ELECTRON:
100% SVR Rate for Once-Daily Sofosbuvir Plus Ledipasvir Plus Ribavirin Given for 12 Weeks in Treatment-Naïve and Previously Treated Patients With HCV GT 1

Reported by Jules Levin
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Conclusions

- 12 weeks SOF + RBV resulted in SVR12 in 84% of treatment-naïve patients, but only in 10% of null responders
- Adding LDV increased efficacy of SOF + RBV
  - 100% SVR12 in both treatment-naïve and prior null responder patients
  - No additional safety or tolerability issues

Clinical Development Plans Going Forward

- Phase 3 program with SOF/LDV fixed-dose combination tablet underway
  - Studies will evaluate efficacy in patients with cirrhosis
  - Studies will evaluate the need for RBV
- Additional studies to explore shorter durations of therapy are under way

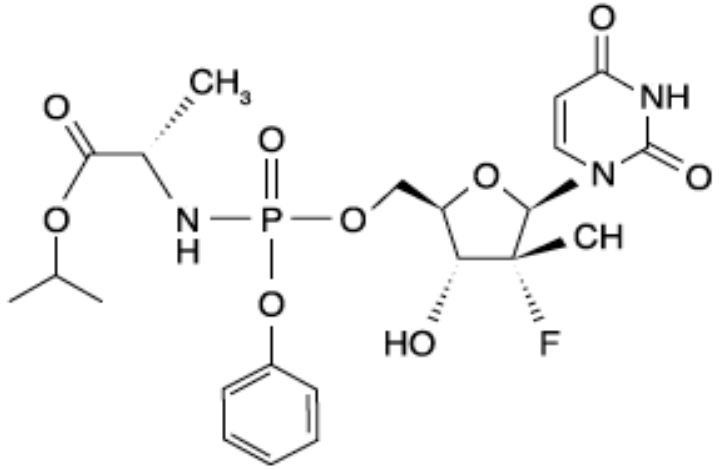
Background

- Up to 170 million people worldwide are chronically infected with hepatitis C virus (HCV)[1]
  - >70% have genotype (GT) 1, the most difficult to treat[2]
- Current treatment for HCV GT1 is a protease inhibitor (PI) + peginterferon (PEG) + ribavirin (RBV) for 24-48 weeks[3]
  - Limitations of current PI regimens include complex dosing schemes, potential for resistance, poor tolerability, and lower response rates in prior null responders
- Need for simpler, shorter, safer, all-oral treatment regimens
- We hypothesized that two potent direct-acting antivirals with different mechanisms of action would improve the rate of response

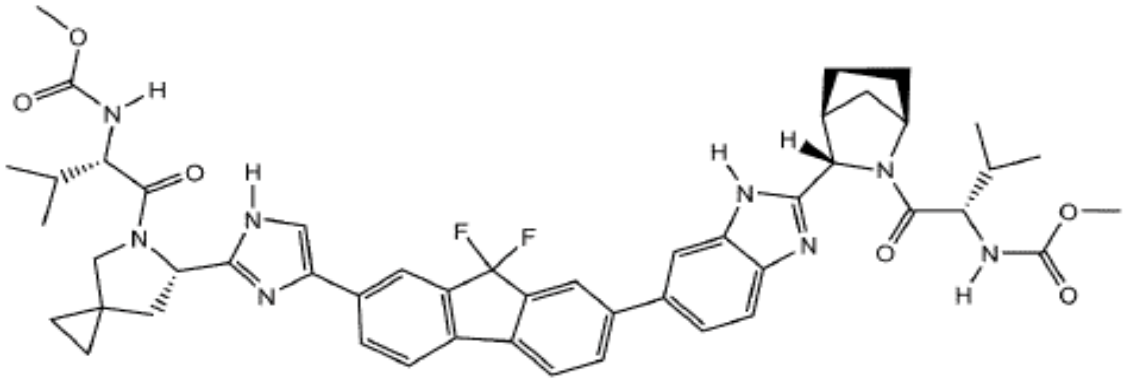
1. Lavanchy D. Liver Int 2009;29(Suppl 1)74-81; 2. Nainan OV, et al. Gastroenterology 2006;131:478-84;
3. Ghany MG, et al. Hepatology 2011;54:1433-44.

