Results of IMPAACT 2032: PK & Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women

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IMPAACT Annual Meeting

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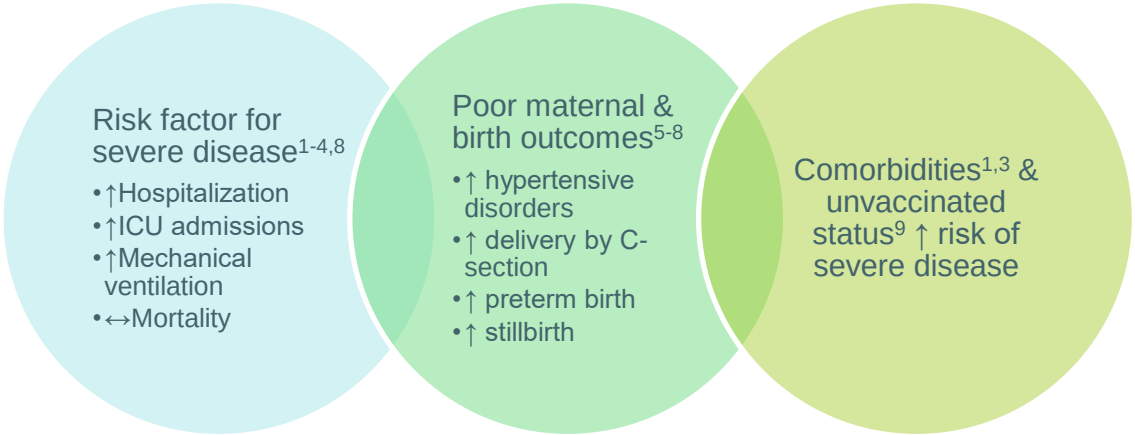
COVID-19 in Pregnancy

- Pregnant women with COVID-19 are at higher risk of adverse clinical outcomes



- Pregnant women need safe and effective therapeutics to reduce morbidities associated with COVID-19

[1]Allotey J, et al. BMJ 2020;370:m3320. [2]Badr. Am J Obstet Gynecol. 2020 [Epub ahead of print]. [3]Ellington S, et al. Morbidity and Mortality Weekly Report. 2020;69(25):769. [4]Collin J, et al. Acta obstetricia et gynecologica Scandinavica. 2020;99(7):819-22. [5]Galang RR, et al. Obstetrics and Gynecology. 2020. [6]Matar R, et al. CID 2020 [Epub ahead of print]. [7]Huntley, et al. Obstet Gynecol. 2020; 136:303. [8]Khoury, et al. Obstet Gynecol 2020; 136:273. [9]Morgan JA, et al. Obstet Gynecol 2022 Jan 1; 139(1):107-109.

Remdesivir in COVID-19 Treatment

- Antiviral medication originally developed for Ebola and then repurposed for COVID-19 treatment
  - PK data limited to healthy volunteers (primarily male) early in the pandemic[1]
- Clinical use in COVID-19 has shifted over time
  - Early data in hospitalized patients showed shorter time to recovery, no mortality benefit in those treated for 5-10 days[2]
  - Later studies with 3-day outpatient regimen showed 87% reduction in hospitalization and death vs. placebo[3]
- Currently the only FDA-approved antiviral for SARS-CoV-2[4]
  - Indicated for use in either hospitalized or non-hospitalized adults and pediatric patients with COVID-19 and at risk for progression to severe disease
  - Data in pregnancy "*insufficient to evaluate drug-associated risk*"

[1]Humeniuk R, et al. Clini Pharmacokin 2021; 60: 569–583 (2021). [2]Beigel JH, et al. N Engl J Med 2020; 383:1813-1826.
[3]Gottlieb RL, et al. N Engl J Med 2022; 386: 305-315. [4]Veklury® [Package Insert]. Foster City, CA: Gilead Sciences, Inc; April 2022.

