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Ravidasvir Pharmacokinetics and ARV Drugs Interactions in HCV+/-HIV Infected Adults

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Background

- Ravidasvir is a NS5A inhibitor that exhibits potent pan-genotypic inhibition of Hepatitis C virus (HCV) replication *in vitro*.
  - ravidasvir is primarily eliminated unchanged by biliary excretion, while renal excretion is negligible.
- Sofosbuvir plus ravidasvir (SOF/RDV) has shown excellent efficacy and safety in genotype 4 HCV-infected adults in Egypt[1].
- SOF/RDV is currently under study in HCV patients (+/- HIV) from South East Asia, where prevalent genotypes are 3, 1 and 6 [ClinicalTrials.gov Identifier: NCT02961426].
  - No data on the pharmacokinetics of RDV in South East Asian adults are available.
  - The impact of concomitant SOF/RDV treatment on antiretroviral (ARV) drug concentrations in adults on antiretroviral treatment (ART) is unknown

[1]*Esmat et al, Effectiveness of ravidasvir plus sofosbuvir in interferon-naive and treated patients with chronic hepatitis c genotype-4. J Hepatol. 2017 Sep 19; PMID: 28935432*

Objectives

- To characterize the pharmacokinetics (PK) of RDV (200 mg, once daily) in combination with SOF (400 mg, once daily) in HCV mono-infected adults in South East Asia
- To assess the impact of SOF/RDV treatment on the concentrations of commonly prescribed antiretrovirals (ARV) in HIV/HCV co-infected adults.

Study Design & Methods

Study Design and Population

- Data were analyzed within the ongoing phase II/III trial assessing the efficacy, safety, tolerance, and PK of SOF/RDV in HCV (+/- HIV)-infected adults in Thailand and Malaysia (NCT01671982).

Intensive Pharmacokinetic Assessment of Ravidasvir

- Twenty-five HCV mono-infected patients had intensive steady-state 24-hour blood sampling 4 weeks after starting SOF/RDV treatment.
  - PK sampling: 0 (pre-dose), 1, 2, 3, 4, 6, 8 and 24 hours post-dose
  - Subjects fasted for at least 6 hours before and until 2 hours after dosing

Impact of SOF/RDF on ARV drug concentrations

- In 65 HIV/HCV co-infected patients, mid-dose or trough ARV drug concentrations were measured before starting SOF/RDV treatment and 4 weeks after starting SOF/RDV treatment (at steady state).

The study was approved by Ethics Committees at the National and local levels.

Drug Level Measurement and PK analysis

- Measurement of RDV plasma drug levels were performed using a LC-MS/MS assay. The method was internally validated over the concentration range of 0.01–10 µg/mL. Average accuracy was 99% to 108% and precision (interassay and intra-assay) was <9% (coefficient of variation).
- Steady-state PK parameters of ravidasvir, AUC_{0-24}, Cmax, Tmax, Cmin, C24, apparent oral clearance (CL/F) was determined using a non-compartmental analysis using Phoenix 64-WinNonLin v7.0 (Pharsight, A Certera Company).
- "Time-Matched" mid-dose or trough ARV drug concentrations at week 0 and Week 4 were compared using a Wilcoxon signed-rank test.

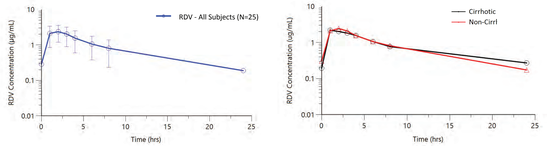
Ravidasvir: Intensive PK Substudy

- 25 subjects were included in the PK analysis
  - 21 patients were non-cirrhotic and 4 patients cirrhotic (all cirrhotic patients were males)

Table 1: Baseline Characteristics of Subjects in PK Substudy

Baseline Characteristics	
Sex	21 /4 (M/F)
Age (Years)	49.2 (21.2-64.0)
Weight (Kg)	65.5 (46.2-88.3)
BMI	23.3 (18.3-30.9).

