FINAL ABBREVIATED CLINICAL STUDY REPORT

Study Title:	A Prospective cohort study on the use of Sofosbuvir-based regimens in HCV-infected patients in clinical practice in France HELIOS: HEpatitis C real-LIfe study for patients On Sofosbuvir
Name of Test Drug:	Sofosbuvir Ledipasvir/Sofosbuvir Fixed Dose Combination (FDC) Sofosbuvir/Velpatasvir FDC
Dose and Formulation:	Sofosbuvir (400 mg) tablet Ledipasvir/Sofosbuvir FDC (90/400 mg) tablet Sofosbuvir/Velpatasvir FDC (400/100 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences SAS 65 quai Georges Gorse 92100 Boulogne-Billancourt France
Study No.:	GS-FR-334-1530 (HELIOS)
Phase of Development:	Phase 4
IND No.:	Not Applicable.
EudraCT No.:	Not Applicable.
ClinicalTrials.gov Identifier:	Not Applicable.
Study Start Date:	13 October 2015 (first patient screened/enrolled)
Study End Date:	15 February 2019 (last patient last visit for the primary endpoint) 17 December 2020 (last patient last visit for this report)

Principal or Coordinating Investigator:	Name: Affiliation:	PPD Hôpital Cochin Service d'Hépato-Gastroentérologie 27 rue du Faubourg Saint-Jacques 75014 Paris
Sponsor Responsible Medical Monitor:	Name: Telephone: Fax:	PPD (as of 15 October 2022) PPD PPD
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Report Date:	26 October 2022	

This study was conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices and Heads of Medicines Agencies Good Pharmacovigilance Practices, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-FR-334-1530
Gilead Sciences SAS
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

Title of Study: A Prospective cohort study on the use of Sofosbuvir-based regimens in HCV-infected patients in clinical practice in France
HELIOS: HEpatitis C real-LIfe study for patients On Sofosbuvir

Investigators: Multicenter study.

Study Centers: 45 sites in France

Publications: Ouzan D, Larrey D, Guyader D, Remy AJ, Riachi G, Heluwaert F, et al. Evolution of Hepatitis C Virus Treatment During the Era of Sofosbuvir-Based Therapies: A Real-World Experience in France. Dig Dis Sci 2021;66 (3):881-98.

Study Period:

13 October 2015 (first patient screened)
15 February 2019 (last patient last visit for the primary endpoint)
17 December 2020 (last patient last visit for this report)

Phase of Development: Phase 4

Study Objectives:

The primary objective of this study is to assess the efficacy of sofosbuvir (SOF)-based regimens in adult patients with chronic hepatitis C virus (HCV) infection treated in routine clinical practice.

The secondary objectives of this study are to assess the following:

- The safety and tolerability of SOF, ledipasvir (LDV)/SOF and SOF/velpatasvir (VEL), ± ribavirin (RBV), in adult patients with chronic HCV infection treated in routine clinical practice.
- The efficacy of SOF, LDV/SOF, and SOF/VEL, ± RBV, in adult patients with chronic HCV infection treated in routine clinical practice.
- The characteristics of patients treated with SOF, LDV/SOF, and SOF/VEL in clinical practice: severity of the liver disease, history of treatment, and HCV genotypes and subtypes.
- The impact of treatment with SOF, LDV/SOF, and SOF/VEL on quality of life.
- Patient adherence.

- Pharmacoeconomic data, including work productivity and activity impairment, number of consultations/hospitalizations due to HCV and/or liver disease and/or HCV treatment during treatment and follow-up (2 years), and treatment occurrence for anemia, thrombopenia, and/or neutropenia.
- Long-term follow-up (2 years posttreatment).

Methodology: This was a multicenter, prospective, noninterventional cohort study to evaluate the use of SOF-based regimens in adult patients with HCV infection treated in routine clinical practice in France. Data were collected from available information in medical records. Patients were those initiating treatment with SOF ± RBV, LDV/SOF fixed-dose combination (FDC) ± RBV, or SOF/VEL FDC± RBV, used in accordance with the respective approved Summary of Product Characteristics (SmPC). The decision to initiate or not to initiate patient treatment with SOF, LDV/SOF, or SOF/VEL was based on the judgment of the prescribing physician.

Clinical data were collected from the patient's medical records at baseline, which was the start of treatment with SOF, LDV/SOF, or SOF/VEL, and at follow-up, which consisted of the end of treatment and 12 weeks, 48 weeks (1 year), and 96 weeks (2 years) after the end of treatment.