Delays in Obtaining PK Pregnancy Data

Pregnant women generally excluded from prelicensure programs

Medications often used clinically in the absence of PK or safety data until opportunistic data available

Cannot afford these delays during a pandemic

Time-to-first published PK data with antiretroviral drugs in pregnancy

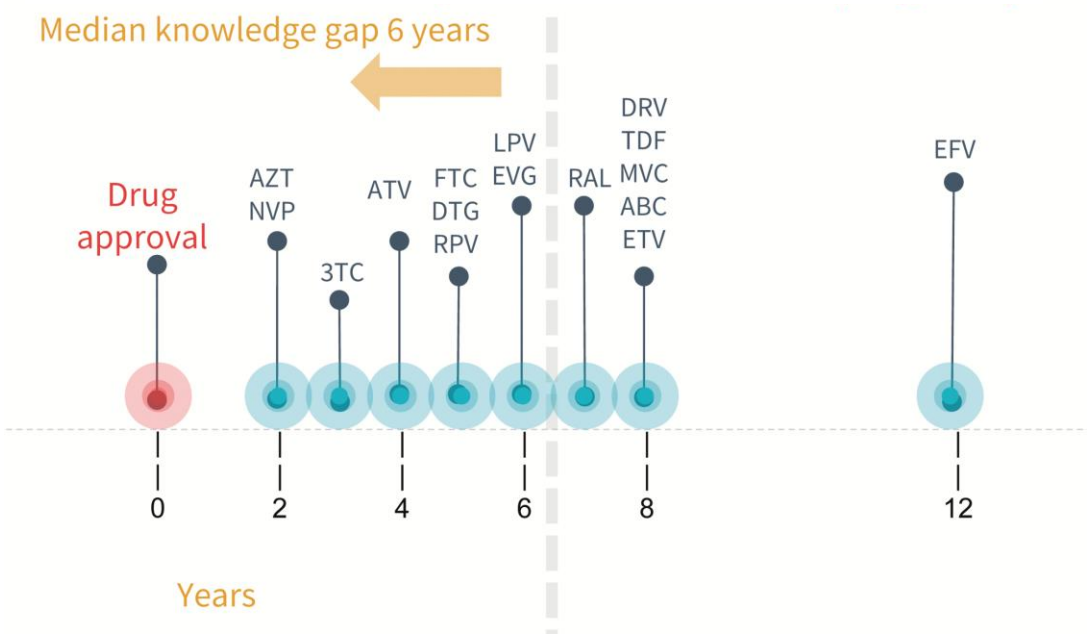


Figure from Colbers A, et al. CID 2019: 69.

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- Phase IV, prospective, open-label, non-randomized, opportunistic study in hospitalized pregnant and non-pregnant women
  - First completed PK study of COVID-19 therapeutics in pregnancy
  - Will help meet post-marketing requirements

- Objectives of our analyses:
  - Describe the PK of remdesivir and its metabolites 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

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Study Design

Arm 1
Pregnant Women
(n=up to 28)

Arm 2
Non-Pregnant Women
(n=up to 28)

Screening/Entry (any time through 4th infusion)

Pre-infusion
- 48 hours prior to remdesivir initiation

RDV infusions
- Treatment up to 5 or 10 days
- Intensive and single PK

Safety follow-up
- Through 4 weeks post-last infusion

Safety assessments: vitals, respiratory status; hepatic, renal, hematologic lab results

Delivery (Arm 1 only)
- Can occur during RDV infusions, safety follow-up, or afterward
- From onset of labor or start of C-section → 24 hours after delivery
- If within 5 days of RDV: single maternal and cord blood sample

