CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Obeldesivir in Participants From Birth to < 5 Years of Age With Respiratory Syncytial Virus (RSV) Infection
Plain Language Short Title:	Study of Obeldesivir to Treat Children With Respiratory Syncytial Virus (RSV) Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	166945
EU CT Number:	2024-517998-24
ClinicalTrials.gov Identifier:	~~Not Available~~ NCT06784973
Diagnosis or Condition:	RSV Infection
Protocol ID:	GS-US-685-6883
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 27 September 2024

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

°C	degrees Celsius
°F	degrees Fahrenheit
A	alemtuzumab
AEs	adverse events
Ag	antigen
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{tau}	area under the concentration versus time curve over the dosing interval
B	bendamustine
c	cobicistat (Tybost®)
CA	chronological age
CAP	capecitabine
CD4	clusters of differentiation 4
CFR	Code of Federal Regulations
CGI-C	Caregiver Global Impression of Change
CGI-S	Caregiver Global Impression of Severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed concentration of drug
COVID-19	coronavirus disease 2019
COX	cyclooxygenase
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTD	Common Technical Document
CTR	Clinical Trials Regulation
C_{trough}	concentration at the end of the dosing interval
d	day
DAIDS	Division of AIDS
DDI	drug-drug interaction
DMC	data monitoring committee
DS	daytime symptom
E	elvitegravir (Vitekta®)
EC	endothelial cell
ECDC	European Center for Disease Prevention and Control
ECG	electrocardiogram
EDC	Electronic data capture
eg	for example

eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
EQ-5D	EuroQoL (5 dimensions)
EQ-5D-5L	EuroQol (5 dimensions, 5 levels)
EQ-5D-Y	EuroQol-5 Dimension-child specific
EQ-5D-Y-3L	EuroQol-5 Dimension-child specific (3 levels)
ET	early termination
EU	European Union
FAPS	Full Analysis Positive Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
g	grams
GA	gestational age
GRCD	Gilead RSV Caregiver Diary
GS	glutamine synthetase
h	hour
HA	hyaluronic acid
HCPGI-S	Health Care Professional Global Impression of Severity
HDPE	high-density polyethylene
His	histidine
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	investigator's brochure
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
ie	that is
IEC	independent ethics committee
IN	integrase
IND	investigational new drug
IRB	institutional review board
IRT	Interactive Response Technology
J	joule
kg	kilogram
KM	Kaplan-Meier
L	liter
LLOQ	lower limit of quantitation
m	Module

MAVs	medically attended visits
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mL	milliliter
NA	not applicable
NHANES	National Health and Nutrition Examination Survey
No.	Number
O	ofatumumab
ObsRO	observer-reported outcome
ODV	obeldesivir
OS	overnight symptom
P	passage
PCR	polymerase chain reaction
PK	pharmacokinetics
PMA	postmenstrual age
PopPK	population PK
PS	Patient Safety
Q	intercompartmental clearance
-R	resistant
RDV	remdesivir
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
SD	standard deviation
SE	standard error
SRT	Safety Review Team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TELAs	treatment-emergent laboratory abnormalities
CCI	[redacted]
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
vs	versus
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

PROTOCOL SYNOPSIS

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

Study Title: A Phase 2, Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Obeldesivir in Participants From Birth to < 5 Years of Age With Respiratory Syncytial Virus (RSV) Infection

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

Regulatory Agency Identifier Number(s):

IND Number: 166945
EU CT Number: 2024-517998-24
ClinicalTrials.gov Identifier: Not Available

Study Sites Planned: Approximately 100 sites globally in Asia, Australia, the European Economic Area, and North America.

Objectives and Endpoints:

Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of obeldesivir (ODV; GS-5245) in pediatric participants with RSV infection	• Proportion of participants experiencing treatment-emergent adverse events by Day 28 • Proportion of participants experiencing Grade 3 or 4 treatment-emergent laboratory abnormalities by Day 28
• To evaluate the efficacy of ODV on duration of time until alleviation of targeted RSV symptoms in pediatric participants with RSV infection	• Time to alleviation of targeted RSV symptoms by Day 28
Secondary Objectives	**Secondary Endpoints**
• To evaluate the plasma pharmacokinetics (PK) of ODV in pediatric participants with RSV infection	• PK parameters (AUC_{tau}, C_{max}, and C_{trough}) for ODV metabolite, GS-441524
• To evaluate the antiviral activity of ODV on RSV nasal swab viral load in pediatric participants with RSV infection	• Change from baseline in RSV nasal swab viral load at Day 5
• To evaluate the efficacy of ODV on duration of time until sustained alleviation of targeted RSV symptoms in pediatric participants with RSV infection	• Time to sustained alleviation of targeted RSV symptoms by Day 28

• To evaluate the efficacy of ODV on duration of time until resolution of targeted RSV symptoms in pediatric participants with RSV infection	• Time to resolution of targeted RSV symptoms by Day 28
• To evaluate acceptability and palatability of ODV in pediatric participants with RSV infection	• Assessment of palatability and acceptability scores of age-specific formulation as assessed by caregiver at Days 1 and 5

Study Design: This is a Phase 2, randomized, multicenter, double-blind, placebo-controlled study comparing the safety, tolerability, PK, and efficacy of ODV with placebo for the treatment of RSV infection in participants from birth to < 5 years of age.

At least 130 nonhospitalized participants will be randomized in a 2:1 ratio to receive ODV or placebo for CCI

Number of Participants Planned: At least 130 participants are planned to be randomized.

Study Population: Nonhospitalized participants < 5 years of age with RSV infection.

Main Eligibility Criteria:

Main Inclusion Criteria:

General

G1. Participants assigned male or female at birth, from birth to < 5 years of age who meet one of the following weight, gestational age (GA), and postmenstrual age (PMA) criteria, where permitted according to local law and approved nationally and by relevant institutional review board or independent ethics committee:

- Cohort 1: children and infants with weight at screening ≥ 3 kg to < 40 kg (Part A) and ≥ 1.5 kg to < 3 kg (Part B)
  - — Children born at term (ie, ≥ 37 weeks GA) with a chronological age of ≥ 28 days to < 2 years
  - — Preterm children (ie, < 37 weeks GA) with a PMA ≥ 44 weeks to < 2 years chronological age
  - — Children ≥ 2 and < 5 years of chronological age
- Cohort 2: neonates with screening weight ≥ 1.5 kg to < 6 kg
  - — Born at term (ie, ≥ 37 weeks GA) and < 28 days chronological age
  - — Born preterm (ie, < 37 weeks GA) and PMA < 44 weeks

Best estimate of GA and PMA values are acceptable for inclusion criteria.

G2. Caregiver willing and able to provide written informed consent prior to performing study procedures. Participants will provide assent, if possible, in accordance with local requirements and the investigator's discretion.

Medical History/Physical Characteristics

MH1. RSV infection diagnosis ≤ 3 days prior to randomization by a locally available approved or authorized antigen (Ag) test or 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.

MH2. Negative test for influenza A/B, and SARS-CoV-2 infection ≤ 7 days prior to randomization by a locally available approved or authorized Ag test or PCR assay, or alternative nucleic acid–based detection, including a respiratory viral panel, or respiratory pathogen panel. Serologic tests will not be accepted.

MH3. Onset of RSV signs or symptoms ≤ 3 days prior to randomization.

MH4. Presence of at least 1 of the following signs or symptoms of RSV infection at screening and at randomization:

a) Nasal congestion

b) Rhinorrhea

c) Cough

d) Tachypnea

e) Feeding difficulty

f) Disturbed sleep

g) Disturbed activity level

Main Exclusion Criteria:

Medical Conditions

MC1. Currently requiring or expected to require hospitalization for RSV infection within 48 hours after randomization.

MC2. Not expected to survive the current RSV-related illness.

MC3. Documented previous infection and/or hospitalization for RSV during the current respiratory virus season.

MC4. Diagnosed with acute concurrent active systemic infections requiring treatment with systemic antiviral, antibacterial, antifungal, or antimycobacterial therapy, or with any documented respiratory viral infection (other than RSV), ≤ 7 days prior to randomization.

MC5. History of asthma or recurrent wheezing (defined as more than 3 episodes of wheezing in the past year that lasted more than a day and affected sleep).

MC6. Neuromuscular disease that affects swallowing.

MC7. Cystic fibrosis.

MC8. Participants who are immunocompromised, including but not limited to:

a) Have a history of cancer (except for nonmelanoma skin 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 are on immunosuppressive therapy at randomization.

c) Have received systemic biologic agents that are immunosuppressive < 12 months prior to randomization.

d) Have chronic use of high-dose corticosteroids (ie, ≥ 1 mg/kg/day of prednisone or equivalent per day administered for ≥ 2 weeks at randomization).

e) Have untreated HIV infection or on active treatment for HIV infection with a CD4 count below 200 cells/mm3 or CD4 percentage below 20% in the last 6 months.

f) Have an immunocompromising genetic disorder other than immunoglobulin A deficiency.

g) Have any underlying condition for which the investigator considers the participant to be immunocompromised < 12 months prior to randomization.

Laboratory Assessment at Screening

LA1. Alanine aminotransferase ≥ 5 × upper limit of normal (ULN).

LA2. Estimated glomerular filtration rate < 90 mL/min/1.73m^2 using bedside Schwartz formula for participants ≥ 1 year of age; creatinine level above the ULN as defined by the local laboratory and appropriate for the GA and chronological age for participants < 1 year of age.

Prior/Concurrent Therapy or Clinical Study Experience

PT1. Concurrent or previous treatment with other agents with actual or possible direct antiviral activity against RSV, received within 28 days or within 5 half-lives, whichever is longer, prior to randomization.

PT2. Received palivizumab within 100 days, or nirsevimab within 1 year, or other RSV specific monoclonal antibody within 5 half-lives of the antibody, prior to randomization.

PT3. Participant whose mother received RSV vaccination during pregnancy and who is < 1 year old prior to randomization.

PT4. Received an investigational product within 28 days or 5 half-lives, whichever is longer, prior to randomization.

PT5. On renal replacement therapies (hemodialysis, peritoneal dialysis, continuous renal replacement therapy).

Test Product, Dose, and Mode of Administration: Oral ODV[redacted], dose defined per age-weight bands.

