# SECOND FINAL SYNOPTIC CLINICAL STUDY REPORT

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| **Study Title:** | A Phase 3b, Randomized, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Treatment-Naive and Treatment-Experienced Japanese Subjects with Chronic Genotype 1 HCV Infection |
| **Name of Test Drug:** | Ledipasvir/sofosbuvir fixed-dose combination (FDC) |
| **Dose and Formulation:** | Ledipasvir/sofosbuvir FDC (90/400 mg) tablet |
| **Indication:** | Hepatitis C virus infection |
| **Sponsor:** | Gilead Sciences, Inc.<br>333 Lakeside Drive<br>Foster City, CA 94404 USA |
| **Study No.:** | GS-US-337-0113 |
| **Phase of Development:** | Phase 3b |
| **IND No.:** | Not applicable |
| **EudraCT No.:** | Not applicable |
| **Study Start Date:** | 15 October 2013 (First Subject Screened) |
| **Study End Date:** | 22 August 2014 (Last Subject Observation) |
| **Principal or Coordinating Investigator:** | Name: Masashi Mizokami, MD<br>Affiliation: PPD |
| **Gilead Responsible Medical Monitor:** | Name: Phil Pang, MD, PhD<br>Telephone: PPD<br>Fax: PPD |
| **Second Final Report Date:** | 10 February 2015 |
| **Previous Final Report Date:** | 01 December 2014 |
| **Previous Report Date(s):** | 15 July 2014 (Interim Clinical Study Report)<br>10 February 2014 (Second Interim Clinical Study Report) |

# STUDY SYNOPSIS

**Study GS-US-337-0113**
**Gilead Sciences, Inc.**
**333 Lakeside Drive**
**Foster City, CA 94404**
**USA**

**Title of Study:** A Phase 3b, Randomized, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Treatment-Naive and Treatment-Experienced Japanese Subjects with Chronic Genotype 1 HCV Infection

**Investigators:** This was a multicenter study.

**Study Centers:** Subjects were randomized and treated at 19 study centers in Japan. Data for subjects randomized across 18 sites are summarized in this report.

**Publications:**

Mizokami M, Izumi N, Yokosuka O, Sakamoto N, Ishizaki A, Betular J, et al. A Phase 3 Study of Ledipasvir/Sofosbuvir Combination ± Ribavirin in Japanese Patients With Chronic Genotype 1 HCV Infection [Presentation]. Japanese Digestive Disease Week (JDDW); 2014 October 23; Kobe Japan.

Mizokami M, Takehara T, Yokosuka O, Sakamoto N, Korenaga M, Mochizuki H, et al. 100% SVR4 in Japanese Patients with Chronic Genotype 1 Hepatitis C Virus Infection Receiving Ledipasvir/Sofosbuvir Fixed Dose Combination for 12 Weeks: Results from a Multicenter Phase 3 Study [Abstract 1929]. American Association for the Study of Liver Disease (AASLD). 2014 October; Boston MA United States.

**Study Period:**

15 October 2013 (First Subject Screened)
22 August 2014 (Last Subject Observation)

**Phase of Development**: Phase 3b

**Objectives:**

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of combination treatment with ledipasvir (LDV)/ sofosbuvir (SOF) fixed-dose combination (FDC) ± ribavirin (RBV) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as hepatitis C virus [HCV] ribonucleic acid [RNA] less than the lower limit of quantitation [< LLOQ] 12 weeks posttreatment)
- To evaluate the safety and tolerability of LDV/SOF FDC ± RBV as assessed by review of the accumulated safety data

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

The exploratory objectives of this study were as follows:

- To identify or validate genetic markers that may be predictive of virologic response to therapy and/or tolerability of therapy through genetic discovery research (eg, pharmacogenomics) in subjects who provided their separate and specific consent
- To assess the effect of treatment with LDV/SOF FDC ± RBV on health-related quality of life

**Methodology**: This Phase 3b, randomized, open-label, multicenter study in Japan assessed the antiviral efficacy, safety, and tolerability of LDV/SOF±RBV administered for 12 weeks in treatment-naive and treatment-experienced subjects with chronic genotype 1 HCV infection.

