Research Article
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Sofosbuvir/Velpatasvir fixed dose combination in Indian patients with chronic hepatitis c virus (HCV) infection: an open-label, single-arm, multicenter phase IV study

Abstract

Background: This Phase IV post-marketing study was conducted to demonstrate the safety and efficacy of sofosbuvir/velpatasvir fixed-dose combination (FDC) in adult Indian patients with HCV infection as per the recommendation of the Drugs Controller General (India).

Methods: This single-arm, open-label, multicenter study was conducted across 22 sites in 409 patients in India. All the eligible patients received once-daily sofosbuvir/velpatasvir (400mg/100mg) FDC for 12weeks. Safety was assessed by monitoring the adverse events (AEs) and efficacy was measured by the proportion of patients achieving sustained virological response (HCV RNA <15 IU/mL or undetectable) at 12weeks after the end of the treatment (SVR12).

Results: Between October 2018 to June 2020, 409 patients were enrolled. Twenty patients discontinued the study due to consent withdrawal or lost to follow-up. The SVR12 rate was 90.8%. Sensitivity analysis showed consistent results with SVR12 rates of more than 93%. The combination was well tolerated and none of the AEs reported were related to the study drug, requiring dose reduction, or discontinuation of the study treatment.

Conclusions: Once daily sofosbuvir/velpatasvir FDC for 12 weeks was found to be safe, well tolerated, and effective in patients with HCV infection.

Trial Registration: The trial is registered at clinical trial registry of India with registration number CTRI/2018/08/015359. (CTRI Trial Data)

Keywords: Sofosbuvir/Velpatasvir, hepatitis C virus, SVR12, pangenotypic, public health

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Parika Amardev Kalra,[1] Asokananda Konar,[2] Hemant Gupta,[3] Jignesh Babulal Patel,[4] Macherla Ramanna,[5] Omesh Goya,[6] Shravan Kumar P,[7] Praveen Sharma,[8] Rajiv Baijal,[9] Rakesh Pravinchandra Patel,[10] Sandeep Shamrao Kulkarni,[11] Sanjay Hadigal,[12] Sanjeev Hegde,[13] Saumin Prakashbhai Shah,[14] Shanti Vijayaraghavan[15]

[1]Department of Medicine, Surat Institute of Digestive Sciences, India
[2]Department of Gastroenterology, Peerless Hospital and Research Ltd, India
[3]Department of Gastroenterology, Samvedna Hospital, India
[4]Department of Gastroenterology, Saviour Hospital, India
[5]Department of Gastroenterology, Osmania General Hospital, India
[6]Department of Gastroenterology, Dayanand Medical College and Hospital, India
[7]Department of Gastroenterology, Gandhi Hospital, India
[8]Department of Gastroenterology, Sir Ganga Ram Hospital, India
[9]Department of Gastroenterology, PSRI hospital, India
[10]Department of Gastroenterology, Meera Hospital, India
[11]Department of Gastroenterology, Sahyadri Super Specialty Hospital, India
[12]Department of Medical Affairs, Viatris, India
[13]Department of Global Clinical Operations, Viatris, India
[14]Department of Clinical Research, Unique Hospital-Multispeciality & Research Institute, India
[15]Department of Gastroenterology, Sri Ramachandra Hospital, India

Correspondence: Dr. Sanjay Hadigal, MD, Global Medical Lead- Infectious Disease / Hepatology / Vaccines & Tail Brands, Viatris (Formerly Mylan Laboratories Limited), India, Tel +91 9611000386, Email sanjay.hadigal@viatris.com

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Abbreviations: AE, adverse event, BLOQ, below the lower limit of quantification, BMI, body mass Index, CI, confidence interval; DAA, direct-acting antiviral; DCGI, drugs controller general of India, eGFR, estimated glomerular filtration rate, EOS, end of study, EOT, end of treatment, ESRD, end-stage renal disease, FAS, full analysis set, FDA, food and drugs administration, FDC, fixed dose combination, GCP, good clinical practice, HCC, hepatocellular carcinoma, HCV, hepatitis C virus, ICH, international conference on harmonization, LLOQ, lower limit of quantification, LOCF, Last observation carried forward, PPS, per-protocol set, SAE, serious adverse event, SAS®, statistical analysis system, SD, standard deviation, SVR, sustained virological response, TEAE, treatment-emergent adverse event

