CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b/2a Study in Participants with Early Stage COVID-19 to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	150732
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT04539262
Indication:	COVID-19
Protocol ID:	GS-US-553-9020
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 31 July 2020 Amendment 1: 26 August 2020 Amendment 2: 14 December 2020 Amendment 3: 13 January 2021

This study will be conducted under US Food & Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area and Switzerland are not included under the IND and are considered non-IND sites.

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 1b/2a Study in Participants with Early Stage COVID-19 to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation
IND Number:	150732
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT04539262
Study Centers Planned:	Up to approximately 50 centers globally
Objectives:	The primary objective of this study is: • To characterize the impact of inhaled remdesivir (RDV) on severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 viral load in participants with early stage coronavirus disease 2019 (COVID-19) The secondary objectives of this study are: • To evaluate the safety and tolerability of inhaled Remdesivir for Injection formulation in participants with early stage COVID-19 • To evaluate the pharmacokinetics (PK) of inhaled Remdesivir for Injection formulation and its metabolites in participants with early stage COVID-19 in Parts A and B • To characterize and evaluate disease progression from baseline • To characterize the efficacy, safety, and tolerability of Remdesivir for Inhalation Solution formulation administered with a mouthpiece in Part C of the study CCI [redacted]

Study Design:

This is a Phase 1b/2a randomized, blinded, placebo-controlled, multicenter study of RDV therapy for outpatients with early stage COVID-19 evaluating inhaled RDV (treatment arm) or placebo-to-match (PTM) (placebo arm).

The study will feature multiple parts: Part A, Part B, and Part C.

The goal of the study is to evaluate the safety, efficacy, and PK of inhaled RDV in participants with early stage COVID-19. Parts A and B of the study will evaluate 2 different nominal dosing regimens (31 mg in Part A and 62 mg in Part B [Remdesivir for Injection formulation]) for up to 5 days of daily dosing. Safety and efficacy of an inhaled RDV formulation with reduced sulfobutylether β-cyclodextrin sodium (SBECD) content (Remdesivir for Inhalation Solution formulation) will be evaluated in Part C of the study. The RDV formulation used within each Study Part is as follows:

Study Part	Formulation	Volume/Nominal Dose (mg)	Duration of Nebulization (minutes)
Part A	Remdesivir for Injection formulation via nebulization	31 mg[a]	17 minutes
Part B	Remdesivir for Injection formulation via nebulization	62 mg[a]	34 minutes
Part C	Remdesivir for Inhalation Solution formulation via nebulization	39 mg[b]	19 minutes

a Sealed Facemask: Nominal dose of 31 mg and 62 mg to achieve a deposited dose of 5 mg and 10 mg, respectively: Overall delivery efficiency 16.1%.
b Mouthpiece: Nominal dose of 39 mg to achieve a deposited dose of 10 mg: Overall delivery efficiency 25.6%.

The term "inhaled remdesivir" refers to both the Remdesivir for Injection formulation and Remdesivir for Inhalation Solution formulation when administered via nebulization using the LC Sprint.

Part A: In Part A, approximately 36 participants who meet all eligibility criteria will be randomized in a 1:1:1 ratio into one of the following 3 treatment groups:

Treatment Group 1: 31 mg inhaled Remdesivir for Injection formulation daily for 5 days

Treatment Group 2: 31 mg inhaled Remdesivir for Injection formulation daily for 3 days followed by PTM daily for 2 days

Treatment Group 3: PTM daily for 5 days

	Part B: In Part B, if supported by evaluation in healthy volunteers in the Phase 1a study, an additional 36 total participants may be randomized in a 1:1:1 ratio into one of the following 3 treatment groups: **Treatment Group 4:** 62 mg inhaled Remdesivir for Injection formulation daily for up to 5 days **Treatment Group 5:** 62 mg inhaled Remdesivir for Injection formulation daily for up to 3 days followed by PTM daily through Day 5 **Treatment Group 6:** PTM daily for 5 days **Part C:** Part C of the study will include an expanded safety and efficacy assessment of an additional 80 participants. Participants in Part C will be enrolled after review of preliminary safety data from Parts A and B through at least Day 7. Approximately 80 participants will be randomized in a 3:1 ratio into one of the following 2 treatment groups: **Treatment Group 7:** 39 mg Remdesivir for Inhalation Solution formulation once daily for 5 days by mouthpiece **Treatment Group 8:** PTM daily for 5 days by mouthpiece
Number of Participants Planned:	Part A and Part B: Approximately 36 participants will be enrolled in each part. Part C: Approximately 80 participants will be enrolled.
Target Population:	Parts A and B: Participants ≥ 18 years of age with polymerase chain reaction (PCR)-confirmed early stage COVID-19 Part C: Participants ≥ 18 years of age with early stage COVID-19 confirmed by nucleic acid testing or direct antigen testing
Duration of Treatment:	RDV and/or PTM will be administered for 5 days.
Diagnosis and Main Eligibility Criteria:	Eligible participants will be at least 18 years of age who meet the following eligibility criteria: Key Inclusion Criteria: • Willing and able to provide written informed consent, or with a legal representative who can provide informed consent • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection first confirmed by PCR (Parts A and B) or by nucleic acid testing or direct antigen testing (Part C) with sample collected ≤ 4 days prior to randomization

- COVID-19 symptom onset ≤ 7 days prior to randomization
- Oxygen saturation as measured by pulse oximetry (SpO_2) > 94% on room air

Key Exclusion Criteria:

- Ongoing or prior participation in any other clinical trial of an experimental vaccine or treatment for COVID-19
- Prior or current hospitalization for COVID-19 or need for hospitalization
- Treatment of COVID-19 with other agents with actual or possible direct antiviral activity against SARS-CoV-2 including IV RDV or administration of any SARS-CoV-2 (or COVID-19) vaccine

  Patients chronically administered chloroquine or hydroxychloroquine for any reason are to be excluded
- Requiring oxygen supplementation
- Positive pregnancy test
- Breastfeeding female
- Known hypersensitivity to the study treatment, its metabolites, or formulation excipient
- Pre-existing pulmonary conditions such as chronic obstructive pulmonary disease or asthma (Parts A and B only)

Study Procedures/ Frequency:

At screening, after the participant has provided informed consent, assessments will include but are not limited to the following: demographic and baseline characteristics, medical history, and concomitant medications will be documented. Body weight and height will be measured. A urine pregnancy test will be performed for women of childbearing potential. Vital signs including heart rate, temperature, blood pressure, and SpO_2 will be recorded. A complete physical examination will be performed.

Study Parts A and B:

On Days 1 through 5, assessments will include a symptom-directed physical examination. A 12-lead electrocardiogram (ECG) will be performed at Day 1. Vital signs will be measured predose and postdose. Concomitant medications and adverse events (AEs) will be documented. Laboratory samples will be obtained for safety assessments (Days 1, 3, 5) and PK assessments (Days 1, 3, 5). Nasopharyngeal, oropharyngeal swab samples and saliva samples for SARS-CoV-2 testing and possible viral resistance testing will be performed on Days 1 through 5. A chest x-ray will be performed at Day 1 to identify any pulmonary infiltrates. Forced expiratory volume

in the first second of expiration (FEV_1) will be performed daily during treatment days and will be performed both predose and 10 minutes postdose. Repeat FEV_1 should be performed at 30 minutes postdose if there is > 15% reduction in FEV_1 at 10 minutes postdose compared with the same day predose FEV_1. FEV_1 assessment may also be performed if there is a clinical concern of bronchospasm. Inhaled Remdesivir for Injection formulation or PTM will be administered at Days 1 through 5. If Day 1 assessments are performed on the same day as the screening assessments, procedures need not be repeated.

Participants will complete the adapted InFLUenza Patient-Reported Outcome (FLU-PRO©) questionnaire daily (Days 1-14).

On Days 7 and 14, assessments will include a symptom-directed physical examination. Vital signs will be measured, concomitant medications and AEs will be documented. Laboratory samples will be obtained for safety assessments, single PK assessment (Day 7), and nasopharyngeal and oropharyngeal swab samples and saliva samples for SARS-CoV-2 testing and possible viral resistance testing.

On Day 28, assessments will include review of AEs and concomitant medications. The Day 28 follow-up assessments may be completed by telephone.

If supported by review of at least 7-day safety data from participants in Parts A and B, then the Remdesivir for Inhalation Solution formulation will be evaluated in Part C.

Pharmacokinetic Assessments:

Sparse plasma PK assessments will be conducted in all participants at selected sites in Parts A and B. Sparse plasma PK samples will be collected at Day 1 (end of nebulization, CCI [redacted]) and Day 3 (predose and end of nebulization).

Up to 6 participants/group in Part A and Part B will have intensive PK assessments. Intensive PK samples will be collected at Day 1 and an additional collection, either at Day 3 or Day 5, at the following time points relative to the end of nebulization: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 24 hours post end of nebulization. An additional single PK sample will be collected on Day 7 visit for subjects who participate in the intensive PK assessments.

Study Part C:

Remdesivir for Inhalation Solution formulation or PTM will be administered Days 1 through 5 with telehealth support as needed.

	On Days 1, 3, 5, and 7, assessments will include a symptom-directed physical examination. Nasopharyngeal, oropharyngeal swab samples and saliva samples for SARS-CoV-2 testing and possible viral resistance testing will be collected predose with the assistance of home nursing on Days 1, 3, 5, and 7. Vital signs will be performed predose on Days 1, 3, and 5 and on Day 7. Concomitant medications and AEs will be documented. Laboratory samples will be obtained for safety assessments predose on Days 1, 3, 5, and 7. Plasma samples will be obtained for PK assessments predose on Days 3 and 5 and Day 7 (anytime sample) in all participants. Participants will complete the adapted FLU-PRO© questionnaire daily (Days 1-14). FEV_1 will be performed daily during treatment days and will be performed both predose and 10 minutes postdose. Repeat FEV_1 should be performed at 30 minutes postdose if there is > 15% reduction in FEV_1 at 10 minutes postdose compared with the same day predose FEV_1. FEV_1 assessment may also be performed if there is a clinical concern of bronchospasm. On Days 14 and 28, assessments will include review of AEs and concomitant medications. The Day 14 and 28 follow-up assessments may be completed by telephone.
Test Product, Dose, and Mode of Administration:	In **Part A and Part B**, the Remdesivir for Injection formulation delivered by inhalation, will be used. In **Part C,** the Remdesivir for Inhalation Solution formulation will be used. Part A: 31 mg (nominal dose) Remdesivir for Injection administered via inhalation once daily at approximately the same time each day Part B: 62 mg (nominal dose) Remdesivir for Injection administered via inhalation once daily at approximately the same time each day Part C: 39 mg (nominal dose) by mouthpiece of Remdesivir for Inhalation Solution formulation administered via inhalation once daily at approximately the same time each day
Reference Therapy, Dose, and Mode of Administration:	Placebo administered via inhalation once daily at approximately the same time each day
Criteria for Evaluation:	
Safety:	Proportion of participants with treatment-emergent AEs and laboratory abnormalities.

