FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b Randomized, Open-label, Controlled Study of the Efficacy, Safety and Tolerability of 12 Weeks of Ledipasvir/Sofosbuvir (LDV/SOF) Treatment for HIV/HCV Co-infected Subjects who Switch to Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) or Emtricitabine/Rilpivirine/Tenofovir Alafenamide (F/R/TAF) prior to LDV/SOF HCV Treatment, the HIV/HCV Co-STARs study (Co-infection treatment with Single Tablet Antiviral Regimens)
Name of Test Drugs:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF); Emtricitabine/Rilpivirine/Tenofovir Alafenamide (F/R/TAF); Ledipasvir/Sofosbuvir (LDV/SOF)
Doses and Formulations:	Fixed-dose combination (FDC) tablet of E/C/F/TAF (150/150/200/10 mg); FDC tablet of F/R/TAF (200/25/25 mg); FDC tablet of LDV/SOF (90/400 mg)
Indications:	HIV-1 infection (E/C/F/TAF; F/R/TAF) Hepatitis C virus infection (LDV/SOF)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-366-1992
Phase of Development:	Phase 3b
IND No.:	123098
EudraCT No.:	2014-004545-27
ClinicalTrials.gov Identifier:	NCT02707601
Study Start Date:	01 April 2016 (First Subject Screened)
Study End Date:	29 September 2017 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Greg Huhn, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Richard Haubrich, MD Telephone: PPD
Report Date:	16 January 2018

STUDY SYNOPSIS

Study GS-US-366-1992

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b Randomized, Open-label, Controlled Study of the Efficacy, Safety and Tolerability of 12 Weeks of Ledipasvir/Sofosbuvir (LDV/SOF) Treatment for HIV/HCV Co-infected Subjects who Switch to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) or Emtricitabine/Rilpivirine/Tenofovir Alafenamide (F/R/TAF) prior to LDV/SOF HCV Treatment, the HIV/HCV Co-STARs study (Co-infection treatment with Single Tablet Antiviral Regimens)

Investigators: Multicenter study

Study Centers: This was a multicenter study with 44 centers in the United States (US; Table 15.8.1.1).

Publications:

Ramgopal M, Jain M, Hinestrosa F, Asmuth D, Huhn G, Slim J, et al. HIV-1/HCV Coinfection Treatment with Single-Tablet Antiviral Regimens (CoSTARs): 12 Weeks of Ledipasvir/Sofosbuvir (LDV/SOF) after Randomized Switch to Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) or Rilpivirine/F/TAF (R/F/TAF) [Poster LB-12]. AASLD: The Liver Meeting 2017 20-24 October; Washington DC.

Huhn G, Jain M, Hinestrosa F, Asmuth D, Huhn G, Slim J, et al. HIV-1/HCV Coinfection Treatment with Single-Tablet Antiviral Regimens (CoSTARs): 12 Weeks of Ledipasvir/Sofosbuvir (LDV/SOF) after Randomized Switch to Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) or Rilpivirine/F/TAF (R/F/TAF) [Poster PE16/52]. European AIDS Conference 2017 25-27 October; Milan Italy.

Study Period:

01 April 2016 (First Subject Screened)

14 September 2017 (Last Subject Last Observation for the Primary Endpoint)

29 September 2017 (Last Subject Observation)

Phase of Development: Phase 3b

Objectives:

The primary objective of this study was as follows:

- To evaluate efficacy of ledipasvir/sofosbuvir (LDV/SOF) as measured by the proportion of subjects achieving hepatitis C virus (HCV) RNA below the lower limit of quantification (LLOQ) 12 weeks after the last dose of LDV/SOF (sustained virologic response [SVR12])

The secondary objectives of this study were as follows:

- To determine the proportion of subjects achieving HCV RNA below LLOQ 4 weeks after the last dose of LDV/SOF (SVR 4)
- To evaluate maintenance of HIV-1 RNA suppression after switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) or emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) 24 weeks from the start of the emtricitabine/tenofovir alafenamide (F/TAF)-based regimen
- To evaluate the safety and tolerability of switching to E/C/F/TAF or F/R/TAF from the current antiretroviral (ARV) therapy (ART) in virologically-suppressed, HIV-1/HCV-coinfected subjects
- To evaluate the safety and tolerability of 12 weeks of treatment for HCV with LDV/SOF in virologically-suppressed, HIV-1/HCV-coinfected subjects who switched to E/C/F/TAF or F/R/TAF

Methodology: Co-STARs was a randomized, multicenter, open-label, 2-part study to assess the efficacy, safety, and tolerability of LDV/SOF treatment in HIV/HCV-coinfected subjects who have been virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of 2 nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) plus a third ARV agent for ≥ 6 consecutive months at screening.

