CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2/3 Single-Arm, Open-label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Obeldesivir in Pediatric Participants With COVID-19
Plain Language Short Title:	Study of Obeldesivir in Children and Adolescents With COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EU CT Number:** **ClinicalTrials.gov Identifier:**	158222 2023-503282-27 Not Available
Population Diagnosis or Condition:	COVID-19
Protocol ID:	GS-US-611-6464
Contact Information:	The medical monitor and study director names and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 09 May 2023 Amendment 0.1 EU: 15 November 2023

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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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AUC	area under the concentration versus time curve
AUCx-xx	partial area under the concentration versus time curve from time "x" to time "xx"
BID	twice daily
CI	confidence interval
C_{max}	maximum observed concentration of drug
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DAIDS	Division of AIDS
DMC	data monitoring committee
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GA	gestational age
GCP	Good Clinical Practice
Gilead	Gilead Sciences
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
Ig	immunoglobulin
IRB	institutional review board
IRT	Interactive Response Technology
KM	Kaplan-Meier
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
ODV	obeldesivir (GS-5245)
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
RDV	remdesivir
RNA	ribonucleic acid

SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SSR	special situations report
TK	toxicokinetic(s)
ULN	upper limit of normal
US	United States

PROTOCOL SYNOPSIS

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

Study Title: A Phase 2/3 Single-Arm, Open-label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Obeldesivir in Pediatric Participants With COVID-19

Plain Language Short Title: Study of Obeldesivir in Children and Adolescents With COVID-19

Regulatory Agency Identifier Numbers:

IND Number: 158222
EU CT Number: 2023-503282-27
ClinicalTrials.gov Identifier: Not Available

Study Sites Planned: Approximately 40 centers globally

Objectives and Endpoints:

Primary Objectives	**Primary Endpoints**
• To evaluate the plasma pharmacokinetic (PK) of obeldesivir (ODV; GS-5245) in pediatric participants with COVID-19	• PK parameters (AUC_{0-12}, C_{max}, and C_{trough}) for ODV metabolite, GS-441524
• To evaluate the safety and tolerability of ODV in pediatric participants with COVID-19	• Incidence of treatment-emergent adverse events (AEs) by Day 35 • Incidence of treatment-emergent laboratory abnormalities by Day 35
Secondary Objectives	**Secondary Endpoints**
• To assess the impact of ODV on time to sustained alleviation of targeted COVID-19 symptoms in pediatric participants with COVID-19	• Time to sustained alleviation of targeted COVID-19 symptoms by Day 35
• To evaluate the antiviral activity of ODV on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nasal swab viral load in pediatric participants with COVID-19	• Change from baseline in SARS-CoV-2 nasal swab viral load at Day 5
• To assess the impact of ODV on the requirement for supplemental oxygen in pediatric participants with COVID 19	• Proportion of participants who require supplemental oxygen support (low flow oxygen, high flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation) by Day 35
• To evaluate palatability and acceptability of ODV in pediatric participants with COVID-19	• Assessment of palatability and acceptability scores of each formulation at Day 5

• To provide data on the use of medications other than remdesivir and ODV for treatment of COVID-19 in pediatric participants with COVID-19	• Proportion of participants with concomitant use of medications other than remdesivir and ODV for treatment of COVID-19 by Day 35
• To assess the impact of ODV on COVID-19-related hospitalizations or all-cause death in pediatric participants with COVID-19	• Proportion of participants with COVID-19-related hospitalization or all-cause death by Day 35

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Study Design: This will be a single-arm, open-label study to evaluate the safety, PK, and efficacy of ODV in pediatric participants with COVID-19 who are at risk of progression to severe disease. Participants will be enrolled in a staggered manner and will receive treatment with ODV. Cohorts will be opened for enrollment based upon availability of a suitable pediatric formulation and availability of preliminary safety and PK data.

Cohort	Description
Pediatric participants ≥ 28 days to < 18 years old	
1	≥ 6 years to < 18 years and weight ≥ 40 kg
2	≥ 6 years to < 18 years and weight ≥ 20 kg to < 40 kg
3	≥ 2 years to < 18 years and weight ≥ 12 kg to < 20 kg
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg
Term neonatal participants 0 days to < 28 days old	
5	≥ 14 days to < 28 days of age, gestational age (GA) ≥ 37 weeks and weight ≥ 2.5 kg
6	0 days to < 14 days of age, GA ≥ 37 weeks and birth weight ≥ 2.5 kg
Preterm neonates and infants 0 days to < 56 days old	
7	0 days to < 56 days of age, GA < 37 weeks and birth weight ≥ 1.5 kg

Number of Participants Planned: At least 52 participants

Study Population: Pediatric participants 0 days to < 18 years of age with COVID-19 who are at risk of progression to severe disease

Diagnosis and Main Eligibility Criteria: Participants with SARS-CoV-2 infection confirmed by polymerase chain reaction or an alternative molecular diagnostic assay who meet following criteria:

- Age and weight criteria:
  - Cohort 1: ≥ 6 years to < 18 years and weight ≥ 40 kg
  - Cohort 2: ≥ 6 years to < 18 years and weight ≥ 20 kg to < 40 kg
  - Cohort 3: ≥ 2 years to < 18 years and weight ≥ 12 kg to < 20 kg
  - Cohort 4: ≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg
  - Cohort 5: ≥ 14 days to < 28 days of age, GA ≥ 37 weeks and weight ≥ 2.5 kg
  - Cohort 6: 0 days to < 14 days of age, GA ≥ 37 weeks and birth weight ≥ 2.5 kg
  - Cohort 7: 0 day to < 56 days of age, GA < 37 weeks and birth weight ≥ 1.5 kg
- Initial onset of COVID-19 signs/symptoms ≤ 5 days before screening with ≥ 1 sign/symptom such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia present at screening
- Presence of ≥ 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness due to COVID-19, including:
  - CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]

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- CCI
- CCI

Test Product, Dose, and Mode of Administration:

- ODV CCI administered orally twice daily for participants aged ≥ 6 years to < 18 years and weighing ≥ 40 kg (Cohort 1).
- ODV CCI administered orally twice daily for participants aged ≥ 6 years to < 18 years and weighing ≥ 20 kg to < 40 kg (Cohort 2).

Reference Therapy, Dose, and Mode of Administration: Not applicable

Duration of Intervention: 5 days

Study Procedures/Frequency:

- Screening: within 48 hours of the baseline (Day 1) visit (screening and baseline visits may occur on the same day)
- Study treatment period: 5 days
  - In-person visits at Days 1 and 5
  - In-person or remote visit at Day 3
- Posttreatment follow-up period: 30 days after the last dose of study drug
  - In-person or remote visits at Days 8 and 14
  - Virtual visits at Days 21 and 28
  - End-of-study in person visit at Day 35

Table 1 outlines the schedule of study procedures.

Statistical Methods:

Safety: Treatment-emergent AEs and selected laboratory test data will be summarized using descriptive statistics and listed by participant. The proportion of participants with concomitant use of medications other than RDV and ODV for treatment of COVID-19 will be provided in summary tables by cohort and overall. Palatability and acceptability will be summarized using descriptive statistics by cohort and overall.

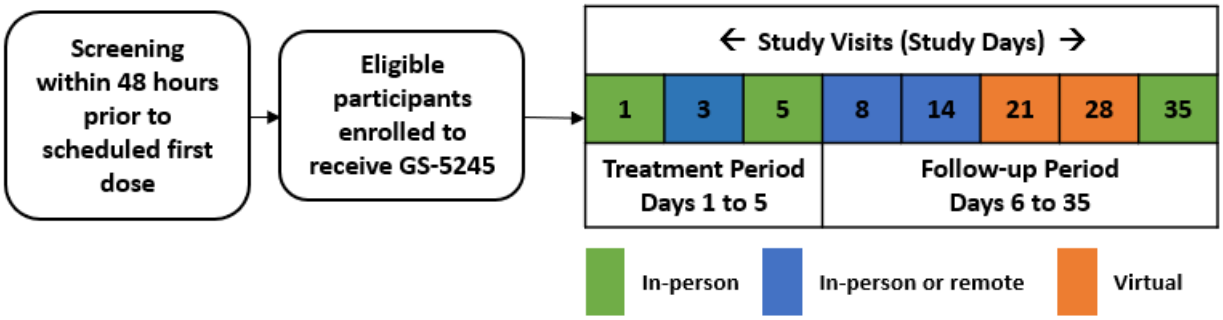
Pharmacokinetics: Plasma concentrations and PK parameters will be listed and summarized for GS-441524 using descriptive statistics by cohort and overall.

Efficacy: The efficacy endpoints will be summarized using descriptive statistics and listed by participant.

