Treatment Experienced

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

SIRIUS

Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.

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SIRIUS Trial: Features

SIRIUS Trial

- **Design**: Phase 2, double-blind, randomized, trial that evaluated ledipasvir-sofosbuvir x 24 weeks or ledipasvir-sofosbuvir plus ribavirin for 12 weeks in treatment-experienced patients with GT1 HCV and compensated cirrhosis
- **Setting**: Multiple sites in France
- **Entry Criteria**
  - Chronic HCV Genotype 1 (n = 155 randomized)
  - 18 years or older
  - Failed prior therapy with sequential PEG + RBV and PEG + RBV + PI
  - Compensated cirrhosis by: (a) biopsy, (b) FibroScan >12.5 kPa, or (c) FibroTest (FibroSURE) >0.75 and APRI >2
  - Excluded if evidence of hepatic decompensation or HCC
- **Primary End-Point**: SVR12

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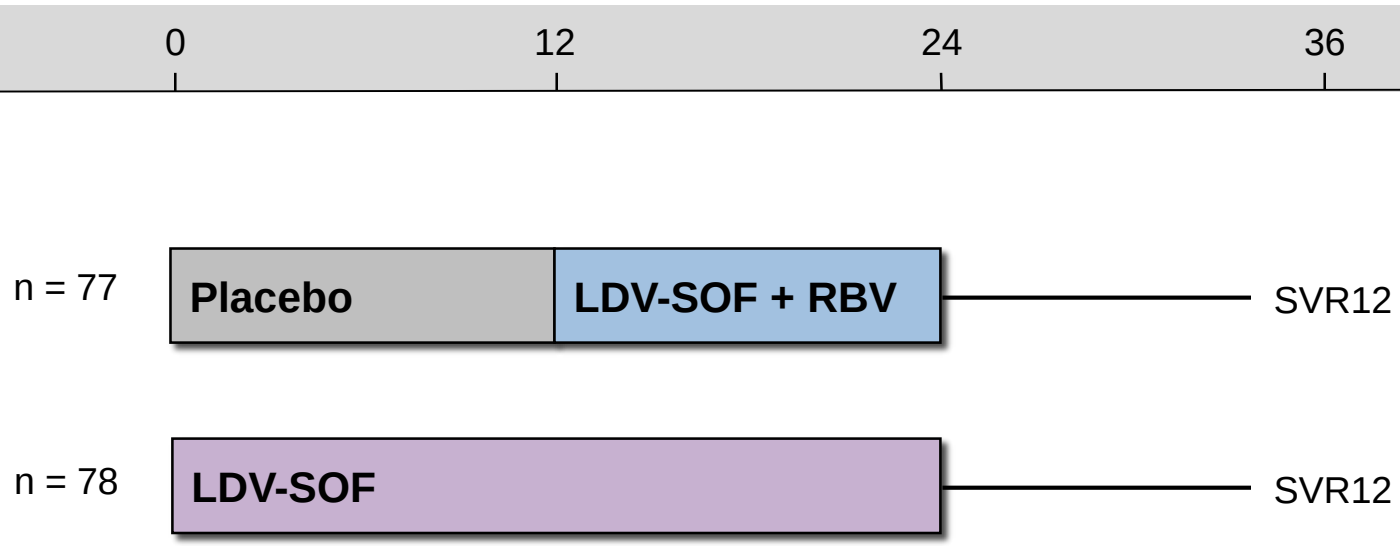
SIRIUS Trial: Study Design



Drug Dosing

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Abbreviations: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

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SIRIUS Trial: Baseline Characteristics

	LDV-SOF + RBV 12 wks N = 77	LDV-SOF x 24 wks N = 78
Age (years)	56	57
BMI, kg/m^2 mean	27.9	26.3
Male sex, n (%)	58 (75)	56 (72)
White Race, n (%)	76 (99)	75 (96)
IL28B CC, n (%)	4 (5)	6 (8)
HCV RNA (log_{10} IU/mL)	6.5	6.5
Mean MELD (range)	7 (6-16)	7 (6-12)
Varices, n (%)	16 (21)	25 (32)
Platelets <100 x 10^9/L	56 (39-74)	57 (23-77)
Albumin < 35 g/L	6 (8)	14 (18)

