of approximately 240 participants is planned for this study. Up to approximately 25% of total enrollment may consist of participants who qualify for inclusion by the age criterion (ie, MH1 risk factor a) alone and with no other risk factors for severe RSV disease. Up to approximately 50% of total enrollment may consist of participants who qualify for inclusion by the presence of chronic cardiovascular disease (ie, MH1 risk factor e) without additional medical comorbidity risk factors (ie, MH1 risk factors b, c, or d). Note that the 50% cap applies to both those participants with MH1 risk factor e alone or those participants with MH1 risk factors a and e. No caps are present for participants with medical history of COPD, asthma or specified chronic lung disease. All the enrolled participants will be randomized 1:1 to receive ODV or placebo-to-match for 5 days. Randomization will be stratified by vaccination status (ever vs never).

3.2. Duration of Intervention

Participants will receive oral ODV or placebo for 5 days.

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participant

3.3.1.1. Criteria for Early Discontinuation From Study Intervention

Study intervention will be discontinued in the following instances:

- 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.
- Baseline or on-treatment eGFR < 50 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation 2021. No confirmatory repeat testing is required to meet this criterion.
- Baseline or on-treatment alanine aminotransferase (ALT) ≥ 5 × upper limit of normal (ULN).
- 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 (Section 3.3.1.1.1).
- Participant noncompliance.
- Pregnancy during the study; refer to Appendix 11.3.
- Loss to follow-up (Section 6.4.3).
- Discontinuation of the study by the sponsor.
- Disaster or public health emergency (Appendix 11.2 provides information on risk assessment and mitigation that may allow continued participation).

3.3.1.1.1. Partial Withdrawal

Participants may decide to partially withdraw from the study (eg, discontinue from study intervention and/or procedures but agree to continue to be followed for study endpoints). Such partial withdrawals should be fully documented.

3.3.1.2. Criteria for Early Discontinuation From the Study

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

- Participant request to discontinue for any reason. (Section 3.3.1.1.1).
- Participant noncompliance.
- Pregnancy during the study; refer to Appendix 11.3.
- Loss to follow-up (Section 6.4.3).
- Disaster or public health emergency (Appendix 11.2 provides information on risk assessment and mitigation that may allow continued participation.).
- Withdrawal of consent.
- Death.

3.3.2. Early Study Termination

The study will be discontinued in the following instances:

- Decision by Gilead (Gilead Sciences) to end the study.
- Discontinuation of the study at the request of a regulatory agency, institutional review board (IRB), or independent ethics committee (IEC).

3.4. Definitions for Primary Analysis Completion and End-of-Study Dates

3.4.1. Primary Analysis Completion Date

The primary analysis completion date is the date when the last participant receives a protocol-specified procedure or assessment for the purposes of final collection of data for the primary endpoint analysis.

3.4.2. End-of-Study Date

The end-of-study date will be the date of the last participant's last observation (or in-person or virtual visit) for all protocol-specified procedures or assessments, including any follow-up procedures or assessments.

A participant is considered to have reached the end of the study when they have completed all periods of the study including follow-up, or when they discontinue the study due to the following reasons, whichever comes first: death, participant withdrawal of consent, loss to follow-up, or the sponsor termination of study.

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 virology, PK, and biomarker data), participant-reported outcomes, and interactive response technology (IRT). Case report forms (CRFs) are not considered source data.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

A total of approximately 240 participants is planned for this study. The target population is nonhospitalized participants 18 years of age or older with acute RSV infection and at least 1 risk factor for severe RSV disease. Every effort will be made to include participants of any race, gender, and across the age range described in the study inclusion and exclusion criteria provided in Section 4.2 and Section 4.3, respectively, of the protocol. The collection of race, ethnicity, sex at birth, and age data allows for the analysis and reporting of safety and efficacy data by demographic subgroups as required by certain health authorities.

Moreover, to ensure a diversity of age range and medical comorbidities studied, enrollment caps will be placed on participants enrolled meeting the risk factor criterion of 60 years of age or older alone (ie, only MH1.a.) and on participants qualifying for inclusion by the cardiovascular disease criterion without other risk factors (ie, only MH1.e. without other risk factors). Further details are provided in Section 3.1 above.

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 of the following inclusion criteria to be eligible for participation in this study. Note that unless otherwise specified, LRTI is defined by RiiQ-measured symptoms (Section 8.1.2.2).

General (G)

G1. Participants ≥ 18 years of age willing and able to provide written informed consent.

G2. Participants assigned male at birth and participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 11.3.

Medical History (MH)/Physical Characteristics

MH1. Exhibits at least 1 of the following risk factors for severe RSV disease:

a) Age ≥ 60 years.

b) Moderate or severe COPD with a history of ≥ 1 exacerbation during the preceding 12 months.

c) Asthma with a history of ≥ 1 exacerbation during the preceding 12 months.

d) One or more of the following chronic lung diseases:

   i) Bronchiectasis

   ii) Interstitial lung disease (eg, idiopathic pulmonary fibrosis)

   iii) Pulmonary hypertension

e) Chronic cardiovascular disease exclusive of treated or untreated hypertension:

   i) CHF

   ii) Past or present history of coronary artery disease (including stable angina) AND receiving 1 or more medications for its treatment (eg, nitrates, beta-blockers, and angiotensin converting enzyme inhibitors)

MH2. RSV infection confirmed ≤ 3 days before randomization by a locally available approved or authorized polymerase chain reaction (PCR) assay or alternative nucleic acid-based detection, including a respiratory viral panel, or respiratory pathogen panel. Serologic tests will not be accepted.

MH3. New onset or increased from baseline of ≥ 2 of the following signs and/or symptoms, and at least one sign/symptom of moderate severity at screening and onset ≤ 3 days before randomization:

a) Nasal congestion.

b) Sore throat.

c) Cough.

d) Wheezing.

e) Shortness of breath (ie, dyspnea).

f) Expectoration (ie, sputum production).

MH4. RSV vaccine status:

a) Participants whose only risk factor is age ≥ 60 years (ie, risk factor a) must not have received, at any time, any doses of investigational or licensed vaccine for RSV.

b) For all other participants, receipt of ≥ 1 dose(s) of investigational or licensed RSV vaccine, at any time prior to randomization, is allowed.

Other Inclusion Criteria (OIC)

OIC1. Willing and able to complete the RiiQ prior to first dose and daily throughout study period.

4.3. Exclusion Criteria

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

Medical History/Physical Characteristics

MH1. Currently requiring or expected to require hospitalization within 48 hours after randomization.

MH2. Documented previous infection and/or hospitalization for RSV during the current respiratory virus season.

MH3. Documented respiratory tract infection < 28 days before randomization.

MH4. Documented to be positive for influenza A or B virus, and/or SARS-CoV-2 ≤ 7 days prior to randomization.

MH5. Concurrent infections requiring treatment with any systemic antibacterial, antifungal, or antimycobacterial therapy ≤ 7 days prior to randomization.

MH6. Any acute medical event within 4 weeks of randomization that is **not** associated with the current RSV illness, including percutaneous coronary intervention planned within 4 weeks of randomization.

MH7. Participants with a history of cystic fibrosis.

MH8. Meets criteria for protocol-defined RSV LRTI at screening or enrollment.