Sofosbuvir (SOF, GS-7977)

- Potent HCV-specific nucleotide analog (chain terminator)
- Safe and well tolerated
  - Once daily, no food effect
  - No significant drug interactions
  - No safety signals in preclinical/clinical studies
- High barrier to resistance
  - No virologic breakthrough to date
- Pangenotypic antiviral effect
- Safe and well tolerated in ~1500 patients in Phase 2 and Phase 3 studies



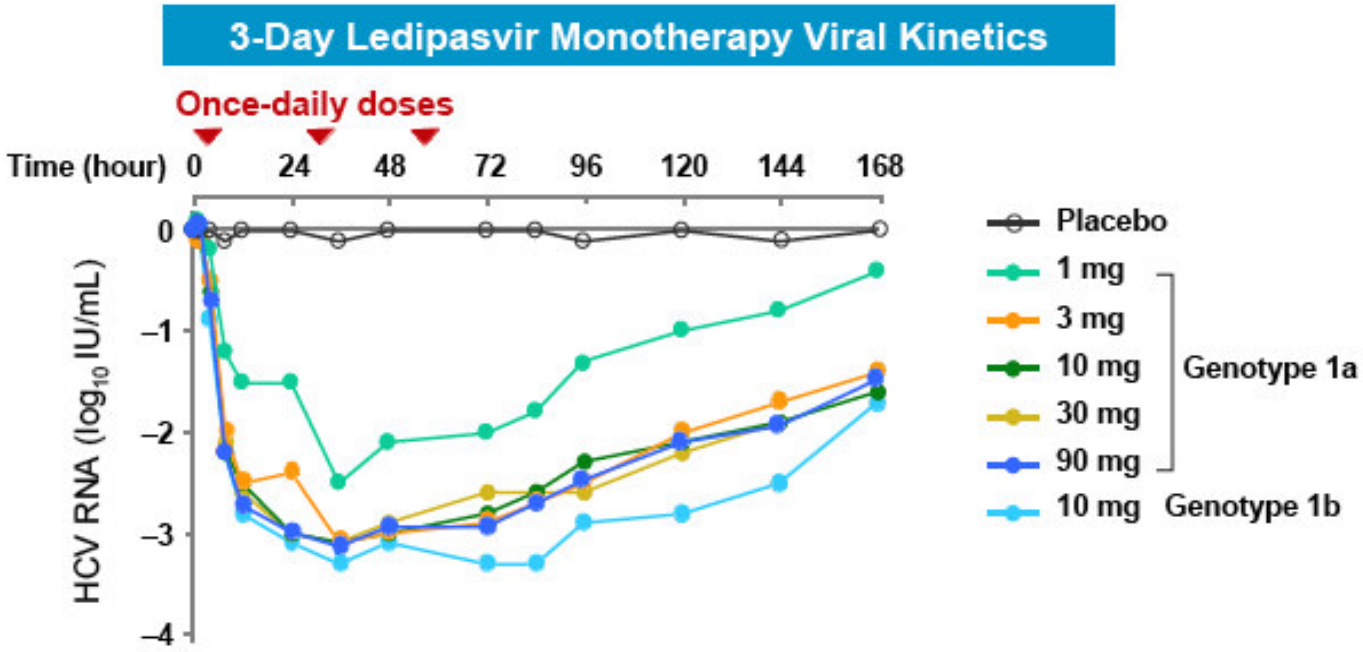
Ledipasvir (GS-5885)



- HCV NS5A inhibitor
  - NS5A essential for RNA replication and post-replication assembly and secretion[1]
- Picomolar potency against genotype 1a and 1b HCV[2]
- Effective against signature NS5B-resistant mutant S282T[3]

1. Guedj J, et al. Proc Natl Acad Sci U S A 2013 [epub]; 2. Lawitz E, et al. EASL 2011, poster 1219;
3. Cheng G, et al. EASL 2012, poster 1172;

Ledipasvir (GS-5885)



