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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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Key points

In this post-hoc analysis of the Phase 3 ION trials evaluating HCV therapy with ledipasvir/sofosbuvir ± ribavirin, current opioid substitution therapy and ongoing drug use during therapy did not impact treatment completion, adherence, sustained virologic response, and safety.

Abstract

Background: Interferon-based HCV therapy is safe and effective among people receiving opioid substitution therapy (OST), but treatment uptake remains low. The aim of this post-hoc analysis was to evaluate the impact of OST and drug use during therapy on completion, adherence, sustained virologic response (SVR12) and safety of ledipasvir/sofosbuvir ± ribavirin.

Methods: The Phase 3 ION studies evaluated a fixed-dose combination of ledipasvir/sofosbuvir ± ribavirin administered for 8/12/24 weeks in patients with chronic HCV genotype 1. People with clinically significant drug use (prior 12 months) or non-cannabinoids detected at screening by urine drug tests (not explained by prescriptions) were ineligible. Stored samples were available from ION-1 for retrospective testing for illicit drugs by ELISA.

Results: Among 1952 patients enrolled in the ION studies, 4% (n=70) were receiving OST. Among those receiving (n=70) and not receiving OST (n=1882), there was no difference in treatment completion (97% vs 98%, *P*=0.40) ≥80% adherence (93% vs 92%, *P*=1.00), SVR12 (94% vs 97%, *P*=0.28), and serious AEs (4% vs 3%, *P*=0.43), respectively. Among participants in the ION-1 trial, 23% (n=196) used illicit drugs during therapy (15%

cannabinoids alone; 8% other illict drugs ± cannabinoids). There was no difference in treatment completion, ≥80% adherence, SVR12 or serious AEs in those with no drug use during treatment compared with those who used cannabinoids and/or other illicit drugs. No cases of HCV reinfection were observed in the 24 weeks following treatment.

Conclusions: OST and drug use during HCV therapy did not impact treatment completion, adherence, SVR12 or safety.

INTRODUCTION

Hepatitis C virus (HCV) infection disproportionally affects people who inject drugs (PWID) [1]. The burden of HCV-related liver disease is increasing among PWID, particularly among older individuals who have been infected for many years [1]. For recent initiates into drug injecting, the risk of acquiring HCV is high and HCV transmission continues among PWID in many settings [2-4] . Therefore, effective HCV treatment for PWID is necessary to prevent the development and progression of liver disease and stop onward transmission [5, 6]. Strategies enhancing HCV testing, linkage to care and treatment are needed.

People with a history of injecting drug use include former injectors who have ceased injecting and "recent PWID" (definitions for "recent" vary from one month to 12 months) [7]. People with a history of injecting drug use may also be receiving opioid substitution therapy (OST, methadone or buprenorphine) for management of opioid dependence, some of whom may also have recently injected drugs.

Interferon-based therapy is safe and effective among those with a history of injecting drug use, people receiving OST and those with recent drug use prior to or during therapy, with

responses similar to that observed in large clinical trials [8-10]. However, data are lacking on HCV treatment outcomes with interferon-free direct-acting antiviral agents (DAAs) among PWID receiving OST or people with illicit drug use during HCV therapy.

Many payers in the United States have implemented restrictions excluding those who have recently used illicit drugs, injecting drugs, or are receiving OST from interferon-free HCV therapies (irrespective of disease stage) [11]. An argument used for restricting access has been the lack of data on treatment outcomes with interferon-free HCV therapies in these populations. However, this is not consistent with international guidelines from the American Association for the Study of Liver Disease (AASLD)/Infectious Diseases Society of America (IDSA), the European Study for the Association of the Liver (EASL), the International Network for Hepatitis in Substance Users (INHSU), and the World Health Organization (WHO), all of whom recommend interferon-free HCV treatment for PWID [5, 12-15] and suggest PWID should be prioritized given the potential to reduce transmission [6]. Interferon-free DAA HCV therapy for recent PWID is also cost-effective, given the prevention benefits [16].

