High Efficacy and Low Relapse Rates Observed with 8 or 12 Weeks of LDV/SOF STR in GT1 HCV Infected Treatment-Naïve, Non-Cirrhotic Patients with Pretreatment HCV RNA < 6 Million IU/mL

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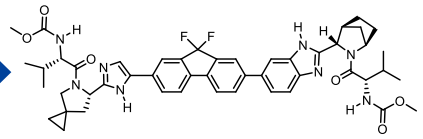
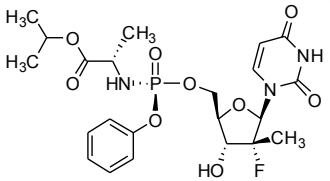
Introduction

LDV
NS5A
inhibitor





SOF - NS5B
nucleotide
polymerase
inhibitor

Ledipasvir (LDV)

Once-daily, oral, 90 mg

Sofosbuvir (SOF)

Once-daily, oral, 400-mg tablet

LDV
NS5A
inhibitor

SOF - NS5B
nucleotide
polymerase
inhibitor

Ledipasvir/Sofosbuvir STR

Once-daily, oral (90/400 mg) single-tablet regimen for HCV

STR: single-tablet regimen; HCV: hepatitis C

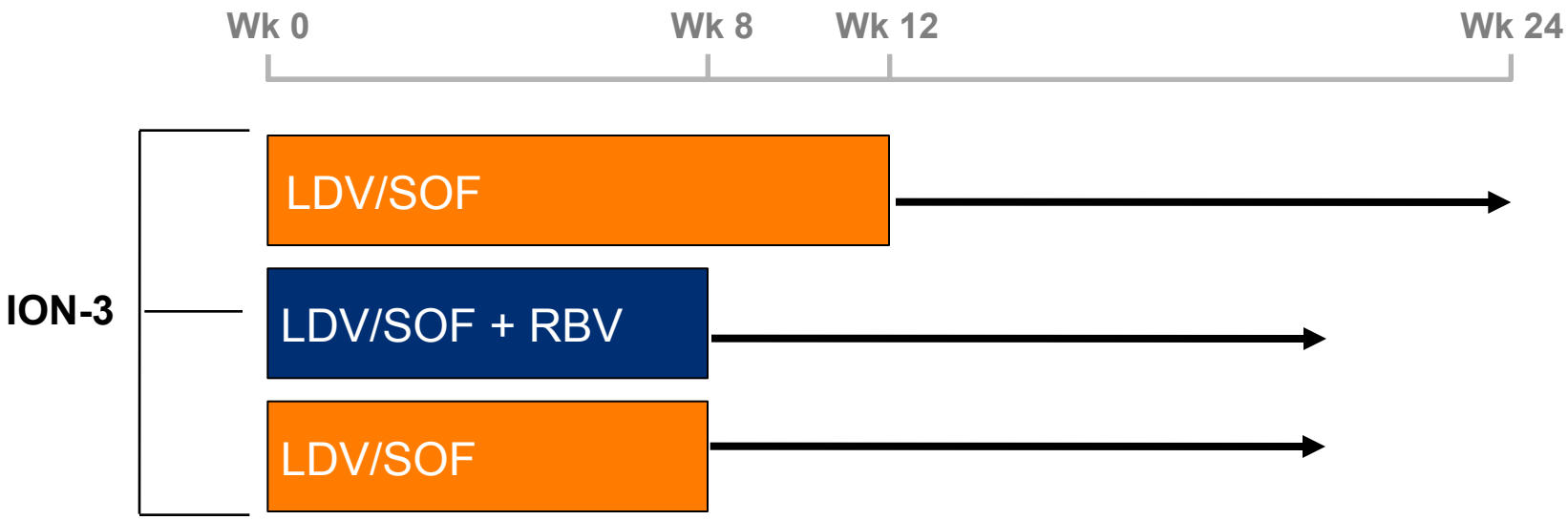
Introduction

- ION-3, a phase 3, randomized, open label study (N=647) evaluated a shortened duration of ledipasvir/sofosbuvir (LDV/SOF) for 8 weeks (+/- RBV) compared to LDV/SOF for 12 weeks in genotype 1 (GT 1) treatment-naïve, non-cirrhotic patients.
- Overall sustained virologic response (SVR) rates were non-inferior between the 8 and 12 week LDV/SOF arms (94% and 96% respectively); however, relapse was numerically higher in those treated for 8 weeks (5.1%) compared to 12 weeks (1.4%). The addition of RBV did not improve SVR.
- A post-hoc analysis of the ION-3 trial was conducted to evaluate baseline factors that might be responsible for the differential in relapse rates between the 8 and 12 week arms of LDV/SOF.

Objectives

- This analysis retrospectively evaluated baseline historical negative predictors in subjects who relapsed to determine factors that would allow the 8 week and 12 week LDV/SOF treatment arms to have comparable SVR12 rates and rates of virologic failure (i.e., relapse rates).
- Baseline historical negative predictors evaluated included: age, gender, race, GT1 subtype, METAVIR fibrosis stage, BMI, IL28B status, and baseline HCV RNA.
- Impact of baseline viral load was assessed at a predefined cutoff of 800,000 IU/ml as well as in 1 million IU/mL increments up to 10million IU/mL.

Methods



Inclusion criteria had no upper limit to age or BMI.

HCV GT1, treatment-naïve, without cirrhosis; N = 647

Absence of cirrhosis is defined as any one of the following:

- Liver biopsy within 2 years of screening showing absence of cirrhosis
- FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 during Screening.

In the absence of a definitive diagnosis of the presence or absence of cirrhosis by the above criteria, a liver biopsy was required; liver biopsy results superseded blood test results and were considered definitive.

