Approvals

IMPAACT 2032

Primary Statistical Analysis Plan

Version 2.0

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

Protocol Version 2.0

ClinicalTrials.gov Identifier: NCT04582266

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11 April 2022

This is IMPAACT 2032 SAP Version 2.0 with names of authors, names of publication writing team members, and analysis timeline redacted.

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Version History

Version	Changes Made	Date Finalized
1	Original Version	9 February 2021

2	Summary of Changes
	• Section 4:
	  ○ Renamed “General Considerations”;
	  ○ Defined analysis sets
	  ○ Added description of how PK variables will be summarized
	  ○ Added description of Arm 1 trimester subgroup
	  ○ Removed Section 4.2 “Analysis Approaches”
	• Section 5:
	  ○ Added “Estimands and Estimation”
	• Section 6:
	  ○ Added Estimands and Estimation, CONSORT Diagram, Safety Evaluability, Retention, and Hospitalization to the report contents
	• Section 8:
	  ○ Edited protocol data and laboratory managers
		11 April 2022

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures of the IMPAACT 2032 study that will be included in the primary manuscript. These outcome measures address the major primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the Primary Analysis Report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Analysis Report are included in the Analysis Implementation Plan (AIP). The pharmacokinetic (PK) analyses to be performed by the IMPAACT 2032 protocol pharmacologist(s) are described in the Pharmacology Statistical Analysis Plan (PK SAP).

Analyses for the Primary Analysis Report will be finalized once the last participant has completed data collection for all primary outcome measures, i.e., the last study visit (primary completion date, PCD) and all queries have been resolved.

Outlines of analyses for other objectives and outcome measures not included in the Primary SAP will be provided in a separate SAP.

1.2 Version History

Current document is Version 2.0, based on Protocol Version 2.0, dated 18 December 2020.

Major modifications from Version 1.0 include the addition of Section 5 “Estimands and Estimation”.

2 Study Overview

2.1 Study Design

IMPAACT 2032 is a Phase IV prospective, open label, non-randomized opportunistic study to describe the pharmacokinetic (PK) properties and safety of remdesivir (RDV) administered intravenously as part of clinical care among hospitalized pregnant and non-pregnant women with coronavirus disease of 2019 (COVID-19). RDV will be provided and managed by the participant’s treating physician and will not be provided as part of this study. This study is comprised of 2 arms specific to the study population. Arm 1 includes pregnant women, while Arm 2 includes non-pregnant women of childbearing potential. PK sampling will be performed during the RDV infusions and women will be followed for safety for 4 weeks after the last infusion; Arm 1 women who are still pregnant at that time will have an additional follow-up at the time of delivery.

The target sample size is 20 PK-evaluable women for each arm (defined in **Section 4** below). If a participant is deemed unevaluable for PK, the Clinical Management Committee (CMC) will determine how to proceed with replacement. There is no randomization or stratification in this study.

The primary and secondary objectives are to describe the pharmacokinetics of RDV and its metabolite, GS-441524, in plasma after administration to pregnant and non-pregnant women as part of clinical care and to describe clinical and laboratory safety outcomes through 4 weeks post-last infusion in pregnant and non-pregnant women receiving RDV as part of clinical care and during delivery in pregnant women. Other objectives that will be addressed in separate SAP(s) are listed in Section 2.2 of the protocol (Version 2.0).

A challenge in designing this study is the current paucity of data on the PK parameters of RDV and its metabolites (e.g., GS-441524, GS-704277, and GS-443902) and their variability, particularly when given to adults with COVID-19, and how they might differ during pregnancy. 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, 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. These analyses will be addressed in a separate SAP.

This study design is opportunistic because it enrolls women who may have received at least one infusion of RDV. Consequently, the results may be overly optimistic. Because participants can be enrolled any time before the 4th infusion, the study population might not include women who started RDV and discontinued it before the 4th infusion due to toxicity, intolerance, virologic failure, or any other reason. Thus, this study may not identify pharmacokinetic, safety, or tolerance issues that occur 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.

2.2 Hypotheses

As the study objectives are descriptive, the study protocol does not specify any hypotheses.

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. Other study objectives in the protocol will be addressed in separate SAP(s).

2.3.1 Primary Objectives

1. Arm 1: Describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to pregnant women as part of clinical care.
2. Arm 1: Describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care.

