Drug Interactions Between Direct-Acting anti-HCV Antivirals Sofosbuvir and Ledipasvir and HIV Antiretrovirals

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Disclosures

- I am an employee of Gilead Sciences, Inc

Sofosbuvir (SOF, Formerly GS-7977)

- HCV NS5B nucleotide analog prodrug with broad genotypic activity
- Activated by sequential metabolic pathways including
  - Low affinity and high capacity hydrolases (CES1, CatA, HINT1)
  - Nucleotide phosphorylation (UMP-CMP kinase, NDP kinase)
- SOF enters hepatocytes and is converted to active SOF-TP
- SOF undergoes extrahepatic metabolism to form GS-331007 (predominant inactive circulating metabolite), principally eliminated in urine
- Safe and well tolerated
  - Once daily dosing
  - Favorable safety profile in preclinical/clinical studies

Ledipasvir (LDV, Formerly GS-5885)

- HCV NS5A inhibitor
- Picomolar potency against GT1a and 1b
- LDV is minimally metabolized and primarily eliminated in the feces
- Safe and well tolerated
  - Once daily dosing
  - Favorable safety profile in preclinical/clinical studies

LDV/SOF (90/400 mg) fixed-dose combination tablet is under US-EU regulatory review for the treatment of HCV GT 1 infection

Pre/Clinical Pharmacology

- LDV and SOF (not GS-331007) are substrates for P-gp and BCRP
- LDV but not SOF is an inhibitor of intestinal P-gp and BCRP
- LDV is an inhibitor of hepatic OATP1B1, 1B3 and BSEP at concentrations exceeding those achieved clinically
- LDV and SOF are not substrates for hepatic OCT1, OATP1B1 or OATP1B3
- GS-331007 is not a substrate for renal transporters OAT1, OAT3, or OCT2
- LDV and SOF are not substrates for UGT1A1
- LDV is subject to slow oxidative metabolism
  - No turnover by CYP450 isozymes (in vitro phenotyping studies)
- SOF is not a substrate for CYP450

Limited potential for clinically significant drug interactions

HIV Antiretrovirals

- Integrase strand transfer inhibitor
  - Raltegravir (RAL, Isentress®)
- NNRTI-based regimens
  - Efavirenz (EFV)/emtricitabine (FTC)/tenofovir DF (TDF) (ATR, Atripla®)
  - Emtricitabine/rilpivirine (RPV)/tenofovir DF (CPA, Complera®)

Objectives

Primary

- To evaluate the drug-drug interaction between LDV and RAL
  - SOF and RAL may be administered without dose adjustment[1]
- To evaluate the drug-drug interaction between LDV/SOF and ATR or CPA

Secondary

- To evaluate the safety and tolerability of co-administration of LDV with RAL and LDV/SOF with ATR or CPA

1. Kirby B, et al. AASLD 2012.

Methods

- Two Phase 1, open-label, randomized, multiple-dose, cross-over DDIs in healthy male and female subjects

Study 1

Fed (N=30)
LDV (90 mg QD) + RAL (400 mg BID)

Days 1-10	Days 11-20	Days 21-30
LDV	RAL	LDV + RAL
LDV	LDV + RAL	RAL
RAL	LDV	LDV + RAL
RAL	LDV + RAL	LDV
LDV + RAL	LDV	RAL
LDV + RAL	RAL	LDV

Study 2

Cohort 1: Fasted (n=32)
LDV/SOF (90/400 mg QD) +
ATR (600/200/300 mg QD)

Days 1-14	Days 16-28
LDV/SOF	LDV/SOF + ATR
ATR	LDV/SOF + ATR

Cohort 2: Fed (n=32)
LDV/SOF (90/400 mg QD) +
CPA (200/25/300 mg QD)