Sample Size: A minimum of 12 evaluable participants from each cohort (Cohorts 1-4) provides > 90% power to reject the null hypothesis that there is at least a 30% difference in GS-441524 AUC_{0-12} and C_{max}, respectively, between pediatric and adult participants, using 2 one-sided tests with each performed at an alpha level of 0.05. This power analysis assumes that the expected geometric mean ratio between the pediatric participants versus the adult group is 1, the equivalency boundary is 70% to 143%, and the interparticipant standard deviations of AUC_{0-12} and C_{max} are 0.19 h•ng/mL and 0.18 ng/mL (natural log scale, preliminary results from Study GS-US-611-6248).

STUDY SCHEMA

Figure 1. Study Schema



An in-person visit will occur either at a medical facility or as a remote visit at home by a healthcare professional (where permitted). Virtual visit is defined as an interaction with a healthcare professional using telephone or online based interaction (eg, telehealth, webcast, videoconferencing).

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table

	Screening/ (D −1)[a]	Baseline/ D 1[a]	D 3	D 5	D 8	D 14	D 21	D 28	EOS/ D 35
	–	–	–	–	± 1 d	± 2 d	± 2 d	± 2 d	± 5 d
	In person		In person or remote[b]	In person	In person or remote[b]		Virtual[c]		In person
Participant and/or parent or legal guardian consent/assent	CCI								
Medical history[d]									
Document SARS-CoV-2 infection									
Complete physical examination[e]									
Symptom-directed physical examination[e]									
Body weight									
Height/length[f]									
Last recorded Apgar score if < 24 hours of age									
Birth weight if < 56 days of age									
Gestational age if < 1 years of age									
Vital signs[g]									
Tanner stage assessment if ≥ 6 years of age									
Hematology, chemistry									
Urinalysis									
Routine coagulation test (PT/aPTT with calculated INR)									
Neonatal bilirubin panel for all neonates < 14 days, and any neonate presenting with jaundice									
Urine pregnancy test[h]									
Midturbinate nasal swab[i]									

	Screening/ (D −1)[a]	Baseline/ D 1[a]	D 3	D 5	D 8	D 14	D 21	D 28	EOS/ D 35
	–	–	–	–	± 1 d	± 2 d	± 2 d	± 2 d	± 5 d
	In person		In person or remote[b]	In person	In person or remote[b]		Virtual[c]		In person
Review inclusion/exclusion criteria	CCI								
Participant and/or caregiver symptom assessment[j]									
PK sample[k]									
Study drug dispensation									
Study drug administration[l]									
Study drug return[m]									
Concomitant medications									
Hospitalization details[n]									
Oxygen supplementation requirement[o]									
Adverse events[p]									
Acceptability/palatability assessment									

aPTT = activated partial thromboplastin time; COVID-19 = coronavirus disease 2019; D/d = day; EOS = end of study; Ig = immunoglobulin; INR = international normalized ratio; MAP = mean arterial pressure; PT = prothrombin time; PK = pharmacokinetic(s); RT-qPCR = reverse transcription-quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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

b An in-person visit will occur either at a medical facility or as a remote visit at home by a health care professional (where permitted).

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

d Medical history will include the date of first COVID-19 symptoms, overall COVID-19 symptoms, all COVID-19 vaccinations prior to screening, demographics, baseline characteristics, allergies, and all other medical history.

e 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 will only be conducted during an in-person visit by a qualified health care professional.

f Record length and head circumference if < 28 days at enrollment.

g Vitals signs include heart rate, temperature, blood pressure (MAP if available, systolic and diastolic), respiratory rate, and oxygen saturation. Vital signs will be collected at in-person visits only.

h For female participants of childbearing potential only.

i The nasal swab sample will be used for SARS-CoV-2 RT-qPCR, potential infectious viral titer assessment, potential resistance testing, and viral coinfection.
j Participant and/or caregiver symptom assessment will be completed on stipulated days via a questionnaire (Section 6.3.7).
k Refer to Section 6.3.5 for PK samples collection timepoints. PK samples will be collected on Days 3 and 5 for Cohorts 1 and 2.
l Study drug administration time will be recorded by investigational site personnel or by participant/parent/caregiver via a diary. Participant to withhold their dose prior to arriving to the site on Day 5, as the dose will be administered at the site.
m Study drug bottle should be returned by the participant on Day 5, if the participant has already completed both doses of study drug. If the participant has the last dose of study drug remaining by the conclusion of the Day 5 in-person visit, the participant may return the study drug bottle if an in-person visit is conducted on any subsequent visits (including EoS visit). Alternatively, the participant may courier the study drug bottle to the site.
n To be collected for hospitalized participants. Information to be collected: hospitalization date, reason for hospitalization, discharge date, and discharge outcome.
o To be collected for hospitalized participants. Refer to Section 6.3.4 for information collection on oxygen supplementation or oxygenation.
p All participants presenting with multisystem inflammatory syndrome in children (MIS-C; https://emergency.cdc.gov/han/2020/han00432.asp) should be monitored and treated as clinically indicated.
q To be collected for hospitalization participants.

1. INTRODUCTION

1.1. Background

A novel coronavirus, SARS-CoV-2, has been identified as the cause of the global pandemic of COVID-19. Children of any age can get COVID-19 {Zimmermann 2020} and the incidence in children has been found to be similar to that in adults {Dawood 2022}. The prevalence of SARS-CoV-2 infection was initially reported to be low, with children and adolescents to represent approximately 1% to 2% of total cases, but the prevalence has increased over time, possibly related to increased testing rates {Nikolopoulou 2022}. As of January 2023, 17.2% of cases in the United States (US) were children from 0 to 17 years of age; with 3.6% cases in the age group 0-4 years, 6.5% cases in the age group 5-11 years, 4.5% cases in the age group 12-15 years, and 2.6% cases in the age group 16-17 years {Centers for Disease Control and Prevention 2022}. In a study conducted in school-aged children in the United Kingdom, median illness duration was longer for children aged 12 to 17 years (7 days) than children aged 5 to 11 years (5 days), with 4.4% of children having an illness duration of at least 28 days and longer duration occurring more commonly in older than younger children (5.1% vs 3.1%, respectively) {Molteni 2021}. Further, in addition to increased prevalence, the overall incidence of SARS-CoV-2 infection and COVID-19–related hospitalizations among children has increased over the course of the pandemic with successive SARS-CoV-2 waves and the emergence of unique variants {Ben-Tov 2022} {Marks 2022}. The percentage of intensive care unit admissions among hospitalized children is comparable to that for hospitalized adults with COVID-19 and hospitalization rates in the US associated with COVID-19 are higher among unvaccinated children than those who are vaccinated {Shi 2022} {Siegel 2021}. Both children and adults present with similar viral loads irrespective of hospitalization or symptom status {Madera 2021}, with fever and cough reported as the most common symptoms {European Center for Disease Prevention and Control 2022} {Nikolopoulou 2022}. Although children with COVID-19 are frequently asymptomatic or have symptoms that are reported as mild or moderate, symptoms can include nausea/vomiting, and upper respiratory complications {Swann 2020}, {Gotzinger 2020}, {Liguoro 2020}, {Zimmermann 2020}. The signs and symptoms of COVID-19 in children may overlap significantly with other respiratory and enteric viral infections. However, as in adults, COVID-19 can result in severe disease in children, leading to respiratory failure and acute respiratory distress syndrome {Bhalala 2022}. Other symptoms in children include gastrointestinal symptoms, sore throat/pharyngitis, shortness of breath, myalgia, rhinorrhea/nasal congestion, and headache, consistent with symptoms observed in adults. Furthermore, underlying conditions such as CCI [redacted], CCI [redacted] and CCI [redacted] children as well as adults to more severe COVID-19 disease; prematurity in infants is also a risk factor for severe disease {Fernandes 2021} {Kompaniyets 2021} {Tsankov 2021} {Uka 2022}.

Remdesivir (RDV, Veklury®) is approved for the treatment of COVID-19 in hospitalized and nonhospitalized patients in the US, the European Union (EU), Japan, and other countries in pediatric and adult patients {VEKLURY 2022a, Veklury 2022b}. The pharmacologically active metabolite of RDV within lung cells is the triphosphate (GS-443902), which is recognized and incorporated in SARS-CoV-2 viral RNA by viral RNA-dependent RNA polymerase as an

alternate substrate, thereby selectively inhibiting the synthesis of viral RNA {Tchesnokov 2020}. Recent in vitro studies confirmed potent antiviral activity of RDV and its parent nucleoside GS-441524 against the SARS-CoV-2 delta variant and other variants of interest, and it is anticipated that future coronavirus (CoV) strains are likely to remain susceptible to RDV as it has potent activity in vitro and in vivo toward both SARS-CoV and Middle East respiratory syndrome CoV, whose polymerase active sites are 100% conserved (Studies PC-540-2021, PC-540-2024, and PC-540-2026). The broader utility of RDV for the treatment of early infection with SARS-CoV-2 and other potential emerging CoV strains is limited due to intravenous administration; therefore, availability of more convenient treatment options using other routes of administration is crucial for early therapy.