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SIRIUS Trial: Baseline Characteristics (continued)

	LDV-SOF + RBV 12 wks N = 77	LDV-SOF x 24 wks N = 78
HCV Genotype		
1a	48 (62%)	50 (64)
1	28 (36%)	27 (35%)
1 (no confirmed subtype)	1 (1%)	1 (1%)
Prior Protease Inhibitor		
Telaprevir	43 (56%)	49 (63%)
Boceprevir	30 (39%)	27 (35%)
Telaprevir and Boceprevir	1 (1%)	1 (1%)
Simeprevir	1 (1%)	2 (3%)
Faldaprevir	2 (3%)	0
Patients with NS3A RAVs	44 (57%)	39 (50%)
Patients with NS5A RAVs	12 (16%)	12 (15%)

Abbreviations: RAVs = Resistant Associated Variants

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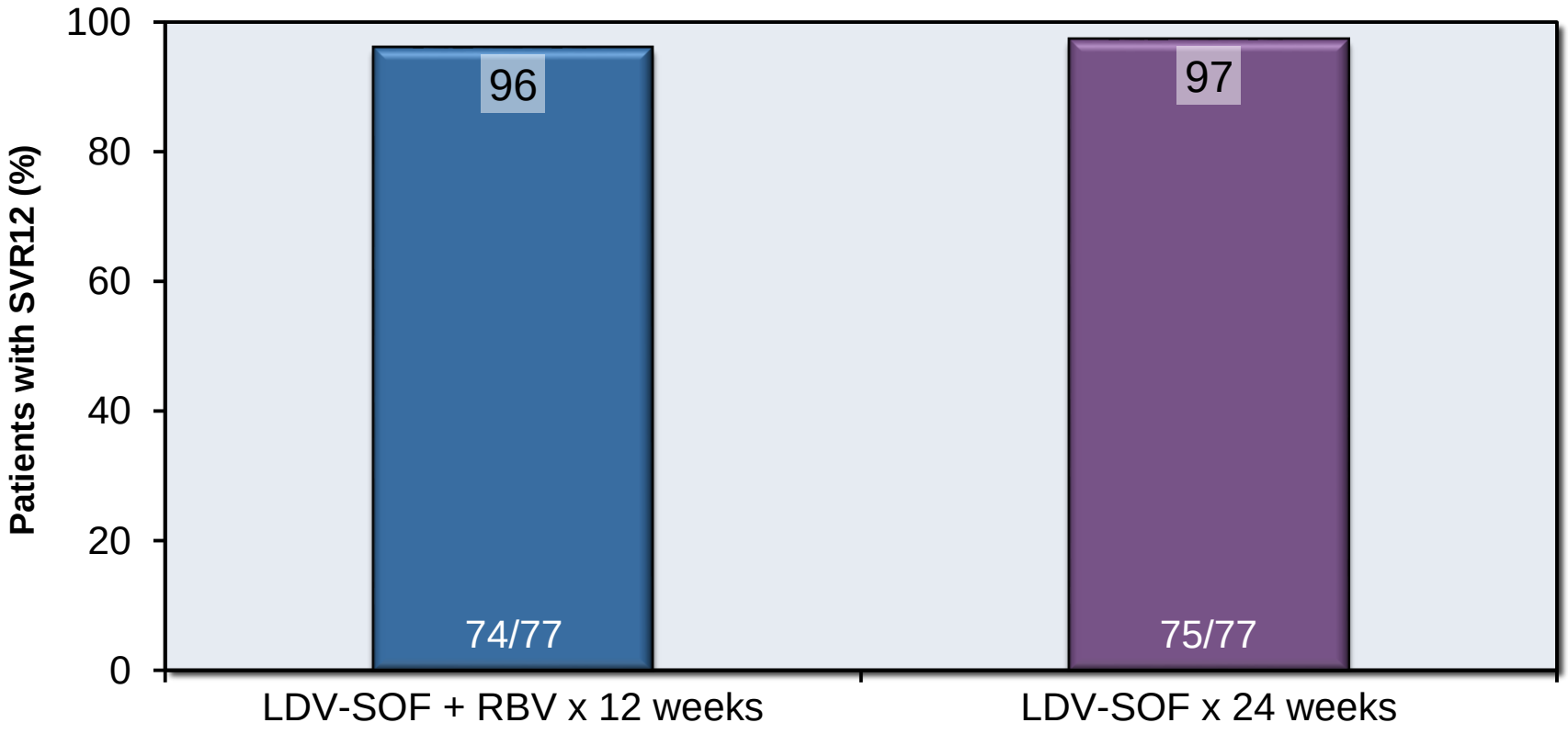
SIRIUS Trial: Results