Days 1-10	Days 11-20
LDV/SOF	LDV/SOF + CPA
CPA	LDV/SOF + CPA

Methods

- PK sampling was collected over 24 hours for LDV, SOF, GS-331007, EFV, RPV, FTC and TFV and over 12 hours for RAL
- Plasma concentrations were determined using validated LC/MS/MS assays
- PK parameters were estimated using noncompartmental methods (WinNonlin® 6.3, Pharsight Corp., USA)
- Geometric least-squares mean ratios and 90% confidence intervals (Test: Reference) were estimated using ANOVA for AUC_{tau}, C_{max} and C_{tau} and compared against lack of PK alteration boundaries of 70-143%
- Adverse event (AE) monitoring, clinical laboratory, physical examination and ECG evaluations were performed throughout study

Subject Enrollment and Demographics

Subjects	Study 1	Study 2	
		Cohort 1	Cohort 2
Enrolled/completed*, n	30/28	32/29	32/29
Mean age, y (range)	32 (22, 45)	35 (20, 45)	35 (23, 45)
Mean weight, kg (range)	80 (56, 101)	77 (57, 102)	75 (50, 99)
Sex (male/female), n	23/7	23/9	19/13
Race, n (%)			
White	23 (77)	26 (81)	20 (63)
Non-white	7 (23)	6 (19)	12 (38)
Ethnicity n (%)			
Hispanic/Latino	25 (83)	25 (78)	24 (75)
Non-Hispanic/Latino	5 (17)	7 (22)	8 (25)

*Study 1: 2 subjects discontinued (DCed) due to adverse events (AE);
Study 2 (Cohort 1): 2 subjects withdrew consent; 1 DCed due to AE;
Study 2 (Cohort 2): 1 subject withdrew consent; 2 DCed due to AE.

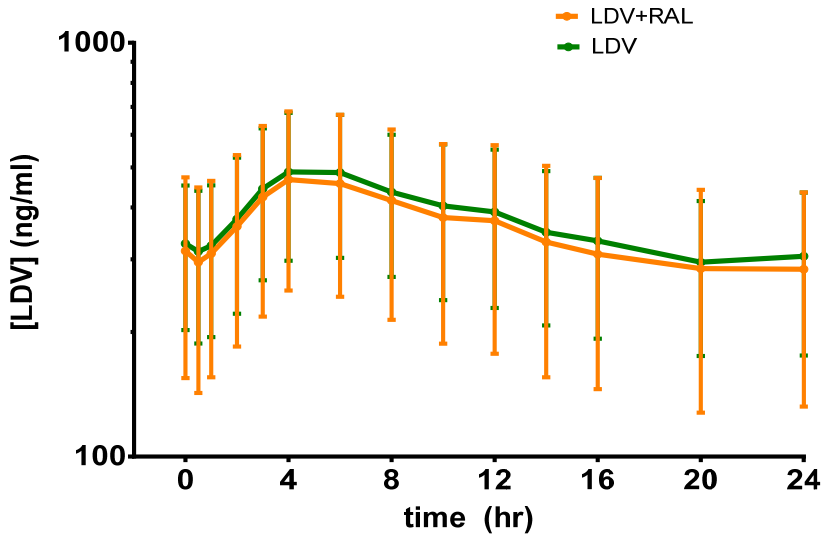
Safety

- No Grade 3 (severe) or Grade 4 (life-threatening) AEs or serious AEs
- Majority of AEs were Grade 1 (mild)

AE by System Organ Class, n of subjects (%)	Study 1 n=30	Study 2	
		Cohort 1 n=32	Cohort 2 n=32
Treatment-Emergent AEs	10 (33)	21 (66)	11 (34)
AEs leading to discontinuation*	2 (7)	1 (3)	1 (3)
Study drug-related AEs	1 (3)	11 (34)	6 (19)
Cardiac disorders			1 (3)
Gastrointestinal disorders	1 (3)	8 (25)	6 (19)
General disorders			1 (3)
Musculoskeletal and connective tissue disorders			1 (3)
Nervous system disorders		2 (6)	
Psychiatric disorders		1 (3)	1 (3)
Reproductive systemic and breast disorders		1 (3)	
Skin and subcutaneous tissue disorders			1 (3)

*Study 1: Grade 2 abdominal pain; Grade 2 furuncle;
Study 2 (Cohort 1): Grade 1 nausea;
Study 2 (Cohort 2): Grade 2 atrial fibrillation.