Efficacy:	Change in SARS-CoV-2 viral load will be measured. A FLU-PRO© questionnaire will be utilized to report COVID-19 symptom severity and duration. Disease progression from baseline will be assessed by duration and change in severity of COVID-19 clinical symptoms and need for medically attended visits (MAVs).
Pharmacokinetics:	For Parts A and B, the plasma concentrations of inhaled RDV and its metabolites will be measured, as appropriate. The following plasma PK parameters will be calculated for each analyte (RDV, GS-441524 and GS-704277), as applicable: $AUC_{0\ 24h}$, AUC_{tau}, AUC_{last}, $CL_{ss/F}$, $t_{1/2}$, $V_{z/F}$, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, C_{tau}. CCI [redacted]
Statistical Methods:	No statistical sample size/power calculation was performed as the sample size of up to approximately 152 participants is deemed feasible and sufficient to provide a descriptive assessment of viral kinetics, safety and tolerability, PK and disease progression in this study. Antiviral activity evaluation will be based on time weighted average change in SARS-CoV-2 viral load (defined as the AUC of viral load change divided by time between baseline to Day 7) and will be summarized by treatment group and each RDV group compared with placebo. Safety: Adverse event data will be listed by participant. Adverse events leading to study treatment discontinuation, treatment-emergent AEs, and serious AEs will be summarized by treatment, system organ class, and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Listings of individual participants laboratory results and change from predose values for selected laboratory values will be summarized by treatment. Incidence of treatment-emergent laboratory abnormalities will be summarized by treatment. Vital signs and ECG data will be summarized by treatment. FEV_1 values will be summarized by treatment. Listings of individual participants progression of COVID-19 symptoms as reported by adapted FLU-PRO© questionnaire will be summarized by treatment.

PK:

For Parts A and B, plasma PK parameters for inhaled RDV and its metabolites will be summarized by treatment group using descriptive statistics (including mean, geometric mean, median, minimum, maximum, and sample size). Concentrations of inhaled RDV and its metabolites in plasma over time will be summarized. CCI [redacted]

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AE	adverse event
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
CI	confidence interval
CL_{ss}/F	apparent oral clearance at steady state after administration of the drug: CLss/F = Dose/AUC_{tau}, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CoV	coronavirus
CRF	case report form
C_{tau}	observed drug concentration at the end of the dosing interval
DAIDS	Division of AIDS
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EudraCT	European Clinical Trials Database
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in the first second of expiration
FLU-PRO©	InFLUenza Patient-Reported Outcome
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
GLPS	Global Patient Safety

IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
IXRS	interactive voice/web response system
LLOQ	lower limit of quantitation
MAV	medically attended visit
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
NOAEL	no observed adverse effect level
PCR	polymerase chain reaction
PI	principal investigator
PK	pharmacokinetic(s)
PT	preferred term
PTM	placebo-to-match
PVE	Pharmacovigilance and Epidemiology
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
RT-qPCR	quantitative reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBECD	sulfobutylether β-cyclodextrin sodium
SDV	source data verification
SpO_2	oxygen saturation as measured by pulse oximetry
SOC	standard of care
SOP	standard operating procedure
SRT	safety review team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)

ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution of the drug

1. INTRODUCTION

1.1. Background

Coronaviruses (CoVs) are positive-sense, single-stranded, enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. However, over the past 2 decades, emerging pathogenic CoVs that can cause life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV;{de Wit 2016, Ksiazek 2003}), Middle Eastern respiratory syndrome coronavirus (MERS-CoV; {Assiri 2013, Choi 2016, Who Mers-Cov Research Group 2013}), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19; {Zhu 2020}). Coronaviruses are known to have high mutation and recombination rates, which may allow them to cross species barriers and adapt to new hosts {Lau 2015}. Bats are reservoir hosts for many types of CoVs and are thought to have spread emerging CoVs to new species. Cross-species transmission to animals and subsequent zoonotic transmission has resulted in disease in humans {de Wit 2016}.

SARS-CoV-2, a single-stranded RNA virus, is identified as the cause of an outbreak of respiratory illness that was first detected in Wuhan, China in December 2019. The virus has now spread globally, resulting in a global pandemic and causing severe respiratory illness throughout the world. Severe cases progress to pneumonia and multi-organ failure, which can lead to death. Gilead Sciences, Inc. (Gilead) has been working closely with global health authorities to respond to the ongoing pandemic and to evaluate the utility of intravenous (IV) remdesivir (RDV; GS-5734™) as a treatment option for COVID-19. Supported by Phase 3 clinical studies, IV RDV has been approved for treatment of COVID-19 in Japan, the European Union (EU), the United States (US), and other countries.

1.2. Remdesivir (RDV; GS-5734) for Inhaled Administration

Remdesivir is being developed by Gilead and is formulated for IV administration and for administration via nebulization.

1.2.1. General Information

Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Metabolism of remdesivir to remdesivir triphosphate has been demonstrated in multiple cell types. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in inhibition of viral replication.

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

1.2.2. Additional Clinical Studies of Remdesivir

1.2.2.1. GS-US-553-9018 Inhaled Remdesivir Phase 1a Study

Study GS-US-553-9018 is an ongoing randomized, blinded, placebo-controlled, single- and multiple-dose study with staggered dose escalation and adaptive dose selection evaluating inhaled RDV. In each cohort, 10 healthy male and nonpregnant, nonlactating, female volunteers, aged 18 through 45, inclusive are randomized 4:1 to receive inhaled RDV or placebo-to-match (PTM). Participants received single doses of 12.5 mg, 31 mg, and 62 mg of Remdesivir for Injection formulation via nebulization in Cohorts 1, 2, and 4 respectively or multiple doses of 31 mg or 62 mg each day for 5 days in Cohorts 3 and 5. Cohorts 1 through 5 received Remdesivir for Injection formulation via nebulization, and Cohort 6 received Remdesivir for Inhalation Solution formulation. Safety data as of 10 September 2020 included all participants in Cohorts 1 through 5. All AEs were mild or moderate. There were no deaths, serious adverse events (SAEs), pregnancies, or study drug discontinuations.

Preliminary plasma PK data in healthy participants are available following administration of inhaled Remdesivir for Injection formulation as single nominal doses of 12.5 mg to 62 mg (2 mg to 10 mg deposited), and as multiple nominal doses of 31 mg (5 mg deposited) and 62 mg (10 mg deposited) for 5 days. Following single nominal dose administration of 12.5 mg, 31 mg, and 62 mg inhaled Remdesivir for Injection formulation, maximal concentrations of RDV and GS-704277 were achieved at the end of nebulization or within 30 minutes after the end of nebulization; plasma concentrations declined rapidly thereafter and were undetectable (below the limit of quantitation) at 2 hours and 4 hours postdose for RDV and GS-704277, respectively. GS-441524 concentrations peaked at 3 to 4 hours postdose and remained detectable up to 48 hours postdose in most participants. Approximately dose proportional increases in the exposures of RDV and the metabolites were observed following 12.5 mg, 31 mg and 62 mg single dose administration. Following multiple dose administration, no accumulation was noted for RDV and GS-704277, consistent with the short half-lives. Accumulation ratios of GS-441524 ranging from 1.2 to 1.6 were observed on Day 5 consistent with its longer half-life ranging from 11.2 hours (31 mg single dose) to 28.6 hours (62 mg multiple doses, Day 5).

Overall, the observed steady-state plasma exposures at the 31 mg and 62 mg nominal dose were substantially below those observed with the 100 mg IV clinical dose at steady-state (IV exposures were approximately 101 and 70-fold higher for RDV, 11 and 6.5-fold higher for GS-704277, and 16 and 8.5-fold higher for GS-441524 compared with the 31 mg, and 62 mg nominal dose of inhaled Remdesivir for Injection formulation, respectively). These results were similar to those observed in the nonclinical inhaled Remdesivir for Injection formulation study in African green monkeys. Comparison of the preliminary human and nonclinical African green monkey PK data indicate that it is reasonable to expect that the 31 mg and 62 mg human nominal inhaled doses (5 mg and 10 mg deposited) may produce similar, or exceeding GS-443902 (triphosphate) levels in respiratory tissues as the 100 mg human IV dose.

1.2.3. Rationale for This Study

The evaluation of inhaled RDV as a treatment for COVID-19 is supported by clinical data from studies of IV RDV in patients with COVID-19, inhaled administration of RDV in healthy volunteers, and nonclinical characterization of inhaled administration in PK, toxicology, and efficacy studies.

Remdesivir for treatment of COVID-19 administered by IV infusion is now approved in Japan, the EU, US, and numerous countries globally. Emerging data suggest that upper airway disease precedes lower airway and lung disease in individuals infected with SARS-CoV-2 {Wolfel 2020}. Delivery of RDV by inhalation could enable antiviral activity in the respiratory tract while achieving lower systemic drug exposures, potentially offering an option in non-hospitalized patients, and enabling use of RDV in patients who are not currently eligible for IV administration of RDV. Inhalation is a less invasive route of administration which will support outpatient administration. Furthermore, drug supply may be more efficiently utilized as there is potentially less total active pharmaceutical ingredient needed for each dose by inhalation versus IV administration. The current lyophilized clinical formulation of IV RDV, Remdesivir for Injection, 100 mg, is suitable for nebulization. Additionally, a new formulation with a reduced content of sulfobutylether β-cyclodextrin sodium (SBECD), Remdesivir for Inhalation Solution, 40 mg, is being evaluated in a Phase 1a study.

Data from nonclinical studies evaluating inhalation of RDV indicate minimal respiratory tract findings in a single dose PK study in African green monkeys, and a 7-day rat repeat-dose toxicity study. These studies demonstrate the localized delivery of RDV and formation of the active triphosphate, GS-443902, in respiratory tissues with lower systemic exposure to RDV and metabolites.