Part 1: In Part 1 of the study, eligible subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

- **Treatment Group 1:** Switch to E/C/F/TAF
- **Treatment Group 2:** Switch to F/R/TAF

At Week 8, subjects who tolerated the switch to E/C/F/TAF or F/R/TAF and maintained HIV-1 RNA < 50 copies/mL continued to Part 2 of the study.

Part 2: In Part 2 of the study, subjects continued treatment with E/C/F/TAF or F/R/TAF and received 12 weeks of LDV/SOF HCV therapy (until Week 20).

After Week 20, subjects continued treatment with E/C/F/TAF or F/R/TAF and attended study visits 4 and 12 weeks after the last dose of LDV/SOF.

Subjects who completed the study through the Post-HCV Treatment Week 12 visit returned to the clinic for a 30-Day Follow-Up visit.

Details of the study plan and data collection are provided in the protocol and protocol amendments in Appendix 16.1.1.

Number of Subjects (Planned and Analyzed):

Planned: A sample size of 240 subjects was originally planned for this study. The study was amended to lower the sample size to approximately 120 subjects (approximately 60 subjects per treatment group) due to slow accrual and general consensus that the study objectives could be achieved with a lower sample size. A sample size of 120 subjects will provide at least 85% power to detect an improvement of at least 8 percentage points in overall SVR12 rate from the performance goal of 88%, by using a 2-sided exact 1-sample binomial test at a significance level of 0.05.

Analyzed:

	E/C/F/TAF +LDV/SOF	F/R/TAF +LDV/SOF	Total
Subjects Randomized	76	74	150
Subjects in Safety Analysis Set	74 (100%)	74 (100%)	148 (100%)
Subjects in Part 2 Safety Analysis Set	72 (97.3%)	72 (97.3%)	144 (97.3%)
Subjects in HIV Full Analysis Set (FAS)	74 (100%)	74 (100%)	148 (100%)
Subjects in HCV FAS	72 (97.3%)	72 (97.3%)	144 (97.3%)
Subjects in Pharmacokinetic (PK) Analysis Set	4 (5.4%)	3 (4.1%)	7 (4.7%)

The denominator for percentage is the number of subjects in the Safety Analysis Set.
Source: Table 15.8.5

Diagnosis and Main Criteria for Inclusion: Eligible subjects were HIV-1 and chronic genotype 1 HCV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of 2 N(t)RTIs plus a third ARV agent for ≥ 6 consecutive months prior to screening, with no documented resistance to any of the study agents at any time in the past, and who met 1 of the following criteria: 1) no cirrhosis and no prior HCV treatment (treatment naive); 2) no cirrhosis and HCV treatment only with interferon (IFN) ± ribavirin (RBV) or IFN + RBV + an HCV protease inhibitor (PI) (treatment experienced); or 3) compensated cirrhosis and treatment naive. Additionally, subjects must have had an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 30 mL/min and no evidence of hepatitis B infection.

Duration of Treatment: Treatment duration was approximately 32 weeks for E/C/F/TAF or F/R/TAF and 12 weeks for LDV/SOF, with a follow-up visit 30 days after the last dose of study drug.

Test Product, Dose, Mode of Administration, and Batch No.:

- E/C/F/TAF (1 × E/C/F/TAF [150/150/200/10 mg] fixed-dose combination [FDC] tablet) administered orally, once daily with food (Batch numbers CP1503B1 and CP1604B1)
- F/R/TAF (1 × F/R/TAF [200/25/25 mg] FDC tablet) administered orally, once daily with food (Batch numbers EF1513B1 and EF1505B1)
- LDV/SOF (1 × LDV/SOF [90/400 mg] FDC tablet) administered orally, once daily with or without food (Batch number DK1405B1)

Reference Therapy, Dose, Mode of Administration, and Batch No.: None

Criteria for Evaluation:

Efficacy: Efficacy was evaluated using scheduled assessments of HCV RNA (performed using COBAS® Ampliprep/COBAS® TaqMan® HCV Quantitative Test, v2.0), HIV-1 RNA (performed using COBAS® TaqMan® HIV RNA Test, v2.0), and CD4 cell count.

Pharmacokinetics: Pharmacokinetic (PK) blood samples were collected at specified visits for potential population PK assessment.

Safety: Adverse events (AEs) were collected at all visits, and clinical laboratory tests were performed at all visits. Blood was collected at specified visits for possible exploratory analyses of bone and renal safety, inflammation, platelet function, and coagulation.