Mean (±SD) RDV Concentration vs Time plots when administered with SOF



- RDV Pharmacokinetic Parameters are shown in Table 2

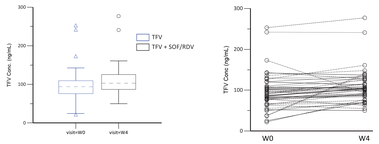
Table 2: PK Parameters of Ravidasvir when administered with Sofosbuvir in HCV mono-infected adults (N=25)

PK Parameters	Median (range)
AUC_{0-24} (µg.hr/mL)	17.3 (3.2-69.9)
Cmax (µg/mL)	2.3 (0.4-6.4)
C24 (µg/mL)	0.11 (0.03-0.90)
Cmin (µg/mL)	0.17 (0.03-1.63)
Tmax (hrs)	2.0 (1.0-3.1)
CL/F (L/hr)	11.6 (2.9-62.3)
T1/2 (hrs)	6.6 (5.3-11.8)

SOF-RDV & ARV DRUGS INTERACTIONS

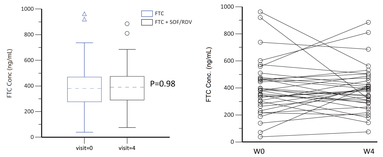
- Tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), efavirenz (EFV) and nevirapine (NVP) were the most commonly prescribed ARVs in HIV/HCV co-infected patients.
- 65 HIV/HCV co-infected subjects were included:
  - median age (range) was 42.9 (23.4-61.5) years and weight 62.0 (45.0-100) kg.
- A total of 47 subjects had 'time-matched' tenofovir (TFV) concentrations before and after SOF/RDV treatment, 34 had FTC, 51 had EFV and 7 had NVP.

Tenofovir-DF +/- SOF+RDV (N=47)



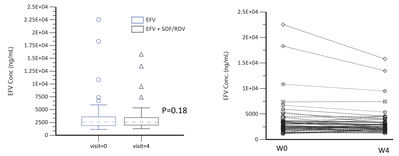
- Day 1: Median TFV Conc. 94 (22-253) ng/mL
- Wk 4: Median TFV Conc. 103 (50-227) ng/mL

Emtricitabine (FTC) +/- SOF+RDV (N=34)



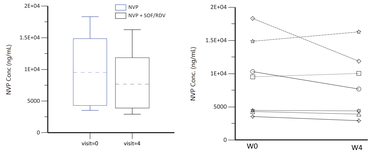
- Day 1: Median FTC Conc. 381 (38-963) ng/mL
- Wk 4: Median FTC Conc. 390 (75-885) ng/mL

Efavirenz +/- SOF+RDV (N=51)



- Day 1: Median EFV Conc. 2,580 (1,173-22,538) ng/mL
- Wk 4: Median EFV Conc. 2,542 (1,266-15,781) ng/mL

Nevirapine +/- SOF+RDV (N=7)



- Day 1: Median NVP Conc. 9,517 (3,535-18,311) ng/mL
- Wk 4: Median NVP Conc. 7,678 (2,519-16,280) ng/mL

Table 3: Summary of ARV concentrations before and after SOF/RDV treatment

	Time Post-dose (hours)		ARV Concentration (ng/mL)			
	Without SOF/RDV (Week 0)	With SOF/RDV (Week 4)	Without SOF/RDV (Week 0)	With SOF/RDV (Week 4)	Ratio Conc. Week 4/Week 0	p-value
Tenofovir (n=47)	12.2 (8.5-15.6)	11.5 (8.0-15.3)	94 (22-253)	103 (50-227)	1.08 (0.54-3.7)	0.0003
Emtricitabine (n=34)	12.0 (8.5-13.8)	11.5 (9.5-15.3)	381 (38-963)	390 (75-885)	1.00 (0.35-5.81)	0.98
Efavirenz (n=51)	12.3 (8.5-15.8)	11.6 (9.4-15.2)	2,580 (1,173-22,538)	2,542 (1,266-15,781)	0.96 (0.51-2.1)	0.18
Nevirapine (n=7)	12.5 (11.6-13.3)	11.9 (11.0-12.9)	9,517 (3,535-18,311)	7,678 (2,915-16,280)	0.91 (0.65-1.1)	0.31

Values: Median (range)

- ARV levels are comparable to historical ranges reported in adults and the recommended cut-off concentrations for virologic efficacy

Conclusion

- SOF/RDV co-treatment had no significant impact on FTC, EFV concentrations.
- TFV concentrations were slightly higher with SOF/RDV use but the magnitude is likely not clinically significant.
- More data on NVP concentrations in the presence of SOF/RDV treatment are needed to draw firm conclusions on any drug-drug interaction.
- Robust PK data of RDV in HCV-infected adults receiving 200 mg once daily is now available and the intensive RDV PK data will guide the development of a population PK model to evaluate the impact of ARVs on RDV exposure.
- Further work to study the impact of non-ARV concomitant drugs on RDV drug exposure are ongoing

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