MH9. Participants who are immunocompromised, ie, fulfill 1 or more of the criteria below.

a) Have a history of cancer (except for nonmelanoma cancer) and who have received 1 or more doses of chemotherapy or immunotherapy or undergone surgical resection < 12 months prior to randomization.

b) Have received solid organ or hematopoietic stem cell transplant and on immunosuppressive therapy at randomization.

c) Have chronic use of high-dose corticosteroids (ie, ≥ 20 mg of prednisone or equivalent per day administered for ≥ 2 weeks at randomization).

d) Have untreated HIV infection or on active treatment for HIV infection with a CD4 count < 200 cells/mm^3 or CD4 percentage < 15% in the last 6 months.

MH10. Breastfeeding (nursing). If willing to discontinue breastfeeding during 5 days of treatment, participant can be enrolled.

MH11. Unwilling to use protocol-mandated contraception.

MH12. Known hypersensitivity to the study drug, its metabolites, or formulation excipient.

MH13. Decompensated cirrhosis (Child-Pugh Class C) or acute liver injury/failure.

MH14. New or increased dose of systemic corticosteroids ≤ 14 days prior to randomization.

Laboratory Assessments (LA)

LA1. Undergoing dialysis, known history of moderate or severe renal impairment, known CL_{cr} < 60 mL/min (as calculated by Cockroft-Gault {Cockcroft 1976}), or eGFR < 60 mL/min/1.73 m^2 within the preceding 6 months prior to randomization.

a) Potential participants meeting laboratory criterion LA1 may be enrolled if test results available before dosing show that renal function no longer meets this criterion.

LA2. Known history of any of the following abnormal laboratory results (< 6 months prior to randomization) unless confirmed as resolved at screening.

a) ALT ≥ 5 × ULN.

b) Positive urine or serum pregnancy test (Appendix 11.3) or pregnant at screening.

Prior/Concurrent Therapy (PT) or Clinical Study Experience

PT1. Received any approved or authorized, direct-acting antiviral drug or monoclonal antibody against RSV < 28 days or < 5 half-lives, whichever is longer, before randomization.

PT2. Received an investigational product < 28 days or < 5 half-lives, whichever is longer, before randomization.

Other Exclusion Criteria (OEC)

OEC1. Any inability to take study drug or comply with study procedures that, in the opinion of the investigator, would make the participant unsuitable for the study.

5. STUDY INTERVENTION AND CONCOMITANT MEDICATIONS

5.1. Randomization, Blinding, and Treatment Code Access

5.1.1. Randomization

Central randomization will be implemented to minimize bias in the assignment of participants to treatment groups. Participants who meet randomization eligibility criteria will be randomized in a 1:1 ratio to receive ODV 700 mg (2 tablets) twice daily on Day 1 followed by 350 mg (1 tablet) twice daily on Days 2 to 5 or placebo-to-match for 5 days starting on Day 1. The IRT will implement the randomization scheme and assign a participant number. Randomization will be stratified by vaccination status (ever vs never).

5.1.2. Blinding

During the study, participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Study personnel who may be unblinded because of the nature of their function or study role without additional documentation, as specified in Gilead procedural documents, include the following:

- 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.

- Individuals in Patient Safety (PS) who review individual case data and/or group-level summaries contained within the safety database when they are involved in activities such as aggregate report generation, signal management, or expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

- Individuals who are involved in bioanalytical/biomarker data transfer and sample/assay review.

  — The Bioanalytical File Administrator in either Bioanalytical Lab Clinical Data Management or Biomarker and Bioanalytical Operations who facilitates the transfer of bioanalytical (eg, PK, antidrug antibody) files between Gilead and bioanalytical laboratories

  — Individuals in Clinical Virology and Biomarker & Bioanalytical Operations performing sample selection for resistance analysis may be unblinded

  — Bioanalytical Chemistry scientists who monitor the development, validation, and performance of bioanalytical assays

  - The personnel in bioanalytical laboratories involved in sample receipt, analysis, data review, and data transfer
  - Personnel (eg, Biomarker Sciences) not serving on the study management team who review assay results for samples collected per the study procedures
- Research and Development Quality personnel not serving on the study management team to support Quality Assurance activities and/or regulatory agency inspections.
- Biostatisticians and programmers employed by contract research organizations (CRO), may be unblinded for datasets creation and analyses (eg, development of randomization schedule, PK merge with clinical data, and analyses).
- Clinical pharmacologist and pharmacometrician may be unblinded for dataset creation and analysis (eg, PK merge, PopPK dataset, and analyses). Specified personnel in the following departments may be unblinded, if applicable, and granted data access per the applicable procedures:
  - Clinical Pharmacology Sciences for purposes of analysis and/or modeling to support program development planning and/or interpretation of PK and/or PD data, if applicable.

5.1.3. Planned Interim Internal Unblinding

Prior to the primary analysis, there is 1 planned interim analysis (Section 8.2.1). This analysis will be conducted using an internal unblinded team independent of the blinded study team (Gilead Data Review Committee [GDRC]). This group will consist of at least 1 representative from Clinical Development, Biostatistics, and PS, and may include other personnel as necessary. The Gilead medical monitor, other Clinical Development, Biostatistics, or PS personnel directly interacting with the study sites or data processing, or analysis will not participate in the internal unblinded team and will not be unblinded to the participant treatment assignment.

The purpose of the analysis is to evaluate safety, explore treatment effects from primary and secondary endpoints, and to support program development and planning of Phase 3 studies.

Gilead personnel included in the unblinded team will be documented in GDRC charter per Gilead's procedure.

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. 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 intervention 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 treatment 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 of Study Intervention(s)

5.2.1. Study Intervention(s)

Table 2 contains information on dosage form, formulation, dose strengths, sourcing, packaging, storage, handling, and labeling for interventions provided as part of the study.

Table 2. Description and Handling of Study Intervention(s)

Intervention Name	ODV (GS-5245)	Placebo
Dosage form	Tablet	Tablet
Formulation description	ODV tablets, 350 mg, are oval shaped, debossed with "GSI" on 1 side and "5245" on the other side, and film-coated light yellow. ODV tablets, 350 mg, contain GS-5245 drug substance, 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. Placebo tablets contain 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.
Unit dose strength(s)	350 mg	Not applicable
Sourcing	Provided by sponsor or designee	
Packaging, storage, and handling	For both ODV and placebo, 10 tablets are packaged in a 60 mL white, HDPE bottle containing polyester coil. Each bottle is capped using a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminum-faced liner. ODV and placebo tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label.	
Labeling	Study drug(s) to be provided and distributed by the sponsor to study sites in the US and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products) for CTD, or Annex 6 for CTR, as applicable, and/or other local regulations.	

CTD = common technical document; CTR = clinical trial regulation; EU = European Union; HDPE = high-density polyethylene; ODV = obeldesivir; US = United States

5.3. Prior and Concomitant Medications

There are no restrictions on concomitant medications based on the potential for PK drug-drug interaction (DDI) with ODV.

Once randomized, for all participants, medical care, including hospitalization, if required, is not restricted. Additionally, medications used for supportive and symptomatic treatment of RSV are allowed without restriction. Permissible medications include but are not limited to anti-inflammatories (eg, ibuprofen, naproxen), antipyretics (eg, paracetamol/acetaminophen), bronchodilators and inhaled corticosteroids (eg, albuterol, fluticasone), systemic corticosteroids at doses deemed necessary by treating clinicians (eg, can exceed 20 mg of prednisone or equivalent per day for ≥ 2 weeks), and any other locally prescribed or over-the-counter treatments for RSV symptoms.

