Original Article

Twelve weeks of ledipasvir/sofosbuvir all oral regimen for patients with chronic hepatitis C genotype 2 infection: Integrated analysis of three clinical trials

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Aim: The combination of ledipasvir and sofosbuvir (LDV/SOF) has been approved for the treatment of various hepatitis C virus (HCV) genotypes across many countries. This article presents an integrated analysis of three prospective phase II/III trials in the Asia Pacific region to evaluate the efficacy and safety of 12 weeks of LDV/SOF in HCV genotype 2 patients without cirrhosis or with compensated cirrhosis.

Methods: A total of 200 patients were included in the integrated analysis. The primary end point was the rate of sustained virologic response for 12 weeks after the end of therapy (SVR12), analyzed by fibrosis stage, treatment history, HCV genotype subtype, and presence of baseline resistance associated substitutions (RAS). Safety was evaluated by adverse events and laboratory abnormalities.

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**INTRODUCTION**

**HEPATITIS C VIRUS (HCV)** remains a major public health concern in Asia. Of the approximately 170 million people worldwide who are infected with HCV, over 50% live in the Asia-Pacific region.\(^1\) Hepatitis C virus is one of the leading causes of cirrhosis and hepatocellular carcinoma.\(^1\) The prevalence of chronic HCV infection among hepatocellular carcinoma cases varies by region, ranging from 12% in China, 20% in Korea, to as high as 79% in Japan.\(^2,3\) According to the Global Burden of Disease Study 2013, HCV was responsible for 416,000–585,000 deaths in the Asia-Pacific region, which accounts for 59–83% of an estimated 704,000 deaths due to HCV globally.\(^4\)

The prevalence of antibodies to HCV (anti-HCV) in this region ranges from 0.3% in New Zealand to 5.6% in Thailand, with some hyper-endemic areas in Japan, Vietnam, and Taiwan.\(^5\) Hepatitis C virus genotype 2 is the second most prevalent genotype, after genotype 1b in East Asian countries such as Korea, Japan, China, and Taiwan, where genotype 2 has a seroprevalence as high as 32–49%.\(^6,7\)

Currently, treatment options for individual patients vary according to factors such as HCV genotype, previous treatment experience, cirrhosis status, or presence of resistance-associated substitutions (RAS) at baseline. Sofosbuvir (SOF) plus ribavirin (RBV) has been the standard treatment for HCV genotype 2 in Asia. However, anemia, as the most common adverse event (AE), has been reported frequently, and the difficult-to-treat populations (e.g. cirrhotic patients with prior treatment failure) are required to receive treatment for a longer duration.\(^8,9\)

The fixed-dose combination of ledipasvir (LDV), a non-structural protein 5A (NS5A) inhibitor, and SOF, an NS5B polymerase inhibitor, is given in a single tablet (90 mg LDV and 400 mg SOF) taken orally once daily. Since 2014, LDV/SOF has been approved in many countries across the world for the treatment of HCV genotypes 1, 4, 5, and 6. With proof-of-concept studies indicating the efficacy and safety of LDV/SOF in genotype 2 HCV infection, 12-week LDV/SOF was further evaluated in phase III trials, which led to its label extension to HCV genotype 2 in Canada, followed by Japan, Taiwan, and Korea.

This article presents an integrated analysis of three clinical trials to evaluate the efficacy and safety of 12-week LDV/SOF without RBV in HCV genotype 2 patients without cirrhosis or with compensated cirrhosis. Pooled efficacy and safety results are reported here.

**METHODS**

**THE INTEGRATED ANALYSIS** included patients from three trials: NCT02202980 (LEPTON),\(^10\) NCT02613871 (HBV/HCV Coinfection),\(^11\) and NCT02738333 (Japan GT 2).\(^12\)