Patient-Reported Outcomes: The following health-related questionnaires were administered at specified visits: HIV medication adherence Visual Analogue Scale (VAS), HIV Treatment Satisfaction (HIVTSQ), Short Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), and Work Productivity and Activity Impairment (WPAI): Hepatitis C questionnaire.

Statistical Methods: All tables, figures, and listings produced for this study are provided in Section 15.1 (tables and figures) and Appendix 16.2 (listings). Documentation of statistical methods is provided in Appendix 16.1.9.

Sample Size and Power: The study enrolled 150 subjects, which provides at least 85% power to detect an improvement of at least 6 percentage points in SVR12 rate from the performance goal of 88% by using a 2-sided exact 1-sample binomial test at significance level of 0.05.

Populations:

Safety Analysis Set: The primary analysis set for safety analyses of the whole study was the Safety Analysis Set, defined as all subjects randomized to the study who received at least 1 dose of study drug (E/C/F/TAF, F/R/TAF, or LDV/SOF).

Part 2 Safety Analysis Set: The primary analysis set for safety analyses of the coadministration period was the Part 2 Safety Analysis Set, defined as all subjects who entered Part 2 of the study and received at least 1 dose of LDV/SOF.

HIV Full Analysis Set: All subjects randomized who received at least 1 dose of HIV study drug (E/C/F/TAF or F/R/TAF).

HCV Full Analysis Set: All subjects randomized who received at least 1 dose of HCV study drug (LDV/SOF).

Efficacy: The primary efficacy endpoint was SVR12 defined as HCV RNA < LLOQ 12 weeks after discontinuation of LDV/SOF. The overall SVR12 rate was compared to the performance goal of 88% using a 2-sided exact 1-sample binomial test at the 0.025 significance level. The 2-sided 95% exact CIs for SVR12 based on the Clopper-Pearson method were provided for the study overall and for each randomized HIV treatment group in the HCV FAS. Subgroup analyses were performed to assess the relationship between SVR12 and baseline demographic and disease characteristics. Point estimates and 95% exact CIs of the SVR12 rates for the study overall and for each randomized HIV treatment group were generated by HCV genotype (1a, 1b, and other if applicable). The secondary HCV efficacy endpoint of SVR4 was analyzed using exactly the same methods used for SVR12, including those used in subgroup analysis for SVR12. The tertiary HCV efficacy endpoints were the proportion of subjects with alanine aminotransferase (ALT) normalization, the proportion of subjects with HCV RNA < LLOQ while on HCV treatment, HCV RNA absolute values and changes from baseline through end of HCV treatment, and the proportion of subjects with virologic failure.

The secondary HIV efficacy endpoint was the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL 24 weeks after start of HIV study drug using the US Food and Drug Administration (FDA)-defined snapshot algorithm (HIV FAS). Subgroup analyses were also performed for the secondary HIV efficacy endpoint. The tertiary HIV efficacy endpoints were proportion of subjects with HIV-1 RNA ≥ 20 copies/mL 24 weeks after start of HIV study drug using the US FDA-defined snapshot algorithm, change from baseline in CD4 cell count and CD4% 24 weeks after start of HIV study drug, and the proportion of subjects with HIV-1 RNA < 50 copies/mL 24 weeks after start of HIV study drug using 2 different data imputation methods (missing = failure [M = F] and missing = excluded [M = E]).

Pharmacokinetics: For subjects in the PK Analysis Set, plasma concentrations were listed for relevant analytes: TAF, tenofovir, rilpivirine, emtricitabine, elvitegravir, cobicistat, LDV, SOF, or the SOF metabolite GS-331007. Population PK assessments will be summarized in a separate report, if conducted.

Safety: Safety data were summarized for Part 1 and the coadministration period, respectively, as well as throughout the whole study, by treatment group and overall. Safety data collected up to 30 days after permanent discontinuation of study drugs were included. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. All AEs and laboratory abnormalities discussed in this report were treatment emergent and are referred to in this report as AEs and laboratory abnormalities, respectively, unless otherwise specified.