2.3.2 Secondary Objectives

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. Arm 2: Describe clinical and laboratory safety outcomes through 4 weeks post-infusion in non-pregnant women of childbearing potential receiving RDV as part of clinical care.

2.4 Overview of Sample Size Considerations

The target number of participants in each arm is 20 PK-evaluable women. This target was selected based on sample size calculations regarding the ability of the study to indicate whether 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.

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. CIs were calculated using the modified Cox approach (Olsson, 2017). At the time of protocol development, there were limited PK data available for RDV in humans (EMA, 2020, Humeniuk 2020, Tempestelli 2020). Coefficient of variation (CV) estimates for RDV and GS-441524 AUCs and C_{max} presented in the European Medicines Agency's summary on compassionate use range from 12.7% to 30.3% (i.e., 0.127 to 0.303), based on data from healthy adult non-pregnant volunteers. 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 1 below illustrates the upper and lower confidence limits and width of the 90% CI for the mean PK parameter (e.g., area under the plasma concentration curve, half-life, or trough concentration), 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 our data suggest a greater than 30% difference from the PK parameter in non-pregnant comparison populations.

Table 1. Percentile range and width of 90% CIs 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%

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 2 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 2. Precision (exact binomial 95% CIs) 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%

Additional sample size details are provided in Section 9.4.1 of the protocol (Version 2.0).

2.5 Formal Interim Monitoring

No formal interim analyses were planned or specified in the study protocol. The plans for study monitoring are described in Section 9.5 of the protocol (Version 2.0).

3 Outcome Measures

3.1 Primary Outcome Measures (Arm 1)

1. [For Primary Objective 1] Non-compartmental PK parameters:
    a. RDV area under the plasma concentration-time curve (AUC)
    b. RDV half-life ($t_{1/2}$)
    c. GS-441524 trough concentration (C_{trough})

2. [For Primary Objective 2] Clinical and laboratory safety outcomes:
    a. Maternal renal adverse events of any grade through 7 days post-last infusion
    b. Maternal hepatic adverse events of any grade through 7 days post-last infusion
    c. Maternal hematologic events of any grade through 7 days post-last infusion
    d. Adverse events through 4 weeks post-last infusion and during delivery:
        i. Maternal Grade 3 or higher adverse events
        ii. Serious adverse events
        iii. Maternal Grade 3 or higher adverse events assessed as related to RDV by the CMC
    e. Labor/delivery outcomes:
        i. Pregnancy loss
        ii. Congenital anomalies
        iii. Preterm birth (< 37 weeks, < 34 weeks)
        iv. Small for gestational age (SGA) (< 10^{th} percentile for gestational age)
    f. Newborn physical exam:
        i. Birth weight
        ii. Length
        iii. Head circumference

Note: Additional non-compartmental PK parameters, described in Table 2 of the PK SAP, will also be summarized for Arm 1 as part of the Primary Analysis Report for RDV, GS-441524, and/or GS-704277 (data permitting).

3.2 Secondary Outcome Measures (Arm 2)

1. [For Secondary Objective 1] Non-compartmental PK parameters:
    a. RDV AUC
    b. RDV $t_{1/2}$
    c. GS-441524 C_{trough}

2. [For Secondary Objective 2] Clinical and laboratory safety outcomes:
    a. Renal adverse events of any grade through 7 days post-last infusion
    b. Hepatic adverse events of any grade through 7 days post-last infusion
    c. Hematologic events of any grade through 7 days post-last infusion
    d. Adverse events through 4 weeks post-last infusion:
        i. Grade 3 or higher adverse events
        ii. Serious adverse events
        iii. Grade 3 or higher adverse events assessed as related to RDV by the CMC

Note: Additional non-compartmental PK parameters, described in Table 2 of the PK SAP, will also be summarized for Arm 2 as part of the Primary Analysis Report for RDV, GS-441524, and/or GS-704277 (data permitting).

4 General Considerations

The derivation of PK parameters will be performed by the IMPAACT 2032 protocol pharmacologist(s), as described in the PK SAP. The statistical summaries to be prepared by the statisticians are described in this Primary SAP.