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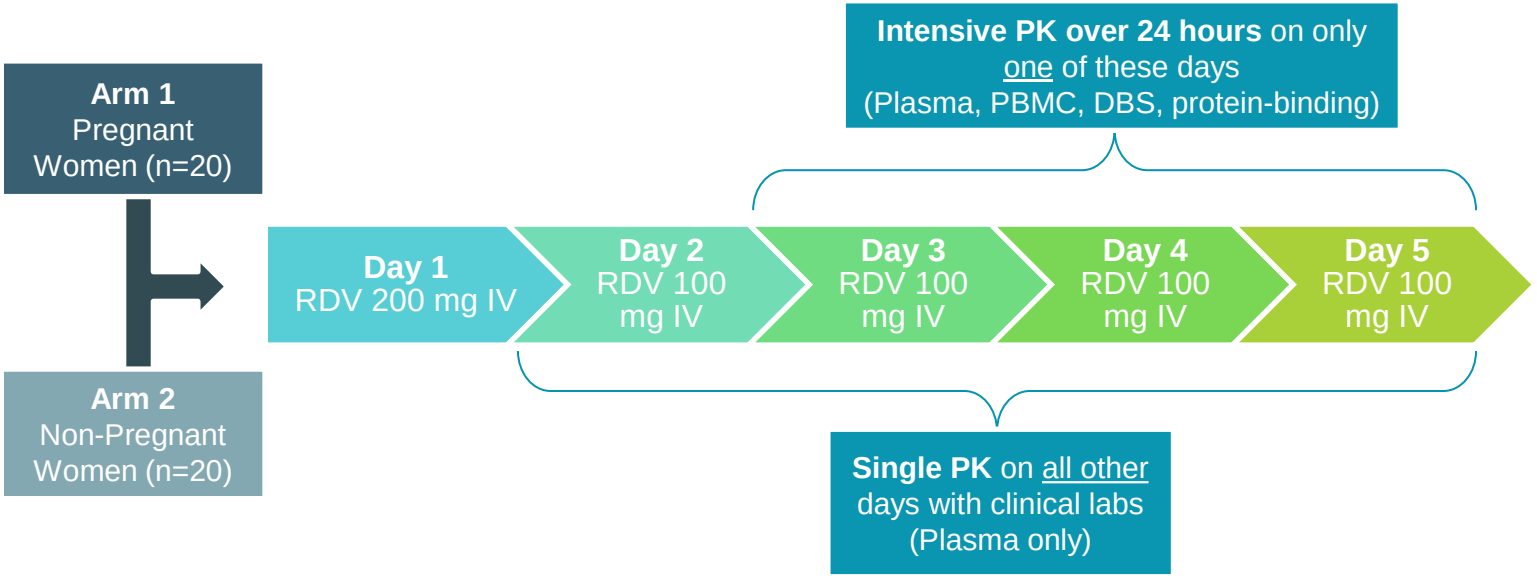
Overview of PK Assessments



Note: no PK sample collections occurred after Day 5 in women who receive RDV for 10 days

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Remdesivir PK is Complex

- Nucleoside prodrug → activated within target cells
- IV administration due to high first pass metabolism
- RDV ~95% protein bound