Nirmatrelvir/ritonavir (Paxlovid™) is authorized for emergency use in the US for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19. No oral medications are currently available for the treatment of COVID-19 in pediatric patients in the EU.

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

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

1.2. Background on Study Interventions

1.2.1. 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), including information on the following:

- Nonclinical pharmacology
- Nonclinical PK
- Toxicology

1.2.1.2. Clinical Studies of Obeldesivir

1.2.1.2.1. Study GS-US-611-6248

Study GS-US-611-6248 was a Phase 1a first-in-human, single and multiple ascending dose study of ODV. This randomized, blinded, placebo-controlled study evaluated single and multiple doses with staggered dose escalation and adaptive ODV dose selection. The study also evaluated the impact of food on bioavailability.

The single ascending dose cohorts evaluated ODV 100 mg, 300 mg, 900 mg, and 1600 mg administered once daily for 5 days and multiple ascending dose cohorts evaluated ODV 500 mg administered BID for 5 days and ODV 900 mg administered once daily for 5 days. Obeldesivir tablets were administered in fasted state (morning dose) or 2 hours after a meal (evening dose) with approximately 240 mL of water.

A total of 70 participants were enrolled into the study, 58 participants received ODV and 12 participants received placebo. A similar proportion of male and female participants (52.9% and 47.1%, respectively) were enrolled in the study. The mean (SD) age was 32 (7.5) years (range: 20 to 45 years).

Following single dose administration of ODV at doses of 100, 300, 900, or 1600 mg under fasted conditions, dose-proportional increases in the GS-441524 plasma PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) were observed across the dose range of 100 to 900 mg. The median T_{max} of GS-441524 in plasma was 0.75 hours postdose and the median $t_{1/2}$ ranged from 6 to 7 hours across the 100 to 900 mg singles doses. Following ODV 500 mg BID administration for 5 days under fasted condition, accumulation of GS-441524 in plasma (approximately 35% based on AUC values) was observed and reached steady state at 5 days. Minimal (approximately 12% based on AUC value) accumulation of GS-441524 was observed after ODV 1600 mg once-daily dosing.

Administration of ODV with high-fat meal decreased the rate but not the extent of absorption; thus, ODV may be administered without regard to food.

Overall, ODV at single doses of 100 mg to 1600 mg and multiple doses of 500 mg BID and 900 mg once daily has been safe and well tolerated. No Grade 3 and severe AEs, SAEs, deaths, pregnancies, or discontinuation of study drug were reported. No Grade 4 laboratory abnormalities reported; 1 Grade 3 lipase elevation was reported on Day 3 which returned to normal at Day 5. Creatinine clearance decreases were generally transient and returned to baseline limits. There were no clinically relevant changes in vital signs, electrocardiograms, or ophthalmologic examinations.

1.2.1.2.2. Study GS-US-611-6409

Study GS-US-611-6409 is an ongoing Phase 1 study to evaluate transporter and cytochrome P450 enzyme (CYP)-mediated DDIs between ODV and probe drug. This is an open-label, multicenter, fixed- (Cohorts 1, 2, 3, 5, and 7) or randomized-sequence (Cohorts 4

and 6) crossover study in healthy participants. The following interactions are planned to be evaluated in each cohort:

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

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

The safety profile of Cohorts 3 and 7 is not yet available. No SAEs, deaths, pregnancies or discontinuations of study drug were reported.

Conclusion

Preliminary data indicates that-

- ODV as a perpetrator: ODV is not an inhibitor of CYP3A (as observed with MDZ) or a clinically relevant inhibitor of OATP1B1/1B3 (as observed with PIT).
- ODV as a victim: There was no clinically significant effect of P-gp inhibition (as observed with coadministration of ODV with ritonavir) on plasma exposure of GS-441524. There was no clinically significant effect of increased gastric pH (as observed with coadministration of ODV with FAM) plasma exposures of GS-441524; thus, ODV may be coadministered with acid-reducing agents including antacids, histamine 2-receptor antagonists, and proton-pump inhibitors.

1.2.1.3. Toxicology

1.2.1.3.1. Phototoxicity

Results of a CCI [redacted] showed that CCI [redacted] was not cytotoxic and did not display an IC_{50} with or without ultraviolet radiation exposure, up to the highest soluble concentration tested CCI [redacted] Administration of ODV is not considered to exhibit a photosafety risk.

1.2.1.3.2. Fertility Study

A fertility and early embryonic development (FEED) study in male and female rats has been conducted. A summary of the results of this study, based on the audited draft report, is provided below.

The objectives of this FEED study were to determine the potential adverse effects/disturbances in the reproductive process resulting from CCI administration of ODV to CCI [redacted] rats, from premating to conception and from conception to implantation. This included identification of deficits in estrous cycling, tubal transport, implantation, development of the preimplantation stages of the embryo in the female, and functional reproductive effects (alterations in libido and epididymal sperm maturation) in the male. In addition, the toxicokinetics CCI [redacted] were determined from a satellite group of nonmated animals.

Four groups of male rats CCI [redacted] were administered ODV by CCI [redacted]

There were no ODV–related effects on male survival, clinical and macroscopic observations, body weights, body weight gains, food consumption, and organ weights at CCI [redacted] Male reproductive performance (mating, fertility, and pregnancy indices and precoital intervals) and spermatogenic parameters were unaffected by ODV administration at CCI [redacted]

There were no ODV–related effects on female survival or clinical observations at CCI [redacted] or on premating and gestation body weights, body weight gains, food consumption, estrous cycle length, reproductive performance, macroscopic findings, or organ weights at CCI [redacted] Intrauterine survival was also not affected by ODV administration at any dose level. All parameters in the CCI [redacted] were comparable to the vehicle control group.

Based on the lack of effects on reproductive performance and spermatogenic parameters, a dose level of CCI was considered to be the no observed adverse effect level (NOAEL) for male reproductive toxicity of ODV when administered CCI to CCI rats. Based on the lack of effects on female reproductive performance, estrous cyclicity, and intrauterine survival, the NOAEL for female reproductive toxicity and embryonic toxicity was considered to be CCI . These doses corresponded to mean CCI

CCI

1.3. Rationale for This Study

There are currently no approved oral therapeutic agents available for the treatment of COVID-19 in children < 12 years of age. All approved COVID-19 drugs for children ≥ 12 to < 18 years of age and weighing ≥ 40 kg are administered via parenteral route. The availability of an effective oral antiviral agent with a favorable benefit-risk profile would address a serious unmet medical need for the treatment of children with COVID-19.

1.4. Rationale for Dose Selection of Study Drug

The proposed dose for evaluation in Cohort 1 (participants aged ≥ 6 years to < 18 years and weighing ≥ 40 kg) is the same dose being evaluated in the adult Phase 3 Study GS-US-611-6273, which is ODV CCI BID. Obeldesivir administered at single doses of 100 mg to 1600 mg and multiple doses of CCI BID or 900 mg once daily for 5 days were generally safe and well tolerated in the Phase 1a study (Section 1.2.1.2.1).

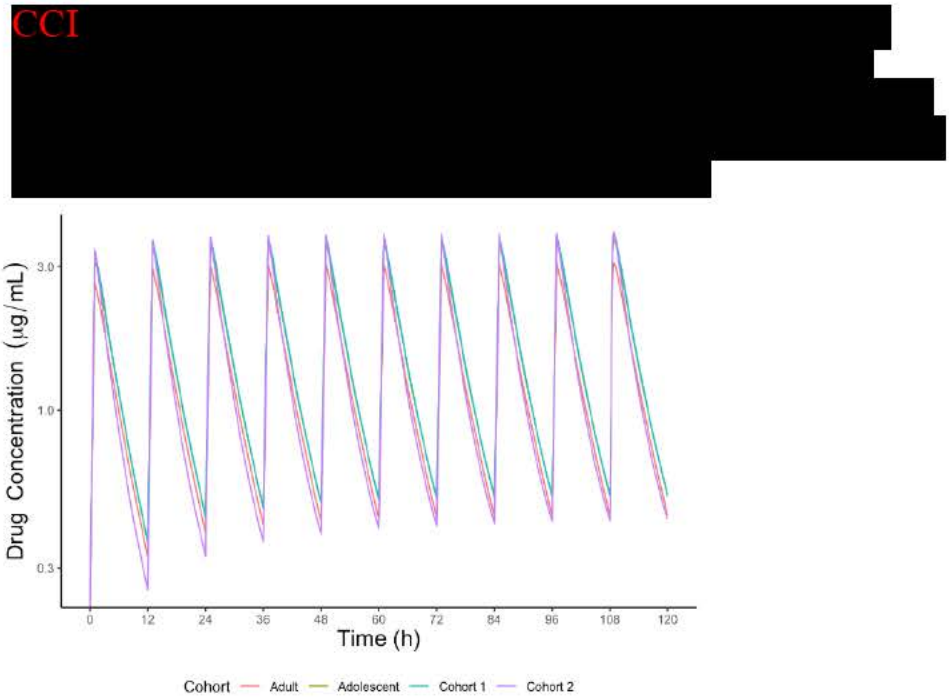
A population pharmacokinetic (PopPK) model developed for ODV based on available adult PK data from the Phase 1 Study GS-US-611-6248 was revised to incorporate allometric scaling based on body weight in order to extrapolate exposures and select doses for pediatric participants ≥ 6 years of age and ≥ 20 kg. Figure 2 displays the resulting PopPK model-predicted GS-441524 concentration versus time profiles for the 5-day administration of CCI BID to adults (≥ 18 years of age and weighing ≥ 40 kg), CCI BID to adolescents (≥ 12 to < 18 years of age and weighing ≥ 40 kg) in the Phase 3 Study GS US 611-6549 and Study GS-US-611-6464 Cohort 1 participants (≥ 6 to < 18 years of age and weighing ≥ 40 kg), and CCI BID to Study GS-US-611-6464 Cohort 2 participants (≥ 6 to < 18 years of age and weighing ≥ 20 to < 40 kg). This figure demonstrates that the predicted PK profiles for each of the pediatric weight groups are predicted to be similar to the anticipated PK profiles in adults. Figure 3 provides the boxplots of the corresponding PK parameters for adults and each of the pediatric weight groups. As the model results demonstrate, administration of CCI for 5 days to pediatric