5.4. Dosage and Administration

5.4.1. Obeldesivir

Obeldesivir will be administered, without regard to food, orally at doses of 700 mg twice daily on Day 1 (ie, 2 tablets each for 2 administrations) followed by 350 mg twice daily on Days 2 to 5 (ie, 1 tablet each for 8 administrations) for a total of 5 days of drug dosing.

On Day 1, 3, and 5, participants will be coming into the clinic in the morning or afternoon. They should withhold either their morning or afternoon dose until they arrive in clinic and that dose should be taken in the clinic.

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. In case the study visit is virtual, drug accountability will be performed virtually, and the participant will be instructed on returning unused study drug bottles.

Each investigational site must keep accountability records that capture:

- The date received, quantity, and condition of study drug bottles.
- The date, participant number, and the quantity of study drug bottles dispensed.
- The date, quantity of used, and unused study drug bottles returned, 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. Study drug accountability records must be filed at the site, and copies provided to Gilead.

If the site does not have an appropriate standard operating procedure for study drug destruction, used and unused study drugs bottles 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 bottle 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 CRO.

6.1. Informed Consent

Written informed consent must be obtained from each participant before initiation of any study related procedures. See Section 9.1.3 for further information regarding informed consent. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study (Section 4.2). The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent 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.

6.1.1. Informed Consent for Optional Research

The site must obtain a specific informed consent for optional research from participants who agree to provide the following, in accordance with applicable regulations:

- Intensive venous and capillary blood PK samples collected on Day 1 and/or Day 5 (up to 4 hours postdose) as part of an optional intensive PK substudy.

- Permission to use the remainder of their already-collected biomarker, and/or PK specimens for optional future research.

The specimens collected for optional future research will be destroyed no later than 15 years after the end of the study or per country requirements, whichever is shorter (Section 9.1.3).

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. If screening and randomization do not occur on the same day, 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. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

6.3. Instructions for Study Procedures

6.3.1. Medical History and Demography

Medical history and demographic information are to be collected according to the Study Procedures Table (Table 1) for each participant at screening as follows:

Review medical history: disease-specific history (including the date of first RSV symptoms), disease-related events (including overall RSV symptoms), available disease treatment history (including RSV vaccinations prior to screening), baseline characteristics, allergies, and medications taken within 30 days of the screening visit.

Obtain demographic information, including sex at birth.

6.3.2. Vital Signs

Vital signs will be recorded according to the Study Procedures Table (Table 1). Vital signs will include blood pressure, heart rate, body temperature, and all vitals will be recorded after the participant has been resting for ≥ 5 minutes.

6.3.3. Physical Examination

Physical examinations will be performed according to the Study Procedures Table (Table 1).

At the screening, baseline (Day 1), and early termination (ET) visits, a complete physical examination should be performed that will 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, and nails; musculoskeletal; and neurological. Genitourinary and reproductive examinations should only be conducted if clinically indicated as determined by the investigator. Symptom-directed physical examinations will be performed on Days 3, 5, 7, 10, 15, and 29, and only during in-person visits.

6.3.4. Clinical Laboratory Assessments

Serum ALT, bilirubin, creatinine, CL_{cr}/eGFR analysis, and urine pregnancy testing (where applicable) will be performed at a local laboratory at screening if deemed necessary by the investigator to confirm eligibility.

All other laboratory analyses will be performed at a central laboratory unless otherwise specified. Reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory analysis data for clinical significance and pathological changes. Laboratory analysis values outside the normal ranges will be flagged and clinical relevance will be assessed by the investigator.

Blood samples for sparse plasma PK and optional intensive plasma PK will be collected according to the Study Procedures Table (Table 1). Intensive PK analysis will be done at a Gilead contracted CRO.

In addition, samples for baseline clinical laboratory assessment will be collected prior to the first study drug dose.

See Table 3 for a summary of the laboratory analytes.

More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator.

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

6.3.4.1. Chemistry

The eGFR will be calculated according to the CKD-EPI creatinine equation 2021 {Delgado 2022, Levey 2010, Levey 2009}.

An online calculator (https://kidney.org/professionals/KDOQI/gfr_calculator) can be used to calculate eGFR and requires values for the serum creatinine, age, and sex with Standardized Assays selected as “Yes” and “Adjust for body surface area” selected as “No”.

Table 3. Laboratory Analytes

Safety Laboratory Measurements		
Chemistry (Serum or Plasma)	**Hematology**	**Other Laboratory Measurements**
Alkaline phosphatase ALT[a] AST Total bilirubin[a] Direct and indirect bilirubin (screening and reflexed from Total bilirubin)[a] Total protein Albumin Bicarbonate BUN Albumin-corrected calcium Chloride CPK Serum creatinine[a] Glucose Phosphorus Magnesium Potassium Sodium Uric acid Lactate dehydrogenase CL_{cr}[a] eGFR[a] Lipase	Hematocrit Hemoglobin Platelet count RBC count WBC count differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils	FSH in amenorrhoeic participants < 54 years of age GS-441524 (PK assessments) Urine/serum pregnancy test[b]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; PK = pharmacokinetic(s); RBC = red blood cell; WBC = white blood cell

a Serum ALT, bilirubin, serum creatinine, CL_{cr}, and eGFR assessments at screening (prior to dosing) are not required unless deemed necessary by the investigator to confirm eligibility, using a local laboratory.

b Urine pregnancy test will be performed at the local laboratory and serum pregnancy test will be performed via central laboratory.

Refer to the Study Procedure Table (Table 1) for collection time points.

6.3.5. Pharmacokinetics

Table 1 summarizes the sparse PK sample collection schedule. Blood samples will be collected relative to study drug administered in the clinic throughout the course of treatment, if 1 dose was administered in the evening of Day 1, PK samples can be collected on Day 6 relative to study drug administration in clinic. Blood samples will be collected for sparse PK assessments after in-clinic dose on Day 1, Day 3, and Day 5, and a single PK sample at the ET visit (if applicable) for all participants as per the Study Procedure Table (Table 1). Participants who consent to the optional intensive PK substudy will not provide samples for sparse PK (Section 6.3.6).

A single PK sample will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose, if applicable. A single PK sample will also be collected at ET visit for all participants who discontinue the study earlier than Day 10, if applicable.

6.3.6. Assessments for Intensive PK Substudy

An optional intensive PK substudy will be performed in a subset of participants who provide consent (approximately 30 participants). In the intensive PK substudy, plasma from venous blood PK samples and capillary blood PK samples will be collected simultaneously relative to study drug administration on Days 1 and 5 (morning or evening dose). Single venous and capillary PK samples will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose, if applicable. Single venous and capillary PK samples will also be collected on ET visit for all participants who discontinue the study earlier than Day 10, if applicable.

6.3.7. Medically Attended Visit and Hospitalization Information

For the purposes of the efficacy analysis, 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.

For the purposes of the efficacy analysis, hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities. This includes specialized acute medical care units within an assisted living facility or nursing home. This does not include hospitalization for the purposes of public health and/or clinical study execution. The date and duration of hospital admission, use of positive pressure ventilation (including NIPPV and mechanical ventilation), and primary reason for hospitalization (including if the hospitalization is related to RSV) will be recorded.

The nature and cause of the visit should be identified, and the cause of the MAV and/or hospitalization (eg, RSV-related or not) will be determined by the investigator. Medically attended visit and hospitalization information should be collected during Days 1, 3, 5, 7, 10, 15, 29, 60, and ET visits as per the Study Procedure Table (Table 1).

