IMPAACT 2032: Remdesivir PK & Safety in Pregnant and Non-Pregnant Women with COVID-19

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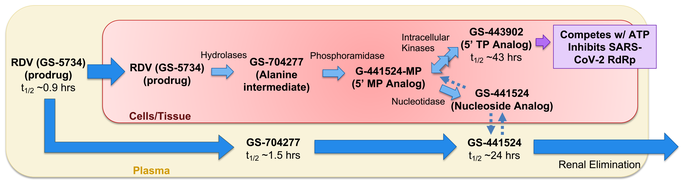
BACKGROUND

- Pregnant people with COVID-19 are at higher risk for severe disease vs. non-pregnant adults[1] and more likely to have adverse pregnancy outcomes.[2]
- Remdesivir (RDV) is an FDA-approved antiviral drug indicated for the treatment of COVID-19 in hospitalized and non-hospitalized adults and adolescents ≥12 years of age at high risk for severe disease.[3]
- RDV has complex pharmacology (**Figure 1**).[4] There are currently no PK data available for RDV in pregnant women. PK data in non-pregnant women with COVID-19 and safety data in pregnancy are also limited.[5]
- PK and safety data are needed to inform the appropriate use of RDV in pregnant women with COVID-19.

FIGURE 1. RDV Pharmacology



ATP = adenosine triphosphate; MP = monophosphate; TP = triphosphate; RdRp = RNA dependent RNA polymerase; RDV = remdesivir; half-life estimates derived from studies in non-pregnant adults without COVID-19.[4,6]

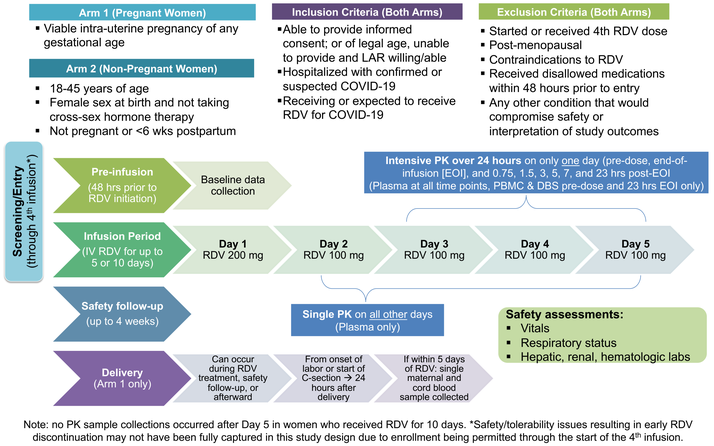
OBJECTIVES

- Describe the PK of RDV, GS-704277, GS-441524 and GS-443902 in pregnant and non-pregnant women with COVID-19.
- Describe safety outcomes through 4 weeks post-last infusion.
- Describe clinical and safety outcomes at delivery.

METHODS

- Ongoing phase IV, prospective, open-label, non-randomized, opportunistic study (NCT04582266) that enrolled women between hospitalization and the start of the 4th RDV infusion (**Figure 2**).
- With the exception of PK sampling, study procedures are mostly done through medical chart abstraction or remote contact.
- No formal statistical comparisons were made in this preliminary analysis.

FIGURE 2. Eligibility Criteria & Study Design



Note: no PK sample collections occurred after Day 5 in women who received RDV for 10 days. *Safety/tolerability issues resulting in early RDV discontinuation may not have been fully captured in this study design due to enrollment being permitted through the start of the 4th infusion.

In this preliminary analysis, RDV and metabolite **exposures were comparable** between pregnant and non-pregnant women and this therapy was **safe and well tolerated.**

RESULTS

- This preliminary analysis included 50 women enrolled prior to 1 October 2021 (**Figure 3**).

FIGURE 3. Analysis Population

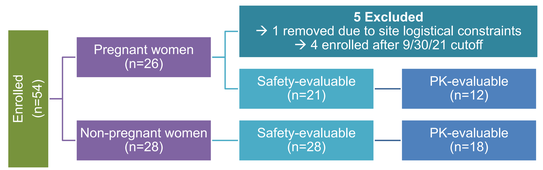
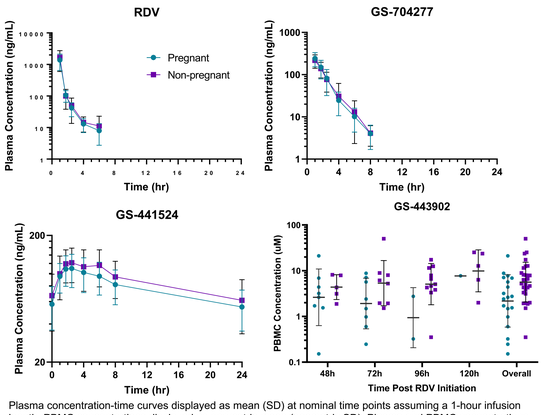