This study will evaluate the potential for a short course of nebulized RDV to prevent progression of COVID-19 in participants with early infection. The doses selected are anticipated to result in similar levels of triphosphate in the lung as that which results from IV administration.

Remdesivir by IV administration has a favorable safety and efficacy profile. Enrollment of this study in multiple parts will allow an initial assessment of safety and antiviral kinetics of nebulized RDV in early stage COVID-19 patients in Parts A and B of the study. Part C of the study will allow for evaluation of safety and efficacy of an inhaled RDV formulation with reduced SBECD content (Remdesivir for Inhalation Solution formulation via a mouthpiece). The use of a mouthpiece allows more drug to be administered over a shorter time period compared to a facemask and is more suitable for self/at-home administration.

1.3. Rationale for the Dose Selection

Remdesivir has been approved for the treatment of COVID-19 in Japan, the EU, and the US at an initial dose of 200 mg IV followed by 100 mg IV for the next 4 or 9 days. This protocol proposes investigation of a new route of administration through the respiratory tract to deliver drug directly to the primary site of infection while reducing overall systemic exposure.

Safety, tolerability, and PK of RDV administered via inhalation are being evaluated in an ongoing Phase 1a study in healthy participants (GS-US-553-9018). Two different RDV formulations, Remdesivir for Injection formulation and Remdesivir for Inhalation Solution formulation, were evaluated in this study at the nominal doses up to 62 mg (estimated 10 mg deposited dose, administered using LC® Sprint (PARI Respiratory Equipment, Inc.) equipped with sealed facemask and an exhaust filter, 16.1% to 17% device efficiency) once daily for 5 days. Safety and preliminary PK data are available for the Remdesivir for Injection formulation, and PK and safety results for Remdesivir for Inhalation Solution formulation are forthcoming. An amendment to protocol GS-US-553-9018 is ongoing to generate additional safety and PK data for LC Sprint equipped with mouthpiece, and Remdesivir for Inhalation Solution formulation. This additional cohort is planned to run in parallel to Part C of the GS-US-553-9020 study, and together will inform on the Phase 3 dose selection for inhaled RDV. Both formulations were well tolerated in the healthy volunteer study up to 62 mg nominal dose (10 mg deposited). Preliminary data are discussed in Section 1.2.2.1.

Based on these results, 31 mg and 62 mg doses are proposed for evaluation in Parts A and B of the current study, respectively. Briefly, a nominal dose of 31 mg Remdesivir for Injection formulation (estimated 5 mg deposited dose; utilizing 16.1% device efficiency) for 3 or 5 days is proposed for evaluation in Part A. This dose is predicted to achieve similar concentrations of the active GS-443902 in respiratory tissues as those expected following a 100 mg human IV dose. A higher nominal dose of 62 mg (estimated 10 mg deposited dose; utilizing 16.1% device efficiency), which may provide increased efficacy when administered to patients, is proposed for Part B. In both Parts, RDV will be administered using LC Sprint equipped with sealed facemask and an exhaust filter.

Part C:

Remdesivir for Inhalation Solution formulation and a new device configuration of LC Sprint utilizing a mouthpiece for drug delivery will be evaluated in Part C. This new formulation contains reduced levels of an excipient, SBECD (7.5% after reconstitution, as compared to 15% for Remdesivir for Injection formulation), which may offer improved safety when RDV is administered via inhalation. Both the new formulation and the new device configuration are being evaluated in healthy participants: Cohort 6 (60 mg Remdesivir for Inhalation Solution formulation or placebo, for 5 days, inhaled via sealed facemask) and Cohort 7 (39 mg Remdesivir for Inhalation Solution formulation or placebo, single dose, inhaled via mouthpiece). In alignment with the doses evaluated in the healthy volunteers study, the nominal dose in Part C is projected to be 39 mg (estimated 10 mg deposited dose; utilizing 25.6% mouthpiece configuration efficiency).

The proposed doses for evaluation in Part A, B, and C are anticipated to be safe and efficacious, based on the cumulative clinical and nonclinical information available to date (Section 1.2.2.1 and inhalation IB). Estimated dose margins based on mg/g lung weight at the lowest and highest nominal doses evaluated in this study are 5.2- and 2.6-fold, respectively (inhalation IB).

Duration of 3 to 5 days of dosing will be evaluated in this study. The 5-day dosing duration is the recommended IV remdesivir duration for treatment of COVID-19 requiring hospitalization and not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation {VEKLURY 2020}. Shorter treatment duration of IV RDV for 3 days is currently being evaluated in an outpatient study (GS-US-540-9012) in COVID-19 patients at risk for disease progression.

1.4. Risk/Benefit Assessment for the Study

Potential risks of a participant's study involvement include unknown adverse events (AEs) due to inhaled RDV. Strategies to mitigate these risks include close monitoring of participant's clinical status and laboratory testing. Parameters for discontinuation of the study treatment due to AEs will be well defined and closely followed.

Transient, Grade ≤ 2, treatment-emergent elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed with daily IV RDV administration in Phase 1 studies in healthy volunteers. Transaminases increased is a listed adverse drug reaction to RDV. However, due to the reduced systemic exposure to RDV compared to the IV regimen, it is anticipated that there will be a lower effect on ALT and AST. Nonetheless, liver function testing will be closely monitored during the study.

Remdesivir contains SBECD, an approved excipient. In nonclinical species, SBECD administration has been associated with kidney vacuolation and hypertrophy. However, nonclinical inhalation toxicology studies and available inhaled clinical data with SBECD support its use in the RDV clinical formulation.

Participants may or may not clinically benefit from participation in the study. If efficacious, benefits might include shorter duration or lower severity of COVID-19 symptoms or reduced progression to severe disease. They may also benefit from increased observations and evaluations by health care professionals. Data from this study may support further evaluation of inhaled RDV in patients with COVID-19.

During a pandemic, additional potential risks to participants may include adequate study treatment availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy.

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

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To characterize the impact of inhaled RDV on SARS-CoV-2 viral load in participants with early stage COVID-19

The secondary objectives of this study are:

- To evaluate the safety and tolerability of inhaled Remdesivir for Injection formulation in participants with early stage COVID-19
- To evaluate the PK of inhaled Remdesivir for Injection formulation and its metabolites in participants with early stage COVID-19 in Parts A and B
- To characterize and evaluate disease progression from baseline
- To characterize the efficacy, safety, and tolerability of Remdesivir for Inhalation Solution formulation administered with a mouthpiece in Part C of the study

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[redacted]

[redacted]

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- Time weighted average change in SARS-CoV-2 viral load which is defined as AUC of viral load change divided by time between baseline through Day 7

The secondary endpoints of this study are:

- Proportion of participants with treatment-emergent AEs (TEAEs) and laboratory abnormalities
- Proportion of participants with TEAEs leading to study treatment discontinuation
- Composite of all-cause medically attended visits (MAVs) (medical visits attended in person by the participant and a health care professional) or death by Day 28
- Composite of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or death by Day 28
- Proportion of participants hospitalized by Day 28
- Characterization of the plasma concentrations of inhaled RDV and its metabolites including $AUC_{0\ 24h}$, AUC_{last}, $CL_{ss/F}$, $t_{1/2}$, $V_{z/F}$, C_{max}, T_{max}, C_{last}, T_{last}, AUC_{tau}, λ_z, and C_{tau} (Parts A and B only)
- Change in SARS-CoV-2 viral load from baseline to Day 5
- Change in SARS-CoV-2 viral load from baseline to Day 7
- Change in SARS-CoV-2 viral load from baseline to Day 14 (Parts A and B only)
- Time to negative SARS-CoV-2 polymerase chain reaction (PCR)
- Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19 adapted InFLUenza Patient-Reported Outcome (FLU-PRO©) questionnaire

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[redacted]

[redacted]

[redacted]

3.2. Study Design

This study is a randomized, blinded, placebo-controlled, multicenter study of inhaled RDV in participants with early stage COVID-19 infection. In Parts A and B of the study, eligible participants will be randomized in equal proportions to 1 of 3 treatment groups.

Part C of this study is a randomized, blinded, placebo-controlled, multicenter study of Remdesivir for Inhalation Solution formulation in participants with early stage COVID-19 infection. Eligible participants will be randomized in a 3:1 ratio to 1 of 2 treatment groups to receive Remdesivir for Inhalation Solution formulation or PTM administered by mouthpiece.

The term "inhaled remdesivir" refers to both the Remdesivir for Injection formulation and Remdesivir for Inhalation Solution formulation when administered via nebulization using the LC Sprint.

3.3. Study Treatments

The study will feature multiple parts: Part A, Part B, and Part C. The planned *nominal* doses are provided below by treatment group.

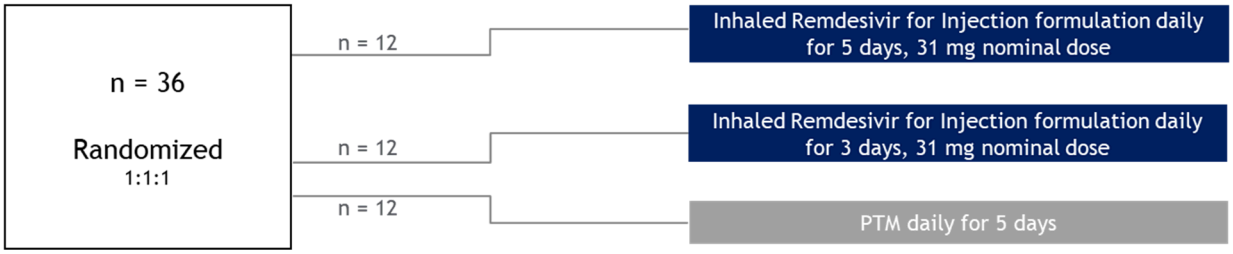
In Part A, approximately 36 participants who meet all eligibility criteria will be randomized in a 1:1:1 ratio into one of the following 3 treatment groups:

Treatment Group 1: 31 mg inhaled Remdesivir for Injection formulation daily for 5 days

Treatment Group 2: 31 mg inhaled Remdesivir for Injection formulation daily for 3 days followed by PTM daily for 2 days