The LEPTON study was a phase II, multicenter, open-label study undertaken in New Zealand, to assess the efficacy and safety of LDV/SOF for 8 or 12 weeks in patients with genotype 2 HCV. The 12-week LDV/SOF arm (\(n=26\)) was included in the analysis. The HBV/HCV Coinfection study was a phase IIIb, open-label, non-randomized study undertaken in Taiwan, to evaluate the efficacy and safety of LDV/SOF for 12 weeks in patients coinfected with genotype 1 or 2 HCV and hepatitis B virus (HBV). The study arm with patients coinfected with genotype 2 HCV and HBV (\(n=43\)) was included in the analysis. The Japan GT 2 study was a phase IIIb, multicenter, open-label, randomized study undertaken in Japan, to investigate the efficacy and safety of 12-week LDV/SOF and 12-week SOF+RBV in patients with genotype 2 HCV infection. The patients treated with LDV/SOF (\(n=131\)) were included in the analysis. Study protocols were approved by local institutional review boards or independent ethics committees, and were carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Informed consent was obtained from all study participants. Details of the study designs have been reported elsewhere,\(^10–12\) and inclusion and exclusion criteria are given in Table S1.
From the three trials, a total of 200 patients who had chronic HCV genotype 2 infection and received 12 weeks of a once-daily, oral, fixed dose of 90 mg LDV and 400 mg SOF were included in the integrated analysis. The primary end-point for the integrated analysis was the rate of sustained virologic response for 12 weeks after the end of therapy (SVR12), defined as HCV RNA below the lower limit of quantification (15 IU/mL), analyzed by fibrosis stage, prior treatment, HCV genotype subtype, and presence of baseline resistance. Safety was evaluated by AEs and laboratory abnormalities. Testing methods used for the assessment of fibrosis stage and RAS are presented in the Table S2. Data from the three trials were pooled and summarized using descriptive statistics. For the primary end-point, results for both intention-to-treat (ITT) and completer analysis were reported. The ITT population was used in the reporting of SVR12 by various subgroups and safety results.

RESULTS
Patient demographics and clinical characteristics
A TOTAL OF 200 patients from the three clinical trials were included in the integrated analysis. All patients were randomized and received at least one dose of assigned study drug, and were included in the ITT analysis. Out of the 200 patients, 197 (98.5%) completed the assigned study treatment and had HCV RNA data observed at post-treatment week 12 or imputed from a later time point, and were included in the completer analysis (Fig. 1).

Most of the study participants were Asian (88%), with a mean age of 59 years. The majority of the patients were treatment-naïve (70%), with a mean HCV RNA level of 6.0 log_{10} IU/mL. Almost half of the patients had fibrosis stage F0–1 (45%), 29% had F2 fibrosis, and 12% and 15% had F3 and F4 fibrosis, respectively. One-third of patients had subtype genotype 2a/2c (34%), one-third had genotype 2b (34%), and the rest had genotype 2 of unspecified subtype. Pretreatment NS5A RAS were detected in 86% of patients. Patient demographics are summarized in Table 1.

Efficacy results of LDV/SOF for 12 weeks
Of the 197 patients included in the completer analysis, 194 (98%; 95% confidence interval [CI]: 96–100%) achieved SVR12 (Fig. 2). The three patients who did not achieve SVR12 in the Japan GT 2 study had undetectable HCV RNA at the end of the treatment but relapsed during follow-up (Fig. 2, Table S3).

Approximately one-quarter of the patients (27%) who completed treatment had advanced fibrosis (F3 or F4), and the SVR12 rate was similar across fibrosis stages: 99% of patients with fibrosis stage F0–1 (85/86; 95% CI, 94–100%), 100% of patients with F2 fibrosis (58/58; 95% CI, 94–100%), 96% (23/24; 95% CI, 79–100%), and 97% (28/29; 95% CI, 82–100%) of patients with F3 and F4 fibrosis, respectively (Fig. 3). Sustained virologic response for 12 weeks after the end of therapy was achieved by 99% (135/136; 95% CI, 96–100%) of treatment-naïve patients and 97% (59/61; 95% CI, 89–100%) of treatment-experienced patients in the integrated analysis. Combination analysis of fibrosis grade and treatment experience are provided in Table S4. Percentage of completer patients achieving SVR12 was also similar across subtypes of genotype 2 (100% [67/67; 95% CI, 95–100%] for genotype 2a/2c, 97% [63/65; 95% CI, 89–100%] for genotype 2b, and 99% [64/65; 95% CI, 92–100%] for patients with unspecified genotype subtype) (Fig. 3).