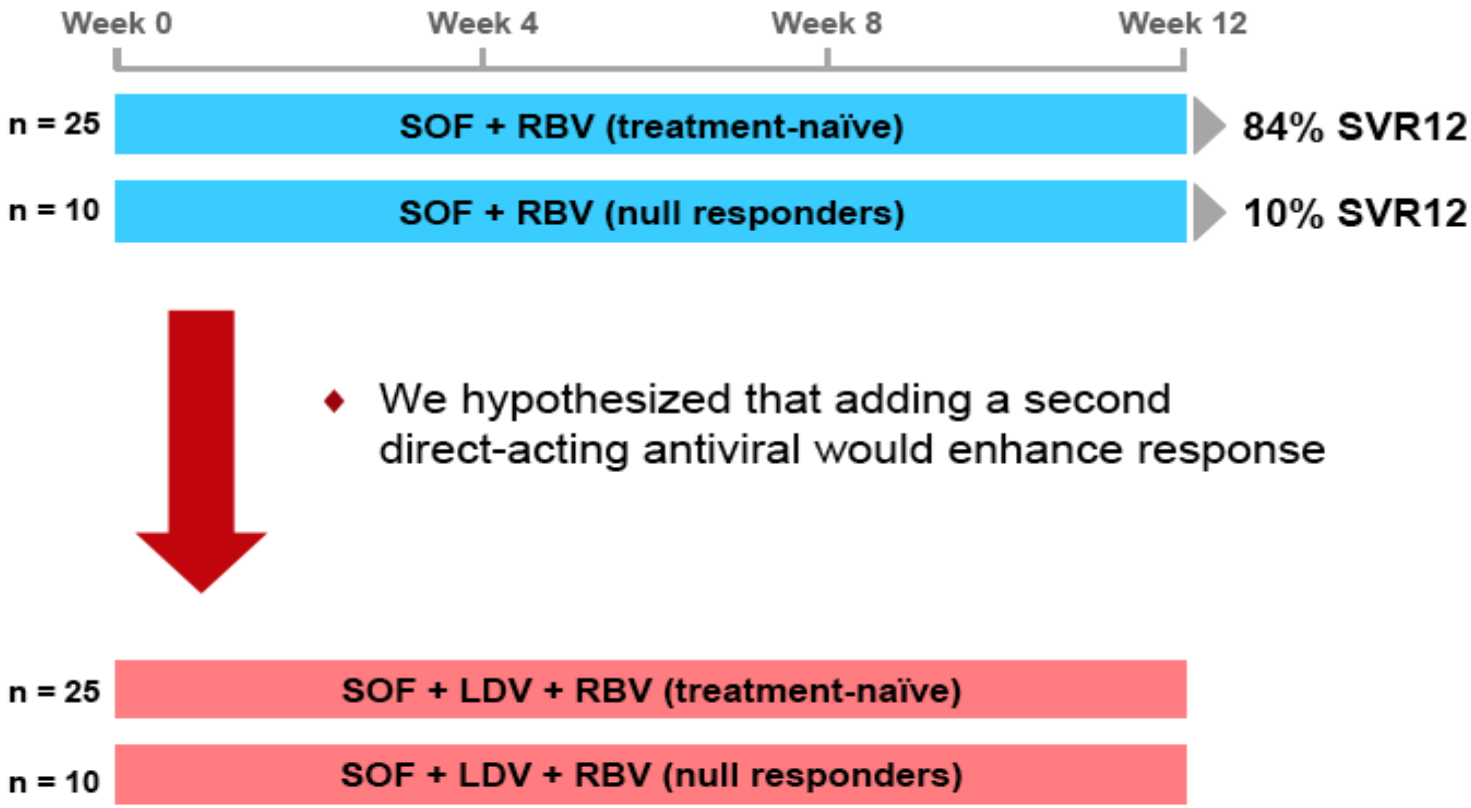
- Safe and well tolerated in >1000 patients in Phase 2[1]
- No clinically significant drug-drug interactions with sofosbuvir [2]