Effect of RAL on LDV/SOF



mean ± SD

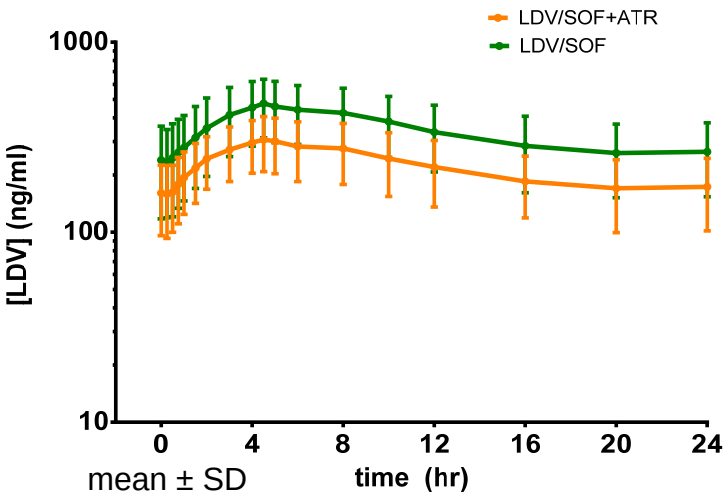
LDV PK Parameters	GMR% (90% CI): LDV + RAL vs LDV
AUC_{tau} (ng·h/mL)	91.5 (84.0, 99.6)
C_{max} (ng/mL)	92.2 (84.9, 100)
C_{tau} (ng/mL)	89.1 (81.3, 97.8)

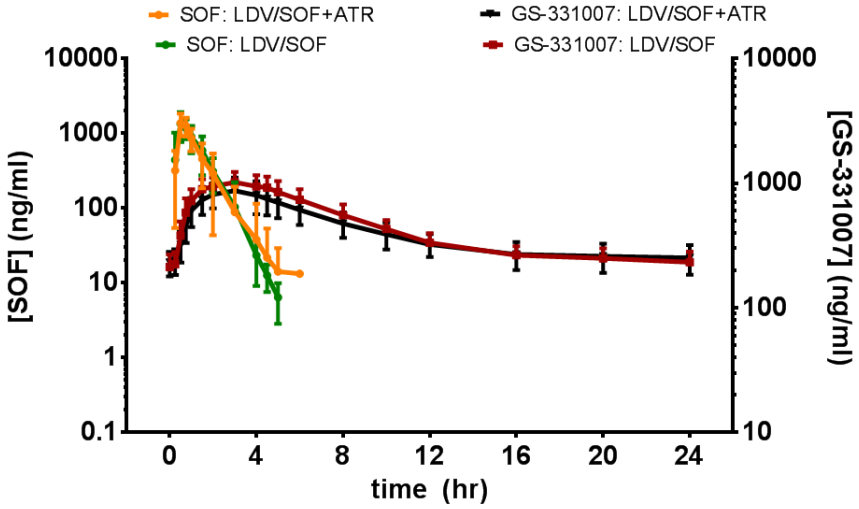
Data presented to 3 significant figures; LDV + RAL: n=28; LDV: n=29.

- No effect of RAL on LDV PK
- Previous data demonstrated no DDI between SOF and RAL[1]

