Efficacy and Safety of Sofosbuvir-Based Direct-Acting Antiviral Therapies for Hepatitis C Virus in Patients Receiving Opioid Substitution Therapy: An Analysis of Phase 3 Studies

Jason Grebely[1], Jordan J Feld[2], David Wyles[3], Mark Sulkowski[4], Liyun Ni[5], Joseph Llewellyn[5], Heshaam M. Mir[5], Nika Sajed[5], Luisa M. Stamm[5], Robert H. Hyland[5], John McNally[5], Diana M. Brainard[5], Ira Jacobson[6], Stefan Zeuzem[7], Marc Bourlière[8], Graham Foster[9], Nezam Afdhal[10], Gregory J Dore[1]

[1]The Kirby Institute, UNSW Sydney, Sydney, New South Wales, Australia; [2]Toronto Centre for Liver Disease, Toronto, Ontario, Canada; [3]Division of Infectious Diseases, Denver Health and Hospital Authority, Denver, Colorado, USA; [4]Johns Hopkins University, Baltimore, Maryland, USA; [5]Gilead Sciences, Inc., Foster City, California, USA; [6]Mount Sinai Beth Israel, New York; New York, USA; [7]Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Germany; [8]Hospital Saint Joseph, Marseille, France; [9]Queen Mary University London, London, UK; [10]Beth Israel Deaconess Medical Center, Boston Massachusetts, USA

Australasian Professional Society on Alcohol and other Drugs 2017 Conference
12-15 November
Melbourne, VIC, AUSTRALIA.

Disclosures

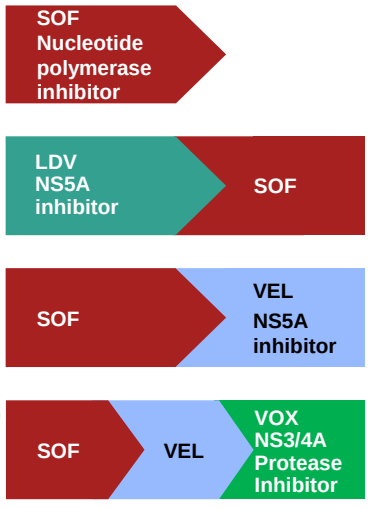
- JG is a consultant/advisor for and has received research grants from AbbVie, Cepheid, Gilead Sciences and Merck/MSD

Acknowledgments

- The authors thank the patients who participated in these studies.
- These studies were funded by Gilead Sciences, Inc.

Sofosbuvir-based therapy for treatment of HCV infection

- **Sofosbuvir (SOF)**
  - Once-daily, oral, 400-mg tablet used in combination with other medications
  - Potent antiviral activity against HCV genotypes (GT) 1–6
- **Ledipasvir (LDV)/Sofosbuvir (SOF)**
  - Once-daily, oral, fixed-dose combination (FDC, 90/400 mg) tablet
  - Single-tablet regimen (STR) for HCV GT 1, 4, 5, 6
- **Sofosbuvir/Velpatasvir (VEL)**
  - Once-daily, oral, FDC (400/100 mg) tablet
  - Pan-genotypic STR for HCV GT 1-6
- **Sofosbuvir/Velpatasvir/Voxilaprevir (VOX)**
  - Once-daily, oral, FDC (400/100/100 mg) tablet
  - Pan-genotypic STR for HCV GT 1-6