Treatment Group 3: PTM daily for 5 days

Part A



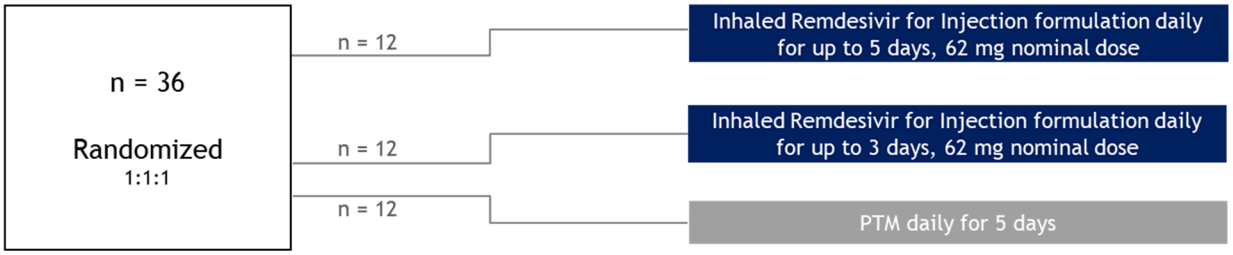
In Part B, if supported by Phase 1a data in healthy volunteers, an additional 36 participants who meet all eligibility criteria may be randomized in a 1:1:1 ratio into one of the following treatment groups:

Treatment Group 4: 62 mg inhaled Remdesivir for Injection formulation daily for up to 5 days

Treatment Group 5: 62 mg inhaled Remdesivir for Injection formulation daily for up to 3 days followed by PTM through Day 5

Treatment Group 6: PTM daily for 5 days

Part B



In Parts A and B, at in-clinic screening, after the participant has provided informed consent, assessments will include but are not limited to the following: demographic and baseline characteristics, medical history, and concomitant medications will be documented. Body weight and height will be measured. A urine pregnancy test will be performed for women of childbearing potential. Vital signs including heart rate, temperature, blood pressure, and SpO_2 will be recorded. A complete physical examination will be performed.

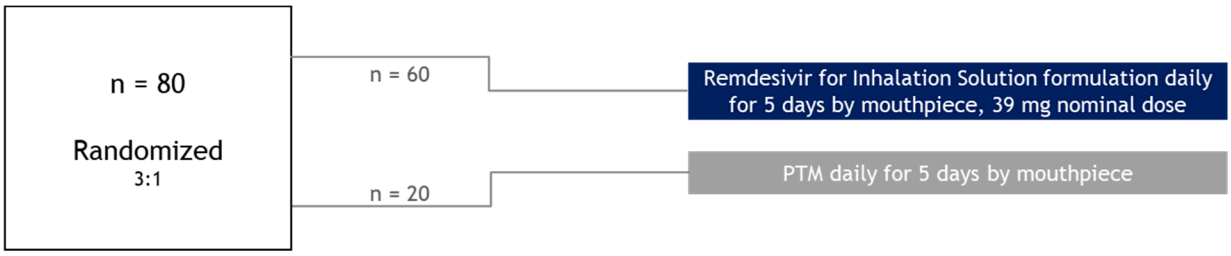
Participants with PCR-confirmed COVID-19 who enroll in the study will return to clinic daily on Days 1 through 5 for study treatment administration and clinical assessments. Participants will return to clinic on Days 7 and 14 for follow-up clinical assessment and undergo a Day 28 follow-up which may be completed by telephone.

Part C

Part C of the study will include an expanded safety and efficacy assessment of an additional 80 participants. Participants in Part C will be enrolled after review of preliminary safety data from Parts A and B through at least Day 7. Approximately 80 participants will be randomized 3:1 to 1 of 2 treatment groups:

Treatment Group 7: 39 mg Remdesivir for Inhalation Solution formulation once daily for 5 days by mouthpiece

Treatment Group 8: PTM daily for 5 days by mouthpiece



At screening, after the participant has provided informed consent, assessments will include but are not limited to the following: demographic and baseline characteristics, medical history, and concomitant medications will be documented. Body weight and height will be measured. A urine pregnancy test will be performed for women of childbearing potential. Vital signs including heart rate, temperature, blood pressure, and SpO_2 will be recorded. A complete physical examination will be performed.

In Part C, participants with nucleic acid testing or direct antigen testing-confirmed COVID-19 who enroll in the study will be administered Remdesivir for Inhalation Solution formulation or PTM on Days 1 through 5. Clinical assessments may be conducted at home with the assistance of home nursing on Days 1, 3, 5, and 7. Participants will undergo Days 14 and 28 telephone contact follow-ups.

3.4. Safety Review Team

A safety review team (SRT) will be established to assess safety and make decisions on dose selection and duration before initiating Part C.

The SRT will include the Gilead medical monitor. Other members of the SRT may include representatives from Global Patient Safety (GLPS) (formerly known as Pharmacovigilance and Epidemiology [PVE]), Clinical Operations, Biostatistics, and/or Clinical Pharmacology. Additional members may be invited to participate if additional expertise is needed. The medical monitor serves as the chair of the SRT. An SRT charter (or similar document) will be agreed upon by all SRT members prior to the first SRT meeting.

The data reviewed at the SRT meetings to make optimal dosing and duration decisions will be defined in the SRT charter, including safety and nonclinical toxicity data. The quality control checks performed on the data reviewed and used for making optimal dosing and duration decisions will also be described in the SRT charter.

Source data verification may not be performed prior to the meetings. Alternative data quality control checks that are performed on data used to make optimal dosing and duration decisions are described in the SRT charter.

3.5. Duration of Treatment

In Parts A and B, participants will receive study treatment with inhaled Remdesivir for Injection formulation or PTM for 5 days. The duration of nebulization for Remdesivir for Injection is approximately 17 minutes for a nominal dose of 31 mg Remdesivir for Injection formulation RDV and approximately 34 minutes for a nominal dose of 62 mg inhaled Remdesivir for Injection formulation.

In Part C, participants will receive study treatment with Remdesivir for Inhalation Solution or PTM for 5 days via a mouthpiece. The duration of nebulization for Remdesivir for Inhalation Solution is approximately 19 minutes for a nominal dose of 39 mg Remdesivir for Inhalation Solution formulation through a mouthpiece.

3.6. Discontinuation Criteria

Study treatment dosing in an individual subject will be placed on hold and may be discontinued following a review of all available clinical data by the medical monitor and discussion with the investigator, if any of the following occurs:

- Any SAE or ≥ Grade 3 AE suspected to be related to RDV
- Any elevations in ALT ≥ 5 × upper limit of normal (ULN); or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, confirmed by immediate repeat testing
- FEV_1 decline of > 15% at 30 minutes postdose compared with same day predose FEV_1

Discontinuation of study medication is not a seriousness criterion.

Subjects, who discontinue the study medication, should be encouraged to remain in the study and attend study visits as described in Section 6 (Study Procedures).

3.7. End of Study

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

3.8. Poststudy Care

The long-term care of the participant will remain the responsibility of their primary treating physician. Remdesivir is being supplied with curative intent. There is no provision for poststudy availability.

3.9. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory, and specialty laboratory (for PK data).

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

In Part A and Part B, approximately 36 participants will be enrolled in each part. Approximately 80 participants will be enrolled in Part C. Participants in Part C may receive study treatment in a home setting.

4.1.1. Subject Replacement

Subjects who discontinue prior to the end of study will not be replaced.

4.2. Inclusion Criteria

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

1) Willing and able to provide written informed consent, or with a legal representative who can provide informed consent

2) Aged ≥ 18 years

3) SARS-CoV-2 infection first confirmed by PCR (Parts A and B) or by nucleic acid testing or direct antigen testing (Part C) with sample collected ≤ 4 days prior to randomization

4) COVID-19 symptom onset ≤ 7 days prior to randomization

5) SpO_2 > 94% on room air

6) Participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5

4.3. Exclusion Criteria

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

1) Ongoing or prior participation in any other clinical trial of an experimental vaccine or treatment for COVID-19

2) Prior or current hospitalization for COVID-19 or need for hospitalization

3) Treatment of COVID-19 with other agents with actual or possible direct antiviral activity against SARS-CoV-2 including IV RDV or administration of any SARS-CoV-2 (or COVID-19) vaccine

    a) Patients chronically administered chloroquine or hydroxychloroquine for any reason are to be excluded

4) Requiring oxygen supplementation

5) Positive pregnancy test (Appendix 5)

6) Breastfeeding female

7) Known hypersensitivity to the study treatment, its metabolites, or formulation excipient

8) Pre-existing pulmonary conditions such as chronic obstructive pulmonary disease or asthma (Parts A and B only)

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

In Part A, approximately 36 participants who meet eligibility criteria will be randomized in a 1:1:1 ratio to receive either of two inhaled 31 mg RDV regimens or PTM starting on Day 1 using an interactive voice/web response system (IXRS) and assigned a subject number. In Part B, an additional 36 participants who meet eligibility criteria will be randomized in a 1:1:1 ratio to receive either of two inhaled 62 mg RDV regimens or PTM starting on Day 1 using an IXRS and assigned a subject number.

In Part C, approximately 80 participants will be randomized 3:1 to 1 of 2 treatment groups to receive either: Remdesivir for Inhalation Solution formulation (nominal dose of 39 mg to achieve 10 mg deposited dose) administered by mouthpiece or PTM administered by mouthpiece starting on Day 1 using an IXRS and assigned a subject number.

5.1.2. Blinding

The study will be sponsor unblinded. During the randomized phase, Gilead personnel and site pharmacist will be unblinded while the investigational site(s) and subjects participating in the study will remain blinded. To mitigate the risks of inadvertently releasing the treatment information, certain Gilead staff will only be provided with the unblinded information when there is a need to access such information for data analysis to support internal dose determination. Should Gilead staff receive unblinding information, they will maintain the confidentiality of the unblinded information, and will not communicate the information to blinded sites, or subjects as specified in Gilead standard operating procedures (SOPs).

During the randomized phase, subjects and all study site personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel may be unblinded based on their study role. Study treatment will be dispensed by an unblinded pharmacist to the subjects. Monitors, who will oversee activities relating to study drug, such as drug storage, drug accountability, and verifying randomization schedules as documented in the Study Monitoring Plan, will remain unblinded. Other non-Gilead personnel who are responsible for ensuring data integrity or participant safety may be unblinded as well. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, who facilitates the data transfer of PK files between Gilead and vendors, will remain unblinded. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IXRS system for purposes of study treatment inventory management will remain unblinded. Individuals in Clinical Virology responsible for the selection of samples for sequencing and/or interpretation of sequencing data will remain unblinded. Individuals in GLPS responsible for safety signal detection, IND safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries. External (ie, contract research organizations) Biostatisticians and Programmers may be unblinded for data monitoring purposes.

Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

5.1.3. Procedures for Breaking Treatment Codes

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

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

5.2. Description and Handling of Remdesivir

5.2.1. Formulation

Remdesivir for Injection, 100 mg, is a preservative-free, white to off-white or yellow, lyophilized solid containing 100 mg of remdesivir that is to be reconstituted with 19 mL of sterile water for injection prior to administration by inhalation through a nebulizer. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 20 mL (100 mg of remdesivir). Remdesivir for Injection, 100 mg, is supplied as a sterile product in a single-use, 30 mL, Type 1 clear glass vial. In addition to the active ingredient, Remdesivir for Injection, 100 mg contains the following inactive ingredients: SBECD, water for injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0.

The supplied Placebo-to-Match Remdesivir for Injection, 100 mg, (PTM Remdesivir for Injection, 100 mg) is identical in physical appearance to the active formulation and contains the same inactive ingredients.

Remdesivir for Inhalation Solution, 40 mg, is a preservative-free, white to off-white or yellow, lyophilized solid containing RDV that is to be reconstituted with 8.4 mL of sterile water for injection prior to administration by inhalation through a nebulizer. Following reconstitution, each vial contains a 5 mg/mL RDV solution with sufficient volume to allow withdrawal of 8 mL (40 mg of RDV). Remdesivir for Inhalation Solution, 40 mg, is supplied as a sterile product in a single-use, 20 mL, Type I clear glass vial. In addition to the active ingredient, Remdesivir for Inhalation Solution, 40 mg, contains the following inactive ingredients: SBECD, water for

injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0.

The supplied Placebo-to-Match Remdesivir for Inhalation Solution, 40 mg, (PTM Remdesivir for Inhalation Solution, 40 mg) is identical in physical appearance to the active formulation and contains the same inactive ingredients.

Detailed information regarding study treatment administration and reconstitution instructions are included in a pharmacy manual provided to the investigator.

5.2.2. Packaging and Labeling

Remdesivir for Injection, 100 mg, and placebo are provided in 30 mL glass vials enclosed with rubber stopper and aluminum seal with a polypropylene flip-off cap. Following reconstitution, each single-use vial contains sufficient volume to allow withdrawal of 20 mL (100 mg RDV or placebo).

Remdesivir for Inhalation Solution, 40 mg, and placebo are provided in 20 mL glass vials enclosed with rubber stopper and aluminum seal with a polypropylene flip-off cap. Following reconstitution, each single-use vial contains sufficient volume to allow withdrawal of 8 mL (40 mg RDV or placebo).

Remdesivir for Injection, 100 mg, Remdesivir for Inhalation Solution, 40 mg, and their matching placebo vials to be distributed to study centers and shall be labeled to meet applicable requirements of the US FDA and/or local regulations.

Sufficient quantities of Remdesivir for Injection, 100 mg, Remdesivir for Inhalation Solution, 40 mg, and their matching placebo vials will be shipped to the investigator or qualified designee from Gilead Sciences Clinical Supplies Management (or its designee).

5.2.3. Storage and Handling

Remdesivir for Injection, 100 mg, and PTM Remdesivir for Injection, 100 mg, vials should be stored below 30 °C prior to use. Remdesivir for Injection and placebo vials are recommended to be reconstituted and diluted within the same day as administration. Remdesivir for Injection and placebo vials do not contain any preservatives and are intended for single-use. Any unused Remdesivir for Injection and placebo material should be discarded.

The total storage time of reconstituted solution containing Remdesivir for Injection or placebo should not exceed 4 hours at room temperature (20 °C to 25 °C) or 24 hours at refrigerated temperature (2 °C to 8 °C). Any unused Remdesivir for Injection and placebo material should be discarded.

Remdesivir for Inhalation Solution, 40 mg, and PTM Remdesivir for Inhalation Solution, 40 mg, vials should be stored below 30 °C prior to use. Remdesivir for Inhalation Solution and placebo vials are recommended to be reconstituted and diluted within the same day as administration, if feasible. Remdesivir for Inhalation Solution and placebo vials do not contain any preservatives and are intended for single-use. Any unused Remdesivir for Inhalation Solution and placebo material should be discarded.

The total storage time of reconstituted solution containing Remdesivir for Inhalation Solution or placebo should not exceed 4 hours at room temperature (20 °C to 25 °C) or 7 days at refrigerated temperature (2 °C to 8 °C). Any unused Remdesivir for Inhalation Solution and placebo material should be discarded.

5.3. Dosage and Administration of Remdesivir

Remdesivir for Injection, 100 mg, and Remdesivir for Inhalation Solution, 40 mg, will be provided by Gilead. Remdesivir for Injection will be administered in Parts A and B of the study and Remdesivir for Inhalation Solution will be administered in Part C of the study.

All study treatments will be administered at approximately the same time each day.

In Parts A and B, RDV or PTM will be administered as an aerosolized solution by inhalation through a sealed facemask coupled with a nebulizer with a single inlet/outlet and exhaust filter. The duration of nebulization is approximately 17 minutes for a nominal dose of 31 mg inhaled Remdesivir for Injection. The duration of nebulization is approximately 34 minutes for a nominal dose of 62 mg inhaled Remdesivir for Injection.

In Part C, RDV or PTM will be administered as an aerosolized solution by inhalation through a mouthpiece coupled with a nebulizer with a single inlet/outlet. The duration of nebulization is approximately 19 minutes for a nominal dose of 39 mg Remdesivir for Inhalation Solution.

Detailed information regarding study treatment administration and reconstitution instructions can be found in the pharmacy manual.

5.4. Dispensing, Accountability, and Disposal or Return of Study Treatment

The investigator (or designee, eg, study center pharmacist) will acknowledge receipt of the study treatment (after reviewing the shipment's content and condition) from Gilead (or designee). The investigator will maintain an accurate inventory of all study drugs. For Parts A and B, each dose of the study treatments administered at the study center will be administered by qualified study center staff. The dose of study treatments administered to subjects in the clinic under the supervision of staff will be accurately recorded on the Study Drug Accountability form provided by Gilead (or on equivalent documentation maintained by the study center), which indicates the date and quantity of each dosage formulation dispensed to individual subjects. For Part C, each dose of study treatment may be administered at home or in-clinic. During study drug dispensation, the dose of study treatment will be accurately recorded on the Study Drug Accountability form provided by Gilead (or on equivalent documentation maintained by the

study center), which indicates the date and quantity of each dosage formulation dispensed to individual subjects. If study drug is administered at the home setting, a home health service provider will be available to provide supervision either in-person or via telehealth. All information and documentation related to home administration of study drug will be provided to the investigator by the home health provider, wherever applicable, in a timely manner.

Gilead recommends that used and unused study treatment should be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study treatment supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic Trial Master File. If study drug is destroyed onsite, the investigator must maintain accurate records for all study treatments destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study treatment. Upon study completion, copies of the study treatment accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study treatment supplies 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 treatment supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during a remote monitoring visit.

5.5. Prior and Concomitant Medications

Due to antagonism observed in vitro with RDV, use of chronically administered chloroquine or hydroxychloroquine for any reason is exclusionary.

Concomitant treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 (including IV RDV) is prohibited.

Medications will be assessed from screening to the Day 28 Follow-up visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 3 and described in the text that follows.

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

6.1. Subject Enrollment and Treatment Assignment

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. In Part C of the study, study visits may be performed in-clinic or at the participant's home via home health and/or telehealth, virtually or remotely, as permitted by local and institutional regulations.

6.2. Pretreatment Assessments

6.2.1. Study Parts A, B, and C: Screening Visit

Subjects will be screened in-clinic within 2 days before randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent, or with a legal representative who can provide informed consent

After the informed consent the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Obtain medical history including the following information (eg, date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics), allergies, and medical history
- Review concomitant medications
- Complete physical examination (urogenital/reproductive/anorectal exams will be performed only if clinically indicated) including vital signs (heart rate, temperature, blood pressure, and SpO_2), body weight, and height
- Urine pregnancy test (females of childbearing potential only)
- Childbearing female participants who are not postmenopausal (see Appendix 5) who do not wish to follow protocol-defined contraception will need a serum follicle-stimulating hormone (FSH) test (FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)

- Documentation of SARS-CoV-2 infection first confirmed by PCR (Parts A and B) or by nucleic acid testing or direct antigen testing (Part C) with sample collected ≤ 4 days prior to randomization

- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent form

In Study Parts A and B, study subjects who qualify should be immediately randomized. Randomization and dosing should occur on the same day if possible.

From the time of obtaining informed consent through the first administration of study treatment, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AEs 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. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Study Parts A and B: Baseline/Day 1 Assessments

The following evaluations are to be completed at the Day 1 visit in-clinic. The investigator must have confirmed eligibility before proceeding with randomization. If the screening and Day 1 visits occur on the same day, no procedures need to be repeated. Participants must complete the following assessments before being administered study treatment, unless otherwise stated:

- Complete symptom-directed physical examination including vital signs (heart rate, temperature, blood pressure, SpO_2)

- Perform 12-lead electrocardiogram (ECG)

- Perform FEV_1 (predose and 10 minutes postdose)

  Repeat of FEV_1 should be performed 30 minutes postdose if there is > 15% reduction in FEV_1 at 10 minutes postdose compared with the same day predose FEV_1. FEV_1 assessment may also be performed if there is a clinical concern of bronchospasm

- Perform chest x-ray

- Complete daily adapted FLU-PRO© questionnaire

- Safety laboratory samples will be collected for the following analyses:

  Hematology

  Coagulation

  Chemistry

- Obtain nasopharyngeal and oropharyngeal swabs, and saliva samples for SARS-CoV-2 quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) testing and possible viral resistance testing
- Sparse plasma PK assessment: end of nebulization CCI [redacted]
- [redacted]
- Review AEs and concomitant medications
- Inhaled Remdesivir for Injection formulation administration:

  Inhaled Remdesivir for Injection formulation will be administered to participants at the site under close supervision.