SIRIUS: SVR 12 by Treatment Duration and Regimen



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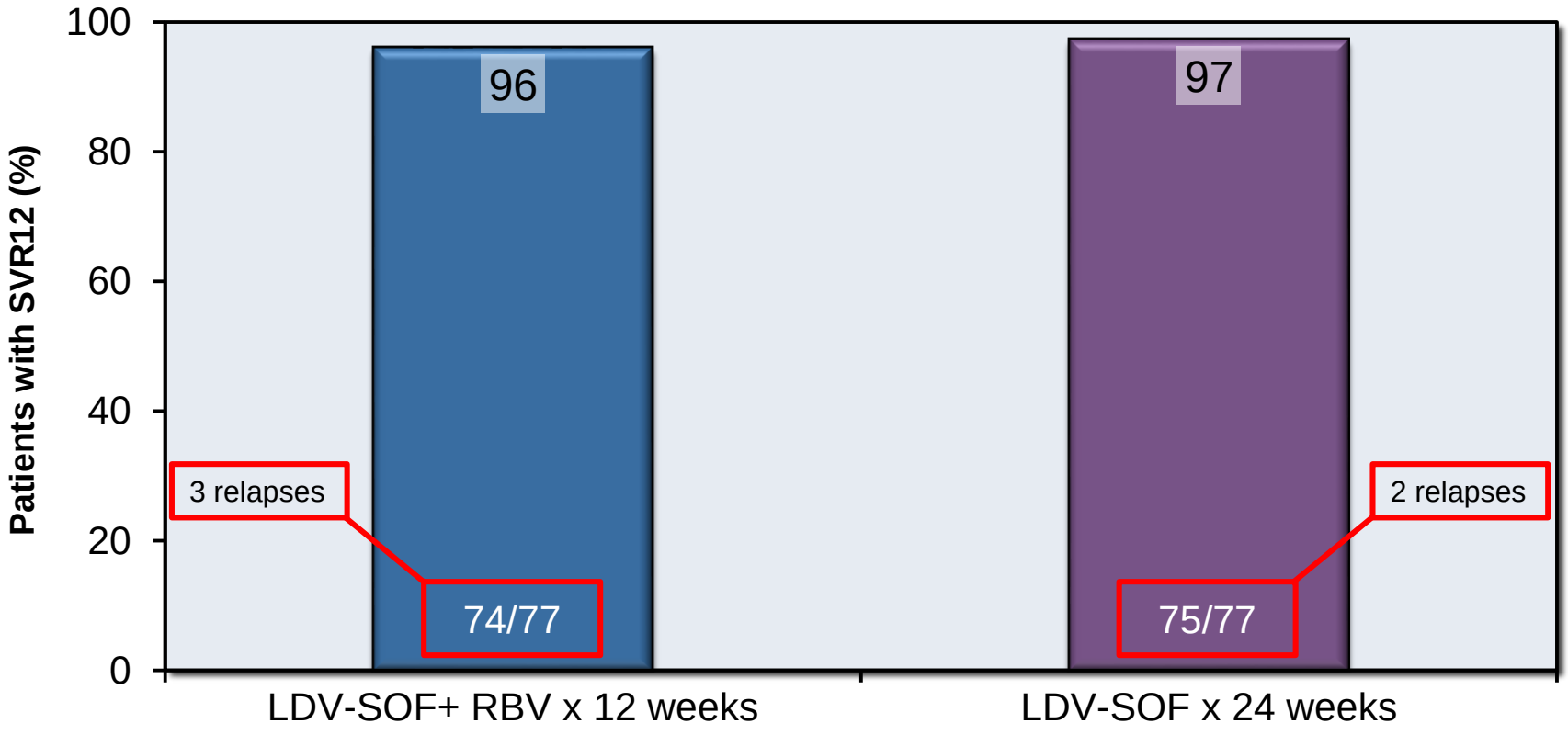
SIRIUS Trial: Results