For primary and secondary PK analyses, the PK Evaluable analysis set will be used. This analysis set will include women who have at least 3 out of 4 of the pre-dose through 3 hours post-end-of-infusion (post-EOI) intensive PK samples, either the 5 hours post-EOI or the 7 hours post-EOI intensive PK sample, and either the pre-dose or 23 hour post-EOI samples 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. PK evaluability will be determined by the protocol pharmacologists and CMC on a case-by-case basis. If a participant is deemed unevaluable for PK, the CMC will determine how to proceed with replacement. For primary and secondary safety analyses, the Safety analysis set will be used. This analysis set includes all women who receive any amount of RDV.

Continuous variables will be summarized by N, N missing, mean, standard deviation, and quantiles of minimum, 25th percentile, median, 75th percentile, and maximum. Categorical variables will be summarized by N (%) in each category, excluding the missing category in the denominator. PK parameters will be also summarized using geometric and 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 (Olsson, 2017). The 90% CI for the geometric mean will be calculated using the t distribution on the log scale.

The Pre-infusion Period will refer to the period 48 hours before initiation of RDV infusions for COVID-19. If there is more than one record before the start of infusions, the last one before it (proximal) will be used, unless otherwise noted. The Infusion Period begins at the start of the first infusion and continues through the day of the last infusion, and 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. This period is divided into 3 data collection time points: 48-Hours, 7-Days, and 4-Weeks

Post-Last Infusion. For Arm 1, the Delivery Period is defined as the period from onset of labor or start of Cesarean section through 24 hours after delivery.

Because women of any gestational age can be enrolled in the study and each trimester of pregnancy provides differing physiological changes that can affect bioavailability of drugs, primary analyses will also be presented by trimester for Arm 1.

5 Estimands and Estimation

5.1 Primary Estimands

5.1.1 First Primary Estimand

<table>
<tr><th colspan="2">Primary Objective 1: To describe the pharmacokinetics of RDV and its metabolite, GS-441524, after administration to pregnant women as part of clinical care</th></tr>
<tr><td>Estimand description</td><td>Geometric mean of PK parameter (RDV AUC/RDV $t_{1/2}$/ GS-441524 C_{trough}) in hospitalized pregnant woman, who tolerated at least 3 RDV infusions for the treatment of COVID-19.</td></tr>
<tr><td>Treatment</td><td>Remdesivir (RDV)</td></tr>
<tr><td>Target population</td><td>Analysis set</td></tr>
<tr><td>Hospitalized pregnant women who received and tolerated at least 3 RDV infusions for treatment of COVID-19</td><td>PK-evaluable women
(PK Evaluable analysis set)

NOTE: Women will be considered PK evaluable if they have at least 3 out of 4 of the pre-dose through 3 hours post-end-of-infusion (post-EOI) intensive PK samples, either the 5 hours post-EOI or the 7 hours post-EOI intensive PK sample, and either the pre-dose or 23 hour post-EOI samples 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. For $t_{1/2}$, women will be PK evaluable if they have the additional requirement of 3 consecutive declining points in the curve.</td></tr>
<tr><td>Variable(s)</td><td>Outcome measure(s)</td></tr>
<tr><td>1. RDV concentration in plasma
2. RDV concentration in plasma
3. GS-441524 concentration in plasma</td><td>Non-compartmental PK parameters:
1. RDV area under the plasma concentration-time curve (AUC)
2. RDV half-life ($t_{1/2}$)
3. GS-441524 trough concentration (C_{trough})</td></tr>
<tr><td>Handling of intercurrent events</td><td>Handling of missing data</td></tr>
<tr><td>The following intercurrent events are relevant to the estimand:
1. Onset of labor
2. Discontinue treatment for toxicity or non-toxicity reasons
3. Maternal death</td><td>Only participants who are deemed PK evaluable will be included in the final analysis (i.e., missing observations due to missing or inadequate sampling are considered missing completely at random).</td></tr>
</table>

These intercurrent events will be addressed using a principal stratum approach.	Participants who do not undergo intensive PK sampling will not be included in the final analysis (i.e., missing observations due to drop out prior to intensive PK sampling are considered missing completely at random). Given the descriptive nature of the primary analyses, there are no planned supplementary or sensitivity analyses.
Population-level summary measure	Analysis approach
Geometric mean of PK parameter (RDV AUC/RDV $t_{1/2}$/ GS-441524 C_{trough}) in hospitalized pregnant women	Geometric mean of PK parameter (RDV AUC/RDV $t_{1/2}$/ GS-441524 C_{trough}), bounded by a 90% CI calculated using the t distribution on the log scale