1. Kirby B, et al. AASLD 2012.

Effect of ATR on LDV/SOF



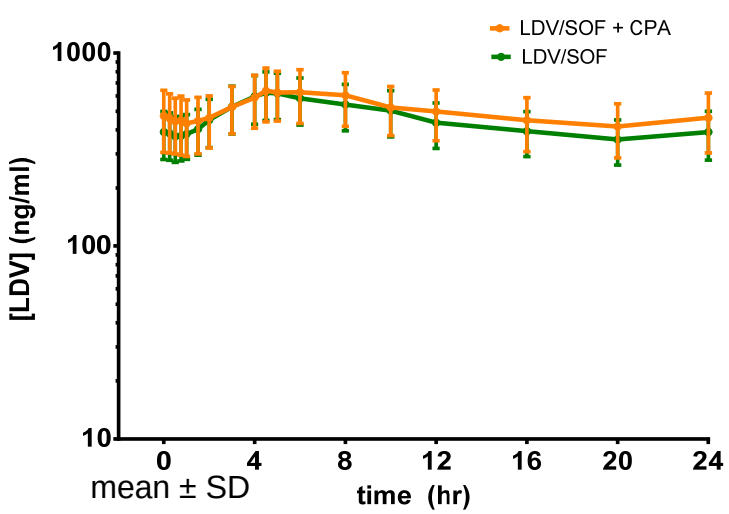


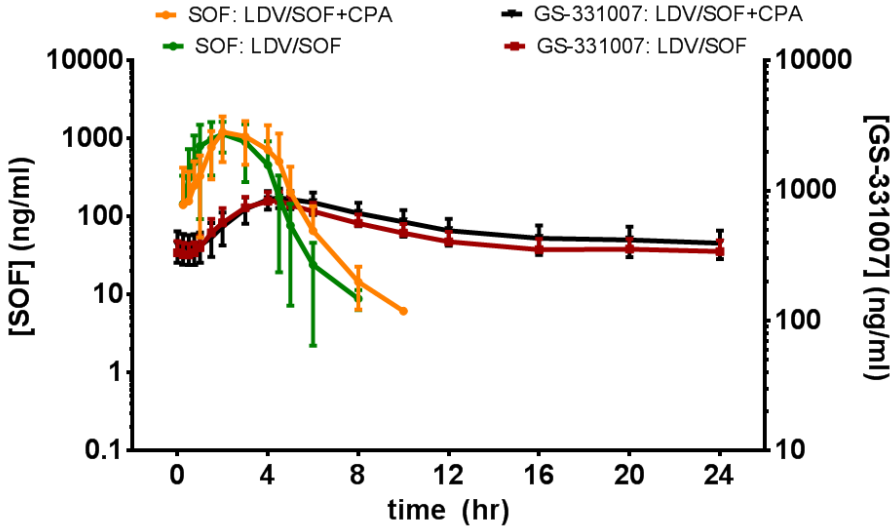
- ~ 30% reduction in LDV PK with ATR
  - Not clinically significant based on exposure-response evaluation
- No impact on SOF or GS-331007 PK

PK Parameters	GMR% (90% CI): LDV/SOF + ATR vs LDV/SOF		
	LDV	SOF	GS-331007
AUC_{tau} (ng·h/mL)	66.4 (58.7, 75.3)	94.3 (81.0, 110)	89.6 (82.8, 96.9)
C_{max} (ng/mL)	66.4 (58.9, 74.9)	103 (86.7, 123)	85.7 (76.2, 96.3)
C_{tau} (ng/mL)	66.1 (57.1, 76.5)		107 (102, 113)

Data presented to 3 significant figures; n=14.

