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Safety and Efficacy of Treatment With Once-Daily Ledipasvir/Sofosbuvir (90/400 mg) for 12 Weeks in Genotype 1 HCV-Infected Patients With Severe Renal Impairment

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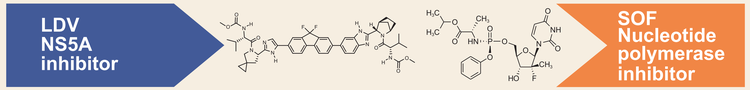
Introduction

Sofosbuvir and Ledipasvir



- **Ledipasvir**
  - Once-daily, oral, 90-mg NS5A inhibitor
- **Sofosbuvir**
  - Once-daily, oral, 400-mg NS5B inhibitor

- **LDV/SOF FDC**
  - Once-daily, oral, FDC (90/400 mg) tablet
  - Single-tablet regimen for HCV

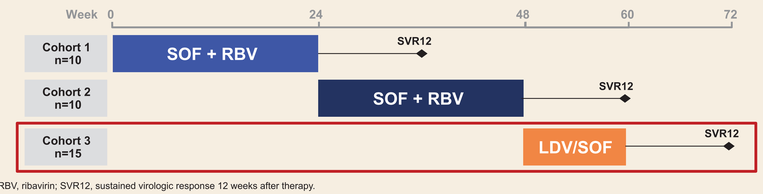
FDC, fixed-dose combination; HCV, hepatitis C virus.

- Despite higher concentrations of the primary circulating SOF metabolite GS-331007 in patients with severe renal impairment (RI), retrospective case series and claims database analyses have suggested substantial use of LDV/SOF in this population with no untoward effects[1-7]

Objectives

- To evaluate the safety and efficacy of LDV/SOF for 12 weeks in patients with chronic HCV genotype (GT) 1 or 4 infection and severe RI not undergoing dialysis

Methods



RBV, ribavirin; SVR12, sustained virologic response 12 weeks after therapy.

- In this Phase 2, open-label study (NCT01958281), patients in Cohort 3 were treated for 12 weeks with LDV/SOF (90/400 mg) daily
- Enrolled at 8 sites in New Zealand and USA
- Key eligibility criteria: severe RI (creatinine clearance [CLcr] ≤30 mL/min [Cockcroft-Gault equation]), HCV GT 1 or 4, and not undergoing dialysis
- Regimens:
  - Cohort 1: SOF 200 mg and RBV 200 mg qd
  - Cohort 2: SOF 400 mg and RBV 200 mg qd
  - Cohort 3: LDV/SOF 90/400 mg
- Primary efficacy endpoint: SVR12
  - HCV RNA <lower limit of quantitation (<15 IU/mL) at posttreatment Week 12 (analyzed by COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 [Roche Molecular Diagnostics, Pleasanton, CA])
- Safety: adverse events (AEs), discontinuations (D/C) due to AEs, laboratory abnormalities, electrocardiograms, and echocardiograms
- Pharmacokinetics (PK): SOF, GS-331007, and LDV area under the curve over the dosing interval (AUC_T)

Results

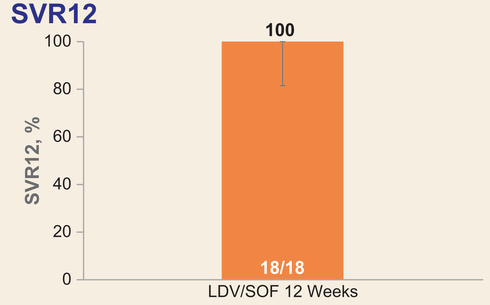
Demographics

	LDV/SOF, 12 Weeks n=18
Mean age, y (range)	57 (32–66)
Male, n (%)	12 (67)
White, n (%)	8 (44)
Black, n (%)	10 (56)
Mean BMI, kg/m^2 (range)	30 (21–39)
Mean eGFR, mL/min/1.73 m^2 (range)	24.9 (9.0–39.6)
Cirrhosis, n (%)	2 (11)
HCV GT 1 (total), n (%)	18 (100)
1a	14 (78)
1b	4 (22)
IL28B non-CC, n (%)	17 (94)
Mean HCV RNA, log_{10} IU/mL (range)	6.2 (5.0–7.1)

BMI, body mass index; eGFR, estimated glomerular filtration rate; IL28B, interleukin-28B.