Finally, a virology analysis that included all patients who completed treatment, SVR assessment, and for whom NS5A sequence was available at baseline showed that 98% of patients (165/168; 95% CI, 94–98%) with NS5A RAS and 100% of patients (28/28; 95% CI, 88–100%) without NS5A RAS achieved SVR12 (Fig. 3). None of the three patients who relapsed had treatment-emergent NS5A RAS. One patient who relapsed had treatment-emergent NS5B nucleoside inhibitor S282T at relapse, which became undetectable 12 weeks post-treatment.

Safety and tolerability results of LDV/SOF
The overall incidence of AEs was similar across all three trials (Table 2). The most common AEs (reported in ≥5% of the cohort) included headache in 11% (n=21), nasopharyngitis in 8% (n=15), fatigue in 5% (n=9), and nausea in 5% (n=9) (Table 2). Serious AEs were infrequent across patient groups, occurring in 3% of participants (n=6), with grade 3–4 AEs in 2% of participants (n=4), none of these events were considered related to study treatment. Only one patient with a medical history of rheumatoid arthritis self-discontinued treatment due to a grade 2 AE of worsening rheumatoid arthritis, which was considered related to treatment. One death was reported in the Japan GT 2 study, in which a patient died 153 days post-treatment from polytrauma due to a fall, which was considered not related to the study drug.

DISCUSSION

EDIPASVIR/SOFOSBUVIR HAS BEEN approved for the treatment of HCV genotypes 1, 4, 5, and 6 across
many countries globally, and its efficacy and safety in these genotypes have been reported in both clinical and real-world studies. The SVR12 of LDV/SOF in HCV genotype 1 ranges from 95% to 98% in global clinical trials and 94% to 100% in real-world cohorts;13 in Asian patients with HCV genotype 1 infection, LDV/SOF has even higher SVR12 rates, with up to 97–100% in clinical trials and real-world experience.14–17 In HCV genotypes 4, 5, and 6, LDV/SOF has been shown to have SVR12 rates of 93–95%.18,19

Ledipasvir was shown to have different antiviral activities against different HCV genotypes in in vitro assays, with the highest potency against genotype 1 virus (half-maximal effective concentration [EC₅₀] ranging from 0.004 nM to 0.031 nM for different subtypes); whereas for genotype 2, the EC₅₀ values ranged from 16 nM to 530 nM, which is approximately 4000–17000-fold higher than that of genotype 1.20 However, when LDV is combined with SOF, which serves as a backbone with a potent antiviral activity and a high genetic barrier against all HCV genotypes,21 the integrated analysis showed that 12-week LDV/SOF was associated with high SVR12 rates (overall 98%) in patients with genotype 2 HCV, irrespective of fibrosis stage or treatment history. The results are consistent with a recently published Taiwan real-world study in genotype 2 patients, which reported an SRV12 of 100% with LDV/SOF (n=39), compared with 94% with SOF + RBV (n=82) and 99% with SOF plus daclatasvir (n=66).22 Similarly, a real-world study in genotype 2 Japanese patients (n=58) reported an SRV12 of 95% with 12-week LDV/SOF, with high efficacy in most subgroups including older age, compensated cirrhosis, and treatment experience.23 A propensity score matched analysis undertaken in the same study showed no statistically significant difference (P=0.57) in SRV12 rates between LDV/SOF (96%) and glecaprevir/pibrentasvir (98%).23 Also, a nationwide randomized controlled trial in Italy reported an SRV12 of 100% in mixed genotype 1b/2a and genotype 2a HCV patients with thalassemia major (n=7).24