Reference Therapy, Dose, and Mode of Administration: Placebo with a dosing schedule same as for the test product.

Duration of Intervention: CCI

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

Statistical Methods:

Efficacy: The median time (days) to symptom alleviation of targeted RSV symptoms along with the associated 95% CI will be estimated by treatment group using the Kaplan-Meier method. A log-rank test will be used to compare the treatment difference in time to alleviation of targeted RSV symptoms between ODV and placebo. Furthermore, a Cox proportional hazards regression model will be used to estimate the hazard ratio and corresponding 95% CI.

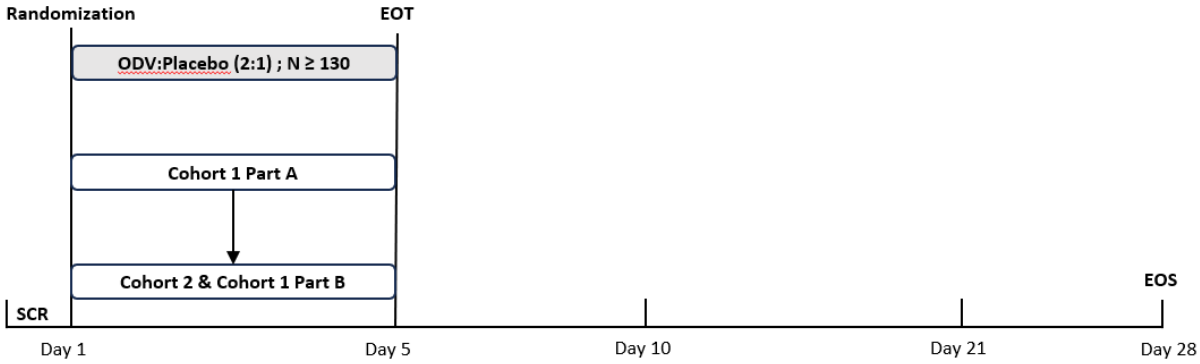
Safety: All safety data during the treatment-emergent period will be summarized by treatment group.

Pharmacokinetics: Plasma concentrations and PK parameters will be listed and summarized for GS-441524 using descriptive statistics.

Sample Size: The target sample size is at least 130 nonhospitalized participants across 2 cohorts with a minimum of 24 participants for Cohort 2. The sample size is determined based on practical considerations. It is not formally powered. The sample size will provide a suitable assessment of the descriptive safety, tolerability, PK, and efficacy profile of ODV.

STUDY SCHEMA

Figure 1. Study Schema



EOS = end of study; EOT = end of treatment; N = number of participants; ODV = obeldesivir (GS-5245); SCR = screening
Screening window is within 48 hours of the Day 1 visit. Day 1 visit may occur the same day as screening.
Cohort definition and staggered enrollment are summarized in Section 3.1.

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table

	Screening[a,b]	Baseline[a]					EOS	ET
Study Day		**Day 1**	**Day 3[c]**	**Day 5**	**Day 10**	**Day 21**	**Day 28**	—
Visit Window	—	—	—	**± 1 d**	**± 2 d**	**± 2 d**	**−4 d/+7 d**	—
Type of Visit	**In Person[d]**					**Virtual[e]**		**In Person[d]**
Assent/caregiver consent	X							
Medical history[f]	X							
Demographics	X							
Documentation of RSV infection[b]	X							
Documentation of SARS-CoV-2 and influenza A/B test negativity[b]	X							
Inclusion/exclusion criteria	X	X						
Complete physical examination[g]	X				X			X
Symptom-directed physical examination[g]		X	X	X				
Body weight	X	X			X			X
Height/length/head circumference[h]	X				X			X
GA and PMA if GA is < 37 weeks for children < 2 years	X							
Vital signs[i]	X	X	X	X	X			X
Hematology, chemistry	X			X	X			X
Neonatal bilirubin panel for all participants < 14 days of age and any neonate as defined in Cohort 2 presenting with jaundice	X							
Nasal midturbinate swab samples[j]		X	X	X	X			X
GRCD[k]		By caregiver–from Days 1 through 28 or ET inclusive						

	Screening[a,b]	Baseline[a]					EOS	ET
Study Day		**Day 1**	**Day 3[c]**	**Day 5**	**Day 10**	**Day 21**	**Day 28**	—
Visit Window	—	—	—	**± 1 d**	**± 2 d**	**± 2 d**	**−4 d/+7 d**	—
Type of Visit	**In Person[d]**					**Virtual[e]**		**In Person[d]**
CGI-S[l]		By caregiver–on Days 1, 3, 5, 10, 28 or ET						
CGI-C[l]		By caregiver–on Days 3, 5, 10, 28 or ET						
HCPGI-S[m]		X	X	X	X			X
WPAI-RSV[n]		By caregiver–on Days 1, 10, 28 or ET						
HRQOL questionnaires[o]		By caregiver–on Days 1, 5, 10, 28 or ET						
PK sample		Refer to Table 2						
Randomization		X						
Study drug dispensation		X						
Study drug administration[p]		Days 1 through 5 inclusive						
Study drug return[q]				X				
Concomitant medications	X	X	X	X	X	X	X	X
MAV/hospitalization/ICU information[r]	X	X	X	X	X	X	X	X
Oxygen supplementation requirements, if hospitalized	X	X	X	X	X	X	X	X
Feeding support information, if hospitalized	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Acceptability and palatability assessment		X		X				

CGI-C = Caregiver Global Impression of Change; CGI-S = Caregiver Global Impression of Severity; d = day; EOS = end of study; EQ-5D-5L = EuroQol (5 dimensions, 5 levels); EQ-5D-Y-3L = EuroQol-5 Dimension–child specific (3 levels); ET = early termination; GA = gestational age; GRCD = Gilead RSV Caregiver Diary; HCPGI-S = Health Care Professional Global Impression of Severity; HRQoL = health-related quality of life; ICU = intensive care unit; MAP = mean arterial pressure; MAV = medically attended visit; ODV = obeldesivir; PK = pharmacokinetic(s); PMA = postmenstrual age; RSV = respiratory syncytial virus; qRT-PCR = quantitative reverse transcriptase-quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WPAI = Work Productivity and Activity Impairment

a Screening window is within 48 hours of the Day 1 visit. Day 1 visit may occur on the same day as screening. If the screening and Day 1 visits are the same day, do not repeat Day 1 assessments.

b Participants anticipated to be eligible for the study and without documented RSV infection ≤ 3 days prior to randomization, and negative influenza A/B, and SARS-CoV-2 testing ≤ 7 days prior to randomization will be consented for RSV, Influenza A/B, and SARS-CoV-2 testing. Participants who are RSV positive and negative for influenza A/B, and SARS-CoV-2 will be approached to consent for entry into the study.
c Day 3 visit is only required if PK samples cannot be collected on Day 5, otherwise it is an optional visit.
d In person is defined as a visit at a medical facility or elsewhere by a health care professional (where permitted).
e Virtual visit is defined as an interaction with a health care professional using telephone or online-based interaction (eg, telehealth, webcast, video conferencing).
f Medical history will include disease-specific history (including the date of first RSV symptom), disease-related events (including RSV symptoms), available disease treatment history (including maternal RSV vaccine or prophylactic treatment for participants), allergies, and medications taken within 30 days of the screening visit.
g A complete physical examination includes source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. Urogenital and reproductive examination should only be completed if clinically indicated. A physical examination is only conducted if a qualified health care professional is available.
h Record length and head circumference for participants < 2 years of age at screening.
i Vital signs include heart rate, body temperature, blood pressure (MAP if available, systolic and diastolic), respiratory rate, and oxygen saturation and will be recorded after the participant has been resting for ≥ 5 minutes.
j The nasal midturbinate swab sample will be used for RSV viral load by qRT-PCR, potential infectious viral titer assessment, potential resistance testing, and respiratory coinfection assessment (Section 6.3.10.1).
k The caregiver symptom assessment will be completed on stipulated days via the GRCD (Appendix 11.5.1), as outlined in Section 6.3.11.1.
l The caregiver global impression of severity and change will be completed on stipulated days via the CGI-S and CGI-C questionnaires, respectively. For days when ODV is administered, the questionnaire should be filled out before study drug administration.
m The health care professional global impression of severity will be completed on in-person visit days via the HCPGI-S questionnaire. The HCPGI-S questionnaire could be completed by a physician or other qualified health care professional. For days when ODV is administered, the questionnaire should be filled out before study drug administration.
n The impact on caregivers on work/education/volunteering will be evaluated on stipulated days via the WPAI-RSV questionnaire. For days when ODV is administered, the questionnaire should be filled out before study drug administration.
o HRQoL will be completed on stipulated days via EQ-5D-Y-3L (for pediatric participants ≥ 4 years of age at screening, to be completed by the caregiver-proxy reported) and EQ-5D-5L (for caregiver, to be completed by caregiver) questionnaires. The EQ-5D-Y-3L assessment will not be required for participants < 4 years of age at screening. For days when ODV is administered, the questionnaire should be filled out before study drug administration.
p Study drug will be administered twice daily, and administration times will be recorded by investigational site personnel or by the caregiver via a diary. Participants receiving only 1 of 2 doses on Day 1 will need to take their last dose on Day 6. Depending on site visit time, participants will be required to withhold their morning or evening dose prior to arriving to the site on Day 5 (or Day 3, if PK samples are collected on Day 3), as the dose will be administered at the site.
q 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 during the subsequent in-person visit.
r 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; ICU admission; or any other in-person visit attended by the participant and a health care professional.