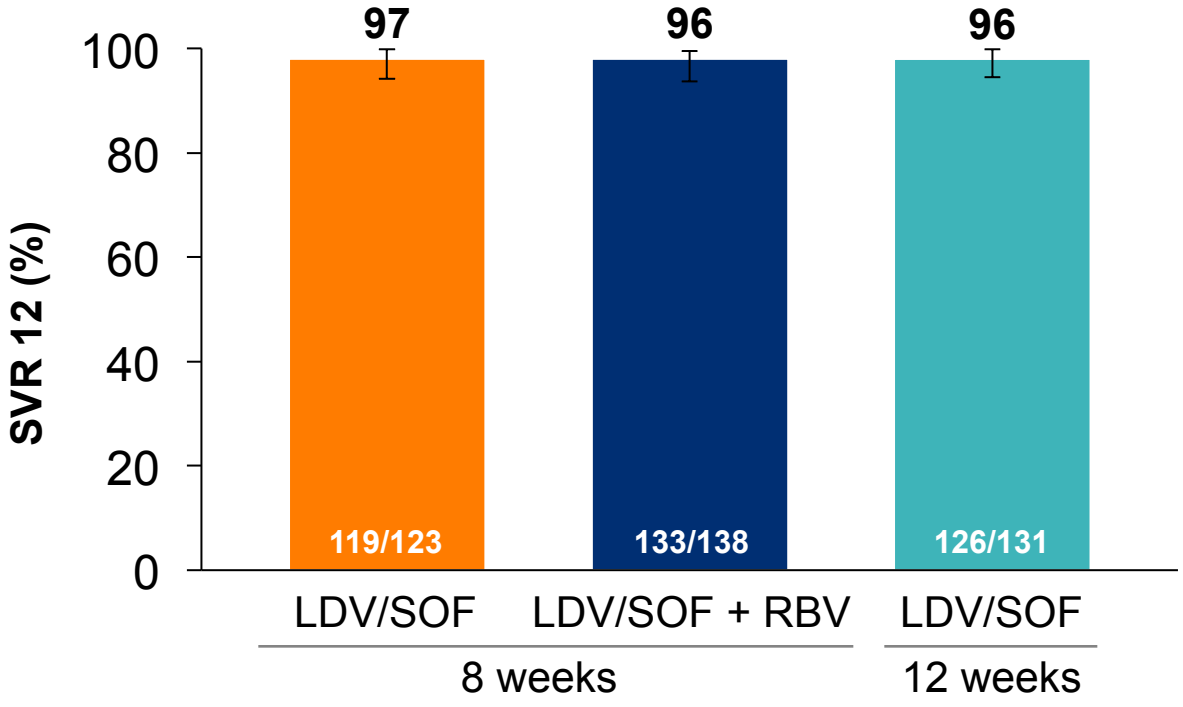
Endpoints

- The primary efficacy endpoint was an HCV RNA level of less than 25 IU/mL at 12 weeks after the end of treatment (sustained virologic response 12).
- A key secondary endpoint was the non-inferiority of 8 weeks LDV/SOF to the other treatment regimens in terms of both, sustained virologic response and virologic failure (e.g., relapse rates).
- HCV RNA analyzed by COBAS® TaqMan® HCV Test v2.0 HPS, with LLOQ of 25 IU/mL

Demographics

Characteristic	LDV/SOF 8 weeks n = 215	LDV/SOF + RBV 8 weeks n = 216	LDV/SOF 12 weeks n = 216
Mean age, years (range)	53 (22-75)	51 (21-71)	53 (20-71)
Mean BMI, kg/m^2 (range)	28 (18-43)	28 (18-56)	28 (19-45)
Male, n (%)	130 (60)	117 (54)	128 (59)
Race, n (%)			
White	164 (76)	176 (81)	167 (78)
Black	45 (21)	36 (17)	42 (19)
HCV genotype 1a, n (%)	171 (80)	172 (80)	172 (80)
Mean HCV RNA, $\log_{10}$ IU/mL (SD)	6.5 ± 0.76	6.4 ± 0.69	6.4 ± 0.76
HCV RNA < 6 million IU/mL, n (%)	123 (57)	138 (64)	131 (61)
***IL28B* genotype Non-CC, n (%)**	159 (74)	156 (72)	160 (74)
Baseline ALT > 1.5 x ULN	87 (40)	95 (44)	99 (46)
Fibrosis Score (liver biopsy), n (%)	156 (73)	136 (63)	156 (72)
F0-F2	127 (59)	108 (50)	127 (59)
F3	29 (13)	28 (13)	29 (13)
Interferon ineligible, n (%)	13 (6)	13 (6)	15 (7)