Patient-Reported Outcomes: All patient-reported outcome data collected up to 30 days after permanent discontinuation of study drugs was summarized by randomized HIV treatment group and overall for the Safety Analysis Set. For the SF-36, FACIT-F, CLDQ-HCV, and WPAI: Hepatitis C questionnaires, a Wilcoxon signed rank test was used to explore changes from baseline within each treatment group. Otherwise, only descriptive statistics were used.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 150 subjects randomized, 148 subjects (E/C/F/TAF 74 subjects, F/R/TAF 74 subjects) received at least 1 dose of HIV study drug and were included in the Safety Analysis Set and HIV FAS (Table 15.8.1.3). A total of 144 subjects (97.3%; E/C/F/TAF 72 subjects; F/R/TAF 72 subjects) entered the coadministration period, received at least 1 dose of HCV study drug (LDV/SOF), and were included in the Part 2 Safety Analysis Set and HCV FAS. In total, 8 subjects (E/C/F/TAF±LDV/SOF 3 subjects; F/R/TAF±LDV/SOF 5 subjects) prematurely discontinued HIV or HCV study drug, as follows (Figure 15.8.1):

- Four subjects discontinued HIV study drug (E/C/F/TAF 2 subjects; F/R/TAF 2 subjects) prior to entering the coadministration period for the following reasons: 1 subject receiving F/R/TAF due to lack of efficacy, 2 subjects receiving E/C/F/TAF due to investigator's discretion, and 1 subject receiving F/R/TAF was lost to follow-up.
- One subject discontinued LDV/SOF during the coadministration period due to noncompliance with study drug but continued on HIV study drug (E/C/F/TAF).
- Three subjects receiving F/R/TAF discontinued HIV study drug after completing LDV/SOF due to AE, death, and subject decision, respectively.

Demographic and baseline characteristics were similar between the E/C/F/TAF and F/R/TAF randomized treatment groups (Table 15.8.3.1.1). Median age of subjects in the Safety Analysis Set was 53 years (range: 25 to 70 years). Most subjects were male (74.3%), white (52.7%) or black (41.2%), and not Hispanic/Latino (81.6%). Median (Q1, Q3) baseline body mass index (BMI) was 25.6 (22.7, 29.5) kg/m^2, and median (Q1, Q3) baseline $eGFR_{CG}$ was 99.8 (77.3, 116.7) mL/min (Table 15.8.3.2.1).

Baseline HIV disease characteristics were generally similar between the E/C/F/TAF and F/R/TAF randomized treatment groups (Table 15.8.3.2.1). The study enrolled a virologically suppressed, HIV-infected population; therefore, at baseline, 99.3% of subjects in the Safety Analysis Set had HIV-1 RNA < 50 copies/mL. Median (Q1, Q3) baseline CD4 cell count was 651 (484, 806) cells/µL, and 74.3% of subjects had a CD4 cell count ≥ 500 cells/µL. The most common HIV risk factors were homosexual sex (46.6%) or heterosexual sex (42.6%), and 27.0% of subjects reported intravenous drug use as the mode of infection. Median (Q1, Q3) duration of prior ART was 12.5 (6.0, 20.0) years.

Baseline HCV disease characteristics were generally similar between the E/C/F/TAF and F/R/TAF randomized treatment groups (Table 15.8.3.2.2). All 144 subjects in the Part 2 Safety Analysis Set had genotype 1 HCV infection: 120 subjects (83.3%) had genotype 1a, 23 subjects (16.0%) had genotype 1b, and 1 subject (< 1%) had genotype 1 with subtype unknown. The majority of subjects had a non-CC (CT or TT) IL28B allele (74.3%). Overall, 17 subjects (11.8%) had cirrhosis. Baseline (for the coadministration period) median HCV RNA was 6.4 log_{10} IU/mL (range: 1.1 to 7.5 log_{10} IU/mL), and most subjects (72.2%) had HCV RNA ≥ 800,000 IU/mL at that time. Most subjects (93.8%) were HCV treatment naive.

Important protocol deviations are listed in Appendix 16.2.2.

Efficacy Results: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after the last dose of LDV/SOF) in the HCV FAS (Table 15.9.1.2.1). The overall SVR12 rate was 97.2% (95% CI: 93.0% to 99.2%), which demonstrated superiority over the performance goal of 88% ($p < 0.001$). The SVR12 rates were comparable between the randomized HIV treatment groups (E/C/F/TAF+LDV/SOF 98.6%; F/R/TAF+LDV/SOF 95.8%).

Subgroup analyses of SVR12 rates showed no impact of important baseline demographic and disease characteristics on SVR12 rates (Table 1). In particular, black subjects had a similar overall rate of SVR12 compared with nonblack subjects (98.3% vs 96.5%). There was no difference in SVR12 by HCV genotype (genotype 1a 96.7%; genotype 1b 100%), age at baseline (< 65 years 97.0%, ≥ 65 years 100%), baseline HCV RNA (< 800,000 IU/mL 100%; ≥ 800,000 IU/mL 96.2%), cirrhosis (yes 94.1%; no 97.6%), or prior HCV treatment experience (treatment naive 97.8%; treatment experienced 88.9%).

