Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

SIRIUS

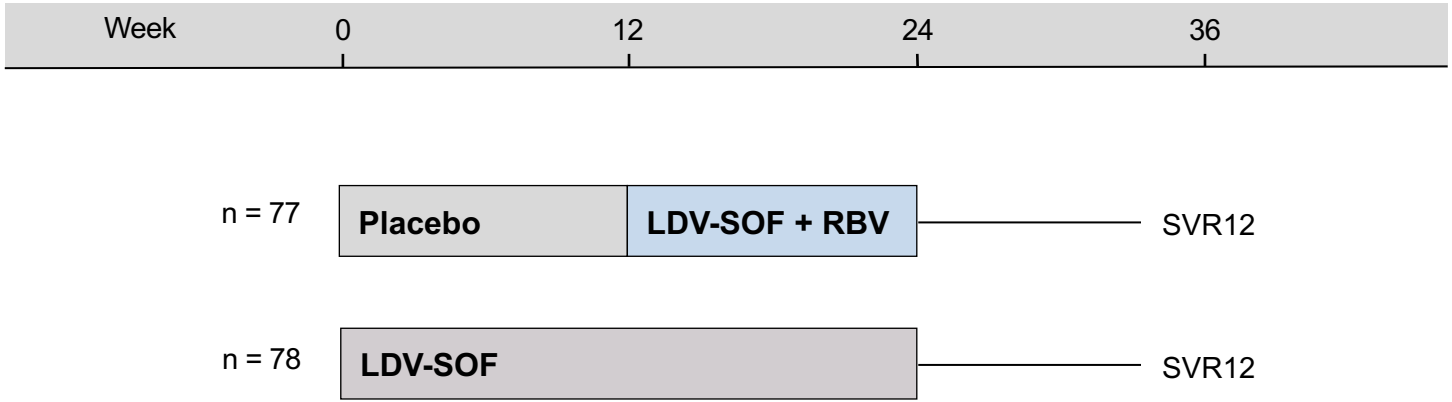
Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis SIRIUS Trial: Features

- **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)
  - Age 18 years or older
  - Failed prior therapy with sequential PEG + RBV and PEG + RBV + PI
  - Compensated cirrhosis by: (1) biopsy, (2) FibroScan >12.5 kPa, or (3) FibroTest (FibroSURE) >0.75 and APRI >2
  - Excluded if evidence of hepatic decompensation or HCC
- **Primary End Point**: SVR12

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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis
SIRIUS Trial: Study Design



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

Drug Dosing: Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily *or* Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis 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, n (%)	14 (18)	13 (17)
Albumin < 35 g/L, n (%)	6 (8)	14 (18)

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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis SIRIUS Trial: Baseline Characteristics (continued)

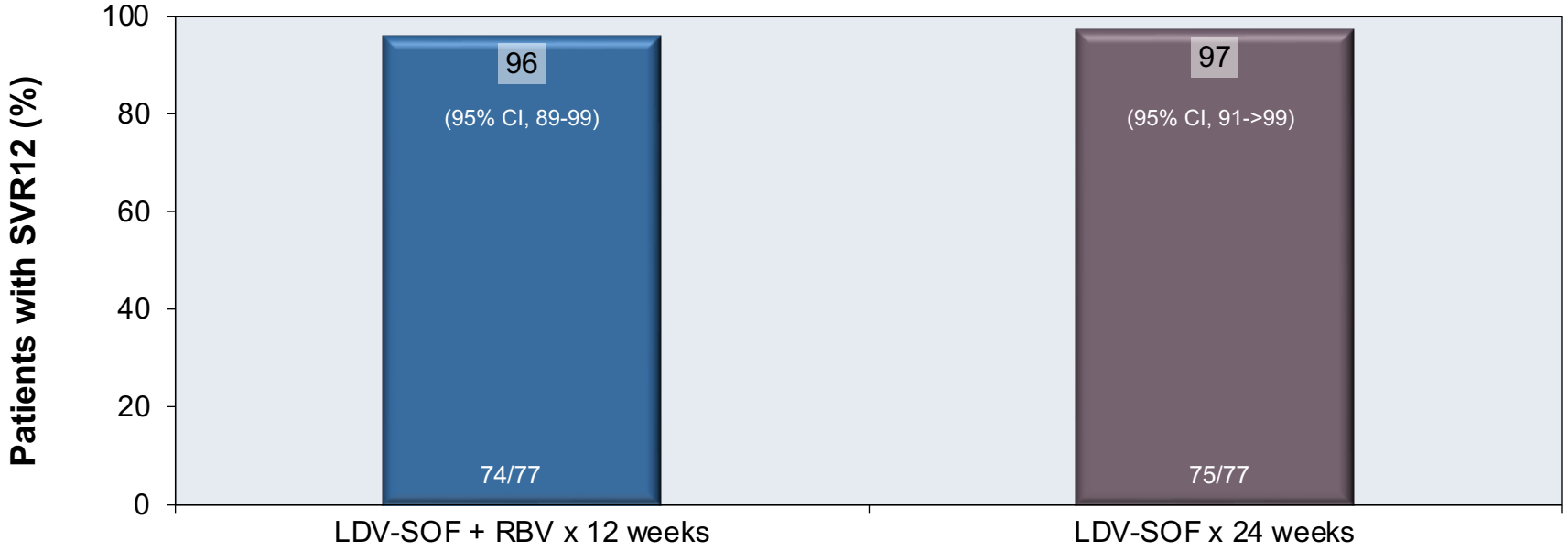
	LDV-SOF + RBV 12 wks (n = 77)	LDV-SOF x 24 wks (n = 78)
HCV Genotype		
1a	48 (62%)	50 (64)
1b	28 (36%)	27 (35%)
1 (no confirmed subtype)	1 (1%)	1 (1%)
Prior Protease Inhibitor		
Telaprevir	43 (56%)	49 (63%)
Boceprevir	30 (39%)	27 (35%)
Telaprevir and Boceprevir	1 (1%)	1 (1%)
Simeprevir	1 (1%)	2 (3%)
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