Effect of CPA on LDV/SOF



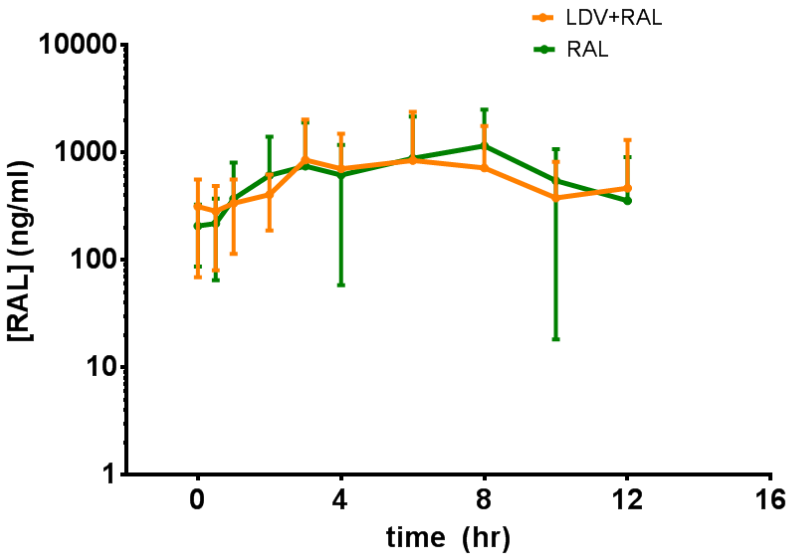


- No impact of CPA on LDV, SOF or GS-331007 PK

PK Parameters	GMR% (90% CI): LDV/SOF + CPA vs LDV/SOF		
	LDV	SOF	GS-331007
AUC_{tau} (ng·h/mL)	108 (102, 115)	110 (101, 121)	115 (111, 119)
C_{max} (ng/mL)	101 (94.6, 107)	105 (92.5, 120)	106 (101, 111)
C_{tau} (ng/mL)	116 (108, 125)		118 (113, 123)

Data presented to 3 significant figures; LDV/SOF+CPA : N=17; LDV/SOF: N=15.

Effect of LDV/SOF on RAL



mean ± SD

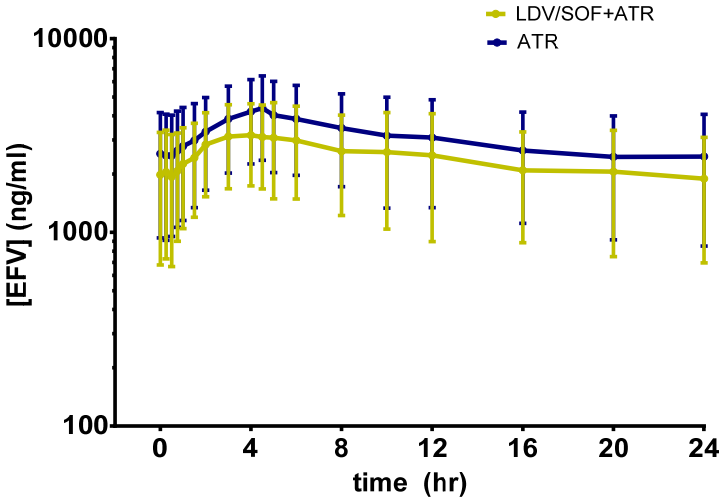
RAL PK Parameters	GMR% (90% CI)
AUC_{tau} (ng·h/mL)	84.5 (69.8, 102)
C_{max} (ng/mL)	82.2 (66.5, 102)
C_{tau} (ng/mL)	115 (90.2, 146)

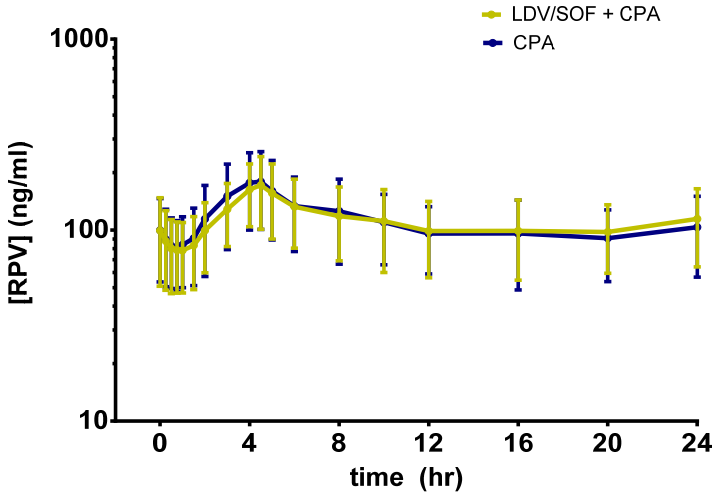
Data presented to 3 significant figures; LDV + RAL: N=28; LDV: N=29.