  Healthcare professionals administering inhaled Remdesivir for Injection formulation should have the appropriate medication available for immediate use in case of hypersensitivity. The participant should be treated according to the standard of care (SOC) for management of hypersensitivity reaction. After dose administration, monitoring should be done as follows:

  - Approximately 30 minutes post dose administration, participants should be observed, and vital signs should be performed prior to discharge

6.3. Study Parts A and B: Daily Study Assessments (Days 2-5)

The following evaluations are to be completed daily and prior to study treatment administration from Days 2-5 in-clinic, unless otherwise stated:

- Complete symptom-directed physical examination including vital signs (heart rate, temperature, blood pressure, SpO_2)
- Complete daily adapted FLU-PRO© questionnaire
- Safety laboratory samples (Days 3 and 5)

- Obtain nasopharyngeal, oropharyngeal swabs, and saliva samples for SARS-CoV-2 RT-qPCR testing and possible viral resistance testing

- Perform FEV_1 (predose and 10 minutes postdose)

  Repeat of FEV_1 should be performed 30 minutes postdose if there is > 15% reduction in FEV_1 at 10 minutes postdose compared with the same day predose FEV_1. FEV_1 assessment may also be performed if there is a clinical concern of bronchospasm

- Sparse plasma PK assessment: predose and end of nebulization (Day 3)

- [redacted]

- Review AEs and concomitant medications

- Inhaled Remdesivir for Injection formulation administration:

  Inhaled Remdesivir for Injection formulation will be administered to participants at the site under close supervision. Healthcare professionals administering inhaled Remdesivir for Injection formulation should have the appropriate medication available for immediate use in case of hypersensitivity. The participant should be treated according to the SOC for management of hypersensitivity reaction. After dose administration, monitoring should be done as follows:

  Approximately 30 minutes post dose administration, participants should be observed, and vital signs should be performed prior to discharge

6.4. Study Parts A and B: Follow-Up Assessments (Days 7 and 14)

The following evaluations are to be completed on Days 7 and 14 (± 3 days) in-clinic:

- Complete symptom-directed physical examination including vital signs (heart rate, temperature, blood pressure, SpO_2)

- Complete daily adapted FLU-PRO© questionnaire

- Safety laboratory samples

- Obtain nasopharyngeal, oropharyngeal swabs, and saliva samples for SARS-CoV-2 RT-qPCR testing and possible viral resistance testing

- Single PK assessment (Day 7)

- Review AEs and concomitant medications

6.5. Study Parts A and B: Day 28 Follow-Up Assessment (± 5 days)

The following evaluations are to be completed on Day 28 and may be completed by telephone:

- Review AEs and concomitant medications

6.6. Study Part C: Baseline/Day 1, Days 3, 5, and 7 Assessments

The investigator must have confirmed eligibility before proceeding with randomization. If the screening and Day 1 visits occur on the same day, no procedures need to be repeated. Whenever possible, Day 1 dosing should occur on the same day as screening. The following evaluations are to be completed at Days 1, 3, 5, and 7. They may be completed at home with the assistance of home nursing. Participants must complete the following assessments before being administered study treatment, unless otherwise stated:

- Complete symptom-directed physical examination including vital signs (heart rate, temperature, blood pressure, SpO_2)
- Complete daily adapted FLU-PRO© questionnaire
- On Days 1 through 5, perform FEV_1 (predose and 10 minutes postdose)

  Repeat of FEV_1 should be performed 30 minutes postdose if there is > 15% reduction in FEV_1 at 10 minutes postdose compared with the same day predose FEV_1. FEV_1 assessment may also be performed if there is a clinical concern of bronchospasm

- Obtain nasopharyngeal and oropharyngeal swabs, and saliva samples for SARS-CoV-2 RT-qPCR testing and possible viral resistance testing
- PK assessments

  Days 3 and 5: Sparse plasma PK assessment at predose

  Day 7: Single anytime plasma PK assessment

- Safety laboratory samples (Days 1, 3, 5, and 7)
- Review AEs and concomitant medications
- Remdesivir for Inhalation Solution formulation administration (Days 1-5):

  Remdesivir for Inhalation Solution formulation may be administered at home to participants with in-person or telehealth support

  For participants with pre-existing pulmonary conditions (ie, chronic obstructive pulmonary disease [COPD] or asthma) enrolled in Part C of the study, prescribed inhalers may not be used ≤ 30 minutes prior to Remdesivir for Inhalation Solution formulation administration

Healthcare professionals overseeing Remdesivir for Inhalation Solution formulation therapy remotely will observe the patient for any signs of adverse event. If any adverse event is observed and cannot be managed remotely appropriate urgent care measures will be implemented.

- Approximately 30 minutes after dose administration, participants should be observed remotely prior to telehealth support session concluding

6.7. Study Part C: Days 2 and 4 Assessments

The following evaluations are to be completed daily and prior to study treatment administration on Days 2 and 4. They may be completed at home with telehealth support, unless otherwise stated:

- Complete daily adapted FLU-PRO© questionnaire
- Perform FEV_1 (predose and 10 minutes postdose)

  Repeat of FEV_1 should be performed 30 minutes postdose if there is > 15% reduction in FEV_1 at 10 minutes postdose compared with the same day predose FEV_1. FEV_1 assessment may also be performed if there is a clinical concern of bronchospasm
- Review AEs and concomitant medications
- Remdesivir for Inhalation Solution formulation administration:

  Remdesivir for Inhalation Solution formulation may be administered at home to participants with in-person or telehealth support

  For participants with pre-existing pulmonary conditions (ie, COPD or asthma) enrolled in Part C of the study, prescribed inhalers may not be used ≤ 30 minutes prior Remdesivir for Inhalation Solution formulation administration

  Healthcare professionals overseeing Remdesivir for Inhalation Solution formulation therapy remotely will observe the patient for any signs of adverse event. If any adverse event is observed and cannot be managed remotely appropriate urgent care measures will be implemented.

  - Approximately 30 minutes after dose administration, participants should be observed remotely prior to telehealth support session concluding

6.8. Study Part C: Follow-Up Assessments (Days 14 and 28)

The following evaluations are to be completed on Day 14 (± 3 days) and Day 28 (± 5 days) and may be completed by telephone:

- Complete daily adapted FLU-PRO© questionnaire (Day 14 only)
- Review AEs and concomitant medications

6.9. Chest X-Ray

In Study Parts A and B, a chest x-ray will be performed at Day 1. If screening visit and Day 1 are the same day, chest x-ray does not need to be repeated if completed as SOC < 2 days before screening.

6.10. FEV_1

FEV_1 will be performed daily during treatment days and will be performed both predose and 10 minutes postdose. Repeat FEV_1 should be performed at 30 minutes postdose if there is > 15% reduction in FEV_1 at 10 minutes postdose compared with the same day pre-dose FEV_1. FEV_1 assessment may also be performed if there is a clinical concern of bronchospasm.

All subjects with >15% reduction in FEV_1 compared with same day predose FEV1 should be monitored until FEV_1 normalizes.

FEV_1 assessments will be performed as per the current American Thoracic Society Standardization.

6.11. Clinical Laboratory Assessments

Clinical laboratory assessments will be performed throughout the study as outlined below and in Appendix 3.

The following clinical laboratory assessments will be performed at screening and analyzed locally at sites:

- Urine pregnancy test (females of childbearing potential only)
- FSH testing (screening only): females who are < 54 years old and have ceased menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure only and do not wish to follow protocol-defined contraception

The following clinical laboratory assessments will be performed at the applicable visits and sent to a central laboratory for analysis:

- Chemistry: alkaline phosphatase, AST, ALT, gamma-glutamyl transferase, total bilirubin, direct and indirect bilirubin, total protein, albumin, lactate dehydrogenase, creatine phosphokinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, uric acid
- Hematology: hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume
- Coagulation panel: prothrombin time, partial thromboplastin time, and international normalized ratio

- Virology assessments: nasopharyngeal and oropharyngeal swab samples and saliva samples will be used to assess SARS-CoV-2 viral load by RT-qPCR. Once viral load testing is complete, the remnant samples may be used to evaluate the emergence of viral resistance by SARS-CoV-2 sequencing and/or phenotypic testing

- Estimated glomerular filtration rate will be determined according to:

  Cockcroft-Gault formula for creatinine clearance for participants ≥ 18 years of age

  Creatinine clearance will be estimated based on screening body weight

  Men: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})}$ creatinine clearance (CLcr) (mL/min)

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

6.12. Pharmacokinetic Assessments

Sparse plasma PK assessments will be conducted in all participants in Parts A, B, and C. In Study Parts A and B, sparse plasma PK samples will be collected at Day 1 (end of nebulization, CCI [redacted]) and Day 3 (predose and end of nebulization). In Study Part C, sparse plasma PK samples will be collected at Days 3 and 5 (predose) and a single anytime PK sample will be collected on Day 7.

Up to 6 participants/group in Part A and Part B will have intensive PK assessments. Intensive PK samples will be collected at Day 1 and an additional collection, either at Day 3 or Day 5, at the following time points relative to the end of nebulization: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 24 hours post end of nebulization. An additional single PK sample will be collected on Day 7 visit for subjects who participate in the intensive PK assessments.

6.13. Assessments for Early Discontinuation from Study

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (see Section 6.13.1, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.13.1. Criteria for Discontinuation of Study Treatment

Study treatment may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing if supported by both investigator and Gilead medical monitor

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Lack of efficacy
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 5
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board (IRB) or independent ethics committee (IEC)
- Any SAE or ≥ Grade 3 AE suspected to be related to RDV
- FEV_1 decline of > 15% at 30 minutes postdose compared with same day predose FEV_1
- Meeting toxicity management criteria necessitating discontinuation, refer to Section 7.7.

6.14. End of Study

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

6.15. Poststudy Care

The long-term care of the participant will remain the responsibility of their primary treating physician. Remdesivir is being supplied with curative intent. There is no provision for poststudy availability.

6.16. Sample Storage

The stored biological samples may be used by Gilead or its research partner for future testing to provide additional 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. If subjects provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of the study or per country requirements.

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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 subject administered a study treatment, which 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 treatment, whether or not the AE is considered related to the study treatment. 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, and transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form (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 treatment 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 subject 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 subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a 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 Treatments and Gilead Concomitant Therapy Special Situations Reports

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

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study treatment while the medication is in the control of a health care professional, patient, 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 treatment by a subject.

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

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

Drug interaction is defined as any drug/drug, drug/food, 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 treatment.