5.1.2 Second Primary Estimand

Primary Objective 2: To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care.	
Estimand description	(A) Probability of a pregnant woman, who received any amount of RDV while hospitalized for the treatment of COVID-19,* having at least one adverse event (maternal renal/hepatic/hematologic of any grade) or death through 7 days post-last infusion. (B) Probability of a pregnant woman, who received any amount of RDV while hospitalized for the treatment of COVID-19,* having at least one adverse event (maternal Grade 3 or higher/serious/maternal Grade 3 or higher assessed as related by the CMC) or death through 4 weeks post-last infusion and at delivery. (C) Probability of a pregnant woman, who received any amount of RDV while hospitalized for the treatment of COVID-19,* having a labor/delivery outcome (pregnancy loss/congenital anomalies/preterm birth < 37 weeks/preterm birth < 34 weeks/SGA), pregnancy loss, or death. *NOTE: This study design is opportunistic in that it enrolls women who may have already received at least one infusion of RDV. 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. Consequently, the results may be overly optimistic.
Treatment	Remdesivir (RDV)

Target population	Analysis set
Pregnant women who received any amount of RDV while hospitalized for treatment of COVID-19* *NOTE: This study design is opportunistic in that it enrolls women who may have already received at least one infusion of RDV.	Pregnant women who received any amount of RDV (Safety analysis set)

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. Consequently, the results may be overly optimistic.	
Variable(s)	Outcome measure(s)
(A) Occurrence of each of the following through 7 days post-last infusion: 1. Maternal renal adverse events of any grade 2. Maternal hepatic adverse events of any grade 3. Maternal hematologic adverse events of any grade (B) Occurrence of each of the following through 4 weeks post-last infusion and during delivery: 1. Maternal Grade 3 or higher adverse events 2. Serious adverse events 3. Maternal Grade 3 or higher adverse events assessed as related to RDV by the CMC (C) Occurrence of each of the following labor/delivery outcomes*: 1. Pregnancy loss 2. Congenital anomalies 3. Preterm birth < 37 weeks 4. Preterm birth < 34 weeks 5. Small for gestational age (SGA) (< 10th percentile for gestational age) *For multiple births, the "worst" outcome within the sibling set will be used.	Outcome measures as defined by the variables
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Maternal death 2. Terminal fetus/infant event Maternal death will be addressed using a composite event approach. Terminal fetus/infant event will be addressed as a composite event for pregnancy loss. A principal stratum approach will be used for congenital anomalies, preterm birth, and SGA.	Missing data will be handled using an "available case" approach. Outcome measures for participants who discontinue follow-up before the time point of interest (i.e., 7 days post-last infusion/4 weeks post-last infusion and delivery) and did not have an event of interest will be missing (i.e., these participants will not be included in the denominator). Labor/delivery outcome measures for participants who discontinued follow-up before delivery will not be included (i.e., missing observations that would be relevant

A supplementary analysis that applies a principal stratum approach for maternal death will be used for relevant outcome measures.	to the variable are considered missing completely at random). As a sensitivity analysis, we will use multiple imputation over a range of potential probabilities, including "best case" (i.e., probability of event = 0) and "worst case" (i.e., probability of event = 1) scenarios.
Population-level summary measure	Analysis approach
(A) Probability of a pregnant woman, who received any amount of RDV for the treatment of COVID-19, having at least one adverse event (maternal renal/hepatic/hematologic of any grade) through 7 days post last infusion (B) Probability of a pregnant woman, who received any amount of RDV for the treatment of COVID-19, having at least one adverse event (maternal Grade 3 or higher/serious/maternal Grade 3 or higher assessed as related by the CMC) through 4 weeks post last infusion and at delivery (C) Probability of a pregnant woman, who received any amount of RDV for the treatment of COVID-19, having at least one labor/delivery outcome (pregnancy loss/congenital anomalies/preterm birth < 37 weeks/preterm birth < 34 weeks/SGA)	(A) Proportion of participants with at least one adverse event (maternal renal/hepatic/hematologic of any grade) through 7 days post last infusion, bounded by an exact 95% CI (B) Proportion of participants with at least one adverse event (maternal Grade 3 or higher/serious/maternal Grade 3 or higher assessed as related by the CMC) through 4 weeks post last infusion, bounded by an exact 95% CI (C) Proportion of participants with at least one labor/delivery outcome (pregnancy loss/congenital anomalies/preterm birth < 37 weeks/preterm birth < 34 weeks/SGA), bounded by an exact 95% CI