Efficacy and Relapse in Subjects with Baseline HCV RNA < 6 Million IU/mL

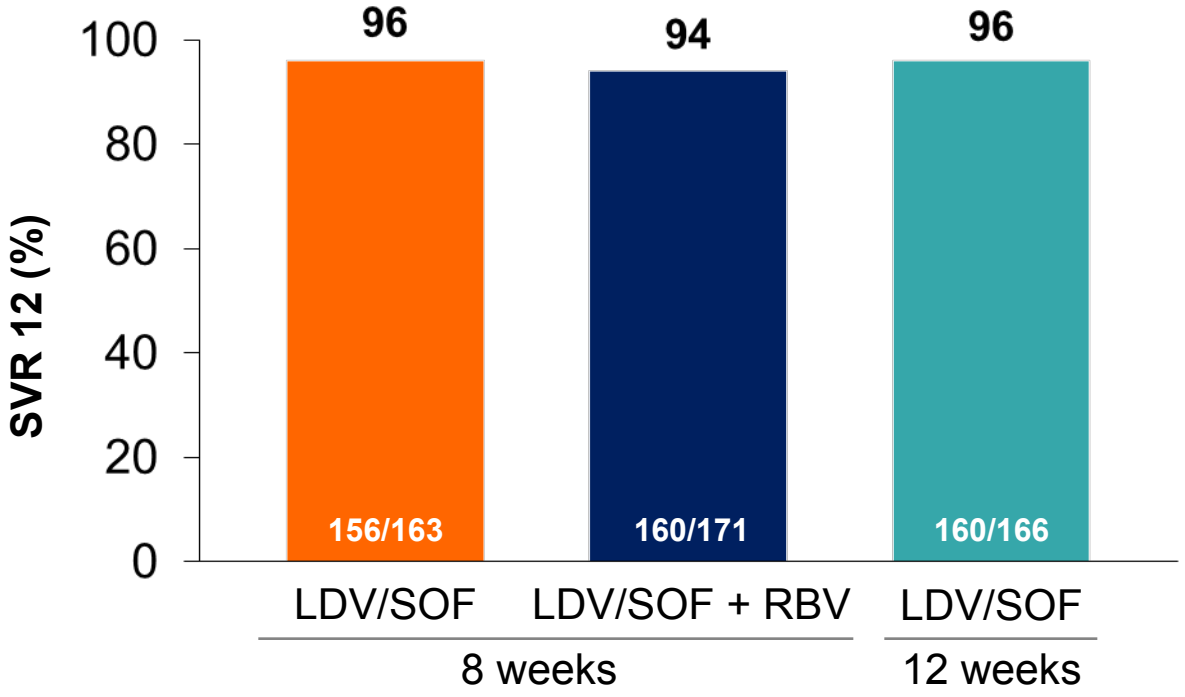


	LDV/SOF 8 weeks	*LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
Relapse Rates < 6M	1.6% (2/123)	2.2% (3/137)	1.5% (2/131)
Relapse Rates ≥ 6M	9.8% (9/92)	7.8% (6/77)	1.2% (1/85)

*2 patients were lost to follow-up after their baseline visit and never achieved HCV RNA < lower limit of quantitation on treatment.

8 weeks of LDV/SOF was non-inferior to 8 weeks of LDV/SOF + RBV and 12 weeks LDV/SOF for both SVR12 and relapse rates.

Efficacy and Relapse in Subjects with Baseline HCV RNA < 10 Million IU/mL



	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
Relapse Rates < 10M	3.1% (5/163)	4.1% (7/171)	1.2% (2/166)
Relapse Rates ≥ 10M	11.5% (6/52)	4.4% (2/45)	2.0% (1/50)

The utility of using a viral load cut-off at <10 million IU/mL was also evaluated. Identical SVR12 rates were observed using <10 million IU/mL and similar relapse rates were observed. This confirmed the validity of using <6 million/IU/mL as the majority of relapses that occurred were at baseline viral loads >10 million IU/mL.

Assessment of SVR Rates by Baseline Demographics*

SVR12, % (n/n)	LDV/SOF 8 weeks (n=215)	LDV/SOF + RBV 8 weeks (n=216)	LDV/SOF 12 weeks (n=216)
SVR12, Overall			
***IL28B* CC**	96% (54/56)	100% (57/57)	100% (54/54)
***IL28B* CT**	94% (112/119)	96% (120/125)	98% (120/122)
***IL28B* TT**	95% (36/38)	86% (24/28)	97% (34/35)
Male	92% (119/129)	93% (106/114)	98% (124/127)
Female	99% (83/84)	99% (95/96)	100% (84/84)
SVR12 (BL HCV RNA <6M)			
***IL28B* CC**	100% (30/30)	100% (36/36)	100% (31/31)
***IL28B* CT**	97% (63/65)	98% (78/80)	99% (72/73)
***IL28B* TT**	100% (26/26)	95% (19/20)	96% (23/24)
Male	97% (64/66)	95% (62/65)	97% (72/74)
Female	100% (55/55)	100% (71/71)	100% (54/54)

*Data excludes those who are lost to follow up and or withdrew consent.