Counterfeit or falsified medicine: Any study treatment 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 Treatments and Procedures

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

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

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

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

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

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

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

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

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events

7.3.1. Requirements for Collection Prior to Study Treatment Initiation

After informed consent, but prior to initiation of study treatment, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study treatment, collect all AEs, regardless of cause or relationship, including the protocol-required posttreatment follow-up period must be reported 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 subject 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 Gilead GLPS (formerly PVE) 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 treatment, 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 treatment, the investigator should promptly document and report the event to Gilead GLPS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Treatment Special Situations Reports

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

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study treatment), that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.4.2.1).

7.3.5.2. Non-Gilead Concomitant Therapy Report

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

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 report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

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

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject 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 subject'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 GLPS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If 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:

Gilead GLPS	Gilead GLPS 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 GLPS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Treatment

- All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from study treatment initiation throughout the duration of the study, including the protocol required post treatment follow-up period.

Gilead GLPS	Gilead GLPS Email PPD or Fax: PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve Gilead concomitant medications that are not considered study treatment must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

Gilead GLPS	Gilead GLPS 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 due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

- The investigator should report pregnancies in female study subjects and/or female partners of male subjects that are identified after initiation of study treatment and throughout the study, including the post study treatment follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead GLPS	Gilead GLPS 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 due to 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 post study must be reported to the Gilead GLPS.

- The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS 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 GLPS. Gilead GLPS contact information is as follows: email PPD and fax: PPD.

- Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

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

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

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

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

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

Severity should be recorded and graded according to the DAIDS scale, Version 2.1. 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.

All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality is demonstrated.

7.7. Toxicity Management

Nebulized RDV will be administered to participants under close supervision.

Inhaled Remdesivir for Injection formulation will be administered to participants at the clinical site (Parts A and B). Healthcare professionals administering inhaled Remdesivir for Injection formulation should have the appropriate medication available for immediate use in case of hypersensitivity. The participant should be treated according to the SOC for management of hypersensitivity reaction. After dose administration, monitoring should be done as follows:

- Approximately 30 minutes after dose administration, participants should be observed, and vital signs should be performed prior to discharge (Parts A and B only)

Remdesivir for Inhalation Solution formulation may be administered to participants in the participant's home with in-person or telehealth support (Part C only). Healthcare professionals overseeing Remdesivir for Inhalation Solution formulation therapy remotely will observe the patient for any signs of adverse event. If any adverse event is observed and cannot be managed remotely, appropriate urgent care measures will be implemented.

- Approximately 30 minutes after dose administration, participants should be observed remotely prior to telehealth support session concluding

For participants with pre-existing pulmonary conditions (ie, COPD or asthma) enrolled in Part C of the study, prescribed inhalers may not be used ≤ 30 minutes prior to Remdesivir for Inhalation Solution formulation administration.

The participant should be treated according to the SOC for management of hypersensitivity or bronchospasm according to site or home health protocol. The medical monitor should be notified prior to study treatment discontinuation when medically feasible. Study treatment dosing in an individual participant will be placed on hold and may be permanently discontinued, following review of all available clinical data by the Medical Monitor and discussion with the investigator, in the following conditions:

- Development of ALT levels ≥ 5 × ULN
- Development of ALT levels ≥ 3 × ULN **and** bilirubin ≥ 2 × ULN
- Acute anaphylactic reaction to RDV
- Estimated creatinine clearance < 30 mL/min based on the Cockcroft-Gault formula
- Any SAEs and Grade 3 and 4 abnormal laboratory results assessed as related to study treatment

For clinical queries, please contact the medical monitor. Study treatment dosing may be resumed if it was held due to laboratory abnormality and is now within acceptable range, if the abnormality was not attributed to study treatment.

Please refer to Appendix 4 for further details on the management of clinical and laboratory AEs.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To characterize the impact of inhaled RDV on SARS-CoV-2 viral load in participants with early stage COVID-19

The secondary objectives of this study are:

- To evaluate the safety and tolerability of inhaled Remdesivir for Injection formulation in participants with early stage COVID-19
- To evaluate the PK of inhaled Remdesivir for Injection formulation and its metabolites in participants with early stage COVID-19 in Parts A and B
- To characterize and evaluate disease progression from baseline
- To characterize the efficacy, safety, and tolerability of Remdesivir for Inhalation Solution formulation administered with a mouthpiece in Part C of the study

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8.1.2. Primary Endpoint

- Time-weighted average change in SARS-CoV-2 viral load which is defined as AUC of viral load change divided by time between baseline through Day 7

8.1.3. Secondary Endpoint

The secondary endpoints of this study are:

- Proportion of participants with TEAEs and laboratory abnormalities
- Proportion of participants with TEAEs leading to study treatment discontinuation
- Composite of all-cause MAVs (medical visits attended in person by the participant and a health care professional) or death by Day 28

- Composite of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or death by Day 28
- Proportion of participants hospitalized by Day 28
- Characterization of the plasma concentrations of inhaled RDV and its metabolites including $AUC_{0\ 24h}$, AUC_{last}, $CL_{ss/F}$, $t_{1/2}$, $V_{z/F}$, C_{max}, T_{max}, C_{last}, T_{last}, AUC_{tau}, λ_z, and C_{tau} (Parts A and B only)
- Change in SARS-CoV-2 viral load from baseline to Day 5
- Change in SARS-CoV-2 viral load from baseline to Day 7
- Change in SARS-CoV-2 viral load from baseline to Day 14 (Parts A and B only)
- Time to negative SARS-CoV-2 PCR
- Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19 adapted FLU-PRO© questionnaire

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8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to 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.

8.2.2. Final Analysis

The unblinded final analysis will be performed at the end of study, after all subjects 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 analysis is defined as the Full Analysis Set, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of study treatment. Participants will be grouped according to the treatment to which they were randomized.

8.3.1.2. Safety

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

8.3.1.3. Pharmacokinetics

Each PK Analysis Set will include all randomized subjects who received at least 1 dose of study treatment and had at least 1 nonmissing PK concentration datum reported by the PK laboratory for each respective analyte.

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 (e.g., 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 trial data. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (i.e., 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.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

SARS-CoV-2 viral load will be summarized by treatment using descriptive statistics in Part A and Part B. For Part C, time weighted average change in SARS-CoV-2 viral load will be compared between the RDV and placebo groups using analysis of covariance with baseline viral load included in the model as a covariate.

8.5.2. Secondary Analyses

The proportion of participants all-cause MAV (medical visits attended in person by the participant and a health care professional) or death by Day 28 will be estimated using Kaplan-Meier methods by treatment group in Part C. The proportion of participants COVID-19 related MAVs or death by Day 28 will be estimated using Kaplan-Meier methods by treatment group in Part C. The proportion of hospitalization by Day 28 will be summarized by treatment group. Kaplan Meier product limit method will be used to estimate time to negative SARS-CoV-2 PCR and time to alleviation (mild or absent) of baseline COVID-19 symptoms by treatment group.

8.6. Safety Analysis

All safety data collected on or after the randomization date through Day 28 will be summarized by treatment group (according to the study treatment received). Data for the pretreatment will be included in data listings.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class, high-level group term, high-level term, preferred term (PT), 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 TEAE will be defined as any AE that begins on or after the date of first dose of study treatment up to the date of last dose of study treatment plus 30 days.

Summaries (number and percentage of subjects) of TEAEs (by system organ class and PT) will be provided by treatment group.

8.6.3. Laboratory Evaluations

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

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

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

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

8.7. Adjustments for Multiplicity

No adjustments for multiple comparison are planned.

8.8. Pharmacokinetic Analysis

For Parts A and B, plasma concentrations and PK parameters (if applicable) for inhaled RDV and its metabolites will be listed and summarized using descriptive statistics by treatment group (including mean, geometric mean, median, minimum, maximum, and sample size). Concentrations of inhaled RDV and its metabolites in plasma over time will be summarized. For Part C, plasma concentration of GS-441524 will be listed and summarized using descriptive statistics by nominal time.

8.9. Sample Size

The sample size in this study is determined based on practical considerations and past experience with similar types of studies. No sample size/power calculation was performed. A sample size up to approximately 152 participants (72 participants for Part A and Part B; 80 participants for Part C) should provide a suitable assessment of the descriptive efficacy, and safety profile in this population.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug during the course of a clinical study. This documentation must be provided prior to 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 subject completes the protocol-defined activities.

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

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject 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 any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

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

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB or IEC or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions or in accordance with local regulations. NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject 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, the study treatment, and any other study information, remain 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 study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, paper or electronic completed subject case report forms (CRFs), IRB or IEC and governmental approval with correspondence, informed consent, 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 subject:

- Subject identification
- Documentation that subject 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 subject 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 treatment, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for ED, if it occurs

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, the US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 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 study 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 subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the Sponsor. Subsequent to data entry, a study monitor will perform source data verification (SDV) within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator or 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 (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials 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 by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). 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.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff 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, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the 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 monitor should have access to any subject records needed to verify the entries in the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of 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 medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority(ies), IRBs, or IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGMENT

A Phase 1b/2a Study in Participants with Early Stage COVID-19 to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation

GS-US-553-9020, Amendment 3, 13 January 2021

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

PPD

Name (Printed)
Medical Monitor

PPD

Signature

13 Jan 2021

Date

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

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

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

These risks can be summarized as follows:

1) Study drug supplies to subjects and sites:

    a) Subjects 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 subject visits. Without study drugs, the subject would not be able to stay on the study drug as planned per protocol.

    Mitigation plan: Study drug supplies may be provided to the subject from the site without a clinic visit, once it is confirmed that the subject may safely continue on study drug as determined by the principal investigator (PI). A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person subject 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 subjects if permitted by local ethics committee/institutional review boards (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 subject would not be able to stay on the study drug as planned per protocol.

    Mitigation plan: The sites' 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 study sites. Manual shipments will be triggered as necessary.

2) Subject safety monitoring and follow-up:

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

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

        i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

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

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

iv) If applicable, confirm subjects 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 subject to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Subjects 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 lab analyses.

Mitigation plan: Local labs may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local lab pregnancy testing is not feasible.

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

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

3) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur 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 subject visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. In compliance with Gilead policy, a remote SDV should not be arranged). The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote 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 subjects 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 due to subjects missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report 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 subjects 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 RDV in study subjects remains unchanged.