Introduction

Chronic hepatitis C virus (HCV) infection is a global concern due to hepatic and extrahepatic complications, including malignancies.[1,2,3] In 2019, the newly infected HCV patients were 1.5million, with an incidence of 19 cases per 100,000 population globally.[4] The Indian scenario is no different, with approximately 1 in 100 individuals being infected by HCV.[5] The disease affected nearly 4.7 to 10.9million population as per 2015 global estimates.[6] Furthermore, the mortality rates continue to remain high and are estimated to be as high as 96,000 every year.[5]

The major challenge in HCV treatment is the prevalence of various HCV genotypes and subtypes and the varying effectiveness

of each direct-acting antiviral drug (DAA) against each genotype.[7] The availability of pan-genotypic DAAs has revolutionized the treatment approach, due to high HCV eradication rates, regardless of the genotype of the patient.[8,9]

The most commonly used pan-genotypic DAAs are sofosbuvir/daclatasvir and sofosbuvir/velpatasvir. Sofosbuvir/velpatasvir has shown to be efficacious with 12 weeks of treatment in cirrhotic patients and has demonstrated its safety and efficacy irrespective of the liver status.[10,11] The sustained virological response (SVR) rates with sofosbuvir/velpatasvir treatment in the global studies ranged from 95-99%.[10,11]

This once-daily, single-dose regimen was approved by Food and Drugs Administration (FDA) for the treatment of chronic Hepatitis C in 2016. The Drugs Controller General India (DCGI) approved the combination in 2017 considering the public health need due to the high prevalence rates of HCV in India. However, the agency required that the sponsor (Mylan Pharmaceuticals Private Limited) conducts a post-marketing phase IV study to show the safety and efficacy of the combination in Indian patients.

Therefore, the objective of the present study was to evaluate the safety and efficacy of the sofosbuvir/velpatasvir fixed-dose combination (FDC) in adult Indian patients with HCV infection.

Material and methods

Study design

This phase IV, multicenter, prospective, open-label, single-arm study was conducted across 22 centers in India from October 2018 to June 2020. The study for each subject consisted of 3 weeks screening period, 12weeks treatment period, and a follow-up phase of another 12weeks after administration of the last dose of study drug (Figure 1). The study design was discussed with the Indian agency (DCGI) prior to the study initiation.

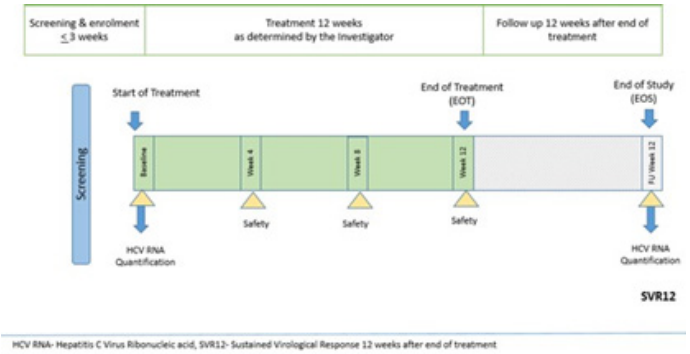

Figure 1 Overall Schema of Study Design.

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines and approved by each center's institutional review board (Supplementary Table 1). A written informed consent was obtained from each patient at screening prior to any study-specific assessment. All authors had access to the study data, and reviewed and approved the final manuscript.

Supplementary Table 1 Details of the IEC and/or institutional review boards approving the study

