Title

Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naïve patients: Findings from two randomized trials

Journal

Liver International, 38(6)

ISSN

1478-3223

Authors

Tam, Edward
Luetkemeyer, Anne F
Mantry, Parvez S
et al.

Publication Date

2018-06-01

DOI

10.1111/liv.13616

Peer reviewed

Article type : Original Articles

Handling Editor: Janus Ong

Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naive patients: findings from two randomized trials

Edward Tam[1], Anne F. Luetkemeyer[2], Parvez S. Mantry[3], Sanjaya K. Satapathy[4], Peter Ghali[5], Minhee Kang[6], Richard Haubrich[7], Xianlin Shen[7], Liyun Ni[7], Gregory Camus[7], Amanda Copans[7], Lorenzo Rossaro[7], Bill Guyer[7], and Robert S. Brown, Jr[8] on behalf of the RESCUE and ACTG A5348 study investigators.

[1]LAIR Centre, Vancouver, BC, Canada

[2]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

[3]The Liver Institute, Methodist Dallas Medical Center, Dallas, TX, USA

[4]Methodist University Hospital Transplant Institute, University of Tennessee Health Sciences Center, Memphis, TN, USA

[5]McGill University Health Centre, Royal Victoria Hospital, Montreal, QC, Canada

[6]Harvard T.H. Chan School of Public Health, Boston, MA, USA

[7]Gilead Sciences, Foster City, CA, USA

[8]Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York City, NY, USA

Corresponding author:

Edward Tam MD FRCPC

LAIR Centre, 305–750 West Broadway

Vancouver, BC V5Z 1H2, Canada.

Tel.: +1 604 876 5122; fax: +1 604 484 3026

E-mail: etam@laircentre.com

Number of figures/tables: 3 figures/4 tables

Abbreviations:

ACTG, AIDS clinical trial group; LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; HCV, hepatitis C virus; SVR, sustained virologic response; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; SVR12, SVR at 12 weeks post-treatment; AE, adverse event; PEG, peginterferon; GT, genotype; SMV, simeprevir; RAS, resistance-associated substitutions; ART, anti-retroviral therapy; SVR4, LLOQ, lower limit of quantification; SVR at 4 weeks post-treatment; SAE, serious adverse event; PPI, proton pump inhibitor; Q, quartile; VEL, velpatasvir; VOX, voxilaprevir; DAA, direct-acting antiviral; BMI, body mass index; NA, not

applicable; CI, confidence interval; IFN, interferon; TVR, telaprevir; CPK, creatine phosphokinase

Conflicts of interest:

ET: Grant/research support, advisory board and speaker: AbbVie, Gilead Sciences, Janssen, Merck; Grant/research support and advisory board: BMS, Intercept; Grant/research support and speaker: PendoPharm; Grant/research support: Boehringer Ingelheim, Genfit, Novartis, Shire; Advisory board: Lupin.

AFL: Grant/research support: AbbVie, BMS, Gilead Sciences, Merck.

PSM: Grant/research support, advisory board and speaker: AbbVie, Gilead Sciences, Intercept, Merck; Advisory board and speaker: Salix; Grant/research support: BMS, Genfit, Novartis, Ocera, Octeta, Shinogi, Tobira.

SKS: Grant/research support, advisory board and speaker: Intercept; Grant/research support and advisory board: Gilead Sciences; Grant/research support: Biotest, Conatus, Genfit, Shire; Advisory board: Abbvie; Speaker: Alexion.

PG: Grant/research support, advisory board and speaker: AbbVie, Gilead Sciences, Merck.

RSB: Grant/research support and advisory board/consulting: AbbVie, BMS, Intercept, Janssen, Merck; Grant/research support: Novartis; Advisory board/consulting: Gilead Sciences.

RH, XS, LN, GC, AC, LR and BG: Employees of Gilead Sciences.

MK: None

Financial support: RESCUE study was funded by Gilead Sciences. A5348 was funded by the National Institutes of Health (NIH) and Gilead Sciences. A5348 work

was supported by the National Institute of Allergy and Infectious Diseases of the NIH under Award Numbers UM1 AI068634, UM1 AI068636 and UM1 AI106701.

Clinical trial numbers: NCT02600351 (RESCUE), NCT02605304 (ACTG A5348)

ABSTRACT

Background & Aims: We report data from two similarly designed studies that evaluated the efficacy, safety, and optimal duration of ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) for retreatment of chronic hepatitis C virus (HCV) in individuals who failed to achieve sustained virologic response (SVR) with prior SOF-based, non-NS5A inhibitor-containing regimens.

Methods: The RESCUE study enrolled HCV mono-infected adults with genotype 1 or 4. Non-cirrhotic participants were randomized to 12 weeks of LDV/SOF or LDV/SOF+RBV. Compensated cirrhotic participants were randomized to LDV/SOF+RBV (12 weeks) or LDV/SOF (24 weeks). The AIDS Clinical Trials Group A5348 study randomized genotype 1 adults with HCV/HIV co-infection to LDV/SOF+RBV (12 weeks) or LDV/SOF (24 weeks). Both studies used SVR at 12 weeks post-treatment (SVR12) as the primary endpoint.

Results: In the RESCUE study, 82 participants were randomized and treated, and all completed treatment. Overall, SVR12 was 88% (72/82); 81-100% in non-cirrhotic participants treated with LDV/SOF or LDV/SOF+RBV for 12 weeks and 80-92% in cirrhotic participants treated with LDV/SOF+RBV for 12 weeks or LDV/SOF for 24 weeks. Adverse events (AEs), mostly mild-to-moderate in severity, were experienced by 78% of participants, with headache and fatigue most frequently reported. One

serious AE, not related to treatment, was observed. No premature discontinuations of study drug, or deaths occurred. In the A5348 study, 7 participants were randomized (cirrhotic n=1; GT1a n=5) and all attained SVR12, with no serious AEs or premature discontinuations.

