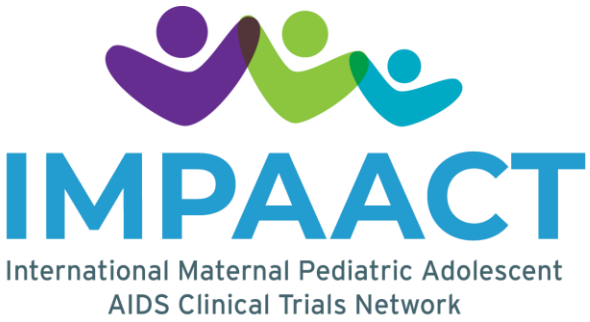

IMPAACT 2032

Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

IND#154,388
DAIDS study ID # 38746

This file contains the current IMPAACT 2032 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #1, dated 12 April 2021
- Protocol Version 2.0, dated 18 December 2020

Clarification Memorandum #1 for:

IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

Version 2.0, dated 18 December 2020

DAIDS Study ID #38746
IND # 154388

Clarification Memorandum Date: 12 April 2021

Summary of Clarifications and Rationale

This Clarification Memorandum (CM) updates protocol specifications to reflect current policies of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), and National Institutes of Health (NIH). It also updates the wording related to the IMPAACT Network Certificate of Confidentiality and adds the protocol IND number. These updates do not impact the study design or study-specific procedures.

Implementation

This CM will be submitted to the Johns Hopkins Medicine Institutional Review Board, which serves as the single Institutional Review Board (sIRB) for IMPAACT 2032, for their information; however, approval of this CM is not required by the study sponsor prior to implementation. Sites may submit this CM to their local IRBs/ECs for their information or, if required by the local IRBs/ECs, for their approval prior to implementation.

IRBs/ECs may have acknowledged and/or approved remote site monitoring strategies prior to the issuance of this CM. If so, sites should file documentation of this acknowledgement and/or approval in their essential document files for IMPAACT 2032. This CM and any applicable IRB/EC correspondence should also be filed in essential document files for IMPAACT 2032.

The information included in this memorandum will be incorporated into the next protocol amendment.

A. DAIDS Policy Updates

1. Protocol Section 12 is updated to reflect current DAIDS policies for clinical site monitoring, which allow for on-site and remote monitoring. The prior contents of this section are replaced with the following:

   Under contract to DAIDS or NICHD, site monitors will inspect study site facilities and review participant study records — including informed consent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the sIRB approved protocol, and accuracy and

completeness of records. Monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by monitors.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by DAIDS or NICHD. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity (1). Site investigators will make study documents available for site monitors to review utilizing a secure platform that is 21 CFR Part 11 and HIPAA compliant. Potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, Medidata Remote Source Review, site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records. Other secure platforms that are 21 CFR Part 11 and HIPAA compliant may be utilized, as allowed by DAIDS or NICHD.

Reference:

1. **FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download**

2. Protocol Section 14.5 refers to the DAIDS policy on identification and classification of critical events. This policy has been retired. Section 14.5 is removed from the protocol and Section 13.1 has been updated to refer to the reporting requirements that still apply for sites conducting this study. In Section 13.1 no changes are made to the first paragraph and the prior contents of the second paragraph are replaced with the following:

   Prior to study initiation, site investigators must obtain sIRB review and approval of this protocol and site-specific informed consent forms in accordance with 45 CFR 46; subsequent to initial review and approval, the sIRB must review the study at least annually. Site investigators must promptly report to the sIRB any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of the sIRB; and any suspension or termination of sIRB approval.

3. Protocol Section 14.6 (now re-numbered as Section 14.5) refers to requirements for entry of study results into ClinicalTrials.gov. To reflect current NIH and regulatory requirements, the prior contents of this section are replaced with the following:

   The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The protocol team will comply with this policy as well as the requirements of 42 CFR 11.

4. Protocol Sections 11.1, 11.2, 11.3, 13.7, 14.3, and 14.4 refer to the following DAIDS policies:

   - Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials
   - Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials
   - Requirements for Clinical Quality Management Plans

- Requirements for Manual of Operational Procedures

These policies have been retired and replaced with instructions for sites that are now contained in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual. Throughout the protocol, references to the above-listed policies are replaced with requirements specified in the DAIDS SCORE Manual (edits not shown here). The SCORE Manual is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

B. Certificate of Confidentiality

The Certificate of Confidentiality described in protocol Section 13.7 has been deemed issued to the IMPAACT Network effective with the start date of the current Network funding cycle (1 December 2020). The first sentence in the last paragraph of this section is replaced with the following:

In addition to the above, a Certificate of Confidentiality has been deemed issued for the IMPAACT Network by the US Department of Health and Human Services.

C. Protocol Cover Page

The IND Number # 154388 is added to the cover page

IMPAACT 2032

Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

Support Provided by:
Gilead Sciences, Inc.

DAIDS Study ID #38746
IND # XXXXX Held by DAIDS

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FINAL Version 2.0
18 December 2020

IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

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DAIDS Study ID #38746

Version 2.0
PROTOCOL SIGNATURE PAGE

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____
Signature of Investigator of Record Date

_____
Name of Investigator of Record
(printed)

IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

ABBREVIATIONS AND ACRONYMS

AAG	α1-acid glycoprotein
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMC	Clinical Management Committee
COVID-19	coronavirus disease of 2019
CRP	C-reactive protein
CV	coefficient of variation
DAIDS	Division of AIDS
DBS	dried blood spots
DMC	Data Management Center
EAE	expedited adverse event
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
EC	ethics committee
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medical Association
FDA	Food and Drug Administration
FDAAA	United States Food and Drug Administration Amendments Act of 2007
GCP	good clinical practices
GFR	glomerular filtration rate
GMR	geometric mean ratio
GS-5734™	remdesivir
GS-441524	remdesivir dephosphorylated nucleoside analog
GS-443902	remdesivir active triphosphate form
HIV	human immunodeficiency virus
hs	high sensitivity
ICU	intensive care unit
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	institutional review board
IND	investigational new drug
INR	international normalized ratio
IoR	Investigator of Record
IV	intravenous
LAR	legally authorized representative

LDH	lactate dehydrogenase
LDMS	laboratory data management system
LPC	laboratory processing chart
MERS-CoV	Middle East respiratory syndrome
MMWR	Morbidity and Mortality Weekly Report CDC
MOG	Management Oversight Group
MOP	manual of procedures
NCA	non-compartmental pharmacokinetic analysis
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
OHRP	Office for Human Research Protection
PBMCs	peripheral blood mononuclear cells
PCD	primary completion date
PID	participant identification number
PK	pharmacokinetic
PRO	Protocol Registration Office
PT	prothrombin time
PTT	partial thromboplastin time
RDV	remdesivir
RSC	Regulatory Support Center
SAE	serious adverse event
SARS-CoV-1	serious acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMC	Study Monitoring Committee
SOF	sofosbuvir
TAF	tenofovir alafenamide

IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

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IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

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IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

SCHEMA

Purpose:	To describe the pharmacokinetic (PK) properties and safety of remdesivir (GS-5734™) (RDV) administered to pregnant and non-pregnant women with COVID-19.
Design:	Phase IV, prospective, open label, non-randomized opportunistic PK study
Study Population:	Pregnant and non-pregnant women of childbearing potential hospitalized and receiving RDV for treatment of COVID-19.
Sample Size:	**Arm 1:** Target enrollment of 20 pregnant women with evaluable PK data **Arm 2:** Target enrollment of 20 non-pregnant women of childbearing potential with evaluable PK data
Drug under study:	RDV will not be provided as part of the study. Participants will be administered RDV intravenously once daily for up to 10 days per clinical care.
Study Duration:	Approximately 15 months total. Accrual is expected to be completed within approximately 6 months from first enrollment. Enrolled women in Arm 1 will be followed for 4 weeks after the last RDV infusion or through delivery, whichever comes later. Enrolled women in Arm 2 will be followed for 4 weeks after the last RDV infusion.

Primary Objectives

Arm 1:

- To describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to pregnant women as part of clinical care.
- To describe the clinical and laboratory safety outcomes through four weeks post-last infusion and during delivery in pregnant women receiving RDV as part of clinical care.

Secondary Objectives

Arm 2:

- To describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to non-pregnant women of childbearing potential as part of clinical care.
- To describe the clinical and laboratory safety outcomes through four weeks post-last infusion in non-pregnant women of childbearing potential receiving RDV as part of clinical care.

Other Objectives

Arm 1:

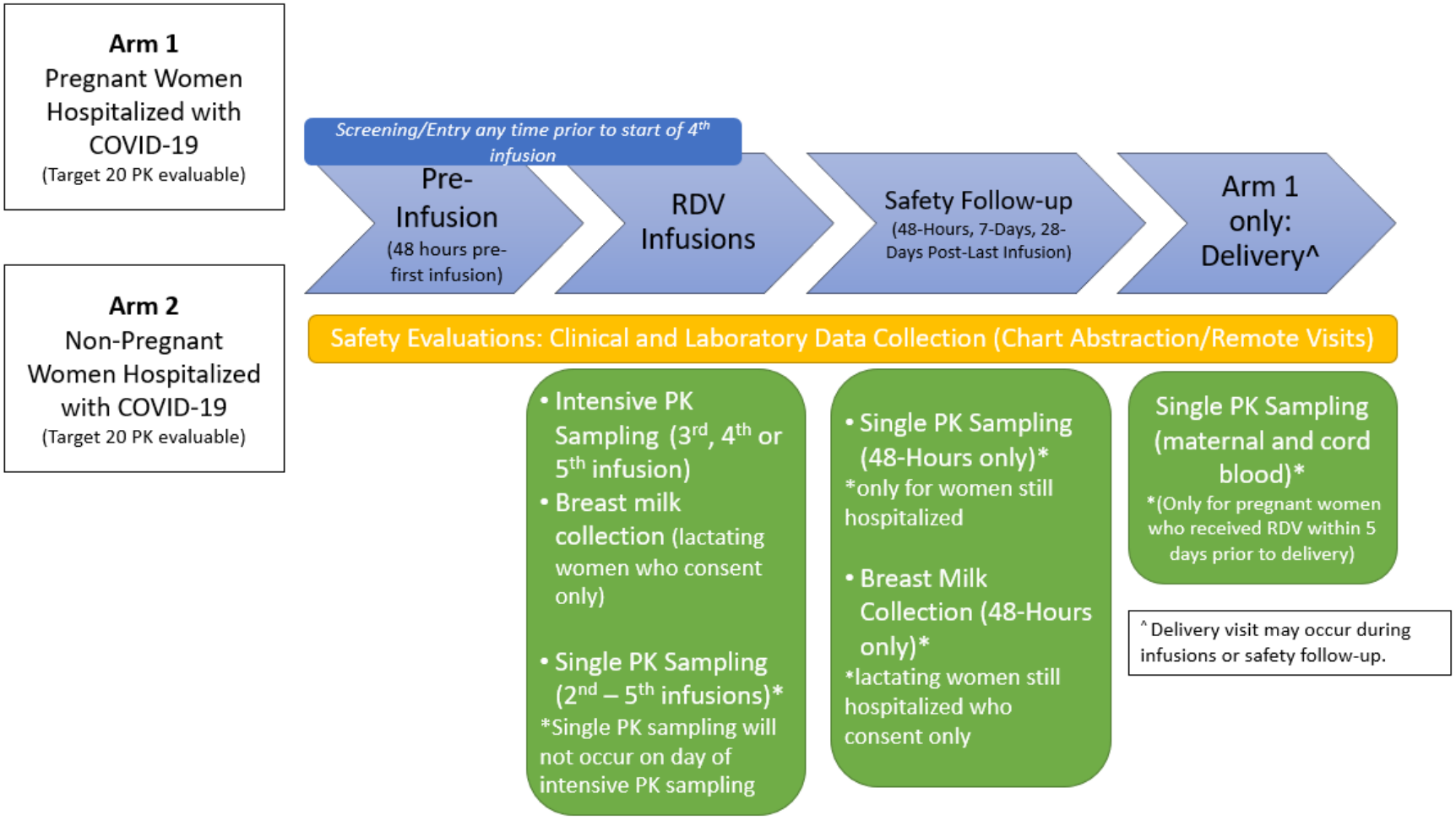
- To describe RDV placenta transfer with collection of plasma and cord blood samples at delivery in mothers who have received a dose of RDV within the preceding 5 days.

Arms 1 and 2:

- To compare the pharmacokinetics of RDV and its metabolite, GS-441524, in pregnant women to those observed in non-pregnant women of childbearing potential.
- To describe and compare intracellular concentrations of RDV's active intracellular nucleotide triphosphate (GS-443902) in pregnant and non-pregnant women of childbearing potential receiving RDV as part of clinical care.
- To develop a population PK (PopPK) model of RDV and its metabolites in pregnant and non-pregnant women receiving RDV and evaluate associations between clinical characteristics and RDV and GS-441524 pharmacokinetics.
- To assess plasma protein binding of RDV in pregnant women and non-pregnant women of childbearing potential.
- To describe the frequency of detection in breast milk and the relative concentrations in breast milk and plasma of RDV and GS-441524 in lactating women undergoing RDV PK sampling.

IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

Figure 1: Overview of Study Design



1 INTRODUCTION

1.1 Background

As of November 23, 2020, Centers for Disease Control and Prevention (CDC) received 12,175,921 COVID-19 case reports for the United States (U)S since January 22, 2020. There were slightly more women (52%) than men (48%) included in these reports (1). The most recent tracking data from CDC includes 39,857 case reports of US pregnant women with COVID-19 received between January 22 and November 23, 2020, with 53 deaths and 8,284 hospitalizations, although these data did not distinguish between hospitalization for COVID-19 conditions from admissions for pregnancy-related indications, such as delivery. The race/ethnicity breakdown of the pregnancy COVID-19 cases was 37% Hispanic, 35% White Non-Hispanic, 19% Black Non-Hispanic, 3%, Asian and 6% Multiple/Other (2). In an earlier MMWR publication describing the period between January 22 and June 7, 2020, CDC reported receiving notifications of 326,335 women of reproductive age (15–44 years) with positive SARS-CoV-2 test results. Of the 91,412 of these women with pregnancy data, 9% (8,207) were pregnant. Hospitalization was reported in 31.5% of pregnant women compared to 5.8% of nonpregnant women but the data did not distinguish between hospitalization for COVID-19 conditions from admissions for pregnancy-related indications, such as delivery. After adjusting for age, presence of underlying medical conditions, and race/ethnicity, pregnant women were significantly more likely to be hospitalized (aRR = 5.4, 95% confidence interval [CI] = 5.1-5.6), to be admitted to the intensive care unit (ICU) (aRR = 1.5, 95% CI = 1.2–1.8) and to receive mechanical ventilation (aRR = 1.7, 95% CI = 1.2–2.4) than nonpregnant women (3). Increased need for intensive care during pregnancy has also been reported in Swedish women with COVID-19 (4). A review of published data on severe coronavirus infections in pregnancy reported adverse pregnancy outcomes, including maternal death, preterm delivery, stillbirth and neonatal death, as well as respiratory compromise requiring ICU care and mechanical ventilation, in pregnant women with COVID-19, although at lower frequency than with MERS-CoV and SARS-CoV-1 (5).

Despite this reported incidence of severe COVID-19 in pregnant women associated with adverse pregnancy and maternal health outcomes, pregnant women are routinely excluded from participation in research protocols within COVID-19 drug development programs(6). The physiological changes associated with pregnancy can have a dramatic impact on drug disposition and use of therapeutic agents during pregnancy poses unique safety concerns(6). As a result, drugs cannot be used safely and effectively during pregnancy without their pharmacokinetics (PK) and safety being evaluated in pregnant women. Only a few of the many COVID-19 clinical treatment trials currently listed on clinicaltrials.gov include pregnant women(7). Those that do involved use of hydroxychloroquine, which has been used extensively in pregnant women for malaria treatment but is no longer recommended for routine use in treatment of COVID-19 due to a lack of proven efficacy in the presence of significant risk of major toxicity(8).