Patients also completed paper questionnaires (EuroQoL – 5 Dimensions [EQ5D], Work Productivity and Activity Impairment [WPAI], and Treatment Adherence) during the study.

Number of Patients (Planned and Analyzed):
Planned: Approximately 1,000 patients
Analyzed: 1031 in the Study Population, which included the following:

- 624 patients in HELIOS1
  - SOF ± RBV, 22 patients
  - SOF+daclatasvir (DAC) ± RBV, 44 patients
  - SOF+simeprevir (SIM) ± RBV, 4 patients
  - LDV/SOF, 554 patients
- 407 patients in HELIOS2 (SOF/VEL ± RBV)

Diagnosis and Main Criteria for Inclusion: Eligible patients were adults at least 18 years of age with HCV infection (ie, HCV RNA positive) who were initiating a SOF-based treatment, including LDV/SOF and SOF/VEL; were not concurrent participants in other clinical studies using an investigational medicinal product; and were expected to be able to be followed for a 2-year duration.

Duration of Treatment: SOF, LDV/SOF, and SOF/VEL were administered according to each product's SmPC. The duration of treatment varied between 8 weeks, 12 weeks, or 24 weeks depending on the treatment received.

Test Product, Dose, and Mode of Administration, and Batch No: Sofosbuvir, ledipasvir/sofosbuvir FDC, and sofosbuvir/velpatasvir FDC were administered according to each product's SmPC. Batch numbers were not collected in this study.

Reference Therapy, Dose, Mode of Administration, and Batch No.: Ribavirin was administered according to the SmPC. Batch numbers were not collected in this study.

Criteria for Evaluation:

Efficacy: The primary endpoint was sustained virologic response rate 12 weeks after treatment discontinuation (SVR12), where virologic response was defined as HCV RNA < 25 IU/mL (lower limit of quantification).

The secondary efficacy endpoints included virologic response rate at 24 weeks posttreatment (SVR24); the rate of viral breakthrough (on-treatment virologic failure), relapse, and late relapse; and clinical outcomes during follow-up including but not limited to diagnosis of hepatocellular carcinoma, liver fibrosis, signs of decompensated cirrhosis.

Pharmacokinetics: No pharmacokinetics (PK) analyses were performed for this study.

Safety: Safety endpoints were evaluated by determining rates of adverse drug reactions (ADRs) leading to permanent discontinuation of treatment with SOF, LDV/SOF, or SOF/VEL.

Other: Other endpoints included the following:

- Quality of life, assessed with the EQ5D questionnaire during treatment and long-term follow-up (2 years).
- Patient adherence to HCV treatment, assessed with a patient questionnaire during the treatment period.
- WPAI assessed with WPAI questionnaire during treatment and long-term follow-up (2 years).
- Rate of consultations/hospitalizations due to HCV and/or liver disease and/or HCV treatment during treatment and follow-up (2 years).
- Treatment occurrence for anemia, thrombopenia, and/or neutropenia during treatment and follow-up (2 years).

Statistical Methods: All enrolled patients in this study who fulfilled the inclusion criteria and received at least 1 dose of known study treatment formed the analysis dataset, which is referred to as the Study Population in this report.

All variables were presented using standard descriptive statistics (number of available data, number of missing data, mean and its 95% confidence interval (CI), standard deviation, first quartile, median, third quartile, minimum, and maximum for quantitative variables and number of available data, number of missing data and percentage for each modality for qualitative variables.

Two-sided tests were performed to identify possible differences between treatment groups. The alpha-significance was set to 0.05.

Qualitative variables were compared using a Chi-squared test that was replaced by the Fisher exact test if the expected frequency in any of the contingency table cells was less than 5.

For the primary efficacy endpoint, a 2-sided CI based on Clopper-Pearson method was provided.

Logistic regressions was used for SVR12 prediction and adherence rate. Odds ratios with their associated 95% CIs were presented.

Safety analyses were mostly descriptive. The rate of ADRs was also estimated by a Poisson regression. Changes from baseline were calculated for laboratory evaluations and vital signs.

Quality of life analysis included descriptive statistics for individual scores, global score, and index. Mixed-model analyses were also performed for all scores (individual, global, and index).

SUMMARY OF RESULTS:

Patient Disposition and Demographics: A total of 1031 adult patients (624 in HELIOS1 and 407 in HELIOS2) were included in the study. In HELIOS1, 70 patients (6.8%) were treated with SOF ± RBV (SOF+RBV, SOF+DAC ± RBV, or SOF+SIM ± RBV) and 554 patients (53.7%) were treated with LDV/SOF. In HELIOS2, 407 patients (39.5%) were treated with SOF/VEL.

