Efficacy and safety of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: Analysis of Phase 3 ION trials

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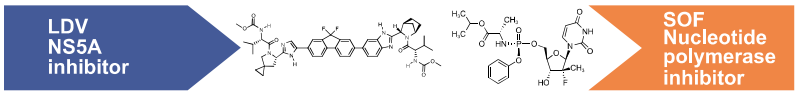
Ledipasvir/sofosbuvir for treatment of HCV infection



- **Ledipasvir**
  - Once-daily, oral, 90-mg NS5A inhibitor
- **Sofosbuvir**
  - Once-daily, oral, 400-mg NS5B inhibitor

- **LDV/SOF FDC**
  - Once-daily, oral, FDC (90/400 mg) tablet
  - Single-tablet regimen for HCV

FDC, fixed-dose combination; HCV, hepatitis C virus.

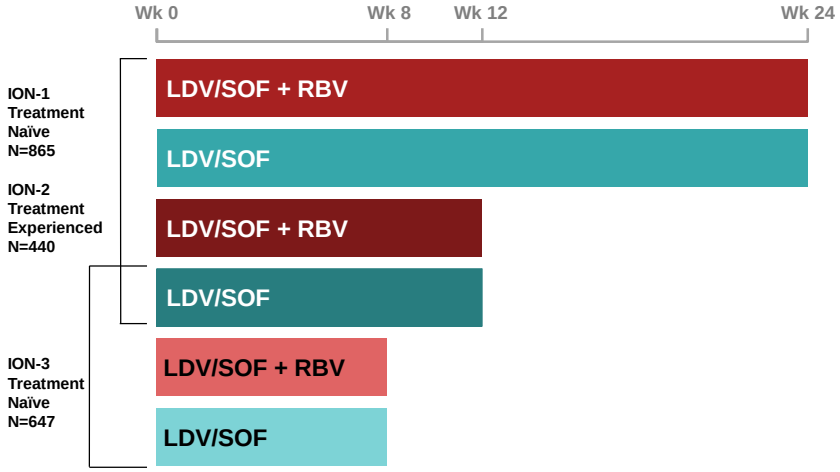
Treatment of HCV infection in people who use drugs

- The burden of HCV infection is growing, including among people on opioid substitution therapy (OST) and those with ongoing drug use
- Interferon-based HCV therapy in people receiving OST and people with ongoing drug use is effective, but is limited by its poor-tolerability
- Simple, tolerable, effective DAA HCV therapies have the potential to improve access for people on OST and people who use drugs
- There are little data on outcomes following DAA HCV therapy in people receiving OST or people who use drugs

Aims

- The aim of this post-hoc analysis of the Phase 3 ION trials was to evaluate the impact of OST and illicit drug use during therapy (tested retrospectively on stored serum samples) on treatment completion, adherence, sustained virologic response 12 weeks post-end of treatment (SVR12) and safety of ledipasvir/sofosbuvir ± ribavirin

LDV/SOF Phase 3 Program (ION-1, ION-2, ION-3)



RBV, ribavirin

Afdhal N, et al. *N Engl J Med* 2014; 370:1889-1898;
Afdhal N, et al. *N Engl J Med* 2014;370:1483-1493;
Kowdley K, et al. *N Engl J Med* 2014;370:1879-1888

Study Population

- A post-hoc analysis was performed using data from ION-1, -2 and -3
- Patients with HCV genotype (GT) 1, treatment naive, with/without compensated cirrhosis received 8, 12, or 24 weeks of LDV/SOF ± RBV
- Participants receiving OST (e.g. methadone or buprenorphine) were eligible for inclusion.
- Patients were excluded from the ION studies if they had clinically significant drug use within 12 months of screening (as assessed by the investigator) or non-cannabinoids detected by a positive urine drug test during the screening phase that was not explained by a prescription medication
- On-treatment screening for clinically significant drug use was not performed

Study Methods

- Stored serum samples from ION-1 retrospectively tested at Week 8 and 12 for illicit drugs (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, oxycodone, phencyclidine, propoxyphene and cannabinoids) by enzyme-linked immunosorbent assay
- 853 of 865 patients treated in the ION-1 study had Week 8 or Week 12 serum sample available for retrospective testing of drugs
- Treatment completion, adherence, SVR12, safety and reinfection were assessed
- Phylogenetic analyses were used to distinguish viral relapse from reinfection

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Demographics by Receipt of OST (ION 1-3)