- Approximately 15-18% change in RAL PK with LDV
  - Similar or higher decreases in RAL PK with TVR/r and EFV[2,3]
- Previous data demonstrated no DDI between SOF and RAL[1]

1. Kirby B, et al. AASLD 2012; 2. Hanley WD, et al. AAC 2009; 3. Iwamoto M, AAC 2008.

Effect of LDV/SOF on EFV (ATR) and RPV (CPA)





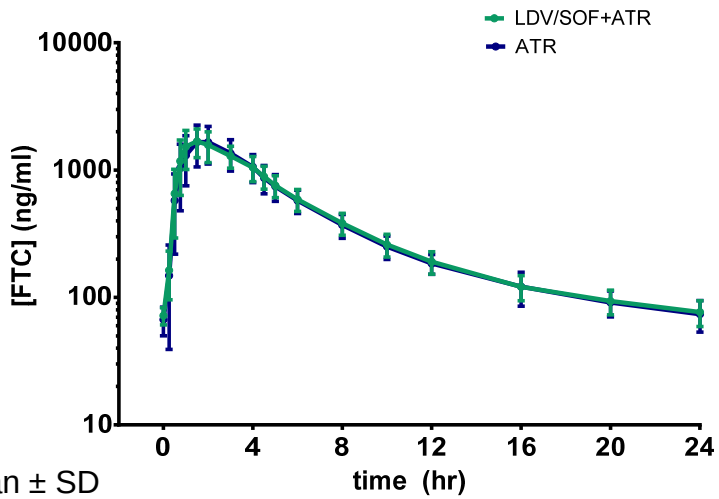
mean ± SD

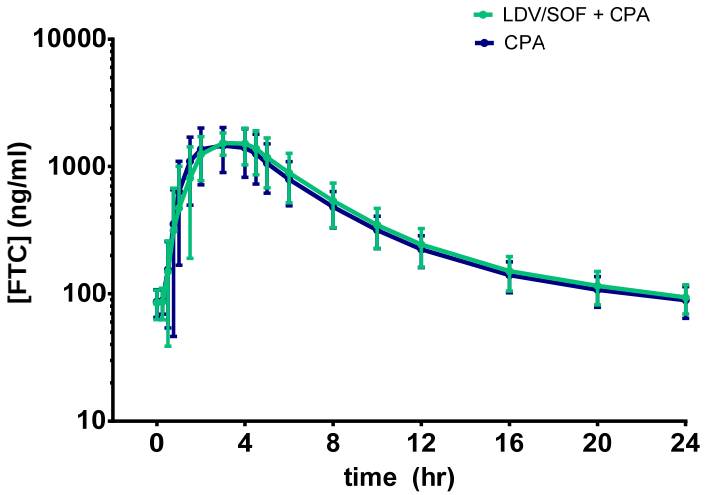
- No impact on EFV or RPV PK by LDV/SOF

PK Parameters	GMR% (90% CI): LDV/SOF + ARV vs ARV	
	EFV	RPV
AUC_{tau} (ng·h/mL)	89.7 (83.9, 95.9)	102 (93.6, 111)
C_{max} (ng/mL)	87.7 (78.6, 96.9)	97.0 (87.9, 107)
C_{tau} (ng/mL)	90.8 (83.1, 99.1)	112 (103, 121)

Data presented to 3 significant figures; LDV/SOF + ATR: n=15; ATR: n=17; LDV/SOF + CPA: n=14; CPA: n=14.

Effect of LDV/SOF on FTC (ATR or CPA)