Remdesivir (GS-5734™) (RDV), a nucleotide prodrug originally developed for the treatment of Ebola virus disease and Marburg virus infections, is the first drug licensed for use against COVID-19, the disease caused by infection with SARS-CoV-2 virus(9). RDV has been shown to shorten time to recovery from severe COVID-19 (10-12). In an activation process analogous to that of tenofovir alafenamide (TAF) and sofosbuvir (SOF), RDV is metabolized to an intracellular nucleotide triphosphate which inhibits viral RNA polymerases. Now that RDV is licensed, hospitalized pregnant women with COVID-19 can receive RDV part of clinical care; however, since all RDV research protocols excluded pregnant women there are no RDV pregnancy PK data and only limited RDV in pregnancy safety data from observational cohorts(13).

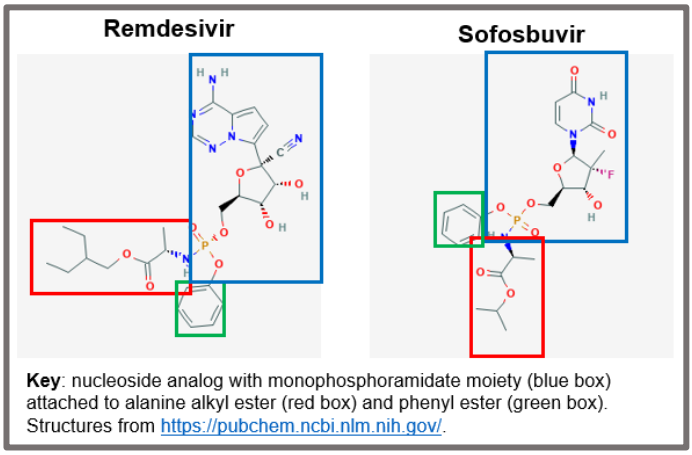
The routine exclusion of pregnant women from drug development programs results in therapeutic agents typically being licensed for use in non-pregnant adults in the absence of pregnancy specific PK and safety

data. As a result, these licensed drugs cannot be employed with evidence-based certainty as to their safety and efficacy in pregnant women until data are available from the requisite pregnancy PK and safety studies, which often require years to complete. Requisite PK and safety studies require years to complete. As an example, it took 3-5 years after licensure of cobicistat before its failure as an effective booster of elvitegravir and darunavir in pregnant women was recognized and warnings against its use in pregnancy were issued, during which time cobicistat was used routinely as part of clinical care for pregnant women living with HIV(6). A similar delay in the availability of pregnancy PK and safety data for drugs shown to be effective against COVID-19 would be tragic, given the incidence, acuity and observed severity of COVID-19 in pregnant women and the current paucity of proven effective therapies.

1.2 Clinical Pharmacology During Pregnancy

RDV is the first drug with preliminary evidence of efficacy in COVID-19(14). RDV is a prodrug that requires several steps of metabolism to generate its active intracellular nucleotide triphosphate (NTP, GS-443902), following a similar activation sequence as SOF (Figure 2). RDV is a monophosphoramidate prodrug of an adenosine analog that is made more lipophilic by the addition of alkyl-alanine and phenyl phosphate esters. RDV is rapidly converted by plasma and liver hydrolases to a nucleoside analog monophosphate. Inside cells the nucleoside analog monophosphate is rapidly converted to the active triphosphate form (GS-443902), which competes with natural adenosine triphosphate (ATP) to selectively inhibit RNA-dependent RNA polymerase. Dephosphorylation of the nucleoside analog results in GS-441524, which is not as efficiently rephosphorylated as RDV.

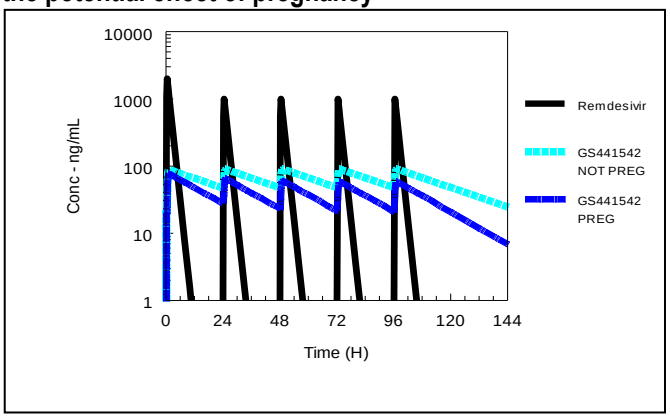
Figure 2: Remdesivir and sofosbuvir structure.



Key: nucleoside analog with monophosphoramidate moiety (blue box) attached to alanine alkyl ester (red box) and phenyl ester (green box). Structures from https://pubchem.ncbi.nlm.nih.gov/.

The in vitro EC50 against SARS-CoV-2 has been reported at 0.137 µM (83 ng/mL) and 0.77 µM (460 ng/mL) in Vero cells (11, 15). In a human lung epithelial cell line (Calu3), in vitro EC50s for RDV and GS-441524 were 0.28 uM (169 ng/mL),and 0.62 uM (181 ng/mL) by plaque assay. RDV demonstrated greater potency in human airway epithelial cells with an EC50 of 0.01 uM (6 ng/mL), likely due to higher GS-443902 concentrations in HAE cells in comparison to the Calu-3 and Vero E6 cell types. Due to poor hepatic stability, RDV should not be given orally as bioavailability is expected to be low. RDV PK data at the currently recommended doses for COVID-19 treatment are primarily limited to healthy non-pregnant adults studied in preparation for studies of RDV use against Ebola(16). See Table 1 below for summary plasma PK parameters. In this study, Day 1 peak plasma concentrations after a 200 mg intravenous (IV) dose administered over 30 minutes were 9.0 µM (5440 ng/mL) for RDV and 0.5 µM (152 ng/mL) for GS-441524. $AUC_{0\text{-}24h}$ were 4.8 µM-h (2920 ng*h/mL) for RDV and 7.7 µM-h (2240 ng*h/mL) for GS-441524 (15). Sparse PK results in a 66 year old female and a 67 year old male with COVID-19 have also been detailed(17). Median peak RDV concentrations of 4.54 uM (2737 ng/mL) and

Figure 3: Expected PK of Remdesivir and GS-441524 and the potential effect of pregnancy



5.50 uM (3317 ng/mL) were measured in each of these patients, respectively, on infusion Days 3-9. GS-441524 $AUC_{0\text{-}24h}$ was 10.7 uM-h (3117 ng*h/mL) in the male patient, and 21.1 uM-h (6131 ng*h/mL) in the female patient, who had 1.96-fold higher levels due to underlying renal dysfunction.

No accumulation of RDV occurred with multiple dosing, consistent with its measured half-life in plasma of just under 1 hour. Following single doses ranging from 3 – 225 mg IV, PK of GS-441524 were linear. GS-441524 reaches steady-state in 4 days and accumulated 1.9-fold based on AUC, consistent with its ~24-hour half-life. The intracellular phosphorylated metabolite GS-443902 has a median half-life of 32.23 to 48.38 hours. Renal and biliary excretion were the major routes of elimination in rats and monkeys.(15) In the mass balance study, mean total recovery of the dose was greater than 92%, consisting of approximately 74% recovered in urine and 18% recovered in feces. The majority of the IV RDV dose recovered in urine was the GS-441524 metabolite (49%) followed by RDV (10%) and other metabolites(18). The impact of pregnancy on hydrolase activity and RDV PK is unknown. A simulation from modelling based on pregnancy PK data for other renally eliminated drugs is presented in Figure 3 (19-22). The modelling and simulation suggest that increased glomerular filtration rate (GFR) and renal tubular secretion associated with pregnancy will increase GS-441524 elimination. Because RDV is 88-94% protein bound, while its metabolites are only 1-2% protein bound (9), pregnancy related changes in plasma protein concentrations due to volume expansion and drug displacement from protein binding sites may also affect unbound RDV concentrations.

Table 1. Plasma PK Parameters of RDV and GS-441524 Following 30-minute IV Infusion(s) of RDV 200 mg on Day 1 and 100 mg Daily on Days 2-5 in Healthy Adults (Preliminary Analysis)(15)

PK Parameter	Remdesivir		GS-441524	
	Day 1 (n=8)	Day 5 (n=7)	Day 1 (n=8)	Day 5 (n=7)
Cmax (ng/mL)	5440 (20.3)	2610 (12.7)	152 (25.9)	142 (30.3)
AUC (hr*ng/mL)	2920 (20.6)	1560 (13.9)	2240 (29.1)	2230 (30.0)
$T_{1/2}$ (h)	0.98 (0.82, 1.03)	0.89 (0.82, 1.09)	NA	25.3 (24.10, 30.32)

C_{max} and AUC summarized as geometric mean (CV%); $t_{1/2}$ summarized as median (Q1, Q3)

RDV is currently licensed for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization(9). The only RDV PK data currently available are from healthy non-pregnant adult volunteers, for which results by sex were not detailed, and sparse PK results from two patients with COVID-19(9, 16, 17). No data describing RDV PK in pregnant women or non-pregnant women with COVID-19 are available. Clinical data with RDV use in pregnancy are limited to the experience of 6 pregnant women in the Democratic Republic of Congo who received RDV as Ebola treatment and 67 pregnant and 19 postpartum women who received remdesivir for COVID-19 under the Gilead compassionate use protocol(13, 23). Remdesivir was well tolerated by the pregnant women treated for Ebola (23). The pregnant and postpartum women who received RDV for COVID-19 under the Gilead compassionate use protocol all had room air oxygen saturation 94% or lower. There was one spontaneous miscarriage and one postpartum women who died but no pregnant woman or live born infant died. None of the pregnant women developed gestational hypertension or pre-eclampsia. Ninety three percent of pregnant women and 89% of postpartum women recovered from COVID-19. Serious adverse events (SAEs) were observed in 29% of women, including deep vein thrombosis, hypertension, hypoxia and pleural effusion. Elevations of laboratory parameters were common, occurring in 67% (13).

The use of RDV in pregnant women in the absence of PK and safety data places pregnant women receiving RDV at risk for both inadequate therapeutic response and unrecognized maternal toxicity including adverse pregnancy outcomes.

1.3 Rationale

Although pregnant women are routinely excluded from COVID-19 experimental treatment protocols, the care providers of pregnant women who develop severe COVID-19 are treating them with potential therapies in the absence of pregnancy specific PK and safety data and outside of research protocols. Under these circumstances, the fastest way to get the urgently needed RDV pregnancy PK and safety data is through an opportunistic RDV PK and safety protocol in pregnant women receiving RDV as part of clinical care. IMPAACT 2032 will follow the opportunistic design of the highly successful IMPAACT P1026s study which between 2004 and 2019 performed intensive PK sampling and safety evaluations for HIV and TB therapeutics in over 1000 pregnant and postpartum women, successfully evaluating the PK and safety of over 25 different HIV and TB medications in pregnant and postpartum women. Because of the duration of treatment of HIV and TB, participants in IMPAACT P1026s were studied both during pregnancy and postpartum, serving as their own controls. This approach is not possible with RDV, which has a treatment duration of 5-10 days. As a result, women treated during pregnancy will generally not be receiving the drug postpartum. Under these circumstances the best comparison group for PK and safety data from pregnant women would be data from non-pregnant adult women of childbearing potential. Since such data are lacking for RDV, IMPAACT 2032 will also simultaneously enroll and study RDV PK and safety in a cohort of COVID-19 positive, non-pregnant women of childbearing potential. These non-pregnant participants will provide the first data describing RDV PK and safety in women receiving RDV for COVID-19 and will serve as a comparison group for the IMPAACT 2032 pregnant women.

The recent recognition of the acuity and severity of COVID-19 in pregnant women mandates rapid development of a streamlined protocol that can be implemented with minimal delay to provide the critical RDV pregnancy specific PK and safety data needed to allow RDV to be used safely and effectively in pregnant women. This protocol was designed with recognition of the challenges posed by performing a research protocol on hospitalized participants acutely ill with COVID-19 during an ongoing and rapidly changing pandemic. Priority has been given to obtaining the urgently needed pregnancy RDV PK and safety data as quickly as possible through protocol activities that pose the least risk of violating RDV infection control measures, to avoid putting clinical staff, research staff and other hospital patients at increased risk of SARS-CoV-2 infection. The protocol team has endeavored to develop a protocol that will acquire RDV PK and safety data in pregnant women as quickly, efficiently and safely as possible under these challenging conditions. The team has elected to design the study to facilitate ease and practicality of implementation and to focus on acquiring only those data necessary to provide an initial evidence base for the use of RDV in pregnant women. This approach is reflected in many aspects of the protocol, including the eligibility criteria, participant data collection procedures, PK sampling and analysis approach, and duration of follow up.

IMPAACT 2032 will provide critical RDV PK and safety data in women, allowing evaluations of exposure of RDV and its metabolites in both pregnant and non-pregnant adult women and of RDV safety when used in these populations. This protocol will provide urgently needed RDV PK and safety data in women with COVID-19, providing evidence necessary to ensure that RDV can be used safely and effectively in both pregnant and non-pregnant women of childbearing potential.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to:

2.1.1 Arm 1: Describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to pregnant women as part of clinical care.

2.1.2 Arm 1: Describe the clinical and laboratory safety outcomes through four weeks post-last infusion and during delivery in pregnant women receiving RDV as part of clinical care.

2.2 Secondary Objectives

The secondary objectives of this study are to:

2.2.1 Arm 2: Describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to non-pregnant women of childbearing potential as part of clinical care.

2.2.2 Arm 2: Describe clinical and laboratory safety outcomes through four weeks post-last infusion in non-pregnant women of childbearing potential receiving RDV as part of clinical care.

2.3 Other Objectives

The other objectives of this study are to:

2.3.1 Arm 1: Describe RDV placenta transfer with collection of plasma and cord blood samples at delivery in mothers who have received a dose of RDV within the preceding 5 days.

2.3.2 Arms 1 and 2: Compare the pharmacokinetics of RDV and its metabolite, GS-441524, in pregnant women to those observed in non-pregnant women of childbearing potential.

2.3.3 Arms 1 and 2: Describe and compare intracellular concentrations of RDV's active intracellular nucleotide triphosphate (GS-443902) in pregnant and non-pregnant women of childbearing potential receiving RDV as part of clinical care.

2.3.4 Arms 1 and 2: Develop a population PK (PopPK) model of RDV and its metabolites in pregnant and non-pregnant women receiving RDV and evaluate associations between clinical characteristics and RDV and GS-441524 pharmacokinetics.

2.3.5 Arms 1 and 2: Assess plasma protein binding of RDV in pregnant women and non-pregnant women of child-bearing potential.

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2.3.6 Arms 1 and 2: Describe the frequency of detection in breast milk and the relative concentrations in breast milk and plasma of RDV and GS-441524 in lactating women undergoing RDV PK sampling.

3 STUDY DESIGN

This is a Phase IV prospective, open label, non-randomized opportunistic study to evaluate the PK and safety of RDV when administered to pregnant and non-pregnant women of childbearing potential for treatment of COVID-19. RDV is not provided as part of this study; a requirement for entry is that participants receive RDV as part of their clinical care (i.e., outside of the study). Participation in this study will have no effect on the cost of care for treatment of COVID-19 or the cost of any RDV received for clinical care. Information on patient support for access to RDV can be found at https://www.vekluryhcp.com/patient-support/. As no investigational drug is being provided to study participants, the study is opportunistic in nature and clinical care decisions are made outside the context of this study, and as the Division of AIDS (DAIDS) at the US National Institutes of Health (NIH), as the study sponsor, is not charging for use of RDV in the context of this study, 21 CFR 312.8 is not applicable to this study.

A target of 20 PK evaluable pregnant women will be enrolled into Arm 1; a target of 20 PK evaluable non-pregnant women of childbearing potential will be enrolled into Arm 2. See Section 10.2 for a definition of PK evaluable. Refer to Sections 4.1 through 4.3 for the eligibility criteria and to Section 4.5 for a description of the recruitment, screening and enrollment process. Study sites will be located in the United States.