6.3.8. Questionnaires/Participant-Reported Outcomes

6.3.8.1. Respiratory Infection Intensity and Impact Questionnaire

The RiiQ will be completed according to the Study Procedures Table (Table 1).

The RiiQ is a patient-reported outcome measure designed to assess symptoms and impacts of RSV infection {Osborne 2023}. The tool asks respondents to indicate the presence, severity, and impact of 6 symptoms related to the upper and lower respiratory tract (eg, congestion, cough, and wheezing), and 7 symptoms related to systemic responses to infection (eg, headache, pain, and fatigue) within the previous 24 hours. Response options range from “None” to “Severe” for the severity rating. For the impact scales, response options for the functional impact scale range from “No difficulty” to “Great difficulty”, response options for the feelings scale range from “Not at all” to “Extremely”, and response options for the concerns scale range from “Not at all concerned” to “Extremely concerned.”

6.3.8.2. Pre-Existing Symptom Questionnaire

The Pre-Existing Symptom Questionnaire will be completed according to the Study Procedures Table (Table 1).

The Pre-Existing Symptom Questionnaire is a patient-reported outcome measure designed to assess the same symptoms as those measured in the RiiQ, focusing on symptoms that were present approximately 1 week prior to the development of RSV infection symptoms. As with the RiiQ, the tool asks respondents to indicate the presence and severity of 6 symptoms related to the upper and lower respiratory tract (eg, congestion, cough, and wheezing), and 7 symptoms related to systemic responses to infection (eg, headache, pain, and fatigue) approximately 1 week prior to development of RSV infection symptoms. As with the RiiQ, response options range from "None" to "Severe".

6.3.8.3. Global Impression of Severity Scales

The Patient Global Impression of Change (PGIC), the Patient Global Impression of Severity (PGIS) and the Health Care Professional Global Impression of Severity (HCPGIS) will be completed according to the Study Procedures Table (Table 1).

The PGIC, PGIS and the HCPGIS are single-item instruments intended to measure a general impression of symptom severity and change. These tools will help to estimate responder definitions for the other participant-reported outcomes. Response options range from "None" to "Severe".

6.3.8.4. EuroQol (5 Dimensions, 5 Levels)

The EQ-5D-5L will be completed according to the Study Procedures Table (Table 1).

The EQ-5D-5L is a HRQOL instrument that evaluates quality of life in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The ED-5D-5L scale allows 243 unique health states or can be converted into EQ-5D index utility scores anchored at 0 for death and 1 for perfect health. The EQ-5D questionnaire also includes a visual analog scale, by which respondents can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status).

6.3.9. Clinical Virology

Midturbinate nasal swab samples will be collected to assess RSV viral load by reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR), potential multiplex respiratory pathogen PCR, potential infectious viral titer assessment, potential resistance testing (by RSV sequencing and/or phenotyping), and potential anti-RSV antibody testing. Nasal swabs will be collected by site personnel on days that the participant is present in the clinic. Nasal swab self-collection will be performed by the participant on days that she/he is not present in the clinic (see Table 1 for details).

6.3.9.1. Nasal Self-swab Training With the Study Participant

On Day 1, the study participants will be invited to practice a nasal self-swab in the presence of study staff to guide them through the instructions and the procedure. Therefore, 2 midturbinate nasal swabs may be collected: 1 by study staff and 1 by the participant. The nasal self-swab training can be repeated at any subsequent visit as needed. If a self-swab is collected as part of the training at any visit, it should be sent to the central laboratory for analysis in addition to the swab collected by study staff. The participant should be reminded by study staff to take a nasal self-swab on Days 7 and 10 if the study visit occurs virtually.

Participants will be provided with self-collection kits and self-swab training on Day 1. Additional kits/training can be provided at subsequent visits as needed.

The participant will be reminded of the storage conditions and return instructions of the swab sample. The self-swab should be returned to the study site or shipped directly to the central laboratory as soon as possible.

If the participant becomes incapable of collecting a nasal self-swab, the swabs may be collected by a family member, caregiver, or health care provider.

6.3.9.2. Virology Samples 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.

6.3.10. Biomarker Testing

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of the study or per country requirements, whichever is shorter (Section 9.1.3).

6.3.10.1. Biomarker Samples to Address the Study Objectives

Biological specimens will be collected from all participants who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dosage selection, and to better understand the biological pathways, biology of RSV or related diseases, and/or the validation of a companion diagnostic for ODV in RSV and related diseases. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to prospectively specify all tests that may be done on the specimens provided. The specific analyses will include but may not be limited to the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state-of-the-art knowledge.

Samples will be collected to measure biomarkers that may include but will not be limited to anti-RSV antibodies (assessment may include evaluating anti-RSV antibody isotypes, titer, quantity, avidity, and/or neutralizing titer) and cytokine profiling from plasma, serum, or midturbinate nasal swab samples collected at the time points specified in the Study Procedures Table (Table 1).

6.3.10.2. Biomarker Samples for Optional Future Research

For participants who provided additional specific consent (Section 6.1.1), any already-collected biomarker, virology, or PK specimens will be stored and retained for optional future research and may be used to advance development of the study drug and/or increase our knowledge and understanding of the biology of RSV and related diseases. These stored samples may be used by Gilead or its research partners for retesting anti-RSV antibodies or cytokines, for testing to learn more about how the study drug has worked, or for clinical laboratory testing to provide additional safety data. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The analysis of optional future research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

6.3.11. 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 CRF. 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.

6.3.12. Concomitant Medications

At each study in-person/virtual visit, the site will record any and all medications taken by the participant since the last in-person/virtual visit or during the visit (as applicable). Concomitant medications include prescription medications, nonprescription medications, therapies, dietary supplements, and minerals.

Any medication or vaccine that the participant is receiving at the time of enrollment or during the study must be recorded along with:

- therapy name
- reasons for use
- dates of administration (including start and end dates)

6.4. Procedures for Early Discontinuation From Study Intervention or From the Study

6.4.1. Procedures for Early Discontinuation From Study Intervention

If a participant discontinues study intervention (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform study-related follow-up and procedures (Section 3.3*).* If this is not possible or acceptable to the participant or investigator, the participant may be partially withdrawn from the study (Section 3.3.1.1.1) to enable collection of study endpoint information or completely withdrawn from the study.

6.4.2. Procedures for Early Discontinuation From the Study

A participant who discontinues the study early will be asked to return to the investigational site within 2 days to attend an ET visit for assessments and procedures specified in the Study Procedure Table (Table 1).

6.4.3. Loss to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to attend protocol-specified visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a scheduled protocol-specified visit (eg, in-person, telephone, or virtual):

The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the protocol-specified visits with at least 3 attempts, including telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's source documents.

Should the participant continue to be unreachable and not responsive within 2 weeks, the participant will be considered lost to follow-up, will be withdrawn from the study, and no additional contact will be required.

6.5. 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, whichever is shorter.

If participants provide additional specific consent for optional future research, residual biological samples may be retained in storage no later than 15 years after the end of the study or per country requirements, whichever is shorter (Section 9.1.3).

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 7.1.4).

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 7.1.4).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form (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).
- Inpatient 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. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

7.1.4. Study Drugs and Gilead Concomitant Medications Special Situations Reports

Special situations 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 report of drug/drug, drug/food, 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.

A "reasonable possibility" of a causal relationship means that there is evidence, facts, and/or other rationale to suggest a causal relationship, rather than a relationship that cannot be ruled out.

