Sofosbuvir/Velpatasvir Pharmacokinetics in Pregnant Women with Hepatitis C Virus

597

Catherine A. Chappell[1,2], Jennifer J. Kiser[3], Riley Randolph[3], Ingrid S. Macio[2], Leslie A. Meyn[1,2], Sam MaWhinney[3], Anne-Marie Rick[1], Gysella B. Muniz[1], Kyung-min Kwon[4], Cathleen Letterio[4], Sarjita Naik[4], Bruce Kreter[4], Sharon L. Hillier[1,2]

[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Magee-Womens Research Institute, Pittsburgh, PA, USA,

[3]University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA,[4]Gilead Sciences, Foster City, CA, USA

BACKGROUND

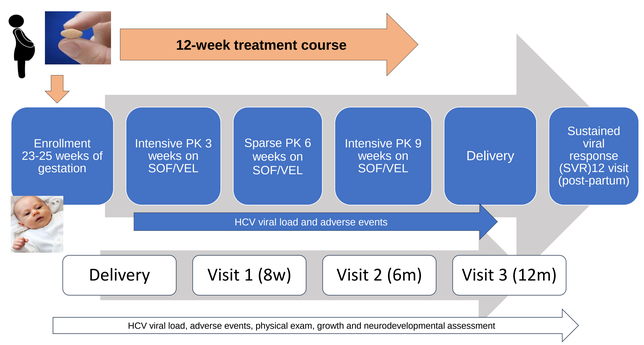
Treatment of hepatitis C virus (HCV) during pregnancy with direct-acting antivirals could have several benefits[1]:

- Curative HCV treatment provided during a time of high healthcare engagement and improved health insurance provision
- Prevention of perinatal HCV transmission
- Reduction of the current the morbidity associated with challenges in postpartum HCV treatment and HCV testing of perinatally exposed children

Due to the physiologic changes in pregnancy, pharmacokinetic (PK) profiles of medications during pregnancy is a critical step. A PK study ledipasvir/sofosbuvir in 9 pregnant women showed similar ledipasvir and sofosbuvir concentrations but lower GS-331007 concentrations (the inactive metabolite of sofosbuvir) with 100% sustained viral response (SVR) and no safety concerns[2]. However, a pan-genotypic HCV treatment regimen was needed. Our objectives were to compare the PK parameters of sofosbuvir/velpatasvir (SOF/VEL) in pregnant versus nonpregnant women, and to assess delivery outcomes and viral response.

METHODS

This is an open-label, phase 1, single site study of SOF/VEL in HIV-negative pregnant women with chronic HCV infection.

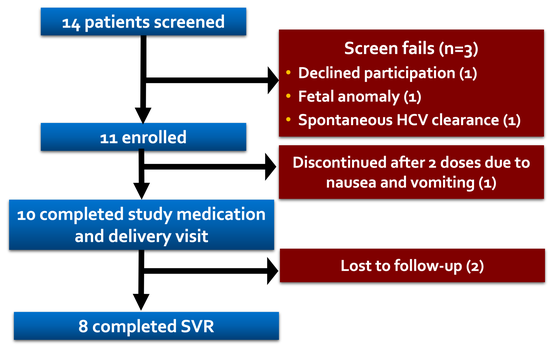


VEL, SOF and GS-331007 in plasma were measured using validated UPLC-MS/MS assays. PK parameters were determined using non-compartmental methods (Phoenix v8.3) and geometric mean ratios and 90% CI compared to historical intensive PK data in non-pregnant women from registrational trials.

SOF/VEL administration during pregnancy showed a favorable PK profile with reassuring preliminary safety and efficacy outcomes.

RESULTS

Participants were enrolled Nov 2020 to July 2022.



10 infants were enrolled at delivery:

- 4 completed the 12 month follow up visit
- 3 remain in follow-up
- 2 were lost to follow-up after delivery
- 1 was lost to follow-up after the first infant visit

Characteristics	Number (%) or Median (range)
Age	30 (25, 39)
White Race	10 (91%)
Black Race	1 (9%)
HCV acquired via drug use	10 (91%)
HCV acquired via needle injury	1 (9%)
HCV Genotype 1	8 (73%)
HCV Genotype 3	3 (27%)