4

Treatment of HCV infection in people who use drugs

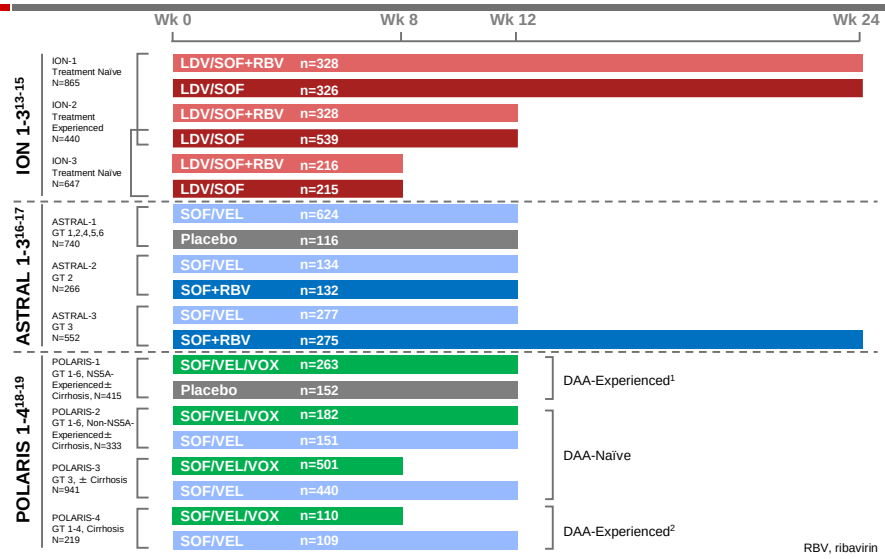
- The burden of HCV infection is growing, including among people on opioid substitution therapy (OST) and those with ongoing drug use
- Interferon-based HCV therapy in people receiving OST and people with ongoing drug use is effective, but is limited by its poor-tolerability
- Simple, tolerable, effective 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

Grebely J, Hazarizadeh B, and Dore GJ. *Nature Reviews in Gastroenterology & Hepatology* 2017

Objective

- The aim of this post-hoc analysis of Phase 3 studies of sofosbuvir-based therapy was to evaluate treatment completion, adherence, SVR12 and safety of sofosbuvir-based therapy (including sofosbuvir/velpatasvir/voxilaprevir) in patients receiving OST and not receiving OST

ION, ASTRAL, POLARIS Study Designs



1. Patients who had previously received a regimen containing an NS5A inhibitor
2. Patients who had previously received a DAA regimen but not an NS5A inhibitor

Study Population

- Phase 3 trials: ION-1, -2 and -3; ASTRAL-1, -2 and -3; and POLARIS-1, -2, -3 and -4
  - Participants receiving OST (e.g. methadone or buprenorphine) were eligible for inclusion
  - Patients were excluded from enrolment in these studies if they had clinically significant drug use within 12 months of screening (as assessed by the investigator) or illicit drug use (excluding cannabinoids) detected by a positive urine drug test during the screening phase that was not explained by a prescription medication

Study Methods

- Post-hoc analysis of Phase 3 trials
- Endpoints included treatment completion, adherence, SVR12, safety, and reinfection
- Adherence was measured by counting the number of unused tablets in the returned bottles to derive the number of administrated tablets
- Participants were monitored for recurrence (viral relapse or reinfection) at 4 weeks, 12 weeks (SVR12), and 24 weeks (SVR24) following the completion of treatment
- Phylogenetic analyses were used to distinguish viral relapse from reinfection

9

Baseline Demographics I

	OST at enrollment (N=194)	No OST at enrollment (N=4549)
Mean Age (SD)	48 (10.7)	54 (10.4)
Male Sex, n (%)	141 (73)	2770 (61)
HCV Genotype, n (%)*		
1a	84 (43)	2109 (46)
1b	12 (6)	816 (18)
2	14 (7)	409 (9)
3	74 (38)	787 (17)
4	10 (5)	269 (6)
5	0	54 (1)
6	0	86 (2)
Mean (SD) HCV RNA $\log_{10}$ IU/mL	6.3 (0.7)	6.3 (0.7)
HCV RNA ≥800,000 IU/mL, n (%)	142 (73)	3456 (76)
Cirrhosis, n (%)	70 (36)	1041 (23)

*19 patients were classified as other, unknown, or missing and all were not receiving OST at enrolment
Abbreviations: HCV, hepatitis C virus; OST, opioid substitution therapy; SD, standard deviation

