Ledipasvir/Sofosbuvir Is Safe and Effective for the Treatment of Patients with Genotype 1 Chronic HCV Infection in Both HCV Mono- and HIV/HCV Coinfected Patients

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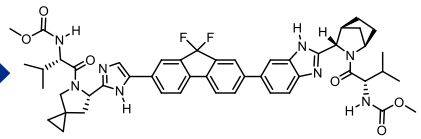
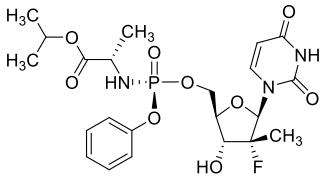
Introduction

- HIV/HCV coinfected patients have faced historical barriers to HCV treatment that include low response rates to PEG-based regimens, comorbidities, drug-drug interactions, and poor tolerability of available regimens.
- With the introduction of Direct Acting Antivirals (DAAs) the recently updated AASLD/IDSA/IAS-USA Guidance state **“**HIV/HCV coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications**”.**
- Ledipasvir/sofosbuvir (LDV/SOF) is FDA approved for HIV/HCV coinfection and dosage recommendations are the same as in HCV monoinfection.

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

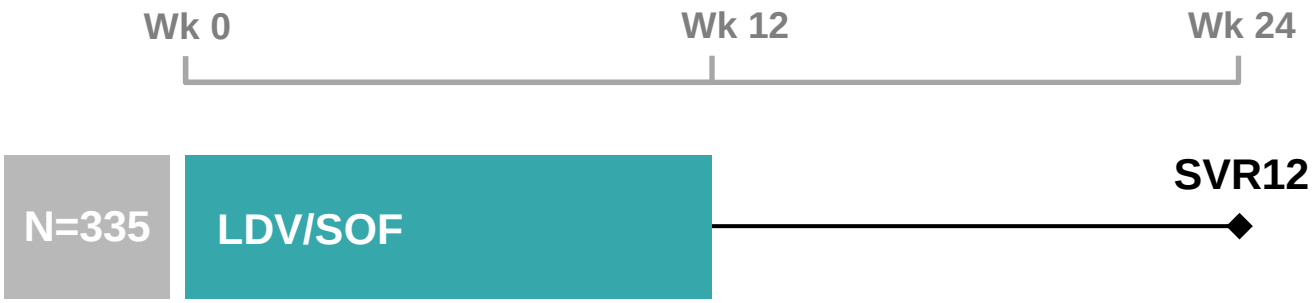
Once-daily, oral (90/400 mg) single-tablet regimen for HCV

STR: single-tablet regimen; HCV: hepatitis C

Objectives & Endpoints

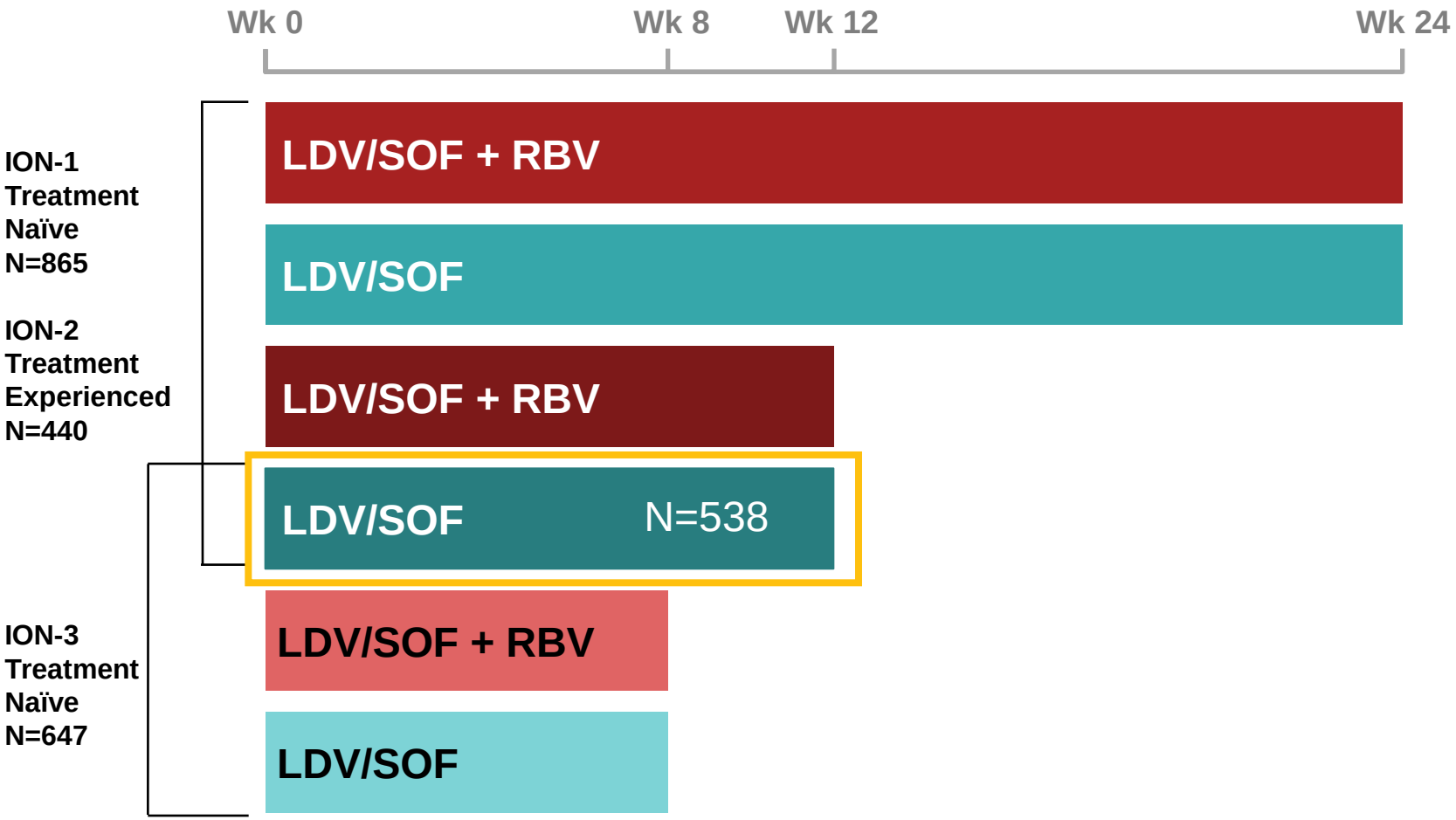
- This analysis retrospectively compared the efficacy and safety of 12 weeks with LDV/SOF in HCV GT 1 HIV/HCV coinfected patients in the Phase 3 ION-4 study with GT 1 HCV mono-infected patients in the Phase 3 ION 1-3 studies.
- The primary efficacy endpoint for each study was sustained virologic response and virologic failure including relapse rates with 12 weeks LDV/SOF in both HCV mono- and HIV/HCV coinfected patients.
  - SVR12 was defined as an HCV RNA level of less than 25 IU/mL at 12 weeks after the end of treatment
  - HCV RNA analyzed by COBAS® TaqMan® HCV Test v2.0 HPS, with LLOQ of 25 IU/mL.
- Safety
  - Adverse events and discontinuations