The baseline viral load cut-off of < 6 million IU/mL normalized any effect of *IL28B*, genotype or gender

Reasons for Not Achieving SVR

Patients, n (%)	8 Weeks		12 Weeks
	LDV/SOF n=215	*LDV/SOF+RBV n=216	LDV/SOF n=216
SVR12	202 (94)	201 (93)	208 (96)
Breakthrough	0	0	0
Relapse	11 (5)	9 (4)	3 (1)
Lost to Follow-Up	1 (<1)	5 (2)	5 (2)
Withdrew Consent	1 (<1)	1 (<1)	0
Relapse Rates by Baseline Viral Load			
HCV RNA < 6M IU/mL	1.6% (2/123)	2.2% (3/137)	1.5% (2/131)
HCV RNA ≥ 6M IU/mL	9.8% (9/92)	7.8% (6/77)	1.2% (1/85)
Relapse Rates < 10M	3.1% (5/163)	4.1% (7/171)	1.2% (2/166)
Relapse Rates ≥ 10M	11.5% (6/52)	4.4% (2/45)	2.0% (1/50)

*2 patients were lost to follow-up after their baseline visit and never achieved HCV RNA < lower limit of quantitation on treatment.

- All virologic failures in this study were due to relapse (n=23)
- 9 subjects had baseline NS5A resistance-associated polymorphisms and 14 subjects did not; 6 subjects had new RAVs at relapse
- 18% of subjects had baseline NS5A resistance-associated polymorphisms, and 90% achieved SVR12