S. No.	Name of committee	Institution name	Date of approval
1	Care Hospital Nagpur Ethics Committee	Ganga Care Hospital Limited	03/08/2018
2	Clinical Research Ethics Committee Peerless Hospitex Hospital And Research Center, Kolkata	Peerless Hospitex Hospital And Research Center Ltd	20/02/2019
3	Drug Trial Ethics Committee, DMCH	Dayanand Medical College and Hospital	25/09/2018
4	Ethics Committee, Guntur medical college and Government General Hospital	Guntur medical college & Government General Hospital	26/10/2018
5	Ethics Committee, Shankar Vidyarthi Memorial Medical College, Kanpur	Ganesh Shankar Vidyarthi Memorial Medical College	11/09/2018
6	Ethics Committee, Unique Hospital-Multispeciality& Research Institute	Unique Hospital-Multispeciality & Research Institute	26/07/2018
7	Fortis Hospital Institutional Ethics Committee, Noida	Fortis Hospital	31/07/2018
8	Institutional Ethics Committee Gleneagles Global Hospitals	Aware Gleneagles Global Hospitals	30/07/2018
9	Institutional Ethics Committee of Meenakshi Mission Hospital and Research Center	Meenakshi Mission Hospital & Research Centre	09/07/2018
10	Institutional Ethics Committee, Gleneagles Global Hospitals, Hyderabad	Gleneagles Global Hospital	26/04/2019
11	Institutional Ethics Committee, Jubilee Mission Medical College	Jubilee Mission Medical College & Research Institute	11/09/2018
12	Institutional Ethics Committee, M.V Hospital and ResearchCentre, Lucknow	M.V Hospital and Research Centre	25/08/2018
13	Institutional Ethics Committee, Osmania General Hospital	Osmania General Hospital	09/01/2019
14	Institutional Ethics Committee, SAL Hospital	SAL Hospital and Medical Institute	19/01/2019
15	Institutional Ethics Committee, Sri Ramachandra Hospital	Sri Ramachandra Hospital	12/11/2018
16	Institutional Ethics Committee Gandhi Medical College and Hospital	Gandhi Medical College and Hospital	27/07/2018
17	Meera Institutional Ethics Committee	Meera Multispeciality Hospital	23/10/2018
18	Pushpawati SinghaniaHospital & Research Institute Ethics Committee	Pushpawati Singhania Hospital & Research Institute	08/05/2019
19	Sahyadri Hospitals Ltd Ethics Committee	Sahyadri Super Specialty Hospital	25/07/2018
20	Samvedna Hospital Ethics Committee,Varanasi	Samvedna Hospital	12/11/2018
21	Saviour Hospital Ethics Committee	Saviour Hospital	28/07/2018
22	Sir Ganga Ram Hospital Ethics Committee	Sir Ganga Ram Hospital	15/02/2019
23	Surat Institute of Digestive SciencesEthics Committee	Surat Institute of Digestive Sciences	06/07/2018

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Study population

Patients between 18-65 years (both inclusive) of age with a confirmed diagnosis of chronic HCV infection were eligible for participation in the study if their BMI was ≥18 kg/m^2 and Child-Pugh Score <10.

Patients with chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alpha 1 antitrypsin deficiency, cholangitis) or a known coinfection with hepatitis B virus and/or human immunodeficiency virus were excluded from the study. Other exclusion criteria included documented or suspected hepatocellular carcinoma (HCC), evidence of hepatic decompensation, haemoglobin levels ≤8.5g/dL (5.27mmol/L), and clinically relevant drug or alcohol abuse within 12months of screening. Patients with renal impairment (estimated glomerular filtration rate [eGFR] <45mL/min/1.73 m^2 or End-stage Renal Disease (ESRD) requiring haemodialysis) or those having any contradictions to receiving sofosbuvir/velpatasvir FDC were also ineligible for participation.

Study treatment

Post-screening, all eligible patients received the approved prescribed dose of sofosbuvir/velpatasvir (400mg/100 mg) FDC, orally once daily with or without food for 12weeks. The patients were instructed to take each dose at the same time each day. All patients were followed-up at week 4, week 8, week 12, and up to 12weeks after the last dose of study drug. Additional telephonic follow-ups were arranged during week 16 and week 20 (Figure 1).

Treatment was discontinued at the discretion of the investigator if the patient developed an adverse event (AE) or failed to respond to the study drugs. If the patient failed to respond to the study drug, and the patient or the Investigator felt it was in the best interests of the patient to seek another treatment, the patient was discontinued from the study. Every effort was made to complete all end-of-the-treatment (EOT) procedures per protocol. Additionally, attempts were made to complete telephonic safety follow-up assessments 4weeks later.

Study assessments and endpoint

Safety was the primary endpoint in this study. Concomitant medications and compliance were assessed, and AEs were recorded during each follow-up visit apart from the regular physical examination. Safety was assessed by recording the AEs, and serious AE, as reported by the patient or appropriate caregiver, throughout the study. Safety assessments also included laboratory results, 12-lead Electrocardiogram, vital signs, and physical examinations. Liver cirrhosis was detected using a non-invasive technique followed in routine clinical practice, which allowed the investigator to evaluate the extent of fibrosis and cirrhosis of the liver.