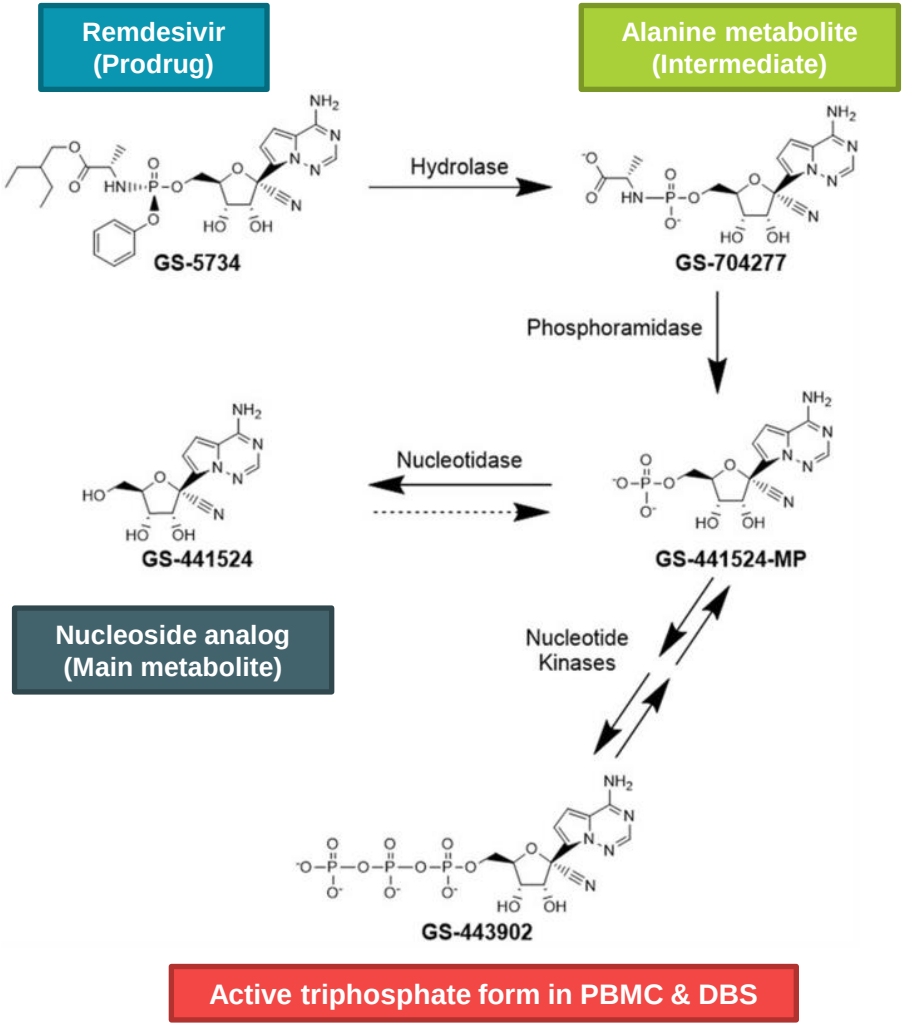
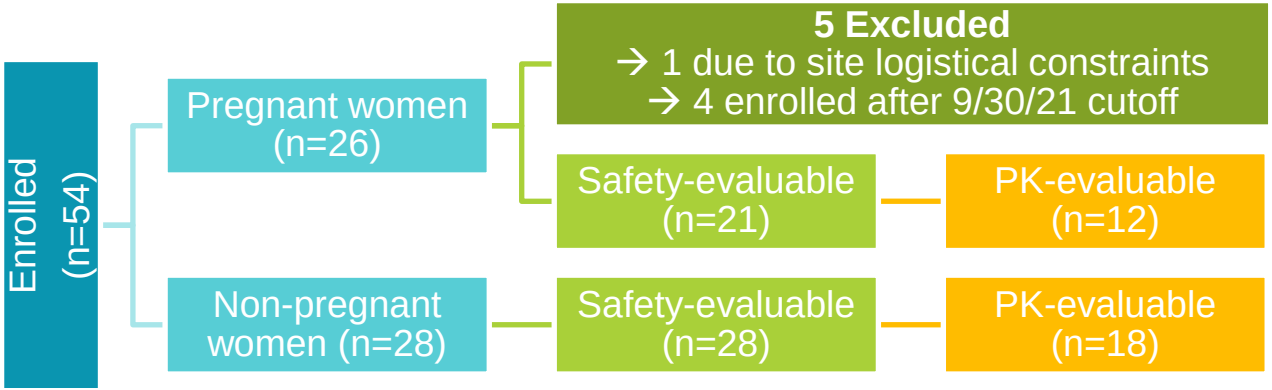


Figure from Humeniuk R, et al. Clini Pharmacokin 2021; 60: 569–583 (2021).

Study Population

- Total of 49 women were included in this preliminary analysis
  - Enrolled from March → September 2021
  - No formal statistical comparisons made