Study Design: ION-4



- **Phase 3, multicenter, open-label study (NCT02073656)**
- **HCV GT 1 or 4 patients in US, Canada, and New Zealand**
- **ART regimens:**
  - Efavirenz + FTC + TDF
  - Raltegravir + FTC + TDF
  - Rilpivirine + FTC + TDF

Study Design: ION-1, ION-2, ION-3

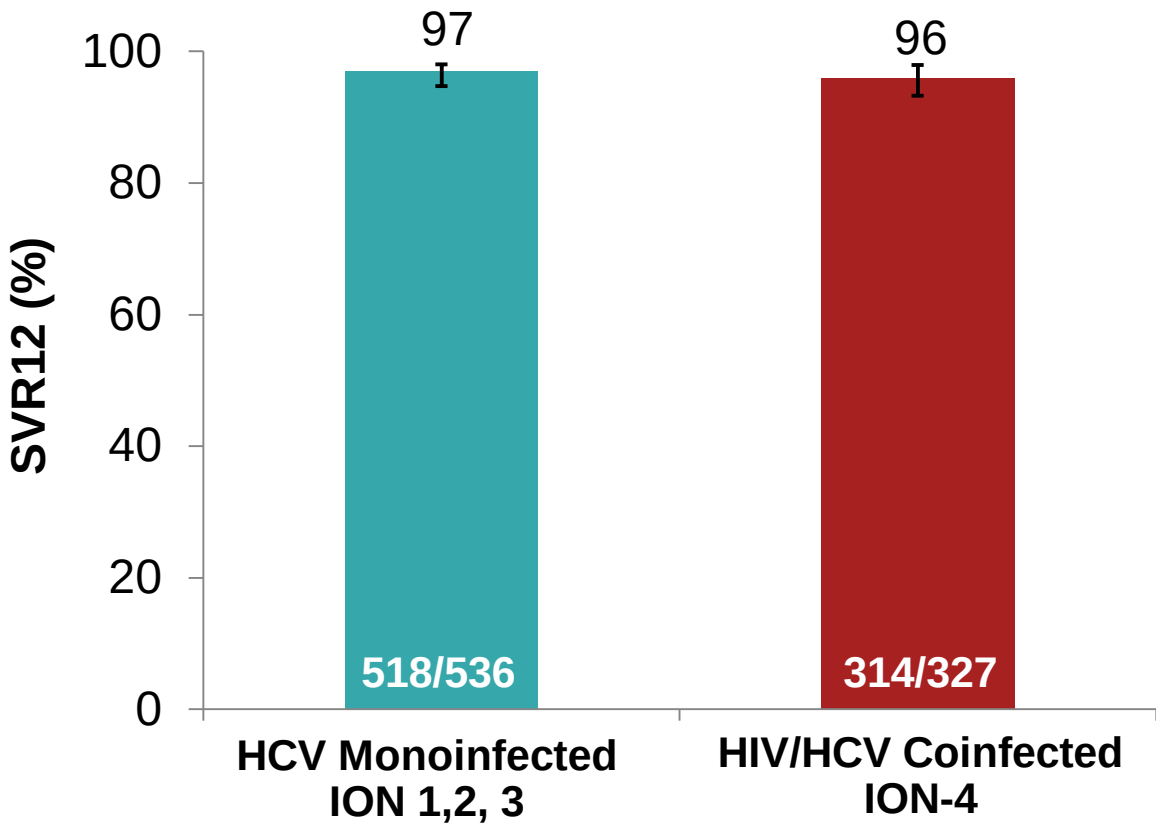


Demographics: ION Phase 3 Studies

Characteristic	LDV/SOF 12 weeks ION 1 n = 214*	LDV/SOF 12 weeks ION 2 n = 109	LDV/SOF 12 weeks ION 3 n = 216	LDV/SOF 12 weeks ION 1 - 3 n = 539*	LDV/SOF 12 weeks ION 4 n = 327
Mean age, years (range)	52 (18-75)	56 (24-67)	53 (20-71)	54 (18-71)	52 (26-72)
Mean BMI, kg/m^2 (range)	27 (18-41)	29 (19-47)	28 (19-45)	28 (18-47)	27 (18-66)