The Phase 3 ION trials evaluated the efficacy and safety of ledipasvir/sofosbuvir ± ribavirin in patients with chronic genotype 1 HCV infection [17-19]. People receiving stable OST were eligible for inclusion, but people with clinically relevant illicit drug use within 12 months of screening were excluded from study participation (confirmed by urine drug test). However, illicit drug use in the period following treatment initiation did not lead to subsequent discontinuation from these trials. Although these clinical trial populations are highly selected, included people on stable OST, excluded people with recent drug use, and may not be

representative of recent PWID populations, there is a paucity of data on interferon-free DAA therapy among people receiving OST.

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.

METHODS

Study Participants and Design

From October 17, 2012, to June 19, 2013, participants were enrolled in three international, multicentre, randomized open-label trials at sites in the United States, France, Germany, Italy, Spain and the United Kingdom, including ION-1 (ClinicalTrials.gov identifier: NCT01701401) [17], ION-2 (ClinicalTrials.gov identifier: NCT01768286) [18], and ION-3 (ClinicalTrials.gov identifier: NCT01851330) [19].

A fixed-dose combination tablet of ledipasvir/sofosbuvir 90 mg/400 mg was administered for 8, 12 or 24 weeks ± ribavirin in patients with chronic HCV genotype 1 infection. Twice daily ribavirin dose was given according to body weight (1000 mg daily <75 kg and 1200 mg daily ≥75 kg).

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. The designs and results of these studies have been described previously [17-19].

Stored serum samples from treatment-naïve HCV genotype 1-infected patients enrolled in ION-1 collected at Weeks 8 and 12 of treatment with ledipasvir/sofosbuvir ± ribavirin were available for retrospective testing for illicit drugs (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, oxycodone, phencyclidine, propoxyphene and cannabinoids) by enzyme-linked immunosorbent assay (ELISA) (Immunalysis, Pomona, United States). Only samples from ION-1 were tested. Information on retrospective testing for illicit drugs was compared to recorded concomitant medications to ensure that individuals who were receiving prescribed medications were not classified as having used illicit drugs (e.g. methadone, buprenorphine, benzodiazepines, barbiturates, opiates, oxycodone, amphetamines, methamphetamines, and cannabinoids).

Study Endpoints

In this analysis, the endpoints included treatment completion, adherence (≥80% of doses), SVR12, safety (adverse events [AEs] serious AEs, and hemoglobin level <10 g/dL), and reinfection. The analysis population included all randomized patients who received ≥1 dose of ledipasvir/sofosbuvir ± ribavirin. Adherence was calculated by dividing the number of total doses received during therapy (determined by pill counts at Week 4, 8, and 12 [where applicable] study visits) by the total expected number of doses. SVR12 was defined as the absence of quantifiable HCV RNA in serum (<25 IU/mL) measured by COBAS® TaqMan® HCV Test, v2.0 (Roche Molecular Systems) at 12 weeks after the end of study treatment. Participants were monitored for recurrence (viral relapse/reinfection) at 4 weeks, 12 weeks (SVR12), and 24 weeks (SVR24) following the completion of treatment. Deep sequencing of

the HCV NS5A and NS5B genes were performed for all patients at baseline and again for all patients with virologic failure in samples obtained at the first timepoint of failure with an HCV RNA >1000 IU/mL [17-19]. Phylogenetic analyses were used to distinguish viral relapse from reinfection.

Statistical Analysis

Descriptive statistics, including means, frequencies, and percentages (with 95% confidence intervals [CIs] for SVR12), were used to summarize the data. The proportion of participants with treatment completion, ≥80% adherence, SVR12, and AEs were compared among people receiving and not receiving OST. Further, the proportion of participants with treatment completion, ≥80% adherence, SVR12, and AEs were compared among people with no illicit drug use, canniboid use only, and illicit drug use (including cannabinoid use) during HCV therapy in the ION-1 study. Comparisons were made using a 2-sided Fisher's exact test. All *P* values are two-sided; a level of 0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participant Characteristics

Of the 1952 patients enrolled and treated in the ION trials (ION-1, n=865; ION-2, n=440; ION-3, n=647), 70 (4%) were receiving OST at enrolment. The clinical characteristics of the study participants are shown in Table 1. Among people receiving OST, 69% (n=48) of participants received ledipasvir/sofosbuvir, 31% (n=22) received ledipasvir/sofosbuvir + ribavirin, 90% (n=63) had no cirrhosis, and 89% (n=62) were treatment-naïve. Among those not receiving OST, 55% (n=1032) of participants received ledipasvir/sofosbuvir, 45%

(n=850) received ledipasvir/sofosbuvir + ribavirin, 88% (n=1660) had no cirrhosis, and 77% (n=1450) were treatment-naïve.