Efficacy was the secondary endpoint in the study, measured as the proportion of patients achieving SVR (HCV RNA <15IU/mL or undetectable) at 12 weeks (SVR12) after the last dose of study medication. Blood samples for determination of HCV RNA levels were collected at screening, week 12 (EOT), and week 24 (or 12weeks after EOT). Full details of the assessment are provided in Supplementary Table 2.

Supplementary Table 2 Schedule of assessments for the 12-week study

12-week regimen	Screening (<3 weeks)	Baseline (Day 1)	Week 4, Week 8 (±5 Days)	End of Treatment Visit (EOT) Week 12 (±5 Days)	Telephonic Follow-up (Week 16, Week 20) ±5 Days	SVR12 Visit/ End of Study (EOS) Week 24 (±7 Days)
Informed consent	X					
Demographics	X					
Inclusion and exclusion criteria	X	X				
Treatment Regimen		X				
Medical history	X					
Prior medication/treatment	X	X				
Height	X					
Weight	X					
Physical examination[a]	X	X		X		X
12-Lead ECG[b]	X			X		
Vital signs (HR, RR, BP, temperature)[c]	X	X		X		X
Assessment of liver stiffness	X					
Pregnancy test[d]	X					X
Hematology and clinical chemistry[e]	X			X		X
Urinalysis[f]	X			X		X
Child-Pugh Score[g]	X					
Concomitant medication	X	X	X	X		X
Adverse events[h]	X	X	X	X	X	X
HCV-RNA levels Quantitative	X			X		X
Dispense study treatment		X	X			

a. A physical examination included the evaluation of general appearance, eyes, head and neck, abdomen, lymph nodes, skin, cardiovascular system, respiratory system, musculoskeletal system and assessment for ascites.

b. A standard 12-lead ECG was recorded after 5 minutes of rest in the supine position.

c. Vital signs were measured by the Investigator or his or her designee after 5 minutes of rest (sitting).

d. Pregnancy test was only required for females of childbearing potential. Serum pregnancy was performed at screening and EOS visit. The urine pregnancy test could be performed additionally at other visits if clinically indicated. If urine pregnancy was found to be positive, serum pregnancy was to be done for confirmation.

e. All hematology and clinical chemistry laboratory assessments were conducted preferably in a fasted state. Clinical chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, glucose, calcium, chloride, cholesterol, creatinine, γ-glutamyltransferase, phosphate, potassium, sodium, total bilirubin, urea (blood urea nitrogen), prothrombin, INR. Hematology: hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, red blood cell count, and white blood cell count with differential count.

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Supplementary Table 2 Continued...

f. Complete urinalysis (dipstick analysis): blood, urobilinogen, ketones, glucose, protein, and urine microscopy.

g. Child-Pugh Score was calculated using table 1 mentioned below.

h. AEs were monitored continuously during the study and were recorded in the eCRF at each study visit, i.e., from the time the informed consent form was signed until the EOS visit (12 weeks after the EOT). All AEs were followed until resolution or deemed stable or until the event was found to be due to another known cause (concurrent condition or medication) and clinical judgment indicated that further evaluation was not warranted. Should an Investigator was made aware of any SAE occurring any time after the active reporting period, the SAE (in case of reasonable causality) was to be reported to sponsor within 24 hours.

Statistical analysis

A sample size of 110 patients was initially chosen for the study that was statistically demonstrated to be a good number to evaluate the safety endpoints, which is defined as the occurrence of AEs in the study. However, the sample size was increased to 400 enrolled patients as per the recommendation from DCGI to make proper evaluations of efficacy outcomes as well. A sample size of 120 to 500 per arm was used in the FDA registration studies[10,11] to evaluate the efficacy of sofosbuvir/velpatasvir combination.

Continuous variables were summarized using the mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables were summarized using frequency counts and percentages. P-values less than 0.001 were considered significant and reported. All tests were two-sided at the α=0.05 level of significance, if not stated otherwise.