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 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Toxicity Grading Scale, Version 2.1 {Division of AIDS 2017}. For each episode, the highest grade attained should be reported as defined in the Toxicity 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, all SAEs and any AEs that are related to protocol-required procedures must be reported on the applicable CRFs.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, throughout the duration of the study including the posttreatment follow-up visit, and report the AEs on the CRFs 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 CRFs and to PS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed. The investigator must report the primary cause of death for any participant who dies during the follow-up period to the sponsor.

Any SAEs and deaths that occur within 30 days of the last dose of study drug or until the Day 60 Follow-up visit, whichever is longer, regardless of causality, should also be reported.

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 PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug special situations that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to PS (Section 7.4.2). Adverse events and SAEs resulting from special situations 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 Situations Report

Special situations 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 PS using the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Medications Report

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

All clinical sequelae in relation to these special situations will be reported as AEs or SAEs at the same time using the AE CRF and/or the SAE CRF. 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 Situations 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 CRF and the SAE narrative section of the Safety Report Form CRF. Results from local laboratory testing done to diagnose and monitor the status of the event should be recorded on the appropriate CRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all initial or follow-up SAE data including updates to the reported event terms on the applicable CRFs in order for the SAE information to be transmitted from the CRFs within 24 hours of the investigator's knowledge of the initial event/updates in order for the SAE information to be transmitted timely to PS. Serious adverse event information must be reported 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, site personnel must record the SAE on the paper Initial or Follow-up SAE Report Form and transmit.by emailing or faxing the report within 24 hours of the investigator's knowledge of the initial event/update using the contact information below:

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 CRF 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 CRFs and transmitted to PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

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

If for any reason it is not possible to record and transmit the SSR information electronically, record the SSR on the paper special situations reporting form and submit 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 CRF 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 CRFs and transmitted to PS.

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 PS using the paper SSR form and transmitted to:

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

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 CRF.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period 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 (Appendix 11.3). Pregnancies should be reported to PS 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 participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to PS 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 PS (email: Safety_FC@gilead.com and 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 of the participant (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 PS; however, if the SAE occurs in a partner, the pregnancy-related SAE will not be captured in CRF but should be reported via the paper pregnancy outcome report form.

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

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States (US) Food and Drug Administration CFR, the European Union (EU) Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014 and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line listings, SADRs, or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014, Gilead or a specified designee will notify worldwide regulatory agencies and the relevant independent ethics committee in concerned Member States of applicable SUSARs 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 or a quarterly SAE line listing notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the institutional review board or independent ethics committee of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

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

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, 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, Toxicity Grading Scale, Version 2.1 {Division of AIDS 2017}. For AEs associated with laboratory abnormalities, the event should be graded based on 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

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor or designee who will have a discussion with the investigator and decide the appropriate course of action. Whether or not the AEs are considered treatment-related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to Day −1 levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

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

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

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

7.7.1. Laboratory Events Meeting Discontinuation Criteria

Laboratory events meeting discontinuation criteria are discussed in Section 3.3.

7.7.2. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.7.3. Grade 3 Laboratory Abnormality or Clinical Event

Participants who have an eGFR < 50 mL/min/1.73 m^2 (by CKD-EPI creatinine equation 2021) will be discontinued from study drug whether considered related to the study drug or not (refer to Section 3.3.1.1).

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 treatment emergent Grade 3 CL_{cr} decrease (by CKD-EPI creatinine equation 2021) or creatinine increase laboratory abnormality, the participant should be followed until the laboratory abnormality returns to baseline or is otherwise explained.

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.

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

7.7.4. 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.

For a treatment emergent Grade 4 CL_{cr} decrease (by CKD-EPI creatinine equation 2021) or creatinine increase laboratory abnormality, the participant should be followed until the laboratory abnormality returns to baseline or is otherwise explained.

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 or designee.

8. STATISTICAL CONSIDERATIONS

This section provides a high-level description of the planned analyses, assessed statistical power with assumptions, and any applicable multiplicity adjustments. Additional details of the statistical methods will be provided in the statistical analysis plan (SAP), 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 efficacy endpoint is the time to alleviation of targeted RSV symptoms as measured by RiiQ through Day 15. Alleviation of targeted symptom is defined as follows:

In participants without preexisting respiratory symptoms:

All targeted symptoms scored as “None” (score = 0) or “Mild” (score = 1) for 2 consecutive assessments.

In participants with preexisting respiratory symptoms:

- Preexisting symptoms that were worse at baseline should have improved by at least 1 point on the RiiQ Symptom Scale from baseline for 2 consecutive assessments; and
- Preexisting symptoms that were present but not worse at baseline should have not worsened from baseline severity for 2 consecutive assessments; and
- Symptoms that were not preexisting at baseline should be scored as “None” (score = 0) or “Mild” (score = 1) on the RiiQ Symptom Scale for 2 consecutive assessments.

The date and time of the first day of the 2 consecutive assessments will be considered the time of symptom alleviation.

Targeted symptoms are the 6 symptoms included in the RiiQ respiratory domain (nasal congestion, sore throat, cough, wheezing, shortness of breath, expectoration [sputum production]).

8.1.2. Secondary Endpoints

8.1.2.1. Time to Sustained Alleviation of Targeted RSV Symptoms as Measured by RiiQ Through Day 15

Sustained alleviation of targeted RSV symptoms is defined similarly to alleviation of targeted RSV symptoms but for 3 consecutive assessments.

8.1.2.2. Time to RSV-related LRTI Through Day 29

Respiratory syncytial virus-related LRTI is defined as:

Based on RiiQ, ≥ 2 of the following symptoms, 1 of which must be reported as at least 'moderate' severity: new or increased cough, new or increased wheezing, new or increased shortness of breath, new or increased expectoration (sputum production) and participant has not met alleviation or endpoints.

8.1.2.3. Time to RSV-related Hospitalization or All-cause Death Through Day 29

Hospitalization is defined in Section 6.3.7 and RSV relatedness will be determined by the investigator.

8.1.2.4. Time to RSV-related Medically Attended Visits or All-cause Death Through Day 29

MAVs are defined in Section 6.3.7 and RSV relatedness will be determined by the investigator

8.1.2.5. Change From Baseline in RSV Viral Load Through Days 3, 5, 7, 10, and 15

8.1.2.6. PK Parameters (AUC_{tau}, C_{trough}, and C_{max}) of GS-441524, as Available

8.2. Planned Analyses

8.2.1. Interim Analysis

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

8.2.1.1. Planned Internal Analysis

A planned internal analysis based upon the primary endpoint will be conducted at the end of Northern hemisphere RSV season (March 2025) or when approximately 50% of planned participants have completed the Day 29 assessments or prematurely discontinued from the study, whichever occurs first. The purpose of the analysis is to evaluate safety, explore treatment effects from primary and secondary endpoints, and to support program development and planning of Phase 3 studies.

A GDRC that includes only internal members independent of study team will review unblinded data.

8.2.2. Primary Analysis

The unblinded primary analysis of the primary endpoint (time to alleviation of targeted RSV symptoms) will be tested at the 1-sided 0.05 significance level. The 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 of the primary endpoint will serve as the final analysis for this endpoint.

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

The analysis sets are defined in Table 4.