Participants will be pregnant and non-pregnant women hospitalized for COVID-19 and will receive daily RDV infusions, typically for 5 days but in some cases for up to 10 days, as part of their clinical care. RDV will be provided and managed by the participants' treating physician and will not be provided as a part of this study. Women may be enrolled prior to starting RDV or after starting RDV but must be enrolled prior to the start of the 4th infusion. Participants will undergo intensive PK sampling on the day of the 3rd, 4th, or 5th infusion (at site discretion), as described in Section 6.4.1. Protein binding capacity of RDV will also be assessed *ex vivo* from the pre-dose intensive PK sample. Participants will also undergo collection of single PK samples with standard of care (SOC) labs drawn on the days of the 2nd, 3rd, 4th, and 5th infusions (with the exception of the day of intensive PK sampling), and also at 48 hours after the last infusion, as described in Section 6.4.2. For Arm 1 participants, maternal and cord blood PK sampling will be performed at delivery for a comparison of maternal and fetal plasma RDV concentrations if the participant received RDV infusion within the preceding 5 days. Additionally, for women in both Arms who are lactating, and who consent to this sample collection, an optional breast milk sample may be collected on the intensive PK sampling day and at 48-hours after the last RDV infusion, to assess breast milk concentrations of RDV and its metabolites.

For all women, clinical and laboratory evaluations will be abstracted from the medical record. Pregnancy, birth, and infant outcomes will be obtained from pregnant women enrolled in Arm 1. See Appendix I and Section 6 for additional details. Arm 1 and Arm 2 participants will be followed through 4 weeks after the last infusion of RDV; Arm 1 women who are still pregnant at that time will have additional follow-up at the time of delivery.

4 STUDY POPULATION

This study will be conducted among hospitalized pregnant and non-pregnant women receiving RDV infusion for treatment of COVID-19 as part of their clinical care (i.e., not as part of this study). Women will be assessed for eligibility per the criteria specified in Sections 4.1 through 4.3, and the requirements in Section 4.4. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.5. Considerations related to participant retention and withdrawal/discontinuation from the study are provided in Sections 4.6 and 4.7, respectively.

4.1 Inclusion Criteria – Arm 1 (Pregnant Women)

Women must meet all of the following inclusion criteria to be enrolled in Arm 1.

4.1.1 Of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with all applicable IRB policies and procedures, and is willing and able to provide informed consent for her own participation in this study.

Or

Of legal age to provide independent informed consent but is unable to provide informed consent (e.g. impaired capacity, as determined by site SOPs and consistent with all applicable IRB policies and procedures) and a Legally Authorized Representative (LAR) is willing and able to provide written informed consent on behalf of the participant in accordance with 21 CFR 50.27.

Note: All sites must follow the policies and procedures of all applicable IRBs; this includes single IRB (sIRB) policies and procedures. Refer to Section 13.1 for more information on sIRB oversight.

4.1.2 At study entry, viable intra-uterine pregnancy of any gestational age, based on medical records.

4.1.3 At study entry, hospitalized AND has confirmed or suspected COVID-19, based on medical records.

4.1.4 At study entry, receiving or expected to receive RDV for COVID-19 clinical care, as prescribed by the clinical care provider and documented in medical records.

Note: The study investigator or designee will confirm that a potential study participant is receiving or expected to receive RDV based on information in the medical record.

4.2 Inclusion Criteria – Arm 2 (Non-Pregnant Women)

Women must meet all of the following inclusion criteria to be enrolled in Arm 2.

4.2.1 Of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with all applicable IRB policies and procedures, and is willing and able to provide informed consent for her own participation in this study.

Or

Of legal age to provide independent informed consent but is unable to provide informed consent (e.g. impaired capacity, as determined by site SOPs and consistent with all applicable IRB policies and procedures) and a LAR is willing and able to provide written informed consent on behalf of the participant in accordance with 21 CFR 50.27.

Note: All sites must follow the policies and procedures of all applicable IRBs; this includes sIRB policies and procedures. Refer to Section 13.1 for more information on sIRB oversight.

4.2.2 At study entry, between 18 and 45 years of age, based on medical records and participant report.

4.2.3 Assigned female at birth and at study entry not taking cross-sex hormone therapy.

4.2.4 At study entry, not suspected to be pregnant, based on participant report and/or investigator or designee determination.

4.2.5 At study entry, hospitalized AND has confirmed or suspected COVID-19, based on medical records.

4.2.6 At study entry, receiving or expected to receive RDV for COVID-19 clinical care, as prescribed by the clinical care provider and documented in medical records.

Note: The study investigator or designee will confirm that a potential study participant is receiving or expected to receive RDV based on information in the medical record.

4.3 Exclusion Criteria – Arms 1 and 2

Women who meet any of the following criteria will be excluded from enrolling in this study:

4.3.1 At study entry, has started or received the 4th RDV infusion.

4.3.2 At study entry, evidence of post-menopausal status (medical or surgical), based on medical records and/or participant report.

4.3.3 At study entry, any contraindications to RDV treatment for COVID-19, based on investigator or designee determination.

4.3.4 Received or administered any disallowed medications listed in Section 5.4 within 48 hours prior to study entry.

4.3.5 At study entry, has any other condition, that, in the opinion of the site investigator or designee, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives.

4.4 Co-Enrollment Considerations

Co-enrollment in this study and other studies is permitted without prior approval of the Protocol Team, as long as requirements of both studies can safely be met and blood draw maximums will

not be exceeded (see Section 6.8.1). All investigational agents must be documented as concomitant medications (see Section 5.3).

4.5 Recruitment, Screening, and Enrollment Process

RDV is an approved drug for treatment of COVID-19 in adults and pediatric patients requiring hospitalization, who are 12 years of age or older and who weigh at least 40 kg. Recruitment methods for this study may vary across sites but are expected to rely on identification of pregnant and non-pregnant women hospitalized for COVID-19 in a facility that is affiliated with an IMPAACT clinical research site and who recently initiated treatment with RDV or who may require treatment with RDV. Clinical research site staff will work with local care providers to identify hospitalized pregnant and non-pregnant women with COVID-19.

Due to COVID-19 infection control measures, hospitalized pregnant and non-pregnant women are expected to be in isolation. Additionally, participants may be incapacitated and determined, per site-specific SOPs and sIRB or other institutional, state, or local guidelines, to be unable to provide independent consent for themselves. Site staff must ensure that information about the study is provided to the potential participant or her LAR (as applicable) including detailed review of the study informed consent form, time to address any questions or concerns the potential participant or LAR may have, and an assessment of understanding, before proceeding to informed consent decision. Refer to Section 13.3 for further information on informed consent procedures for this study, including allowable consenting options in the context of COVID-19. The informed consent process will be conducted in accordance with sIRB and other institutional and local policies and procedures, and fully documented consistent with the NIAID DAIDS policies referenced in Section 11.2 and with 45 CFR 46.117.

Eligibility screening will be initiated after informed consent is provided. Screening evaluations must be completed prior to enrollment. Screening evaluations may be performed up to and on the day of enrollment; however, all required screening outcomes must be available prior to enrollment.

Each site must establish SOPs for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of entry.

Prior to enrollment, and after informed consent is obtained, sites will assign a participant identification number (PID) to the participant. The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to enroll participants in this study. For women found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID), for each enrolled participant. Refer to Section 9.5 for more information on monitoring participant accrual in this study.

For Arm 1, only maternal participants will be enrolled in the study; fetuses/infants will not be enrolled. However, as some limited data will be collected on infant outcomes at birth as well as newborn physical exam findings, participants will be asked to provide consent for data collection on their infants, as described in the sample consent forms in Appendix II. PIDs will not be assigned to infants and these data will be collected on maternal eCRFs.

4.6 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain her for the protocol-specified duration of follow-up, thereby maximizing evaluability and statistical power and minimizing potential biases associated with loss to follow-up. Study sites are responsible for developing and implementing local procedures to reach this goal. Refer to Section 9.5 for more information on monitoring participant retention in this study.

4.7 Participant Withdrawal or Discontinuation from the Study

Regardless of the participant retention procedures referenced above, participants or their LAR may voluntarily withdraw from the study. Participants may also be discontinued from study participation by the site investigator or designee under the following circumstances:

- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the Clinical Management Committee (CMC).
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or the sIRB.
- Site participation in the study is cancelled by the sponsors, government or regulatory authorities, or the sIRB.
- The participant does not initiate RDV within 7 days from study entry.

For any participant who withdraws or is discontinued from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or discontinuation in detail and enter the reason into the appropriate eCRF. No final evaluations are required in the case of early study discontinuation or withdrawal.

5 DRUG UNDER STUDY

No study drug is provided as a part of this study. The drug being evaluated in this study is remdesivir (RDV) (GS-5734™) and is referred to as the "drug under study." RDV will not be supplied as part of this study. RDV is approved by the FDA and is expected to be accessed by hospitals via existing drug distribution pathways external to the study and will be administered by the treating physician consistent with the prescribing information.

The RDV Prescribing Information is available at:
https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf

5.1 Remdesivir Formulations

RDV is available in two different formulations: lyophilized powder for reconstitution (100 mg) and premixed injection solution 5mg/mL (100 mg). RDV should be stored consistent with details as provided by the non-study sources who supply the drug to the participants. The formulation administered to each participant at each infusion will be captured on eCRFs as described in Section 6.4.

5.2 Dose, Preparation and Administration

RDV should be prepared and administered consistent with details as provided in the prescribing information. The standard dosage of RDV is a single loading dose of 200 mg infused intravenously over 30 to 120 minutes on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously over 30 to 120 minutes for up to 10 infusions (30 minute infusion administration is recommended where possible). Based on the prescribing information, it is expected that participants who do not require invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) will receive a 5-day course of treatment, and participants requiring invasive mechanical ventilation or ECMO will receive a 10-day course of treatment; however, treatment may be discontinued early in either case as determined by the treating physician. After an infusion is complete, at least 30 mL of 0.9% saline will be used to flush the line. The prepared diluted solution will not be administered with any other medications. The compatibility of RDV injection with IV solutions and medications other than saline is not known. The dose and volume administered to each participant at each infusion will be captured on eCRFs as described in Section 6.4.

5.3 Concomitant Medications

The term concomitant medications refers to medications (prescription and non-prescription as well as other investigational agents) other than RDV received by enrolled participants. All concomitant medications must be source documented; a subset of concomitant medications will be entered into eCRFs as part of the medical and medication histories obtained at data collection timepoints as described in Section 6.

RDV is rapidly metabolized by hydrolases to a nucleotide monophosphate, which can be further phosphorylated to the active triphosphate form, or dephosphorylated to GS-441524. GS-441524 is predominantly eliminated renally and does not affect common drug metabolism pathways. It is not anticipated that RDV will impact the PK of other medications. However, RDV is a substrate for P-glycoprotein and OATP1B1 and its transport may be affected by inducers or inhibitors of these transporters. PK results will be carefully evaluated in relation to concomitant medications during data analysis.

5.4 Disallowed Medications at Entry

Due to potential interactions with RDV or the formation of its active triphosphate metabolite, GS-443902, the following medications are exclusionary if taken or administered within 48 hours prior to entry: carbamazepine, hydroxychloroquine, chloroquine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, rifabutin, ritonavir, St. John’s wort.

6 STUDY PROCEDURES AND DATA COLLECTION REQUIREMENTS

An overview of study procedures including PK sampling, blood volumes and data collection requirements are presented in the Schedule of Evaluations (SOE) in Appendix I. Presented in this section is additional information on study procedures and data collection requirements for each study period as follows: baseline, infusion, safety-follow-up, and delivery (for women enrolled in Arm 1).

Because study participants will be hospitalized with COVID-19 at study entry and while receiving RDV infusions, and given COVID-19 infection control measures, IMPAACT 2032 study staff are expected to have limited contact with study participants. The treating physician (not affiliated with the study) is responsible for RDV management and clinical care. Study procedures for this study are limited to data collection and blood specimens for PK. The study procedures described in this section are the responsibility of the IMPAACT 2032 study staff. With the exception of PK sampling, study procedures will largely be done via medical chart abstraction and/or remote contact or telemedicine visit. Refer to Section 10 for more details on PK design and analysis. Refer to the IMPAACT 2032 Laboratory Processing Chart (LPC) for collection, processing, and shipping instructions for PK samples.

All procedures must be performed at the approved clinical research site or approved associated facilities. All procedures must be documented in accordance with the DAIDS policies for source documentation; refer to Section 11 for more information on documentation requirements and entry of eCRFs. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

In addition to the protocol-specified procedures described in this section and the SOE Appendix, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; and providing instructions for contacting study staff. All such tasks should be documented consistent with site SOPs.

6.1 Data Collection Requirements

Collection of clinical and laboratory data is required throughout the study beginning at 48 hours before the first infusion and continuing through 4 weeks after the last infusion. Additionally, data will be collected at the time of delivery for participants in Arm 1, and limited data will also be collected from the birth and newborn exam records of their infants. The specific data collection requirements are described in each sub-section below specific to each time period. All information should be obtained based on available medical records or remote or telemedicine visit, in order to minimize physical contact with the participant. Data abstraction and reporting should be targeted to occur as close as possible to the data collection timepoint indicated in the SOE; for the infusion time period in particular, sites are encouraged to key data each day that infusions are administered, if possible.

Documented medical conditions will be assessed for severity as described in Section 7.2.1, and new conditions occurring after infusions begin will also be assessed for relationship to RDV as described in Section 8. Relevant dates will be recorded for all conditions and medications.

Abnormal findings identified prior to initiation of RDV infusions will be entered into medical history eCRFs, and abnormal findings identified after initiation of RDV infusions will be entered into adverse events eCRFs. Administration of RDV will be recorded on an Infusion Treatment Log eCRF and use of concomitant medications in the time periods specified below will be recorded on the Concomitant Medication Log eCRF. Laboratory test results will be recorded on laboratory eCRFs as specified in Section 6.

6.2 Screening/Entry

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process.

Screening procedures may be performed at any point after hospitalization and COVID-19 diagnosis (or presumed diagnosis), up to and including the day of enrollment. Participants or their LAR (as applicable) must provide consent before any activities are performed to determine eligibility. See Section 13.3 for more information on the informed consent process. For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined.

Entry may occur at any time after hospitalization and prior to the start of the 4th RDV infusion. **Entry should be targeted for prior to or as close to the start of RDV infusions as possible**. Women who are enrolled but do not initiate RDV within 7 days of entry will be discontinued from the study per Section 4.7.

Procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination. Final eligibility determination must precede enrollment. In the event that a woman is found to be ineligible on the day of enrollment, enrollment should not occur.

Screening and entry procedures include the following:

- Obtain informed consent
- Assign PID to woman
- Obtain participant medical records
- Document eligibility requirements and demographics in SES
- Complete final eligibility determination and confirmation (Entry visit only, prior to enrollment)
- Complete paper-based eligibility checklist, enter checklist data into SES to enroll the woman, print and file a copy of the confirmation file (Entry visit only)
- Complete Visit Tracking eCRF

6.3 Pre-infusion

The Pre-infusion period is defined as 48-hours priors to initiation of RDV infusions for COVID-19. Clinical and laboratory data will be collected per Table 2 for this time period (unless alternate time period is specified for specific data elements). If Screening/Entry occurs within or after 48-hours prior to the first RDV infusion, the clinical and laboratory data for the Pre-infusion period will be collected retrospectively after study entry.