Safety assessments were conducted using the Safety Analysis Set which included all patients who received at least one dose of study treatment. Efficacy was evaluated using the Full Analysis Set (FAS) as the primary analysis, to include all treatment-allocated patients with at least one post-baseline evaluable efficacy assessment. The proportion of patients achieving SVR12 was estimated and presented along with 95% CI for single proportions based on exact Clopper-Pearson method. Patients who had missing virological response at 12weeks after the EOT were considered as non-responders in the primary analysis and were imputed using the Last Observation Carried Forward (LOCF) approach. In addition, the analysis was repeated using a complete case analysis (non-responders who had completed the study) and Per-Protocol Set (PPS) (PPS included all patients who received the study treatment and had achieved both endpoints with no major protocol deviations). The Virological response was also summarized descriptively by visits. Patients who had HCV viral load count values below the Lower Limit of Quantification (LLOQ) were imputed with values of LLOQ/2 for actual data and zero for Log10 transformed value for summarizing descriptive statistics. All data were analyzed using SAS® Version 9.4 (SAS Institute Inc., USA).

Results

Patient characteristics

Subject disposition: A total of 553 patients were screened of which 409 eligible patients were enrolled in the study (Figure 2). Of the 409 enrolled patients, 389 (95.1%) patients completed the study, and 20 patients discontinued due to consent withdrawal (n=12), lost to follow-up (n=4), protocol violation (n=3), and death (n=1).

Subject characteristics

The study population was predominantly male patients (n=225, 55%) with a mean (SD) age of 42.9 (12.54) years. The baseline assessment suggested that 80.9% (n=331) of patients were not having any clinically examined or reported fibrosis or cirrhosis. Since sofosbuvir/velpatasvir FDC is a pan-genotypic regimen, genotyping is not essential for starting the medication. However, if patients had done genotyping previously, the data was collected. Genotyping data was available in 16.6% patients (n=68) and the remaining 83.4% (n=341) patients did not have genotyping data (Table 1). The mean treatment duration was 85.44 (±9.853) days per patient with 95.1% having compliance of 80% to 120% (Table 2).

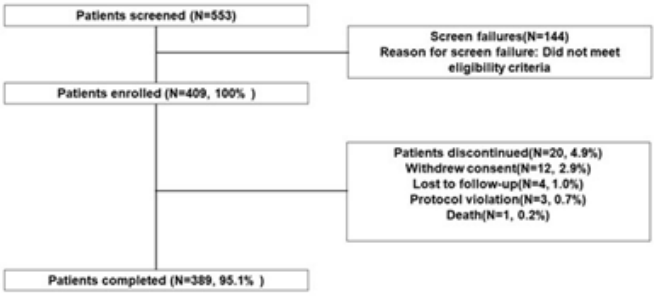

Figure 2 Subject Disposition.

Table 1 Baseline demography and disease characteristics

Demographic characteristic	All patients (N=409)
Age, years; mean (SD)	42.9 (12.54)
Gender, n(%)	
Male	225 (55.0)
Female	184 (45.0)
BMI, kg/m^2; mean (SD)	24.1 (3.66)
Genotypes from prior history, n(%)	
1	19 (4.6)
2	0
3	45 (11.0)
4	4 (1.0)
5	0
6	0
Unknown	341 (83.4)
Fibrosis and/or cirrhosis, n(%)	78 (19.1)
Mean (SD) HCV RNA, $\log_{10}$ IU/mL	5.82 (±0.960)
Median (range) ALT, U/L	57 (6, 538)

Abbreviations: BMI, body mass index; n, number of patients; N, total number of patients; SD, standard deviation, HCV, Chronic hepatitis C virus, ALT, alanine aminotransferase

Table 2 Treatment Compliance as recorded for all the patients

Characteristic (Unit)	Statistics	All patients (N =409)
Compliance(%)	N	408
	Mean (SD)	101.78 (10.622)
	Median	101.19
	Min, Max	2.4, 133.3
Compliance(%)	n(%)	
< 80%		9 (2.2)
≥80% - ≤120%		389 (95.1)
> 120%		10 (2.4)

Abbreviation: Max, maximum; Min, minimum; SD, standard deviation, N, total number of patients

Medical history and concomitant medication

Assessment of the medical history of the patients suggested that 43.2% of the patients (173/409) were having at least one medical

history that included metabolism and nutrition disorder (11%), prior surgical or medical procedure (10%), gastrointestinal complication (9.3%), and hepatobiliary disorder (8.3%). All the patients were treatment naïve and had not received any prior treatment for HCV infection. Prior and concomitant medication intake by the patients were analyzed with 6.4% (n=26) and 42.5% (n=174) patients receiving at least one prior and one concomitant medication, respectively. The most common medications received by the patients were drugs related to gastric acid-related disorders (2.0%), vitamins (1.7%), antibacterial medications for systemic use (1.5%), drugs associated with bile and liver therapy (1.2%), and beta blockers (1.0%).