Table 1. GS-US-366-1992: SVR12 by Subgroup, HCV FAS

	E/C/F/TAF +LDV/SOF (N = 72)	F/R/TAF +LDV/SOF (N = 72)	Total (N = 144)
HCV Genotype			
1a	61/62 (98.4%)	55/58 (94.8%)	116/120 (96.7%)
1b	10/10 (100%)	13/13 (100%)	23/23 (100%)
Age at Baseline (Years)			
< 65	64/65 (98.5%)	66/69 (95.7%)	130/134 (97.0%)
≥ 65	7/7 (100%)	3/3 (100%)	10/10 (100%)
Race			
Black	29/30 (96.7%)	29/29 (100%)	58/59 (98.3%)
Nonblack	42/42 (100%)	40/43 (93.0%)	82/85 (96.5%)
Baseline HCV RNA (IU/mL)			
< 800,000	19/19 (100.0%)	21/21 (100%)	40/40 (100%)
≥ 800,000	52/53 (98.1%)	48/51 (94.1%)	100/104 (96.2%)
Cirrhosis			
Yes	8/8 (100%)	8/9 (88.9%)	16/17 (94.1%)
No	63/64 (98.4%)	61/63 (96.8%)	124/127 (97.6%)
Prior HCV Treatment Experience			
Treatment-Naive	65/66 (98.5%)	67/69 (97.1%)	132/135 (97.8%)
Treatment-Experienced	6/6 (100%)	2/3 (66.7%)	8/9 (88.9%)

The denominator for percentage was the number of subjects in the HCV FAS. Baseline refers to Part 2 Baseline for LDV/SOF dosing.
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with LLOQ 15 IU/mL.
SVR12 was sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing Post-HCV Week 12 value was imputed as a failure.
One subject was identified as having HCV genotype 1 by local assay with unknown subtype (1a or 1b), therefore grouped as Genotype 1 Unknown.
Source: Table 15.9.1.3.2

Table 2 provides case details for the subjects who did not achieve SVR12 and results of their HCV resistance testing. Complete results of virology resistance analyses are summarized in a separate Virology Report (PC-366-2002). For the 4 subjects who did not achieve SVR12, 1 subject had HCV relapse (achieved SVR4 and 4.4 million IU/mL at Post-HCV Week 12), 1 subject had HCV rebound (HCV RNA 82 IU/mL after 4 weeks of LDV/SOF treatment and HCV RNA 1.6 million IU/mL after 8 weeks of LDV/SOF treatment), and 2 subjects missed the Post-HCV Week 12 visit (1 subject with HCV RNA < LLOQ at the end of the coadministration period who died prior to the Post-HCV Week 4 visit due to metastatic cancer of unknown primary and 1 subject who achieved SVR4 who withdrew consent prior to the Post-HCV Week 12 visit).

Table 2. GS-US-366-1992: Case Details and HCV Resistance Results for Subjects with HCV Virologic Failure or Other HCV Virologic Outcome at Post-HCV Week 12, Part 2 Safety Analysis Set

Subject ID (Randomized HIV Treatment Group)	Virologic Outcome at Post-HCV Week 12	HCV GT/ IL28B GT/ ±Cirrhosis	Prior HCV Tx Experience/ BL HCV RNA LDV/SOF Adherence	Result of HCV Resistance Testing
PPD (F/R/TAF)	HCV Relapse[1]	1a/ CT/ Cirrhotic	Treatment Naive/ 3.8 million IU/mL 100%	No NS5A/B RAS at baseline or at confirmation of failure Achieved SVR4
PPD (E/C/F/TAF)	HCV Rebound[2]	1a/ CT/ Non-Cirrhotic	Treatment Naive/ 8.4 million IU/mL 92.7%	No NS5A/B RAS at baseline Failure (Week 8 of LDV/SOF treatment) RAS: NS5A-Q30R, H58D; NS5B-none
PPD (F/R/TAF)	Missing due to death[3]	1a/ CT/ Non-Cirrhotic	Treatment Naive/ 7.2 million IU/mL 52.4%	Not applicable HCV RNA < LLOQ at completion of LDV/SOF therapy
PPD (F/R/TAF)	Missing due to withdrawal of consent[4]	1a/ TT/ Non-Cirrhotic	Treatment Experienced/ 1.0 million IU/mL 100%	Not applicable Achieved SVR4

BL = baseline; GT = genotype; RAS = resistance-associated substitution; Tx = treatment

1 HCV RNA at the Post-HCV Week 12 visit was 4.4 million IU/mL. No HCV resistance testing performed at baseline. No evidence of HCV reinfection (genotype 1a at both time points). Both NS5A and NS5B genes have 98.7% homology at the nucleotide level between the Week 8 sample and retest. At the amino-acid level, these 2 samples have 99% homology in NS5A and 100% homology in NS5B. Therefore, the 2 samples had the same HCV viruses. The patient experienced viral relapse with wild type HCV. HIV-1 RNA < 50 copies/mL at all but 1 study visit (baseline to end of study). HIV-1 RNA was 1140 copies/mL at Week 12.