1. Everson G, et al. AASLD 2012, poster 783; 2. German P, et al. AASLD 2012, poster 1888.

Aim

- To evaluate the safety and efficacy of the nucleotide NS5B inhibitor sofosbuvir (SOF) given in combination with the NS5A inhibitor ledipasvir (LDV) in treatment-naïve and prior null responder patients with chronic HCV GT 1 infection

Study Design: Genotype 1 Cohorts



LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Results: Baseline Characteristics

	SOF + RBV		SOF + LDV + RBV	
	Treatment-naïve (n = 25)	Null responder (n = 10)	Treatment-naïve (n = 25)	Null responder (n = 9)
Mean age (range)	48 (21–68)	48 (29–57)	45 (25–59)	50 (26–61)
Male	60%	70%	32%	78%
Caucasian	80%	90%	92%	100%
Mean BMI (range)	25.7 (19.6–37.9)	28.1 (19.5–36.2)	25.2 (19.8–37.3)	25.6 (21.8–28.2)
IL28B genotype **CC** **CT** **TT**	 44% 48% 8%	 20% 50% 30%	 36% 56% 8%	 0 78% 22%
GT 1a	88%	90%	80%	89%
Mean baseline HCV RNA, $\log_{10}$ IU/mL	6.1 (4.4–7.2)	6.8 (5.6–7.5)	5.9 (3.4–7.4)	6.9 (6.6–7.3)

Absence of cirrhosis was demonstrated by transient elastography or biopsy.
BMI, body mass index; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Results: Efficacy

Patients with HCV RNA <LOD* over Time, n/N (%)

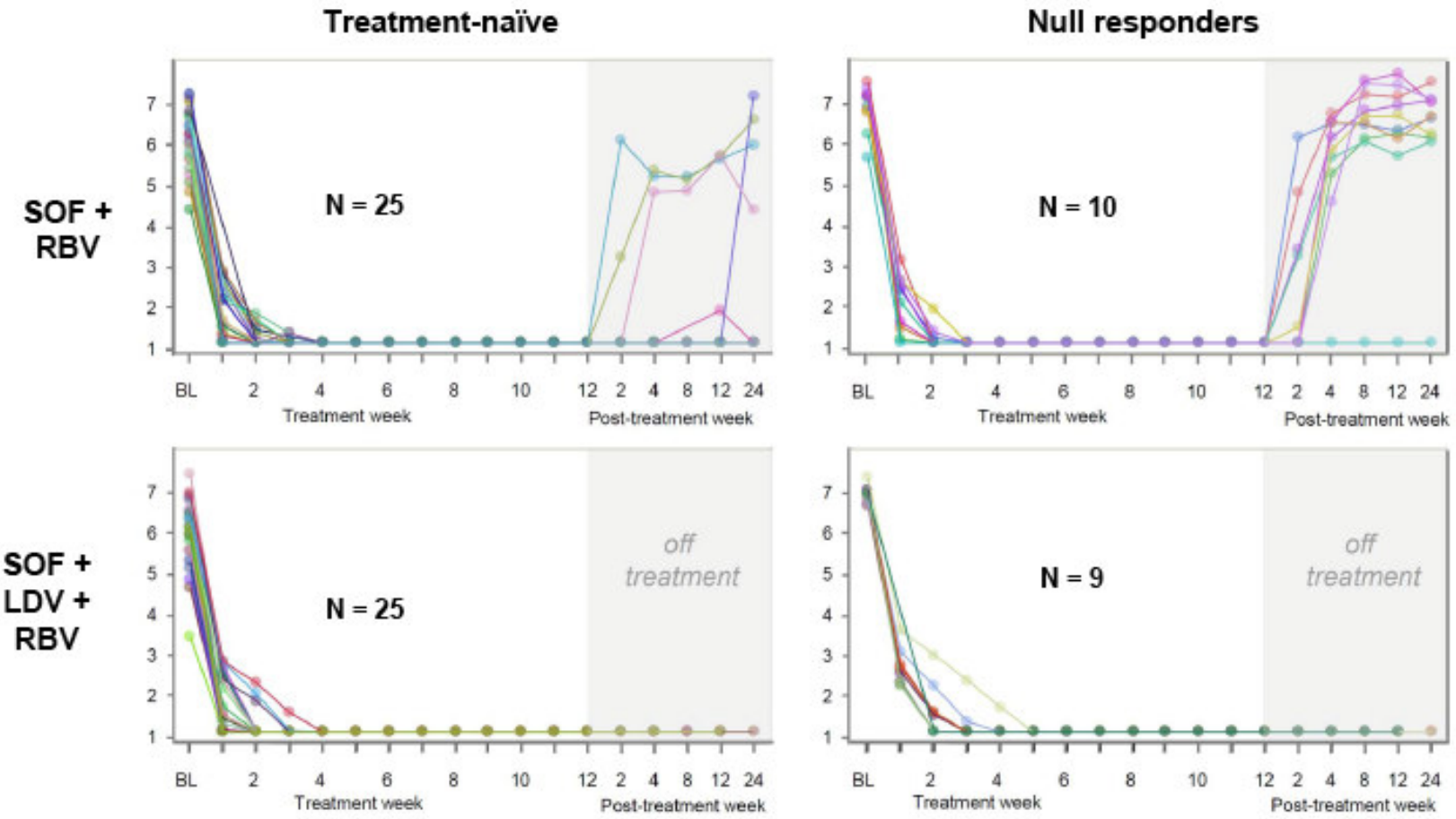
	SOF + RBV		SOF + LDV + RBV	
	Treatment-naïve (n = 25)	Null responder (n = 10)	Treatment-naïve (n = 25)	Null responder (n = 9)
Week 1	8/25 (32)	1/10 (10)	11/25 (44)	0/9 (0)
Week 2	17/25 (68)	7/10 (70)	22/25 (88)	4/9 (44)
Week 4	25/25 (100)	10/10 (100)	25/25 (100)	8/9 (89)
EOT	25/25 (100)	10/10 (100)	25/25 (100)	9/9 (100)
SVR4	22/25 (88)	1/10 (10)	25/25 (100)†	9/9 (100)
SVR12	21/25 (84)	1/10 (10)	25/25 (100)	9/9 (100)