Approximately 150 treatment-naive subjects were to be randomized (1:1) to 1 of the following 2 groups:

- LDV/SOF 12 Week treatment-naive group (Group 1): LDV/SOF FDC (90/400 mg) tablet once daily for 12 weeks
- LDV/SOF+RBV 12 Week treatment-naive group (Group 2): LDV/SOF FDC (90/400 mg) tablet once daily + RBV (weight-based dosing; 600, 800, or 1000 mg/day, divided twice daily) for 12 weeks

Approximately 150 treatment-experienced subjects were to be randomized (1:1) to 1 of the following 2 groups:

- LDV/SOF 12 Week treatment-experienced group (Group 3): LDV/SOF FDC (90/400 mg) tablet once daily for 12 weeks
- LDV/SOF+RBV 12 Week treatment-experienced group (Group 4): LDV/SOF FDC (90/400 mg) tablet once daily + RBV (weight-based dosing; 600, 800, or 1000 mg/day, divided twice daily) for 12 weeks

Treatment-naive status was defined as having never received treatment for HCV with any interferon (IFN), RBV, or other approved or experimental HCV-specific direct-acting antiviral (DAA) agent. Treatment-experienced status was categorized as nonresponse, relapse/breakthrough, or IFN intolerant.

Randomization of treatment-naive subjects into Groups 1 and 2 was stratified by the presence or absence of cirrhosis at screening. Randomization of treatment-experienced subjects into Groups 3 and 4 was stratified by the presence or absence of cirrhosis at screening and by response to prior HCV treatment (ie, nonresponse, relapse/breakthrough, or IFN intolerant). Up to 40% of subjects randomized in each group may have had Child-Pugh Class A compensated cirrhosis at screening.

A total of 341 subjects were randomized and treated at 19 study centers in Japan. Good Clinical Practice (GCP) noncompliance observations related to the sponsor/in-country representative were made at 1 participating study center that had randomized 23 subjects into the study PPD , as outlined in Section 8.2 of the second interim clinical study report (CSR). The GCP noncompliance observations were assessed by Gilead, the investigator, and associated personnel at the affected site. Although the principal investigator and institutional review board (IRB) concluded that there were no deviations from the protocol and that no revision to the informed consent form was warranted, the observations were considered critical from the GCP point of view at the participating center, and GCP inspections by the Pharmaceuticals and Medical Devices Agency identified as the GCP noncompliance. Therefore, all data for these 23 subjects were excluded from the analyses presented in this second final CSR, resulting in a reanalysis based on the remaining subjects (N = 318). The first final synoptic CSR dated 01 December 2014 presents data from all 19 study sites.

**Number of Subjects (Planned and Analyzed):**
Planned: Approximately 300 subjects (150 treatment-naive and 150 treatment-experienced)

Analyzed: 318 subjects (159 treatment-naive and 159 treatment-experienced) after excluding 23 subjects due to GCP noncompliance observations.

- Efficacy analysis set: 318 subjects
- Safety analysis set: 318 subjects
- Pharmacokinetics (PK) analysis set: 318 subjects
- PK substudy analysis set: 23 subjects

In the original analysis, all randomized subjects with genotype 1 HCV infection who received at least 1 dose of study treatment were included in the full analysis set (FAS) (N = 341) for the efficacy analysis. The same 341 subjects were included in the original safety and PK analysis sets. In this report, 23 subjects from 1 site with GCP noncompliance observations (related to the sponsor/in-country representative) were excluded from the full, safety, and PK analysis sets, and the term "reanalysis population" (N = 318) is used to describe the remaining subjects included in the efficacy, safety, and PK analyses in this report.

None of the 23 subjects originally included in the PK substudy analysis set were among those excluded from the reanalysis described in the second interim CSR.

**Diagnosis and Main Criteria for Inclusion**: Eligible subjects were males or nonpregnant/nonlactating females ≥ 20 years of age, with chronic genotype 1 HCV infection, who had screening HCV RNA levels ≥ $10^5$ IU/mL; were HCV treatment-naive or treatment-experienced; had documentation of the presence or absence of cirrhosis; and had a body weight ≥ 40 kg.

**Duration of Treatment:** Treatment duration was 12 weeks.

**Test Product, Dose, Mode of Administration, and Lot No.:**

- LDV/SOF was administered orally to all subjects at a dose of 90/400 mg (1 FDC tablet once daily).
- RBV (Copegus®) was administered orally to subjects in Groups 2 and 4 at a total daily dose of 600, 800, or 1000 mg/day (3, 4, or 5 × 200-mg tablets divided twice daily), depending on the subject's weight.