Among the 865 patients treated with ledipasvir/sofosbuvir ± ribavirin in the ION-1 study, 853 patients had a Week 8 or Week 12 serum sample available for retrospective testing of drugs (Table 2). Overall, 15% (126/853) tested postitive for cannibinoids alone and 8% (70/853) tested positive for any drug use not explained by prescribed medications (± cannabinoids). Among those testing positive for any drug use not explained by prescribed medications (± cannabinoids), this included 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%). The baseline characteristics stratified by drug use during therapy were similar in the three groups (Table 3).

HCV Treatment Completion

The proportion of participants completing HCV therapy was 97% (68/70; 95% CI: 90% to >99%) among participants receiving OST, compared to 98% (1846/1882; 95% CI: 97% to 99%) among those not receiving OST (P = 0.40, Table 4). The reasons for treatment discontinuation among people receiving OST (n = 2) included one participant who withdrew consent and one participant with lack of efficacy. The reasons for treatment discontinuation among people not receiving OST (n = 36) included AEs (n = 13), consent withdrawal (n = 6); protocol violation (n = 6); lack of efficacy (n = 1); non-compliance (n = 1); pregnancy (n = 1); and lost to follow-up (n = 8). The proportion of participants completing HCV therapy was similar among those with no illicit drug use during therapy (98%, 95% CI: 96% to 99%;

Table 4) compared with those with cannabinoid use only (98%, 95% CI: 94% to >99%; *P* = 1.00) or those with any illicit drugs ± cannabinoids (97%, 95% CI: 90% to >99%; *P* = 0.66).

HCV Treatment Adherence

The proportion of participants with ≥80% adherence to therapy was 93% (65/70; 95% CI: 84% to 98%) among participants receiving OST, compared to 92% (1737/1882; 95% CI: 91% to 93%) among those not receiving OST (*P* = 1.00, Table 3). The proportion of participants with ≥80% adherence to therapy was similar among those with no illicit drug use during therapy (91%, 95% CI: 89% to 93%; Table 4) compared to those with cannabinoid use only (92%, 95% CI: 86% to 96%; *P* = 0.86) or those with any illicit drugs ± cannabinoids (91%, 95% CI: 82% to 97%; *P* = 1.00).

HCV Treatment Outcomes

Among all participants receiving ledipasvir/sofosbuvir (± ribavirin), the proportion with SVR12 among those receiving OST (94%, 95% CI: 86% to 98%) was similar to those not receiving OST (97%, 95% CI: 96% to 98%; *P* = 0.28, Table 3). SVR12 stratified by treatment duration for participants receiving and not receiving OST is shown in Figure 1. There was no difference in SVR12 in those receiving methadone and buprenorphine, respectively [95% (95% CI: 83% to 99%) vs. 93% (95% CI: 77% to 99%), *P* = 1.00]. The proportion of participants with SVR12 was similar among those no illicit drug use during therapy (99%, 95% CI: 98% to >99%; Table 4) compared to those with cannabinoid use only (98%, 95% CI: 93% to >99%; *P* = 0.12) or those with any illicit drugs ± cannabinoids (97%, 95% CI: 90% to >99%; *P* = 0.14). Among those with any illicit drugs ± cannabinoids (n=70), there was no difference in SVR12 among those receiving and not receiving OST [100% (95% CI: 74% to 100%) vs. 97% (95% CI: 88% to >99%), *P* = 1.00).