Analysis set

All the eligible patients (n=409) were enrolled for the safety analysis. The FAS of this study (n=404) for efficacy analysis did not contain another 5 patients due to early termination following the missing viral load. The PP analysis (n=375) excluded 34 patients due to non-availability of viral load information impacted by the COVID-19 situation.

Safety evaluation

Overall, 116 (28.4%) patients reported at least one treatment-emergent AE (TEAE) and none of the TEAEs were related to the study drug. The most-reported TEAEs in ≥2% of patients were pyrexia (9.8%), fatigue (3.9%), headache (2.9%), cough (2.2%), nausea, and vomiting (2.0% each) (Table 3). Most of the AEs were recovered/resolved by the end of the study period. One patient (0.2%) had severe TEAE (unrelated to the study drug) which was captured as serious AEs (SAE) (pneumonia, hepatic encephalopathy, and sepsis), and died during the study. None of the patients had an AE requiring dose reduction or temporary discontinuation of study treatment.

Efficacy evaluation

Virologic response: The efficacy analysis conducted using FAS showed SVR12 response rates of 90.8% (95% CI 87.6%-93.5%). The SVR12 response rate in sensitivity analysis for the LOCF approach, complete case, and PP set were 94.8% (95% CI 92.2%-96.8%), 93.9% (95% CI 91.0%-96.0%), and 94.4% (95% CI 91.6%-96.5%), respectively. All sensitivity analysis showed consistent results with the primary analysis demonstrating an SVR12 response rate of more than 93% (Table 4).

The virological response was also analyzed by treatment visit by measuring the HCV RNA levels at screening, week 12 (EOT), and week 24 (end of the study). After receiving the treatment for 12weeks, 99.8% of the patients achieved undetectable HCV RNA levels and 94.4% of patients sustained the virological response till the end the of study (EOS) visit (week 24). This showed that all the patients achieved sustained virological response following 12 weeks of treatment with sofosbuvir/velpatasvir FDC.

Table 3 Safety outcomes analysis results for all the patients

	All patients (N=409)
Patients with at least one TEAE	116 (28.4)
Patients with at least one SAE	1 (0.2)
Adverse Event Related to study drug	0
Adverse Events Leading to Study Medication Discontinuation	0
Adverse Events Leading to Death	1 (0.2)
TEAEs in ≥2 Patients	
Pyrexia	40 (9.8)
Fatigue	16 (3.9)
Headache	12 (2.9)
Cough	9 (2.2)
Nausea	8 (2.0)
Vomiting	8 (2.0)

Abbreviation: TEAE, treatment emergent adverse event

Viral load estimation

The mean HCV RNA viral load below the lower limit of quantification was reported in all the patients at end of 12 weeks of treatment. The Log10 transformed HCV RNA viral load was similar to the actual values. The Log10 transformed mean (SD) HCV RNA viral load at baseline was 5.82 (±0.960) and was below the lower limit of quantification (BLOQ) at the end of 12weeks of treatment.

Subgroup analysis

The analysis of SVR12 rates was also presented by the following subgroups: cirrhotic or non-cirrhotic. The percentage of patients achieving SVR at 12weeks was higher in patients without cirrhosis and/or fibrosis (92.1%; 95% CI 88.6%-94.8%) as compared to patients with cirrhosis and/or fibrosis (85.5%; 95% CI 75.6%-92.6%) (Table 5).

Table 4 Sustained virologic response after 12 weeks of the last dose of study drug

Efficacy endpoint	**Analysis set**	**Missing data imputation method**	**N (%)**	**95% CI***
Primary Analysis				
SVR 12 Response	FAS	Non-responder	367/404 (90.8)	(87.6, 93.5)
Sensitivity Analysis				
SVR 12 Response	FAS	LOCF	383/404 (94.8)	(92.2, 96.8)
	FAS	None/Complete Cases	367/391 (93.9)	(91.0, 96.0)
	PPS	None/Complete Cases	354/375 (94.4)	(91.57, 96.50)

Note: *Two-sided 95% CI is constructed using the exact Clopper-Pearson method for single proportion

Abbreviations: CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward; PPS, per-protocol set; SVR, sustained virologic response after 12 weeks of end of treatment