The lot numbers of study drugs administered in this study were as follows:

- LDV/SOF: DK1208B1R, DK1209B1R, and DK1209B1R-A
- RBV: 11G011D and 11G011D-A

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

**Criteria for Evaluation:**

**Efficacy:** This CSR provides analyses of HCV RNA levels at posttreatment Week 24. Efficacy analyses at all other scheduled assessment time points were described in the second interim CSR (SVR12). The COBAS® TaqMan HCV® Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study, with an LLOQ of 25 IU/mL.

**Pharmacokinetics**: The second interim CSR describes details on collection of blood samples for PK analyses.

**Safety:** The second interim CSR provided analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, physical examinations, vital sign measurements, and 12-lead electrocardiograms (ECGs). This second final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported treatment-emergent AEs between the data cuts for the interim CSR and the final CSR PPD . Additionally, all serious adverse events (SAEs) collected after the data cutoff for the interim CSR to the end of the study (posttreatment Week 24) are summarized. Serious adverse events occurring > 30 days after the last dose of study drug were considered nontreatment-emergent.

**Quality of Life:** The second interim CSR provided analyses of the quality of life questionnaire (Short Form Health Survey [SF-36]) to assess the effect of treatment on health-related quality of life. This second final CSR summarizes any additional data or changes to data that were previously reported in the period between the data cutoff dates for the interim CSR and the final CSR (without subjects from the Hyogo College of Medicine [Dr. Hirayuku Enomoto]).

**Statistical Methods:**

All tables, figures, and listings produced for this study are provided in Section 15.1 and Appendix 16.2. Documentation of statistical methods is provided in Appendix 16.1.9 of this report and described in detail in Section 7.7 of the second interim CSR.

**Efficacy:** For efficacy analyses, data were analyzed by prior treatment experience (treatment-naive or treatment-experienced) and treatment (LDV/SOF or LDV/SOF+RBV) using the reanalysis population. The primary efficacy endpoint was the proportion of subjects with

SVR12 (defined as HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the reanalysis population.

In treatment-naive noncirrhotic subjects, the SVR12 rates in Group 1 (LDV/SOF) and Group 2 (LDV/SOF+RBV) were compared to the adjusted historical SVR null rate of 63% using a 2-sided exact 1-sample binomial test. The adjusted historical SVR rate of 63% calculated for this study was based on the expected historical SVR rate of 73% (92 of 126) for noncirrhotic, treatment-naive Japanese subjects with chronic genotype 1 HCV infection taking pegylated interferon alpha (Peg-IFNα) + RBV + telaprevir (TVR) and allowing a 10% discount due to the expected improved safety profile and shorter treatment duration. A Hochberg procedure was used to ensure control of the family-wise type I error rate at the 0.05 significance level. In treatment-naive cirrhotic subjects and in treatment-experienced subjects, no statistical hypothesis testing was performed. Point-estimates with 2-sided 95% exact confidence intervals (CIs) using the binomial distribution (Clopper-Pearson method) were constructed for the SVR12 rates.

Secondary efficacy endpoints included the proportion of subjects with SVR4, SVR24, virologic failure (on-treatment virologic failure and relapse), and HCV RNA < LLOQ (ie, < 25 IU/mL) by visit; absolute HCV RNA and change from baseline through Week 12 (end of treatment); and emergence of viral resistance to LDV and SOF during treatment and after treatment discontinuation.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

SVR24 rates were calculated using the same method as described for SVR12. If a subject achieved SVR12 and had no further HCV RNA measurement, the subject was counted as a success for SVR24 due to the high correlation between these 2 endpoints {24697}. In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed.

**Pharmacokinetics:** Concentrations of SOF (and its metabolites) and LDV in plasma were determined using validated bioanalytical assays. The population PK parameters for SOF, GS-331007, and LDV were computed for all subjects from concentration data (intensive PK samples were collected over 24 hours postdose at the Week 2 or 4 on-treatment visit [N = 23] and sparse samples were collected from all subjects at all on-treatment visits) using the previously established SOF, GS-331007, and LDV population PK models. Descriptive statistics (sample size, mean, SD, coefficient of variation [%CV], median, Q1, Q3, minimum, and maximum) were presented. Results for all PK analyses are presented in the second interim CSR.

**Safety:** Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs, ECGs, and physical examinations. For safety analyses, data were analyzed grouped together by treatment (LDV/SOF or LDV/SOF+RBV) only, unless otherwise specified (eg, AEs by treatment and age group [< 65 years and ≥ 65 years]), and included all data collected on or after the first dose of any study drug up to the date of the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0.