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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis SIRIUS Trial: Results

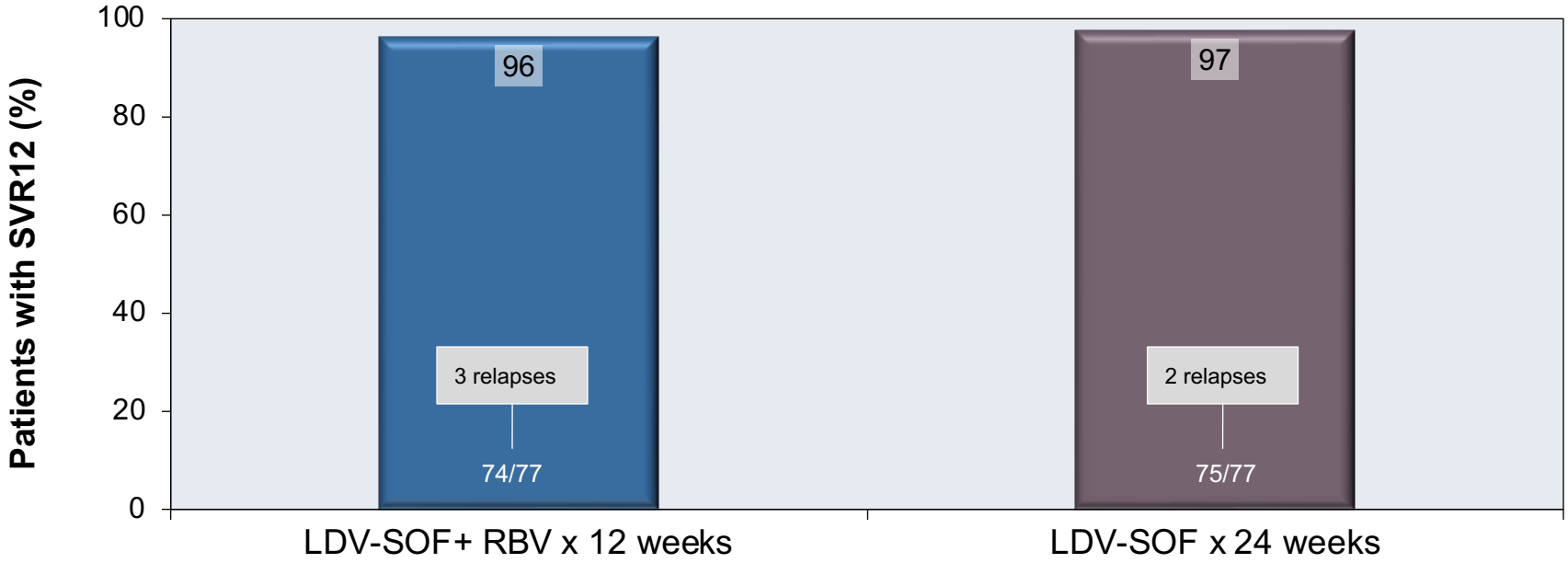
SIRIUS: SVR 12 by Treatment Duration and Regimen