Table 2: Data Collection Requirements for Pre-infusion Period

Evaluation	Enter into eCRFs or SES
Medical History	Record the following as available in the medical records: • All medical conditions of any grade occurring or ongoing within 48 hours prior to the first infusion of RDV. These will be considered pre-existing conditions and unrelated to RDV. • Arm 1: Major obstetrical diagnoses during the current pregnancy prior to start of RDV infusions • Arm 1: Gestational age at 48 hours prior to first infusion. • Arm 1: Prior pregnancy information (number and dates of prior pregnancies, outcome of prior pregnancies) • Last menstrual period

Evaluation	Enter into eCRFs or SES
	• Hospitalization for COVID-19 (COVID-19 status at hospitalization, COVID-19 symptoms onset date, hospitalization onset date, discharge date)
Concomitant Medications	Record the following medications available in the medical records EXCEPT RDV: • All prescription medications • Blood products and transfusions • All investigational drugs

Vital Signs	Record the following measurements that are available in the medical records:
	• Record only once:
	  ○ Height
	  ○ Weight
	• Record the most abnormal measurement in a 24-hour period:
	  ○ Highest systolic blood pressure
	  ○ Temperature
	  ○ Pulse rate
	  ○ Pulse oximetry

Respiratory Status	• Record the respiratory and/or ventilation status

Laboratory Test Results	For each of the following laboratory test results from tests conducted for clinical care and documented in the medical record:
	• Record the most recent results of any grade for each of the following
	  ○ AST, ALT, alk phos, and bilirubin (direct and total)
	  ○ Creatinine and estimated creatinine clearance and method of determination, and estimated GFR (eGFR)
	  ○ CBC with differential and platelets
	  ○ Coagulation factors (prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT))
	  ○ COVID-19 test results (first positive result only)
	  ○ All other laboratory results
	• Record the following results only once - at the time closest to the start of the first infusion either in the Pre-infusion or Infusion period:
	  ○ Inflammatory markers (lactate dehydrogenase (LDH), procalcitonin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), high sensitivity (hs) CRP, D-dimer, ferritin, troponin I, hs troponin I)

6.4 Infusion Period

The infusion period begins at the start of the first infusion and continues through the day of last infusion, regardless of the duration of RDV treatment. The procedures to be completed for this period include clinical and laboratory data collection per Table 3, and PK sampling as described below.

Note: If a participant is enrolled after initiation of RDV infusions, the clinical and laboratory data should be abstracted retrospectively after study entry, starting with the Pre-infusion period and continuing through any portion of the Infusion period that has already passed.

Table 3: Data Collection Requirements for Infusion Period

Evaluation	Enter into eCRFs
Medical History and Medical Events	Updates to any medical conditions that were previously ongoing, and occurrence of any new conditions available in the medical records, as follows: • Infusion reactions of any grade • All Grade 3 and higher events • All serious adverse events (SAEs) • Updates to hospitalization for COVID-19
Concomitant Medications	Record the following medications available in the medical records EXCEPT RDV: • All prescription medications • Blood products and transfusions • All investigational drugs Also record any modifications to medications previously recorded during this period.

Vital Signs	Record the following measurements available in the medical record, as follows:
	• Record only once, if not recorded in Pre-infusion period:
	  ○ Height
	  ○ Weight
	• Record the most abnormal measurement in a 24-hour period:
	  ○ Highest systolic blood pressure
	  ○ Temperature
	  ○ Pulse rate
	  ○ Pulse oximetry

Respiratory Status	• Record the respiratory and/or ventilation status

Evaluation	Enter into eCRFs
Laboratory Test Results	Record highest grade daily result for each of the following available laboratory test results from labs drawn for clinical care and available in the medical records: • AST, ALT, alk phos, and bilirubin (direct and total) of any grade • Creatinine and estimated creatinine clearance of any grade and eGFR • Albumin • CBC with differential and platelets of any grade • Coagulation factors (PT, INR, PTT) • COVID-19 test results (first positive result only, if not reported in a previous data collection period) • All grade 3 or 4 other laboratory test results Record the following results only once - at the time closest to the start of the first infusion either in the Pre-infusion or Infusion period: • Inflammatory markers (LDH, procalcitonin, ESR, CRP, hs CRP, D-dimer, ferritin, troponin I, hs troponin I)
Remdesivir Treatment	For EACH RDV infusion, from the first through the last infusion, record: • Infusion number • Date of infusion • Start time of infusion • Stop time of infusion • Formulation of RDV • Dose • Interruption or modifications of dose (stopped or slowed) • Anatomical location and side of infusion • Initial rate of infusion • Volume of infusion prepared and administered

6.4.1 Intensive PK Sampling and Optional Breast Milk Sampling

Intensive PK samples will be collected around either the 3rd, 4th, or 5th infusion. Sites may choose which infusion is most convenient for collection of the intensive PK samples. Intensive PK sample collection must be completed within a single dosing interval (i.e., specific timepoints may not be spread over different infusions). Intensive PK timepoints are shown in Table 4 below.

RDV administration will begin after the pre-dose sample is drawn. PK samples should be collected from the opposite arm than the one used for infusion to prevent sample contamination. If not already in place, an intravenous catheter will be placed in an arm vein for serial blood collection. Plasma will be stored at each timepoint; additionally, PBMC and DBS will be isolated and stored from these samples at the pre-dose and 23-hour post-end of infusion (EOI) timepoints to assess intracellular concentrations of GS-443902. Additional blood volume will be collected at the pre-dose sample to assess the protein binding capacity of RDV, and will be processed separately from the intensive PK plasma samples (see LPC). Plasma will also be isolated from the pre-dose sample for quantification of α1-acid glycoprotein (AAG).

For lactating women who have consented to provide a breast milk sample, an optional breast milk sample will be collected once on the intensive PK day, at either the EOI, 0.75-hour, 1.5-hour, 3-hour, or 5-hour EOI PK timepoint (at site discretion). Breast milk must be collected within 90 minutes *after* one of these timepoints. If the participant has consented to provide this sample but circumstances do not permit collection of the breast milk sample (e.g., breast pump not permitted in participant room due to infection control measures, participant too sick to express milk), collection of this sample may be omitted. The date and time of breast milk sample collection will be source documented and entered into eCRFs. See the LPC for processing instructions.

A study staff member must be physically present for each PK sample collection timepoint; samples within each block may be collected either by a non-study clinical care provider under the supervision of the study staff, or by a study staff member (see Section 6.4.3). Due to the unique processing requirements of the specimens (see the LPC), PK sample collection has been organized into 4 suggested sample collection "blocks" which do not exceed 4 hours each. The IMPAACT 2032 study staff member is responsible for batch transporting specimens to the processing lab at the end of each block. Samples may be transported to the processing lab more frequently than at the end of each block if time, resources and infection control measures permit, as long as a study staff member is able to supervise PK sample collection at each timepoint.

Table 4: Intensive PK Schedule and Volumes

Suggested Sample Collection Block	1	2				3		4
Timepoint	**Pre-dose**	**End of Infusion (EOI)**	**0.75 hrs after EOI**	**1.5 hrs after EOI**	**3 hrs after EOI**	**5 hrs after EOI**	**7 hrs after EOI**	**23 hrs after EOI**
Plasma Volume	8 mL*	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
PBMC Volume	8 mL	n/a	n/a	n/a	n/a	n/a	n/a	8 mL
DBS Volume	1 mL	n/a	n/a	n/a	n/a	n/a	n/a	1 mL
AAG	X[#]							
Breast milk (optional)	n/a	[5 mL]^	[5 mL]^	[5 mL]^	[5 mL]^	[5 mL]^	n/a	n/a
Window	-1 hr	+/- 15 mins	+/- 15 mins	+/- 15 mins	+/- 15 mins	+/- 30 mins	+/- 30 mins	+/- 1 hr

*6 mL to be processed for protein binding studies (see LPC)
[#]Plasma for AAG to be isolated from the DBS blood sample
^ Breast milk to be collected once, at **one** timepoint only (at site discretion), and only from women who are lactating and have consented to providing this sample. 5 mL is the optimal sample size, but any volume >0.5 mL will be accepted.

Refer to the study-specific Manual of Operations (MOP) for additional PK sample collection procedures. Specific processing instructions for samples at each timepoint are detailed in the LPC.

The timing, dose, formulation and duration of each infusion will be source documented and entered into eCRFs as described in Table 4. The date and time of PK sample collection, and the anatomical location of blood draw, will also be source documented and entered into eCRFs.

6.4.2 Single Plasma PK Sampling with Standard of Care Labs

A convenience single plasma PK sample will be collected on infusion days 2 through 5, as feasible, ideally whenever blood samples are drawn as part of clinical care for standard of care (SOC) labs. If possible, a Pre-infusion blood draw should be targeted for this sample collection. This sample should be omitted on the day of intensive PK sampling. If no blood samples are drawn for clinical care on a particular day, then the single PK sample may be collected by itself if circumstances permit; if circumstances do not permit, this sample collection may be omitted for that day. Single PK specimens are also subject to the unique PK specimen processing requirements (see the LPC). See the LPC for additional instruction. The date and time of PK sample collection will also be source documented and entered into eCRFs.

6.4.3 PK Sampling Supervision by IMPAACT 2032 Study Staff

As described above in Section 6, while the IMPAACT 2032 study staff may not actually collect the PK samples, they are ultimately responsible for the samples and for ensuring samples are collected and processed in accordance with the IMPAACT 2032 protocol and procedures. Study staff must be present for the entire duration of PK sample collection, are responsible for all data collection around PK sampling, and must provide direct supervision to any clinical care providers who collect the PK samples. If PK sampling cannot be performed by the IMPAACT 2032 study staff given COVID-19 infection control measures, PK sampling must be done by a non-study clinical care provider under direct supervision of the IMPAACT 2032 study staff. Blood draws will be done by the non-study clinical care provider in accordance with hospital standard policies and procedures for phlebotomy. Individuals collecting specimens from COVID-19 infected participants and all research personnel involved in the study will strictly follow local hospital institutional standard operating procedures for infection control.

Direct supervision of clinical staff by research staff for PK sampling should be conducted through real-time video or in-person visual observation of the procedures, while allowing the study staff member to maintain physical distance from the participant and avoiding the need for personal protective equipment that may be in short supply. The IMPAACT 2032 study staff are responsible for ensuring samples are collected in the appropriate tubes at the appropriate timepoints, tubes are labeled correctly, and specimens are processed per protocol. Sites must determine the best process for interacting with and supervising the non-study clinical care providers for successful completion of PK sampling.

6.5 Safety Follow-up Period (48-Hour, 7-Day and 4-Week Post-Last Infusion)

The Safety Follow-up period begins from the first day after the last RDV infusion and continues for 4-weeks after the last RDV infusion. The last infusion may be the 5th infusion, or may be an infusion earlier (if RDV was discontinued by the treating physician), or an infusion between 5 and 10 days depending on the treatment course for the participant. The procedures for this period include clinical and laboratory data collection per Table 5, as well as collection of one single PK sample, and optional collection of breast milk in lactating women at 48-hours after the last infusion.

This period is divided into three data collection timepoints: 48-Hour, 7-Day, and 4-Week Post Last Infusion. In addition to chart abstraction, telemedicine visits may be used to obtain and/or supplement or clarify medical history information after the participant has been discharged from the hospital. At each data collection timepoint, a data lookback will take place beginning from the

first day after the end of the prior data collection timepoint until the current data collection timepoint; only the data elements specified in Table 5 for that data collection timepoint period will be recorded on eCRFs.

For Arm 1 participants who deliver within the Safety Follow-up period, and for all Arm 2 participants, study participation will conclude and participants will be taken off study once the 4-week post-last infusion data collection is complete. For Arm 1 participants, who deliver after the Safety Follow-up period, study participation will end after delivery data collection period is complete.

NOTE: For Arm 1 participant if delivery falls within the Safety Follow-up period, data for both periods should still be collected and reported. If there is a gap in time between the Safety Follow-up and Delivery periods, no data are to be collected during that time unless specified in Table 6.

Table 5: Data Collection Requirements for Safety Follow-up Period

Evaluation	Enter into eCRFs or SES
Medical History and Medical Events	Updates to any medical conditions that were previously ongoing at the time of the prior data collection timepoint, and occurrence of any new conditions since the prior data collection timepoint as follows: • All Grade 3 and higher events • All SAEs • Updates to hospitalization for COVID-19
Concomitant Medications	Record the following medications: • All prescription medications • All investigational drugs Also record any modifications to medications previously recorded.

Vital Signs	Record the following measurements that are available in the participant chart:
	• Record only once, if not recorded at Pre-infusion or Infusion periods:
	  ○ Height
	  ○ Weight
	• Record the most abnormal measurement since the last data collection timepoint:
	  ○ Highest systolic blood pressure
	  ○ Temperature
	  ○ Pulse rate
	  ○ Pulse oximetry

Respiratory Status	Record the most recent respiratory and ventilation status at each data collection timepoint

Evaluation	Enter into eCRFs or SES
Laboratory Test Results	Record: a) the highest grade; **and** b) the resolution value (if abnormal and since resolved), or the most recent value (if normal or not resolved), for each of the following available laboratory test results from labs drawn for clinical care **since the last data collection timepoint** : • AST, ALT, alk phos, and bilirubin (direct and total) of any grade • Creatinine and estimated creatinine clearance of any grade and eGFR • CBC with differential and platelets of any grade • Coagulation factors (PT, INR, PTT) • COVID-19 test results (only if a positive result was not reported at any previous timepoint) • Any new (since the last data collection timepoint) grade 3 or 4 other laboratory test results

6.5.1 Single Plasma PK at 48-hours Post Last Infusion

For women who are still hospitalized 48 hours after receiving their last infusion **only**, a single plasma PK sample will be collected at the 48-hour post-last infusion data collection timepoint (within a window of +/- 12 hours). Ideally this sample will be drawn at a time when other blood samples are drawn as part of clinical care for SOC labs. If no blood samples are drawn for clinical care within the window for the 48-hour post-last infusion PK sample, then the single PK sample should be collected by itself if circumstances permit. If circumstances do not permit, this sample collection may be omitted. This single PK specimen is also subject to the unique PK specimen processing requirements (see the LPC for additional instruction). The date and time of PK sample collection will also be source documented and entered into eCRFs.

6.5.2 Breast Milk Sample Collection at 48-Hours Post Last Infusion

At the 48-Hour Post Last Infusion data collection timepoint **only**, an optional breast milk sample will be collected from postpartum lactating women who are still hospitalized and who consented to provide a breast milk sample.

Breast milk samples may be collected within a window of +/- 12 hours of the 48-Hour Post Last Infusion timepoint. If possible, collection of breast milk should be targeted to within 90-minutes on either side of the 48-Hour Post Last Infusion single plasma PK sample collection. If circumstances do not permit collection of the breast milk sample within +/-12-hour window (e.g., breast pump not permitted in participant room due to infection control measures, participant too sick to express milk), collection of this sample may be omitted. The date and time of breast milk sample collection will be source documented and entered into eCRFs. See the LPC for processing instructions.

6.6 Delivery Period (Arm 1)

The Delivery period is for Arm 1 women only. The Delivery period is defined as from onset of labor or start of Cesarean section through 24 hours after delivery. In the Delivery period, procedures include collection of clinical and laboratory data per Table 6 for the mother and infant; as well as PK sampling for the subset of participants **who have received a RDV infusion within 5 days prior to delivery** per Section 6.6.1.

If delivery occurs after the end of the Safety Follow-up period, study participation will conclude and participants will be taken off study after the Delivery period data collection is complete. If delivery falls within the Safety Follow-up period, data collection should be collected for both periods, and study participation will conclude and participants will be taken off study after the Safety Follow-up period data collection is complete.

Table 6: Data Collection Requirements for Delivery Period

Evaluation	Enter into eCRFs or SES
Medical History and Medical Events	Updates to any medical conditions that were ongoing at last data collection period, and occurrence of any new conditions from onset of labor or Cesarean section through 24 hours after delivery that meet the following requirements: • All congenital anomalies of the infant • All Grade 3 and higher events • All SAEs • Updates to hospitalization for COVID-19
Concomitant Medications	Only collect: • Prescription medications for new onset conditions at time of delivery • All investigational drugs Routine labor and delivery medications should NOT be reported. Also record any modifications to medications previously recorded, if available.
Vital Signs	Record the following measurements that are available in the medical record as follows: • Record the most abnormal measurement in a 24-hour period: o Highest systolic blood pressure o Temperature o Pulse rate o Pulse oximetry
Respiratory Status	Record the most recent respiratory and ventilation status.
Laboratory Test Results	Record the following results available in the medical record: • Any new grade 3 or 4 laboratory test results
Pregnancy/ Birth Outcomes	• Pregnancy outcome (outcome of pregnancy, congenital anomalies, date of outcome, narrative) • Birth outcome (outcome location, type of delivery, infant date of birth, infant time of birth, infant gestational age, intrauterine growth classification, infant birth weight, infant biological sex at birth, Apgar scores, infant head circumference).