In genotype 2 patients, NS5A RAS polymorphisms are highly prevalent – 86% (168/196) of patients in the complete analysis had NS5A RAS at baseline. In vitro studies showed that L31M, one of the most common NS5A RAS polymorphisms in genotype 2,25 confers a 12-fold and 33-fold reduction in LDV antiviral activity in genotypes
2a and 2b, respectively. Despite the reduction in LDV activity, LDV/SOF for 12 weeks was still associated with high SVR12 rates irrespective of genotype 2 subtype or baseline NS5A RAS presence in this integrated analysis. Treatment with LDV/SOF for 8 weeks was also studied in parallel in the LEPTON study; nevertheless, only 74% (20/27) achieved SVR12, and of the seven genotype 2a and six genotype 2b patients with baseline NS5A RAS, 29% (2/7) and 83% (5/6) achieved SVR12, respectively. It was unclear whether the low SVR12 for 8-week LDV/SOF was associated with NS5A RAS or with genotype 2a, because of the small number of patients. The high SVR12 for 12-week LDV/SOF treatment in genotype 2 could be attributable to the sufficient treatment duration (i.e. 12 weeks), the high NS5B inhibitor activity of SOF, which is fully active against a panel of NS5A mutants showing reduced susceptibility to LDV in vitro, or a combination of both factors.

Treatments with LDV/SOF and SOF+RBV for 12 weeks have comparable efficacy in HCV genotype 2, with an SVR12 of 98% for LDV/SOF in the integrated analysis, with an SVR12 of 100% in Taiwan, and 97% in Korea and Japan for SOF+RBV in trials. However, RBV has been associated with AEs such as anemia,

| Table 1 Demographics of patients with chronic hepatitis C genotype 2 infection treated with 12 weeks of ledipasvir/sofosbuvir |
|---------------------------------------------------------------|
| **Baseline demographics**                                      |
| Age, mean (SD)                                                | 53 (11.1) | 56 (8.1) | 61 (11.6) | 59 (11.3) |
| Male sex, n (%)                                               | 17 (65)   | 16 (37)  | 58 (44)   | 91 (46)   |
| Body mass index, mean (SD)                                   | 26 (3.8)  | 25 (3.7) | 24 (3.6)  | 24 (3.7)  |
| Asian, n (%)                                                  | 2 (8)     | 43 (100) | 131 (100) | 176 (88)  |
| **Baseline disease characteristics**                          |
| Treatment naïve, n (%)                                        | 21 (81)   | 33 (77)  | 85 (65)   | 139 (70)  |
| Fibrosis stage, n (%)                                         | 18 (69)   | 12 (28)  | 59 (45)   | 89 (45)   |
| F0–F1                                                        | 4 (15)    | 15 (35)  | 39 (30)   | 58 (29)   |
| F2                                                           | 2 (8)     | 8 (19)   | 14 (11)   | 24 (12)   |
| F3                                                           | 2 (8)     | 8 (19)   | 19 (15)   | 29 (15)   |
| HCV RNA, log10 IU/mL, mean (SD)                               | 6.1 (0.66)| 5.9 (0.80)| 6.0 (0.77)| 6.0 (0.77)|
| **Genotype 2 subtype, n (%)**                                 |
| 2 with unspecified subtype                                    | 2 (8)     | 14 (33)  | 50 (38)   | 66 (33)   |
| 2a or 2a/2c                                                   | 8 (31)    | 15 (35)  | 44 (34)   | 67 (34)   |
| 2b                                                           | 16 (62)   | 14 (33)  | 37 (28)   | 67 (34)   |
| NS5A RAS, n/N (%)                                             | 16/25 (64)| 35/43 (81)| 118/129 (91)| 169/197 (86)|

†Genotype based on VERSANT INNO-LiPA 2.0 Assay analysis.
‡Number of patients with baseline non-structural protein 5A (NS5A) sequence data.

2a and 2b, respectively. Despite the reduction in LDV activity, LDV/SOF for 12 weeks was still associated with high SVR12 rates irrespective of genotype 2 subtype or baseline NS5A RAS presence in this integrated analysis. Treatment with LDV/SOF for 8 weeks was also studied in parallel in the LEPTON study; nevertheless, only 74% (20/27) achieved SVR12, and of the seven genotype 2a and six genotype 2b patients with baseline NS5A RAS, 29% (2/7) and 83% (5/6) achieved SVR12, respectively. It was unclear whether the low SVR12 for 8-week LDV/SOF was associated with NS5A RAS or with genotype 2a, because of the small number of patients. The high SVR12 for 12-week LDV/SOF treatment in genotype 2 could be attributable to the sufficient treatment duration (i.e. 12 weeks), the high NS5B inhibitor activity of SOF, which is fully active against a panel of NS5A mutants showing reduced susceptibility to LDV in vitro, or a combination of both factors.