	OST at enrollment (n = 70)	No OST at enrollment (n = 1882)
Mean (SD) age, years	47 (11)	53 (10)
Male sex, n (%)	48 (69)	1127 (60)
Race, n (%)		
White	63 (90)	1537 (82)
Black	6 (9)	302 (16)
Mean (SD) BMI	28 (6)	27 (5)
OST, n (%)		
Methadone	40 (57)	N/A
Buprenorphine	29 (41)	N/A
Naloxone*	2 (3)	N/A
HCV GT1a, n (%)	63 (90)	1380 (73)
IL28B CC, n (%)	28 (40)	455 (24)
Mean (SD) HCV RNA log10 IU/mL	6.4 (0.8)	6.4 (0.7)
Cirrhosis, n (%)	7 (10)	217 (12)
Treatment-experienced n (%)	8 (11)	432 (23)

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; OST, opioid substitution therapy; SD, standard deviation; ULN, upper limit of normal. *One patient was receiving naloxone plus methadone; one patient was taking naloxone following back surgery.

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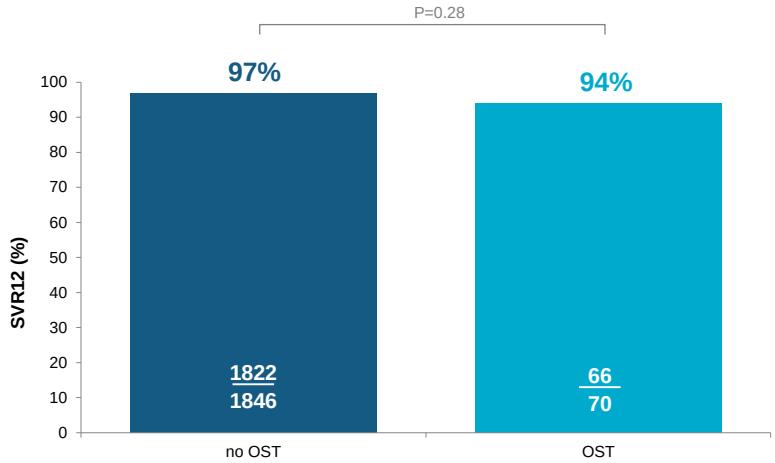
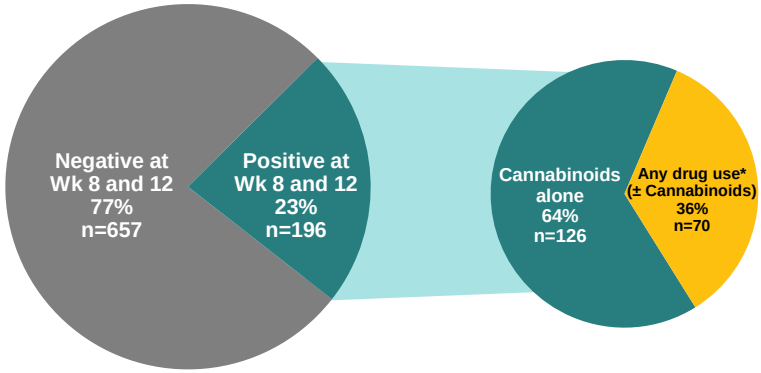
SVR12 by Receipt of OST (ION 1-3)



Outcomes – By OST Therapy At Baseline (ION1-3)

Characteristic	Treatment completion n (%)	≥80 adherence n (%)	SVR12 n (%)	Adverse events n (%)	Serious adverse events n (%)
Opioid substitution therapy					
No (n = 1,882)	1846 (98%)	1737 (92%)	1822 (97%)	1498 (80%)	49 (3%)
Yes (n = 70)	68 (97%)	65 (93%)	66 (94%)	62 (89%)	3 (4%)

Positive Drug Test without Prescription = Drug use (ION-1)



*Includes non-prescribed benzodiazepines (n=19, 27%),opiates/oxycodone/methadone (n=11, 16%), cocaine (n=9, 13%), methamphetamine/amphetamine (n=7, 10%), and barbiturates (n=7, 10%).