6.6.1 Delivery PK

For Arm 1 women who have received at least one RDV infusion within the 5 days preceding delivery, transplacental passage of RDV will be assessed by measurement of drug concentrations in cord blood and maternal plasma at the time of delivery. For these women only, a sample will be drawn at delivery at the time the cord is clamped (within 1 hour). A sample will also be obtained from the umbilical cord, immediately after the cord is clamped (or within 1 hour). Delivery PK specimens are also subject to the unique PK specimen processing requirements (see

the LPC). The date and time of PK sample collection will also be source documented and entered into eCRFs.

6.7 Early Discontinuation of Remdesivir

Women who discontinue RDV after initial PK sampling but prior to the 5th infusion will have no further PK sampling done. These women will be followed for safety and clinical outcomes throughout the duration of the study follow-up period, and clinical and laboratory data will continue to be collected as indicated in the SOE.

6.8 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:
https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

6.8.1 Specimen Collection

Specimens will be collected for this study as indicated in the SOE and per detailed guidance provided in the LPC, which will be available on the study-specific webpage at: http://impaactnetwork.org/studies/IMPAACT_2032.asp.

In accordance with NIH recommendations, for participants 18 years of age or older, adult blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. For participants less than 18 years of age, pediatric blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period.

Site investigators should review the participant chart to ensure that blood volume limits have not been exceeded prior to PK sampling. If limits will be reached, PK sampling should not be done or should be limited. In the event that blood collection must be limited, available specimens should be prioritized for use in the following order: (1) plasma for PK, (2) DBS for PK, (3) PBMC for PK. In this event, the CMC should also be notified and may provide guidance.

6.8.2 Specimen Preparation, Testing, Storage, and Shipping

PK specimens are subject to unique plasma processing requirements: blood samples must be kept on ice before processing, a precisely measured proportion of stabilizing agent must be added to the specimens during plasma separation, and processed plasma samples must be frozen at -70 degrees Celsius or colder within 4 hours of specimen collection. All specimens collected for this study will be labeled, transported, processed, tested, stored, and/or shipped in accordance with the DAIDS policy referenced in Section 6.8, site and local laboratory SOPs, and the LPC. The frequency of specimen collection will be directed by the SOE. Plasma, DBS, and PBMC specimens will be stored on-site and shipped for batch testing, according to the schedule listed in the LPC. Refer to the LPC for additional instruction related to PK specimens shipping. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in LPC.

6.8.3 Biohazard Containment

Transmission of SARS-CoV-2 and other respiratory pathogens are transmitted primarily by inhalation of droplet nuclei. Transmission of blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Appropriate respiratory, blood, and secretion precautions will be employed by all personnel in the collection of clinical samples and the shipping and handling of all clinical samples for this study, as currently recommended by the CDC in the United States, the World Health Organization (WHO) internationally and the NIH. The current CDC guidelines for SARS-CoV-2 specimen collection and handling are available: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources.html.

All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for United Nations (UN) 3373, Biological Substance, Category B, and Packing Instruction 650. If samples are processed through an intermediate location, central lab or other, should again decontaminate the outside of the Styrofoam shipment container prior to shipment to lab. Samples from this study must be shipped separately from any other studies. No sharing of a single container for multiple studies.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Section 7 describes safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the Protocol Team and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in Section 7.1 and described in greater detail in Section 9.5. Unless otherwise noted, the specifications of this section apply to all study arms.

7.1 Safety-Related Roles and Responsibilities

IMPAACT 2032 is an opportunistic study and RDV is not provided as part of this study; it is expected that site investigators will not be the treating physicians of COVID-19 infected patients receiving RDV. The treating physician has primary responsibility for RDV clinical management and toxicity monitoring. It is expected that RDV will be provided, administered, and managed by the participants' non-study treating physician consistent with the prescribing information for RDV.

7.1.1 IMPAACT 2032 Site Investigators

IMPAACT 2032 site investigators are responsible for additional close monitoring of safety data as described in Section 7.2 and for alerting the Protocol Team if unexpected concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in Section 7.2 and complete EAE reporting as indicated in Section 7.3. Site investigators are also responsible for prompt reporting of any unanticipated problems involving risks to participants or others to the sIRB and any other applicable review bodies, per the procedures of each applicable review body. All investigators must follow sIRB requirements for prompt reporting, which are available at: https://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/prompt_reporting_policy.html

7.1.2 Clinical Management Committee

The following Protocol Team Members comprise the Clinical Management Committee (CMC): Chair and Vice-Chairs, Medical Officers, Protocol Investigators, Pharmacologists, Statisticians, Data Managers, and Clinical Trial Specialists. The CMC will provide guidance as needed including but not limited to participant eligibility and PK sampling procedures.

On behalf of the full Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in Section 9.5.1, and will review adverse event (AE) reports to assess and/or confirm initial investigator assessment of relatedness to RDV. Refer to Section 8 for more information on participant management including relatedness assessments.

7.2 Safety-Related Data Collection

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to all participants, beginning at the time of the first infusion until 4 weeks after the last infusion (and for Arm 1 participants, during the Delivery period, if that occurs after Safety Follow-up period). Any untoward medical conditions occurring prior to the first infusion will be considered pre-existing conditions.

Pre-existing conditions, adverse events, and laboratory test results will be graded initially by the site investigator according to Section 8 and entered into eCRFs as specified below and in Section 6.

7.2.1 Pre-Existing Conditions

All pre-existing conditions that meet the criteria specified below will be entered into Medical History eCRFs.

- All medical conditions of any grade occurring or ongoing within 48 hours prior to the first infusion of RDV.
- Arm 1: Major obstetrical diagnoses during the current pregnancy prior to start of RDV infusions.
- Arm 1: Gestational age at 48 hours prior to first infusion.
- Hospitalization for COVID-19

7.2.2 Adverse Events

The following adverse events that meet the criteria and specific to the time periods listed below will be entered into Adverse Event log eCRFs.

<u>Infusion and Safety Follow-up Periods:</u>

- Infusion reactions of any grade
- All Grade 3 and higher events
- All SAEs as defined in Version 2.0 of the DAIDS EAE Manual

<u>Arm 1: Delivery Period (onset of labor through 24 hours after delivery):</u>

- All congenital anomalies of the infant
- All Grade 3 and higher events

- All SAEs as defined in Version 2.0 of the DAIDS EAE Manual

7.2.3 Laboratory Test Results

All laboratory test results that are available in medical records from lab tests done for clinical care, and that meet the criteria and specific to the time periods below, will be entered into laboratory eCRFs as specified.

Pre-infusion Period:
Record the most recent result for each of the following laboratory test results of any grade from labs drawn within 48 hours prior to infusion and up until the start of the first infusion:

- AST, ALT, bilirubin (direct and total)
- Creatinine and estimated creatinine clearance and method of determination and eGFR
- CBC with differential and platelets
- Coagulation factors (PT, INR, PTT)
- All other laboratory results
- Inflammatory markers (LDH, procalcitonin, ESR, CRP, hs CRP, D-dimer, ferritin, troponin I, hs troponin I) (record any available markers only once, refer to Table 2 and 3)

Infusion Period:
Record any available inflammatory markers (LDH, procalcitonin, ESR, CRP, hs CRP, D-dimer, ferritin, troponin I, hs troponin I) only once, refer to Table 2 and 3.

Record highest grade daily result for each of the following from labs drawn after the start of the first infusion through the day of the last infusion:

- AST, ALT, and bilirubin (direct and total) of any grade
- Creatinine and estimated creatinine clearance and eGFR of any grade
- Albumin
- CBC with differential and platelets of any grade
- Coagulation factors (PT, INR, PTT)
- COVID-19 test results(first positive result only, if not reported previously)
- All grade 3 or 4 other laboratory test results

Safety Follow-up Period:
At each data collection timepoint (48-Hour, 7-Day, and 4-Week Post Last Infusion), record the highest grade as well as either the resolution value (if abnormal and since resolved) or the most recent value (if normal or not resolved), since the last data collection timepoint, for each of the following:

- AST, ALT, alk phos, and bilirubin (direct and total) of any grade
- Creatinine and estimated creatinine clearance of any grade and eGFR
- CBC with differential and platelets of any grade
- Coagulation factors (PT, INR, PTT)
- COVID-19 test results (only if a positive result was not reported in any previous timepoint)
- Any new (since the last data collection timepoint) grade 3 or 4 other laboratory test results

Delivery Period:
Record the following results from onset of labor through 24 hours after delivery:

- Any new grade 3 or 4 laboratory test results

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available at: https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available at: https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at: CRMSSupport@niaid.nih.gov

Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at: DAIDSRSCSafetyOffice@tech-res.com

7.3.2 EAE Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

Expedited reporting will be required for remdesivir (RDV), the drug under study.

In addition to the SAE Reporting Category identified above, any fetal loss under 20 weeks of gestational age, or fetal death 20 weeks of gestational age or over, must be reported in an expedited manner (i.e., as an EAE).

7.3.3 Grading the Severity of Events (applies to EAEs and all other adverse events)

Adverse events will be graded, initially by the IMPAACT 2032 site investigator as described in Section 8, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, which is available on the RSC website at: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

For participants who are entering the study during pregnancy (Arm 1), creatinine and creatinine clearance will be graded based on absolute values only and not change from baseline.

Note: The DAIDS AE Grading Table Parameter for unintentional weight loss excludes postpartum weight loss. Therefore, maternal weight loss after delivery in Arm 1 women will not be graded in this study.

7.3.4 EAE Reporting Period

The EAE reporting period for this study begins at the first RDV infusion administration and ends when the participant completes all study follow-up. This includes any gap in time between the end of the Safety Follow-up Period and Delivery for women in Arm 1 -- EAEs should be reported for this time period if the site becomes aware of them.

After the protocol-defined EAE reporting period, unless otherwise noted, only suspected unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT

No study drug is provided as a part of this study. As such, all clinical management and toxicity monitoring of participants receiving RDV will be the responsibility of the non-study treating physician.

All adverse events identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in Section 11. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3). Relationship assessments will be made initially by the IMPAACT 2032 site investigator with guidance, as is feasible, from the treating physician. If relationship assessment is not able to be made by the site investigator, the attribution should be marked as "unknown." The CMC will review and confirm all classifications; in cases where relationship was marked as "unknown," the CMC will be responsible for classifying the event if possible. Where there is discordant assessment between the IMPAACT 2032 site investigator and the CMC, the site will be queried for more information. Ultimately, the CMC classification will be used for data analysis. Relationship assessments will be according to the following categories and definitions:

Related	There is a reasonable possibility that the adverse event may be related to RDV
Not related	There is not a reasonable possibility that the adverse event may be related to RDV

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in Section 7.2 above.

All grade 3 or higher adverse events considered related to RDV must be followed to resolution (return to baseline) or stabilization, while the participant is on study.

With respect to IMPAACT 2032 data collection, adverse events should be entered into eCRFs per Section 6.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase IV prospective, open label, non-randomized opportunistic study to describe the PK properties and safety of RDV administered intravenously as part of clinical care among hospitalized pregnant and non-pregnant women with COVID-19. This study is comprised of two arms specific to the study population. The first arm will include pregnant women, while the second arm will include non-pregnant women of childbearing potential. PK sampling will be performed during the RDV infusions and women will be followed for safety for four weeks after the last infusion; Arm 1 women who are still pregnant at that time will continue to be followed for safety at delivery.

The target sample size is 20 PK-evaluable women for each arm. A participant's PK data will be deemed unevaluable by a protocol pharmacologist for a specific analysis if they do not have adequate PK evaluations to determine the PK parameter of interest for that analysis (see Sections 9.6 and 10.2 for details). If a participant is deemed unevaluable for PK, the CMC will determine how to proceed with replacement. All women who receive any amount of RDV after enrollment will be evaluable for the safety analyses.

The primary objectives are to describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to pregnant women as part of clinical care and to describe clinical and laboratory safety outcomes in pregnant women receiving RDV as part of clinical care. The secondary objectives are to describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to non-pregnant women of childbearing potential as part of clinical care, and to describe clinical and laboratory safety outcomes in non-pregnant women receiving RDV as part of clinical care. Other objectives are to describe placental transfer with collection of plasma and cord blood samples at delivery in mothers who have received RDV within the preceding 5 days, to compare the pharmacokinetics of RDV and its metabolite, GS-441524, in pregnant women to those observed in non-pregnant women of childbearing potential, to describe and compare intracellular concentrations of RDV's active intracellular nucleotide triphosphate (GS-443902) in pregnant and non-pregnant women, to develop a PopPK model of RDV and its metabolites in pregnant and non-pregnant women and evaluate associations between clinical characteristics and RDV and GS-441524 pharmacokinetics, to assess plasma protein binding of RDV in pregnant women and non-pregnant women of childbearing potential, and to describe the frequency of detection and the relative concentrations in breast milk and plasma of RDV and GS-441524 in lactating women undergoing RDV PK sampling.

A challenge in designing this study is the current paucity of data on the PK parameters of RDV, particularly when given to adults with COVID-19, and their variability, as well as how they might differ during pregnancy. As discussed in more detail in Section 10.5, while pregnancy is expected to alter RDV and GS-411524 drug disposition, the differences in RDV PK in pregnant versus non-pregnant women are not expected to be of sufficient magnitude to require dosing modifications from the standard adult doses of RDV. A preliminary analysis approach for this study is to assess if drug exposure during pregnancy is within 30% of the PK outcome measure(s) for a comparison population of non-pregnant adults, including healthy non-COVID-19 infected adults (see Table 1 in Section 1.2) as well as adults with COVID-19 and non-pregnant women enrolled in Arm 2 of this study. Additional analyses to assess adequacy of dosing during pregnancy will be performed as more information on the PK and pharmacodynamics of RDV in adults with COVID-19 becomes available, including data from Arm 2 (non-pregnant women) of this study. The statistical analysis plan (SAP) will be updated as more data become available.

This study design is opportunistic in that it enrolls women who may have already received at least one infusion of RDV. Consequently, the results may be overly optimistic. Because participants can be enrolled any time prior to the 4th infusion, the study population will potentially not include women who started RDV and discontinued it prior to the 4th infusion due to toxicity, intolerance, virologic failure, or any other reason. Thus, this study may not be able to identify pharmacokinetic, safety, or tolerance issues that occur very soon after drug initiation and estimates of the frequency of adverse outcomes may be overly optimistic. The fact that the results of this study may not generalize to the full population of women who start RDV will be discussed as a limitation of the study in presentations and publications of results.

The Primary Completion Date (PCD) for this study will be the date on which data collection is complete for all the primary outcome measures, i.e., the last study visit. The primary data analyses will be performed after study completion.

9.2 Outcome Measures

Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in Section 2.

Primary and secondary outcome measures listed below in Table 7 will be addressed in the study's primary SAP, which will define the content of the Primary Analysis Report. This report will form the basis for the primary manuscript and results reporting to ClinicalTrials.gov. Outcomes of interest for other objectives intended for subsequent publications are listed under "Other Outcome Measures".