Male, n (%)	127 (59)	74 (68)	128 (59)	329 (61)	272 (83)
Race, n (%)					
Black	24 (11)	24 (22)	42 (19)	90 (17)	114 (35)
Hispanic	26 (12)	7 (6)	14 (7)	47 (9)	55 (17)
Cirrhosis	34 (16)	22 (20)		56 (10)	67 (20)
Mean HCV RNA, $\log_{10}$ IU/mL (SD)	6.4 (± 0.69)	6.5 (± 0.44)	6.4 (± 0.8)	6.4 (± 0.64)	6.7 (± 0.65)
HCV genotype 1a, n (%)	145 (68)	86 (79)	172 (80)	403 (75)	250 (76)
***IL28B* genotype Non-CC, n (%)**	159 (74)	99 (91)	160 (74)	474 (88)	247 (76)
Baseline ALT > 1.5 x ULN	119 (56)	53 (49)	99 (46)	271 (50)	135 (41)
Treatment experienced		109 (100)		109 (20)	181 (55)

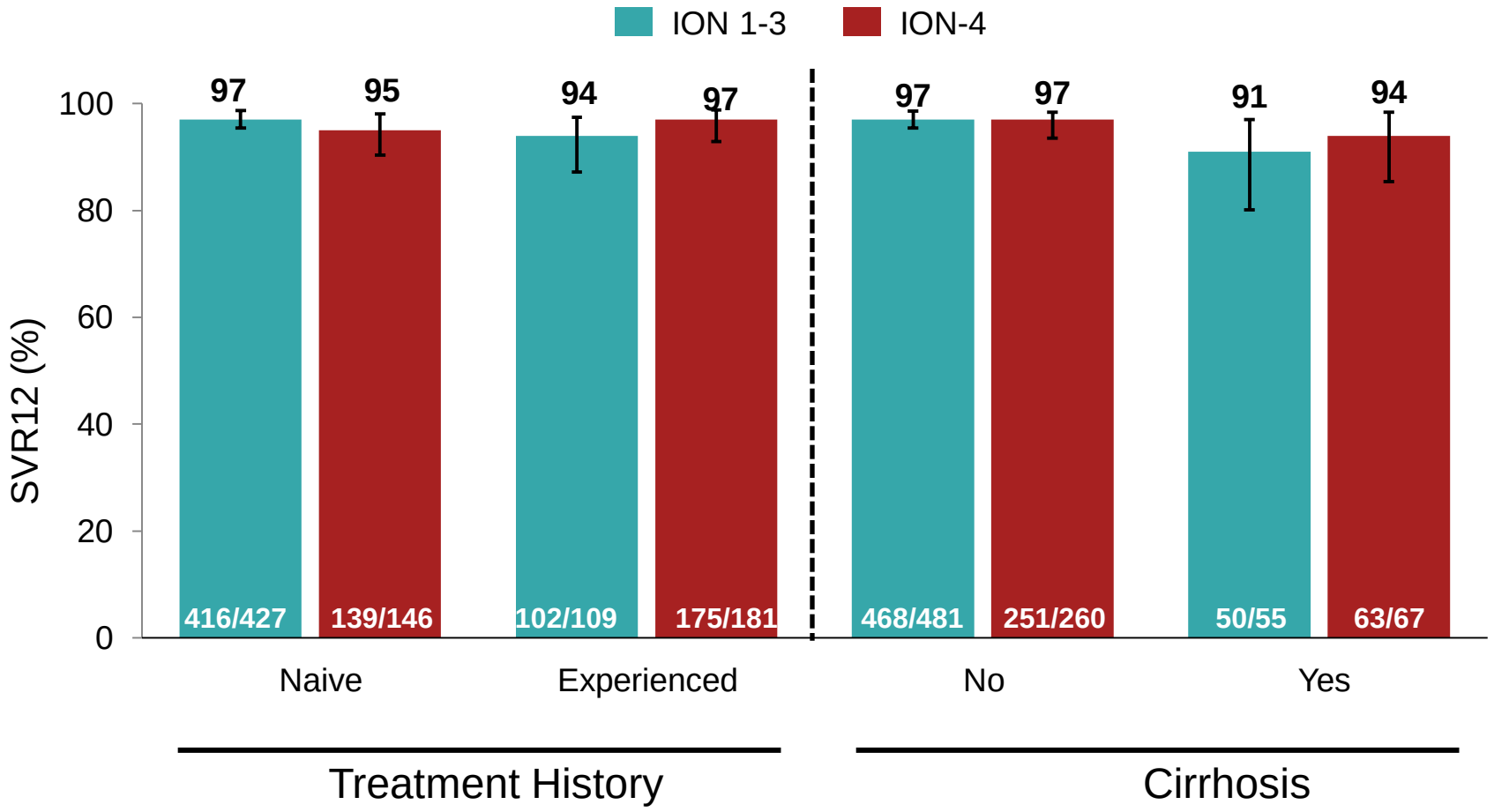
* Includes 1 GT4 patient and 2 patients with missing genotype