Conclusions: In this SOF-experienced NS5A inhibitor-naïve population, which included participants with cirrhosis or HCV/HIV co-infection, high SVR12 rates were achieved.

Keywords: Ledipasvir; Sofosbuvir; HCV; HIV; Treatment-experienced.

Key points:

- Two similarly designed studies evaluated the optimal ledipasvir/sofosbuvir-containing treatment regimens for the retreatment of HCV
- All patients had failed previous non-NS5A sofosbuvir-based therapy and difficult-to-treat patients, such as those with cirrhosis and/or co-infected with HIV, were included
- The highest SVR12 rates were obtained with 12 weeks of ledipasvir/sofosbuvir + ribavirin in non-cirrhotic participants and 24 weeks of ledipasvir/sofosbuvir in cirrhotic individuals
- Ledipasvir/sofosbuvir remains an important therapeutic option for the treatment of HCV even in SOF-based treatment-experienced patients and those coinfected with HIV

Introduction

The fixed-dose combination therapy of ledipasvir/sofosbuvir (LDV/SOF) for the treatment of hepatitis C virus (HCV) combines inhibitors of NS5A (LDV) and NS5B polymerase (SOF). There is evidence to suggest that individuals who failed to achieve a sustained virologic response (SVR) after prior treatment with SOF + ribavirin (RBV) ± peginterferon (PEG) may respond well to LDV/SOF combination therapy. The ELECTRON-2 study included 19 participants with genotype (GT) 1 HCV who relapsed after SOF+RBV-based therapy.[1] Following a 12-week treatment regimen with LDV/SOF+RBV, all participants achieved SVR at week 12 post-treatment (SVR12; Gilead Sciences, data on file). Similar high SVR rates have been observed in other small retreatment studies.[2,3] The ION-4 study evaluated LDV/SOF for 12 weeks in 335 participants co-infected with HIV.[4] Relapsers from the ION-4 study were eligible for retreatment with LDV/SOF+RBV for 24 weeks and 8 out of 9 achieved SVR12.[5] However, retreatment rescue regimens for HCV-mono-infected and co-infected individuals have not been standardized.

There are limited data on the retreatment of individuals who have failed simeprevir (SMV) + SOF treatment. Individuals who failed to respond to SMV+SOF regimens may respond to LDV/SOF due to the different mechanisms of action of SMV and LDV, the retained activity of SOF even after failed SOF-based therapies, and the extremely rare development of NS5B resistance-associated substitutions (RAS).[2,3] Two small studies have reported overall SVR rates of 85-96% in participants who, having previously failed treatment with SMV+SOF±RBV, were retreated with LDV/SOF±RBV for up to 24 weeks.[6,7]

Based on the rationale outlined above, LDV/SOF±RBV for 12-24 weeks is recommended for the treatment of individuals in whom a previous SOF+RBV±PEG

regimen has failed.[8] Additional data are needed to more fully evaluate LDV/SOF regimens for retreatment of HCV in NS5A inhibitor-naïve individuals including those who are co-infected with HIV and failed to achieve SVR with prior SOF-based therapy.

We report SVR12 data from two prospective randomized studies (RESCUE [GS-US-337-1746] and A5348). These studies evaluated efficacy, safety, and optimal duration of LDV/SOF±RBV for the treatment of GT1 or 4 HCV-mono and HCV/HIV co-infected participants with prior virologic failure after SMV+SOF±RBV or SOF+RBV±PEG regimens.

Patients and Methods

Study participants

Both the RESCUE and A5348 studies enrolled chronic GT1 HCV-infected adults (≥18 years) with or without compensated cirrhosis. Presence of cirrhosis was determined by liver biopsy, transient elastography, or measurement of hepatic fibrosis (see online supplementary appendix for details). The RESCUE study also enrolled GT4 HCV-infected participants (up to 5% of population). All participants had prior virologic failure (specifically relapse) after treatment with a SOF-based regimen (SMV+SOF±RBV or SOF+RBV±PEG). Individuals who had received prior therapy with an NS5A inhibitor or any nucleoside or nucleotide polymerase inhibitors other than SOF were excluded from both studies. In the A5348 study, only individuals co-infected with HIV who had previously failed treatment with SMV+SOF±RBV or SOF+RBV±PEG were eligible. Conditions of permitted antiretroviral therapy (ART) and detailed inclusion/exclusion criteria for the two studies are presented in the online supplementary appendix.

Study design and treatment

The RESCUE study was a phase IIIb randomized, multicenter, open-label study in the USA and Canada (NCT02600351). Participants were enrolled based on cirrhosis status. Non-cirrhotic participants were randomized to receive either LDV/SOF or LDV/SOF+RBV for 12 weeks. Participants with compensated cirrhosis were randomized to receive either LDV/SOF+RBV for 12 weeks or LDV/SOF for 24 weeks. Participants received LDV/SOF as a fixed-dose, once-daily tablet (Harvoni®, Gilead Sciences Inc., Foster City, CA, USA) containing LDV(90 mg)/SOF(400 mg). Weight-based RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg) was administered in a divided dose, twice-daily. An interactive web response system was used to manage participant randomization and treatment assignment. Randomization was stratified by prior regimen and genotype.