2 Duration of exposure to LDV/SOF was 10.9 weeks. HCV RNA at Week 4 of LDV/SOF treatment was 82 IU/mL. HCV RNA 2 days after discontinuation of LDV/SOF was 23.2 million IU/mL. HIV-1 RNA ≥ 50 copies/mL at multiple study visits. HIV-1 RNA (copies/mL) = 70 (screening); 67 (Week 16); 1510 & 3070 (Week 24); 86 & 115 (Week 32).

3 Death due to metastatic carcinoma of unknown primary between completion of LDV/SOF therapy and Post-HCV Week 4 visit.

4 Withdrew consent after Post-HCV Week 4 visit. Subject did not return to clinic for HCV RNA testing with treating physician.

Source: Listings 16.2.4.4, 16.2.5.1, 16.2.6.1.1, 16.2.6.2.2, 16.2.6.2.3, and 16.2.7.6

The overall SVR4 rate (secondary HCV efficacy endpoint) was 98.6% (95% CI: 95.1% to 99.8%), which also demonstrated superiority over the performance goal of 88% ($p < 0.001$; Table 15.9.1.1.1). Subgroup analyses of SVR4 rates are presented in Table 15.9.1.3.1.

The following tertiary HCV efficacy endpoints are presented in tables: percentage of subjects with ALT normalization (Table 15.9.1.2.5); percentage of subjects with HCV RNA < LLOQ while on HCV treatment (Table 15.9.1.2.3); and HCV RNA (log_{10} IU/mL) values and changes from baseline through end of treatment (Table 15.9.1.2.4).

The percentages of subjects in the HIV FAS with HIV-1 RNA ≥ 50 copies/mL 24 weeks after start of HIV study drug as determined by the US FDA-defined snapshot algorithm (secondary HIV efficacy endpoint) were as follows (Table 15.9.2.1.1): E/C/F/TAF 1.4%; F/R/TAF 1.4%; difference in percentages: 0.0% (−6.1% to 6.1%).

The percentages of subjects in the HIV FAS with HIV-1 RNA < 50 copies/mL 24 weeks after start of HIV study drug as determined by the US FDA-defined snapshot algorithm were as follows: E/C/F/TAF 95.9%; F/R/TAF 94.6%. Four subjects discontinued study drug prior to Week 8 (as discussed above) and did not develop HIV drug resistance. Median changes from baseline in CD4 cell count (observed data) at Week 24 were as follows (Table 15.9.2.3.1): E/C/F/TAF 16 cells/µL; F/R/TAF 49 cells/µL (p = 0.30). Subgroup analyses of the percentage of subjects with HIV-1 RNA < 50 copies/mL 24 weeks after start of HIV study drug as determined by the US FDA-defined snapshot algorithm are presented in Table 15.9.2.1.3.

The following tertiary HIV efficacy endpoints are presented in tables: percentage of subjects with HIV-1 RNA ≥ 20 copies/mL 24 weeks after start of HIV study drug as determined by the US FDA-defined snapshot algorithm (Table 15.9.2.1.2); change from baseline in CD4 cell count (LOCF imputation) 24 weeks after start of HIV study drug (Table 15.9.2.3.2); change from baseline in CD4% 24 weeks after start of HIV study drug (Table 15.9.2.3.3); percentages of subjects with HIV-1 RNA < 50 copies/mL 24 weeks after start of HIV study drug using 2 different data imputation methods (Table 15.9.2.2.1 [M = F] and Table 15.9.2.2.2 [M = E]).

Results of virology resistance analyses are summarized in a separate Virology Report (PC-366-2002). No subject developed HIV drug resistance after switching to E/C/F/TAF or F/R/TAF.

Pharmacokinetics Results: Population PK assessments will be summarized in a separate report, if conducted.

Safety Results: Median (Q1, Q3) exposure to HIV study drug was as follows (Table 15.11.1.1): E/C/F/TAF 32.1 (32.0, 32.4) weeks; F/R/TAF 32.1 (32.0, 32.4) weeks. Overall median (Q1, Q3) exposure to LDV/SOF was 12.1 (12.0, 12.3) weeks (Table 15.11.1.2).