participants weighing ≥ 40 kg and CCI BID for 5 days to pediatric participants weighing ≥ 20 kg to < 40 kg results in exposures comparable to those anticipated in adult participants following CCI BID administration, and within the range of observed exposures associated with safe doses administered to adults in the Phase 1 Study GS-US-611-6248.

Therefore, the proposed doses are ODV CCI BID and CCI BID for Cohort 1 and Cohort 2, respectively (Table 2). The weight range associated with proposed dose for Cohort 2 may be confirmed prior to enrollment, based on update to the PopPK model using available additional PK data from adult Phase 1 and Phase 3 studies (including but not limited to GS-US-611-6248, GS-US-611-6273, and GS-US-611-6549).

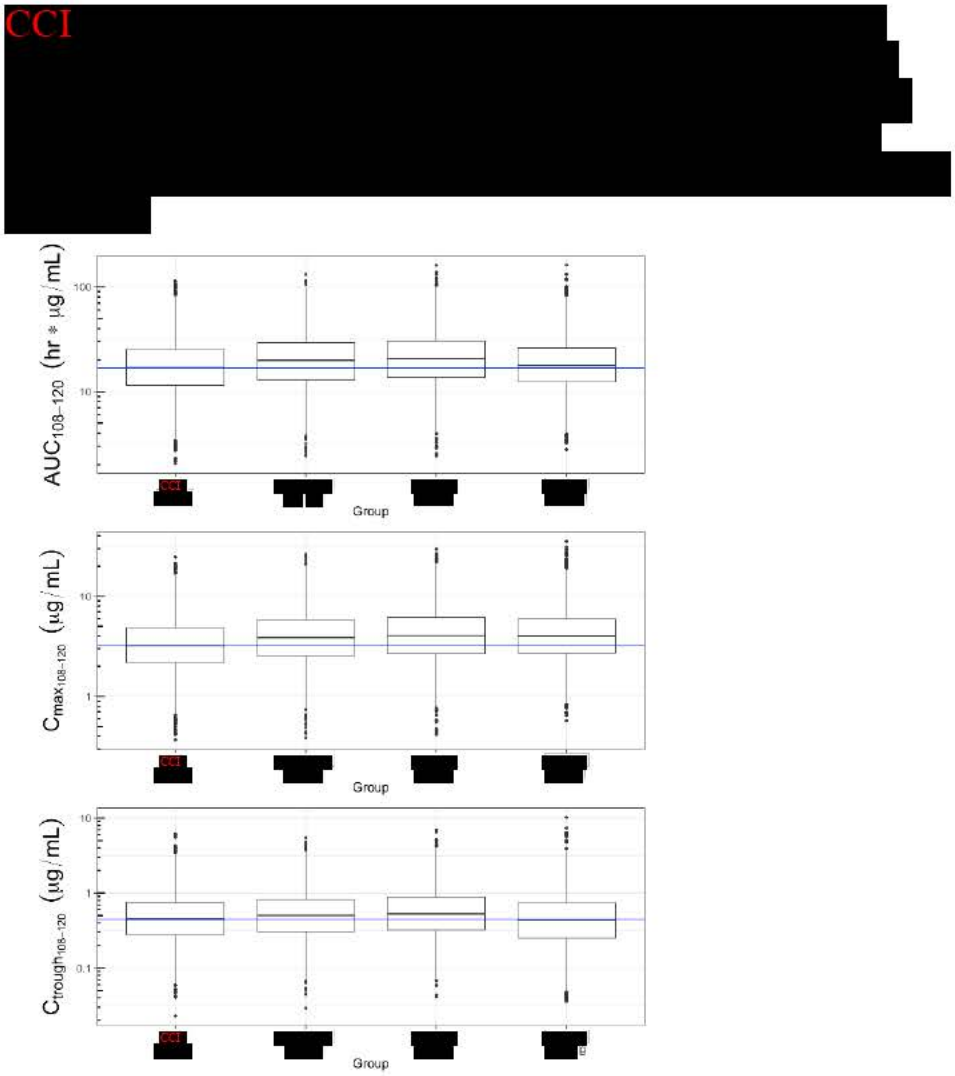
The dose(s) for Cohorts 3 to 5 will be determined prior to enrollment using PK modeling based on data from the relative bioavailability study for the pediatric dosing formulation and any other available PK data from this pediatric study and adult studies (including but not limited to GS-US-611-6248, GS-US-611-6273, and GS-US-611-6549). Similarly, the dose(s) for Cohorts 6 and 7 will be determined using modeling based on available cumulative PK data from this pediatric study and adult studies prior to enrollment (including but not limited to GS-US-611-6248, GS-US-611-6273, and GS-US-611-6549).

Figure 2.



BID = twice daily; ODV = obeldesivir (GS-5245); PK = pharmacokinetic; y = year (age)
Adolescent refers to Study GS-US-611-6549 participants ≥ 12 years to < 18 years of age and weighing ≥ 40 kg. Cohorts 1 and 2 refer to pediatric Study GS-US-611-6464 Cohort 1 (participants ≥ 6 years to < 18 years of age and weighing ≥ 40 kg) and Cohort 2 (participants ≥ 6 years to < 18 years of age and weighing ≥ 20 kg to < 40 kg).

Figure 3.



AUC108-120 = partial area under the concentration versus time curve from time 108 hours to time 120 hours (the evening dose on Day 5); BID = twice daily; C_{max} = maximum observed concentration of drug; C_{trough} = concentration at the end of the dosing interval; ODV = obeldesivir (GS-5245); PK = pharmacokinetic; y = year (age)
Adolescent refers to Study GS-US-611-6549 participants ≥ 12 years to < 18 years of age and weighing ≥ 40 kg. Cohorts 1 and 2 refer to pediatric Study GS-US-611-6464 Cohort 1 (participants ≥ 6 years to < 18 years of age and weighing ≥ 40 kg) and Cohort 2 (participants ≥ 6 years to < 18 years of age and weighing ≥ 20 kg to < 40 kg).

1.5. Benefit-Risk Assessment for the Study

Obeldesivir has shown to have activity in animal models and shares the same active triphosphate metabolite as the approved COVID-19 treatment drug, RDV.

Obeldesivir has also been evaluated in a Phase 1 (single and ascending dose) study where it was safe and well tolerated. Obeldesivir is currently being evaluated in 2 Phase 3 adult population studies (GS-US-611-6273 and GS-US-611-6549). Enrollment in this study will be initiated following the review of safety data from the first occurring Data Monitoring Committee (DMC) of the adult program:

- Data from the first 200 participants, who completed Day 29 visit or prematurely discontinued from the study, in GS-US-611-6273 have been reviewed by the DMC

  OR

- Data from the first 150 participants, who completed Day 29 visit or prematurely discontinued from the study, in GS-US-611-6549 have been reviewed by the DMC.

Obeldesivir has the potential benefit to be the first oral COVID treatment for children, which will facilitate treatment of outpatients as well as inpatients.

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 infectious disease pandemic may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.3 for further details on the risks and risk mitigation strategy.