Table 7. Outcome Measures

Primary Outcome Measures		
Arm 1	**9.2.1.1**	Non-compartmental PK parameters: • RDV area under the plasma concentration-time curve (AUC) • RDV half-life (T1/2) • GS-441524 trough concentration (C_{trough})

	9.2.1.2	• Maternal renal adverse events of any grade through 7 days post-last infusion
		• Maternal hepatic adverse events of any grade through 7 days post-last infusion
		• Maternal hematologic events of any grade through 7 days post-last infusion
		• Adverse events through four weeks post-last infusion and during delivery:
		  ○ Maternal Grade 3 or higher adverse events
		  ○ Serious adverse events
		  ○ Maternal Grade 3 or higher adverse events assessed as related to RDV by the CMC (see Section 8)
		• Labor/delivery outcomes:
		  ○ Pregnancy loss
		  ○ congenital anomalies
		  ○ preterm birth (< 37 weeks, < 34 weeks)
		  ○ small for gestational age (SGA) (< 10^{th} percentile for gestational age)
		• Newborn physical exam:
		  ○ birth weight
		  ○ length
		  ○ head circumference

Secondary Outcome Measures		
Arm 2	**9.2.2.1**	Non-compartmental PK parameters: • RDV AUC • RDV T1/2 • GS-441524 C_{trough}

	9.2.2.2	• Renal adverse events of any grade through 7 days post-last infusion
		• Hepatic adverse events of any grade through 7 days post-last infusion
		• Hematologic events of any grade through 7 days post-last infusion
		• Adverse events through four weeks post-last infusion and during delivery:
		  ○ Grade 3 or higher adverse events
		  ○ Serious adverse events
		  ○ Grade 3 or higher adverse events assessed as related to RDV by the CMC (see Section 8)

Other Outcome Measures		
Arm 1	**9.2.3.1**	• Ratio of cord blood/maternal plasma RDV and GS-441524 concentrations
Arms 1 and 2	**9.2.3.2**	PopPK parameters: • RDV AUC • GS-441524 AUC
	9.2.3.3	• Intracellular GS-443902 concentrations (DBS and PBMC)

	9.2.3.4	PopPK parameters: • RDV clearance (CL) • RDV volume of distribution (V) • RDV AUC • GS-441524 CL • GS-441524 V • GS-441524 AUC
	9.2.3.5	• RDV free fraction
	9.2.3.6	• Detection of RDV in breast milk • Detection of GS-441524 in breast milk • RDV maternal breast milk/maternal plasma concentration ratio • GS-441524 maternal breast milk/maternal plasma concentration ratio

9.3 Randomization and Stratification

There is no randomization or stratification in this study.

9.4 Sample Size and Accrual

9.4.1 Sample Size

As noted in Section 9.1, the target number of participants in each arm is 20 PK-evaluable women. This target was selected based on sample size calculations (below) regarding the ability of the study to indicate whether or not the PK outcome measures in pregnant women are within 30% of the PK outcome measures for non-pregnant comparison populations. We also calculated the precision provided for estimating the risk of adverse events and the probability of observing zero events and of observing 1-10 event(s). As described in more detail in Section 9.5.2, the data analyses that address the primary objectives will include descriptive statistics for the PK parameter of interest at specified timepoints as well as descriptive statistics of safety outcomes.

To determine an appropriate sample size for the PK primary objective, we considered the precision for estimating the PK parameter with different target sample sizes, as measured by the width of the resulting confidence intervals (CI) expressed as a percentage of the mean value. CI were calculated using the modified Cox approach(24). Currently, there is limited PK data available for RDV in humans(15, 16). As was shown in Table 1, coefficient of variation (CV) estimates for RDV and GS-441524 AUCs and C_{max} range from 12.7% to 30.3% (i.e., 0.127 to 0.303), based on data from 8 healthy adult non-pregnant volunteers(15). Because the protocol team expects study participants will have a wider range in age, disease severity, and stage of pregnancy (for Arm 1), resulting in a higher variability than the available data, we describe the precision with an assumed CV of 0.2, 0.3, or 0.4.

Table 8 below illustrates the upper and lower confidence limits and width of the 90% CI for the mean PK parameter (e.g., AUC, T1/2, or C_{trough}), expressed as a percentage of the mean, for different N and CV. With a sample size of 20 evaluable women and a CV equal to 0.3, the 90% CI will range from 89 – 112.3% of the mean, and the corresponding CI width will be 23.3% of the mean. This relatively narrow CI would provide a very good indication of whether or not our data suggest a greater than 30% difference from the PK parameter in non-pregnant comparison populations.

Table 8. Percentile range and width of 90% Confidence Intervals for the mean PK parameter

N	CV = 0.2		CV = 0.3		CV = 0.4	
	Range	Width	Range	Width	Range	Width
15	91.3- 109.5%	18.2%	87.2- 114.6%	27.4%	83.4- 120.0%	36.6%
20	92.6- 108.0%	15.5%	**89.0- 112.3%**	**23.3%**	85.7- 116.7%	31.1%
25	93.4- 107.1%	13.7%	90.2- 110.8%	20.6%	87.2- 114.7%	27.5%

Because an important objective, if feasible, is to compare PK parameters between Arm 1 and Arm 2, we also calculated the power to achieve this objective, namely correctly detecting whether or not the PK parameter during pregnancy is more than 30% different from the PK parameter in non-pregnant women. We used an equivalence framework; i.e., we used PASS 15 to calculate the power to conclude that the 90% CI for the geometric mean ratio (GMR) of the PK parameter is within 0.7 to 1.43 (25).

Table 9 below presents the power to conclude that the PK parameter in study pregnant women is not more than 30% different than the PK parameter in non-pregnant women (i.e.: the 90% CI of the GMR is within 0.7 to 1.43) under the assumption that the geometric means of the PK parameter are the same (GMR = 1.0) or the geometric mean of pregnant women is 10% less than the geometric mean of non-pregnant women (GMR = 0.9). For a GMR = 0.9, the power to conclude that there is evidence that the PK parameters are not more than 30% different for N = 20 in both arms is 0.99, 0.84, or 0.63 with CVs=0.2, 0.3, or 0.4, respectively. Thus, a sample size of at least 20 evaluable women in each arm is necessary to provide a power above 63% if the CV is 0.4 or less. With a sample size of 20 evaluable pregnant women and only 10 evaluable non-pregnant women, the probability would still be above 68% if the CV is 0.3 or less but only 42% if the CV is 0.4.

Table 9. Power to conclude that pharmacokinetic parameters are not more than 30% different (90% CI within 0.7 – 1.43)

N Arm 1 (Pregnant Women)	N Arm 2 (Non-pregnant Women)	GMR = 1.0			GMR = 0.9		
		CV = 0.2	CV = 0.3	CV = 0.4	CV = 0.2	CV = 0.3	CV = 0.4
15	10	99.2	78.6	42.3	91.5	63.4	34.9
	20	100.0	93.4	68.7	97.7	78.9	55.3
20	10	99.6	84.3	50.8	94.0	68.5	41.5
	20	100.0	96.7	78.1	**98.9**	**84.4**	**63.0**
25	10	99.8	87.5	56.4	95.3	71.8	45.7
	20	100.0	98.1	83.6	99.4	87.7	67.9

For the safety primary objective, we calculated the precision for potential proportions of participants experiencing Grade 3 or higher adverse events or adverse pregnancy outcome that may be observed and the probability of observing events with sample sizes ranging from 15 to 25. Table 10 below presents the exact binomial (Clopper-Pearson) 95% upper and lower confidence limits. With a sample size of 20 evaluable women and an observed adverse event rate of 20%, the 95% CI will range from 6% – 44%.

Table 10. Precision (exact binomial 95% confidence interval) for estimating the percentage of participants experiencing a ≥ Grade 3 adverse event or adverse pregnancy outcome

N	n (%) with ≥Grade 3 Adverse Events or Adverse Pregnancy Outcome	Exact 95% CI
15	0 (0%)	0% - 22%
20	0 (0%)	0% - 17%
25	0 (0%)	0% - 14%
15	2 (13%)	2% - 40%
20	2 (10%)	1% - 32%
25	3 (12%)	3% - 31%
15	3 (20%)	4% - 48%
20	**4 (20%)**	**6% - 44%**
25	5 (20%)	7% - 41%
15	5 (33%)	12% - 62%
20	6 (30%)	12% - 54%
25	8 (32%)	15% - 54%
15	6 (40%)	16% - 68%
20	8 (40%)	19% - 64%
25	10 (40%)	21% - 61%
15	8 (53%)	27% - 79%
20	10 (50%)	27% - 73%
25	13 (52%)	31% - 72%

Table 11 below presents the probability of observing no event (e.g., ≥ Grade 3 or higher adverse event or adverse pregnancy outcome) and of observing at least 1-10 event(s) for sample sizes ranging from 15-25. With a sample size of 20 evaluable women and a true event probability of 20%, the probability of observing at least two events is 93%. Note that the non-negligible probability of observing zero events when the true event rate is less than 10% indicates that this study may not detect such events; the protocol team acknowledges this as a limitation.

Table 11. Probability of observing no event and of observing 1-10 event(s)

N	True probability of an event	Probability of observing				
		0 events	≥1 event	≥2 events	≥5 events	≥10 events
15	1%	86%	14%	1%	0%	0%
20	1%	82%	18%	2%	0%	0%
25	1%	78%	22%	3%	0%	0%
15	5%	46%	54%	17%	0%	0%

20	5%	36%	64%	26%	0%	0%
25	5%	28%	72%	36%	1%	0%
15	10%	21%	79%	45%	1%	0%
20	10%	12%	88%	61%	4%	0%
25	10%	7%	93%	73%	10%	0%
15	20%	4%	96%	83%	16%	0%
20	**20%**	1%	99%	**93%**	37%	0%
25	20%	0%	100%	97%	58%	2%
15	30%	0%	100%	96%	48%	0%
20	30%	0%	100%	99%	76%	5%
25	30%	0%	100%	100%	91%	19%
15	40%	0%	100%	99%	78%	3%
20	40%	0%	100%	100%	95%	24%
25	40%	0%	100%	100%	99%	58%
15	50%	0%	100%	100%	94%	15%
20	50%	0%	100%	100%	99%	59%
25	50%	0%	100%	100%	100%	89%

9.4.2 Accrual

Each arm will open to accrual independently and will accrue independently over approximately 6 months from the first enrollment in each arm. If it takes longer to reach the accrual target for Arm 2 (non-pregnant women) than for Arm 1 (pregnant women), the protocol team may decide to close accrual to Arm 2 if it has not yet fully accrued when 20 PK-evaluable Arm 1 women have completed their study follow-up, since the study primary objectives only involve Arm 1 women and do not involve Arm 2 women.

The initial enrollment limit will be 25 in each arm, based on an anticipated 20% unevaluable. The determination of evaluable participants is done by the protocol pharmacologists (see Section 10.2). The CMC may increase the enrollment limit in either arm to achieve the target number of 20 PK-evaluable women. Changes to the enrollment limit will be implemented in the Statistical and Data Management Center's (SDMC) enrollment system and sites will be notified and instructed via email. The IMPAACT Management Oversight Group (MOG) will also be notified.

Refer to Section 9.5.2 for the definitions of unevaluable for PK and Section 9.6 for the definition of unevaluable for safety.

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. Detailed plans for study monitoring will be outlined in a Study Progress, Data, and Safety Monitoring Plan (SPDSMP) developed by the SDMC prior to enrollment of the first participant. Sections 11 and 12 provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.5.1 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct.

The Protocol Team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and actual accrual following activation. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these. If relatively few of the eligible sites have been activated after the study has been opened to accrual, the team will periodically re-assess the feasibility of the study and the reasons why sites have not been activated and may make adjustments as needed.

The team will closely monitor total study accrual based on reports that will be generated at least monthly by the SDMC. Accrual performance will be reported by the DMC, by site and across sites, and the team will review and discuss study progress at least monthly. If Arm 1 has not yet enrolled at least 10 pregnant women within 6 months after the first Arm 1 enrollment, or has not fully enrolled within 12 months after the first Arm 1 enrollment, the protocol team will assess whether the study remains feasible or needs modification and will make a recommendation to the IMPAACT MOG regarding study continuation or modification.

The Protocol Team will similarly review participant retention and other key indicators of the quality of study conduct (e.g., data and specimen completeness) based on reports generated by the SDMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Determination of PK evaluability will be made by a protocol pharmacologist and tracked in the study database (see Section 10.2 for the definition of PK unevaluable). If a participant is deemed unevaluable, the CMC will determine how to proceed with replacement, and the SDMC will implement the decision in the data management system and SES.

Participant Safety

On behalf of the Protocol Team, the CMC will closely review participant safety through routine review of safety data reports generated by the SDMC. These reports will provide listings of adverse events specified for entry into eCRFs, as described in Section 7.2. The CMC will review these reports via conference call or other meeting at least monthly (see Section 8 for details of the review of the assessed relationship of adverse events to RDV). At the time of each call, the DAIDS Medical Officer may, when possible, also review any EAEs (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports. As drugs are not being provided in this study, there are no planned safety-related study action triggers or stopping rules; however, the CMC (and specifically, the clinician members) will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern. If recurrent instances of a serious toxicity are observed, appropriate authorities, such as the FDA and/or the pharmaceutical company, may be notified.

9.5.2 Monitoring by the IMPAACT MOG and Study Monitoring Committee (SMC)

An independent IMPAACT SMC will review the SPDSMP in an introductory initial review, following policies described in the IMPAACT MOP.

After the initial review, SMC reviews will only occur on an *ad hoc* basis if any issues or concerns arise, as determined by the IMPAACT MOG. The MOG will regularly review, at a minimum, accrual and retention reports. Also, as described above in Section 9.5.1, the CMC will closely monitor the study and will raise any issues or concerns to the IMPAACT MOG, particularly with regard to accrual, feasibility, and participant safety. The MOG will then determine if an *ad hoc* SMC review should be convened. For *ad hoc* SMC reviews, limited data will be reviewed, focusing on the events that triggered the reviews.

Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

9.6 Analyses

This section provides a brief summary of the planned statistical analyses. Details will be specified in a separate, comprehensive SAP. Section 10.4 describes the pharmacology data analyses and modelling, including the non-compartmental and population PK analyses.

The data analyses to address the primary and secondary PK and safety objectives will include descriptive statistics. PK outcome measures will be summarized using geometric means, arithmetic means, % CVs, and 90% CIs. The 90% CI for the arithmetic mean will be calculated on the log scale using the modified Cox approach(24). Continuous safety outcome measures, such as newborn birth weight, will be summarized using mean and median as measures of location and the standard deviation and quantiles of minimum, 25th percentile, 75th percentile, and maximum as measures of dispersion. Categorical safety outcome measures will be summarized using proportions and exact binomial (Clopper-Pearson) 95% CIs. Descriptive statistics will also be presented by trimester for Arm 1

For the objectives that compare PK parameters between arms, 90% CIs for the geometric mean ratio (GMR) of the PK parameters in study pregnant women versus non-pregnant women will be calculated to assess whether or not there is a greater than 30% difference in exposure in pregnant women versus non-pregnant women. The confidence coefficient will be 90% rather than 95% to match the usual practice in the PK literature. We will use Schuirmann's two one-sided tests (TOST) approach to show that the means of the two groups do not differ by more than the 30% margin of equivalence, i.e.: the 90% CI of the GMR is between 0.7 and 1.43(26). As discussed in Section 9.1, the 30% margin is a preliminary analysis approach (due to paucity of available data), and the SAP will be updated to include additional analyses to assess adequacy of dosing during pregnancy as more information on the PK and pharmacodynamics of RDV in adults with COVID-19 becomes available.

For women who deliver within 5 days after receiving RDV, placental transfer will be assessed by comparing the drug concentrations of RDV and GS-441524 in plasma from cord blood with concentrations in maternal plasma at delivery using the GMR with a 90% CI.

The intracellular concentrations of GS-443902 at each timepoint and in each arm will be summarized using descriptive statistics and compared between pregnant and non-pregnant women using the GMR with a 90% CI. Individual-level concentrations over time will also be visualized using spaghetti plots and compared within individual .

The RDV free fraction from *ex vivo* experiments will be summarized using descriptive statistics for pregnant and non-pregnant women, as will the unbound RDV concentrations (calculated as follows: total concentration x free fraction) and the Albumin and AAG concentrations.

For lactating women meeting breast milk collection criteria, the number and percentage of women with detectable maternal breast milk concentrations for RDV and GS-441524, and the breast milk/plasma ratios, will be calculated and summarized using descriptive statistics. Timing of breast milk and plasma sample collection since EOI will also be summarized.

All analyses will include all participants with evaluable data for that analysis (see Section 10.2 for the definition of PK-unevaluable. For the safety analyses, a participant will only be deemed unevaluable if she does not receive any amount of RDV.

10 CLINICAL PHARMACOLOGY PLAN

The design and analysis plans for the primary, secondary and other pharmacology objectives are described in this section. Detailed PK sample collection, processing, storage and shipping instructions are provided in the LPC.