Safety

The proportion with AEs [89% (95% CI: 79% to 95%) vs 80% (95% CI: 78% to 81%), *P* = 0.07; Tables 4 and 5] and serious AEs [4% (95% CI: 1% to 12%) vs 3% (95% CI: 2% to 3%), *P* = 0.43, Tables 4 and 5) were similar among participants receiving and not receiving OST. AEs were mostly mild or moderate in severity. Hemoglobin levels <10 g/dL were mainly limited to those who received ledipasvir/sofosbuvir + ribavirin, in those receiving and not receiving OST (5% vs 7%, *P* = 1.00). The proportion of participants with AEs was similar among those with no illicit drug use during therapy (86%, 95% CI: 83% to 88%; Table 4) compared to those with cannabinoid use only (83%, 95% CI: 75% to 89%; *P* = 0.34) or those with any illicit drugs and cannabinoids (90%, *P* = 0.46). The proportion of participants with serious AEs was similar among those with no illicit drug use during therapy (4%, 95% CI: 3% to 6%; Table 4) compared to those with cannabinoid use only (2%, 95% CI: <1% to 6%; *P* = 0.21) or those with any illicit drugs ± cannabinoids (4%, 95% CI: 1% to 12%; *P* = 1.00).

HCV Reinfection

There were no cases of documented reinfection or relapse between post-treatment week 12 and post-treatment week 24.

DISCUSSION

This post-hoc analysis of data from the ION clinical trials demonstrates that there is no difference in treatment completion, adherence, SVR12 and AEs among people receiving and not receiving OST who received treatment with ledipasvir/sofosbuvir ± ribavirin. Further, among people without drug use at the time of therapy initiation, subsequent illicit drug use

during therapy did not have a major impact on treatment completion, adherence, SVR12 and AEs. These findings support current international clinical recommendations supporting HCV treatment for PWID receiving OST [5, 12-15].

In this analysis, there were no differences in the proportion with treatment completion or adherence among people receiving OST or those with illicit drug use during ledipasvir/sofosbuvir therapy. The comparable completion and adherence in this post-hoc analysis are consistent with previous data demonstrating similar treatment completion and adherence to interferon-based HCV therapy among people receiving OST and those with ongoing illicit drug use as compared to people without drug use [8-10, 20]. In a meta-analysis of interferon-based studies among PWID, engagement in addiction treatment was associated with higher treatment completion [10]. Further efforts are needed to expand the integration of interferon-free HCV therapy in drug and alcohol clinics and community health clinics that also provide OST.

The proportion of participants with SVR12 was >97% across all treatment regimens and durations among participants receiving and not receiving OST. Further, there was no impact of ongoing drug use during therapy on SVR12. Treatment was also well-tolerated. The comparable SVR12 and reported AE and serious AEs in this post-hoc analysis are consistent with a high SVR12 (97%) and safety analysis observed in a phase 2, open-label, single-arm trial of 38 non-cirrhotic individuals receiving OST and an interferon-free regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir + ribavirin for 12 weeks [21]. These data are also consistent with data from the phase 3 C-EDGE CO-STAR study [22]. Among people with HCV genotypes 1/4/6 on stable OST (recent injecting drug use at screening was permitted) receiving elbasvir/grazoprevir for 12 weeks, an SVR of 91% was observed [22].

Further, these data are consistent with previous data demonstrating that interferon-based HCV therapy is safe and effective among people receiving OST and those with ongoing drug use [8-10, 20, 23].

There were no cases of HCV reinfection observed in this study through 24 weeks after treatment completion. This is consistent with low HCV reinfection rates of 1–4% per 100 person-years following successful interferon-based therapy among PWID that have previously been reported [9, 24, 25]. However, the sample size and duration of follow-up in this study are limited and further long-term studies of HCV reinfection among PWID are required to more fully characterize the risk of HCV reinfection and associated risk factors.

This study has several other limitations. People with active drug use at baseline were excluded from participating in the ION trials, and as such, enrolled participants represented a selected population likely to be engaged in care. Therefore, these findings may not be generalizable to other PWID populations (particularly those not receiving stable OST or recent PWID). Additionally, the sample size of participants receiving OST with ongoing drug use excluding cannabinoids was small. Further, this was a post-hoc analysis of the Phase 3 ION studies and this analysis was not specified *a priori*. Given the paucity of data on interferon-free treatment outcomes among people receiving OST and people with illicit drug use, these data still provide important guidance for HCV management in these populations.