Table 4. Analysis Set Definitions

Analysis Set	Description
Full Analysis Set (FAS)	The 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.
Full Analysis Positive Set (FAPS)	The FAPS will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) are respiratory syncytial virus (RSV) positive at baseline by a central laboratory test. This is the primary analysis set for efficacy analyses.
Safety Analysis Set	The primary analysis set for safety analyses is defined as Safety Analysis Set, which includes 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.
Virology Analysis Set	The Virology Analysis Set will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have a baseline RSV viral load greater than or equal to the lower limit of quantitation (LLOQ). Participants will be grouped according to the treatment they received.
Sparse Pharmacokinetics (PK) Analysis Set	The sparse PK Analysis Set will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) had ≥ 1 nonmissing PK concentration datum reported by the PK laboratory for each respective analyte.
Intensive PK Analysis Set	The intensive PK Analysis Set will include all participants who (1) are randomized into the study and enrolled into the optional intensive PK, (2) have received at least 1 dose of study drug, and (3) had ≥ 1 nonmissing PK concentration datum reported by the PK laboratory for each respective analyte.
Biomarker Analysis Set	The Biomarker Analysis Set will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have 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 0 at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

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

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

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

8.4. Demographic and Baseline Characteristics Analysis

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

Demographic summaries will include sex, race/ethnicity, randomization stratification group, and age.

Baseline data will include a summary of weight, height, and body mass index.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

Primary estimand supporting the primary efficacy objective is defined as:

Population: nonhospitalized adult participants 18 years of age or older with acute RSV infection and at least 1 risk factor for severe RSV disease; the study population.

Variable: time to alleviation of targeted RSV symptoms in the absence of rescue medication.

Treatments: ODV and placebo-to-match.

Intercurrent Events: Hospitalization for the treatment of RSV, all-cause death, use of rescue medication, and discontinuation of randomized treatment prior to alleviation of targeted RSV symptoms. Hospitalization for the treatment of RSV or all-cause death means “never achieve alleviation of targeted RSV symptoms” (composite strategy). The use of rescue medication prior to “achieve alleviation of targeted RSV symptoms” means “never achieve alleviation of targeted RSV symptoms” (composite strategy). Discontinuation of randomized treatment will be ignored (treatment policy).

Population Summary: Difference in median time to alleviation of targeted RSV symptoms between ODV and placebo.

The primary estimand is the difference in median time (days) to alleviation of targeted RSV symptoms through Day 15 in the absence of rescue medication or hospitalization for the treatment of RSV between ODV and placebo in adult participants with RSV infection. This will be estimated irrespective of adherence to randomized treatment.

For participants with symptom alleviation by Day 15 (event), time to alleviation of targeted RSV symptom is calculated as symptom alleviation date and time minus the first dose date and time.

For participants who complete Day 15 of the study or discontinue from the study before Day 15 without alleviation of targeted symptoms (censored), the time will be calculated as the last date and time on which the symptom alleviation is assessed by Day 15 minus the first dose date and time or Day 14 whichever occurs first.

Participants who experience RSV-related hospitalization, all-cause death, or discontinuation from the study prior to alleviation of symptoms, use of rescue medications prior to alleviation of symptoms will be censored at Day 15.

The median time to alleviation of targeted RSV symptoms 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 alleviation of RSV symptoms.

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

To support the analysis of the primary endpoint, 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.

A sensitivity analysis using a generalized Hodge-Lehmann estimator for the difference in median time to alleviation of RSV symptoms may be performed.

The Full Analysis Positive Set (FAPS) will be used for the primary efficacy endpoint analysis.

8.5.2. Secondary Analyses

The estimand for time to sustained alleviation of targeted RSV symptoms through Day 15 is defined as:

Population: nonhospitalized adult participants 18 years of age or older with acute RSV infection and at least one risk factor for severe RSV disease; the study population.

Variable: time to sustained alleviation of targeted RSV symptoms in the absence of rescue medication

Treatments: ODV and placebo-to-match.

Intercurrent Events: hospitalization for the treatment of RSV, all-cause death, use of rescue medications, and discontinuation of randomized treatment prior to sustained alleviation of targeted RSV symptoms. Hospitalization for the treatment of RSV or all-cause death means “never achieve sustained alleviation of targeted RSV symptoms” (composite strategy). The use of rescue medications prior to “achieve sustained alleviation of targeted RSV symptoms” means “never achieve sustained alleviation of targeted RSV symptoms” (composite strategy). Discontinuation of randomized treatment will be ignored (treatment policy).

Population Summary: difference in median time to sustained alleviation of targeted RSV symptoms between ODV and placebo.

The estimand for time to sustained alleviation of targeted RSV symptoms through Day 15 is the difference in median time to sustained alleviation of targeted RSV symptoms in the absence of rescue medication or hospitalization for the treatment of RSV between ODV and placebo in the study population. This will be estimated irrespective of adherence to randomized treatment.

The time to sustained alleviation of targeted RSV symptoms through Day 15 will be analyzed in a similar manner to the primary endpoint using the FAPS.

The estimands for time to RSV-related LRTI through Day 29, time to RSV-related hospitalization or all-cause death through Day 29, and time to RSV-related MAVs or all-cause death through Day 29 are defined in Table 5.

Table 5. Estimands for Three Other Secondary Efficacy Endpoints

<table>
<tr><td>Population</td><td colspan="3">Nonhospitalized adult participants 18 years of age or older with acute RSV infection and at least 1 risk factor for severe RSV disease.</td></tr>
<tr><td>Variable/follow-up time</td><td>Time to RSV-related LRTI through Day 29.</td><td>Time to RSV-related hospitalization or all-cause death through Day 29.</td><td>Time to RSV-related MAVs or all-cause death through Day 29.</td></tr>
<tr><td>Treatments</td><td colspan="3">ODV and placebo-to-match.</td></tr>
<tr><td>Intercurrent events and corresponding strategies</td><td></td><td></td><td></td></tr>
<tr><td>Hospitalization for the treatment of RSV or all-cause death</td><td rowspan="2">Composite strategy means “meeting an RSV-related LRTI” on the date of the intercurrent event(s).</td><td>NA</td><td>NA</td></tr>
<tr><td>Use of rescue medications</td><td>Treatment policy means ignoring the occurrence of intercurrent events (using observed outcome).</td><td>Treatment policy means ignoring the occurrence of intercurrent events (using observed outcome).</td></tr>
<tr><td>Discontinuation of randomized treatment</td><td colspan="3">Treatment policy means ignoring the occurrence of intercurrent events (using observed outcome).</td></tr>
<tr><td>Population summary</td><td colspan="3">Hazard ratio,
Kaplan-Meier estimates.</td></tr>
<tr><td>Estimator</td><td colspan="3">Estimate hazard ratio from a Cox regression model with stratification factor as a covariate.</td></tr>
<tr><td rowspan="2">Censoring rules</td><td colspan="3">Participants who complete Day 29 of the study without meeting the endpoint will be censored at Day 29.</td></tr>
<tr><td>Participants who discontinue from the study before Day 29 without RSV-related LRTI will be censored at the last assessment of RiiQ.</td><td colspan="2">Participants who discontinue from the study before Day 29 without meeting the endpoint will be censored at the last study date.</td></tr>
</table>

LRTI: lower respiratory tract infection; MAV = medically attended visit; RiiQ = Respiratory Infection Intensity and Impact Questionnaire; RSV = respiratory syncytial virus; RT-qPCR = reverse transcriptase-quantitative polymerase chain reaction

Detail of the analyses of other secondary endpoints will be included in the SAP.

8.5.3. Adjustments for Multiplicity

No adjustments for multiple comparisons are needed for the primary analysis of this study as only 1 primary endpoint will be tested.