Reasons for Not Achieving SVR (cont'd)

- In the ION-3 trial, approximately 60% of treatment-naïve, non-cirrhotic subjects had baseline HCV RNA of < 6 million IU/mL. For these subjects, there was no difference in SVR rates (97% and 96%) nor relapse rates (1.6% and 1.5%) between 8 and 12 weeks of LDV/SOF treatment
- SVR rates were identical for the 8 week and 12 week arms (96%) in patients with pretreatment HCV RNA < 10 million IU/mL, and relapse occurred in 3.1% vs. 1.2%, respectively. The majority of failures in ION-3 who were treated for 8 weeks had a baseline HCV RNA greater than 10 million IU/mL
- Although higher overall rates of relapse were observed for males and subjects who were *IL28B* non CC, sex and IL28B status had no effect on outcome among those with a pretreatment HCV RNA < 6 million IU/mL

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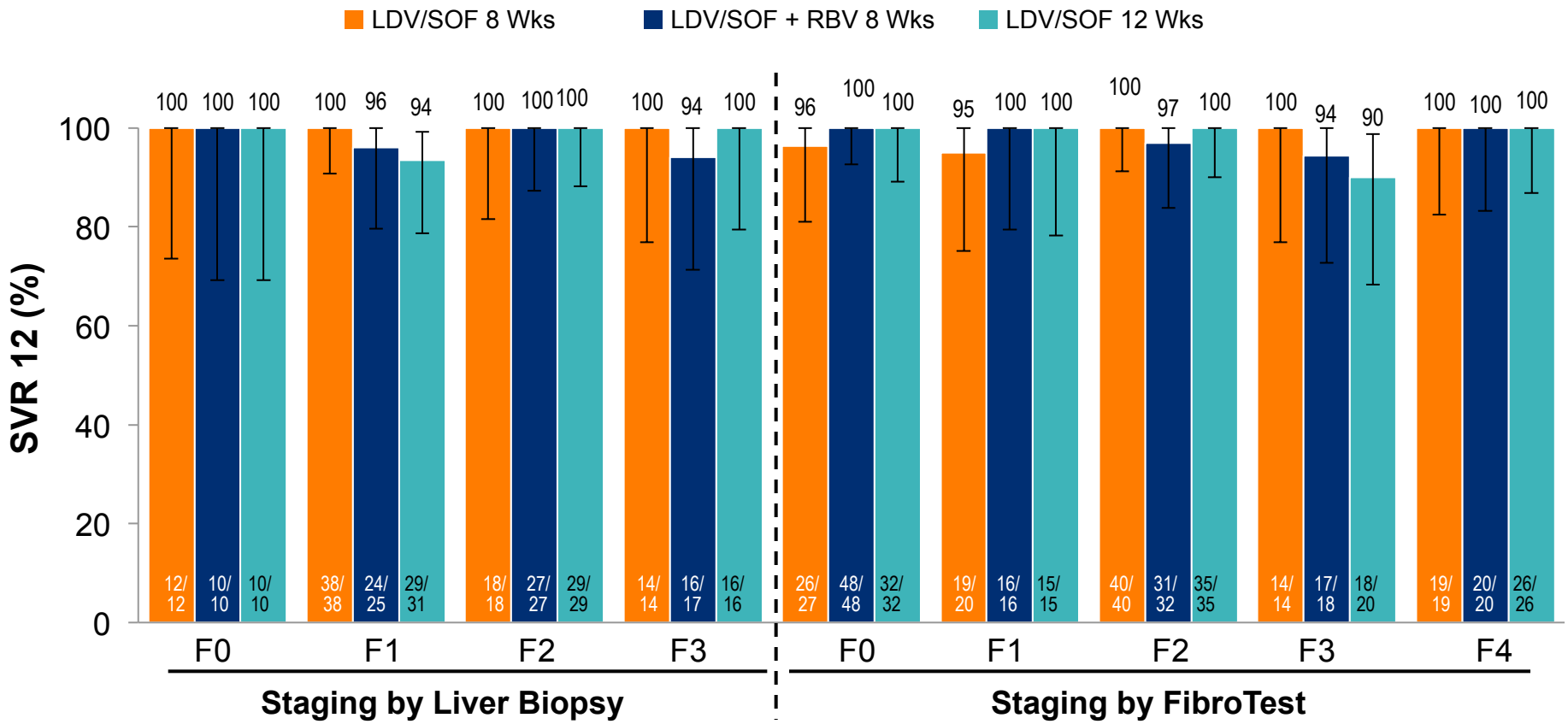
SVR12 by Fibrosis Scores Among Patients with Baseline HCV RNA < 6 Million IU/mL