SIRIUS: SVR 12 by Treatment Duration and Regimen



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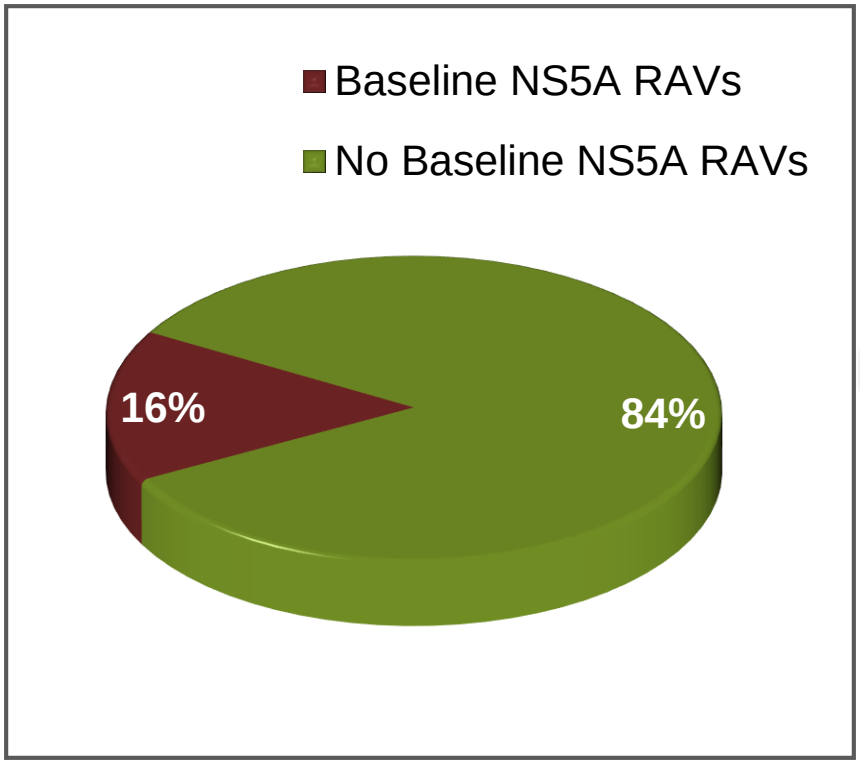
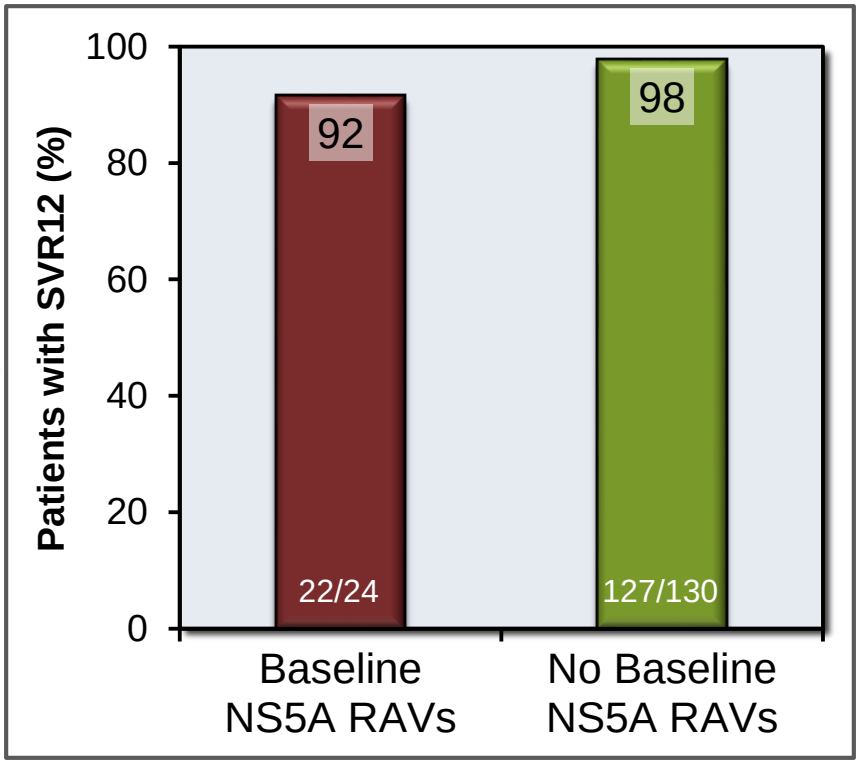
SIRIUS Trial: Results HCV Sequence Analysis