Data available as of data cutoff; final PK and safety analyses are underway

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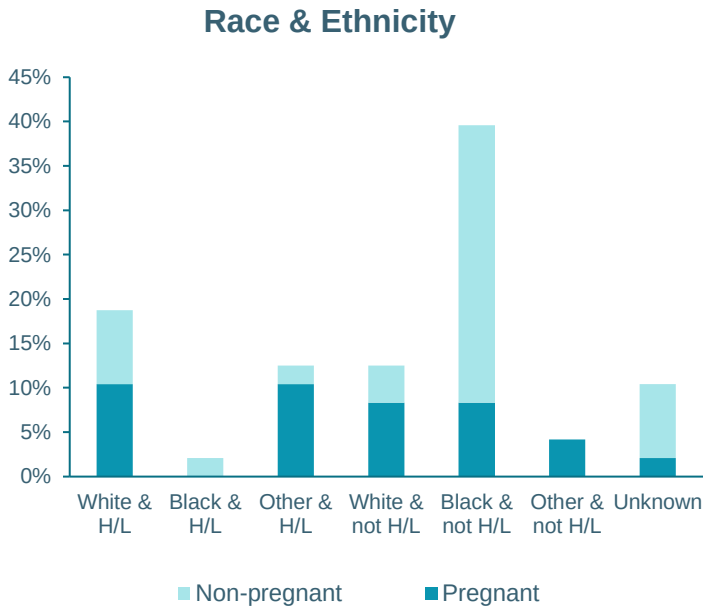
Demographics & Baseline Characteristics



Characteristic	Pregnant Women (n=21)	Non-Pregnant Women (n=28)
Age (yr)	33 (27, 38)	38 (32, 41)
Weight (kg)	77 (71, 93)	102 (82, 139)
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)	--
Trimester		
Second[a]	11 (58%)	--
Third	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%)
eGFR (mL/min/1.73 m^2)	129 (119, 134)	112 (89, 118)

Continuous variables presented as median (IQR), except gestational age which is presented as median (range); categorical variables presented as count (%).
Key: ALT = alanine aminotransferase; eGFR = estimated glomerular filtration rate, NIPPV = noninvasive positive pressure ventilation. Baseline is defined as the value closest (and prior to) the first infusion. No women were on vasopressor/inotropic support at baseline.

Treatment Course

Completed treatment (n=36)

- 5 days: 15 pregnant, 20 non-pregnant
- 10 days: 1 pregnant

Early discontinuation (n=13)

- 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)
- Participant requested to discontinue RDV (n=1)

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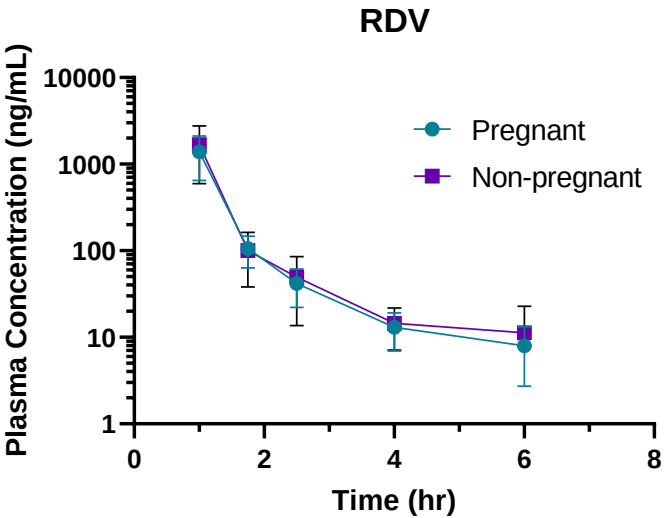
Plasma PK Results: Remdesivir



Plasma concentration-time curves displayed as mean (SD) at nominal time points normalized to a 1-hour infusion length.

PK Parameters	Pregnant Women (n=11)	Non-Pregnant Women (n=16)
Infusion Duration (hr)	0.98 (0.5, 1.12)	1.0 (0.5, 1.0)
$AUC_{0\text{-}24h}$ (ng·h/mL)[a]	888 (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%)

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; $t_{1/2}$ = 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.