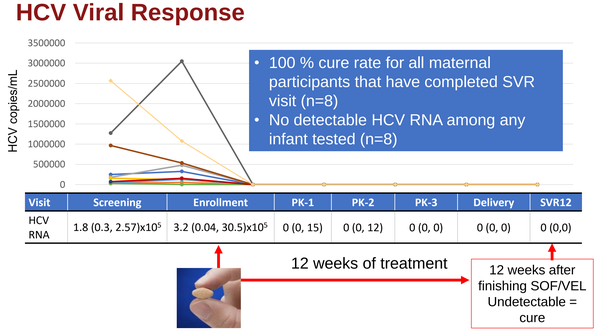
PK Parameter Geomean (%CV)		Pregnant Women (N=10)[a]	Non-Pregnant Women (N=25)[b]	%GMR (90%CI)
SOF	AUC_{tau} (hr*ng/mL)	2039.62 (29.75)	1483.83 (66.43)	1.38 (1.06, 1.78)
	C_{max} (ng/mL)	1455.09 (43.92)	1226.16 (59.46)	1.19 (0.88, 1.60)
GS-331007	AUC_{tau} (hr*ng/mL)	9588.94 (18.75)	15361.31 (22.35)	0.62 (0.55, 0.71)
	C_{max} (ng/mL)	752.66 (21.85)	1312.17 (32.55)	0.57 (0.49, 0.67)
VEL	AUC_{tau} (hr*ng/mL)	3244.45 (39.89)	3570.65 (72.04)	0.91 (0.67, 1.23)
	C_{max} (ng/mL)	381.93 (38.35)	449.39 (77.12)	0.85 (0.63, 1.15)
	C_{tau} (ng/mL)	40.56 (49.00)	49.77 (66.37)	0.82 (0.59, 1.13)

Abbreviations: AUC_{tau}, area under the concentration-time curve of the dosing interval; C_{max}, maximum concentration, C_{tau}, concentration at the end of the dosing interval; CI, confidence interval; CV, coefficient of variation; GMR, geometric mean ratio

a Geometric mean of individual participants PK parameters from 2 PK visits were used for summarization.

b Subset of non-pregnant women from registrational trials administered SOF/VEL with intensive PK assessments.

HCV Viral Response



RESULTS, cont.

Outcome	N (%) or Median (Min, Max)
Gestational age at delivery (weeks + days)	39+0 (35+4, 39+3)
Preterm Birth (<37 weeks of gestation)	2 (18%)
Birth weight (g)	2,900 (2,580, 3,810)
Infant Length of Hospital Stay (days)	3 (2, 6)
NICU Admission*	3 (30%)

Maternal Adverse Events

52 adverse events reported. Of those, 12 were related to SOF/VEL including headache (4), nausea (3), vomiting (2), heartburn (2) and fatigue (1). One (vomiting) resulted in discontinuation of study medication.

CONCLUSIONS

In pregnancy, VEL exposures and SOF maximum concentration (C_{max}) were similar to historic data, but SOF area under the curve (AUC) was 38% higher and GS-331007 AUC and C_{max} were 38% and 43% lower, respectively. This could be due to slowed gastrointestinal motility and increased renal clearance in pregnancy. In this small study, SOF/VEL was highly effective without any adverse safety concerns. A multicenter study (NCT05140941) is currently underway that will provide additional safety and efficacy data to support antenatal HCV treatment, a critical need for global HCV elimination.

REFERENCES

1. Curtis MR, Chappell CA. Evidence for Implementation: HIV/HCV Coinfection and Pregnancy. Curr HIV/AIDS Rep. 2023 Feb;20(1):1-8. doi: 10.1007/s11904-022-00643-9. Epub 2023 Jan 18. PMID: 36652107; PMCID: PMC9846668.
2. Chappell CA, Scarsi KK, Kirby BJ, Suri V, Gaggar A, Bogen DL, Macio IS, Meyn LA, Bunge KE, Krans EE, Hillier SL. Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study. Lancet Microbe. 2020 Sep;1(5):e200-e208. doi: 10.1016/S2666-5247(20)30062-8. Epub 2020 Jul 27. PMID: 32939459; PMCID: PMC7491553.

ACKNOWLEDGEMENT

We thank our brave study participants without whose contribution this work would not be possible. We also thank our study team: Danielle Litzinger, Rachel Gallagher, Jamie Haggerty, Tracy Campbell, Rachel Merritt, Todd Spencer, Shaina Watson, Tony Thompson, May Beamer, Gina Bonura and Hilary Avolia. This study was supported by the National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development (R21HD101996) and Gilead Sciences (IN-US-342-5634).

AUTHOR CONTACT

Email: chappellca@upmc.edu