TABLE 1. Demographics & Baseline Clinical Characteristics

Characteristic	Pregnant Women (n=21)	Non-Pregnant Women (n=28)
Demographics		
Age (yr)	33 (27, 38)	37.5 (31.5, 40.5)
Race & Ethnicity		
White & Hispanic/Latina	5 (24%)	4 (14%)
Black & Hispanic/Latina	0 (0%)	1 (4%)
Other & Hispanic/Latina	5 (24%)	1 (4%)
White & not Hispanic/Latina	4 (19%)	2 (7%)
Black & not Hispanic/Latina	4 (19%)	15 (54%)
Other & not Hispanic/Latina	2 (10%)	0 (0%)
Unknown & Unknown	1 (5%)	5 (18%)
Baseline Clinical Characteristics		
Weight (kg)	77 (71.1, 93.4)	102.1 (82, 138.6)
BMI (kg/m^2)	30.2 (27.9, 37.2)	37.4 (32.8, 50.8)
Gestational age (wks)	26.6 (21.9-32.7)	--
Second trimester[a]	11 (58%)	--
Third trimester	8 (42%)	--
Respiratory Support Type[b]		
Low-flow oxygen therapy	11 (55%)	13 (65%)
High-flow oxygen therapy	7 (35%)	5 (25%)
NIPPV	1 (5%)	2 (10%)
Laboratory Measurements[c]		
eGFR (mL/min/1.73 m^2)	129.3 (118.5, 133.9)	111.7 (88.5, 117.8)
Albumin (g/dL)	3.3 (3.1, 3.4)	3.8 (3.3, 3.9)
ALT (U/L)	30.6 (13.0, 47.6)	26.1 (16.0, 50.1)
Lymphocytes (10^9/L)	1.06 (0.82, 1.28)	1.01 (0.56, 1.50)
Hemoglobin (g/dL)	11.1 (10.0, 11.7)	11.8 (10.4, 12.6)
C-reactive protein (mg/L)	60.0 (37.7, 134.0)	64.0 (41.0, 109.0)

Continuous variables summarized as median (IQR) and categorical variables summarized as count (%), except gestational age which is reported as median (range). Key: ALT = alanine aminotransferase; eGFR = estimated glomerular filtration rate, NIPPV = noninvasive positive pressure ventilation.
[a]Two pregnant women with missing data; [b]1 pregnant women and 8 non-pregnant women missing data. Baseline is defined as the highest recorded value from 48 hours prior to through the day of the first infusion.; [c]Baseline is defined as the value closest (and prior to) the first infusion. No women were on vasopressor/inotropic support at baseline.

FIGURE 4. Plasma concentration-time curves for RDV, GS-704277, and GS-441524 & PBMC Concentration by Study Arm



Plasma concentration-time curves displayed as mean (SD) at nominal time points assuming a 1-hour infusion length. PBMC concentrations displayed as geometric mean (geometric SD). Plasma and PBMC concentrations were analyzed using validated LC-MS-MS methods by QPS LLC.[6,7]

TABLE 2. Intensive PK Results

PK Parameters	Pregnant Women	Non-Pregnant Women
Infusion Duration (hr)	0.98 (0.5, 1.12)	1.0 (0.5, 1.0)
RDV	**N=11**	**N=16**
$AUC_{0\text{-}inf}$ (ng*h/mL)[a]	888.1 (63.0%)	1095 (65.3%)
C_{max} (ng/mL)	973 (170%)	1092 (141%)
T_{max} (hr)	1.07 (0.66, 1.44)	1.20 (0.63, 1.37)
$t_{1/2}$ (hr)[a]	0.95 (36.2%)	1.14 (38.8%)
CL (L/hr)	112.6 (70.5%)	91.3 (65.2%)
Vd (L)	155 (86.5%)	150.8 (76.1%)
GS-704277	**N=11**	**N=17**
$AUC_{0\text{-}inf}$ (ng*h/mL)	424.6 (35.3%)	415.3 (36.7%)
C_{max} (ng/mL)	210 (46.0%)	208 (36.4%)
T_{max} (hr)	1.2 (0.63, 1.37)	1.08 (0.66, 1.53)
$t_{1/2}$ (hr)	1.31 (23.7%)	1.19 (25.2%)
GS-441524	**N=12**	**N=18**
$AUC_{0\text{-}24h}$ (ng*h/mL)[b]	1804 (30.0%)	2126 (33.5%)
C_{max} (ng/mL)	108.7 (29.5%)	123.9 (28.2%)
C_{24h} (ng/mL)[c]	51.7 (34.5%)	57.7 (41.7%)
T_{max} (hr)	2.18 (2.0, 2.6)	2.65 (2.0, 5.13)
$t_{1/2}$ (hr)[d]	20.3 (15.3%)	20.5 (30.7%)