Baseline Demographics II

	OST at enrollment (N=194)	No OST at enrollment (N=4549)
Treatment-experienced, n (%)	42 (22)	1568 (34)
Therapy		
Ledipasvir/sofosbuvir + ribavirin (8 weeks)	8 (4)	423 (9)
Ledipasvir/sofosbuvir + ribavirin (12 weeks)	32 (17)	835 (18)
Ledipasvir/sofosbuvir + ribavirin (24 weeks)	13 (7)	641 (14)
Sofosbuvir/velpatasvir (12 weeks)	92 (47)	1643 (36)
Sofosbuvir/velpatasvir/voxilaprevir (8 weeks)	41 (21)	570 (13)
Sofosbuvir/velpatasvir/voxilaprevir (12 weeks)	8 (4)	437 (10)
OST at Enrollment, n (%)		
Methadone	113 (58)	-
Buprenorphine	35 (18)	-
Buprenorphine/Naloxone	40 (21)	
Other	6 (3)	-

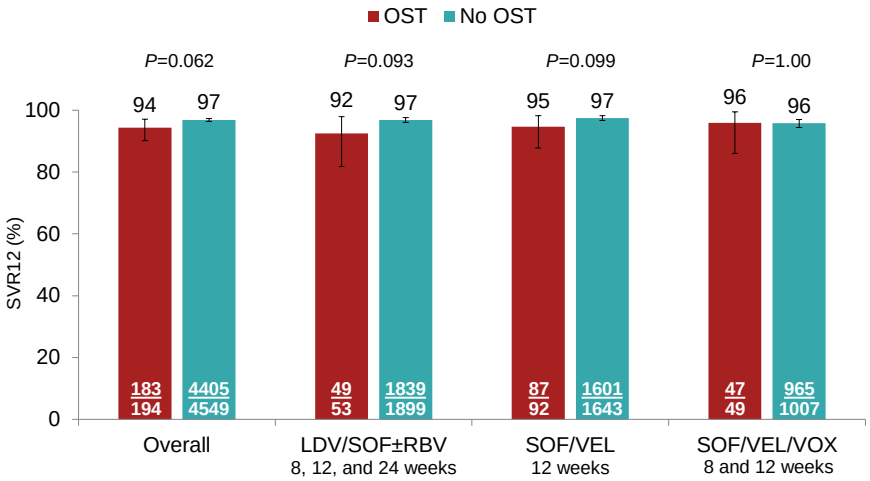
Abbreviations: HCV, hepatitis C virus; OST, opioid substitution therapy; SD, standard deviation

Treatment Completion

Characteristic	OST at enrollment	No OST at enrollment	*P*
Overall, % (n/N) [a]	189/194 (97.4)	4501/4549 (98.9)	0.06
Ledipasvir/sofosbuvir + ribavirin, % (n/N)	51/53 (96.2)	1863/1899 (98.1)	0.28
Sofosbuvir/velpatasvir, % (n/N)	89/92 (96.7)	1634/1643 (99.5)	0.02
Sofosbuvir/velpatasvir/voxilaprevir, % (n/N)	49/49 (100.0)	1004/1007 (99.7)	1.00

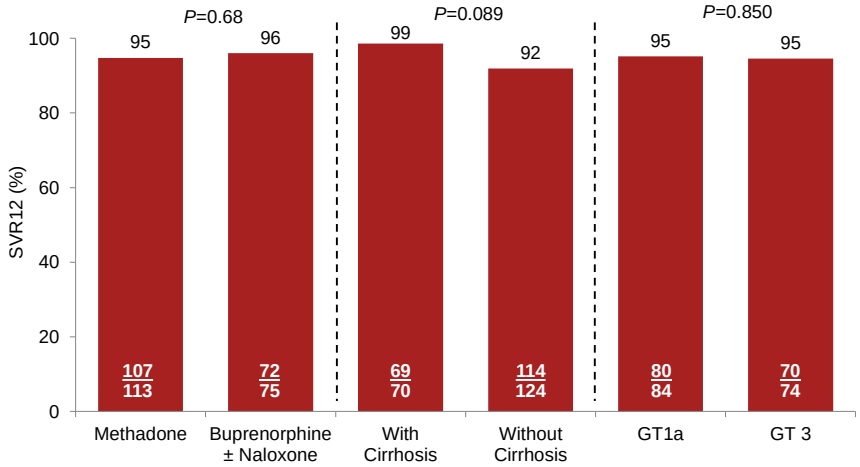
[a]The reasons for treatment discontinuation among patients receiving OST (n=5) included AEs (n=1); lost to follow-up (n=1); consent withdrawal (n=1); lack of efficacy (n=1); and non-compliance (n=1). The reasons for treatment discontinuation among patients not receiving OST (n=48) included AEs (n=19); lost to follow-up (n=10); consent withdrawal (n=6); protocol violation (n=6); lack of efficacy (n=4); non-compliance (n=1); and pregnancy (n=2).