A5348 was a phase II randomized, open-label study conducted in the USA (NCT02605304), which randomized participants 1:1 to receive LDV/SOF+RBV for 12 weeks or LDV/SOF only for 24 weeks. Randomization was stratified by cirrhosis status. The study was randomized due to clinical equipoise and not with the intent to compare treatment arms.

In both studies, dose reductions for RBV could be performed according to product label or investigator discretion. RBV could be permanently discontinued due to adverse events (AEs) without stopping LDV/SOF.

Study assessments

A detailed overview of the assessments performed in each study is presented in the online supplementary appendix (Tables S1 and S2).

In both studies, HCV RNA was measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0 (Roche Diagnostics, Rotkreuz, Switzerland).

To evaluate for the presence of RAS, samples for HCV RNA sequencing were collected in the RESCUE study at baseline/day 1 and every visit thereafter. In the A5348 study, samples were collected at study entry and at the time of HCV virologic failure confirmation.

For A5348, on-study HIV-1 RNA testing was performed at a central laboratory using Abbott RealTime HIV-1 assay (Abbott Laboratories, Lake Bluff, IL, USA). In the event of confirmed HIV-1 virologic failure (HIV-1 viral load ≥200 copies), a plasma specimen was obtained and analyzed for drug resistance.

Endpoints

In both studies, the primary efficacy endpoint was SVR12 (HCV RNA <lower limit of quantification [LLOQ] at 12 weeks post-treatment). HCV RNA <LLOQ at 4 weeks post-treatment (SVR4) was a secondary efficacy endpoint.

Exploratory endpoints included prevalence of pre-existing RAS at baseline, and emergence of RAS upon virologic failure (viral breakthrough or relapse). RAS were evaluated using deep-sequencing at a 15% cut-off both at baseline and at the time of virologic failure. In the RESCUE study, NS3/4A, NS5A, and NS5B RAS were monitored, whereas, in the A5348 study, only NS5A RAS were monitored. Detailed lists of investigated RAS can be found in the online supplementary appendix (Table S3).

In the RESCUE study, the primary safety endpoint was the proportion of participants who discontinued study treatment due to an AE. An additional secondary efficacy

endpoint was the proportion of participants with virologic failure. Sequencing analysis was performed to differentiate between relapse and reinfection as the cause of virologic failure.

In the A5348 study, the primary safety endpoint was any AE of Grade 3 or higher or serious AE (SAE) while on-study treatment and up to 30 days post-treatment, or an AE that required permanent discontinuation of study treatment. Creatinine and creatinine clearance was monitored and suspected renal toxicity (development of ≥Grade 2 renal dysfunction or development of new or worsened proteinuria or glucosuria) was a secondary safety endpoint. Additional secondary safety endpoints included HIV-1 RNA >50 copies/mL and change in CD4+ cell count from baseline.

Oversight of studies

Both studies were approved by the institutional review board or independent ethics committee at each participating site (see online supplementary appendix for list of sites and committees). The A5348 study was monitored by an independent AIDS Clinical Trials Group (ACTG) Study Monitoring Committee. The studies conformed to Good Clinical Practice guidelines and Declaration of Helsinki Principles. All participants provided written informed consent.

Statistical analyses

Due to active retreatment of SOF-based regimen failures, a declining pool of eligible participants resulted in both studies closing early with a lower number of participants enrolled than initially planned. The RESCUE study was designed to enroll 430 participants (180 non-cirrhotics; 250 with cirrhosis). However, 87 participants were randomized and 82 received at least one dose of study drug. The A5348 study was designed to randomize 40 participants (20 per arm), but ultimately 7 participants

were enrolled. Due to the lower than anticipated numbers of participants and early study closures, the studies were not statistically powered as originally planned.

The primary efficacy analyses for the RESCUE study were conducted in the full analysis set (as-randomized population), which included all participants who took at least one dose of study drug. Four participants were randomized erroneously to the wrong treatment groups based on an incorrect assessment of baseline cirrhosis status (n=3) or lack of RBV dispensing by the local pharmacy (n=1). These participants were reassigned to the treatment groups as shown in Figure 1A. Due to these randomization errors, analyses were also performed in the as-treated analysis set (as-treated population), which included participants who met the eligibility criteria and initiated study treatment. In the A5348 study, all 7 participants received study treatment and were included in the efficacy endpoint analyses. In both studies, the primary safety analysis set included all participants who took at least one dose of study drug (safety population). AEs were mapped according to MedDRA Version 19.1. Laboratory abnormalities were graded using either the Gilead Sciences Inc. Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (version 01, April 2015; RESCUE) or the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.0, November 2014; A5348).

In both studies, the SVR12 rate (primary endpoint) was summarized by treatment groups and for the RESCUE study by treatments according to subgroup analyses. The 2-sided 95% exact confidence interval of SVR12 was calculated using the Clopper-Pearson method. No statistical hypothesis testing was performed.

RESULTS

RESCUE study results

Baseline characteristics and disposition

The RESCUE study was conducted at 39 centers in the USA and Canada and enrolled 87 GT1 or GT4 HCV-positive adults between November 2015 and June 2016. Five participants discontinued prior to study drug initiation due to site administrative issues. Of the remaining 82 participants, 4 were reassigned treatment groups due to randomization errors (Figure 1A). Overall, 16 non-cirrhotic participants received LDV/SOF for 12 weeks and 17 received LDV/SOF+RBV for 12 weeks. Of the 49 participants with cirrhosis, 25 received LDV/SOF+RBV for 12 weeks and 24 received LDV/SOF for 24 weeks. All participants completed study treatment.