Table 2. PK Sample Collection Schedule

Cohort 1–Part A (Full Sampling Scheme)
N = at least the first 24 participants with weight ≥ 6 kg at baseline
Day 1: 15 minutes (± 3 minutes), 45 minutes (± 9 minutes), and 2 hours (± 24 minutes) postdose
Day 5 (± 1 day) (**or** Day 3): predose, and at 2 hour 30 minutes (± 30 minutes) and 3 hour 30 minutes (± 40 minutes) postdose
Cohort 1–Part A (Reduced Sampling Scheme)
N = rest of the participants in Cohort 1 Part A
Day 5 (± 1 day) (**or** Day 3): predose and at 45 minutes (± 9 minutes), and 1 hour 45 minutes (± 21 minutes) postdose
Cohort 1–Part B
Participants with ≥ 1.5 to < 3 kg weight at baseline
Day 1: 45 minutes (± 9 minutes) postdose **OR** Day 5 (± 1 day) (**or** Day 3): 2 hours (± 24 minutes) postdose
Day 5 (± 1 day) (**or** Day 3): predose (< 5 minutes)
Cohort 2
Participants with weight at baseline ≥ 3 to < 6 kg
Day 1: 45 minutes (± 9 minutes) postdose (optional sample at 15 minutes (± 3 minutes) postdose)
Day 5 (± 1 day) (**or** Day 3): predose and at 2 hour 30 minutes postdose (± 30 minutes)
Participants with weight ≥ 1.5 to < 3 kg at baseline
Day 1: 0.75 hour (± 9 minutes) postdose **OR** Day 5 (± 1 day) (or Day 3): 2 hours (± 24 minutes) postdose
Day 5 (± 1 day) (**or** Day 3): predose (< 5 minutes)
A single PK sample should be collected on Day 5 (±1 day) for all participants who discontinue study drug earlier than the last scheduled dose. **A single PK sample should be collected at ET visit for all participants who discontinue study earlier than Day 10.**

PK = pharmacokinetic(s)
The PK samples must be collected relative to the study drug administered in clinic.
If PK samples cannot be collected on Day 5 (± 1 day), then they should be collected on Day 3; in any case, PK samples should not be collected at both Day 3 and Day 5 visits.
Only if 1 dose was administered in the evening of Day 1, PK samples can be collected on Day 6 relative to the study drug administered in clinic.

1. INTRODUCTION

1.1. Background

Respiratory syncytial virus (RSV) is a circulating pathogen of acute respiratory infections of all ages and is a leading cause of acute lower respiratory tract infections in infants and young children worldwide {Oey 2023}. Among children, the most affected by RSV-associated severe disease are those below 5 years of age while nearly all children are infected by RSV by the age of 2 years {European Center for Disease Prevention and Control (ECDC) 2022, European Centre for Disease Prevention and Control (ECDC). 2023}. The burden of the disease is significant; it has been estimated that there were approximately 33 million cases of RSV-associated lower respiratory tract infection resulting in 3.6 million hospital admissions and 101,400 RSV attributable overall deaths among children below 5 years of age annually worldwide in 2019 {Li 2022}.

The clinical course of RSV infection can consist of a wide range of acute upper and lower respiratory tract infections, leading to symptoms spanning from mild rhinitis to severe bronchiolitis and respiratory tract failure. It is estimated that 25% to 40% of children with a primary infection progress to having a lower respiratory tract infection {Khan 2022}. The main risk factors for severe disease caused by RSV in the pediatric setting are age younger than 6 months, prematurity, bronchopulmonary dysplasia, congenital heart disease, Down syndrome, neuromuscular diseases that prevents effective clearing of the airway, cystic fibrosis and immunodeficiency {Khan 2022}, (EMEA/CHMP/257022/2017; {European Medicines Agency (EMA) 2018}). However, the majority of children hospitalized with RSV-associated disease are previously healthy, with no clinical risk factors for severe disease {Hall 2009}. Limited data are available about the prevalence of risk factors for severe disease in the outpatient setting. A prospective, population-based surveillance of acute respiratory infections among children < 5 years of age conducted in the United States (US) reported that 27% of 355 outpatient children had underlying conditions associated with high risk for severe RSV-related illness {Hall 2009}.

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 (DDI), 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 infection.

1.2. Background on Study Intervention(s)

A list of study interventions and their marketing authorization status is provided in Appendix 11.2.

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).

1.2.1.2. Relevant Nonclinical Data

For further information on ODV, refer to the current IB.

1.2.1.3. Clinical Studies of ODV

Obeldesivir has been evaluated in the COVID-19 clinical development program. Early and late phase studies in the ODV COVID-19 program characterized the pharmacokinetics (PK) profile and evaluated the DDI potential of ODV. Obeldesivir was safe and well tolerated at single doses of 100 mg to 1600 mg and multiple doses of 500 mg twice daily and 900 mg once daily for CCI In 2 Phase 3 studies, ODV CCI CCI, and it was found to be safe and well tolerated in adults and adolescents with COVID-19 (approximately 2400). In a Phase 2 study, ODV CCI CCI was found to be safe and well tolerated in 3 pediatric participants (≥ 6 to < 18 years of age) with COVID-19.

For further information on ODV refer to the current IB.

1.2.2. Information About Auxillary Medicinal Products/Noninvestigational Medicinal Products

Auxiliary medicinal products/noninvestigational medicinal products are not used in this study.

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 oral treatments for the pediatric population {Borchers 2013, Oey 2023, Rocca 2021}.

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 nucleoside 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 nonhospitalized pediatric participants from birth to < 5 years of age with RSV infection 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 symptom improvement, a shorter duration of illness, reduced progression to severe disease, and reduced incidence of medically attended visits (MAVs) or hospitalizations.

1.4. Rationale for Dose Selection of Study Drug

The PK 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 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 doses up to 1600 mg and multiple doses of CCI , 500 mg twice daily, and 900 mg once daily for CCI in healthy participants and CCI CCI in participants with COVID-19.

A preliminary 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 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. The preliminary model was also used to facilitate the initial development of the age-appropriate pediatric CCI formulation. This model was updated with the PK data obtained from the relative bioavailability study of ODV (GS-US-611-6468) that evaluated the pediatric CCI formulation relative to the ODV tablet and from data obtained from 3 pediatric participants from the Phase 2/3 pediatric study of ODV in treatment of COVID-19 (GS-US-611-6464).

After incorporating an age-based renal maturation function in the pediatric PopPK model, exposures were extrapolated to pediatrics to select ODV doses to be evaluated in RSV pediatric participants < 5 years of age. Virtual pediatric subpopulations were used for the dose projection simulations, based on information from 3 public databases: World Health Organization (WHO), National Health and Nutrition Examination Survey (NHANES), and Fenton Preterm Growth Calculations.

For each age-weight group, ODV doses were selected to match predicted GS-441524 exposures associated with the Phase 2 adult dosing regimen (Study GS-US-685-6819). CCI [redacted] CCI 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. Predicted plasma exposures of GS-441524 following this adult dosing regimen were used as the target exposure level for selecting pediatric ODV doses.

The developed PopPK model was used to select ODV doses for pediatric participants who will be enrolled in Cohort 1 Part A of this Phase 2 study (GS-US-685-6883). Upon availability of PK and safety data from a subset of participants in Cohort 1, the PopPK model will be updated to confirm ODV doses to be administered in Cohort 1 Part B and Cohort 2 and allow enrollment of neonate participants in this study (Section 3.1).

1.5. Benefit-Risk Assessment for the Study

Participants in this study will receive either ODV or placebo. Conducting a Phase 2 study to investigate the safety, tolerability, PK, 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 was found to be safe and well tolerated in participants evaluated in the COVID-19 program.

Obeldesivir has the potential benefit to be the first oral RSV treatment for children.

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.

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 (Section 7.7).

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

2. OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints
• To evaluate the safety and tolerability of ODV in pediatric participants with RSV infection	• Proportion of participants experiencing treatment-emergent adverse events (TEAEs) by Day 28 • Proportion of participants experiencing Grade 3 or 4 treatment-emergent laboratory abnormalities (TELAs) by Day 28
• To evaluate the efficacy of ODV on duration of time until alleviation of targeted RSV symptoms in pediatric participants with RSV infection	• Time to alleviation of targeted RSV symptoms by Day 28
Secondary Objectives	**Secondary Endpoints**
• To evaluate the plasma PK of ODV in pediatric participants with RSV infection	• PK parameters (AUC_{tau}, C_{max}, and C_{trough}) for ODV metabolite, GS-441524
• To evaluate the antiviral activity of ODV on RSV nasal swab viral load in pediatric participants with RSV infection	• Change from baseline in RSV nasal swab viral load at Day 5
• To evaluate the efficacy of ODV on duration of time until sustained alleviation of targeted RSV symptoms in pediatric participants with RSV infection	• Time to sustained alleviation of targeted RSV symptoms by Day 28
• To evaluate the efficacy of ODV on duration of time until resolution of targeted RSV symptoms in pediatric participants with RSV infection	• Time to resolution of targeted RSV symptoms by Day 28
• To evaluate acceptability and palatability of ODV in pediatric participants with RSV infection	• Assessment of palatability and acceptability scores of the age-specific formulation as assessed by caregiver at Days 1 and 5
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the efficacy of ODV on duration of time until alleviation of targeted RSV symptoms, CCI [redacted], in pediatric participants with RSV infection	• Time to alleviation of targeted RSV symptoms by Day 28, CCI [redacted]
• To evaluate the efficacy of ODV on duration of time until sustained alleviation of targeted RSV symptoms, CCI [redacted] in pediatric participants with RSV infection	• Time to sustained alleviation of targeted RSV symptoms by Day 28, CCI [redacted]
• To evaluate the efficacy of ODV on duration of time until resolution of symptoms CCI [redacted] in pediatric participants with RSV infection	• Time to resolution of targeted RSV symptoms by Day 28, CCI [redacted]