In general, the incidence of AEs in the individual study parts (during Part 1 or the coadministration period) and in the study as a whole was proportional to the duration of the study part (Table 3). The incidence of AEs during each study part was not corrected for duration of follow-up. Throughout the study, AEs were reported in a total of 81.8% of subjects (121 of 148 subjects). Grade 3 or 4 AEs were reported in 11.5% of subjects (17 subjects), study drug-related AEs were reported in 14.9% of subjects (22 subjects), and SAEs were reported in 12.8% of subjects (19 subjects). One subject discontinued F/R/TAF due to AE (worsening of pre-existing hypercholesterolemia) during the post-HCV follow-up period. One subject (in the F/R/TAF treatment group) died during the study due to metastatic carcinoma of unknown primary site.

Table 3. GS-US-366-1992: Overall Summary of Safety, Safety Analysis Set

Subjects, n (%)	Part 1 (8 weeks of E/C/F/TAF or F/R/TAF alone) (N = 148)	Coadministration Period (12 weeks of E/C/F/TAF or F/R/TAF + LDV/SOF) (N = 144)	Whole Study (32 weeks total: Baseline through post-HCV Week 12) (N = 148)
Any AE	77 (52.0%)	95 (66.0%)	121 (81.8%)
Grade 2, 3, or 4 AE	24 (16.2%)	42 (29.2%)	64 (43.2%)
Grade 3 or 4 AE	5 (3.4%)	10 (6.9%)	17 (11.5%)
Study drug-related AE	10 (6.8%)	14 (9.7%)	22 (14.9%)
Any SAE	3 (2.0%)	12 (8.3%)	19 (12.8%)
Study drug-related SAE	0	0	0
AE leading to DC of HIV study drug	1 (0.7%)[a]	1 (0.7%)[a]	1 (0.7%)[a]
AE leading to DC of HCV study drug	0	0	0
Death	0	0	1 (0.7%)

DC = discontinuation
a Only 1 subject had an AE leading to discontinuation of HIV study drug (Listing 16.2.7.9). The AE (worsening of hypercholesterolemia) that led to premature study drug discontinuation began in Part 1, continued in Part 2, and resulted in discontinuation of HIV study drug at post-HCV Week 4.
Source: Table 15.11.2.1.2

Generally, the incidence of AEs in either of the individual study parts or in the study as a whole was similar between the E/C/F/TAF±LDV/SOF group and the F/R/TAF±LDV/SOF group (Table 15.11.2.1.1). The incidence of AEs throughout the study was as follows: E/C/F/TAF±LDV/SOF 83.8%; F/R/TAF±LDV/SOF 79.7%. The incidence of AEs during the coadministration period was as follows: E/C/F/TAF+LDV/SOF 62.5%; F/R/TAF+LDV/SOF 69.4%. Two differences between randomized HIV treatment groups were noted, as follows:

- The incidence of study drug-related AEs (either to HIV or HCV study medication) in the study as a whole was 17.6% (13 of 74 subjects) for the E/C/F/TAF±LDV/SOF group and 12.2% (9 of 74 subjects) for the F/R/TAF±LDV/SOF group.
- In the coadministration period, the incidence of SAEs was 5.6% (4 of 72 subjects) for the E/C/F/TAF+LDV/SOF group and 11.1% (8 of 72 subjects) for the F/R/TAF+LDV/SOF group. For the study as a whole, the incidence of SAEs was 9.5% (7 of 74 subjects) for E/C/F/TAF±LDV/SOF group and 16.2% (12 of 74 subjects) for the F/R/TAF±LDV/SOF group. None of the SAEs were considered related to HIV or HCV study medication.

Adverse events reported in ≥ 5% of subjects in the study as a whole are presented in Table 4. Generally, the incidence of these AEs was comparable between Part 1 and the coadministration period.

Table 4. GS-US-366-1992: Adverse Events Reported in ≥ 5% of Subjects in the Study as a Whole, Safety Analysis Set

Subjects, n (%)	Part 1 (8 weeks of E/C/F/TAF or F/R/TAF alone) (N = 148)	Coadministration Period (12 weeks of E/C/F/TAF or F/R/TAF + LDV/SOF) (N = 144)	Whole Study (32 weeks total: Baseline through post-HCV Week 12) (N = 148)
Cough	7 (4.7%)	7 (4.9%)	16 (10.8%)
Upper respiratory tract infection	5 (3.4%)	8 (5.6%)	14 (9.5%)
Headache	3 (2.0%)	11 (7.6%)	12 (8.1%)
Arthralgia	4 (2.7%)	8 (5.6%)	12 (8.1%)
Urinary tract infection	4 (2.7%)	4 (2.8%)	12 (8.1%)
Nausea	5 (3.4%)	5 (3.5%)	10 (6.8%)
Fatigue	2 (1.4%)	7 (4.9%)	9 (6.1%)
Diarrhoea	3 (2.0%)	5 (3.5%)	9 (6.1%)
Abdominal pain	1 (0.7%)	5 (3.5%)	8 (5.4%)