Baseline demographics and treatment characteristics for the as-treated population were generally well balanced across treatment arms (Table 1). The study population (n=82) was 74% male, 70% white, with a mean age of 59 years. Overall, 60% of participants had cirrhosis, 89% had GT1 infection (GT1a=66%), and 95% had an IL28B non-CC genotype. Thirty-seven percent of participants had previously received treatment with SMV+SOF±RBV and 63% with SOF+RBV±PEG. Concomitant proton pump inhibitor (PPI) administration was recorded in 22 subjects (27%) from across all treatment groups during the study.

Efficacy

The overall SVR12 rate was 88% (72/82 participants). In non-cirrhotic and cirrhotic participants, the rates were 91% and 86%, respectively (as-treated population) (Table 2). All the non-cirrhotic participants treated with LDV/SOF+RBV for 12 weeks

achieved SVR12. The SVR12 rate for non-cirrhotic participants who received LDV/SOF for 12 weeks was 81% (Figure 2). In cirrhotic participants, the SVR12 rates were 80% and 92% in the LDV/SOF+RBV for 12 weeks and LDV/SOF for 24 weeks treatment groups, respectively. For HCV GT1a participants, SVR12 rates ranged from 69% (cirrhotic participants LDV/SOF+RBV 12 weeks) to 100% (non-cirrhotic participants LDV/SOF+RBV 12 weeks). Only 1/17 participants with GT1b failed to achieve SVR12. This individual had cirrhosis and was treated with LDV/SOF for 24 weeks. Two participants with GT1 but no confirmed subtype; both achieved SVR12, as did all GT4 participants (Table 2). The SVR12 rates for the as-randomized population ranged from 81-94% (online supplementary appendix Table S4). Of the 22 participants who received PPI therapy during the study, 91% (20/22) achieved SVR12 compared with 87% of participants (52/60) who did not receive PPIs. Prior treatment regimens did not influence the proportion of non-cirrhotic participants with GT1 achieving SVR12 with LDV/SOF or LDV/SOF+RBV for 12 weeks (Figure 3). In cirrhotic participants, a higher proportion achieved SVR12 with LDV/SOF+RBV for 12 weeks if they had received SOF+RBV±PEG previously compared with SMV+SOF (93% versus 64%, respectively).

A post-hoc analysis of relevant baseline data for all study participants revealed that 6, who were originally diagnosed with compensated cirrhosis, most likely had decompensated disease at time of enrollment or historically. Five of these participants were treated with LDV/SOF for 24 weeks and 1 received 12 weeks of LDV/SOF+RBV. All 6 individuals achieved SVR12.

No participants experienced on-treatment virologic failure. Ten participants experienced relapse resulting in virologic failure (3 non-cirrhotic participants and 7

cirrhotic participants; Table 2). The majority were GT1a (9/10) and all were male; 6 had received SMV+SOF-based regimens previously (Table 3).

Virology

Twelve of the 82 participants (15%) had baseline NS5A RAS using a 15% sensitivity threshold. All but 1 of the 12 participants with NS5A RAS had received SOF+RBV±PEG previously (11/52, 21.2%) compared with SMV+SOF (1/30, 3.3%). Ten of 12 (83%) achieved SVR12, as compared to 62/70 (88%) participants with no NS5A RAS at baseline. The 2 participants who experienced virologic failure with pre-existing NS5A RAS (one with GT1a received LDV/SOF for 12 weeks and one with GT1b received LDV/SOF for 24 weeks) had NS5A-L31M at baseline. Another individual with L31M at baseline achieved SRV12. Five participants had baseline NS5B nucleoside inhibitor RAS, but S282T was not detected. All 5 participants with NS5B RAS achieved SVR12. Forty-three participants (52%) had baseline NS3/4A Class RAS: 26/36 (72%) who were previously treated with NS3 protease inhibitors, and 17/46 (37%) who never received NS3 protease inhibitors. The presence of NS3 RAS at baseline did not impact the treatment outcome: SVR12 rates were 86% and 90% for participants with or without baseline NS3 RAS, respectively.

Sequencing confirmed the virologic failures were due to relapse. NS5A RAS were observed post-treatment in the 10 participants who relapsed. Eight of 9 participants with GT1a infection had an emergent substitution at position 30 and three had a substitution at position 93 (Table 3). The individual with GT1b who experienced virologic failure had emergent Y93H at relapse. No NS5B nucleoside inhibitor RAS were observed in any participant at virologic failure.

Safety

Overall, 78% of participants experienced an AE, with 57% considered treatment-related. One treatment-unrelated serious AE (upper gastrointestinal hemorrhage) occurred in an individual with cirrhosis who received LDV/SOF for 24 weeks. There were no LDV/SOF or RBV discontinuations due to AEs, or deaths during the study (Table 4). The proportion of participants (non-cirrhotics and cirrhotics) experiencing AEs was similar in both study arms that received LDV/SOF for either 12 or 24 weeks (69% and 71%, respectively). Headache and fatigue were the most common AEs. The incidence of AEs was higher in the participants who received RBV in addition to LDV/SOF (86% versus 70% for LDV/SOF alone). Fatigue, insomnia, or rash were reported approximately twice as often by participants who received LDV/SOF+RBV compared with LDV/SOF only. Six participants experienced a Grade 3 AE; 2 received LDV/SOF for 12 weeks (headache and migraine), 2 received LDV/SOF+RBV for 12 weeks (increased blood bilirubin and syncope), and 2 received LDV/SOF for 24 weeks (upper gastrointestinal hemorrhage due to portal hypertensive gastropathy and arthralgia). Grade 3 laboratory abnormalities included: anemia (n=5), low platelets (n=2), blood clotting anomalies (n=1), hyperglycemia (n=1), lipase elevation (n=1), and hyperbilirubinemia (n=1). Grade 4 laboratory abnormalities were observed in 1 individual at one time point only (high aspartate aminotransferase and creatine kinase elevation at week 2). Hemoglobin levels of <10 g/dL occurred in 3 participants (4%; all had cirrhosis) and 2 participants with cirrhosis recorded a Grade 3 low platelet count (Table 4).