• To evaluate the efficacy of ODV on severity of RSV symptoms in pediatric participants with RSV infection	[redacted] • Proportion of participants with RSV symptom alleviation per Health Care Professional Global Impression of Severity (HCPGI-S) scale at Days 1, 3, 5, and 10 • Proportion of participants with RSV symptom alleviation per Caregiver Global Impression of Severity (CGI-S) scale at Days 1, 3, 5, 10, and 28 • Proportion of participants with RSV symptom alleviation per Caregiver Global Impression of Change (CGI-C) scale by Days 3, 5, 10, and 28
• To evaluate the impact of ODV on child health utility using the EuroQol-5 Dimension–child specific (3 levels) (EQ-5D-Y-3L; including visual analogue scale [VAS]) to be completed by the caregiver for the pediatric participant (proxy reported)	• Change from baseline in index scores at Days 5, 10, and 28 • Change from baseline in the VAS at Days 5, 10, and 28
• To evaluate the impact of ODV on caregiver health utility using the EuroQol (5 dimensions, 5 levels) (EQ-5D-5L; including VAS) to be completed by the caregiver	• Change from baseline in index scores for the caregiver at Days 5, 10, and 28 • Change from baseline in the VAS for the caregiver at Days 5, 10, and 28
• To evaluate the impact of ODV on caregiver burden using the Work Productivity and Activity Impairment (WPAI)-RSV questionnaire	• Change from previous visit in absenteeism/presenteeism in work/education/volunteering at Days 10 and 28
• To evaluate the antiviral activity of ODV on RSV nasal swab throughout the study period in pediatric participants with RSV infection	• Proportion of participants with negative RSV nasal swab viral load and infectious viral titer at Days 1, 3, 5, and 10, as applicable • Change from baseline in RSV nasal swab viral load at Days 3 and 10, as applicable • Change from baseline in RSV nasal swab infectious viral titer at Days 3, 5, and 10, as applicable
• To evaluate the emergence of viral resistance to ODV in pediatric participants with RSV infection	• Emergence of viral resistance to ODV
• To evaluate the efficacy of ODV in treating RSV in pediatric participants with respiratory coinfection	• Symptom duration and virologic response in pediatric participants with respiratory coinfections
• To evaluate the efficacy of ODV on duration of time until occurrence of RSV-related MAVs[a], hospitalization[b], or death as assessed by the investigator in pediatric participants with RSV infection	• Time to RSV-related MAVs, RSV-related hospitalization, or RSV-related death by Day 28
• To evaluate the efficacy of ODV on duration of time until occurrence of MAVs[a], hospitalization[b],	• Time to all-cause MAVs, all-cause hospitalization, or all-cause death by Day 28

or death from any cause in pediatric participants with RSV infection	

a. MAV is defined as a medical visit attended in person by the participant and a health care professional, including primary pediatrician, urgent care visit, and emergency department visit.
b. Hospitalization is defined as observation at an emergency department or hospital admission for > 24 hours.

3. STUDY DESIGN

3.1. Study Design Overview

This is a Phase 2, randomized, multicenter, double-blind, placebo-controlled study comparing the safety, tolerability, PK, and efficacy of ODV with placebo for the treatment of RSV infection in participants from birth to < 5 years of age with and without risk factors for severe RSV disease.

At least 130 nonhospitalized participants are planned to be randomized for this study across the following cohorts:

- Cohort 1 (approximately 106 participants): children and infants with weight at screening ≥ 3 kg to < 40 kg (Part A) and ≥ 1.5 kg to < 3 kg (Part B)
    - Children born at term (ie, ≥ 37 weeks gestational age [GA]) and ≥ 28 days to < 2 years chronological age
    - Preterm children (ie, < 37 weeks GA) with postmenstrual age (PMA) ≥ 44 weeks to < 2 years chronological age
    - Children ≥ 2 to < 5 years chronological age
- Cohort 2 (N ≥ 24): neonates with screening weight ≥ 1.5 kg to < 6 kg
    - Born at term (ie, ≥ 37 weeks GA) and < 28 days chronological age
    - Born preterm (ie, < 37 weeks GA) and PMA < 44 weeks

This study will initially enroll participants in Cohort 1 Part A. Enrollment in Cohort 2 and Cohort 1 Part B will be initiated following a review of safety and available PK data by a Safety Review Team (SRT) and a review of safety data by an independent data monitoring committee (DMC) after approximately 24 participants from Cohort 1 Part A have completed at least Day 5 assessments or prematurely discontinued the study. All cohorts will then continue to enroll participants in parallel. It is noteworthy that there will be no enrollment pause in Cohort 1 Part A during SRT/DMC reviews.

As ODV doses are defined based on weight groups, participants will be divided into different weight groups within each cohort. Within each cohort/weight group, enrolled participants will be randomized in a 2:1 ratio to receive ODV:placebo for CCI. Within each cohort, the dose administered to a participant will be based on their weight at baseline. The weight group categorizations for both cohorts are outlined in Section 5.4.

Gilead Sciences (Gilead) may close, delay, or suspend enrollment for any cohort or weight group at any time. Thus, not all cohorts or weight groups may be open for enrollment during the study.

3.1.1. Dose Selection/Modification for Cohorts

The first SRT will confirm the ODV doses being used in Cohort 1 Part A after review of safety and available PK data from approximately 24 participants from Cohort 1 Part A who have completed at least Day 5 assessments or prematurely discontinued from the study. In addition, the first SRT will also confirm the ODV doses to be evaluated in Cohort 2 and Cohort 1 Part B.

The second SRT will confirm the ODV doses being used in Cohort 2 (and Cohort 1 Part B, if data are available) after review of safety and available PK data from approximately 12 participants from Cohort 2 who have completed at least Day 5 assessments or prematurely discontinued from the study.

The composition and summary of the SRT is provided in Appendix 11.3.1.

3.2. Duration of Intervention

CCI [redacted]

3.2.1. Poststudy Care

The long-term care of the participant will remain the responsibility of their primary treating physician.

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:

- Any serious adverse event (SAE) suspected to be related to study drug.
- Any Grade 3 or higher AE suspected to be related to study drug.
- An AE or worsening of clinical condition requiring clinical intervention, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- 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.
- Caregiver request to discontinue for any reason (Section 3.3.1.1.1).
- Participant noncompliance.

- Any Grade 3 or higher clinically significant laboratory abnormality (if confirmed by repeat testing) suspected to be related to study drug.
- Alanine aminotransferase (ALT) ≥ 5 × upper limit of normal (ULN).
- Participants ≥ 1 year of age who have a confirmed eGFR < 80 mL/min/1.73 m^2 by bedside Schwartz formula.
- Participants < 1 year of age who have a confirmed creatinine level above the ULN as defined by the local laboratory and appropriate for the GA and chronological age.

3.3.1.1.1. Partial Withdrawal

Participants/caregivers 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 in the following instances:

- Caregiver request to discontinue for any reason (Section 3.3.1.1.1).
- Discontinuation of the study by sponsor.
- Participant noncompliance.
- Loss to follow-up (Section 6.4.1).
- Disaster or public health emergency (Appendix 11.4 provides information on risk assessment and mitigation that may allow continued participation.)
- Withdrawal of consent/assent.
- Death.

3.3.2. Early Study Termination

The study will be discontinued in the following instances:

- Decision by Gilead 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 completes 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 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, dosing diary), central laboratory, local laboratory, and specialty laboratory (for virology and PK data), caregiver or health care professional–reported outcomes, and Interactive Response Technology (IRT). Electronic data capture (EDC) is not considered source data.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

At least 130 nonhospitalized participants will be randomized into the study. The target population is nonhospitalized participants from birth to < 5 years of age with RSV infection, with and without risk factors for severe RSV disease.

Approximately 30% of nonhospitalized participants will have at least 1 of the risk factors for severe RSV disease as listed below:

- Infants ≤ 6 months of age.
- Infants < 1 years of age and born prematurely (GA < 37 weeks).
- Children with congenital heart disease.
- Children with bronchopulmonary dysplasia.
- Children with down syndrome.
- Children with neuromuscular conditions including cerebral palsy.

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, gender, and age data allow for the analysis and reporting of safety and efficacy data by demographic subgroups as required by certain health authorities.

4.1.1. Participant Replacement

Replacement participants will not be enrolled for participants who discontinue the study due to a study drug-related AE.

4.2. Inclusion Criteria

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

General

G1. Participants assigned male or female at birth, from birth to < 5 years of age who meet one of the following weight, GA, and PMA criteria, where permitted according to local law and approved nationally and by relevant IRB or IEC:

- Cohort 1: children and infants with weight at screening ≥ 3 kg to < 40 kg (Part A) and ≥ 1.5 kg to < 3 kg (Part B)

    — Children born at term (ie, ≥ 37 weeks GA) with a chronological age of ≥ 28 days to < 2 years

    — Preterm children (ie, < 37 weeks GA) with a PMA ≥ 44 weeks to < 2 years chronological age

    — Children ≥ 2 and < 5 years of chronological age

- Cohort 2: neonates with weight at screening ≥ 1.5 kg to < 6 kg

    — Born at term (ie, ≥ 37 weeks GA) and < 28 days chronological age

    — Born preterm (ie, < 37 weeks GA) and PMA < 44 weeks

Best estimate of GA and PMA values are acceptable for inclusion criteria.

G2. Caregiver willing and able to provide written informed consent prior to performing study procedures. Participants will provide assent, if possible, in accordance with local requirements and the investigator's discretion.

Medical History/Physical Characteristics

MH1. RSV infection diagnosis ≤ 3 days prior to randomization by a locally available approved or authorized antigen (Ag) test or 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.

MH2. Negative test for influenza A/B, and SARS-CoV-2 infection ≤ 7 days prior to randomization by a locally available approved or authorized Ag test or PCR assay, or alternative nucleic acid–based detection, including a respiratory viral panel, or respiratory pathogen panel. Serologic tests will not be accepted.

MH3. Onset of RSV signs or symptoms ≤ 3 days prior to randomization.

MH4. Presence of at least 1 of the following signs or symptoms of RSV infection at screening and at randomization:

a) Nasal congestion

b) Rhinorrhea

c) Cough

d) Tachypnea

e) Feeding difficulty

f) Disturbed sleep

g) Disturbed activity level

Laboratory Assessment

Not applicable.

Other Inclusion Criteria

OI1. Caregiver willing and able to complete the observer-reported outcomes 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 Conditions

MC1. Currently requiring or expected to require hospitalization for RSV infection within 48 hours after randomization.

MC2. Not expected to survive the current RSV-related illness.

MC3. Documented previous infection and/or hospitalization for RSV during the current respiratory virus season.

MC4. Diagnosed with acute concurrent active systemic infections requiring treatment with systemic antiviral, antibacterial, antifungal, or antimycobacterial therapy, or with any documented respiratory viral infection (other than RSV), ≤ 7 days prior to randomization.

MC5. History of asthma or recurrent wheezing (defined as more than 3 episodes of wheezing in the past year that lasted more than a day and affected sleep).

MC6. Neuromuscular disease that affects swallowing.

MC7. Cystic fibrosis.