Appendix 3. Study Procedures Tables

Appendix Table 1. Study Parts A and B: Study Procedures Table

		TREATMENT PERIOD					FOLLOW-UP PERIOD		
Schedule of Assessments	**Screening**	**Day 1[a]**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 7**	**Day 14 (± 3 days)**	**Day 28[b] (± 5 days)**
Obtain Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Documentation of SARS-CoV-2	X								
ECG[c]		X							
Complete or Symptom-Directed Physical Examination	X	X	X	X	X	X	X	X	
Body Weight	X								
Height	X								
Vital Signs (Heart Rate, Temperature, Blood Pressure, SpO_2)	X	X	X	X	X	X	X	X	
Completion of Daily Adapted FLU-PRO© Questionnaire[d]		X	X	X	X	X	X	X	
Chest X-Ray[e]		X							
FEV_1		X	X	X	X	X			
Safety Laboratory Assessments (Hematology, Chemistry, Coagulation)		X		X		X	X	X	
Pregnancy Test (Urine)	X								
Serum FSH Test[f]	X								
Nasopharyngeal and Oropharyngeal Swabs and Saliva Samples for SARS-CoV-2 RT-qPCR Testing and Possible Viral Resistance Testing		X	X	X	X	X	X	X	
Sparse Plasma PK Assessments[g]		X		X					

Schedule of Assessments	Screening	TREATMENT PERIOD					FOLLOW-UP PERIOD		
		Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14 (± 3 days)	Day 28[b] (± 5 days)
CCI									
CCI									
Inhaled Remdesivir for Injection Formulation or PTM Administration[j]		X	X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; FEV_1 = forced expiratory volume in the first second of expiration; FLU-PRO© = InFLUenza Patient-Reported Outcome; FSH = follicle-stimulating hormone; PCR = polymerase chain reaction; PK = pharmacokinetic(s); RT-qPCR = quantitative reverse transcriptase polymerase chain reaction; RDV = (remdesivir, GS 5734™); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation as measured by pulse oximetry

a If the screening and Day 1 visits occur on the same day, no procedures need to be repeated.
b Day 28 assessments may be completed by telephone.
c ECG will not be required at screening. However, ECG should be performed prior to dosing on Day 1. If subject randomizes and doses on the same day as screening, then ECG will be done at screening.
d Adapted FLU PRO© questionnaire is to be completed daily (Days 1 14).
e Chest x ray will be performed at Day 1. If screening visit and Day 1 are the same day, chest x ray does not need to be repeated if completed as SOC < 2 days before screening.
f Serum FSH test: Childbearing female participants who are not postmenopausal (see Appendix 5 who do not wish to follow protocol defined contraception will need a serum FSH test (FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)
g Sparse plasma PK will be collected at Day 1 (end of nebulization, CCI) and Day 3 (predose and end of nebulization).
[redacted]
j Inhaled Remdesivir for Injection formulation will be administered to participants at the site under close supervision. Healthcare professionals administering inhaled Remdesivir for Injection formulation should have the appropriate medication available for immediate use in case of hypersensitivity. The participant should be treated according to the SOC for management of hypersensitivity reaction. After dose administration, monitoring should be done as follows: Approximately 30 minutes post dose administration, participants should be observed, and vital signs should be performed prior to discharge.

Appendix Table 2. Study Part C: Study Procedures Table

Schedule of Assessments	Screening[a]	TREATMENT PERIOD					FOLLOW-UP PERIOD		
		Day 1[b]	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14[c] (± 3 days)	Day 28[c] (± 5 days)
Obtain Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Documentation of SARS-CoV-2[d]	X								
Complete or Symptom-Directed Physical Examination	X	X		X		X	X		
Body Weight	X								
Height	X								
Vital Signs (Heart Rate, Temperature, Blood Pressure, SpO_2)	X	X		X		X	X		
Completion of Daily Adapted FLU-PRO© Questionnaire[e]		X	X	X	X	X	X	X	
FEV_1		X	X	X	X	X			
Safety Laboratory Assessments (Hematology, Chemistry, Coagulation)		X		X		X	X		
Pregnancy Test (Urine)	X								
Serum FSH Test[f]	X								
Nasopharyngeal and Oropharyngeal Swabs and Saliva Samples for SARS-CoV-2 RT-qPCR Testing and Possible Viral Resistance Testing		X		X		X	X		
Sparse/Single Plasma PK Assessments[g]				X		X	X		

Schedule of Assessments	Screening[a]	TREATMENT PERIOD					FOLLOW-UP PERIOD		
		Day 1[b]	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14[c] (± 3 days)	Day 28[c] (± 5 days)
Remdesivir for Inhalation Solution Formulation or PTM Administration[h]		X	X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

COPD chronic obstructive pulmonary disease; ECG electrocardiogram; FEV_1 forced expiratory volume in the first second of expiration; FLU PRO© InFLUenza Patient Reported Outcome; FSH follicle stimulating hormone; PCR polymerase chain reaction; PK pharmacokinetic(s); RT qPCR quantitative reverse transcriptase polymerase chain reaction; RDV (remdesivir, GS 5734™); SARS CoV 2 severe acute respiratory syndrome coronavirus 2; SpO_2 oxygen saturation as measured by pulse oximetry

a Study visits, with the exception of the screening visit, may be performed in clinic or at the participant's home via home health and/or telehealth, virtually or remotely, as permitted by local and institutional regulations.

b If the screening and Day 1 visits occur on the same day, no procedures need to be repeated.

c Days 14 and 28 assessments may be completed by telephone.

d Documentation of SARS CoV 2 infection first confirmed by nucleic acid testing or direct antigen testing with sample collected ≤ 4 days prior to randomization

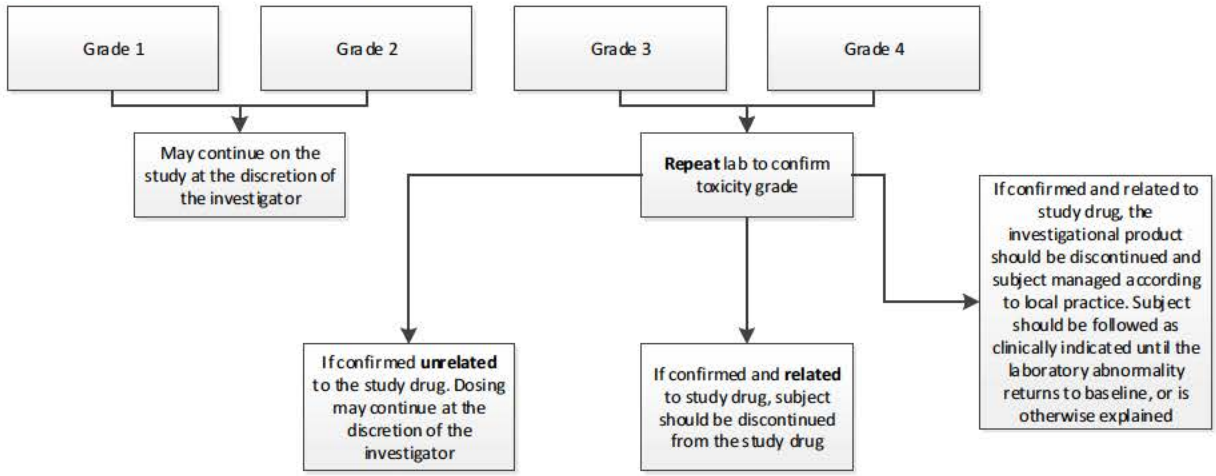
e Adapted FLU PRO© questionnaire is to be completed daily (Days 1 14).

f Serum FSH test: Childbearing female participants who are not postmenopausal (see Appendix 5) who do not wish to follow protocol defined contraception will need a serum FSH test (FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)

g Sparse plasma PK will be collected at Days 3 and 5 (predose). A single anytime PK sample will be collected on Day 7 visit.

h Remdesivir for Inhalation Solution formulation may be administered to participants in the participant's home with in person or telehealth support. For participants with pre existing pulmonary conditions (ie, COPD or asthma) enrolled in Part C of the study, prescribed inhalers may not be used ≤ 30 minutes prior to Remdesivir for Inhalation Solution formulation administration. Healthcare professionals overseeing Remdesivir for Inhalation Solution formulation therapy remotely will observe the patient for any signs of adverse event. If any adverse event is observed and cannot be managed remotely, appropriate urgent care measures will be implemented. Approximately 30 minutes after dose administration, participants should be observed remotely prior to telehealth support session concluding.

Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born participant is considered of childbearing potential until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Participants

a. Study Drug Effects on Pregnancy and Hormonal Contraception

In nonclinical reproductive toxicity studies, RDV demonstrated no adverse effect on embryofetal development when administered to pregnant animals. Embryonic toxicity was seen when RDV was initiated in female animals prior to mating and conception, but only a at a systemically toxic dose. RDV has not yet been studied in pregnant women. Before enrolling participants into studies with RDV, women of childbearing potential must have pregnancy testing performed at screening.

Available data indicate that RDV potentially causes an interaction with hormonal contraception, but the effect is considered to be of limited clinical significance. Hormonal methods must be used together with a barrier method.

Refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female participants of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative urine pregnancy test at screening prior to enrollment. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following until Day 28:

- 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 one of the following methods of birth control listed below:

  Non-hormonal intrauterine device (IUD)

  Hormonal IUD (must be used with a barrier method)

  Tubal sterilization

  Essure® micro-insert system (provided confirmation of success 3 months after procedure)

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  Or

- Barrier methods

  Female barriers: Diaphragm with spermicide, cervical cap with spermicide, or sponge with spermicide

  Male barriers: Male condom (with or without spermicide)

  Or

- Hormonal methods are restricted to drugs associated with the inhibition of ovulation. Each method must be used with a barrier method, preferably male condom. Hormonally-based contraceptives permitted for use in this protocol are as follows:

  Oral contraceptives (either combined or progesterone only)

  Injectable progesterone

Subdermal contraceptive implant

Transdermal contraceptive patch

Contraceptive vaginal ring

Female participants must also refrain from egg donation and in vitro fertilization during treatment and until the last investigational product dose.

3) Contraception Requirements for Male Participants

During the study, male participants with female partners of childbearing potential should use condoms until Day 28 when engaging in intercourse of reproductive potential.

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 will be instructed to notify the investigator and discontinue investigational product immediately, if they become pregnant at any time during the study. Participants whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.