The baseline viral load cut-off of < 6 million IU/mL has high efficacy for all fibrosis stages

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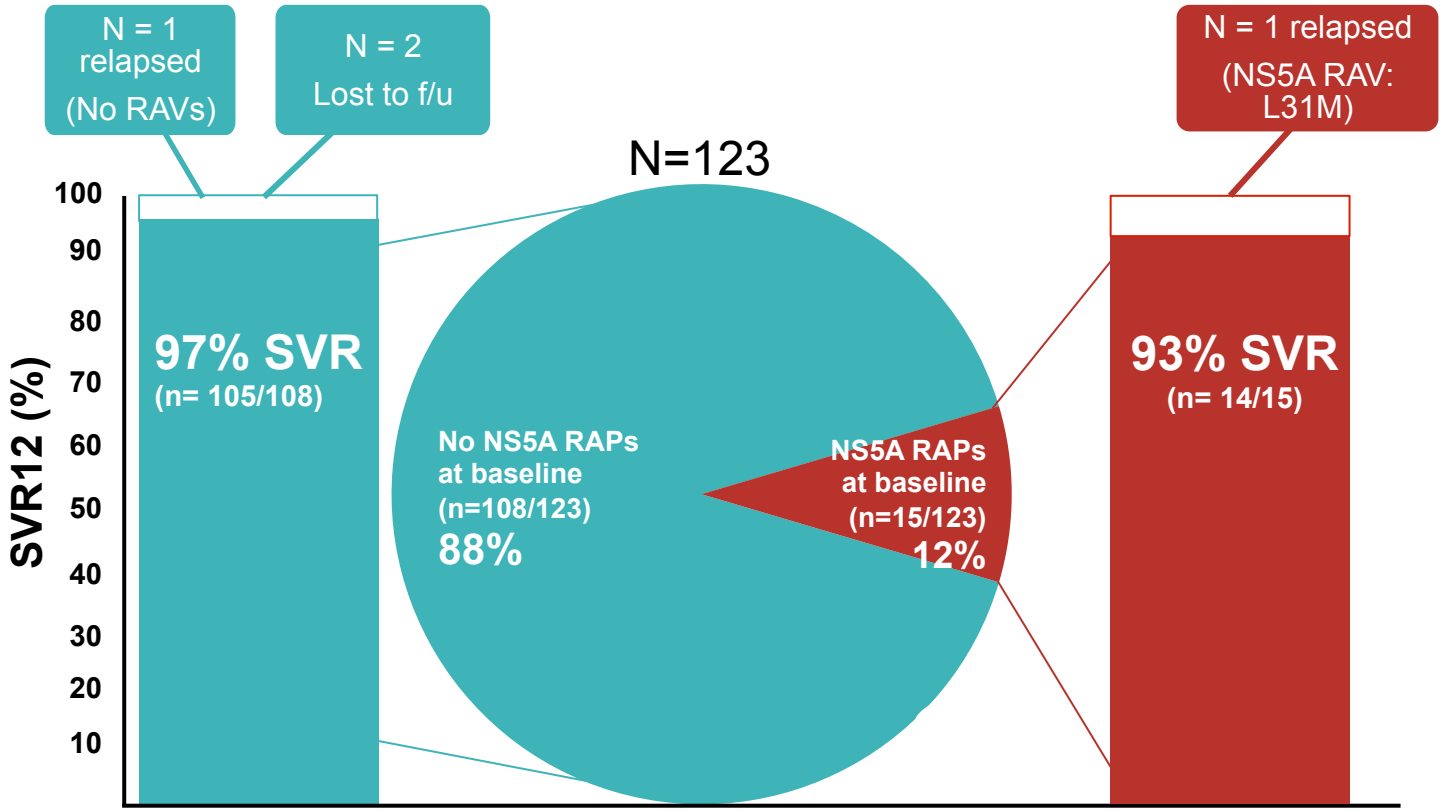
Effect of Baseline NS5A Resistance-Associated Polymorphisms on SVR in the LDV/SOF 8 Week Arm Subjects with Baseline HCV RNA <6M IU/mL