RDV PK comparable between arms

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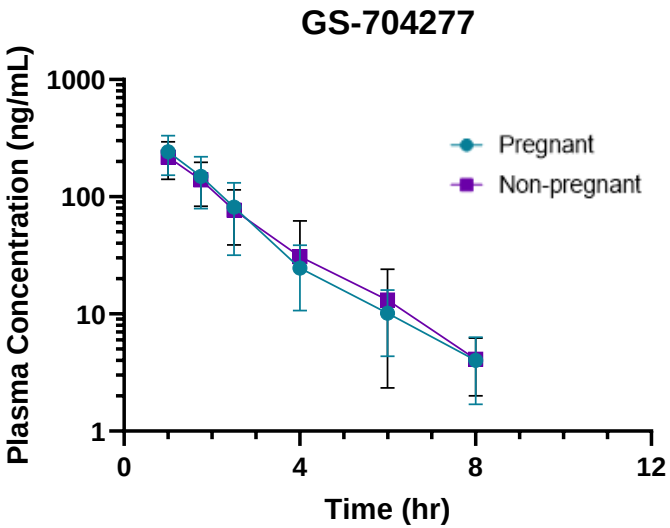
Plasma PK Results: GS-704277



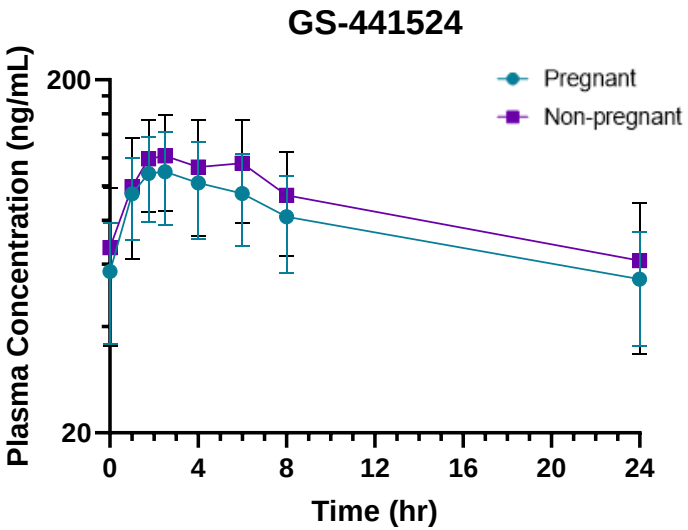
Plasma concentration-time curves displayed as mean (SD) at nominal time points normalized to a 1-hour infusion length.

PK Parameters	Pregnant Women (n=11)	Non-Pregnant Women (n=17)
$AUC_{0\text{-}24h}$ (ng·h/mL)	425 (35.3%)	415 (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%)

Key: $AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 through 24 hours; C_{max} = maximum concentration; $t_{1/2}$ = 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).

GS-704277 PK comparable between arms

Plasma PK Results: GS-441524



Plasma concentration-time curves displayed as mean (SD) at nominal time points normalized to a 1-hour infusion length.

PK Parameters	Pregnant Women (n=12)	Non-Pregnant Women (n=18)
$AUC_{0\text{-}24h}$ (ng·h/mL)[b]	1804 (30.0%)	2126 (33.5%)
C_{max} (ng/mL)	109 (29.5%)	124 (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; $t_{1/2}$ = half-life; T_{max} = time to maximum concentration. Intensive PK results analyzed using noncompartmental analysis (Phoenix WinNonlin, Certara, Inc.). Data presented as geometric mean (CV%), except T_{max} which is reported as median (IQR).
[b]16 pregnant and 12 non-pregnant; [c]10 pregnant and 9 non-pregnant; [d]17 pregnant and 12 non-pregnant