MC8. Participants who are immunocompromised, including but not limited to:

a) Have a history of cancer (except for nonmelanoma skin 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 are on immunosuppressive therapy at randomization.

c) Have received systemic biologic agents that are immunosuppressive < 12 months prior to randomization.

d) Have chronic use of high-dose corticosteroids (ie, ≥ 1 mg/kg/day of prednisone or equivalent per day administered for ≥ 2 weeks at randomization).

e) Have untreated HIV infection or on active treatment for HIV infection with a CD4 count below 200 cells/mm^3 or CD4 percentage below 20% in the last 6 months.

f) Have an immunocompromising genetic disorder other than immunoglobulin A deficiency.

g) Have any underlying condition for which the investigator considers the participant to be immunocompromised < 12 months prior to randomization.

MC9. Known hypersensitivity to the study drug, its metabolites, or formulation excipient.

MC10. Any underlying condition that in the opinion of the investigator makes the patient not an appropriate candidate for the clinical study.

Laboratory Assessment at Screening

LA1. ALT ≥ 5 × ULN.

LA2. eGFR < 90 mL/min/1.73m^2 using bedside Schwartz formula for participants ≥ 1 year of age; creatinine level above the ULN as defined by the local laboratory and appropriate for the GA and chronological age for participants < 1 year of age.

Prior/Concurrent Therapy or Clinical Study Experience

PT1. Concurrent or previous treatment with other agents with actual or possible direct antiviral activity against RSV, received within 28 days or 5 half-lives, whichever is longer, prior to randomization.

PT2. Received palivizumab within 100 days, or nirsevimab within 1 year, or other RSV specific monoclonal antibody within 5 half-lives of the antibody, prior to randomization.

PT3. Participant whose mother received RSV vaccination during pregnancy and who is < 1 year old prior to randomization.

PT4. Received an investigational product within 28 days or 5 half-lives, whichever is longer, prior to randomization.

PT5. On renal replacement therapies (hemodialysis, peritoneal dialysis, continuous renal replacement therapy).

Other Exclusion Criteria

OE1. Any inability to take study drug or comply with study procedures that, in 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. Baseline/Day 1 may occur on the same day as screening. Within each cohort/weight group, participants who meet randomization eligibility criteria will be randomized in a 2:1 ratio to receive ODV twice daily, or placebo twice daily for CCI starting on Day 1. The IRT will implement the randomization scheme and assign a participant number.

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 functional 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 Laboratory 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 and 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 statistical programmers employed by contract research organizations may be unblinded for datasets creation and analyses (eg, development of randomization schedule, PK merge with clinical data, PopPK datasets and analyses).

- Clinical pharmacologist and pharmacometrician may be unblinded for dataset creation and analysis (eg, PK merge, PopPK datasets 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 pharmacodynamic data, if applicable.

5.1.3. Planned Interim Internal Unblinding

If required, a Gilead internal unblinded team independent of the blinded study team may be assembled, to assess the safety, PK, and/or efficacy of ODV for planning and development of this compound. 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 and Clinical Development personnel directly interacting with the study site will not be unblinded to the participant treatment assignment.

Gilead personnel included in the internal unblinded team will be documented per Gilead's procedures.

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 intervention 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 3 contains information on dosage form, formulation, dose strengths, sourcing, packaging, storage, handling, and labeling for interventions provided as part of the study.

CCI [redacted]

Intervention Name	ODV	Placebo
CCI [redacted]	CCI	CCI
CCI [redacted]	CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]	CCI [redacted]
Sourcing	Provided by sponsor or designee.	
Packaging, storage, and handling	ODV CCI and placebo CCI are packaged in white, HDPE bottles with silica gel desiccant. Each bottle is closed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner. ODV CCI and placebo CCI should be stored below 30 °C (86 °F). Storage conditions are specified on the label. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused investigational product should be disposed of in accordance with local requirements.	
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 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 Trials Regulation; EU = European Union; FDA = Food and Drug Administration; HDPE = high-density polyethylene; ODV = obeldesivir; US = United States; CCI [redacted]

5.3. Prior and Concomitant Medications

There are no restrictions on concomitant medications based on the potential for PK 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.

5.4. Dosage and Administration

Participants randomized to receive ODV will be administered ODV CCI orally at dose levels defined in Table 4 without regard to food. Participants randomized to receive placebo will be administered placebo CCI orally without regard to food.

As summarized in Section 3.1.1. the SRT will confirm the ODV doses to be evaluated in Cohort 2 and Cohort 1 Part B from the dose ranges specified in Table 4.

Table 4 Obeldesivir Doses Based on Weight/Age Groups

Cohort	Group	Full Term	Preterm	Weight at Baseline (kg)	ODV Dosing Regimen (mg)[a]
Children and infants with baseline weight ≥ 3 kg to < 40 kg (Part A) and ≥ 1.5 kg to < 3 kg (Part B)					
1 Part A	1	If born full term: (GA ≥ 37 weeks and CA ≥ 28 days	If born preterm: GA < 37 weeks and PMA ≥ 44 weeks	≥ 20 to < 40	291.5 mg twice on Day 1 and 175 mg twice daily on Days 2 to 5
	2			≥ 12 to < 20	175 mg twice on Day 1 and 116.6 mg twice daily on Days 2 to 5
	3			≥ 6 to < 12	116.6 mg twice on Day 1 and 58.3 mg twice daily on Days 2 to 5
	4			≥ 3 to < 6	50 mg twice on Day 1 and 30 mg twice daily on Days 2 to 5
CCI					

Cohort	Group	Full Term	Preterm	Weight at Baseline (kg)	ODV Dosing Regimen (mg)[a]
Neonates with baseline weight ≥ 1.5 kg to < 6 kg					
CCI					CCI

CA = chronological age; GA = gestational age; NA = not applicable; ODV = obeldesivir; PMA = postmenstrual age
a Participants receiving only 1 of 2 doses on Day 1 will need to take their last dose on Day 6.
b The SRT will confirm the ODV doses to be evaluated in Cohort 2 and Cohort 1 Part B from the specified dose ranges (Section 3.1.1).

5.4.1. Obeldesivir Dosing Preparation

Guidance will be provided for the formulation preparation, handling, and storage conditions for the ODV CCI and the placebo CCI

5.5. Accountability for Study Drug

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 and/or CCI tablets dispensed.

- The date, quantity of used and unused study drug bottle and/or CCI tablets 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 are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

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

6. STUDY PROCEDURES

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

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

6.1. Informed Consent

Each participant and/or participant's caregiver must sign an informed consent form (ICF) or assent form, as required by IRB/IEC/local or national requirements, prior to the conduct of any screening procedures.

6.2. Screening, Participants Enrollment, and Treatment Assignment

Participants will be screened within 48 hours before enrollment in the study. Each participant will be assigned a unique screening number using an IRT. 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 48 hours of screening for randomization into the study.

6.3. Instructions for Study Procedures

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-required procedures, on the AE case report form (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.

6.3.2. Concomitant Medications

Refer to Table 1 for concomitant medication collection time point(s). Concomitant medications include prescription medications, nonprescription medications, therapies, dietary supplements, and minerals.

In case new therapies need to be administered during the study, the benefit-risk to the participant should be carefully assessed and consideration given to the timing of any necessary introduction of new therapies.

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

6.3.3. Medical History and Demographics

Medical history and demographic information are to be collected for each participant at screening as follows:

- Review medical history including disease-specific history (including the date of first RSV symptom), disease-related events (including RSV symptoms), available disease treatment history (including maternal RSV vaccine or prophylactic treatment for participants), allergies, and medications taken within 30 days of the screening visit.

- Obtain demographic information including sex at birth.

6.3.4. Vital Signs

Refer to Table 1 for vital signs collection time points.

Vital signs will include, heart rate, body temperature, blood pressure (mean arterial pressure if available, systolic and diastolic), respiratory rate, oxygen saturation, and will be recorded after the participant has been resting for ≥ 5 minutes. In addition, body weight and height/length will be collected.

6.3.5. Physical Examination

Refer to Table 1 for physical examinations assessment time points. A physical examination will only be conducted by a qualified health care professional.

A complete physical examination includes source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. Urogenital and reproductive examination should only be conducted if clinically indicated.

6.3.6. Clinical Laboratory Assessments

Refer to Table 1 for clinical laboratory assessment time points.

The following laboratory assessments will be performed at a local laboratory:

Hematology: Complete blood count with differential

Comprehensive metabolite panel (Chemistry 14): ALT, albumin, alkaline phosphatase, aspartate aminotransferase (AST), direct and total bilirubin (and neonatal bilirubin for participants aged < 14 days and neonates as defined in Cohort 2 presenting with jaundice), blood urea nitrogen, creatinine, eGFR using bedside Schwartz formula if ≥ 1 year of age, ionized calcium, carbon dioxide, chloride, total serum protein, potassium, sodium.

The smallest possible blood vials, such as microtainer tubes, should be used for participants weighing < 15 kg.

Clinical laboratory assessments at other days may be conducted if required by clinical need or local practice. The results of all clinical laboratory tests that are performed as part of clinical care, even if not required by the protocol, should be reported.

6.3.7. Age-Specific Assessments

Refer to Table 1 for the following age-specific assessments:

- Age:
  - Birth month and year for participants ≥ 2 years of age
  - Birth date for participant < 2 years of age
- Length and head circumference for participants < 2 years of age
- Best estimate of GA and PMA for participants with GA < 37 weeks and < 2 years of age
- Neonatal bilirubin panel for all participants < 14 days of age and any neonate as defined in Cohort 2 presenting with jaundice

6.3.8. Medically Attended Visits and Hospitalization

Refer to Table 1 for MAVs, hospitalization, intensive care unit (ICU), oxygen supplementation, and feeding support information collection time points.

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.

Hospitalization is defined as ≥ 24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs. 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.

If a participant is hospitalized, then the following will be collected, as applicable:

- oxygenation/oxygen supplementation information.
- feeding support information.

If a participant is admitted to the ICU during the study, then the ICU admission information will be collected, as applicable.

6.3.9. Pharmacokinetics

Table 2 summarizes the PK sample collection schedule. Blood samples will be collected relative to the study drug administered in 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 the study drug administered in clinic.

A full sampling scheme will be performed in at least the first 24 participants with ≥ 6 kg weight at baseline from Cohort 1 Part A. For the rest of participants in Cohort 1 Part A, as well as participants in Cohort 1 Part B and Cohort 2, reduced sampling schemes are considered as detailed in Table 2.