*** Deep sequencing analysis using 1% cutoff**

RAPs: Resistance associated polymorphisms (present at baseline)
RAVs: Resistance associated variants (treatment-emergent)

Data on file. Gilead Sciences, Inc.

SVR12 by Early Viral Response in Subjects with Baseline HCV RNA <6 million IU/mL

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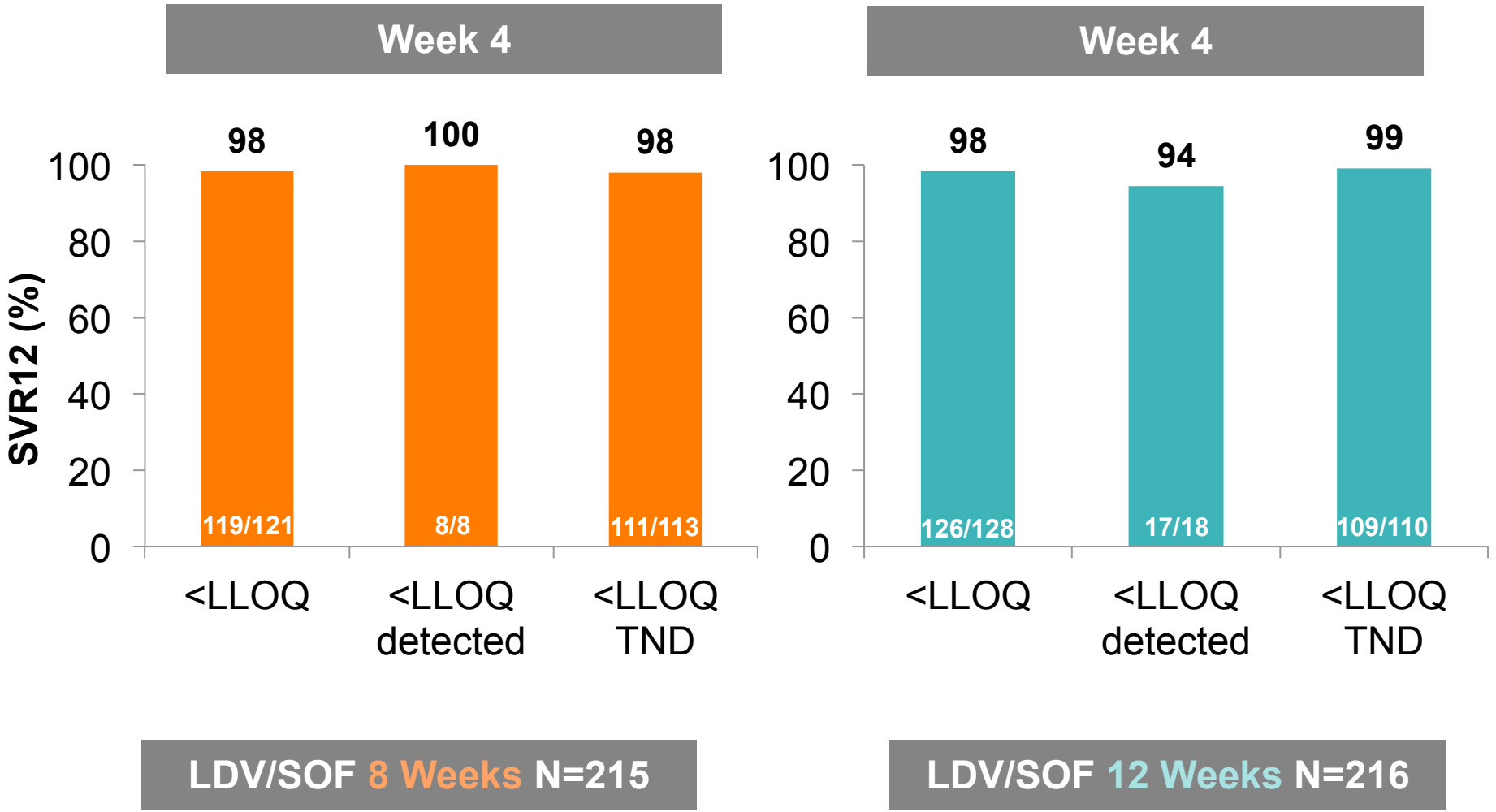

LDV/SOF ± RBV Safety Summary

Patients, n (%)	LDV/SOF 8 Weeks n=215	LDV/SOF+RBV 8 Weeks n=216	LDV/SOF 12 Weeks n=216
AEs	145 (67)	165 (76)	149 (69)
Grade 3–4 AEs	2 (<1)	8 (4)	7 (3)
Serious AEs	4 (2)	1 (<1)	5 (2)
Treatment D/C due to AEs	0	1 (<1)	2 (1)
Death	0	0	0
Grade 3–4 laboratory abnormality	7 (3)	18 (8)	16 (7)
Hemoglobin <10 g/dL	0	11 (5)	1 (<1)
Hemoglobin <8.5 g/dL	0	0	0

Conclusions

- A baseline HCV RNA < 6 million IU/mL in treatment-naïve, non-cirrhotic GT1 patients correlated with similar SVR and relapse rates for 8 weeks or 12 weeks of LDV/SOF single tablet regimen regardless of other patient characteristics.
- The analysis with a baseline HCV RNA <10 million IU/mL confirms the validity of using a <6 million IU/mL baseline viral load cut-off as the majority of relapses occurred in patients with viral load >10 million IU/mL.
- Treatment response did not differ based upon METAVIR fibrosis stage. The presence or absence of baseline NS5A resistance associated variants (RAVs) was also not associated with a significant difference in response.
- This shortened duration could improve adherence and affordability of HCV treatment without a compromise in efficacy (i.e.,SVR12 rates or relapse rates).

References

1. Data on File. Gilead Sciences.
2. HARVONI® [PI]. Gilead Sciences, Inc. Foster City, CA March 2015
3. Jacobson I, et al. AASLD, 2014, Poster #1945.
4. Kowdley K, EASL, 2014, O56
5. Kowdley K, et al. N Engl J Med 2014;370:1879-1888