There remains a reluctance to treat HCV infection among PWID (including those receiving OST). In the United States, 88% of US State Medicaid committees have implemented restrictions that exclude those who either have recently used illicit drugs, are injecting drugs, or are receiving OST from newer (or DAA-based) therapies (irrespective of disease stage)

[11]. Justifications for these restrictions towards PWID are typically described as lack of adherence to the treatment regimen, worse outcomes than non-PWID at comparable disease stages, likelihood of HCV reinfection, and lack of data on treatment outcomes with interferon-free DAA HCV therapies [11, 26]. Decisions to provide DAA HCV treatments to people with drug and alcohol use, including PWID, must be undertaken on the basis of clinical and public health requirements rather than a common co-existing disorder, such as addiction [26]. These data argue against restrictions for DAA therapy that are being imposed on PWID in some countries and provide important data to inform international recommendations for the management of HCV among PWID [12-15].

In conclusion, these data demonstrate that ledipasvir/sofosbuvir HCV therapy is well tolerated and effective among PWID receiving OST and those with illicit drug use during HCV therapy. This study also highlights the importance and urgency for further research and clinical trials with larger sample sizes to evaluate the safety and efficacy of interferon-free therapy among people receiving OST and PWID with ongoing drug use. Clinical trials are evaluating interferon-free therapy among PWID with recent drug use (SIMPLIFY, NCT02336139; HERO, NCT02824640) and PWID with recent drug use and/or those receiving OST (D3FEAT, NCT02498015) are ongoing and should provide further data in this regard. Strategies to enhance HCV testing, linkage to care and treatment among PWID and those receiving OST will be critical to address the growing burden of HCV infection globally.

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Conflicts of interest

Jason Grebely is a consultant/advisor and has received research grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck and Merck Sharp & Dohme. Stefan Mauss is a consultant/advisor for AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Janssen, Merck Sharp & Dohme and has been a speaker on behalf of AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Merck Sharp & Dohme. Ashley Brown has served as an advisor/consultant for and has been a speaker for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Merck Sharp & Dohme, and has been a speaker for and has received clinical research grants from Gilead Sciences. Jean-Pierre Bronowicki has been a clinical investigator, speaker, and/or consultant for Abbvie, Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohmeand has received grants from Gilead Sciences. Massimo Puoti has received research grants and/or fees as a member of temporary advisory boards and/or as a speaker at events or internal courses by Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Roche and ViiV. David Wyles is a paid consulatant/advisor to AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck and has received research grants (paid to UC Regents) from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck. Greg Dore is a consultant/advisor to and has received research grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck,Roche, GlaxoSmithKline, and Abbott Diagnostics. Macky Natha, Yanni Zhu, Junming Yang, Bruce Kreter, Diana M Brainard, Chohee Yun, and Val Carr are employees of Gilead Sciences.

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Table 1. Baseline demographic and clinical characteristics of patients with chronic genotype 1 HCV infection receiving ledipasvir/sofosbuvir with or without ribavirin in the ION Phase 3 clinical trials, stratified by receipt of opioid substitution therapy

Characteristic	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)
Asian	1 (1)	21 (1)
Other	0	19 (1)
Not disclosed	0	3 (0.2)
Region, n (%)		
United States	51 (73)	1548 (82)
Europe	19 (27)	334 (18)
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 genotype, n (%)		
1a	63 (90)	1380 (73)
1b	7 (10)	490 (26)

Other	0	12 (1)
IFNL3 genotype, n (%)		
CC	28 (40)	455 (24)
CT	34 (49)	1072 (57)
TT	8 (11)	355 (19)
Mean (SD) HCV RNA $\log_{10}$ IU/mL	6.4 (0.8)	6.4 (0.7)
HCV RNA ≥800,000 IU/mL, n (%)	56 (80)	1541 (82)
Cirrhosis, n (%)		
Yes	7 (10)	217 (12)
No	63 (90)	1660 (88)
Missing	0	5 (0.3)
ALT >1.5 x ULN, n (%)	25 (36)	929 (49)
Prior treatment experience, n (%)		
Treatment-naïve	62 (89)	1450 (77)
Treatment-experienced	8 (11)	432 (23)
Therapy		
Ledipasvir/sofosbuvir	48 (69)	1032 (55)
Ledipasvir/sofosbuvir with ribavirin	22 (31)	850 (45)

Abbreviations: ALT, alanine aminotransferase; 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.