Correlation of Baseline NS5A RAVs and SVR12 Responses





No statistically significant difference in SVR12 based on baseline NS5A mutations

Abbreviations: RAVs = Resistant Associated Variants

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SIRIUS Trial: Safety Summary

Patients, N (%)	LDV-SOF + RBV x 12 Weeks			LDV-SOF x 24 Weeks	
	Placebo 12 Wk N = 78	LDV/SOF+ RBV 12 Wk N = 77	Overall Period N = 78	First 12 Wk N = 77	Overall Period N = 77
Any adverse event	63 (81%)	66 (86%)	75 (96%)	65 (84%)	67 (87%)
Treatment D/C due to AEs	1 (1%)	0	1 (1%)	0	0
Serious adverse event	1 (1%)	3 (4%)	4 (5%)	3 (4%)	8 (10%)
Grade 3-4 lab abnormalities	18 (23)	8 (11)	24 (31)	15 (19)	11 (14)
Hemoglobin <100 g/L	1 (1%)	1 (1%)	2 (3%)	0	1 (1%)
Hemoglobin <85 g/L	1 (1%)	1 (1%)	2 (3%)	0	0

Abbreviations: LDV-SOF = Ledipasvir-sofosbuvir; AE = adverse event; D/C = discontinued

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SIRIUS Trial: Adverse Events ≥10%

Patients, N (%)	LDV-SOF + RBV x 12 Weeks			LDV-SOF x 24 Weeks	
	Placebo 12 Wk N = 78	LDV/SOF+ RBV 12 Wk N = 77	Overall Period N = 78	First 12 Wk N = 77	Overall Period N = 77
Asthenia	24 (31%)	29 (38%)	45 (58%)	28 (36%)	35 (45%)
Headache	16 (21%)	13 (17%)	21 (27%)	27 (35%)	31 (40%)
Pruritus	14 (18%)	11 (14%)	22 (28%)	4 (5%)	7 (9%)
Insomnia	9 (12%)	7 (9%)	17 (22%)	11 (14%)	13 (17%)
Nausea	8 (10%)	8 (10%)	14 (18%)	7 (9%)	8 (10%)
Fatigue	3 (4%)	5 (6%)	7 (9%)	13 (17%)	15 (19%)
Dry skin	6 (8%)	4 (5%)	11 (14%)	4 (5%)	4 (5%)
Arthralgia	5 (6%)	0	6 (8%)	6 (8%)	12 (16%)
Bronchitis	1 (1%)	4 (5%)	4 (5%)	4 (5%)	13 (17%)

Abbreviations: LDV-SOF = Ledipasvir-sofosbuvir; AE = adverse event; D/C = discontinued

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SIRIUS Trial: Interpretation

Interpretation: “Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore, be useful to treat treatment-experienced patients with cirrhosis if longer-term treatment is not possible.”

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This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online

www.hepatitisc.uw.edu

Hepatitis Web Study

http://depts.washington.edu/hepstudy/

Funded by a grant from the Centers for Disease Control and Prevention.

Hepatitis web study