5.1.3 Third Primary Estimand

Primary Objective 2: To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care.	
Estimand description	Mean of weight, length, and head circumference from newborn physical exam for all live infants born to women, who received any amount of RDV while hospitalized for the treatment of COVID-19.* *NOTE: This study design is opportunistic in that it enrolls women who may have already received at least one infusion of RDV. 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. Consequently, the results may be overly optimistic.
Treatment	Remdesivir (RDV)

Target population	Analysis set
Live infants born to women who received any amount of RDV for the treatment of COVID-19 while hospitalized* *NOTE: This study design is opportunistic in that it enrolls women who may have already received at least one infusion of RDV. Because participants	Live infants born to women who received any amount of RDV (Safety analysis set)

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. Consequently, the results may be overly optimistic.	
Variable(s)	Outcome measure(s)
1. Birth weight (g) 2. Length (cm) 3. Head circumference (cm) For multiple births, only one infant from the sibling set, chosen at random, will be included.	Outcome measures as defined by the variables
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Maternal death 2. Terminal fetus/infant event (for newborn physical exam outcome measures) These intercurrent events will be addressed using a principal stratum approach.	Infants born to women who discontinued follow-up before delivery or did not have available information will not be included (i.e., missing observations that would be relevant to the variable are considered missing completely at random). Given the descriptive nature of the primary analyses, there are no planned supplementary or sensitivity analyses. NOTE: The trial is designed to limit the frequency of missing data. For all women, clinical and laboratory evaluations will be abstracted from medical records and/or remote contact or telemedicine visits.
Population-level summary measure	Analysis approach
Mean weight, length, and head circumference from newborn physical exam for live infants born to women who received any amount of RDV for the treatment of COVID-19 while hospitalized	Mean of weight, length, and head circumference from newborn physical exam, bounded by a 95% CI calculated using the t distribution

5.2 Secondary Estimands

5.2.1 First Secondary Estimand

Secondary Objective 1: 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	
Estimand description	Geometric mean of PK parameter (RDV AUC/RDV $t_{1/2}$/ GS-441524 C_{trough}) in hospitalized non-pregnant woman of childbearing potential, who tolerated at least 3 RDV infusions for the treatment of COVID-19.
Treatment	Remdesivir (RDV)

Target population	Analysis set
Hospitalized non-pregnant women of childbearing potential who received and tolerated at least 3 RDV infusions for the treatment of COVID-19	PK-evaluable women (PK Evaluable analysis set) NOTE: Women will be considered PK evaluable if they have at least 3 out of 4 of

	the pre-dose through 3 hours post-end-of-infusion (post-EOI) intensive PK samples, either the 5 hours post-EOI or the 7 hours post-EOI intensive PK sample, and either the pre-dose or 23 hour post-EOI samples 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. For $t_{1/2}$, women will be PK evaluable if they have the additional requirement of 3 consecutive declining points in the curve.
Variable(s)	Outcome measure(s)
1. RDV concentration in plasma 2. RDV concentration in plasma 3. GS-441524 concentration in plasma	Non-compartmental PK parameters: 1. RDV area under the plasma concentration-time curve (AUC) 2. RDV half-life ($t_{1/2}$) 3. GS-441524 trough concentration (C_{trough})
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Discontinue treatment for toxicity or non-toxicity reasons 2. Death These intercurrent events will be addressed using a principal stratum approach.	Only participants who are deemed PK evaluable will be included in the final analysis (i.e., missing observations due to missing or inadequate sampling are considered missing completely at random). Participants who do not undergo intensive PK sampling will not be included in the final analysis (i.e., missing observations due to drop out prior to intensive PK sampling are considered missing completely at random). Given the descriptive nature of the primary analyses, there are no planned supplementary or sensitivity analyses.
Population-level summary measure	Analysis approach
Geometric mean of PK parameter (RDV AUC/RDV T1/2/ GS-441524 C_{trough}) in hospitalized non-pregnant women of childbearing potential	Geometric mean of PK parameter (RDV AUC/RDV T1/2/ GS-441524 C_{trough}), bounded by a 90% CI calculated using the t distribution on the log scale