*Analyzed by TaqMan® HCV Test 2.0 with limit of detection (LOD) of 15 IU/mL.

†Includes 1 patient who stopped all treatment due to an SAE at week 8; this patient subsequently achieved SVR24.

EOT, end of treatment; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Results: HCV RNA Viral Kinetics



Results: Adverse Events

	SOF + RBV		SOF + LDV + RBV	
	Treatment-naïve (n = 25)	Null responder (n = 10)	Treatment-naïve (n = 25)	Null responder (n = 9)
SAEs*	1 (4)	0	2 (8)	0
AEs that led to discontinuation	0	0	1 (4)†	0
≥Grade 2 AEs‡	10 (40)	3 (30)	12 (48)	2 (22)
Anemia	0	1 (10)	5 (20)	0
Depression	0	1 (10)	2 (8)	0
Headache	1 (4)	0	1 (4)	0
Ligament sprain	1 (4)	1 (10)	0	0

*SAEs considered unrelated to SOF (urethral injury, pyelonephritis, enterovesical fistula + divertivulitis + diverticular perforation).
†Stopped all treatment at Week 8 at time of partial colectomy for diverticular perforation.
‡In more than 1 patient.
AE, adverse event; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir.

Results: Grade 3 and 4 Lab Abnormalities

	SOF + RBV		SOF + LDV + RBV	
	Treatment-naïve (n = 25)	Null responder (n = 10)	Treatment-naïve (n = 25)	Null responder (n = 9)
Grade 4	0	0	0	0
Grade 3	11 (44)	4 (40)	13 (52)	2 (22)
Urine occult blood*	5 (20)	2 (20)	9 (36)	0
Hemoglobin 7 to <9 g/dL†	3 (12)	3 (30)	5 (20)	2 (22)
Prothrombin time >1.5 to 3 x ULN	1 (4)	0	2 (8)	0
ALT >5 to 10 x ULN	1 (4)	0	0	0
Total bilirubin 2.6 to 5.0 x ULN	1 (4)	0	0	0

*Majority of occult blood findings unconfirmed or in females.
†Or any decrease of ≥4.5 g/dL from baseline.