Table 2. Drug test results tested on stored serum samples from patients with chronic genotype 1 HCV infection receiving ledipasvir/sofosbuvir with or without ribavirin in the ION-1 trial (n = 853)

Characteristic, n (%)	Positive for drug use at Week 8 (n = 853)	Positive for drug use at Week 12 (n = 847)	Positive for drug use during therapy (n = 853)
Any drug use	156 (18)	172 (20)	196 (23)
Cannabinoids	134 (16)	147 (17)	166 (19)
Benzodiazepines	10 (1)	13 (2)	19 (2)
Opiates/oxycodone/methadone	6 (<1)	9 (1)	11 (1)
Methamphetamine/amphetamine	5 (<1)	5 (<1)	7 (<1)
Cocaine	5 (<1)	8 (<1)	9 (1)
Barbiturates	4 (<1)	6 (<1)	7 (<1)

Table 3. Baseline demographic and clinical characteristics of patients with chronic genotype 1 HCV infection receiving ledipasvir/sofosbuvir with or without ribavirin in the ION Phase 3 clinical trials, stratified by illicit drug use during therapy

Characteristic, 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.

Table 4. Treatment completion, adherence, efficacy and safety outcomes among patients enrolled in the ION studies, stratified by OST therapy at enrollment and illicit drug use during therapy

Characteristic	Treatment completion n (%) (95% CI)	*P*	≥80 adherence n (%) (95% CI)	*P*	SVR12 n (%) (95% CI)	*P*	Adverse events n (%) (95% CI)	*P*	Serious adverse events n (%) (95% CI)	*P*
Opioid substitution therapy										
No (n = 1,882)	1846 (98%) (97%, 99%)	-	1737 (92%)(91%, 93%)	-	1822 (97%) (96%, 98%)	-	1498 (80%) (78%, 81%)	-	49 (3%) (2%, 3%)	-
Yes (n = 70)	68 (97%) (90%, >99%)	0.40	65 (93%) (84%, 98%)	1.00	66 (94%) (86%, 98%)	0.28	62 (89%) (79%, 95%)	0.07	3 (4%) (1%, 12%)	0.43
Illicit drug use during therapy										
None (n = 657)	643 (98%) (96%, 99%)	-	598 (91%) (89%, 93%)	-	652 (99%) (98%, >99%)	-	564 (86%) (83%, 88%)	-	27 (4%) (3%, 6%)	-
Cannabinoids only (n = 126)	124 (98%)	1.00	116 (92%)	0.86	123 (98%)	0.12	104 (83%)	0.34	2 (2%)	0.21

	(94%, >99%)		(86%, 96%)		(93%, >99%)		(75%, 89%)		(<1%, 6%)	
Illicit drugs ± cannabinoids (n = 70)	68 (97%) (90%, >99%)	0.66	64 (91%) (82%, 97%)	1.00	68 (97%) (90%, >99%)	0.14	63 (90%) (80%. 96%)	0.46	3 (4%) (1%, 12%)	1.00

Abbreviations: OST, opioid substitution therapy; SVR12, sustained virologic response 12 weeks post-end of therapy. The 2-sided 95% exact CI based on the Clopper Pearson method is reported. The p-value from the 2-sided Fisher's exact test is reported. No multiplicity adjustment is performed.

Table 5. Adverse events among patients with chronic genotype 1 HCV infection receiving ledipasvir/sofosbuvir with or without ribavirin in the ION phase 3 clinical trials, stratified by receipt of opioid substitution therapy

Adverse event, n (%)	OST at enrollment		No OST at enrollment	
	Ledipasvir/ sofosbuvir (n = 48)	Ledipasvir/ sofosbuvir plus ribavirin (n = 22)	Ledipasvir/ sofosbuvir (n = 1032)	Ledipasvir/ sofosbuvir plus ribavirin (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)

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

Figure 1. Sustained virologic response in patients receiving and not receiving OST following 8, 12, or 24 weeks of therapy with ledipasvir/sofosbuvir or ledipasvir/sofosbuvir plus ribavirin in the ION studies. Error bars represent 95% confidence intervals. Abbreviation: OST, opioid substitution therapy