A single PK sample should be collected on Day 5 (± 1 day) for all participants who discontinue the study drug earlier than the last scheduled dose. A single PK sample should be collected at the early termination (ET) visit for all participants who discontinue study earlier than Day 10.

The PK sampling scheme ensures that the drawn blood volumes are within the daily and monthly recommended limits for the respective age/weight groups.

6.3.10. Clinical Virology

6.3.10.1. Virology Samples to Address Study Objectives

Midturbinate nasal swab samples will be collected (Table 1) to assess RSV viral load by reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR), respiratory coinfection by multiplex respiratory pathogen PCR, potential infectious viral titer assessment, and potential resistance testing (by sequencing and/or phenotyping). Nasal swabs will be collected by site personnel on days that the participant is present in the clinic or at participants home for sites with that service available.

6.3.10.2. Virology Sample Storage

Any remaining specimens from nasal swab samples collected during the study will be stored and retained for possible future virology-related testing. These stored samples may be used by the sponsor 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.

6.3.11. Questionnaires–Caregiver/Health Care Professional–Reported Outcomes

6.3.11.1. Gilead RSV Caregiver Diary

CCI [redacted]. Previous qualitative and quantitative research established the content validity of the GRCD in populations of caregivers of children < 24 months of age who were hospitalized and not hospitalized due to RSV {Lewis 2018}. Additionally, a preliminary psychometric evaluation of the GRCD, conducted using data collected in the context of an observational primary data collection study in a usual care setting, supported the scoring and structure of the GRCD, as well as the validity, reliability, and responsiveness of the tool for assessing RSV in children < 24 months of age {Williams 2018}. CCI [redacted]

CCI [redacted]
CCI [redacted]

CCI [redacted]
CCI [redacted]

The GRCD will be administered at all visits specified in Table 1 and should be administered prior to study drug administration, where applicable. The GRCD should be ideally filled out by the same caregiver throughout the study.

CCI [redacted]

6.3.11.2. Global Impression of Severity Scales

CCI [redacted]

The CGI-S and the HCPGI-S, with a 24-hour recall period, will be administered at all visits specified in Table 1 and for days when ODV is administered, the questionnaire should be filled out prior to study drug administration.

CCI [redacted]

6.3.11.3. Global Impression of Change Scale

CCI [redacted]

The CGI-C, with a recall period since they started the study drug, will be administered at all visits specified in Table 1 and for days when ODV is administered, the questionnaire should be filled out prior to study drug administration.

CCI [redacted]

6.3.11.4. Health-related Quality of Life

The EuroQol-5 Dimensions (EQ-5D) is a health utility instrument that evaluates quality of life in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D 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 analogue 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) {EuroQol Research Foundation 2024a}.

The EQ-5D-Y will be completed, by the caregiver for pediatric participants ≥ 4 years of age at screening (proxy reported), at all visits specified in Table 1. The EQ-5D-Y assessment will not be required for participants < 4 years of age at screening {EuroQol Research Foundation 2024b}. The EQ-5D-5L will be completed by the caregiver at all visits specified in Table 1.

For days when ODV is administered, both EQ-5D-Y (3 levels; EQ-5D-Y-3L) and EQ-5D-5L should be filled out prior to study drug administration.

6.3.11.5. Work Productivity and Activity Impairment–Respiratory Syncytial Virus

The WPAI questionnaire is an instrument to measure impairments in work and activities. The scale consists of 6 questions that generate a scaled expression of 4 main outcomes: percentage of work missed due to health, percentage of impairment while working due to health, percentage of overall work impairment due to health, and percentage of activity impairment due to health.

The WPAI-RSV will be administered at all visits specified in Table 1 and should be administered prior to study drug administration, where applicable.

The questionnaire is provided in Appendix 11.5.4.

6.3.11.6. Palatability and Acceptability Questionnaires

To assess palatability and acceptability of study drug, the caregiver will rate acceptability and palatability of the applicable formulation using a 5-point facial recognition scale.

The caregiver may answer additional questions regarding preparation and dosing of the age-appropriate formulation.

The questionnaire will be administered at all visits specified in Table 1 after study drug administration.

6.3.11.7. Procedures to Minimize Missing Questionnaire Data

To minimize missing data, the following steps are put in place to help participants remain compliant with questionnaire completion per protocol-required time points:

- The caregiver may receive reminders/notifications on stipulated days (Table 1) to complete the questionnaire.
- Site staff and the study monitor will review questionnaire data completion reports to monitor compliance.
- Site staff will contact the caregiver regarding the missing data (or their close contact in case of nonresponse, where feasible).
- The caregiver may be provided with a Value Sheet (if available) to highlight the significance of questionnaire data and importance of participant compliance for the purpose of this study.

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

If a participant discontinues study intervention early (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.

If a participant discontinues from the study early, the participant will be asked to return to the investigational site within 2 days to attend an ET visit for assessment and procedures specified in Table 1.

6.4.1. 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 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 and will be withdrawn from the study, and no additional contact will be required.

6.4.2. Procedures for End of Study

A participant who completes or discontinues from the study early will have an end-of-study (or ET) visit for assessments and procedures specified in Table 1.

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.

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 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 Division of AIDS (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.

The DAIDS scale is available at:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

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, until 30 days after last administration of study drug 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 after the posttreatment follow-up visit but within 30 days of the last dose of study drug, 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.

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

All clinical sequelae in relation to these 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 SAE data on the applicable CRFs in order for the SAE information to be transmitted from the CRF to PS within 24 hours of the investigator's knowledge of the event from the time of the ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SAE information electronically, 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

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

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

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable 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 IEC 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 IRB or IEC 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 [ECG], x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the

definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2.. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 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

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

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

7.7.1. Laboratory Events Meeting Discontinuation Criteria

Laboratory events meeting discontinuation criteria are discussed in Section 3.3.1.1.

7.7.2. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.7.3. Grades 3 and 4 Laboratory Abnormality or Clinical Event

For a clinically nonsignificant Grade 3 or higher laboratory abnormality, study drug may be continued without dose interruption.

For a clinically significant Grade 3 or higher laboratory abnormality, confirmed by repeat testing, or clinical event, **that is considered to be related** to the study drug, **the participants will be discontinued from the study drug**. The participant should be managed according to local practice. The participant should be followed as clinically indicated until the laboratory value returns to baseline or is otherwise explained, whichever occurs first, or until the clinical event resolves or stabilizes.

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

All Grade 3 or higher laboratory abnormalities occurring by Day 10, regardless of clinical significance, should be retested until they have resolved or returned to baseline levels, or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

A clinically significant Grade 3 or higher laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

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

Grade 3 and Grade 4 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 Grade 3 and Grade 4 AEs must be monitored periodically until symptoms subside, and any Grade 3 or Grade 4 abnormal laboratory values should be retested until they have resolved or returned to baseline levels, or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

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

8. STATISTICAL CONSIDERATIONS

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 time to alleviation of targeted RSV symptoms by Day 28.

For nonhospitalized participants, alleviation of targeted RSV symptoms is defined as:

- Improvement in score by at least 1 point reported at 2 daily consecutive assessments (ie, 24-hour period) for any targeted RSV symptom for which the baseline score is > 1 (ie, ranging from very mild to very severe)
- No increase in score reported at 2 daily consecutive assessments (ie, 24-hour period) for any targeted RSV symptom for which the baseline is 1 (ie, no symptom)

The date of the first day of the 2 daily consecutive assessments will be considered the time of alleviation of targeted RSV symptoms. Note: GRCD is collected twice daily as both daytime and overnight symptoms are assessed.

Targeted RSV symptoms refers to the RSV symptoms included in the GRCD global composite score (cough, respiratory signs, RSV signs, behavior impact) assessed by GRCD.

8.1.2. Secondary Endpoints

8.1.2.1. Time to Sustained Alleviation of Targeted RSV Symptoms by Day 28

For nonhospitalized participants, sustained alleviation of targeted RSV symptoms is defined similarly to alleviation of targeted RSV symptoms but for 3 daily consecutive assessments (ie, 48-hour period).

8.1.2.2. Time to Resolution of Targeted RSV Symptoms by Day 28

For nonhospitalized participants, resolution of targeted RSV symptoms is defined as:

- Improvement in score resulting in score of ≤ 2 (ie, no symptom or very mild) reported at 2 daily consecutive assessments (ie, 24-hour period) for any targeted RSV symptom for which the baseline score is > 2 (ie, ranging from mild to very severe)

- No increase or an improvement in score resulting in score of ≤ 2 (ie, no symptom or very mild) reported at 2 daily consecutive assessments (ie, 24-hour period) for any targeted RSV symptom for which the baseline score is 2 (ie, very mild)

- No increase in score reported at 2 daily consecutive assessments (ie, 24-hour period) for any targeted RSV symptom for which the baseline score is 1 (ie, no symptom)

The date of the first day of the 2 daily consecutive assessments will be considered the time of resolution of targeted RSV symptoms. Note: GRCD is collected twice daily as both daytime and overnight symptoms are assessed.

Targeted RSV symptoms refers to the RSV symptoms included in the GRCD global composite score (cough, respiratory signs, RSV signs, behavior impact) assessed by the GRCD.

8.2. Planned Analyses

8.2.1. Interim Analysis

Before the final analysis, interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program. Also, interim analyses may be used for publication and/or presentation at scientific meetings.

8.2.1.1. Dose Confirmation Analysis

There will be 2 planned SRT meetings in this study.

The first SRT will confirm the ODV doses being used in Cohort 1 Part A after review of safety and available PK data from approximately 24 participants from Cohort 1 Part A who have completed at least Day 5 assessments or prematurely discontinued from the study. In addition, the first SRT will also confirm the ODV doses to be evaluated in Cohort 2 and Cohort 1 Part B.

The second SRT will confirm the ODV doses being used in Cohort 2 (and Cohort 1 Part B, if data are available) after review of safety and available PK data from approximately 12 participants from Cohort 2 who have completed at least Day 5 assessments or prematurely discontinued from the study.

Further details will be provided in the SRT charter.

8.2.1.2. Data Monitoring Committee Analysis

There will be 2 planned DMC meetings in this study.