**Quality of Life:** The health-related quality of life survey (SF-36) was completed by subjects at Day 1 (baseline); Weeks 4, 8, and 12; early termination (if applicable); and posttreatment Weeks 4 and 12. A Wilcoxon signed rank test explored within prior treatment experience (ie, treatment-naive or treatment-experienced) and treatment (ie, LDV/SOF or LDV/SOF+RBV) changes in status from baseline to each of the time points, and from end of treatment to posttreatment time points. A Wilcoxon rank sum test explored differences between groups within treatment-naive and treatment-experienced subjects (ie, the differences between Groups 1 and 2, and the differences between Groups 3 and 4) for changes in status from baseline to each of the time points.

**SUMMARY OF RESULTS:**

**Subject Disposition and Demographics:**

After excluding 23 subjects due to GCP noncompliance observations at 1 study site, a total of 318 subjects were randomized in the study: 159 treatment-naive and 159 treatment-experienced subjects. All of the 318 randomized subjects had genotype 1 HCV infection, received at least 1 dose of study drug, and were included in the reanalysis population. Of the 318 subjects randomized in the study, 316 subjects (99.4%) completed the study treatment. Two subjects (0.6%), in the LDV/SOF+RBV 12 Week treatment-naive group, prematurely discontinued study treatment (Subject PPD discontinued study treatment due to an AE of morbilliform rash and Subject PPD discontinued study treatment due to death from cardiac arrest) (Appendix 16.2, Listings 3, 13.2, and 16). Full details on subject disposition are reported in Section 8 of the second interim CSR and subject disposition at posttreatment Week 24 is summarized in Section 15.1, Table 3.

There were no differences in demographics between the second interim SVR12 analyses and the second final SVR24 analyses (Section 15.1, Table 4 and Appendix 16.2, Listing 4.1). An update was made to the SVR24 final database changing the number of subjects in the treatment-experienced group who failed prior therapy with Peg-IFNα+RBV+PI [protease inhibitor] (Section 8.1 of the second interim CSR). The PI information for 3 subjects (Subjects PPD [simeprevir], PPD [simeprevir], and PPD [faldaprevir]) was not captured in the SVR12 data cut. A total of 36 of 159 (22.6%) treatment-experienced subjects had failed prior treatment with a Peg-IFNα+RBV+PI regimen (including 14 subjects who failed telaprevir, 12 subjects who failed simeprevir, 7 subjects who failed the investigational PI vaniprevir, and 3 subjects for failed the investigational PI faldaprevir) (Section 15.1, Adhoc Table 7059.1; Appendix 16.2, Listing 4.5). The increase in treatment-experienced subjects (36 versus 33 subjects) who had failed prior treatment with a Peg-IFNα+RBV+PI regimen and a small number of additions and changes to concomitant medications did not change the interpretation of the study results (Section 15.1, Table 6 and Appendix 16.2, Listing 7). Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 through 7 and Figure 1, and Appendix 16.2, Listings 1.1 through **7**. In addition, an Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

**Efficacy Results:**

Analysis of the primary efficacy endpoint is reported in Section 9 of the second interim CSR. Results for SVR24, a secondary efficacy endpoint, are summarized in this second final CSR.

The proportion of subjects with SVR12 and SVR24 is presented in the table below. The SVR12 and SVR24 rates were the same for all treatment groups, with a 100% concordance between SVR12 and SVR24 (Section 15.1, Tables 8.2, 9, and 12, and Appendix 16.2, Listing 8.1).

| | **Treatment-Naive** | | **Treatment-Experienced** | |
|---|---|---|---|---|
| | **LDV/SOF 12 Weeks (N = 78)** | **LDV/SOF+RBV 12 Weeks (N = 81)** | **LDV/SOF 12 Weeks (N = 79)** | **LDV/SOF+RBV 12 Weeks (N = 80)** |
| SVR12 | 78/78 (100.0%) | 78/81 (96.3%) | 79/79 (100.0%) | 80/80 (100.0%) |
| 95% CI | 95.4% to 100.0% | 89.6% to 99.2% | 95.4% to 100.0% | 95.5% to 100.0% |
| SVR24 | 78/78 (100.0%) | 78/81 (96.3%) | 79/79 (100.0%) | 80/80 (100.0%) |
| 95% CI | 95.4% to 100.0% | 89.6% to 99.2% | 95.4% to 100.0% | 95.5% to 100.0% |