SVR12: Overall and by Treatment Regimen (Intention-to-Treat Analysis)



Overall, and by regimen, there was no significant difference in SVR12 between those who were and were not receiving OST therapy

SVR12 in OST Group:* by OST Type, Cirrhosis Status and GT 3 vs. GT 1a (Intention-to-Treat Analysis)



Patients receiving OST therapy achieved high SVR12 regardless of type of OST, cirrhosis status or if the patient had GT1a or GT3

*Pooled data across treatment regimens and durations

Adverse Events

Characteristic	OST at enrollment	No OST at enrollment	*P*
Overall, % (n/N)			
Adverse events	152/194 (78.4)	3517/4549 (77.3)	0.79
Severe adverse events	7/194 (3.6)	108/4549 (2.4)	0.24
Ledipasvir/sofosbuvir + ribavirin			
Adverse events	47/53 (88.7)	1513/1899 (79.7)	0.12
Severe adverse events	2/53 (3.8)	50/1899 (2.6)	0.65
Sofosbuvir/velpatasvir			
Adverse events	68/92 (73.9)	1251/1643 (76.1)	0.62
Severe adverse events	4/92 (4.3)	33/1643 (2.0)	0.13
Sofosbuvir/velpatasvir/voxilaprevir			
Adverse events	37/49 (75.5)	753/1007 (74.8)	1.00
Severe adverse events	1/49 (2.0)	25/1007 (2.5)	1.00

Adverse Events in >10% of Subjects

Adverse event, n (%)	OST at enrollment			No OST at enrollment		
	Ledipasvir/ sofosbuvir ± ribavirin (n=53)	Sofosbuvir/ velpatasvir (n=92)	Sofosbuvir/ velpatasvir/ voxilaprevir (n=49)	Ledipasvir/ sofosbuvir ± ribavirin (n=1899)	Sofosbuvir/ velpatasvir (n=1643)	Sofosbuvir/ velpatasvir/ voxilaprevir (n=1007)
Adverse events in >10%						
Headache	12 (22.6)	20 (21.7)	8 (16.3)	443 (23.3)	450 (27.4)	269 (26.7)
Fatigue	19 (35.8)	18 (19.6)	11 (22.4)	556 (29.3)	364 (22.2)	222 (22.0)
Nausea	12 (22.6)	14 (15.2)	12 (24.5)	253 (13.3)	184 (11.2)	150 (14.9)
Diarrhea	4 (7.5)	7 (7.6)	5 (10.2)	151 (8.0)	110 (6.7)	183 (18.2)
Insomnia	5 (9.4)	5 (5.4)	3 (6.1)	232 (12.2)	112 (6.8)	59 (5.9)
Vomiting	4 (7.5)	6 (6.5)	6 (12.2)	60 (3.2)	42 (2.6)	24 (2.4)

Reinfection

- Two subjects were found to have reinfection with a different genotype than at baseline. Neither subject was receiving OST at baseline.
- One patient enrolled in ASTRAL-3 had genotype 3a at baseline and received SOF/VEL for 12 weeks. The patient achieved SVR4 and was found to have genotype 1a 12 weeks after the completion of therapy
- Another patient enrolled in POLARIS-2 had genotype 1a and received SOF/VEL for 12 weeks. The patient achieved SVR12, but was found to have genotype 3a 24 weeks after therapy

Conclusions

- This post hoc analysis of sofosbuvir-based therapies from the ION, ASTRAL, and POLARIS studies demonstrated high SVR12 rates among patients receiving OST, including those with HCV genotype 3 receiving sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir
- Similar treatment completion, SVR12, and AE rates were observed among patients with chronic HCV genotypes 1-6 receiving and not receiving OST
- Collectively, these data add to the body of evidence supporting the efficacy and safety of DAA treatment for HCV among people receiving stable OST, consistent with international recommendations