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

2. OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints
• To evaluate the plasma PK of ODV in pediatric participants with COVID-19	• PK parameters (AUC_{0-12}, C_{max}, and C_{trough}) for ODV metabolite, GS-441524
• To evaluate the safety and tolerability of ODV in pediatric participants with COVID-19	• Incidence of treatment-emergent AEs by Day 35 • Incidence of treatment-emergent laboratory abnormalities by Day 35
Secondary Objectives	**Secondary Endpoints**
• To assess the impact of ODV on time to sustained alleviation of targeted COVID-19 symptoms in pediatric participants with COVID-19	• Time to sustained alleviation of targeted COVID-19 symptoms by Day 35
• To evaluate the antiviral activity of ODV on SARS-CoV-2 nasal swab viral load in pediatric participants with COVID-19	• Change from baseline in SARS-CoV-2 nasal swab viral load at Day 5
• To assess the impact of ODV on the requirement for supplemental oxygen in pediatric participants with COVID 19	• Proportion of participants who require supplemental oxygen support (low flow oxygen, high flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation) by Day 35
• To evaluate palatability and acceptability of ODV in pediatric participants with COVID-19	• Assessment of palatability and acceptability scores of each formulation at Day 5
• To provide data on the use of medications other than RDV and ODV for treatment of COVID-19 in pediatric participants with COVID-19	• Proportion of participants with concomitant use of medications other than RDV and ODV for treatment of COVID-19 by Day 35
• To assess the impact of ODV on COVID-19-related hospitalizations or all-cause death in pediatric participants with COVID-19	• Proportion of participants with COVID-19-related hospitalization or all-cause death by Day 35
[redacted]	


CCI

3. STUDY DESIGN

3.1. Study Design Overview

This will be a single-arm, open-label study to evaluate the safety, PK, and efficacy of ODV in pediatric participants with COVID-19 who are at risk of progression to severe disease.

After screening procedures, eligible participants will receive treatment with ODV.

At least 52 participants aged 0 days to < 18 years will be enrolled as described in Table 2. Participants will be enrolled in a staggered manner. Cohorts will be opened for enrollment based upon availability of a suitable pediatric formulation and availability of preliminary safety and PK data.

Figure 1 provides an overview of study design.

Table 2. Study Cohort Description

Cohort	Description
Pediatric participants ≥ 28 days to < 18 years old	
1	≥ 6 years to < 18 years and weight ≥ 40 kg
2	≥ 6 years to < 18 years and weight ≥ 20 kg to < 40 kg
3	≥ 2 years to < 18 years and weight ≥ 12 kg to < 20 kg
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg
Term neonatal participants 0 days to < 28 days old	
5	≥ 14 days to < 28 days of age, GA ≥ 37 weeks and weight ≥ 2.5 kg
6	0 days to < 14 days of age, GA ≥ 37 weeks and birth weight ≥ 2.5 kg
Preterm neonates and infants 0 days to < 56 days old	
7	0 days to < 56 days of age, GA < 37 weeks and birth weight ≥ 1.5 kg

GA = gestational age

3.2. Duration of Intervention

Duration of dosing is 5 days.

3.2.1. Poststudy Care

The long-term care of the participant will remain the responsibility of his/her primary treating physician.

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participants

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

Study drug will be discontinued in the following instances:

- Any SAE suspected to be related to study drug.
- Any ≥ Grade 3 AE suspected to be related to study drug.
- An AE, or worsening of clinical condition requiring clinical intervention, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Any ≥ Grade 3 clinically significant laboratory abnormality (if confirmed by repeat testing) suspected to be related to study drug.
- eGFR < 50 mL/min/1.73 m2 (≥ 1 year of age) using the Bedside Schwartz formula.
- Alanine aminotransferase (ALT) ≥ 5 × upper limit of normal (ULN).
- Bilirubin ≥ 2 ´ ULN (≥ 3 × ULN for participants with Gilbert's syndrome).
- Unacceptable toxicity, as defined in Section 7.7, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the participant's best interest.
- Participant request to discontinue for any reason.
- Participant noncompliance with the study protocol.
- Pregnancy (refer to Appendix 11.4).
- Discontinuation of the study by sponsor.
- Creatinine level above the thresholds described in Table 3 if < 1 year or age.

Table 3. Creatinine Value Cutoff by Age Group

Gestational age	Chronological age	Creatinine Value Cutoff in mg/dL
≥ 24 to ≤ 27 weeks	0 to < 28 days	CCI
≥ 28 to ≤ 29 weeks	0 to < 14 days	CCI
≥ 30 to < 32 weeks	0 to < 7 days	CCI
	≥ 7 days to 1 month	CCI
	≥ 1 to < 2 months	CCI
	≥ 2 months to < 1 year	CCI
≥ 32 weeks	0 to < 2 days	CCI
	≥ 2 to < 7 days	CCI
	≥ 7 days to 2 months	CCI
	≥ 2 months to < 1 year	CCI

* Creatinine values CCI

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

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

- Withdrawal of consent/assent
- Death

3.3.2. Criteria for Early Discontinuation of the Study

The study will be discontinued in the following instances:

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

3.3.3. Loss to Follow-up

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

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

3.4.1. Primary Endpoint

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

3.4.2. End of Study

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

3.5. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, participant charts), central laboratory, local laboratory, and specialty laboratory (for PK data), participant (or caregiver)-reported outcomes, and Interactive Response Technology (IRT). Electronic data capture is not considered source data.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

At least 52 participants will be enrolled into the study including 12 evaluable participants per cohort from Cohorts 1-4 and a minimum of 4 evaluable participants from Cohort 5. Participants in Cohorts 6 and 7 will only be enrolled once ODV exposures have been evaluated from preceding cohort(s) and a dose has been determined. There is no minimum number of participants to be enrolled in Cohorts 6 and 7 due to the rarity of such participants.

4.1.1. Participant Replacement

If necessary, and with Gilead approval, replacement participants may be enrolled if a participant is considered non-evaluable for primary safety and/or PK analysis (Sections 8.3.1.2 and 8.3.1.3). Replacement participants will not be enrolled for participants who discontinued 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:

1) Participant or legal guardian 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 investigator's discretion.

2) Aged < 18 years who meet one of the following weight criteria and gestational age (GA) criteria where applicable (where permitted according to local law and approved nationally and by relevant IRB or IEC):

   a) Cohort 1: ≥ 6 years to < 18 years and weight ≥ 40 kg

   b) Cohort 2: ≥ 6 years to < 18 years and weight ≥ 20 kg to < 40 kg

   c) Cohort 3: ≥ 2 years to < 18 years and weight ≥ 12 kg to < 20 kg

   d) Cohort 4: ≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg

   e) Cohort 5: ≥ 14 days to < 28 days of age, GA ≥ 37 weeks and weight ≥ 2.5 kg

   f) Cohort 6: 0 days to < 14 days of age, GA ≥ 37 weeks and birth weight ≥ 2.5 kg

   g) Cohort 7: 0 days to < 56 days of age, GA < 37 weeks and birth weight ≥ 1.5 kg

3) SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) or an alternative molecular diagnostic assay ≤ 5 days before screening.

4) Initial onset of COVID-19 signs/symptoms ≤ 5 days before screening with ≥ 1 sign/symptom such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia present at screening.

5) Presence of ≥ 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness due to COVID-19, including:

   a) CCI [redacted]

   b) CCI [redacted]

   c) CCI [redacted]

   d) CCI [redacted]

   e) CCI [redacted]

   f) CCI [redacted]

   g) CCI [redacted]

   h) CCI [redacted]

   i) CCI [redacted]

4.3. Exclusion Criteria

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

1) Anticipated access to and use of authorized or approved COVID-19 therapies during the current COVID-19 illness < 5 days after screening (therapies including but not limited to nirmatrelvir/ritonavir, molnupiravir, intravenous RDV, monoclonal antibodies).

2) Vaccination for SARS-CoV-2 or self-reported history of SARS-CoV-2 infection < 4 months prior to screening.

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

4) CCI [redacted]

5) Any of the following abnormal laboratory results at screening:

   a) CCI [redacted]

   b) eGFR < CCI [redacted]

   c) Serum creatinine: CCI [redacted]

Gestational age	Chronological age	Creatinine Value Cutoff in mg/dL
≥ 24 to ≤ 27 weeks	0 to < 28 days	CCI [redacted]
≥ 28 to ≤ 29 weeks	0 to < 14 days	CCI [redacted]
≥ 30 to < 32 weeks	0 to < 7 days	CCI [redacted]
	≥ 7 days to 1 month	CCI [redacted]
	≥ 1 to < 2 months	CCI [redacted]
	≥ 2 months to < 1 year	CCI [redacted]
≥ 32 weeks	0 to < 2 days	CCI [redacted]
	≥ 2 to < 7 days	CCI [redacted]
	≥ 7 days to 2 months	CCI [redacted]
	≥ 2 months to < 1 year	CCI [redacted]

* Creatinine values CCI [redacted]

6) CCI [redacted].

7) CCI [redacted].

8) CCI [redacted].