Source: Table 15.11.2.2.2

Throughout the study, graded laboratory abnormalities were reported in a total of 94.6% of subjects (139 of 147 subjects; Table 15.11.6.8.1.2). The majority of laboratory abnormalities were Grade 1 (33.3%, 49 subjects) or Grade 2 (38.1%, 56 subjects) in severity. Generally, the incidence of Grade 3 or 4 laboratory abnormalities by analyte was comparable between Part 1 and the coadministration period.

Minimal changes in serum creatinine and $eGFR_{CG}$ were observed in both randomized HIV treatment groups throughout the study (Tables 15.11.6.3.23 and 15.11.6.3.24, respectively). Overall, median baseline $eGFR_{CG}$ was 99.8 mL/min and median changes from baseline were as follows: Week 8 (beginning of coadministration period) 2.2 mL/min, Week 20 (end of coadministration period) −0.9 mL/min, and Post-HCV Week 12 −0.1 mL/min.

Among the subjects with ALT above the upper limit of normal (ULN) at baseline of the coadministration period, normalization was observed in 89.8% (79 of 88 subjects) after 4 weeks of LDV/SOF treatment, in 90.9% (80 of 88 subjects) at the end of the coadministration period, and in 96.6% (84 of 87 subjects) at Post-HCV Week 12 (Table 15.9.1.2.5).

Fasting metabolic laboratory values (total cholesterol, direct low-density lipoprotein, high-density lipoprotein (HDL), total cholesterol to HDL ratio, triglycerides, and glucose) and changes from baseline through end of study are summarized in Tables 15.11.6.4.1 to 15.11.6.4.6. Bone safety laboratory values (serum parathyroid hormone and 25-hydroxy vitamin D) and changes from baseline through end of study are summarized in Tables 15.11.6.5.1 and 15.11.6.5.2, respectively. Renal safety laboratory values (urine protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR], urine retinol binding protein to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, and urine creatinine), changes from baseline through end of study, and categorical shifts in UPCR and UACR are summarized in Tables 15.11.6.6.1.1 to 15.11.6.6.5.

There were no notable changes in median vital signs values (systolic blood pressure, diastolic blood pressure, pulse, respiration, and temperature; Tables 15.11.7.1.1 to 15.11.7.1.5) or body weight (Table 15.11.7.2) during the study.

Patient-Reported Outcome Results: Results from the HIVTSQ showed increases in treatment satisfaction in both randomized HIV treatment groups across all categories evaluated (Table 15.12.2). Overall, results from SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C questionnaires indicated that quality-of-life parameters improved from baseline to end of study (Tables 15.12.3 to 15.12.6). Results from the HIV medication adherence VAS are provided in Tables 15.12.1.1 and 15.12.1.2.

CONCLUSIONS: The overall conclusions from this study are as follows:

- Following 12 weeks of treatment with LDV/SOF, the overall SVR12 rate in HIV/HCV-coinfected subjects was 97.2%, demonstrating superiority over the performance goal of 88% ($p < 0.001$).
  - SVR12 rates were comparable between the E/C/F/TAF+LDV/SOF and F/R/TAF+LDV/SOF treatment groups.
  - SVR12 rates were not impacted by important baseline demographic and disease characteristics (including race [black vs nonblack] or HCV genotype [1a vs 1b]).
- Coadministration of LDV/SOF with E/C/F/TAF or F/R/TAF was well tolerated.
  - There were no discontinuations of HCV or HIV study drugs due to clinical AEs during the coadministration period.
  - There were minimal differences between randomized HIV treatment groups in AEs, graded laboratory abnormalities, or changes from baseline in $eGFR_{CG}$, confirming that any minor differences in HIV and HCV drug exposure are not clinically meaningful.
- Subjects reported significant improvements in satisfaction with HIV treatment for both E/C/F/TAF and F/R/TAF.
- For HIV/HCV-coinfected subjects, switching to E/C/F/TAF or F/R/TAF from a stable regimen of 2 N(t)RTIs plus a third ARV agent resulted in low rates of HIV-1 RNA ≥ 50 copies/mL 24 weeks after start of HIV study drug (E/C/F/TAF 1.4%; F/R/TAF 1.4%).