8.5.4. Rescue Medications

Rescue medications are direct-acting antiviral drugs for the treatment of RSV (eg, ribavirin or an investigational product) or monoclonal antibodies for the treatment of RSV (whether approved or unapproved).

8.6. Safety Analysis

Analysis of safety data will be conducted in the Safety Analysis Set (Section 8.3.1). The treatment-emergent period is defined as the time period from the first dose of study drug up to the date of last dose of study drug plus 30 days. All safety data during the treatment-emergent period will be summarized by treatment group (according to the study drug received). Data for the pretreatment and treatment-free follow-up periods will be included in data listings.

The safety variables to be analyzed include exposure to study treatment, AEs, deaths, clinical laboratory test results (hematology and chemistry), and vital sign measurements. Categorical safety data, including number and percentage of participants with AEs and categorizations of laboratory test data, will be summarized using frequencies and percentages. Continuous safety data, including laboratory test data, will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error, and range). Details are noted below.

8.6.1. Extent of Exposure

Data for a participant's extent of exposure to study drug will be generated from the study drug administration and drug accountability 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 based on 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 or any AE that leads to discontinuation of study drug.

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, Toxicity Grading Scale, Version 2.1 {Division of AIDS 2017}. The DAIDS scale is available at:

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

Number and percentage of participants with TELA will be summarized by treatment group. A treatment-emergent laboratory abnormality will be defined as any values that increases at least 1 toxicity grade from baseline during the treatment-emergent period. If baseline data are missing, 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 ≥ 30 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications, medical history, and vital signs will be provided.

8.7. Pharmacokinetic Analysis

PK parameters AUC_{tau}, C_{trough}, and C_{max} will be listed and summarized for GS-441524 using descriptive statistics by treatment for the Sparse PK Analysis Set or the Intensive PK Analysis Set as applicable. Exposure-safety and exposure-efficacy analyses may be conducted as needed if sufficient data are available.

8.8. Sample Size

A total sample size of approximately 240 participants provides at least 80% power to detect a difference of 36 hours (placebo to ODV HR 0.7) between ODV over placebo, assuming a median time to symptom alleviation in the placebo group of 5 days (120 hours), a reduction in median time to symptom alleviation in the ODV group to 3.5 days (84 hours) using a 2-sided significance level of 0.1.

A median time to alleviation of symptoms of 80 to 88 hours in placebo group was reported in CAPSTONE-1 study {Hayden 2018}which included 7 symptoms similar those to be evaluated in this study. A slightly longer median time to symptom alleviation of 5 days (120 hours) was assumed for the placebo group in this Phase 2 study for the nonhospitalized adult participants with ≥ 1 risk factors for severe RSV disease. A 1.5-day (ie, 30%) reduction in median time to alleviation of symptoms in the ODV group compared to the placebo group was assumed to reflect a response that is likely to be clinically meaningful.

The sample size calculation was performed using software EAST (Version 6.5, module for log-rank test given accrual duration and study duration).

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the study drug. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study, as defined in Section 3.4.2.

9.1.2. 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.

9.1.3. 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 (where permitted), the person conducting the consent discussion (investigator or designee), and an impartial witness (if required by IRB/IEC or local requirements). A copy of the signed ICF will be provided to the participant or the participant's legally authorized representative, as applicable.

The ICF will inform participants about genomic testing and/or 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 and/or to allow the use of the remainder of their already-collected specimens for optional future research, 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, whichever is shorter; but participants may at any time request that their stored samples be destroyed.

9.1.4. 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, an 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 and local regulations as appropriate. 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, CRFs, 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.

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

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

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

Case Report Forms

A CRF 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 CRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonEDC vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment CRFs should be completed only after all data

related to eligibility are available. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. In addition to signatures applied to document ongoing oversight and review, the investigator will apply their electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents before any interim, final, or other time points (as instructed by Gilead). At the conclusion of the study, Gilead will provide the site with access to download a read-only electronic archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.6. Investigator Inspections

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

9.1.7. 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 (ICH 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 study agreement. Study results will be made publicly available (including posted to the Clinical Trials Information System and ClinicalTrials.gov) in accordance with local regulatory requirements.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Regulatory and Ethical Considerations

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

- The ethical principles of the Declaration of Helsinki
- ICH Good Clinical Practice
- Applicable laws and regulatory requirements including Regulation (EU) No. 536/2014 (CTR Annex I, Section D, No. 17, Letter a).

9.3.2. 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.

9.3.3. 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 CRF. The study monitor is responsible for routine review of the CRF 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, on-site) are resolved.

9.3.4. 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.

9.3.5. Study Termination

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at their 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 participant′ interests.

9.3.6. Data Protection

Enterprise level technical and organizational controls have been developed at Gilead for the purpose of data protection. This includes user authentication and identification, fine grained access controls, end-to-end data encryption, security monitoring, network segregation, and physical security controls. Users of Gilead systems are provided training for security awareness and privacy.

To prepare for the possibility of a data security breach, Gilead maintains a business continuity and disaster recovery plan and conducts regular disaster recovery testing to ensure that Gilead systems are recoverable if a cyber or data security incident is experienced. Gilead's detailed incident response plan for any cyber or data security incident is based on the following 5 steps: detection, analysis, containment, eradication, and recovery. Gilead's standard clinical study agreement with study sites also includes data privacy language and arrangements in case of data security breaches as follows:

Gilead and institutions will both act in accordance with the applicable data protection law. Furthermore, the study site and Gilead will cooperate with each other to take the necessary measures in order to comply with the applicable data protection law. Both Gilead and the study site shall implement appropriate technical and organizational measures to meet the requirements of the EU General Data Protection Regulation. If either party becomes aware of a personal data breach related to data processed under this agreement, that party shall promptly notify the other party. In such a case, parties will fully cooperate with each other to remedy the personal data breach and promptly fulfill the (statutory) notification obligations. A personal data breach refers to a personal data breach as described in Article 4, Article 33, and Article 34 of the EU General Data Protection Regulation and applicable national data protection laws.

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11. APPENDICES

11.1. Investigator Signature Page

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

A Phase 2 Randomized, Placebo-controlled Study of the Safety and Efficacy of Obeldesivir to Treat Nonhospitalized Adults With Acute Respiratory Syncytial Virus (RSV) Infection

Amendment 2: 21 October 2024

CLINICAL STUDY PROTOCOL ACKNOWLEDGMENT

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. Disaster and Public Health Emergency Risk Assessment and Mitigation Plan

During an ongoing disaster or public health emergency (hereafter referred to as an event), 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 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 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 study procedures. A qualified courier may be used 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. Study staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow-up:

a) Participant 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 adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

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

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

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

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

b) Participant 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 used 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 event will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

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

Mitigation plan: the study 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 event must be reported in the case report form and described in the clinical study report (CSR). Any remote study visits that are conducted in lieu of clinic visits because of the event will be documented as a protocol deviation.

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

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

4) Missing data and data integrity:

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

   Mitigation plan: implications of an event 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 event 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 obeldesivir (ODV; GS-5245) in study participants remains unchanged.

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

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty until becoming postmenopausal 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 ≥ 54 years of age with cessation of previously occurring menses for ≥ 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 medical documentation of permanent sterility.

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

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Obeldesivir (ODV; GS-5245) CCI [redacted]

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 on Days 1 and 15, and at the early termination visit.

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

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

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

Or

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

- Hormonal or nonhormonal intrauterine device
- 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 after initiation of study drug and throughout the duration of the study including the posttreatment follow-up visit. 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 after initiation of study drug and throughout the duration of the study including the posttreatment follow-up visit must also report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

11.4. Questionnaires/Participant-Reported Outcome Instruments

The questionnaire is not included in full since there are no study sites in Europe.