Table 5 Analysis of SVR 12 Response by Cirrhotic and/or Fibrotic Status – FAS

Statistics efficacy endpoint		**Cirrhotic and/or fibrotic (N=76)**	**Non-cirrhotic and/or non-fibrotic (N=328)**
SVR 12 Response	n(%)	65 (85.5)	302 (92.1)
	95% CI*	(75.58, 92.55)	(88.60, 94.76)

Note1: Patients with missing HCV RNA results at End of Study are considered as non-responder

Note2: *Two-sided 95% CI is constructed using the exact Clopper-Pearson method for single proportion

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Discussion

The FDC of sofosbuvir/velpatasvir was approved in 2016 and is in clinical practice for years for the treatment of HCV infection. The safety and efficacy of the FDC were well-established globally. However, this was considered as a new drug formulation in India. Hence, the Indian regulatory agency had asked the sponsor to conduct a post-marketing study to assess the safety and efficacy of this formulation in Indian patients.

Overall, the treatment with sofosbuvir/velpatasvir FDC was found to be safe and well-tolerated. The most common AEs reported in this study are similar to the ASTRAL1 trial[10] which reported headache, fatigue, and nausea. However, the frequency of AEs reported in this study was comparatively less. Underreporting of AEs is a widespread challenge in countries like India[12] and could be a possible reason for the smaller number of TEAEs reported in this study. In ASTRAL 210 and ASTRAL 311 trials, the percentage of patients in the sofosbuvir/velpatasvir treatment arm reporting the SAEs was 1% and 2% respectively, whereas in the current study only one patient (0.2%) experienced SAE. Two patients from ASTRAL 2 trial11 and three patients from ASTRAL 3 trial11 died during the study. In the current study, one death was reported. However, the deaths reported (including the ASTRAL trials) were unrelated to the study drug or categorized as unknown. One patient from ASTRAL 1 trial10 and one patient in ASTRAL 2 trial11 receiving sofosbuvir/velpatasvir discontinued the treatment. In the current study, no interruptions or early terminations were seen.

The efficacy analysis conducted using primary analysis showed SVR12 response rates of 90.8%. The results are comparable to the previously conducted Phase 3 ASTRAL trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3), where the SVR 12 rates in patients with HCV genotype 1-6 with and without compensated cirrhosis was 95-99%.[10,11] The results of the current study are more in line with ASTRAL 3 trials11 (95% SVR), as genotype 3 is the most prevalent one with around 63.85% cases in India[13,14] which was the population studied in the ASTRAL-3 trial.11 The result of the present study was also equivalent to a phase 3 study conducted in 129 Indian adult patients with HCV infection that achieved an SVR12 of 93%.[15] Another Indian study conducted in 100 HCV-infected patients has demonstrated SVR 12 rates of 99%.[16]

Compared with the FDA registration trials and other real-world studies, the SVR12 rates in the current study were marginally less. However, the sensitivity analysis conducted using the LOCF approach, complete case, and PPS showed SVR12 response rates of 94.8%, 93.9%, and 94.4%. In the Primary analysis, the missing SVR12 assessments were considered as non-responders, whereas in sensitivity analysis, these patients were excluded from the analysis. Therefore, increased compliance rates can demonstrate high SVR12 response rates suggesting that low SVR rates may reflect non-compliance and not efficacy.

In this study, the sofosbuvir-velpatasvir FDC was administered without prior genotype testing, and this is the major advantage of the pan-genotype combination. In countries with low resource settings, effective and safe treatment with minimal diagnostic testing would help in combating the hepatitis B and HCV infections and achieving the goal set by the World Health Organization.[17]

The strength of the study is that it is a prospective multicenter phase IV study evaluating the safety and efficacy of this product in the Indian population. Routine pharmacovigilance would not be able to elucidate the safety and efficacy data of this product. However, no genotype-specific analysis or comparison was done in this trial which can be considered a limitation of the study.

Conclusion

In summary, our phase 4 results suggest that the sofosbuvir/velpatasvir FDC therapeutic regimen was safe and well tolerated in Indian adult patients with chronic HCV infection up to 12weeks of treatment. Data obtained during the study also showed sofosbuvir/velpatasvir FDC was effective in achieving SVR at 12weeks after EOT in the study subjects which is in line with the product label.

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Conflicts of interest

Sanjeev Hegde and Sanjay Hadigal are employees of Viatris. Authors have no other competing interests to declare.

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