9) CCI [redacted]

10) CCI [redacted]

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Enrollment, Blinding, and Treatment Code Access

5.1.1. Enrollment

Participants who meet eligibility criteria will be enrolled to receive ODV starting on Day 1 and assigned a participant number.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Obeldesivir

5.2.1. Formulation

The ODV tablets are available in strengths of CCI [redacted].

The ODV CCI [redacted] strength tablets are capsule shaped, debossed with "GSI" on one side and a bisect on the other side, and film-coated white. In addition to the active ingredient, each film-coated tablet contains the following inactive ingredients: microcrystalline cellulose, crospovidone, magnesium stearate, macrogol polyvinyl alcohol graft copolymer, talc, titanium dioxide, glyceryl mono and dicaprylocaprate (glyceryl monocaprylocaprate type I), and polyvinyl alcohol.

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

5.2.2. Packaging and Labeling

The ODV tablets, CCI [redacted], are packaged in white, high-density polyethylene bottles. Each bottle contains 10 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to participating centers shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), the EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), or Annex 6 for CTR, the Japan-GCP (Ministerial Ordinance on GCP for Drugs), as applicable, and/or other local regulations, as applicable.

5.2.3. Storage and Handling

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

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

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

5.3. Prior and Concomitant Medications

5.3.1. Prior and Concomitant Medications That Are Prohibited or Used With Caution

Medications in Table 4 are prohibited or to be used with caution while participants are taking study drugs. In instances where a prohibited medication is initiated before discussion with the Gilead medical monitor, the investigator must notify Gilead as soon as he/she is aware of the use of the prohibited medication.

There are no restrictions on the symptomatic treatment of COVID-19 other than those indicated in Table 4. There are no restrictions on concomitant medications based on potential for PK DDI with ODV.

Table 4. Prior and Concomitant Medications That Are to Be Used With Caution or That Are Prohibited Because of Impact on Efficacy Assessments or Participant Safety

Medication Class	Medications to Be Used With Caution	Prohibited Medications[a]
COVID-19 medications	—	RDV, molnupiravir, nirmatrelvir/ritonavir, monoclonal antibodies against COVID-19

COVID-19 = coronavirus disease 2019; RDV = remdesivir

a Concomitantly with ODV.

5.4. Dosage and Administration

Participants aged ≥ 6 years to < 18 years and weighing ≥ 40 kg will receive ODV CCI [redacted] administered orally BID for 5 days.

Participants aged ≥ 6 years to < 18 years and weighing ≥ 20 kg to < 40 kg will receive ODV CCI [redacted] administered orally BID for 5 days.

The doses should be taken approximately 12 hours apart.

Obeldesivir may be administered with or without food.

Participant to withhold their dose prior to arriving to the site on Day 5, as the dose will be administered at the site.

For participants aged < 6 years and weighing < 20 kg, dose will be informed by PK modeling (Section 1.4), and an age appropriate formulation will be developed and additional information will be provided in a protocol amendment.

5.5. Accountability for Study Drugs

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

Each investigational site must keep accountability records that capture:

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

5.5.1. Study Drug Return or Disposal

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

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

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

6. STUDY PROCEDURES

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

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

6.1. Informed Consent

Each participant and/or participant's parent or legal guardian 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, Participant Enrollment, and Treatment Assignment

Participants will be screened within 48 hours before enrollment in the study. Each participant will be assigned a unique screening number using an IRT. Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the investigational site within 48 hours for enrollment into the study. Screening and enrollment can occur on the same day, where possible.

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

Once written informed consent/assent has been obtained, all screening and admission tests and assessments have been assessed (including recording the date of the latest COVID-19 vaccination shot or booster), and study eligibility has been confirmed, participants will be enrolled to receive ODV on Day 1.

Participants will receive ODV as described in Section 5.4.

6.3. Instructions for Study Procedures

An in-person visit will occur either at a medical facility or as a remote visit at home by a health care professional (where permitted).

6.3.1. Adverse Events

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

6.3.2. Safety Assessments

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

6.3.2.1. Physical Examination

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

The complete physical examination conducted at screening will also include the following assessments:

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

6.3.2.2. Vital Signs

Refer to Table 1 for vital signs collection time points. Vital signs will be collected at in-person visits only.

Vital sign measurements include heart rate, temperature, blood pressure (mean arterial pressure if available, systolic and diastolic), respiratory rate, and oxygen saturation.

6.3.2.3. Concomitant Medications

Refer to Table 1 for concomitant medications assessment time points and Section 5.3 for more information about concomitant medications.

6.3.2.4. Clinical Laboratory Assessments

Refer to Table 1 for clinical laboratory assessment time points.

Following laboratory assessments will be performed:

- Hematology: Complete blood count (CBC) with differential
- Comprehensive metabolite panel (Chemistry 14): ALT, albumin, alkaline phosphatase, aspartate aminotransferase (AST), total bilirubin (and neonatal bilirubin for participants aged <14 days and participants presenting with jaundice), blood urea nitrogen and creatinine

(include BUN:Cr ratio, and eGFR using bedside Schwarz formula if ≥ 1 year of age), ionized calcium, carbon dioxide, chloride, total serum protein, potassium, sodium

- Urinalysis

The smallest possible blood vials, such as microtainer tubes, must 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.

6.3.2.5. Age-Specific Assessments

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

- Length and head circumference for participants < 28 days of age
- Apgar score assessment for participants < 24 hours of age
- Birth weight for participants < 56 days of age
- GA assessment for participants < 1 year of age
- Tanner stage assessment (Appendix 11.5) for participants ≥ 6 years of age. Date of first menses will be documented.
- Neonatal bilirubin panel for participants < 14 days of age

6.3.2.6. Pregnancy Tests

Urine pregnancy tests will be conducted only for female participants of childbearing potential. Refer to Appendix 11.4 for participants of childbearing potential.

6.3.3. Hospitalization Details

Following information will be collected for hospitalized participants:

- hospitalization date
- reason for hospitalization
- discharge date
- discharge outcome

6.3.4. Oxygenation/Oxygen Supplementation

Oxygenation/oxygen supplementation information will be collected for hospitalized participants.

The following information need to be collected:

- Oxygen supplementation:
  - room air (no O_2 supplementation)
  - low-flow O_2 (L/min and %)
  - high-flow O_2 (L/min and %)
  - continuous positive airway pressure/bilevel positive airway pressure (fraction of inspired oxygen [FiO_2] or %)
  - high-frequency oscillating ventilation (FiO_2 or %)
  - mechanical ventilation (FiO_2 or %)
  - extracorporeal membrane oxygenation
- Oxygenation:
  - peripheral oxygen saturation or partial pressure of oxygen

6.3.5. Pharmacokinetics

As many of the specific PK samples should be obtained from each participant as is feasible.

- Cohorts 1-2: samples collected on CCI
  - Day 3: 1 sample between CCI
  - Day 5: predose CCI and at CCI CCI postdose
  - Day 5: CCI postdose for hospitalized participants only

The PK sample collection timepoints for Cohorts 3-7 will be provided in a protocol amendment.

6.3.6. Clinical Virology

6.3.6.1. Virology Testing

6.3.6.1.1. Virology Samples to Address the Study Objectives

Midturbinate nasal swab samples will be used to assess SARS-CoV-2 viral load by reverse transcription-quantitative PCR at the time points specified in Table 1. Once viral load testing is complete, the remnant samples may be used to evaluate SARS-CoV-2 viral titer, emergence of viral resistance (by SARS-CoV-2 sequencing and/or phenotypic testing), and viral coinfection.

6.3.6.1.2. Virology Sample Storage

Any remaining specimens from midturbinate 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.

6.3.7. Participant Symptom Assessment

Participant and/or parent/caregiver will complete participant symptom assessment daily from Day 1 through Day 14 and at Days 21, 28, and 35 via a symptom score questionnaire.

The questionnaire will consist of severity (on 4- or 5-point scale, as applicable) of select symptoms (listed below), frequency of select symptoms (diarrhea and vomiting) in 24 hours before the assessment, and smell and taste assessment.

The select symptoms for severity assessment on 4- or 5-point scale will include:

- Stuffy or runny nose
- Sore throat
- Shortness of breath
- Cough
- Low energy or tiredness
- Muscle or body aches
- Headache
- Chills or shivering

- Feeling hot or feverish
- Nausea

6.3.7.1. Procedures to Minimize Missing Symptom Data

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

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

6.3.8. Assessment of Palatability and Acceptability

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

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

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

6.4.1. Assessments for Early Discontinuation From Study Intervention

If a participant discontinues study dosing prematurely (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (see Section 3.3). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.4.2. Assessments for End of Study

A participant who completes the study undergo end of study visit as specified in Table 1.

6.5. Poststudy Care

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

6.6. Sample Storage

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

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

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

An AE does not include the following:

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

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

7.1.2. Serious Adverse Events

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

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

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

7.1.3. Study Drugs and Gilead Concomitant Medications Special 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 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.

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

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

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

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Toxicity Grading Scale, Version 2.1 (corrected, July 2017). 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, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs that are related to protocol-required procedures.