Results: Overall SVR12 in HCV Monoinfected and HIV/HCV Coinfected for GT1 Treated with LDV/SOF x 12 Weeks



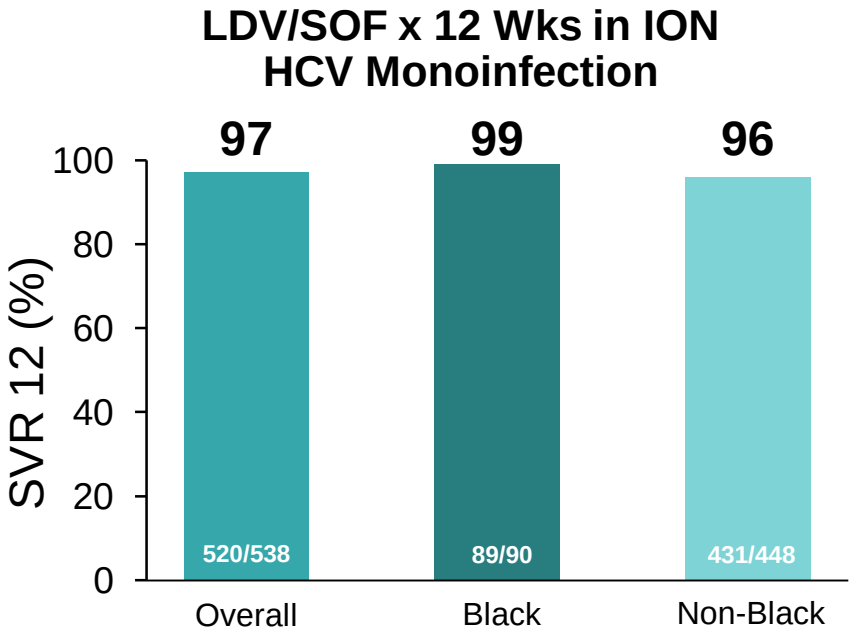
Similar response rates in HIV/HCV coinfected patients compared to HCV monoinfected patients

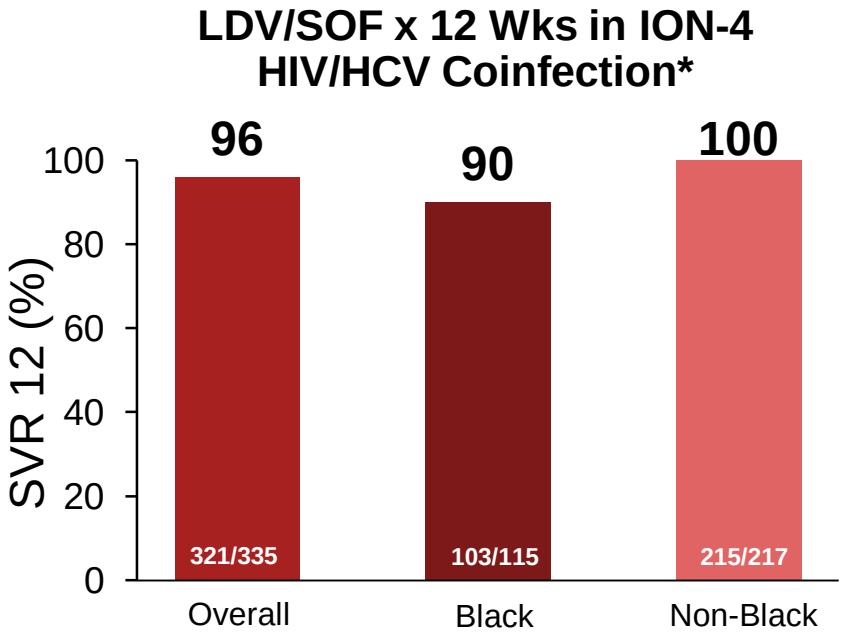
Results: SVR12 by Prior Treatment Experience and Cirrhosis Status



Comparable efficacy between monoinfected and HIV-1 coinfected

Results: SVR12 in Black and Non-Black Patients





- No difference in SVR in HCV monoinfected ION program (12 weeks) for black (89/90, 99%) versus non-black (431/448, 96%) treated with 12 weeks of LDV/SOF
- Overall in ION-4, 10 patients had virologic relapse. All ten were black, seven had the TT allele of the *IL28B* gene, and eight received efavirenz.
  - In the multivariate analysis, black race was identified as the only independent, statistically significant predictor of relapse.
  - A comprehensive genome-wide association study (GWAS) of LDV/SOF treatment relapsers in ION-4 revealed no significant genomic associations with HCV relapse.

* All patients who reported their race were included in the analysis.

ION-4: LDV/SOF x 12 weeks in HIV/HCV Coinfection§

Race Did Not Impact PK Parameters of LDV, SOF, and GS-331007

	Mean Parameter (%CV)*	Black n=115	Non-Black n=217	%GMR (90% CI)
LDV	AUC_{τ}, ng•h/mL	6160 (53.4)	5830 (54.4)	107 (96.9, 118)
	C_{max}, ng/mL	278 (48.6)	263 (48.3)	106 (97.2, 116)
	C_{τ}, ng/mL	183 (56.5)	167 (56.4)	111 (99.5, 123)
SOF	AUC_{τ}, ng•h/mL	1310 (23.1)	1330 (24.2)	98.3 (94.1, 103)
	C_{max}, ng/mL	716 (25.0)	685 (27.7)	106 (99.8, 112)
GS-331007	AUC_{τ}, ng•h/mL	12,900 (32.3)	13,600 (24.9)	93.2 (88.5, 98.1)
	C_{max}, ng/mL	814 (30.4)	845 (27.2)	95.2 (90.3, 100)

*PK parameters presented to 3 significant digits; 3 patients with undisclosed race information were excluded from analyses.