10.1 Pharmacology Overview and Objectives

This is an opportunistic study designed to assess the PK and safety of RDV in pregnant and non-pregnant women with COVID-19. Arm 1 of this study will include women at any stage of pregnancy who have COVID-19 and will receive RDV as part of their clinical care, at the standard adult dose of 200 mg IV on day 1, followed by 100 mg IV on days 2 through 5 to 10. Arm 2 of this study will include non-pregnant women of childbearing potential who have COVID-19 and will receive RDV as part of their clinical care, at the standard adult dose of 200 mg IV on day 1, followed by 100 mg IV on days 2 through 5 to 10. Intensive PK samples will be collected on the day of the 3rd, 4th, or 5th infusion (at site discretion), as described in Section 6.4.1. PMBC and DBS for intracellular assessments of GS-443902 will be isolated with the pre-dose

and 23-hour post-dose samples on the intensive PK day. Additional blood will be collected with the pre-dose intensive PK sample to assess RDV protein binding ex vivo. A sparse PK sample will also be collected with standard of care (SOC) labs on the days of the 2nd, 3rd, 4th, and 5th infusions, as described in Section 6.4.2, and 48 hours after the last RDV infusion in women who are still hospitalized, as described in Section 6.5.1. Sparse samples will not be collected on the day that intensive PK samples are collected. For women who receive a RDV dose within 5 days prior to delivery, a single maternal sample at delivery and a cord blood sample at the time when the cord is clamped will also be collected. For lactating women meeting breast milk collection criteria, breast milk samples will also be collected at one of the scheduled time points between EOI and 5 hours EOI during the intensive PK assessments, and at the 48 hour post-last infusion time point.

The pharmacology objectives for this protocol include all of the objectives listed in Section 2, except 2.1.2 and 2.2.2.

10.2 Definition of PK Evaluable

Women will be considered PK evaluable for the intensive PK assessment if at least 3 out of 4 of the 1st block (pre-dose through 3 hours post-EOI) intensive PK samples are collected, and at least 1 sample in the 2nd block (5 or 7 hours post-EOI), and either the pre-dose or 23 hour post-EOI sample is collected. In addition to these minimum requirements for sample collections, drug concentrations will also be reviewed once available to further assess whether the participant is PK evaluable. Profiles with missing samples will be assessed for evaluability by the pharmacologists and CMC on a case-by-case basis. Participants deemed unevaluable will be replaced to achieve a target of 20 PK evaluable participants in each Arm. Every effort should be made to collect all timepoints of interest. PK results from women who had incomplete PK sampling due to early discontinuation of RDV may be included in population PK modeling and simulations.

10.3 Pharmacology Outcome Measures

Pharmacology outcome measures are described in Section 9.2.

10.4 Pharmacology Data Analysis and Modeling

10.4.1 Non-Compartmental PK Analyses

Descriptive presentation of the concentrations and the various collection times will be summarized. A non-compartmental PK analysis (NCA) will be performed on the plasma concentration-time data generated for each participant. Calculated PK parameters will include, as permitted by data:

- RDV AUC
- RDV C_{max}
- GS-441524 C_{trough}
- RDV terminal elimination rate constant (λ_z) and
- RDV the terminal elimination half-life ($T_{1/2}$).

RDV C_{max} will be taken directly from the observed concentration-time data and is expected to occur at the end of the infusion. Data permitting, the RDV terminal slope, λ_z, will be determined from log-linear portion of the curve and the terminal half-life ($T_{1/2}$) calculated as $0.693/ \lambda_z$. RDV

AUC will be determined using the linear trapezoidal method. In absence of adequate PK data to perform an NCA, other appropriate compartmental analyses may be undertaken to describe the plasma PK of RDV and GS-441524. The random sparse (single) PK sample concentrations on days 2-5 and 48 hours post-last-infusion, intracellular concentrations in DBS and PBMC, RDV protein binding results, and among lactating women, frequency of RDV and/or GS-441524 detection in breast milk and maternal breast milk/plasma ratio will be summarized descriptively.

10.4.2 Population PK Analyses

Population PK analyses will be performed for RDV and GS-441524 using the IMPAACT 2032 PK data alone using appropriate methodology. These data may be combined with other non-pregnant adult PK data, as they become available. PK analyses of collected data, including population PK evaluations, may be performed to assist the study team with assessment of safety or adequacy of dosing during pregnancy. With data from 20 pregnant and 20 non-pregnant women, the population PK modeling and approximately 12 PK samples per participant, the power to build complex PK models will be limited. Thus, the population PK analysis will focus on determination of mean clearance (CL) and volume of distribution (V) for GS-4451524 and RDV and their variabilities. A limited number of key clinical variables will be assessed as potential covariates including pregnancy stage, gestational age, weight, renal function and age.

10.5 Anticipated Outcomes

Based on simulations presented in Section 1.2, RDV and GS-441524 exposures in pregnant women are expected to achieve concentrations within the range of those observed in healthy adults. While pregnancy is expected to alter RDV and GS-441524 drug disposition, the pathways responsible for RDV metabolism and elimination have not been previously studied in pregnancy. It is expected that the PK of RDV and its metabolites will differ between pregnant and non-pregnant women but that these will not be of sufficient magnitude to require dosing modifications from the standard adult doses of RDV. A preliminary analysis approach for this study is to assess if drug exposure during pregnancy is within 30% of the PK outcome measures for a comparison population of non-pregnant adults, including healthy non-COVID infected adults (see Table 1 in Section 1.2) as well as adults with COVID-19 and nonpregnant women enrolled in Arm 2 of this study. If toxicities are noted, relationships with RDV and GS-441524 exposures may be explored. Additional analyses to assess adequacy of dosing during pregnancy will be performed as more information on the PK and pharmacodynamics of RDV in adults with COVID-19 becomes available, including data from Arm 2 (non-pregnant women) of this study. Since this is an observational and opportunistic study, which does not dictate therapy, actual dose modifications in study participants will not occur and are not applicable.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.5, data on enrollment in this study will be collected using the DMC SES. Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled women, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 11.2).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at: https://www.frontierscience.org.

11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, Gilead Sciences, Inc., the US Food and Drug Administration, site drug regulatory authorities, the sIRB and any applicable local IRBs, Office for Human Research Protections (OHRP), and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

12 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records — including informed consent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the sIRB approved protocol, and accuracy and completeness of records.

The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

The Johns Hopkins Medicine IRB serves as the single IRB (sIRB) for IMPAACT studies at US sites; site IRBs also provide local context reviews for US sites. Site investigators are responsible for awareness of and adherence to the policies and procedures of all applicable IRBs. All such policies and procedures must be followed and complete documentation of all correspondence to and from all applicable IRBs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 14.2).

Prior to study initiation, site investigators must obtain sIRB review and approval of this protocol and site-specific informed consent and assent forms in accordance with 45 CRF 46; subsequent to initial review and approval, the sIRB must review the study at least annually. Site investigators must also promptly report to the sIRB any changes in the study and any unanticipated problems involving risks to participants or others.

13.2 Pregnant Women, Children, and Vulnerable Participants

The NIH is mandated by law to ensure that pregnant women and children be included in clinical research when appropriate(27, 28). Recent national and international guidance also recommends the inclusion of pregnant women in clinical trials(29, 30). This study responds to these mandates and will provide clinical research data to inform treatment of COVID-19 in pregnant women. Per the US Code of Federal Regulations (CFR), the sIRB and local IRB must consider the potential risks and benefits to maternal participants, and their fetuses, as described in 45 CFR 46 Subpart B (for pregnant women, fetuses, and neonates) and 45 CFR 46 Subpart D (for children). Additionally, women who are severely ill with COVID-19 to the point of being incapable of giving consent would be considered vulnerable per the definition of ICH E6 (R2) 1.61, and thus the sIRB and local IRB must pay special attention to safeguarding the rights, safety, and well-being of these participants. While fetuses/infants of Arm 1 participants will not be enrolled in this study, participants in Arm 1 will be asked to consent to collection of a limited amount of data on the outcomes of their infants at birth.

With respect to 45 CFR 46 Subpart B, the specifications of 45 CFR 46.204 (d) are expected to apply to this study. There is no prospect of direct benefit for the woman nor the fetus, risk to the fetus from participation in this study (which is limited to blood draws on the mother while the fetus is *in utero*) is not greater than minimal, and the purpose of this research is the development of important biomedical knowledge that cannot be obtained by any other means (as further described in Section 1.3). Therefore, pregnant participants (or their LAR) will be asked to provide informed consent for their own study participation (including abstraction of infant outcome data) under 45 CFR 46 Subpart A, and as described in Section 13.3.

With respect to 45 CFR 46 Subpart D as it applies to collection of infant data after birth, the specifications of 45 CFR 46.404 are expected to apply. The extent of the research activities with the infant are limited to collection of clinical data that would otherwise be collected in the medical record. No procedures are performed directly on the infant. As such, the research is not greater than minimal risk. Per 45 CFR 46.408 (b), it is expected that the sIRB will find that the consent of one parent is sufficient for research to be conducted under 46.404.

13.3 Informed Consent

Refer to Section 4.5 and the study-specific MOP for further information on informed consent procedures for this study. A sample informed consent form is provided in Appendix II.

Informed consent for study participation will be obtained from each participant before any study-specific procedures are performed. If the participant is unable to provide informed consent (e.g. impaired capacity, as determined by site SOPs and consistent with sIRB policies and procedures) written informed consent will be obtained from the participant's LAR on behalf of the participant in accordance with 21 CFR 50.27.

Per FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency dated March 2020, updated May 14, 2020, while FDA regulations generally require that the informed consent of a participant be documented by the use of a written consent form that has been approved by the IRB and signed and dated by the participant at the time of consent (21 CFR 50.27(a)), in light of COVID-19 infection control measures, if the participant is in COVID-19 isolation, electronic methods of obtaining informed consent and verbal confirmation will be considered as determined by site SOPs and consistent with sIRB and local IRB policies and procedures. The method used to assess the decision-making capacity of the

participant and how consent was obtained must be documented in the participant's research record.

In obtaining and documenting informed consent, the site investigator must comply with applicable regulatory requirements, ICH GCP guidelines, and ethical principles. The informed consent form must be approved by the sIRB prior to its use. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation.

In light of the circumstances presented by conducting research during COVID-19, the informed consent SOPs for all sites must include the following information:

- The method to be used to assess the decision-making capacity of participants.
- The process for obtaining consent when a participant is not capable to consent on her own behalf (i.e., lacks decision-making capacity).
- Information about who can serve as a LAR and the process for LAR selection, in accordance with applicable local laws.

13.4 Potential Benefits

There will be no direct benefit to participants who take part in this study. Information learned from this study may be of benefit to participants and others in the future.

13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures. Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted.

13.6 Reimbursement/Compensation Plan

Pending sIRB approval, participants will be compensated for time and inconvenience associated with completing data collection and PK sampling visits as part of this study. Specific compensation amounts will be determined by the sIRB in collaboration with local IRB and will take into consideration local cost of living and intensity of each visit/data collection. Participants will be compensated one payment between $10 - $50 for each data collection time period (i.e., baseline, infusion period, safety follow-up, and delivery) for a total of up to 4 payments just for data collection. On days where there is also PK sampling, participants will receive an additional $50-250 for each PK sampling day depending on intensity of sampling as determined in consultation with the sIRB and local context review. Participants will not be compensated for the cost of their COVID-19 treatment.

13.7 Privacy and Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11.2. Data or information from the study may be shared with drug companies who have agreements with

IMPAACT and/or the US NIH, or regulatory entities, but individual participants will not be identified.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site will be identified by PID only. Likewise, communications between study staff and Protocol Team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US Federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants.

13.8 Management of Incidental Findings

The results of PK evaluations are not planned to be provided to participants as these evaluations will be performed after follow-up has been completed and are not expected to be relevant to clinical care and management, especially given the short treatment duration of RDV. If, however, new information becomes available during the course of the study indicating that the results of these evaluations are of clinical relevance, the results will be provided to study participants.

13.9 Management of New Information Pertinent to Study Participation

Participating women will be provided with any new information learned over the course of the study that may affect their willingness to remain in follow-up in the study.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which are part of the United States National Institutes of Health (NIH). Gilead Sciences, Inc. provide funding to support limited aspects of this study but will not provide regulatory sponsorship or oversight of the study.

Within the NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to remdesivir prior to and during the conduct of the study, in accordance with its sponsor obligations.
NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 12. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved by the sIRB and, as applicable, their local IRBs/ECs and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received.

Site-specific ICFs will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final sIRB and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website:
https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the study-specific website: https://impaactnetwork.org/studies/IMPAACT2032.asp

Study implementation at each site will also be guided by site-specific SOPs. The DAIDS policy on Requirements for Manual of Operations specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to the sIRB and any other applicable review bodies in accordance with the policies and procedures of these review bodies; this includes the sIRB, per the prompt reporting requirements available at the website cited in Section 7.1.1. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT MOP.

14.5 Critical Event Reporting

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at: https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf

14.6 ClinicalTrials.gov

This protocol is subject to the United States Food and Drug Administration Amendments Act of 2007 (FDAAA), including registration in ClinicalTrials.gov.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT MOP.

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APPENDICES
Appendix I
Schedule of Evaluations

Period	Baseline		Infusion						Safety Follow-up[4]			Delivery[4,5] (Arm 1 ONLY)
	Screening / Entry[1]	Pre-infusion[2]	First	Second	Third	Fourth	Fifth	Post-Fifth[3]	48-hours Post Last Infusion	7-Days Post Last Infusion	4-Weeks Post Last Infusion	
CLINICAL DATA COLLECTION												
Informed Consent/Subject Enrollment System	X											
Medical and Medications History/Chart Abstractions[6]		X	X	X	X	X	X	X	X	X	X	X
LABORATORY DATA COLLECTION[6]												
Chemistries - Cr, eGFR, ALT, AST, alk phos, bilirubin		X	X	X	X	X	X	X	X	X	X	
Albumin			X	X	X	X	X	X				
Coagulation factors – (PT, INR, PTT)		X	X	X	X	X	X	X	X	X	X	
Hematology – CBC with differential and platelets		X	X	X	X	X	X	X	X	X	X	
Other laboratory test results		X	X	X	X	X	X	X	X	X	X	X
Inflammatory markers - (LDH, procalcitonin, ESR, CRP, hs CRP, D-dimer, ferritin, troponin I, hs troponin I)		[X]	[X]	[X]	[X]	[X]	[X]	[X]				
PHARMACOLOGY												
Intensive PK plasma sampling[7]					[16 mL]	[16 mL]	[16 mL]					
Intracellular PK sampling (store DBS, PBMC) [7]					[18 mL]	[18 mL]	[18 mL]					
Protein binding plasma sample[7,8]					[6 mL]	[6 mL]	[6 mL]					

Period	Baseline		Infusion						Safety Follow-up[4]			Delivery[4,5] (Arm 1 ONLY)
	Screening / Entry[1]	Pre-infusion[2]	First	Second	Third	Fourth	Fifth	Post-Fifth[3]	48-hours Post Last Infusion	7-Days Post Last Infusion	4-Weeks Post Last Infusion	
CLINICAL DATA COLLECTION												
Alpha-1 acid glycoprotein[9]					[X]	[X]	[X]					
Single PK sampling with SOC labs (plasma)				2 mL[10]	[2 mL][10]	[2 mL][10]	[2 mL][10]		[2 mL][11]			
Breast milk sample[12]					[5 mL][13]	[5 mL][13]	[5 mL][13]		[5 mL] [11]			
Single maternal delivery PK sample (plasma)[14]												[2 mL]
Cord blood PK sample[14]												[2 mL]
TOTAL MAXIMUM PK BLOOD VOLUME	**0 mL**	**0 mL**	**0 mL**	**2 mL**	**40 mL**	**40 mL**	**40 mL**	**0 mL**	**2 mL**	**0 mL**	**0 mL**	**4 mL**

[ ] indicate procedures that are not required at each time indicated or not for all participants.