7.3.2. Adverse Events

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

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

7.3.3. Serious Adverse Events

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

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 Gilead Patient Safety.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

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

7.3.5. Concomitant Medications Reports

7.3.5.1. Gilead Concomitant Medications Special Situations Report

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

7.3.5.2. Non-Gilead Concomitant Medications Report

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

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

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

7.4. Reporting Process for Serious Adverse Events and Special 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 eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

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

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

Gilead Patient Safety
Email: PPD
or
Fax: PPD

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

7.4.2. Special 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 eCRFs and from there transmit the SSR information within 24 hours of the investigator's knowledge to Gilead Patient Safety from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

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

Gilead Patient Safety
Email: PPD
or
Fax: PPD

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

See Section 7.4.2.2 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

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

Gilead Patient Safety
Email: PPD
or
Fax: PPD

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

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

7.4.2.3. Pregnancy Reporting Process

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

Gilead Patient Safety
Email: PPD
or
Fax: PPD

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

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion because of complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after the study must be reported to the Gilead Patient Safety.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead Patient Safety using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Patient Safety. Gilead Patient Safety contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

Refer to Appendix 11.4 for Pregnancy Precautions, Definition for Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Regulation 536/2014 and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions. In accordance with the EU Regulation 536/2014, Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable suspected unexpected serious adverse reactions as outlined in current regulations.

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

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

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

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, 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 for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (corrected, July 2017). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The DAIDS scale is available at:

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

7.7. Toxicity Management

7.7.1. Obeldesivir

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

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

7.7.1.1. Laboratory Events Meeting Discontinuation Criteria

Laboratory events meeting discontinuation criteria are discussed in Section 3.3.1.1.

7.7.1.2. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.7.1.3. Grade 3 Laboratory Abnormality or Clinical Event

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

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

Additionally, participants who have an eGFR < 50 mL/min/1.73 m^2 by Bedside Schwartz formula will be discontinued from study drug whether considered related to the study drug or not (refer to Section 3.3.1.1).

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

7.7.1.4. Grade 4 Laboratory Abnormality or Clinical Event

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

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

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

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

8. STATISTICAL CONSIDERATIONS

Details of the statistical methods will be provided in the statistical analysis plan (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. Secondary Endpoints

Additional information on the secondary endpoints listed in Section 2 is provided below.

- Time (days) to sustained alleviation of targeted COVID-19 symptoms by Day 35

This secondary efficacy endpoint will be assessed via the participant symptom assessment. Symptom alleviation is defined as follows: all targeted symptoms scored moderate or severe at baseline are scored as mild or none for at least 48 consecutive hours, and all targeted symptoms scored mild or none at baseline are scored as none for at least 48 consecutive hours; the first day of the 48 consecutive hours will be considered the symptom alleviation date. Details of the COVID-19 symptoms to be assessed are provided in Section 6.3.7.

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 or to request extension of indication to include the applicable age/weight band(s).

8.2.1.1. Planned Internal Analysis

For the purpose of assessing the dosing regimen, interim analyses of relevant safety and PK data will be conducted by Gilead. Further details will be provided in the safety review team (SRT) charter.

8.2.1.2. Data Monitoring Committee Analysis

An external DMC will review the progress of the study and perform interim review(s) of safety and available PK data. The DMC membership, activities, and meeting schedule will be defined in a DMC charter.

8.2.2. Final Analysis

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

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analyses is defined as the Full Analysis Set (FAS). This will include all participants who (1) are enrolled into the study and (2) have received at least 1 dose of study drug.

8.3.1.2. Safety

The primary analysis set for safety analyses is defined as the Safety Analysis Set. This will include all participants who (1) are enrolled into the study and (2) have received at least 1 dose of study drug.

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

8.3.1.3. Pharmacokinetics

The PK Analysis Set will include all participants who (1) are enrolled into the study, (2) have received at least 1 dose of study drug, and (3) have at least 1 nonmissing PK concentration datum reported by the PK laboratory for GS-441524.

8.3.1.4. Virology

The Virology Analysis Set will include all participants who (1) are enrolled into the study, (2) have at least 1 dose of study drug, and (3) have positive SARS-CoV-2 viral load at baseline.

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 weight, height, and body mass index.

No formal statistical testing is planned.

8.5. Efficacy Analysis

For all efficacy analyses, the FAS will be used, unless specified otherwise. No formal statistical testing is planned.

8.5.1. Primary Analysis

There is no primary efficacy analysis for this study; all efficacy endpoints are either secondary or exploratory.

8.5.2. Secondary Analyses

The time to sustained alleviation of targeted COVID-19 symptoms by Day 35 is calculated as the symptom alleviation date minus the first dose date plus 1 day. In case, prior to data cutoff a participant:

- Completes the study without alleviation of targeted COVID-19 symptoms
- Discontinues from the study early prior to alleviation of targeted COVID-19 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 COVID-19 symptoms will be calculated as the last date on which the symptom alleviation is assessed by Day 35 minus the first dose date plus 1 day or Day 34, whichever occurs first.

In addition, if prior to data cutoff a participant:

- Dies from any cause prior to alleviation of targeted COVID-19 symptoms
- Takes rescue medication prior to alleviation of targeted COVID-19 symptoms

he/she will be regarded as not having the event of interest and will be censored at Day 34.

The timing to sustained alleviation of targeted COVID-19 symptoms will be estimated by cohort and overall using the Kaplan-Meier (KM) method. The median time to sustained alleviation of targeted COVID-19 symptoms along with the 95% CI will be presented. The proportion of participants with sustained alleviation of targeted COVID-19 symptoms using KM estimates will be provided in summary tables and plots by cohort and overall.

For continuous variables, data and change from baseline at all scheduled time points will be summarized by cohort and overall. For categorical variables, the number and percentage of participants in each category within a variable will be presented by cohort and overall.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days will be summarized for the Safety Analysis Set by cohort and overall. Data for the pretreatment period and after date of last dose of study drug plus 30 days will be included in data listings.

Descriptive summaries will be provided for the primary safety endpoints of incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities. No formal statistical testing is planned.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

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

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

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

8.6.3. Laboratory Evaluations

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

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

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

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

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

8.6.4. Other Safety Evaluations

The proportion of participants with concomitant use of medications other than RDV and ODV for treatment of COVID-19 will be provided in summary tables by cohort and overall.

Palatability and acceptability will be summarized using descriptive statistics by cohort and overall.

8.7. Adjustments for Multiplicity

No adjustments for multiplicity are planned for this study.

8.8. Pharmacokinetic Analysis

For all PK analyses, the PK Analysis Set will be used.

Plasma concentrations and PK parameters will be listed and summarized for GS-441524 using descriptive statistics by cohort and overall.

8.9. Sample Size

The total sample size will be at least 52 participants.

A minimum of 12 evaluable participants from each cohort (Cohorts 1-4) provides > 90% power to reject the null hypothesis that there is at least a 30% difference in GS-441524 AUC_{0-12} and C_{max}, respectively, between pediatric and adult participants, using 2 one-sided tests with each performed at an alpha level of 0.05. This power analysis assumes that the expected geometric mean ratio between the pediatric participants versus the adult group is 1, the equivalency boundary is 70% to 143%, and the interparticipant standard deviations of AUC_{0-12} and C_{max} are 0.19 h•ng/mL and 0.18 ng/mL (natural log scale, preliminary results from Study GS-US-611-6248).

A sample size of at least 52 participants will provide a reasonable assessment of the safety profile of ODV.

Sample size and power calculations were made using the software package nQuery Advisor(R), Version 8.5.

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. Study completion is defined as the date when the last participant completes the protocol-defined activities.

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 participant.

9.1.3. Informed Consent (or Assent)

The investigator is responsible for obtaining informed consent from parents and/or legal guardians as well as assent (age < 18 years, where locally and nationally approved) 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 (or assent as applicable) for documenting written informed consent and assent. Each ICF (and assent as applicable) will be appropriately signed and dated by the participant or the participant's parent or legal guardian and the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements).

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 or year of birth, as applicable) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. 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, eCRF, 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, eCRF, IRB/IEC, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Participant identification
- Documentation that participant meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent

- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, the US, Europe, or Japan) and until there are no pending or planned marketing applications in an International Council for Harmonisation (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

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a non-EDC vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the 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. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

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 IRB/IEC, 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 participant, 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 trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Regulatory and Ethical Consideration

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 (GCP)
- Applicable laws and regulatory requirements, including Regulation [EU] No 536/2014 (Regulation [EU] no 536/2014 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 eCRF. The study monitor is responsible for routine review of the case report form/eCRF 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 Discontinuation

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

10. REFERENCES

Ben-Tov A, Lotan R, Gazit S, Chodick G, Perez G, Mizrahi-Reuveni M, et al. Dynamics in COVID-19 symptoms during different waves of the pandemic among children infected with SARS-CoV-2 in the ambulatory setting. Eur J Pediatr 2022;181 (9):3309-18.