Overall, 1002 patients (97.1%) (608 in HELIOS1 and 394 in HELIOS2) completed the study treatment period (8, 12, or 24 weeks). A total of 550 patients (53.3%) (370 in HELIOS1 and 180 in HELIOS2) fully completed the study. Among the patients who did not fully complete the study, the most common reason was the lost to follow-up (212 patients in HELIOS1 and 171 patients in HELIOS2).

Demographics and baseline characteristics were similar in all treatment groups. The median age was 55.0 years in each group and the majority of patients in each group were male and White. At baseline, addiction (defined as current excessive alcohol consumption and/or current recreational drug abuse) was reported in 11.8% in the SOF ± RBV group, 13.7% in the LDV/SOF group, and 17.6% in the SOF/VEL group. The percentage of patients with at least 1 comorbidity was 37.1% in the SOF ± RBV group, 26.9% in the LDV/SOF group, and 28.0% in the SOF/VEL group, with diabetes and arterial hypertension as the most frequently reported comorbidities.

In the SOF ± RBV group, the following were the most common HCV genotypes: HCV genotype 1 in patients receiving SOF+RBV (21 of 21 patients [100%]), HCV genotype 3 in patients receiving SOF+DAC ± RBV (35 of 42 patients [83.3%]), and HCV genotype 4 in patients receiving SOF+SIM ± RBV (3 of 4 patients [75.0%])/ In the LDV/SOF and SOF/VEL groups, HCV genotype 1 was the most common genotype (456 of 533 patients [85.6%] and 190 of 382 patents [49.7%], respectively).

Efficacy Results: The primary endpoint was SVR12, defined as sustained virologic response (HCV RNA < 25 IU/mL) rate 12 weeks after treatment discontinuation. In HELIOS1, the total SVR12 rate was 100% in the SOF ± RBV group (SOF, SOF+DAC, and SOF+SIM) and 98.3% in the LDV/SOF group. In HELIOS2 (SOF/VEL), the total SVR12 rate was 99.6%. Overall, 7 patients were reported as not achieving SVR12 (6 treated with LDV/SOF and 1 treated with SOF/VEL). There were no statistically significant differences in SVR12 rate between treatment groups, either overall or by genotype. Similar SVR12 results for treatment group and genotype were observed when analyzed according to RBV use. SVR12 results for HCV RNA ≤ 15 IU/mL were similar to those for HCV RNA < 25 IU/mL.

A key secondary endpoint was sustained virologic response (HCV RNA < 25 IU/mL) rate 24 weeks after discontinuation (SVR24). Of the patients with available SVR24 data in HELIOS1, 98.4% (125 of 127 patients) in the LDV/SOF group achieved SVR24, and of the patients with available SVR24 data in HELIOS2 (SOF/VEL), 97.2% (35 of 36 patients) achieved SVR24. The low number of patients with SVR24 data was mainly due to loss to follow up. There were no significant differences between treatment groups in SVR24 overall.

Virologic response during treatment (HCV RNA < 25 IU/mL) occurred in most patients in HELIOS1 (100%, 90%, and 100% for patients in the SOF ± RBV group [SOF, SOF+DAC, and SOF+SIM, respectively] and 91.4% for patients in the LDV/SOF group, and in most patients in HELIOS2 (SOF/VEL) (94.6%). Relapse, defined as virologic response at the end of treatment followed by HCV RNA value of ≥ 25 IU/mL 12 weeks after discontinuation of treatment, was not reported in any patients with available data in HELIOS1 or HELIOS2. Late relapse, defined as achievement of SVR12 followed by an HCV RNA value of ≥ 25 IU/mL 24 weeks after discontinuation of treatment, was reported in 1 patient (1.3%) in HELIOS1 (LDV/SOF group) and 1 patient (4.2%) in HELIOS2 (SOF/VEL). On-treatment virologic failure (viral breakthrough), defined as patients who did not have a virologic response at the end of treatment, occurred in 4 patients (1.0%) in HELIOS1 (all in the LDV/SOF group) and 3 patients (1.1%) in HELIOS2 (SOF/VEL).

Clinical outcomes such as addiction, extrahepatic manifestations, and current employment generally remained stable or decreased during the follow-up period of the study.

Pharmacokinetics Results: No PK analyses were performed for this study.