A5348 study results

Baseline characteristics and disposition

The A5348 study was conducted from February 2016 to March 2017 at 3 sites in the USA. Overall, 7 GT1 adults with HCV/HIV co-infection with controlled HIV were randomized to receive either LDV/SOF+RBV for 12 weeks (n=4) or LDV/SOF for 24 weeks (n=3) (Figure 1B). Five participants (71%) were male, 4 (57%) were white, and the mean age was 55 years. Five were GT1a (71%), 1 participant (14%) was cirrhotic, and 6/7 (86%) were IL28B non-CC (Table 1). All participants were on HIV ART with HIV RNA <50 copies/mL. The median CD4+ cell count was 528 cells/mm^3 (quartile [Q]1, Q3: 341, 628).

Efficacy and virology

All participants in both treatment arms achieved SVR4 and SVR12 (Figure 2 and Table 2). There were no LDV-specific RAS detected at baseline.

HIV outcomes

No participants experienced an increase in HIV RNA to >50 copies/mL post-entry or had detectable HIV viremia during the study. The median change in CD4+ cell count from baseline to week 12 was -28 cells/mm^3 (Q1, Q3: -102, 196).

Safety

There were no SAEs or deaths. No AEs occurred that required permanent discontinuation of study treatment. Two participants experienced a Grade 3 laboratory abnormality: increased direct bilirubin and decreased creatinine clearance. No Grade 4 laboratory abnormalities occurred. Two participants met the suspected renal toxicity endpoint definition. Both had creatinine clearance events of

≥Grade 2 which were ongoing from study entry. Both participants were receiving ART; one was taking Atripla and one was on ritonavir-boosted darunavir and dolutegravir. One of the participants had an increase in creatinine clearance to Grade 3 and had urinalysis protein of 1+ at the treatment completion visit.

Discussion

There is an ongoing need to understand appropriate retreatment options for HCV-infected individuals who fail non-NS5A inhibitor-containing, SOF-based regimens. In the SOF-experienced, NS5A inhibitor-naïve populations reported here, overall SVR12 rates with LDV/SOF±RBV retreatment for 12 or 24 weeks were high (88% and 100% for RESCUE and A5348 studies, respectively). The LDV/SOF±RBV combination regimens were well-tolerated; no participants discontinued due to AEs or died, and only 1 serious AE was observed. Recorded AEs were similar to reports from previous LDV/SOF±RBV studies.[9-12]

Retreatment options for HIV-co-infected individuals may be impacted by potential HCV/HIV drug-drug interactions.[13] Therefore, the high SVR rates (100%) and good tolerability observed in co-infected participants is encouraging. Although the sample size in the HCV/HIV co-infected population studied was small, these data should reassure physicians regarding the potential use of LDV/SOF±RBV in this population. It is also encouraging that high SVR rates were obtained in cirrhotic participants, given that these individuals are at a considerably higher risk of death and complications versus non-cirrhotic individuals.[14-16] Overall, our findings suggest that the highest SVR12 rates were obtained with 12 weeks of LDV/SOF+RBV in non-cirrhotic participants and by extending the duration of LDV/SOF treatment to 24 weeks in cirrhotic individuals. Prior treatment regimens had no effect on response to

LDV/SOF in non-cirrhotic participants; the response rate was numerically lower for cirrhotic participants previously treated with SMV.

Although NS5A and NS5B RAS were observed at baseline in some RESCUE participants, these substitutions did not have an impact on-treatment outcome. Ten participants (12%) did not attain SVR12 and 5/10 did not achieve SVR4, all due to virologic relapse. Nine of the 10 treatment failures were GT1a. Similarly, in the POLARIS-1 and -4 studies, among subjects treated with 12-week sofosbuvir/velpatasvir/voxilaprevir, 2/7 relapsers were GT1 and both GT1a. In the POLARIS-4 control arm with 12-week sofosbuvir/velpatasvir, 6/14 relapsers were GT1, 5/6 were GT1a and one GT1b.[17] Consequently, among GT1 subjects being retreated with a DAA, there does appear to be a trend for subtype 1a to be more frequently associated with treatment failure than subtype 1b. Further studies are required to confirm this observation. Two of the relapsed participants had confirmed NS5A RAS at baseline, however, all 10 had emergent mutations at position 30 and/or 93. The NS5A RAS observed in these studies have previously been attributed to reduced efficacy of LDV *in vitro* and detected at treatment failure in phase III studies.[11,18,19] No emergent NS5B RAS were observed in any of the relapsed participants.