Treatments with LDV/SOF and SOF+RBV for 12 weeks have comparable efficacy in HCV genotype 2, with an SVR12 of 98% for LDV/SOF in the integrated analysis, with an SVR12 of 100% in Taiwan, and 97% in Korea and Japan for SOF+RBV in trials. However, RBV has been associated with AEs such as anemia,
hyperuricemia, and fatigue, as well as genotoxicity and teratogenicity in younger patients. Apart from a better safety profile, LDV/SOF, as an RBV-free regimen, has been associated with a better health-related quality of life (HRQOL) in chronic HCV patients both during and after treatment, compared with RBV-containing regimens. An analysis of 494 genotype 1 and genotype 2 HCV patients in Japan treated with LDV/SOF+RBV and SOF+RBV with similar HRQOL scores at baseline found that more AEs were experienced during treatment by those who received RBV-free regimens (46% vs. 22%). Patients who received RBV-containing regimens also had mild HRQOL decreases, whereas patients treated with LDV/SOF not only showed high efficacy but also HRQOL improvement. Other than being RBV-free, the absence of protease inhibitors could also contribute to the favorable safety profile of LDV/SOF, which does not require dosage modification regardless of hepatic impairment severity (Child–Pugh class A, B, or C). Moreover, being a 12-week fixed treatment duration regimen regardless of fibrosis stage, LDV/SOF eliminates the requirement of fibrosis stage testing, particularly for borderline patients. This integrated analysis shows that LDV/SOF had a high SVR12 of 97% and a good safety profile even in patients with F4 fibrosis. Although patients with more advanced hepatic impairment (i.e. decompensated cirrhosis) were not included in this analysis, LDV/SOF plus RBV has been shown to be efficacious and safe in genotype 1 and genotype 4 HCV patients with decompensated cirrhosis.

### Table 2: Safety results from three trials of 200 patients who had chronic hepatitis C virus (HCV) genotype 2 infection treated with 12 weeks of ledipasvir/sofosbuvir

| Patients, n (%) | LEPTON (n = 26) | HBV/HCV Coinfection (n = 43) | Japan GT 2 (n = 131) | Total (n = 200) |
|----------------|----------------|-----------------------------|-------------------|----------------|
| Any AE | 17 (65) | 22 (51) | 78 (60) | 117 (59) |
| Grade 3–4 AE | 1 (4) | 0 (0) | 3 (2) | 4 (2) |
| Serious AE | 1 (4) | 2 (5) | 3 (2) | 6 (3) |
| Treatment discontinuation due to AE | 0 (0) | 0 (0) | 1 (<1) | 1 (<1) |
| Death | 0 (0) | 0 (0) | 1 (<1) | 1 (<1) |
| Common AEs | | | | |
| Headache | 6 (23) | 3 (7) | 12 (9) | 21 (11) |
| Nasopharyngitis | 0 (0) | 2 (5) | 13 (10) | 15 (8) |
| Fatigue | 6 (23) | 2 (5) | 1 (<1) | 9 (5) |
| Nausea | 4 (15) | 0 (0) | 5 (4) | 9 (5) |

AE, adverse event; GT, genotype; HBV, hepatitis B virus; HCV, hepatitis C virus.