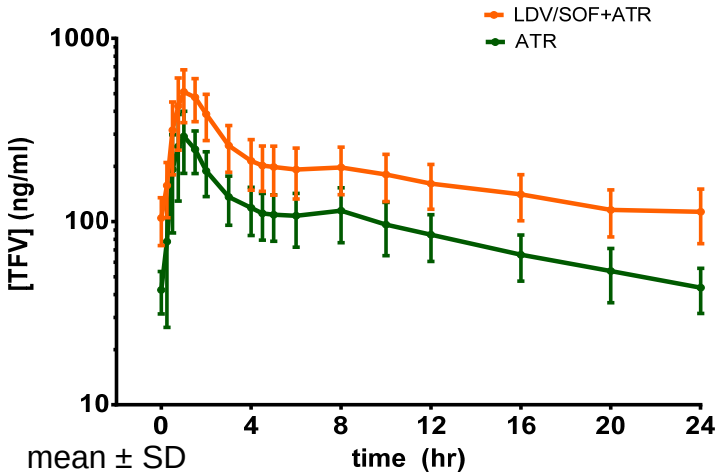
mean ± SD

- No impact on FTC PK by LDV/SOF

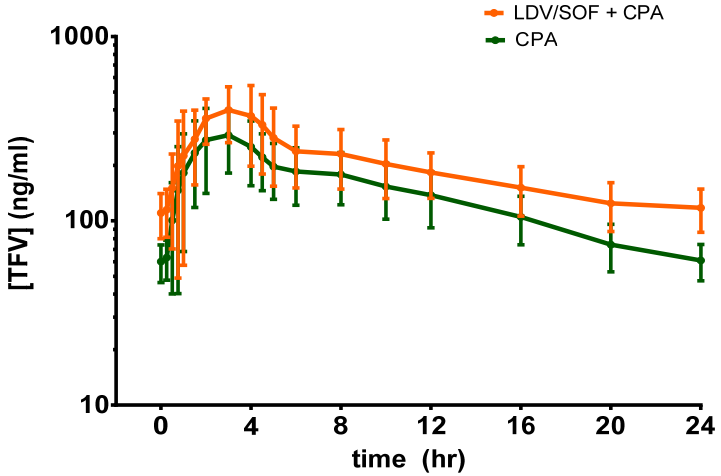
FTC PK Parameter	GMR% (90% CI): LDV/SOF + ARV vs ARV	
	ATR	CPA
AUC_{tau} (ng·h/mL)	105 (98.1, 111)	104 (102, 108)
C_{max} (ng/mL)	108 (97.0, 121)	102 (97.9, 106)
C_{tau} (ng/mL)	103 (98.0, 111)	106 (97.1, 115)

Data presented to 3 significant figures; LDV/SOF + ATR: n=15; ATR: n=17; LDV/SOF + CPA: n=14; CPA: n=14.

Effect of LDV/SOF on TFV (ATR or CPA)



mean ± SD



TFV PK Parameter	Mean (%CV)		GMR% (90% CI): LDV/SOF + ARV vs ARV	
	LDV/SOF + ATR	LDV/SOF + CPA	ATR	CPA
AUC_{tau} (ng·h/mL)	4400 (27.1)	4780 (28.6)	198 (177, 223)	140 (131, 150)
C_{max} (ng/mL)	527 (29.9)	490 (24.1)	179 (156, 204)	132 (125, 139)
C_{tau} (ng/mL)	113 (33.0)	118 (26.4)	263 (237, 297)	191 (174, 210)

Data presented to 3 significant figures; LDV/SOF + ATR: n=15; ATR: n=17; LDV/SOF + CPA: n=14; CPA: n=14.

- LDV/SOF increased TFV exposure
  - Similar **absolute** TFV exposures (within ATR or CPA) with LDV/SOF
    - TFV exposures in LDV/SOF + NNRTI-based regimens are similar to those with boosted HIV PIs
  - Lack of marked changes in TFV Cl_{renal} (data on file)

Conclusions and Next Steps

- LDV/SOF and RAL, ATR or CPA (or components) may be co-administered without dose adjustment
- Study treatments were well tolerated
- ION-4: Phase 3 HIV/HCV co-infection trial of LDV/SOF
  - Allowed HIV ARV regimens: RAL + FTC/TDF; ATR or CPA (or components)
- Planned/ongoing Phase 1 DDI evaluation of LDV/SOF with ARVs
  - Boosted PI regimens
  - EVG/COBI/FTC/TDF (Stribild®)
  - EVG/COBI/FTC/TAF
  - Dolutegravir

Acknowledgments

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