11.5. Country-Specific Requirements

Not applicable.

11.6. Amendment History

A high-level summary of amendment history is provided in tabular form below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

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

11.6.1. Amendment 2 (21 October 2024)

Description and Rationale for Key Changes Included in Amendment 2	Affected Sections
Based on feedback from the Food and Drug Administration (FDA), the Patient Global Impression of Change (PGIC) questionnaire was added.	Table 1 and Section 6.3.8.3
Footnote ‘u’ was added to PGIC procedure to clarify the collection time points.	Table 1
To reduce the burden on participants completing questionnaires throughout the study period, collection of PGIC was removed on Day 5, 7 and 10 and collection of Health Care Professional Global Impression of Severity (HCPGIS) was removed on Day 7 and 10. PGIS and PGIC will not be collected on the same study days and only the Respiratory Infection Intensity and Impact Questionnaire (RiiQ) will be required on days with study visits.	Table 1
Text updated to clarify that the collection of race, ethnicity, sex at birth, and age data allows for the analysis and reporting of safety and efficacy data by demographic subgroups as required by certain health authorities.	Section 4.1
Inclusion criterion was revised to allow the inclusion of a broader population of participants with chronic obstructive pulmonary disease or asthma, ensuring a more representative group of participants who may benefit from the treatment.	Synopsis and Section 4.2
Inclusion criterion was revised to avoid redundancy and clarify that the symptoms must also be present at the time of screening.	Synopsis and Section 4.2
Removed antiviral therapy for concurrent infections to allow for participants taking antiviral therapy to be included in the trial (eg, participants with HIV on antiretrovirals)	Synopsis and Section 4.3
To clarify that participants with any acute medical events not associated with respiratory syncytial virus (RSV) illness are excluded.	Section 4.3
Exclusion criteria were added to ensure that participants enrolled in the study are on a stable dose of systemic corticosteroids prior to randomization.	Section 4.3
Added detail regarding the independent Gilead unblinded team and outlined the purpose of planned interim analysis.	Sections 5.1.3 and 8.2.1.1
Inconsistency was corrected in the text to match Table 1 (footnote k) regarding physical examination.	Section 6.3.3
Corrected error in Table 3, where the text was amended from ‘leucocytes’ to ‘lymphocytes’ for safety laboratory measurements.	Table 3 in Section 6.3.4.1
Blood sample collection on Day 3 was added for sparse PK assessment to ensure consistency in text with Table 1.	Section 6.3.5

Description and Rationale for Key Changes Included in Amendment 2	Affected Sections
To clarify the scheduling of required PK assessments in cases of early discontinuation from study drug and study.	Table 1, Section 6.3.5, and Section 6.3.6,
To clarify that the purpose of the medically attended visit and hospitalization information was for the efficacy analysis, and the definition of hospitalization was expanded to include not only those related to RSV but all hospitalizations.	Table 1 and Section 6.3.7
Text revised to remove redundant language.	Section 6.3.7
Corrected error: cytokine profiling samples will be collected from serum sample .	Section 6.3.10.1
Removed text regarding administration of new therapies to provide flexibility for physicians.	Section 6.3.12
Text for recording dosage information, along with any medication or vaccine, was removed, as this information will not be collected.	Section 6.3.12
Section 6.4.1 created to clarify procedures for early discontinuation from the study drug and from the study.	Section 6.4
Text updated to ensure consistency within the protocol.	Section 6.4.1
Section revised to clarify the intended timing of the early termination visit.	Section 6.4.2
Removed previous Section 6.4.3 (Procedures for End of Study), as there are no procedures planned after Day 60 follow-up visit.	Section 6.4.3
Text for adverse event collection was updated to ensure consistency in follow-up language throughout protocol.	Section 7.3.2
Revised the serious adverse event (SAE) reporting language to clarify recording and reporting requirements for initial and follow-up SAE data for electronic and paper case report forms.	Section 7.4.1.1
Text updated to clarify the definition for RSV-related lower respiratory tract infection.	Section 8.1.2.2
Plasma concentration was removed from the PK analysis, as PK parameters are more relevant for evaluation of PK characteristics.	Synopsis, Section 2, Section 8.1.2.6, and Section 8.7
Corrected text to reflect that the primary estimand supports only primary efficacy objective.	Section 8.5.1
Text updated to clarify that there are no prohibited medications in this study.	Sections 8.5.1
Text updated from ‘symptom alleviation’ to ‘alleviation of targeted RSV symptoms’ to ensure consistency throughout protocol.	Section 8.5.1
Added estimand framework for the 4 secondary endpoints for the secondary analyses.	Section 8.5.2
Added rescue medications in accordance with FDA feedback.	Section 8.5.4
Added justification for assumption of median time to alleviation of symptoms for placebo and obeldesivir groups.	Section 8.8
Revised pregnancy reporting language to be consistent within the protocol.	Appendix 11.3
Minor changes to correct editorial and typographic errors.	Throughout, as needed

11.6.2. Amendment 1 (06 August 2024)

Description and Rationale for Key Changes Included in Amendment 1	Affected Sections
Revisions from the Protocol Clarification Letter 0.0.1 (10 June 2024) are incorporated.	Table 1. Study Procedures Table footnote p; Section 1.5
Removed height measurement requirement at baseline.	Table 1. Study Procedures Table
Clarified that provision of self-swab kits and collection training are optional on Days 3, 5, 7, and 10.	Table 1. Study Procedures Table
Clarified when self-swab collection could take place and specified collection and analysis procedures.	Table 1. Study Procedures Table, footnote p, Section 6.3.9.1
Added the Pre-Existing Symptom Questionnaire.	Table 1. Study Procedures Table; Section 6.3.8.2
Specified that the RiiQ will be administered predose on Day 1 and preferably predose on Days 2-5.	Table 1. Study Procedures Table footnote t
Corrected terminology for analysis of 3 secondary endpoints from “proportion of participants” to “time to event.”	Synopsis, Sections 2, 8.1.2.2, 8.1.2.3, 8.1.2.4, and 8.5.2
Added 4 exploratory endpoints to evaluate the impact of obeldesivir on prevention of intensive care unit admission, need for noninvasive positive pressure ventilation or mechanical ventilation, duration of hospitalization, and the prevalence of persistent symptoms.	Section 2
Clarified information about the Respiratory Infection Intensity and Impact Questionnaire response options.	Section 6.3.8.1
Clarified that adverse and serious adverse event information should be collected until the Day 60 Follow-up visit if the visit occurs later than 30 days after the last dose of study drug.	Sections 7.3.2 and 7.3.3
Clarified handling of missing data and added sensitivity analysis.	Section 8.5.1
Minor changes to correct typographic errors.	Throughout, as needed

11.7. Sponsor Signature Page

GILEAD SCIENCES, INC.
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USA

A Phase 2 Randomized, Placebo-controlled Study of the Safety and Efficacy of Obeldesivir to Treat Nonhospitalized Adults With Acute Respiratory Syncytial Virus (RSV) Infection

Amendment 2: 21 October 2024

APPROVAL OF CLINICAL STUDY PROTOCOL

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

PPD	*[See appended electronic signature]*
Director, Clinical Development	Signature
[See appended electronic signature]	
Date	

Prot-GS-US-685-6819-amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	18-Oct-2024 17:23:30