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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis SIRIUS Trial: Results

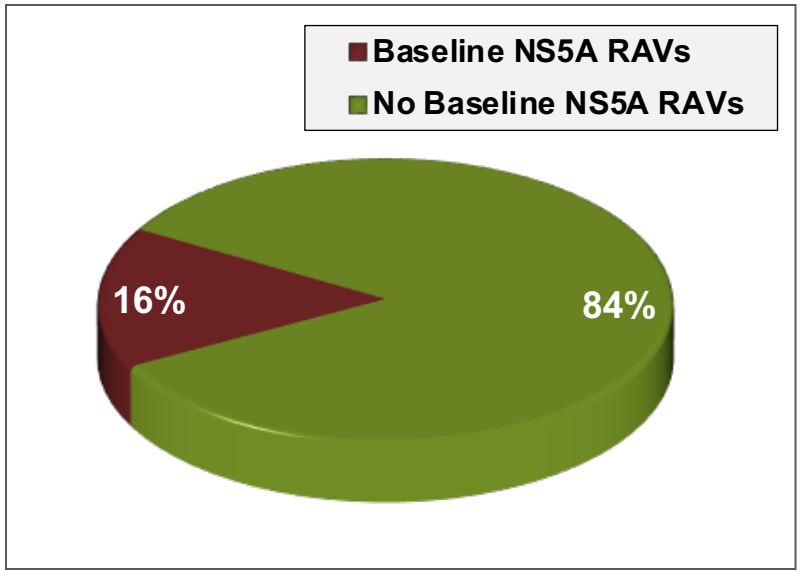
SIRIUS: SVR 12 by Treatment Duration and Regimen

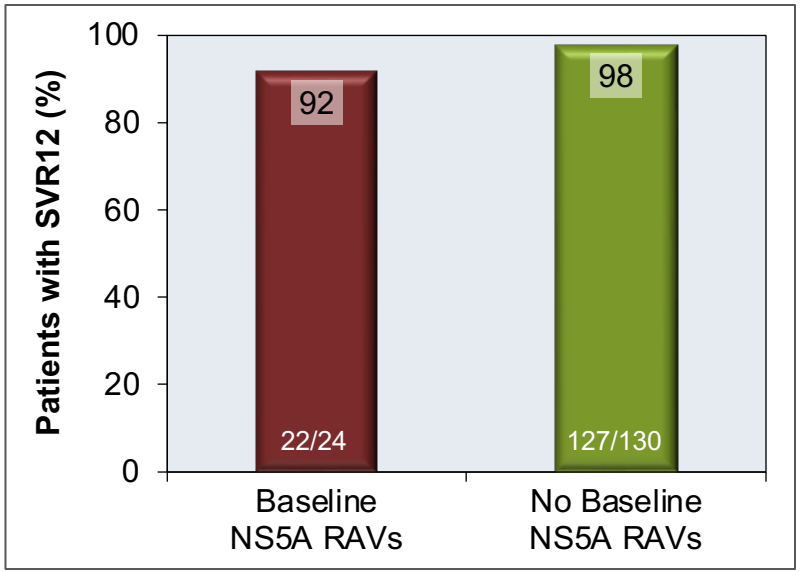


Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis 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

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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis SIRIUS Trial: Safety Summary

Patients, n (%)	LDV-SOF + RBV x 12 Weeks			LDV-SOF x 24 Weeks	
	Placebo 12 Wks (n = 78)	LDV/SOF + RBV 12 Wks (n = 77)	Overall Period (n = 78)	First 12 Wks (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 (10%)	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

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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis SIRIUS Trial: Adverse Events ≥10%

	LDV-SOF + RBV x 12 Weeks			LDV-SOF x 24 Weeks	
	Placebo 12 Wks (n = 78)	LDV/SOF + RBV 12 Wks (n = 77)	Overall Period (n = 78)	First 12 Wks (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

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

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis 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.”

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

Acknowledgments

Hepatitis C Online is funded by a cooperative agreement from the Centers for Disease Control and Prevention (CDC-RFA- PS21-2105). This project is led by the University of Washington Infectious Diseases Education and Assessment (IDEA) Program.

HEPATITIS B ONLINE

HEPATITIS C ONLINE

IDEA INFECTIOUS DISEASES EDUCATION & ASSESSMENT