Pharmacokinetic analyses in ION-4 did not reveal clinically relevant differences in the concentrations of ledipasvir, sofosbuvir or GS-331007 based on race

90% CIs of %GMRs were within PK lack-of-alteration boundaries of 70–143%

Results are consistent with population PK findings from Phase 2/3 LDV/SOF program

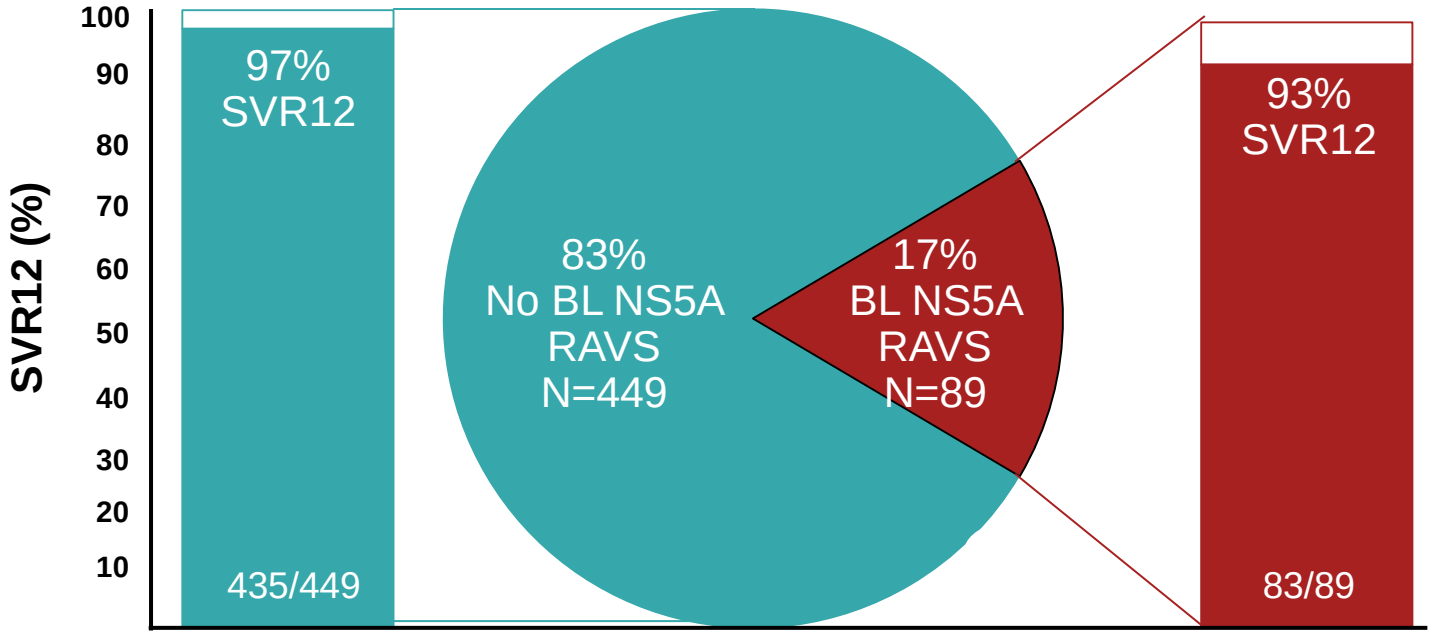
§ All patients who reported their race were included in the analysis

Reasons for Not Achieving SVR: ION Phase 3 Studies

Patients, n (%)	LDV/SOF 12 weeks ION 1 n = 214	LDV/SOF 12 weeks ION 2 n = 109	LDV/SOF 12 weeks ION 3 n = 216	LDV/SOF 12 weeks ION 1 - 3 n = 539	LDV/SOF 12 weeks ION 4 n = 327
SVR12	210 (99)	102 (94)	206 (95)	518 (96)	313 (96)
Breakthrough	0	0	0	0	2 (<1)
Relapse	1 (<1)	7 (6)	3 (1)	11 (2)	10 (3)
Lost to Follow-Up	2 (<1)	0	7 (3)	9 (<2)	1 (<1)*
Withdrew Consent	0	0	0	0	0
Deaths	0	0	0	0	1 (<1)*