An external DMC will review the progress of the study and perform interim review(s) of safety and available PK data.

The first DMC meeting will be conducted after approximately 24 participants in Cohort 1 Part A have completed at least their Day 5 assessments or prematurely discontinued from the study. This meeting will also confirm the initiation of Cohort 2 and Cohort 1 Part B.

The second DMC meeting will be conducted after approximately 12 participants in Cohort 2 have completed at least their Day 5 assessments or prematurely discontinued from the study.

The DMC membership, activities, and meeting schedule will be defined in a DMC charter. No formal stopping rules will be used by the DMC for safety outcomes. A clinical assessment will instead be made to determine if the nature, frequency, and severity of AEs associated with a study drug regimen warrant the early termination of the study in the best interest of the participants.

8.2.2. Final Analysis

The unblinded final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

The analysis sets are defined in Table 5.

Table 5. Analysis Set Definitions

Analysis Set	Description
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.
FAPS	The primary analysis set for efficacy analyses is defined as all participants who (1) are randomized into the study, (2) have received at least 1 dose of study drug, (3) are RSV positive at baseline by a central laboratory test. Participants will be grouped according to the treatment to which they were randomized.
Safety Analysis Set	The primary analysis set for safety analyses is defined as 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 LLOQ. Participants will be grouped according to the treatment they received.

Analysis Set	Description
PK Analysis Set	The PK Analysis Set will include all participants who (1) are randomized in the study, (2) have received ≥ 1 dose of study drug, and (3) have ≥ 1 nonmissing result for PK evaluation of GS-441524. Participants will be grouped according to the treatment they received.

FAPS = Full Analysis Positive Set; FAS = Full Analysis Set; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); RSV = respiratory syncytial virus

8.3.2. Data Handling Conventions

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

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

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

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

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

8.4. Demographic and Baseline Characteristics Analysis

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

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

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

No formal statistical testing is planned.

8.5. Efficacy Analysis

For all efficacy analyses, the Full Analysis Positive Set (Section 8.3.1) will be used, unless otherwise specified. No formal statistical testing is planned.

8.5.1. Primary Analysis

The analysis of the primary efficacy endpoint will be based on the primary estimand outlined in Table 6.

Table 6. Primary Estimand for Primary Efficacy Endpoint

Attribute	Details
Target population	Study population as defined by protocol eligibility criteria
Treatment condition(s)	ODV and placebo, regardless of treatment discontinuation/modification, RSV-related hospitalization, or RSV-related MAVs
Variable	Time (days) to alleviation of targeted RSV symptoms by Day 28 in the absence of rescue medication and all-cause death
Handling of ICEs	The following scenarios if they occur prior to alleviation of targeted RSV symptoms by Day 28 will be considered: • Treatment discontinuation/modification: treatment policy (included as part of the treatment condition(s) attribute) • Use of rescue medication: composite strategy (included as part of the variable attribute). Note: details on the applicable rescue medications will be provided in the SAP • All-cause death: composite strategy (included as part of the variable attribute) • RSV-related hospitalization: treatment policy (included as part of the treatment condition(s) attribute) • RSV-related MAVs: treatment policy (included as part of the treatment condition(s) attribute)
Population-level summary	Difference in median variable (as defined in the variable attribute) between ODV and placebo

ICE = intercurrent events; MAV = medically attended visit; ODV = obeldesivir; RSV = respiratory syncytial virus; SAP = statistical analysis plan

The estimate of the primary estimand is the difference in median time (days) to alleviation of targeted RSV symptoms by Day 28 in the absence of rescue medication and all-cause death between ODV and placebo as defined by protocol eligibility criteria. This will be estimated regardless of treatment discontinuation/modification, RSV-related hospitalization, or RSV-related MAVs (ie, treatment policy).

The time to alleviation of targeted RSV symptoms by Day 28 is calculated as the symptom alleviation date minus the first dose date. In case, prior to data cutoff a participant:

- Completes the study without alleviation of targeted RSV symptoms
- Prematurely discontinues from the study prior to alleviation of targeted RSV symptoms (due to AE, lack of efficacy, investigator's discretion, noncompliance with study drug, protocol violation, participant decision, lost to follow-up)

The time to sustained alleviation of targeted RSV symptoms will be calculated as the last date on which the symptom alleviation is assessed minus the first dose date or Day 27, whichever occurs first.

If a participant takes rescue medication or dies prior to alleviation of targeted RSV symptoms (ie, composite strategy) the participant will be censored at the last date on which symptom alleviation is assessed prior to the start of rescue medication or death.

The median time (days) to symptom alleviation along with the associated 95% CI will be estimated by treatment group using the Kaplan-Meier (KM) method. A log-rank test will be used to compare the treatment difference in time to alleviation of targeted RSV symptoms between ODV and placebo. The proportion of participants with alleviation of targeted RSV symptoms using KM estimates will be provided in tables and plots by treatment group.

Furthermore, to support the analysis of the primary efficacy endpoint, a Cox proportional hazards regression model will be used to estimate the hazard ratio and corresponding 95% CI.

Sensitivity analysis associated with the primary endpoint may be performed:

- A nonparametric analysis where the median time (days) to symptom alleviation of targeted RSV symptoms along with the associated 95% CI will be estimated by treatment group using the methodology of Hodges-Lehmann.
- Missing targeted RSV symptom alleviation status will be imputed using multiple imputation assuming missing at random.
- Restricted mean time to alleviation of targeted RSV symptoms will be provided by treatment group.

Subgroup analysis of the primary efficacy endpoint will be performed to investigate the impact of important demographic and other baseline characteristics (eg, cohort, sex, race, risk factors for severe RSV disease). In addition, if important respiratory coinfections are identified at Day 1, a further subgroup analysis of the primary efficacy endpoint to assess the impact of respiratory coinfections will be performed. More details on subgroup analyses will be provided in the SAP.

The number and percentage of participants experiencing an intercurrent event by treatment group will also be provided.

8.5.2. Secondary Analyses

The estimand for time to sustained alleviation of targeted RSV symptoms by Day 28 is the difference in median time (days) to sustained alleviation of targeted RSV symptoms in the absence of rescue medication and all-cause death between ODV and placebo in the study population. This will be estimated regardless of treatment discontinuation/modification, RSV-related hospitalization, or RSV-related MAVs. Similar analyses as outlined in Section 8.5.1 will be performed.

The estimand for time to resolution of targeted RSV symptoms by Day 28 is the difference in median time (days) to resolution of targeted RSV symptoms in the absence of rescue medication and all-cause death between ODV and placebo in the study population. This will be estimated

regardless of treatment discontinuation/modification, RSV-related hospitalization, or RSV-related MAVs. Similar analyses as outlined in Section 8.5.1 will be performed.

Analysis of virology data will be conducted in the Virology Analysis Set (Section 8.3.1). The estimand for change from baseline in RSV nasal swab viral load at Day 5 is the difference in least square means of change from baseline in RSV nasal swab viral load at Day 5 in the absence of rescue medication and all-cause death between ODV and placebo in the study population. This will be estimated regardless of treatment discontinuation/modification, RSV-related hospitalization, or RSV-related MAVs. The difference in change from baseline in RSV nasal swab viral load at Day 5 between ODV and placebo along with the associated 95% CI will be constructed using a mixed-effects model for repeated measures, including baseline RSV nasal swab viral load as a covariate and treatment group (ODV vs placebo), visit, and treatment group-by-visit interaction as fixed effects. The change from baseline in RSV nasal swab viral load at Day 5 will also be summarized by treatment group using descriptive statistics.

8.5.3. Adjustments for Multiplicity

No adjustments for multiplicity are planned for this study as the primary efficacy evaluation is exploratory in nature. Nominal 95% CIs and tests performed at the nominal 0.05 alpha level will be provided.

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 to the earlier of 30 days after the last dose of study drug. 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 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 the primary safety endpoints associated with the 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, SD, SE, and range). No formal statistical testing is planned.

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 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 lowest-level term will be attached to the clinical database.

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

Summaries (number and percentage of participants) of TEAEs (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 the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Toxicity Grading Scale, Version 2.1 {Division of AIDS 2017}.

The number and percentage of participants with TELAs will be summarized by treatment group. A TELA will be defined as any value that increases ≥ 1 toxicity grade from baseline during the treatment-emergent period. If baseline data are missing, any graded laboratory 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, vital signs, and palatability and acceptability will be provided.

8.7. Pharmacokinetic Analysis

Plasma concentrations and PK parameters will be listed and summarized for GS-441524 using descriptive statistics for the PK Analysis Set.

A complete list of PK parameters will be provided in the SAP.

Exposure-safety and exposure-efficacy analyses may be conducted as needed if sufficient data are available.

8.8. Sample Size

The target sample size is at least 130 nonhospitalized participants across 2 cohorts with a minimum of 24 participants for Cohort 2.

Within each cohort/weight group, participants will be randomized in a 2:1 ratio to ODV or placebo. The sample size is determined based on practical considerations. It is not formally powered. The sample size will provide a suitable assessment of the descriptive safety, tolerability, PK, and efficacy profile of ODV.

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 (or assent as applicable) 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. In addition to the study-specific informed

consent form to be signed by each participant participating in the study, participants will be required to document additional consent to provide additional samples for optional genomic research. 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 date 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/assent
- 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.

9.1.6. Case Report Forms

A CRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the 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 nonelectronic data capture 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.

9.1.7. 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.

9.1.8. 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 trial 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.

10. REFERENCES

Doe JF, Doe JP, Smith FT Jr, Smith WJ. A study to evaluate the safety and effectiveness of a novel anti-inflammatory agent in Subjects with advanced arthritis of the hands. Arthritis Rheum 1994;29 Suppl 190:988-97.

Jones MK, Chen Y, Davis RO, Vasquez RC, Williams PR, Wilson D, et al. Incidence of community acquired pneumonia (CAP) in New York City public schools. Am J Pub Health 1998;44(Pt 7):54-9.

Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus--a comprehensive review. Clin Rev Allergy Immunol 2013;45 (3):331-79.

Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1. July, 2017.