The high SVR rates we observed in SOF-experienced, NS5A inhibitor-naïve participants with GT1 or 4 across the treatment arms (80-100%) are generally aligned with those observed with LDV/SOF-based retreatment in small pilot studies. Two such studies examined LDV/SOF regimens in participants with prior virologic failure with SOF+RBV±PEG. An SVR12 of 100% was observed following LDV/SOF for 12 weeks in participants who previously failed to achieve SVR with 24 weeks of SOF+RBV (n=14)[2] and 98% SVR12 was achieved with LDV/SOF+RBV for 12 weeks

in participants in whom prior treatment with SOF+RBV+PEG or SOF+RBV had failed (n=45).[3] Data on retreatment of SMV+SOF failures are more limited. Interim data from one study in participants who failed 12 weeks of SMV+SOF±RBV therapy indicated reasonable response rates to 12-24 weeks of LDV/SOF±RBV, with 85% of participants (11/13) achieving SVR12.[6] A retrospective cohort study reported 96% of participants (25/26) who had failed prior therapy with SMV+SOF±RBV achieved SVR12 with LDV/SOF±RBV for up to 24 weeks.[7] It has been suggested that PPI use can negatively affect SVR12 rates achieved with LDV/SOF.[20] In this study, PPIs had no impact on SVR agreeing with a recent real-world study that found no significant association between PPI use and treatment outcome in patients (n=1,979) treated with LDV/SOF.[21]

The POLARIS-4 study examined a fixed-dose combination of 3 pan-genotypic drugs (SOF, velpatasvir [VEL], and voxilaprevir [VOX]), targeting different pathways (NS5B, NS5A, and NS3/4A, respectively) for the retreatment of individuals who had failed prior non-NS5A containing direct-acting antiviral agent (DAA) regimens.[22] Twelve weeks of therapy with this triple combination led to SVR rates of 97% (76/78) in GT1 and 100% (19/19) in GT4 HCV-infected participants. In the control arm of the study, retreatment with SOF/VEL for 12 weeks resulted in SVR rates of 91% in GT1 participants. This triple regimen may become a preferred salvage therapy for DAA-experienced individuals (especially those individuals with a prior NS5A failure) and for certain patient groups. Nevertheless, the LDV/SOF±RBV regimen is likely to remain of interest in access-limited settings (such as countries where SOF/VEL/VOX will not be commercially available or the timeline for approval is prolonged), in patients with liver disease where protease inhibitors may be undesirable, and in individuals on concomitant medications (such as certain HIV antiretrovirals) who may

experience drug-drug interactions with an HCV protease inhibitor. A notable finding of our study was that 6 participants who were later identified as having probable decompensated cirrhosis all achieved SVR12. The SOLAR studies reported SVR rates of 84–85% with 12 weeks of LDV/SOF+RBV and 88–90% with 24 weeks of LDV/SOF+RBV in subjects infected with HCV GT1 or GT4 with decompensated cirrhosis; 75% of the 329 subjects enrolled had failure to previous treatment.[23,24] Similar SVR rates were observed in a real-world study involving similar GT1 patients.[25]

In conclusion, in SOF-experienced NS5A inhibitor-naïve participants infected with HCV GT1 or GT4, high SVR12 rates were achieved with LDV/SOF±RBV retreatment for 12 or 24 weeks, including in HCV/HIV co-infected individuals.

Acknowledgements

We extend our thanks to the participants and their families, participating sites, site investigators and study staff, and the A5348 and Gilead Sciences study teams. Third party medical writing support was provided by Ryan Woodrow (Aspire Scientific Ltd, Bollington, UK) and was funded by Gilead Sciences Inc., Foster City, CA, USA. Gilead Sciences Inc. sponsored this study, contributed to its design, and participated in the collection, analysis and interpretation of the data. Authors from Gilead Sciences (Richard Haubrich, Xianlin Shen, Liyun Ni, Gregory Camus, Amanda Copans, Lorenzo Rossaro, and Bill Guyer) were involved in the writing, reviewing and approval of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Gane EJ, Hyland RH, An D, et al. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. Presented at: 49th Annual Meeting of The European Association for the Study of the Liver (EASL); April 9–13, 2014; London, UK.

2. Osinusi A, Kohli A, Marti MM, et al. Re-treatment of chronic hepatitis C virus genotype 1 infection after relapse: an open-label pilot study. *Ann Intern Med* 2014;161:634-638.

3. Wyles D, Pockros P, Morelli G, et al. Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. *Hepatology* 2015;61:1793-1797.

4. Naggie S, Cooper C, Saag M, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. *N Engl J Med* 2015;373:705-713.

5. Cooper C, Naggie S, Saag M, et al. Retreatment of HCV/HIV-coinfected patients who failed 12 weeks of LDV/SOF. Presented at: Conference on Retroviruses and Opportunistic Infections; February 22–25, 2016; Boston, MA.

6. Gonzales GR, Gonzalez SA, Nazario HE, et al. Safety and efficacy of ledipasvir plus sofosbuvir with or without ribavirin in hepatitis C genotype 1 patients who failed previous treatment with simeprevir plus sofosbuvir. Presented at: American Association for the Study of Liver Diseases (AASLD); November 13–17, 2015; San Francisco, CA.

7. Pungpapong S, Leise MD, Watt KD, Vargas HE, Keaveny AP, Aqel BA. Multicenter experience using sofosbuvir/ledipasvir with or without ribavirin to treat hepatitis C genotype 1 relapsers after simeprevir and sofosbuvir treatment.

Presented at: American Association for the Study of Liver Diseases (AASLD); November 13–17, 2015; San Francisco, CA.

8. Lai CL, Wong VW, Yuen MF, et al. Sofosbuvir plus ribavirin for the treatment of patients with chronic genotype 1 or 6 hepatitis C virus infection in Hong Kong. *Aliment Pharmacol Ther* 2015;43:96-101.

9. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;370:1483-1493.

10. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370:1889-1898.

11. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014;370:1879-1888.

12. Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis* 2015;15:397-404.

13. Kaur K, Gandhi MA, Slish J. Drug-drug interactions among hepatitis C virus (HCV) and human immunodeficiency virus (HIV) medications. *Infect Dis Ther* 2015;4:159-172.

14. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006;3:47-52.

15. Bruno S, Zuin M, Crosignani A, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. *Am J Gastroenterol* 2009;104:1147-1158.