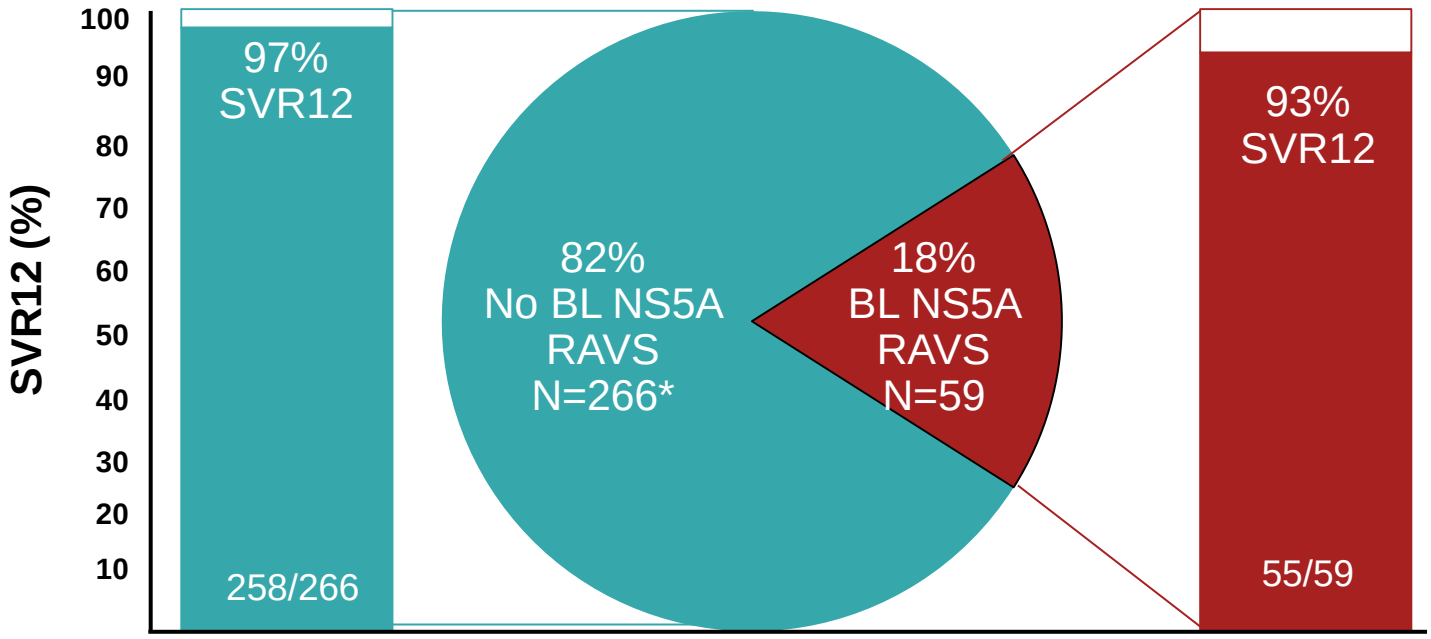
* One patient with confirmed IV drug user developed *Staphylococcus aureus* sepsis, endocarditis with associated embolic brain abscesses, and multi-organ system failure.

ION 1-3: SVR12 by Baseline NS5A Substitutions



- NS5A RAVs were observed in 10 of the 11 patients at time of virologic failure
- No NS5B S282T was observed in any patient at baseline or at time of virologic failure

ION-4: SVR12 by Baseline NS5A Substitutions



- NS5A RAVs were observed in 10 of the 12 patients at time of virologic failure (8 of 10 at time of relapse, 2 of 2 at time of viral breakthrough)
- No NS5B S282T was observed in any patient at baseline or at time of virologic failure

* Analysis done for all available samples and includes 8 GT4 patients.

LDV/SOF x 12 Weeks
Safety in HCV Monoinfected and HIV/HCV Coinfected

Patients, n (%)	LDV/SOF 12 weeks ION 1 n = 214	LDV/SOF 12 weeks ION 2 n = 109	LDV/SOF 12 weeks ION 3 n = 216	LDV/SOF 12 weeks ION 1 - 3 n = 539*	LDV/SOF 12 weeks ION 4 n = 335*
AEs	169 (79)	73 (67)	149 (69)	391 (73)	257 (77)
Grade 3–4 AEs	4 (2)	2 (2)	7 (3)	13 (2)	14 (4)
Serious AEs	1 (<1)	0	5 (2)	6 (1)	8 (2)
Treatment D/C due to AEs	0	0	2 (1)	2 (<1)	0
Death	0	0	0	0	1 (<1)
Grade 3–4 laboratory abnormality	10 (5)	5 (5)	16 (7)	31 (6)	36 (11)
Hemoglobin <10 g/dL	0	0	1 (<1)	1 (<1)	1 (<1)
Hemoglobin <8.5 g/dL	0	0	0	0	0

* Safety analysis done for all patients enrolled.

Common Adverse Events : ION Phase 3 Studies*

Patients, n (%)	LDV/SOF 12 weeks ION 1 n = 214	LDV/SOF 12 weeks ION 2 n = 109	LDV/SOF 12 weeks ION 3 n = 216	LDV/SOF 12 weeks ION 1 - 3 n = 539	LDV/SOF 12 weeks ION 4 n = 327
Headache	53 (25)	28 (26)	33 (15)	114 (21)	83 (25)
Fatigue	44 (21)	23 (21)	49 (23)	116 (22)	71 (21)
Diarrhea	24 (11)	7 (6)	9 (4)	40 (7)	36 (11)
Nausea	24(11)	13 (12)	24 (11)	61 (11)	33 (10)
Insomnia	17 (8)	10 (9)	15 (7)	42 (8)	0
Arthralgia	0	7 (6)	16 (7)	23 (4)	22 (7)

* Safety analysis done for all patients enrolled.