Safety Results: Most patients had a study treatment adherence rate of at least 80% at end of treatment (in HELIOS1, 100% of patients receiving SOF+RBV, 85.3% of patients receiving SOF+DAC ± RBV, 100% of patients receiving SOF+SIM ± RBV, and 94.3% of patients receiving LDV/SOF; in HELIOS2, 98.6% of patients receiving SOF/VEL).

Per the study protocol, only ADRs related to HCV treatment, adverse events (AEs) leading to death, and special situations reports, including pregnancy, were collected and reported in the study.

A total of 131 patients (21.0%) experienced at least 1 ADR in HELIOS1 (SOF ± RBV and LDV/SOF) and 56 patients (13.8%) experienced at least 1 ADR in HELIOS2 (SOF/VEL). No serious ADRs and no ADRs leading to death were reported in HELIOS1 or HELIOS2. Two patients (0.3%) in HELIOS1 and 1 patient (0.2%) in HELIOS2 had at least 1 ADR leading to permanent treatment discontinuation. Asthenia and pruritus, both related to RBV, were reported in 1 patient each in HELIOS1, and general physical condition abnormal, drug use disorder, and drug interaction, each related to SOF/VEL, were reported in 1 patient in HELIOS2.

Most of the ADRs in the study were Grade 1, with Grade 3 ADRs were reported in 2 patients (0.3%) in HELIOS1 and 2 patients (0.5%) in HELIOS2. No Grade 4 ADRs occurred during the study. In HELIOS1, the ADRs reported in most patients (101 patients, 16.2% overall) were assessed as related to LDV/SOF. In HELIOS2, all ADRs were assessed as related to SOF/VEL with the exception of 1 patient (0.2%), who had a ADR related to RBV.

At least 1 AE leading to death occurred in 6 patients in HELIOS1 (1 in the SOF ± RBV [SOF+DAC] group and 5 in the LDV/SOF group) and 5 patients in HELIOS2. Except in 1 patient, all fatal AEs occurred more than 30 days after treatment discontinuation. One patient in the LDV/SOF group had treatment-emergent hepatorenal syndrome during the treatment period that led to death. No ADRs leading to death were reported in HELIOS1 or HELIOS2.

No pregnancies were reported in the study.

In both HELIOS1 and HELIOS2, there were decreases from baseline in median alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and alpha fetoprotein values during the study. No other trends were observed for other chemistry parameters. There were no trends in median change-from-baseline values for hematology or coagulation parameters in either HELIOS1 or HELIOS2.

Other Results: In HELIOS 1 (SOF ± RBV and LDV/SOF), the mean (SD) EQ5D global score improved from 70.0 (18.2) at baseline to 77.5 (17.8) at the end of treatment and remained stable during the follow-up period (79.8 [17.1] at 2 years posttreatment). Similar results were observed in HELIOS2 (SOF/VEL), with an improvement in the mean (SD) EQ5D global score between baseline (72.4 [20.2]) and end of treatment (77.9 [18.2]), which remained stable during the follow-up period (77.7 [19.4] at 2 years posttreatment). This trend was also observed on individual domains in both HELIOS1 and HELIOS2.

The rate of current employment remained stable during the follow-up period in HELIOS1 and HELIOS2 (45.5% at baseline and 42.2% at 2 years posttreatment in HELIOS1 and 41.9% at baseline and 38.7% at 2 years posttreatment in HELIOS2). Consultation at hospital occurred mainly between baseline and the end of treatment (53.4% of patients in HELIOS1 and 54.0% of patients in HELIOS2), and decreased after the end of treatment (21.8% between 1 year posttreatment and 2 years posttreatment in HELIOS1 and 17.2% between 1 year posttreatment and 2 years posttreatment in HELIOS2). The level of hospitalization was not more than 3.0% at any time during the follow-up periods in HELIOS1 and HELIOS2.

CONCLUSIONS: The conclusions of Study GS-FR-334-1530 are as follows:

- The SOF-based regimens examined in this study were safe and well tolerated in this real-world population.
- The SVR12 rate was high in each treatment regimen (100% for SOF ± RBV, 98.3% for LDV/SOF, and 99.6% for SOF/VEL). For patients with available data, SVR24 rates were high (98.4% [125 of 127 patients] for LDV/SOF and 97.2% [35 of 36 patients] for SOF/VEL). The low number of patients with SVR24 data was mainly due to loss to follow up.
- Clinical outcomes, including addiction, extrahepatic manifestations, and employment, remained stable up to 2 years posttreatment.