GS-441524 comparable between arms

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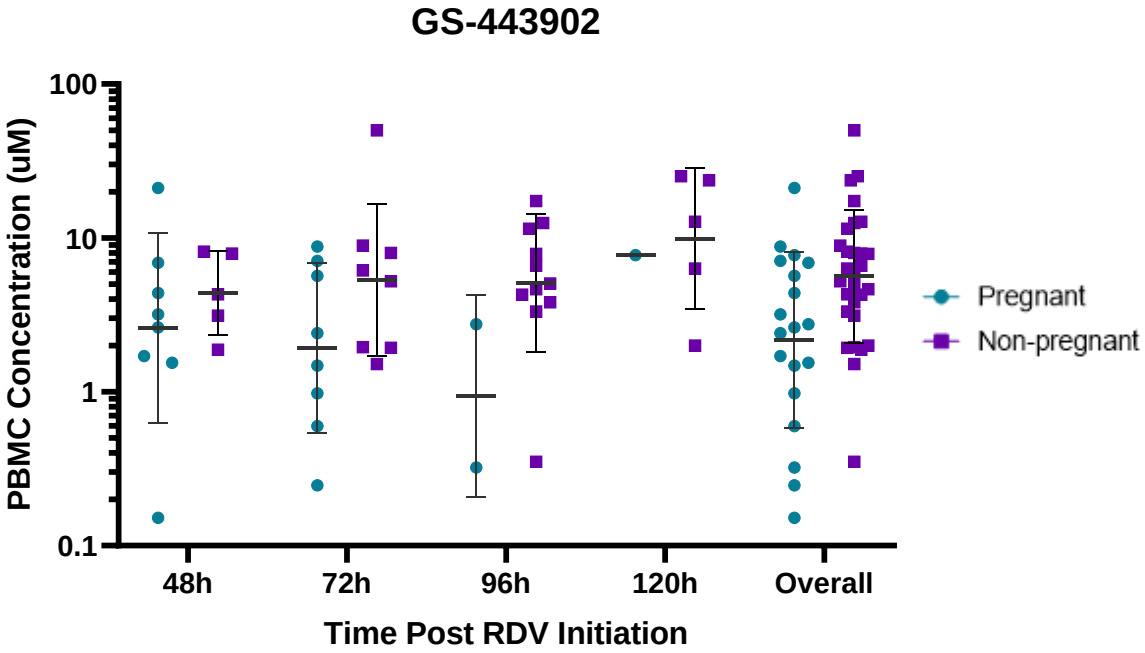
Intracellular PBMC PK Results



PBMC concentrations displayed as geometric mean (geometric SD).

PBMCs comparable between arms

DBS results forthcoming

AEs through Follow-up Week 4

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

Serious Adverse Events (SAEs)

Pregnant women (n=4)

- Asthenia (grade 3), hypotension (grade 4), respiratory failure (grade 4), and fetal death (grade 3)
- Pulmonary embolism (grade 3)
- Superimposed pre-eclampsia (grade 4)
- Acute respiratory failure (grade 4)

Non-pregnant women (n=2)

- Acute respiratory failure (grade 4) and hemoglobin decrease (grade 3)
- Acute respiratory distress (grade 4)

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AEs Related to Remdesivir

- One grade 3 eGFR decrease in a non-pregnant woman
  - Later resolved without intervention
- Two grade 2 bradycardia events in two non-pregnant women
  - Both resulted in treatment discontinuation (after dose 2 and 4)

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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%)
Birth 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.

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Conclusions

- In this preliminary analysis:
  - The PK of remdesivir and its metabolites were comparable between pregnant and non-pregnant women with COVID-19
  - Remdesivir was safe and well tolerated
- Final PK and safety analyses await availability of data from women enrolled after October 1st, 2021
  - Last enrollment in December 2021, last follow-up visit in April 2022
- Regulatory submission anticipated in December 2022

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Acknowledgements

Participants & Families

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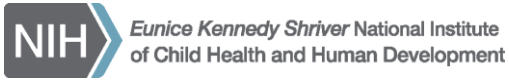

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Site	Pregnant Women	Non-Pregnant Women	Total
4001	6 (23%)	8 (29%)	14 (26%)
5114	3 (12%)	9 (32%)	12 (22%)
5092	6 (23%)	4 (14%)	10 (19%)
5040	6 (23%)	0 (0%)	6 (11%)
5112	1 (4%)	4 (14%)	5 (9%)
5127	2 (8%)	0 (0%)	2 (4%)
5128	1 (4%)	1 (4%)	2 (4%)
5030	1 (4%)	0 (0%)	1 (2%)
5052	0 (0%)	1 (4%)	1 (2%)
5083	0 (0%)	1 (4%)	1 (2%)