Key: $AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 through 24 hours; C_{max} = maximum concentration; C_{24h}: concentration at 24 hours post-dose; CL = clearance; Vd = volume of distribution; $t_{1/2}$ = half-life; T_{max} = time to maximum concentration. Intensive PK results analyzed using noncompartmental analysis with linear up-log down trapezoidal rule (Phoenix WinNonlin, Certara, Inc.). Data presented as geometric mean (CV%), except T_{max} which is reported as median (IQR). [a]Results in 9 pregnant and 13 non-pregnant women; [b]16 pregnant and 12 non-pregnant women; [c]10 pregnant and 9 non-pregnant women; [d]17 pregnant and 12 non-pregnant women

RESULTS (CONTINUED)

- 36 women received RDV infusions through either 5 days (15 pregnant, 20 non-pregnant) or 10 days (1 pregnant).
- Reasons for early RDV discontinuation included: provider discretion (n=6), AEs related to treatment (n=2), hospital discharge (n=2), withdrawal from study (n=1), left against medical advice (n=1), or patient requested to discontinue RDV (n=1)

TABLE 3. AEs through Infusion and 4 Weeks Post-Last Infusion Periods

Outcome	Pregnant Women		Non-Pregnant Women	
	Infusion	Week 4[a]	Infusion	Week 4[a]
AE of any grade	13/21 (62%)	14/20 (70%)	12/28 (43%)	12/23 (52%)
Renal AE of any grade	0/21 (0%)	0/17 (0%)	1/28 (4%)	1/21 (5%)
Hepatic AE of any grade	1/21 (5%)	2/17 (12%)	2/28 (7%)	2/22 (9%)
Hematologic AE of any grade	6/21 (29%)	6/19 (32%)	5/28 (18%)	6/21 (29%)
Grade 3/4 AE	13/21 (62%)	14/20 (70%)	10/28 (36%)	10/22 (46%)
Serious AE (SAE)	3/21 (14%)	4/17 (24%)	2/28 (7%)	2/21 (10%)
Grade 3/4 AE related to RDV[b]	0/21 (0%)	0/17 (0%)	1/28 (4%)	1/21 (5%)

[a]Denominators include women who had follow-up through 4 weeks and women with the relevant event who discontinued earlier; [b]Relatedness was assessed by the study Clinical Management Committee

- AEs deemed related to RDV included the following:
  - Two grade 2 bradycardia events in two non-pregnant women resulting in treatment discontinuation (after dose 2 and 4).
  - One grade 3 eGFR decrease in a non-pregnant woman that resolved without intervention.
- SAEs through 4 weeks post-last infusion (none related to RDV):
  - Pregnant women: 1 woman experienced asthenia (grade 3), hypotension (grade 4), respiratory failure (grade 4), and fetal death (grade 3); a 2nd woman experienced pulmonary embolism (grade 3); a 3rd woman experienced superimposed pre-eclampsia (grade 4); and a 4th woman experienced acute respiratory failure (grade 4).
  - Non-pregnant women: 1 woman experienced acute respiratory failure (grade 4) and hemoglobin decrease (grade 3); and a 2nd woman experienced acute respiratory distress (grade 4).

TABLE 4. Pregnancy Outcomes

Outcome	Pre-infusion in 2nd Trimester	Pre-infusion in 3rd Trimester	Overall
Fetal death[a]	1/6 (17%)[b]	0/5 (0%)	1/11 (9%)
Gestational age at birth (wk)	37.6 (34.0- 40.4)	37.7 (36.9- 38.9)	37.6 (34.0- 40.4)
Preterm birth (<37 wk)[a]	1/5 (20%)	2/5 (40%)	3/10 (30%)
SGA (wt <10th percentile)[a]	1/5 (20%)	0/5 (0%)	1/10 (10%)
Weight (g)	2892 (2120- 3560)	3190 (2580- 4593)	3085 (2120- 4593)

Continuous variables summarized as median (range) and categorical variables summarized as count (%); [a]Denominators reflect total number of births with outcomes available; [b]Intrauterine fetal demise (IUFD) occurred at 26 weeks and was deemed unrelated to RDV.

CONCLUSIONS

- In this preliminary analysis, the PK of RDV and its metabolites were comparable between pregnant and non-pregnant women with COVID-19, and RDV was safe and well tolerated.
- Final PK and safety analyses await availability of data from women enrolled after 1 October 2021.

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