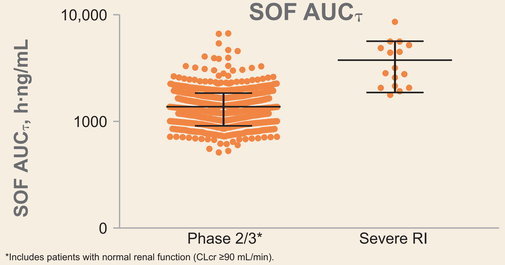
- All 18 patients completed treatment

SVR12



- All patients achieved SVR12
  - Only 1 patient had a baseline resistance-associated substitution (RAS): NS5A RAS M28V

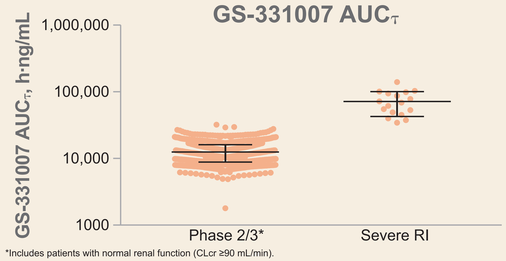
Pharmacokinetics



*Includes patients with normal renal function (CLcr ≥90 mL/min).

- Mean SOF exposure was 103% higher in patients with severe RI (n=17) than in the LDV/SOF Phase 2/3 population (N=1118)
  - The observed change is less than that observed in a Phase 1 study evaluating the impact of RI on SOF PK, where mean SOF exposure in subjects with severe RI was 170% higher vs those with normal renal function[8,9]

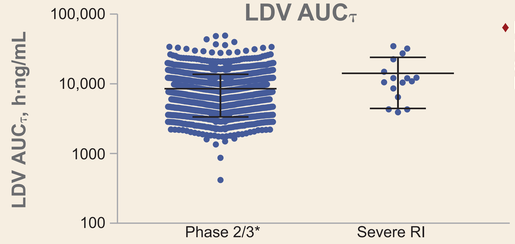
Pharmacokinetics



*Includes patients with normal renal function (CLcr ≥90 mL/min).

- Mean GS-331007 exposure was 501% higher in patients with severe RI (n=17) than in the LDV/SOF Phase 2/3 population (N=1602)
  - This result is consistent with the PK difference observed following administration of a single dose of SOF to subjects with severe RI or normal renal function in a Phase 1 study[8,9]

Pharmacokinetics



- Mean LDV exposure was 57% higher in patients with severe RI (n=17) than in the LDV/SOF Phase 2/3 population (N=1602)
  - This result is consistent with the PK difference observed following administration of a single LDV dose to subjects with severe RI or normal renal function in a Phase 1 study

*Includes patients with normal renal function (CLcr ≥90 mL/min).

Safety Summary

	Patients, n (%)	LDV/SOF, 12 Weeks n=18
Overall Safety	Any AE	13 (72)
	AE in >15% of patients	
	Fatigue	4 (22)
	Headache	4 (22)
	Hyperkalemia	3 (17)
	Grade 3–4 AE	5 (28)
	Serious AE*	4 (22)
	Treatment-related serious AE	0
	Treatment D/C due to AE	0
	Death	0
Laboratory Abnormalities	Grades 3–4†	10 (56)

*Acute kidney injury and noncardiac chest pain (n=1); dehydration and hypotension (n=1); acute renal failure (n=1); hypotension and syncope (n=1); †Elevated creatinine (Grade 3, n=3; Grade 4, n=1); decreased hemoglobin (Grade 3, n=3; Grade 4, n=1); elevated glucose (Grade 3, n=3); decreased bicarbonate (Grade 3, n=1); decreased lymphocytes (Grade 3, n=3).

- AEs were consistent with those expected for this population
- There was no clinically meaningful change in eGFR: there was a 1.2-mL/min/1.73m^2 decrease from baseline to end of treatment

Cardiac Safety

- There were no treatment-related cardiac AEs, including bradycardia
- There were no clinically meaningful changes in QTc intervals or other electrocardiographic parameters during treatment
- Comparison of echocardiograms obtained at baseline and Week 12 did not reveal any clinically significant changes; mean ejection fractions were 58% (range 53–70%) and 57% (49–63%), respectively

Conclusions

- Treatment with the single-tablet regimen of LDV/SOF for 12 weeks resulted in a 100% SVR12 rate in patients with severe RI
- Treatment was safe and well tolerated
  - AEs were consistent with those anticipated for this patient population
- Plasma concentrations of the terminal SOF metabolite GS-3310007 were ~6-fold higher than in the LDV/SOF Phase 3 trials
  - LDV and SOF plasma concentrations were similar to those observed in patients with normal, mild, or moderate RI

References

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Disclosures

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