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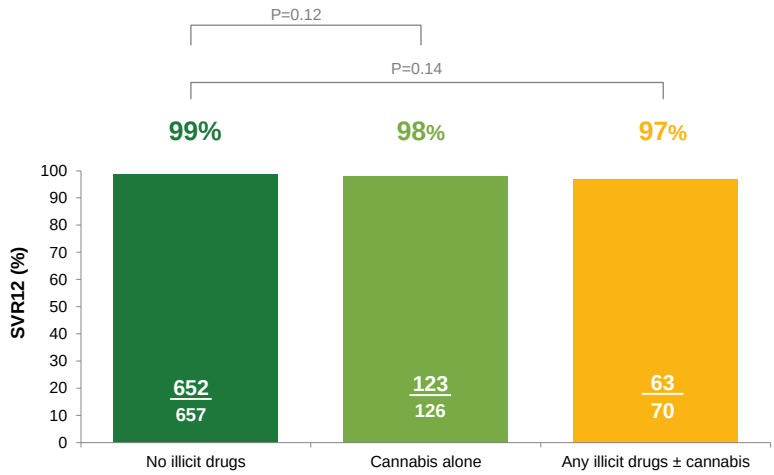
SVR12 by drug use during therapy (ION-1)



Outcomes – By Drug Use During Therapy (ION-1)

Characteristic	Treatment completion n (%)	≥80 adherence n (%)	SVR12 n (%)	Adverse events n (%)	Serious adverse events n (%)
Drug use during therapy					
None (n = 657)	643 (98%)	598 (91%)	652 (99%)	564 (86%)	27 (4%)
Cannabinoids only (n = 126)	124 (98%)	116 (92%)	123 (98%)	104 (83%)	2 (2%)
Illicit drugs ± cannabinoids (n = 70)	68 (97%)	64 (91%)	68 (97%)	63 (90%)	3 (4%)

- There were no cases of HCV reinfection observed in this study through 24 weeks after treatment completion

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Adverse Events

Adverse event, n (%)	OST at enrollment		No OST at enrollment	
	LDV/SOF (n = 48)	LDV/SOF + RBV (n = 22)	LDV/SOF (n = 1032)	LDV/SOF + RBV (n = 850)
Any	43 (90)	19 (86)	766 (74)	732 (86)
Serious	2 (4)	1 (5)	32 (3)	17 (2)
Most common (>10% in any treatment group)				
Fatigue	15 (31)	8 (36)	227 (22)	325 (38)
Headache	12 (25)	4 (18)	212 (21)	227 (27)
Nausea	9 (19)	8 (36)	103 (10)	145 (17)
Insomnia	5 (10)	4 (18)	78 (8)	150 (18)
Irritability	3 (6)	4 (18)	44 (4)	91 (11)
Asthenia	1 (2)	4 (18)	37 (4)	52 (6)
Decreased appetite	5 (10)	1 (5)	23 (2)	34 (4)
Back pain	4 (8)	3 (14)	40 (4)	38 (5)
Rash	3 (6)	3 (14)	45 (4)	91 (11)
Cough	3 (6)	1 (5)	39 (4)	90 (11)
Hypertension	2 (4)	3 (14)	24 (2)	19 (2)
Hemoglobin level <10 g/dL	0	1 (5)	1 (<0.1)	57 (7)

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Conclusions

- The ION clinical trials demonstrates that there is no difference in treatment completion, adherence, SVR12 and AEs among people receiving and not receiving OST or people who used illicit drugs who received treatment with LDV/SOF +/- RBV
- There were no cases of HCV reinfection observed in this study through 24 weeks after treatment completion
- Clinical trials evaluating interferon-free therapy among people who inject drugs (PWID) with recent drug use and/or those receiving OST are ongoing

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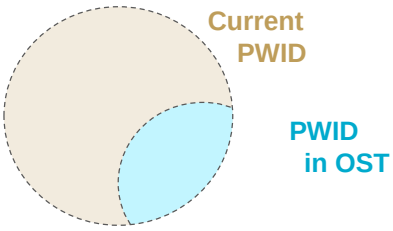
Future work

UNSW/Kirby Institute sponsored; Gilead funded; International open-label; n=100
GT1-6; treatment naïve; F0-4
Commenced enrolment March 2016 (110 screened, 103 enrolled)
Post-treatment follow-up for 3 years

simplify



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Acknowledgments

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- This study was funded by Gilead Sciences, Inc.

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Baseline Demographics Stratified by IDU (ION-1)

Characterisitc, n (%)	No illicit drugs (n = 657)	Cannabinoids only (n = 126)	Any illicit drugs ± cannabinoids (n = 70)
Mean (SD) age, years	53 (11)	51 (11)	51 (10)
Male sex	376 (57)	90 (71)	40 (57)
White race	553 (84)	109 (87)	64 (91)
OST	20 (3)	3 (2)	12 (17)
IFNL3 CC genotype	178 (27)	44 (35)	29 (41)
HCV genotype 1a	415 (63)	102 (81)	54 (77)
No cirrhosis	550 (84)	107 (85)	58 (83)

Abbreviations: HCV, hepatitis C virus; SD, standard deviation.

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