16. Chiaramonte M, Stroffolini T, Vian A, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;85:2132-2137.

17. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med* 2017;376:2134-2146.

18. Nkuize M, Sersté T, Buset M, Mulkay JP. Combination ledipasvir-sofosbuvir for the treatment of chronic hepatitis C virus infection: a review and clinical perspective. *Ther Clin Risk Manag* 2016;12:861-872.

19. Harvoni 90 mg/400 mg film-coated tablets. Summary of product characteristics. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003850/WC500177995.pdf Accessed 19 July 2017.

20. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of Ledipasvir-Sofosbuvir Combination in Patients With Hepatitis C Virus Infection and Factors Associated With Sustained Virologic Response. *Gastroenterology* 2016;151:1131-1140.e1135.

21. Tapper EB, Bacon BR, Curry MP, et al. Evaluation of proton pump inhibitor use on treatment outcomes with ledipasvir and sofosbuvir in a real-world cohort study. *Hepatology* 2016;64:1893-1899.

22. Zeuzem S, Flamm SL, Tong M, et al. Randomized, controlled, phase 3 trial of sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir/velpatasvir for 12 weeks in direct-acting antiviral-experienced patients with genotype 1–6 HCV infection: The POLARIS-IV study. Presented at: American Association for the Study of Liver Diseases (AASLD); November 11–15, 2016; Boston, MA.

23. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology* 2015;149:649-659.

24. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. *Lancet Infect Dis* 2016;16:685-697.

25. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. *Hepatology* 2016;64:405-414.

FIGURE 1. Participant disposition in (A) the RESCUE study and (B) the A5348 study.

LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

*Four participants were reassigned treatment groups due to incorrect assessment of baseline cirrhosis status (n=3) or lack of RBV dispensing by the local pharmacy (n=1).

FIGURE 2. Proportion of participants achieving SVR12 in the RESCUE study (as-treated population) and A5348 study (as-randomized population).

Error bars represent 95% confidence intervals.

LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks post-treatment.

FIGURE 3. RESCUE SVR12 by prior treatment regimen in non-cirrhotic and cirrhotic participants (as-treated population).

LDV, ledipasvir; PEG, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks post-treatment.

TABLE 1. Baseline demographic characteristics of participants from the RESCUE study (as-treated population) and A5348 study (as-randomized population).

	RESCUE study				A5348 study	
	Non-cirrhotic		Cirrhotic		HCV/HIV	
Characteristic	LDV/SOF for 12 weeks (n=16)	LDV/SOF + RBV for 12 weeks (n=17)	LDV/SOF + RBV for 12 weeks (n=25)	LDV/SOF for 24 weeks (n=24)	LDV/SOF + RBV for 12 weeks (n=4)	LDV/SOF for 24 weeks (n=3)
Age, years, mean (min, max)	58 (48, 65)	57 (40, 64)	58 (40, 71)	60 (51, 67)	53 (48, 61)	57 (49, 65)
Male sex, n (%)	10 (63)	13 (76)	19 (76)	19 (79)	4 (100)	1 (33)
Race, n (%)						
White	10 (63)	11 (65)	17 (68)	19 (79)	3 (75)	1 (33)
Black	6 (38)	5 (29)	6 (24)	3 (13)	1 (25)	2 (67)
Hispanic ethnicity, n (%)	2 (13)	3 (18)	4 (16)	7 (29)	2 (50)	1 (33)
BMI, kg/m^2, mean (min, max)	30 (21, 48)	31 (20, 39)	31 (24, 50)	32 (19, 47)	25 (19, 31)	31 (23, 36)
HCV genotype*, n (%)						
1a	14 (88)	11 (65)	16 (64)	13 (54)	2 (50)	3 (100)
1b	1 (6)	4 (24)	5 (20)	7 (29)	2 (50)	0
4	1 (6)	2 (12)	3 (12)	3 (13)	NA	NA

HCV RNA						
log_{10} IU/mL, mean (min, max),	6.5 (5.6, 7.2)	6.4 (5.6, 7.2)	6.1 (4.3, 7.0)	6.0 (3.0, 6.9)	6.2 (5.6, 6.7)	7.1 (6.7, 7.5)
≥800,000 IU/mL, n (%)	15 (94)	13 (76)	18 (72)	16 (67)	3 (75)	3 (100)
Compensated cirrhosis, n (%)	0	0	25 (100)	24 (100)	1 (25)	0
IL28B genotype, n (%)						
CC	1 (6)	2 (12)	0	1 (4)	0	1 (33)
CT	12 (75)	11 (65)	16 (64)	17 (71)	2 (50)	2 (67)
TT	3 (19)	4 (24)	9 (36)	6 (25)	2 (50)	0
Previous HCV treatment, n (%)						
SMV+SOF	6 (38)	4 (24)	11 (44)	9 (38)	0	0
SMV+SOF+RBV	0	0	0	0	0	0
SOF+RBV	4 (25)	5 (29)	3 (12)	6 (25)	2 (50)	1 (33)
SOF+RBV+PEG	6 (38)	8 (47)	11 (44)	9 (38)	2 (50)	2 (67)
HIV positive, n (%)	0	0	0	0	4 (100)	3 (100)
On antiretroviral therapy**, n (%)	NA	NA	NA	NA	4 (100)	3 (100)
HIV RNA <50 copies/mL, n (%)	NA	NA	NA	NA	4 (100)	3 (100)

CD4+ cell count, cells/mm^3, median (Q1, Q3)	NA	NA	NA	NA	564 (435, 614)	387 (200–1150)

BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; NA, not applicable; PEG, pegylated interferon; Q, quartile; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

*Two cirrhotic participants had no confirmed GT1 subtype (LDV/SOF 24 weeks, n=1; LDV/SOF+RBV 12 weeks, n=1).