Figure 3: Efficacy in completers of 12 weeks of ledipasvir/sofosbuvir for chronic hepatitis C genotype 2 infection, by subgroup. Error bars represent 95% confidence intervals, derived from the Clopper–Pearson method. NS5A, non-structural protein 5A; RAS, resistance associated substitution; SVR12, sustained virologic response 12 weeks after treatment; TE, treatment experienced; TN, treatment naïve.
The use of LDV/SOF in patients with advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m²) might be of concern to some physicians, as SOF and its metabolite GS-331007 are mainly eliminated through renal clearance. However, a recent update to LDV/SOF’s FDA prescribing information in March 2020 determined that no LDV/SOF dose adjustment is required in patients with any degree of renal impairment, including end-stage renal disease on dialysis, affirming that LDV/SOF could be used safely in this population. This update was based on the well-tolerated safety profile of LDV/SOF reported in two open-label, phase II studies in renally impaired patients: Trial 0154 with 12-week LDV/SOF in 18 genotype 1 patients with severe renal impairment not requiring dialysis; and Trial 4063 with 8-, 12-, or 24-week LDV/SOF in 95 genotype 1, 2, 4, 5, and 6 patients with end-stage renal disease on dialysis. Despite reporting a higher area under curve exposure to the SOF metabolite GS-331007 in patients, there were no treatment-related serious AEs, discontinuation due to AEs, or virologic failures in both trials. In addition, as the HCV patient population in Asia could represent an elderly demographic, with the majority of patients having comorbidities and receiving concomitant medications, careful evaluation of potential drug–drug interactions between direct-acting antivirals (DAAs) and concomitant medications is important. For example, cotreatment of LDV/SOF with amiodarone is not recommended due to the risk of serious bradycardia, although its mechanism is unknown.

Given LDV/SOF’s efficacy and safety profiles in HCV genotypes 1 and 2, it can potentially treat most HCV patients in countries where these genotypes account for the majority of the HCV population. More importantly, high SVR12 rates and a good safety profile with minimal on-treatment monitoring requirements allow LDV/SOF to play a crucial role in helping these countries achieve the WHO’s goal of HCV elimination by 2030. A real-world study undertaken in rural Mongolia, where genotype 1 is the most prevalent HCV genotype, confirmed the safety and efficacy of LDV/SOF as part of a test-and-treat model of care for HCV microelimination. Patients recruited from primary care clinics were screened with HCV rapid diagnostic tests, and all HCV patients were offered LDV/SOF. Of the 1019 patients who completed treatment, 99% achieved SVR12. This showed the value of LDV/SOF with a fixed dose and a fixed treatment duration in helping to promote health equity and universal healthcare for HCV patients in resource-limited settings in lower and middle income countries. Similarly, in Georgia, LDV/SOF enables the implementation of a large-scale national HCV elimination program, and has already played a significant role in the program. In 2015, the anti-HCV prevalence in Georgia was estimated at 7.7%, with genotypes 1, 2, and 3 accounting for 41%, 25%, and 34% of HCV infections, respectively. As part of the elimination program, which aims to reduce the HCV prevalence by 90% (to 0.5%) by 2020, 2006 patients have been treated with LDV/SOF plus RBV, and the overall SVR across genotypes 1–3 was 98%. In 2016, the fixed dose combination of SOF and velpatasvir (VEL) was approved as a pan-genotypic DAA regimen first in the USA, and it was then recommended for HCV elimination by the WHO in 2019, given its high SVR12 rates regardless of genotype, treatment experience, and cirrhosis status. Depending on region and health-care system, LDV/SOF and SOF/VEL, both with proven efficacy and safety profiles, might play complimentary roles. In countries with limited access to SOF/VEL, LDV/SOF still remains a good treatment option.

A limitation to the current integrated analysis is that it includes genotype 2 patients from only three Asia-Pacific countries, rather than being representative of a more general genotype 2 patient population across regions. Moreover, it did not specifically investigate the efficacy and safety of LDV/SOF in special populations with genotype 2 HCV, such as patients coinfected with HIV or patients with liver decompensation, who could have a higher potential for AEs, compared with general HCV patients.

In conclusion, LDV/SOF for 12 weeks provides a highly effective and safe treatment for patients with genotype 2 HCV, including those with advanced fibrosis.

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**SUPPORTING INFORMATION**

ADDITIONAL SUPPORTING INFORMATION may be found online in the Supporting Information section at the end of the article.

Table S1. Inclusion and exclusion criteria

Table S2. Assessment of fibrosis stage and resistance-associated substitutions

Table S3. Details of three cases of treatment failures in completer analysis

Table S4. Sustained virologic response for 12 weeks after the end of therapy (SVR12) by fibrosis grade and treatment experience

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