5.2.2 Second Secondary Estimand

Secondary Objective 2: To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion in non-pregnant women of childbearing potential receiving RDV as part of clinical care.	
Estimand description	(A) Probability of a non-pregnant woman of childbearing potential, who received any amount of RDV while hospitalized for the treatment of COVID-19,* having at least one adverse event (renal/hepatic/hematologic of any grade) or death through 7 days post last infusion. (B) Probability of a non-pregnant women of childbearing potential, who received any amount of RDV while hospitalized for the treatment of

	COVID-19,* having at least one adverse event (Grade 3 or higher/serious/Grade 3 or higher assessed as related by the CMC) or death through 4 weeks post last infusion and at delivery. *NOTE: This study design is opportunistic in that it enrolls women who may have already received at least one infusion of RDV. 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. Consequently, the results may be overly optimistic.
Treatment	Remdesivir (RDV)

Target population	Analysis set
Non-pregnant women of childbearing potential who received any amount of RDV while hospitalized for treatment of COVID-19* *NOTE: This study design is opportunistic in that it enrolls women who may have already received at least one infusion of RDV. 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. Consequently, the results may be overly optimistic.	Non-pregnant women who received any amount of RDV (Safety analysis set)
Variable(s)	**Outcome measure(s)**
(A) Occurrence of each of the following through 7 days post-last infusion: 1. Renal adverse events of any grade 2. Hepatic adverse events of any grade 3. Hematologic adverse events of any grade (B) Occurrence of each of the following through 4 weeks post-last infusion: 1. Grade 3 or higher adverse events 2. Serious adverse events 3. Grade 3 or higher adverse events assessed as related to RDV by the CMC	Outcome measures as defined by the variables
Handling of intercurrent events	**Handling of missing data**
The following intercurrent event is relevant to the estimand: 1. Death This intercurrent event will be addressed using a composite event approach. A supplementary analysis that applies a principal stratum approach for maternal death will be used for relevant outcome measures.	Missing data will be handled using an "available case" approach. Outcome measures for participants who discontinue follow-up before the time point of interest (i.e., 7 days post-last infusion/4 weeks post-last infusion) and did not have an event of interest will be missing (i.e., these participants will not be included in the denominator).

	As a sensitivity analysis, we will use multiple imputation over a range of potential probabilities, including “best case” (i.e., probability of event = 0) and “worst case” (i.e., probability of event = 1) scenarios.
Population-level summary measure	Analysis approach
(A) Probability of a non-pregnant women of childbearing potential, who received any amount of RDV for the treatment of COVID-19, having at least one adverse event (renal/hepatic/hematologic of any grade) through 7 days post last infusion (B) Probability of a non-pregnant women of childbearing potential, who received any amount of RDV for the treatment of COVID-19, having at least one adverse event (Grade 3 or higher/serious/ Grade 3 or higher assessed as related by the CMC) through 4 weeks post last infusion	(A) Proportion of participants with at least one adverse event (renal/hepatic/hematologic of any grade) through 7 days post last infusion, bounded by an exact 95% CI (B) Proportion of participants with at least one adverse event (Grade 3 or higher/serious/ Grade 3 or higher assessed as related by the CMC) through 4 weeks post last infusion, bounded by an exact 95% CI

6 Report Contents

This section lists the major report contents for the Primary Analysis Report. Detailed descriptions of the content of each of the following sections are given in the AIP.

1 Introduction
2 Background
- I. Study Design
- II. Objectives
- III. Outcome Measures

3 Study History and Monitoring History
4 Statistical Considerations
- I. General Considerations
- II. Estimands and Estimation

5 Disposition
- I. CONSORT Diagram
- II. Accrual
- III. Evaluability

6 Baseline Characteristics
7 Study Status and Retention
8 Status of Drug under Study and Hospitalization
9 Primary Analyses [Arm 1]
- I. Non-compartmental PK Outcome Measures
- II. Additional Non-compartmental PK Parameters
- III. Safety Outcome Measures

10 Secondary Analyses [Arm 2]
- I. Non-compartmental PK Outcome Measures

7 References

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