European Center for Disease Prevention and Control (ECDC). Intensified circulation of respiratory syncytial virus (RSV) and associated hospital burden in the EU/EEA. Stockholm: 2022:

European Centre for Disease Prevention and Control (ECDC). RSV virus expected to add pressure on hospitals in many EU/EEA countries this season. Available at: https://www.ecdc.europa.eu/en/news-events/rsv-virus-expected-add-pressure-hospitals-many-eueea-countries-season. Updated on 23 Nov 2022. Accessed on 04 Aug 2023. 2023:

European Medicines Agency (EMA). Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease. EMA/CHMP/257022/2017. October 2018. 2018:

EuroQol Research Foundation. EQ-5D-5L: About. Available at: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/. Accessed: 26 September. 2024a:

EuroQol Research Foundation. EQ-5D-5Y-3L: About, accessed at https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-y-3l/. Accessed: 26 September. 2024b:

Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The Burden of Respiratory Syncytial Virus Infection in Young Children. N Engl J Med 2009;360 (6):588-98.

Khan L. Respiratory Syncytial Virus. Pediatr Ann 2022;51 (10):e376-e8.

Lewis S, DeMuro C, Block SL, Senders S, Wisman P, Toback S, et al. Development of a novel observer-reported outcome measure for the assessment of Respiratory Syncytial Virus (RSV) infection symptoms in pediatric clinical trials. Journal of Patient-Reported Outcomes 2018;2:9.

Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis [Author Manuscript]. Lancet 2022;399 (10340):2047-64.

Oey A, McClure M, Symons JA, Chanda S, Fry J, Smith PF, et al. Lumicitabine, an orally administered nucleoside analog, in infants hospitalized with respiratory syncytial virus (RSV) infection: Safety, efficacy, and pharmacokinetic results. PLoS One 2023;18 (7):e0288271.

Rocca A, Biagi C, Scarpini S, Dondi A, Vandini S, Pierantoni L, et al. Passive Immunoprophylaxis against Respiratory Syncytial Virus in Children: Where Are We Now? Int J Mol Sci 2021;22 (7).

Williams V, DeMuro C, Lewis S, Williams N, Wolynn T, Wisman P, et al. Psychometric evaluation of a caregiver diary for the assessment of symptoms of respiratory syncytial virus. J Patient Rep Outcomes 2018;2 (1):10.

World Health Organization (WHO). Respiratory Syncytial Virus (RSV) disease. Available at: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/respiratory-syncytial-virus-disease Accessed: 02 May. 2024:

11. APPENDICES

11.1. Investigator Signature Page

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

A Phase 2, Randomized, Multicenter, Double-blind, Placebo-controlled, Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Obeldesivir in Participants From Birth to < 5 Years of Age With Respiratory Syncytial Virus (RSV) Infection

Original: 27 September 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. Marketing Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in ≥ 1 Country Following EU Regulation No. 536/2014	Authorized in ≥ 1 ICH Country	Authorized by Swissmedic
Obeldesivir	Study drug	No[a]	No	No

EU = European Union; ICH = International Council for Harmonisation
a Rationale described in Section 1.

11.3. Committees

11.3.1. Safety Review Team and Charter

A Safety Review Team (SRT) will make dose selection/modification decisions for individual cohorts based on data described in Section 3.1.1. Decisions made will be communicated to the study sites.

A SRT charter defining the team membership, meeting conduct, and decision-making process will be agreed upon by all team members before the first participant is dosed in the study. The data reviewed at the team meetings to make dose confirmation decisions will be defined in the charter. The quality control checks performed on the data reviewed and used for making dose selection and/or dose modification decisions will also be described in the charter.

Source data verification may not be performed before SRT meetings. Alternative data quality control checks that are performed on data used to make dose escalation decisions will be described in the SRT charter (or similar document).

11.3.2. Data Monitoring Committee

A multidisciplinary data monitoring committee (DMC) consisting of non–Gilead Sciences (Gilead) personnel will review the progress of the study, perform interim reviews of data, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse events associated with study treatment warrant the early termination of the study in the best interests of the participant, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design. No formal stopping rules will be used by the DMC for safety outcomes.

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

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

There will be 2 planned DMC meetings in this study. The first DMC meeting will be conducted after approximately 24 participants in Cohort 1 Part A have completed at least their Day 5 assessments or prematurely discontinued from the study. This meeting will also confirm the initiation of Cohort 2 and Cohort 1 Part B.

The second DMC meeting will be conducted after approximately 12 participants in Cohort 2 have completed at least their Day 5 assessments or prematurely discontinued from the study.

11.4. 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 virtual visit, via phone or video conferencing, must be performed before study drug resupply, if applicable. 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 (IRB)/regulatory authority as applicable and with sponsor's approval.

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

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

2) Participant safety monitoring and follow-up:

    c) 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.

d) 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.

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

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

3) Protocol and monitoring compliance:

f) 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.

g) 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.

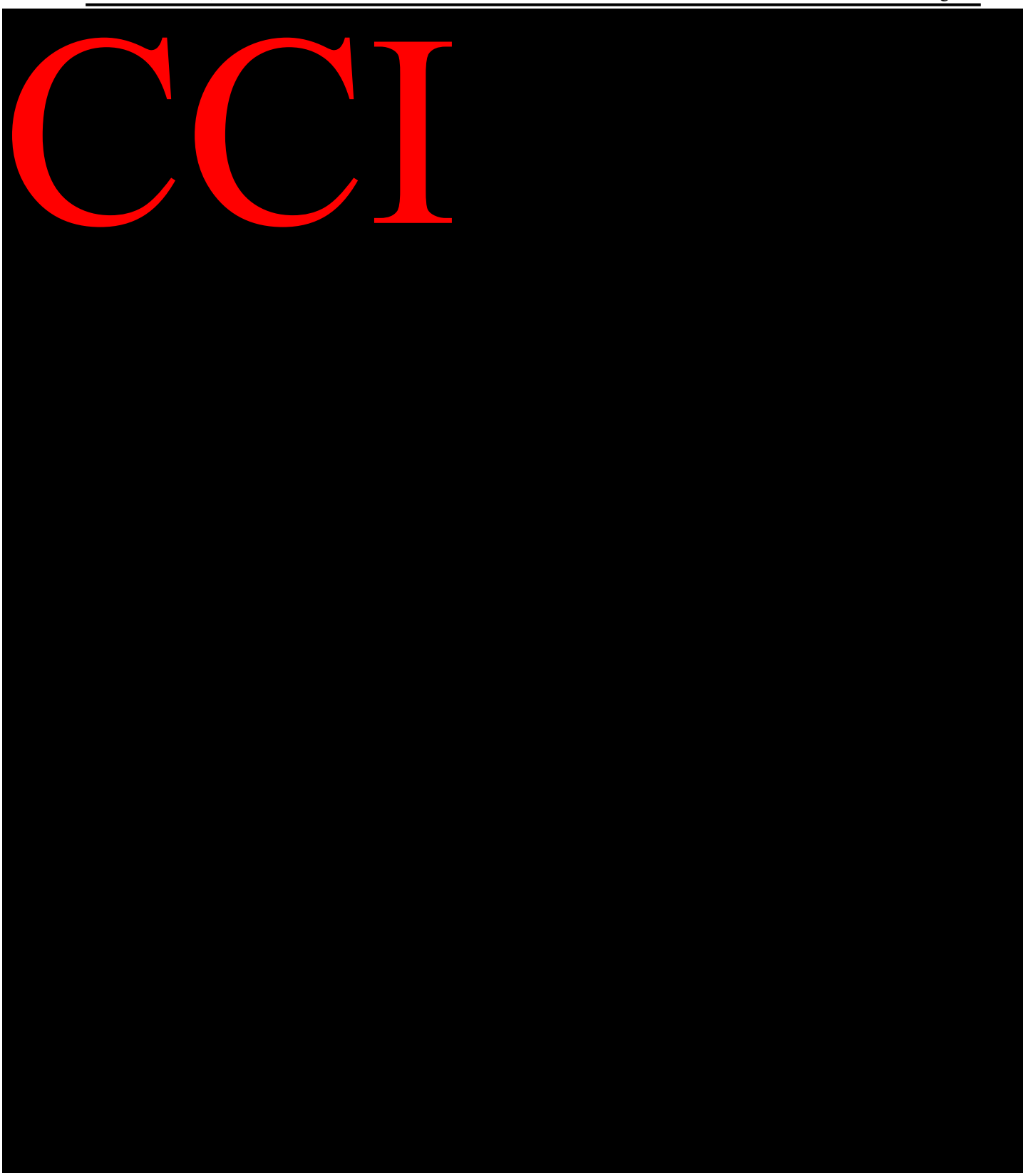
Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the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

11.5. Questionnaires/Participant-Reported Outcome Instruments

CCI [redacted]


CCI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[redacted]

CCI


CCI

11.5.4. Work Productivity and Activity Impairment – Respiratory Syncytial Virus

Work Productivity and Activity Impairment Questionnaire:
Respiratory Syncytial Virus V2.0 (WPAI-RSV)

The following questions ask about the effect of your child's respiratory syncytial virus (RSV) on your ability to work and perform regular activities. *Please choose a response, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the past seven days, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your child's RSV? Include hours you missed on sick days, times you went in late, left early, etc., because of your child's RSV. Do not include time you missed to participate in this study.

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your child's RSV affect your productivity while you were working?
   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your child's RSV affected your work only a little, choose a low number. Choose a high number if your child's RSV affected your work a great deal.

   Consider only how much your child's RSV affected productivity while you were working.

My child's RSV had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	My child's RSV completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your child's RSV affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your child's RSV affected your activities only a little, choose a low number. Choose a high number if your child's RSV affected your activities a great deal.

   Consider only how much your child's RSV affected your ability to do your regular daily activities, other than work at a job.

My child's RSV had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	My child's RSV completely prevented me from doing my daily activities

CIRCLE A NUMBER

Adapted from: Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993; 4(5):353-365.

11.6. Sponsor Signature Page

GILEAD SCIENCES, INC.
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A Phase 2, Randomized, Multicenter, Double-blind, Placebo-controlled, Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Obeldesivir in Participants From Birth to < 5 Years of Age With Respiratory Syncytial Virus (RSV) Infection

Original: 27 September 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]*
Senior Director, Clinical Development	Signature
[See appended electronic signature]	
Date	

protocol GS-US-685-6883 (word file)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	27-Sep-2024 17:07:04