APPENDIX I FOOTNOTES

1. Entry may occur at any point after hospitalization and prior to the start of the 4th infusion.
2. Pre-infusion period is defined as 48 hours prior to start of first infusion. Collect data retrospectively if enrollment occurs after this 48-hour window has started or passed.
3. For any participants whose treatment is continued past the 5th infusion, clinical and laboratory data will be abstracted and recorded for each infusion day while infusions are ongoing per Section 6.4.
4. The Safety Follow-up Period may occur before or after Delivery. For Arm 1 women, if Delivery occurs within the Safety Follow-up Period, data for both periods should still be collected and reported.
5. Delivery procedures are for Arm 1 women only. If an RDV infusion was NOT given within 5 days preceding delivery, PK sampling will not be performed. Delivery period is from onset of labor through 24-hours after delivery.
6. See Section 6 for data collection requirements for each period.
7. Only perform intensive PK sampling schedule **once**, with the 3rd, 4th or 5th infusion. See Section 6.4.1 for collection timepoints.
8. Collect only once on the intensive PK day, with the pre-dose sample only.
9. To be measured from leftover blood sample used for DBS, see LPC.
10. Collect when blood samples are drawn as part of clinical care (preferably prior to infusion administration on that day) – if no SOC bloods are drawn on a given day, single PK sample may be collected if circumstances permit, but if unable to collect, the sample may be omitted for that day. Do not collect on the day that intensive PK sampling is performed.

11. Only collect samples for women still hospitalized. If the participant has already been discharged, omit this sample collection. If still hospitalized and if possible, collect single PK sample when blood samples are drawn as part of clinical care. If no bloods are drawn on this day for clinical care, draw blood specifically for single PK sample. See Section 6.5.
12. Only for women who have consented to provide breast milk samples, and only if women are lactating at the time of PK sampling.
13. Collect only one breast milk sample, on the intensive PK day. See Section 6.4.1 for collection timepoints. 5 mL is the optimal volume, but any volume >0.5 mL will be accepted.
14. Only perform if RDV received within 5 days prior to delivery. See Section 6.6.1 for collection details.

Do not use this form for consenting research participants unless a stamp appears here.

<<US sites only.>>
Lead Study Investigator:
Master Informed Consent Approval Date:
Site Specific Consent Information Approval Date:
JHM IRB Application No.:

Appendix II: Sample Informed Consent Forms

Appendix II, Part 1: MASTER Sample Informed Consent Form

[Sites may NOT modify Part 1 of this consent form]

PART 1: MASTER INFORMED CONSENT FORM

IMPAACT 2032
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

Version 2.0, 18 December 2020

Introduction

You are being asked to take part in the research study named above.

This consent form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as needed to fully understand the study. We will ask you questions to see if we have explained the study clearly.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. Part 1 of the consent form includes general study information that applies to all study sites. Part 2 of the consent form includes information only about the study site where you are being asked to enroll. Before making your decision, both parts of this form will be reviewed with you. You will have the opportunity to discuss any questions about this form and both of its parts with your site's study team.

Key Information

Here is a summary of important information about the study:

- You are being asked to take part in this study because you are hospitalized with COVID-19 and are currently getting, or may get in the future, remdesivir medication for treatment of COVID-19.
- You will not receive remdesivir through this study if you choose to join this study. You will continue to get care and treatment for COVID-19 by your clinical care provider. Participation in this study will not impact whether or not you receive remdesivir for treatment of COVID-19.
- The primary purpose of the study is to determine how much of the remdesivir medication is in a woman's blood. Another purpose is to look at how safe remdesivir is for a woman.
- If you choose to join the study, you will have blood samples taken at the same time that you are having remdesivir infusions.

- If you choose to join this study, information from your medical records will be collected for the time right before you start remdesivir, while you are receiving remdesivir, and for one month after you finish your remdesivir.
- If you choose to join this study, the study staff may contact you up to three times during the month after your last remdesivir infusion to ask you questions about your health.
- If you choose to join the study and you are pregnant, information from your medical records will also be collected about your pregnancy and your delivery. Information will also be collected from your medical records and/or your baby's newborn medical records about your baby's examination(s) within the first day of life.
- It is possible to join this study and then not receive remdesivir infusions. If you do not start remdesivir infusions within 7 days after joining the study, you will not stay in the study.
- There is no direct benefit to you from being in the study. However, this study may help doctors learn information that will help in the treatment of future patients with remdesivir for COVID-19.
- The most likely risk to you is from blood drawing- including pain, which is usually minor, and infection, which is rare.
- There could be risks of disclosure of your information.
- Your decision about this study will have no effect on the medical care that you would normally receive from your clinical care provider, the cost of your care, or your clinical care provider's decision to treat you with remdesivir. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in both parts of this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether to participate. After you understand the study, and if you decide that you will join the study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep. You do not give up any rights by signing this form.

About the study

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT).

The study will measure the amount of remdesivir in the blood of pregnant women and non-pregnant women. The study will include about 40 women who are in the hospital for treatment of COVID-19 in the United States. You will be in this study while you are receiving remdesivir infusions and for one month after. In addition if you are pregnant we will collect information on your delivery and birth outcome. We will also collect information on your baby from the physical examination done on your baby by your clinical care provider on the day of your baby's birth. We may also collect breast milk from women who are lactating (making breast milk).

The United States National Institutes of Health and Gilead Sciences, Inc. are paying for this study.

1. The study will measure the amounts of remdesivir in the blood of pregnant women and non-pregnant women being treated for COVID-19.

The amount of remdesivir needed during pregnancy to treat COVID-19 while being safe for pregnant women and their babies has not yet been studied. In this study, we will measure the levels of remdesivir medicine in the blood

of pregnant and non-pregnant women and compare them to each other. For women who are pregnant and deliver their baby after recently receiving remdesivir, we will also measure the amount of remdesivir found in blood from the baby's umbilical cord and compare that to the amount of remdesivir in mother's blood at the time of delivery. We will also try to measure the amount of remdesivir found in breast milk of women whose bodies are making breast milk around the time of receiving remdesivir.

2. Only pregnant women and non-pregnant women who are eligible can join the study.

If you decide to join the study, we will first talk to you about the study and collect some information about you to find out if you are eligible. More information about this is given in section #4 below. If you are eligible, you can join the study. If you are not eligible, you cannot join the study.

3. It is your decision whether or not you join the study.

Deciding to join the study is voluntary (your choice). If you are eligible, you can choose if you want to join the study or not. You are free to join or not join. Your decision will have no effect on the medical care that you would normally receive from the hospital, including your care provider's decision to treat you with remdesivir, or the cost of your care. Your access to services, and the benefits and rights you normally have, will not be affected. If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

4. Finding out if you are eligible for the study and entering the study

To find out if you can join, we will talk to you about what you will have to do if you decide to join the study. We will collect some information from your medical records about you and your health. If you are pregnant, we will collect information about your pregnancy. We will tell you if you <u>are</u> or <u>are not</u> eligible for the study. If you are eligible, you will enter the study.

Being in the study

5. You will continue to receive care for COVID-19.

Remdesivir or any other medicines you are receiving are not supplied as part of this study. If you join the study, you will continue to be taken care of by your clinical care provider for COVID-19. If you have already started to take remdesivir, you will continue to take remdesivir if that is what your clinical care provider decides. If you have not yet started to take remdesivir, the decision as to whether or not to start remdesivir will be made by you and your clinical care provider. Participation in this study will not change the care that you will receive. If you join the study and do not start remdesivir within 7 days, your study participation will end.

6. You will have medical information collected from your medical records.

Information about your health, including any medications taken and any clinical laboratory test results that you have, will be recorded from your medical records. We will collect information from your medical records

beginning a couple days before you started taking remdesivir, while you are taking remdesivir, and about a month after your last remdesivir infusion. We may also contact you by phone up to three times during the month after your last infusion to see how you are doing.

7. If you are pregnant, we will collect information about you and your baby at birth.

If you are pregnant, information from your medical records about your pregnancy and your delivery will be collected. For your delivery, we will only collect information from the time you start labor through one day after you give birth. We will also collect information from your medical records and/or your baby's newborn medical records about the health of your baby when you deliver, and your baby's physical examination(s) within the first day of life.

8. You will have multiple samples drawn to measure remdesivir in your blood.

If you enroll in the study and receive remdesivir, you will have blood collected while you are receiving remdesivir.

- On **one** infusion day (either your 3rd, 4th or 5th infusion), 8 samples over 24 hours will be collected. For the first sample, we will draw 17 mL (a little over 3 teaspoons). For the next 6 samples, at each collection time we will draw 2 mL (about ½ teaspoon) of blood, for a total of 12 mL (about 2.5 teaspoons). For the last sample, we will collect 11 mL (a little more than 2 teaspoons) of blood. If one is not already there, a small plastic catheter (soft tube) will be placed in a vein in your arm on this day before we start collecting the blood samples, so that blood can be drawn multiple times without having to stick you with a needle several times. The tube may stay in place until all of the blood samples are drawn for this day.

- On **each** infusion day from your **2nd infusion through your 5th infusion**, one 2 mL blood sample will be collected at the time you are having blood drawn for other reasons on that day. If no blood is drawn for other reasons on that day, we may try to collect this sample separately, or you may not have this sample collected. This sample will not be drawn on the one day you have the 8 blood samples collected over 24 hours. Additionally, if you are still in the hospital on the second day *after* completing your remdesivir treatment (2 days after your last infusion), we will also collect this 2mL blood sample in the same way.

If you start receiving remdesivir, but then stop receiving it before your 5th infusion, we will not collect any more blood samples from you after you stop your remdesivir, but you will stay in the study and we will continue to collect information from your medical records.

9. If you are pregnant and received remdesivir close to the time you deliver, you will have blood drawn at the time of delivery.

If you received remdesivir within 5 days before you give birth, at or near the time of delivery, we will:

- Draw one 2 mL sample from you (about a ½ teaspoon).
- Draw a small amount of blood from the umbilical cord that is attached to the placenta after the cord is clamped, right after your baby is born. This will be used to measure the amount of remdesivir that may get into your baby's blood, but this blood comes from the placenta, and not from your baby.

10. *For women who are pregnant or lactating only.* If you are lactating around the time you received remdesivir, and if you agree, we may collect a breast milk sample.

If you have recently given birth and your body is making breast milk (lactating) around the time you received remdesivir, we would like to collect a sample (5 mL, about a teaspoon) of your breast milk. If you agree, we will collect this sample on the day you have the 8 blood samples taken over 24 hours, and also around 2 days after your last remdesivir infusion, if you are still in the hospital at the time.

You do not have to agree to provide this breast milk sample. You can still join this study even if you do not agree to provide this breast milk sample.

Pregnant or lactating women: Please write your initials or make your mark below to indicate your decision about providing a breast milk sample.

If I am making breast milk (lactating) around the time of receiving remdesivir:

_____ I AGREE to have samples of my breast milk collected.

_____ I DO NOT AGREE to have samples of my breast milk collected.

11. Tests to determine the amount of remdesivir in your samples will be sent to a laboratory in the US that is not in this hospital.

Tests to determine the amount of remdesivir in your samples will be done at other laboratories in the US that have special tests for this. **You or your doctor will not be told the results of these tests. You will not be told the level of remdesivir that is in your blood or your breast milk (if you provide it).**

12. We may take you off of the study early.

The study doctor or nurse may need to take you off the study early without your permission if:

- The study is stopped for any reason.
- We determine that staying in the study might harm you.
- You do not start remdesivir within 7 days of joining the study.

13. Please tell us if you want to leave the study.

You are free to leave the study at any time for any reason. The care that you receive at this hospital will not be affected, but it is important for us to know about your decision.

Risks of the study

Taking part in this study may involve some risks and discomfort.

14. Risk from blood draws

Blood drawing may cause pain, fainting, lightheadedness or some discomfort. In about 1 in 10 cases a small amount of bleeding under the skin will produce a bruise. The risk of a blood clot forming in the vein is about 1 in 100 while the risk of infection or significant blood loss is about 1 in 1000.

15. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Benefits of the study

16. There is no direct benefit to you from being in the study.

If you take part in this study, there is no direct benefit to you. Information learned from this study may help others who have COVID-19.

Other information about the study

17. There are no costs from being in the study.

There is no cost for the study-related visits, blood draws and test results. Participation in this study will have no effect on the cost of your care outside of this study for treatment of COVID-19. Remdesivir is not provided to study participants as part of this study. More information about patient support for access to remdesivir can be found at: https://www.vekluryhcp.com/patient-support/.

18. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- The United States Food and Drug Administration (FDA)
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- Gilead Sciences, Inc.
- The IRB(s) overseeing this study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your study information may be given to other authorities if required by law.

19. What will happen with your data and specimens after the study.

The samples collected from you will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about COVID-19. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you may be used. Your information will be labeled with a code number, and the only link between the code number and your name will be kept at this site. Your name will not be given to other researchers.

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the US NIH, or regulatory entities, but you will never be identified personally.

20. Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

PART 2: SITE-SPECIFIC CONSENT INFORMATION

Site Name:
Study Title: Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States
JHM IRB Application Number: *<<insert>>*
Site Investigator of Record:
Site Principal Investigator Contact Information:
Emergency Contact:
Other Study Contact(s):

Introduction

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

Costs to Study Participants:

<<Brief description of costs to participants. Only include if different than costs as described in the main consent document. >>

Payment for Study Participation:

<<Brief description of payments and/or reimbursements. >>>>

Compensation for Research-Related Injury:

Your health is important to us. We will make every effort to protect your well-being and minimize risks.

<<Add any locally-required language for research-related injury and contact information outlining who participants should call in the event of any research-related injuries. Sites may not delete the statement about no compensation through the US NIH.>>
If you are injured as a result of being in this study, you will be given immediate treatment for your injury. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation through the United States National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

Contact Information:

If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study:
  << insert name and telephone number of investigator or other study staff >>

- If you have any health or other problems that may be related to study participation:
  << insert name and telephone number of investigator or other study staff >>

- If you want to leave the study:
  << insert name and telephone number of investigator or other study staff >>

- This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB protects the rights and welfare of the people taking part in those studies. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study. If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  - For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites. You may contact the Johns Hopkins IRB at **410-502-2092** or **jhmeirb@jhmi.edu** with your questions or concerns.
  - You may also contact the [*site specific IRB contact information*] with your questions or concerns. *<< If your site wishes to include local IRB contact information, please include this here. If this is not required, please delete this section. >>*

Additional information about your local site:

<<Please insert any additional required language for your site, as applicable for this study. Examples may include

- *Local regulatory authorities that may review study records (in addition to those listed in Part 1 #18)*
- *Local language regarding state law requirements for reporting of communicable diseases or other mandated reporting requirements*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines*
- *Local conflict of interest disclosures*

How will your privacy be maintained and how will the confidentiality of your data be protected?

<< Insert locally-required HIPAA authorization language. The following language has already been approved by the JHM IRB. Please consider whether this language may be used at your site:

- *If this language is acceptable, it may remain in this section.*
- *If this language is not acceptable, and locally-approved HIPAA authorization language is required, please delete the language and replace it with your own language.*
- *Alternatively, if your site requires use of a separate HIPAA authorization, please delete this section and include the following sentence: "[Add site name] requires that you sign a separate authorization form related to the use of your protected health information for this research study. This is required for participation in this study." >>*

HIPAA Authorization for Disclosure of Protected Health Information

What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information and, if you are pregnant, your baby's private health information. By signing this document, you agree that your health care providers may release your, and your baby's (if applicable) private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at *<< insert site name >>*, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of *<< insert site name >>*. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

Do not use this form for consenting research participants unless a stamp appears here.

<<US sites only.>>
Lead Study Investigator:
Master Informed Consent Approval Date:
Site Specific Consent Information Approval Date:
JHM IRB Application No.:

Signature Lines:

<< If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section >>

If you agree to participate in this study, please sign or make your mark below.

Name of Participant (print)	Signature of Participant	Date

OR

Name of Legally Authorized Representative (LAR)	Signature of LAR	Date

Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date

Name of Witness (as appropriate; print)	Signature of Witness	Date