Discontinuation Rates:

0%	0%	<1%	<1%	0%
LDV/SOF ION 1 N=214*	LDV/SOF ION 2 N=109	LDV/SOF ION 3 N=216	**LDV/SOF** ION 1 - 3 N=539*	**LDV/SOF** ION 4 N=327

Conclusions

- Efficacy rates with 12 weeks LDV/SOF in HIV/HCV coinfected patients (SVR12 96%) were similar to those seen in HCV monoinfected patients (SVR12 97%).
  - Prior HCV treatment status or the presence or absence of cirrhosis did not impact outcome
  - LDV, SOF, and GS-331007 exposures were comparable in black and non-black subjects
- Safety profile of 12 weeks LDV/SOF in HIV/HCV coinfected patients was similar to HCV monoinfected patients.
  - Most common adverse events (>10% reported in any arm) were fatigue, headache, and nausea
  - No adverse impact on HIV disease (CD4 or HIV RNA) or on tolerability of antiretroviral therapy
- LDV/SOF represent a highly effective treatment option for patients with HIV/HCV coinfection and HCV monoinfection.

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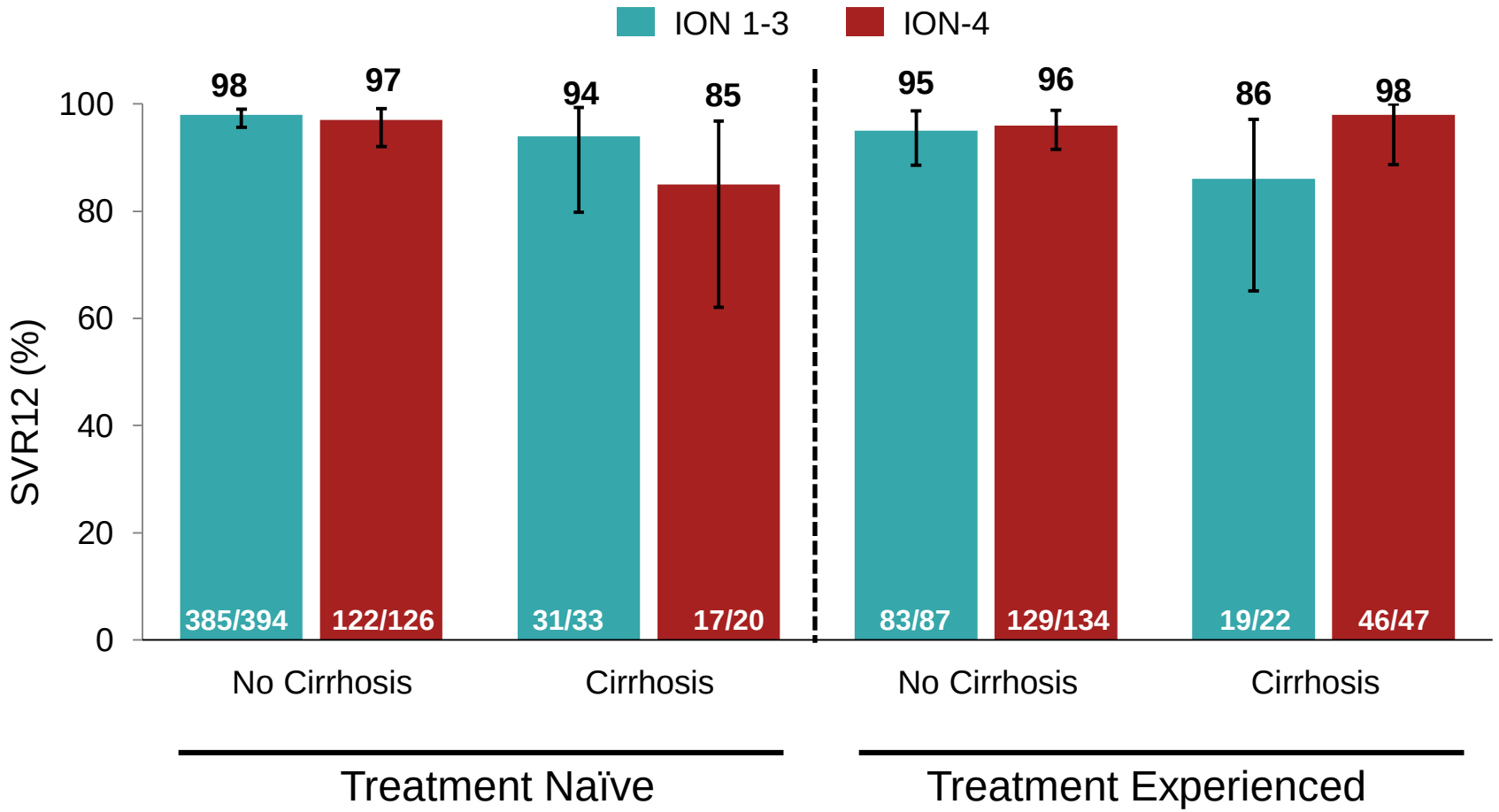
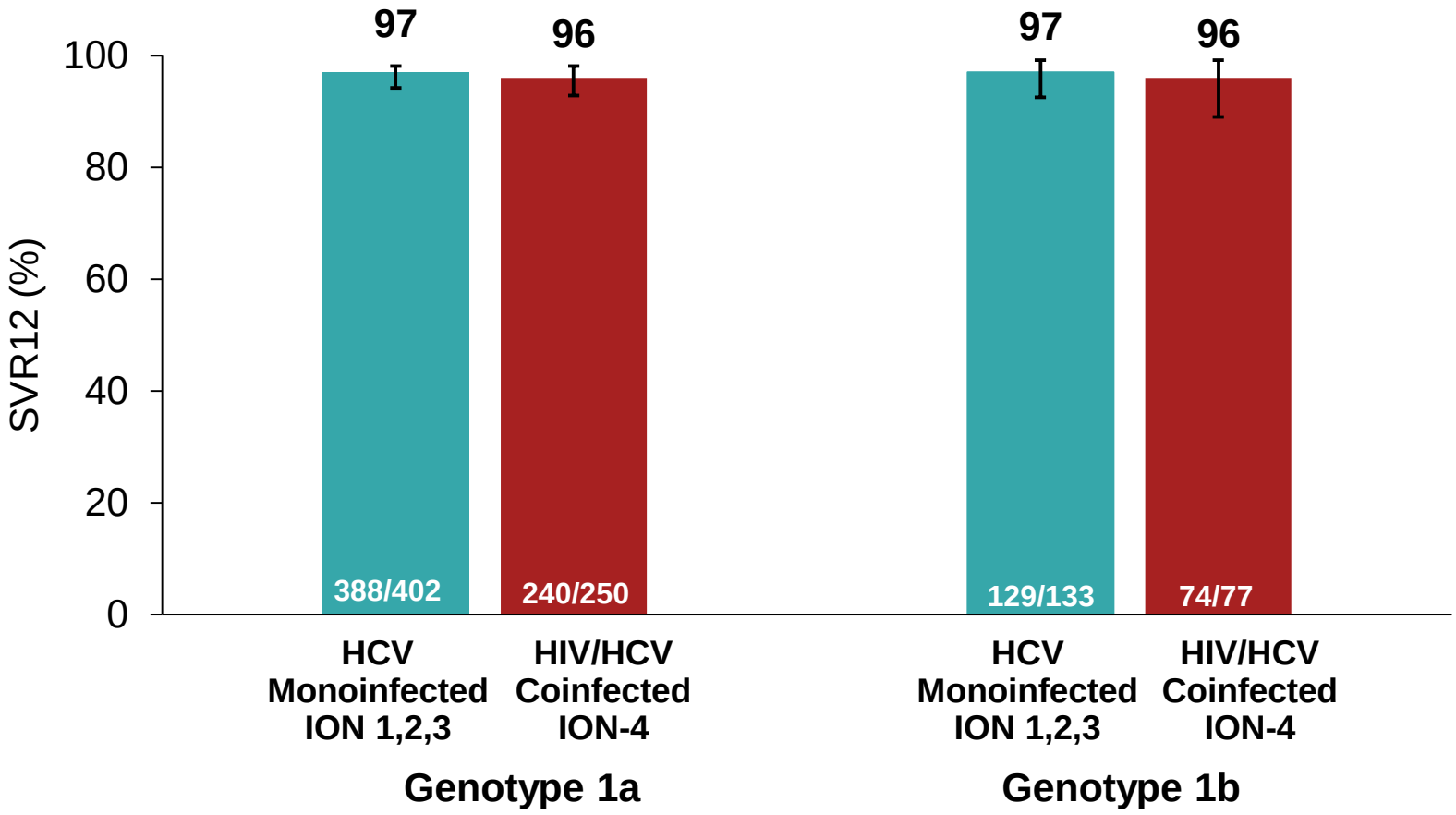
Back-Up