**Antiretroviral therapies included: Atripla (n=2), ritonavir-boosted darunavir and dolutegravir (n=1), Triumeq (n=1), Truvada and dolutegravir (n=1), and Truvada and ritonavir-boosted darunavir (n=2).

TABLE 2. Response following treatment in the RESCUE study (as-treated population) and A5348 study (as-randomized population).

	RESCUE study				A5348 study	
	Non-cirrhotic		Cirrhotic		HCV/HIV	
Response*	LDV/SOF for 12 weeks (n=16)	LDV/SOF + RBV for 12 weeks (n=17)	LDV/SOF + RBV for 12 weeks (n=25)	LDV/SOF for 24 weeks (n=24)	LDV/SOF + RBV for 12 weeks (n=4)	LDV/SOF for 24 weeks (n=3)
HCV RNA <LLOQ						
SVR4	15 (94)	17 (100)	22 (88)	23 (96)	4 (100)	3 (100)
SVR12	13 (81)	17 (100)	20 (80)	22 (92)	4 (100)	3 (100)
95% CI for SVR12	54–96	81–100	59–93	73–99	40–100	29–100
SVR12 in GT1a	11/14 (79)	11/11 (100)	11/16 (69)	12/13 (92)	2/2 (100)	3/3 (100)
SVR12 in GT1b	1/1 (100)	4/4 (100)	5/5 (100)	6/7 (86)	2/2 (100)	0
SVR12 in GT4	1/1 (100)	2/2 (100)	3/3 (100)	3/3 (100)	NA	NA
Virologic failure						
On-treatment viral breakthrough	0	0	0	0	0	0
Relapse	3 (19)	0	5 (20)	2 (8)	0	0

CI, confidence interval; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; LLOQ, lower limit of quantification; NA, not applicable; RBV, ribavirin; SOF, sofosbuvir; SVRn, sustained virologic response at n weeks post-treatment.

*All values are n (%) unless stated otherwise.

TABLE 3. Selected baseline characteristics of participants who had virologic failure due to relapse in the RESCUE study.

HCV genotype	Age (years)	Gender	Race	Cirrhosis	Prior HCV treatment (weeks)	Week post-treatment of virologic failure	NS5A RASs (15% cut-off)	
							Baseline	Relapse
1a	59	Male	Black	Yes	SOF+PEG+RBV (12)	4	None	Q30E
1a	50	Male	White	No	SOF+PEG+RBV (12)	4	L31M	L31M Q30R
1a	61	Male	White	No	IFN (unknown) SOF+PEG+RBV (12)	12	None	Q30Q/H Y93Y/H
1a	60	Male	White	Yes	PEG+RBV (54) SMV+SOF (12)	4	None	Q30K
1a	60	Male	White	Yes	PEG+RBV (36) SMV+SOF (24)	12	None	Q30R
1a	58	Male	White	Yes	PEG+RBV (24) SMV+SOF (24)	12	None	Y93C
1a	60	Male	White	Yes	PEG+RBV (12) SMV+SOF (12)	4	None	Q30R
1a	64	Male	White	No	PEG+RBV (54) TVR+PEG+RBV (24) SMV+SOF (12)	12	None	Q30H Y93H
1a	56	Male	Hispanic	Yes	SMV+SOF (14)	4	None	Q30E
1b	62	Male	White	Yes	PEG+RBV (48) SOF/RBV (24)	12	L31M	L31M Y93H

HCV, hepatitis C virus; IFN, interferon; PEG, pegylated interferon; RAS, resistance-associated substitution; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

TABLE 4. Common AEs reported in the RESCUE study (safety population).

	Non-cirrhotic		Cirrhotic	
Event*	LDV/SOF for 12 weeks (n=16)	LDV/SOF+ RBV for 12 weeks (n=17)	LDV/SOF+ RBV for 12 weeks (n=25)	LDV/SOF for 24 weeks (n=24)
Discontinuation of treatment owing to an AE	0	0	0	0
Serious treatment-emergent AE	0	0	0	1 (4)
Any treatment-emergent AE	11 (69)	14 (82)	22 (88)	17 (71)
Treatment-related AE	7 (44)	12 (71)	17 (68)	11 (46)
Death	0	0	0	0
Common AEs**				
Headache	5 (31)	2 (12)	9 (36)	7 (29)
Fatigue	2 (13)	6 (35)	7 (28)	4 (17)
Insomnia	1 (6)	5 (29)	3 (12)	3 (13)
Rash	1 (6)	2 (12)	5 (20)	2 (8)
Vomiting	3 (19)	1 (6)	1 (4)	1 (4)
Cough	0	3 (18)	2 (8)	0
Muscle spasms	0	0	4 (16)	0
Nausea	2 (13)	1 (6)	3 (12)	3 (13)
Chills	0	2 (12)	0	2 (8)
Increased blood CPK	0	2 (12)	0	1 (4)

Dry mouth	0	2 (12)	0	0
Hypoesthesia	0	2 (12)	0	0
Hematologic events				
Hemoglobin <10 g/dL	0	0	1 (4)	2 (8)
Lymphocyte count 350 to <500 per mm^3	0	0	0	0
Neutrophil count 500 to <750 per mm^3	0	0	0	0
Platelet count 25,000 to <50,000 per mm^3	0	0	0	2 (8)

AE, adverse event; CPK, creatine phosphokinase; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

*All values are n (%) unless stated otherwise.

**The listed AEs occurred in at least 10% of the participants in any group.