Bhalala US, Gist KM, Tripathi S, Boman K, Kumar VK, Retford L, et al. Characterization and Outcomes of Hospitalized Children With Coronavirus Disease 2019: A Report From a Multicenter, Viral Infection and Respiratory Illness Universal Study (Coronavirus Disease 2019) Registry. Critical care medicine 2022;50 (1):e40-e51.

Centers for Disease Control and Prevention. Demographic Trends of COVID-19 cases and deaths in the US reported to CDC. Available at: https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed: 25 September 2022. Last updated: 23 September 2022. 2022:

Colantonio DA, Kyriakopoulou L, Chan MK, Daly CH, Brinc D, Venner AA, et al. Closing the Gaps in Pediatric Laboratory Reference Intervals: A CALIPER Database of 40 Biochemical Markers in a Healthy and Multiethnic Population of Children. Clin Chem 2012;58 (5):854-68.

Dawood FS, Porucznik CA, Veguilla V, Stanford JB, Duque J, Rolfes MA, et al. Incidence Rates, Household Infection Risk, and Clinical Characteristics of SARS-CoV-2 Infection Among Children and Adults in Utah and New York City, New York. JAMA pediatrics 2022;176 (1):59-67.

European Center for Disease Prevention and Control. Clinical characteristics of COVID-19. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/clinical. Accessed: 17 June 2022. Last updated: 17 February 2022. 2022:

Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth. J Pediatr 2021;230:23-31 e10.

Gotzinger F, Santiago-Garcia B, Noguera-Julian A, Lanaspa M, Lancella L, Calo Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020;4 (9):653-61.

Kompaniyets L, Agathis NT, Nelson JM, Preston LE, Ko JY, Belay B, et al. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. JAMA Netw Open 2021;4 (6):e2111182.

Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr 2020;179 (7):1029-46.

Madera S, Crawford E, Langelier C, Tran NK, Thornborrow E, Miller S, et al. Nasopharyngeal SARS-CoV-2 viral loads in young children do not differ significantly from those in older children and adults. Sci Rep 2021;11 (1):3044.

Marks KJ, Whitaker M, Agathis NT, Anglin O, Milucky J, Patel K, et al. Hospitalization of Infants and Children Aged 0-4 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 2020-February 2022. MMWR. Morbidity and mortality weekly report 2022;71 (11):429-36.

Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. Lancet Child Adolesc Health 2021;5 (10):708-18.

Nikolopoulou GB, Maltezou HC. COVID-19 in Children: Where do we Stand? Archives of medical research 2022;53 (1):1-8.

Shi DS, Whitaker M, Marks KJ, Anglin O, Milucky J, Patel K, et al. Hospitalizations of Children Aged 5-11 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 2020-February 2022. MMWR. Morbidity and mortality weekly report 2022;71 (16):574-81.

Siegel DA, Reses HE, Cool AJ, Shapiro CN, Hsu J, Boehmer TK, et al. Trends in COVID-19 Cases, Emergency Department Visits, and Hospital Admissions Among Children and Adolescents Aged 0-17 Years - United States, August 2020-August 2021. MMWR. Morbidity and mortality weekly report 2021;70 (36):1249-54.

Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020;370:m3249.

Tchesnokov EP, Gordon CJ, Woolner E, Kocinkova D, Perry JK, Feng JY, et al. Template-dependent inhibition of coronavirus RNA-dependent RNA polymerase by remdesivir reveals a second mechanism of action. J Biol Chem 2020;295 (47):16156-65.

Tsankov BK, Allaire JM, Irvine MA, Lopez AA, Sauve LJ, Vallance BA, et al. Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis. Int J Infect Dis 2021;103:246-56.

Uka A, Buettcher M, Bernhard-Stirnemann S, Fougere Y, Moussaoui D, Kottanattu L, et al. Factors associated with hospital and intensive care admission in paediatric SARS-CoV-2 infection: a prospective nationwide observational cohort study. Eur J Pediatr 2022;181 (3):1245-55.

VEKLURY, Gilead Sciences Inc. VEKLURY® (remdesivir) for injection, for intravenous use. VEKLURY® (remdesivir) injection, for intravenous use. U.S. Prescribing Information. Foster City, CA. Revised: June. 2022a:

Veklury, Gilead Sciences Ireland UC. Veklury 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. County Cork, Ireland. Revised April. 2022b:

Vieux R, Hascoet JM, Merdariu D, Fresson J, Guillemin F. Glomerular Filtration Rate Reference Values in Very Preterm Infants. Pediatrics 2010;125 (5):e1186-92.

Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19. An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. Pediatr Infect Dis J 2020.

11. APPENDICES

11.1. Investigator Signature Page

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

A Phase 2/3 Single-Arm, Open-label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Obeldesivir in Pediatric Participants With COVID-19

GS-US-611-6464, Original Protocol, 09 May 2023

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. Committees

11.2.1. Safety Review Team

An SRT will make dose selection decision for future cohorts based on data described in Section 1.4.

An 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 for cohorts required dose selection. The data reviewed at the team meeting to make dose selection decisions will be defined in the charter. The quality control checks performed on the data reviewed and used for making dose selection 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 selection decisions are described in the SRT charter (or similar document).

11.2.2. Data Monitoring Committee

A multidisciplinary DMC consisting of non-Gilead personnel will review the progress of the study, perform interim reviews of safety and PK (if available) data, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the participant, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

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.

11.3. Pandemic Risk Assessment and Mitigation Plan

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

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

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

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

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

        Mitigation plan: For participant 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 videoconferencing, to assess the participant within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

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

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

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

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

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

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

6) Participant may be unable or unwilling to attend the study visit to sign an updated ICF 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:

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

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

a. Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and GCP 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 participant on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

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

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

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

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

1) Definitions

a) Definition of Childbearing Potential

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

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

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

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

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

a) Study Drug Effects on Pregnancy and Hormonal Contraception

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

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

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

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

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

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

Or

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

- Nonhormonal intrauterine device
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success)

Or

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

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

— Sponge with spermicide

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

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

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

3) Contraception Requirements for Participants Assigned Male at Birth

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

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

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

4) Unacceptable Birth Control Methods

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

5) Procedures to Be Followed in the Event of Pregnancy

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

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

11.5. Tanner Stages

1. Pubic hair (male and female)	
Tanner I	No pubic hair at all (prepubertal Dominic state)
Tanner II	Small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females)
Tanner III	Hair becomes more coarse and curly, and begins to extend laterally
Tanner IV	Adult-like hair quality, extending across pubis but sparing medial thighs
Tanner V	Hair extends to medial surface of the thighs
2. Genitals (male) (One standard deviation around mean age)	
Tanner I	Testes, scrotum, and penis about same size and proportion as in early childhood
Tanner II	Enlargement of scrotum and testes; skin of scrotum reddens and changes in texture; little or no enlargement of penis (10.5-12.5)
Tanner III	Enlargement of penis, first mainly in length; further growth of testes and scrotum (11.5-14)
Tanner IV	Increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin (13.5-15)
Tanner V	Genitalia adult in size and shape
3. Breasts (female)	
Tanner I	No glandular tissue: areola follows the skin contours of the chest
Tanner II	Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen
Tanner III	Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
Tanner IV	Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
Tanner V	Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla

11.6. Blood Volume Tables for Clinical Laboratory Studies

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

Table 5. Cohorts 1 and 2 - Blood Volume

Assessment	Screening/Day 1	Day 3	Day 5	Day 35/EOS	Total (mL)[a,b]
Hematology	1.2	1.2	1.2	1.2	4.8
Chemistry	1.1	1.1	1.1	1.1	4.4
Coagulation	1.8		1.8		3.6
PK		1	5		6
Additional PK (for hospitalized participants)			1		1
Total	**4.1**	**3.3**	**9.1**	**2.3**	**18.8**
Total (for hospitalized participants)	**4.1**	**3.3**	**10.1**	**2.3**	**19.8**

EOS = end of study; PK = pharmacokinetic(s);
a. Cohort 1 blood volume limits (≥ 40 kg participant): 80 mL for 24 hour maximum and 160 mL for 30 day maximum.
b. Cohort 2 blood volume limits (≥ 20 kg to < 40 kg participant): 40 mL to ≤ 80 mL for 24 hour maximum and 80 mL to ≤ 160 mL for 30 day maximum.

Blood volume tables for Cohort 3 onwards will be provided in a protocol amendment.

11.7. Amendment History

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

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

11.7.1. Amendment 0.1 (15 November 2023)

Rationale for Key Changes Included in Amendment 0.1	Affected Sections
In response to EU CTR comment, reference to relevant European Union regulation was added	Section 9.3.1

protocol GS-US-611-6464 amd 0.1 EU

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	16-Nov-2023 09:19:26