Results: SVR12 for Combined Treatment History and Cirrhosis Status



Results: SVR12 by Genotype 1 Subtype



Characteristics of Virologic Relapsers

Study	Age (years)	Sex	Race	Prior HCV Treatment	HCV Genotype	*IL28B*	NS5A RAVs at Baseline	NS5A RAVs Post-treatment
ION 1	56	M	White	N/A	1a	TT	L31M	L31M
ION 2	64	M	White	PI+Peg-IFN+RBV	1b	CT	None	L31M, Y93H
ION 2	62	M	White	Peg-IFN+RBV	1b	CT	None	L31V
ION 2	64	M	White	PI+Peg-IFN+RBV	1a	CT	None	Q30H, Y93H
ION 2	61	M	White	Peg-IFN+RBV	1b	CT	Y93H	Y93H
ION 2	58	F	White	PI+Peg-IFN+RBV	1a	CT	Q30R, Y93N	Y93N
ION 2	57	F	White	PI+Peg-IFN+RBV	1a	CT	M28T, Q30R, L31M	Q30R, L31M
ION 2	54	M	White	Peg-IFN+RBV	1a	CT	Q30H, Y93H	Q30H, Y93H
ION 3	56	M	Black	N/A	1b	TT	None	L31I, Y93H
ION 3	44	M	Black	N/A	1a	CT	Y93F, Y93N	Y93N
ION 3	51	M	Other	N/A	1a	CT	None	None
ION 4	35	M	Black	N/A	1a	CT	None	None
ION 4	58	M	Black	Peg-IFN+RBV	1a	TT	Y93F, Y93N	Y93N
ION 4	61	M	Black	N/A	1a	TT	L31M, Y93N	L31M, Y93N
ION 4	61	F	Black	Peg-IFN+RBV	1a	CT	None	L31M
ION 4	51	M	Black	NS5a+Peg-IFN+RBV	1a	TT	L31M, H58D	L31M, H58D
ION 4	65	F	Black	N/A	1b	TT	None	L31V
ION 4	60	M	Black	N/A	1a	CT	None	None
ION 4	63	M	Black	Peg-IFN+RBV	1a	TT	None	Y93N
ION 4	55	M	Black	Peg-IFN+RBV	1a	TT	None	Q30R, L31M, Y93H
ION 4	58	M	Black	Peg-IFN+RBV	1b	TT	Y93H	L31I, Y93H