Note: HCV RNA analyzed using Roche TaqMan V2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL
Note: SVRx is sustained virologic response (HCV RNA < LLOQ) × weeks after stopping study treatment
Note: A missing SVR value is imputed as a success if it is bracketed by values that are termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR value is imputed as a failure. TND = target not detected
Note: The exact 95% CI for the proportion is based on the Clopper-Pearson method.
Note: A total of 341 subjects were randomized and received study drug in this study; 23 subjects were removed from this analysis due to GCP noncompliance observations, resulting in a reanalysis based on 318 remaining subjects (ie, reanalysis population).
Source: Section 15.1, Table 8.2 and Table 12

No subjects in any group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse) (Section 15.1, Table 10, and Appendix 16.2, Listing 8.2).

A total of 3 of 318 subjects (0.94%) did not achieve SVR12 or SVR24; all were in the LDV/SOF+RBV 12 Week treatment-naive group. One subject relapsed at the posttreatment Week 4 visit (Appendix 16.2, Listing 8.2), 1 subject discontinued study treatment due to an AE (morbilliform rash), and 1 subject did not complete the study treatment and study due to death (cardiac arrest). All subjects who had achieved SVR12 also achieved SVR24 (Section 15.1, Table 12, and Appendix 16.2, Listings 8.1 and 8.2). A total of 36 of 36 subjects (100%) who failed prior therapy with Peg-IFNα+RBV+PI achieved SVR12 and SVR24 (Appendix 16.2, Listings 4.5 and 8.1). Removal of 23 subjects from the original efficacy analyses did not impact the efficacy profile of LDV/SOF±RBV in this study population.

All efficacy analyses are provided in Section 15.1, Tables 8.1 through 14, Figures 2 through 4.4, and Appendix 16.2, Listings 8.1 and 8.2. Full details on the resistance analysis are reported in Section 9.3.2 of the second interim CSR. No additional resistance analyses were performed since no subjects relapsed during posttreatment Week 12 through Week 24.

**Pharmacokinetic Results:**

Full details on the PK analysis are reported in Section 10 of the second interim CSR.

**Safety Results:**

All AEs and laboratory abnormalities discussed in this CSR were treatment-emergent and are referred to as AEs and laboratory abnormalities in this report, unless otherwise specified. Evaluation of safety through 30 days after the last dose of study drugs were summarized in Section 11 of the second interim CSR.

Adverse Events and Serious Adverse Events

A small number of updates were made to previously reported AE data due to the ongoing nature of the study and data reconciliation. These changes included actions taken to treat the AE (ie, medication), change in onset date, newly reported Grade 1 AEs, newly reported nontreatment-emergent AEs, and removal of previously reported AEs (Appendix 16.2, Listing 10, and Adhoc Listing 7059.1). The 2 previously reported AEs were in the LDV/SOF 12 Week treatment-experienced group:

- A Grade 1 AE of hepatopathy was reported by the investigator for Subject PPD and was considered by the investigator to be related to study drug. Following the review of the complete clinical information for this subject, the investigator reclassified the event and the AE was removed from the database.
- A Grade 2 AE of "drug-induced liver injury" was reported by the investigator for Subject PPD and was considered by the investigator to be related to study drug (Section 11.2.3 of the second interim CSR). During the final analysis, the investigator reviewed the clinical laboratories (ALT, AST, bilirubin, and alkaline phosphatase), clinical signs, and symptoms of the subject and decided they did not meet the criteria for "drug-induced liver injury." As a result, the Grade 2 AE of "drug-induced liver injury" for Subject PPD was removed from the database.

There was an additional Grade 1 AE (nasopharyngitis) reported for 1 subject in the LDV/SOF+RBV group. Adhoc Listing 7059.1 provides a detailed listing of any newly reported AEs and any changes in previous reported AEs between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points. These changes did not impact the overall interpretation or conclusion of the safety profile of LDV/SOF with or without RBV in this study.

There were no additional treatment-emergent SAEs. Two additional nontreatment-emergent SAEs were reported and were not considered related to study drug (Appendix 16.2, Listing 10, Listing 14, and Adhoc Listing 7059.1). Subject PPD in the LDV/SOF+RBV 12 Week treatment-experienced group, was a 58-year-old female subject who had a Grade 3 event of ureteral calculus on posttreatment Day 116 (resolved on posttreatment Day 125). Subject PPD in the LDV/SOF 12 Week treatment-experienced group, was a 52-year-old male subject who had a Grade 3 event of duodenal ulcer on posttreatment Day 152 (resolved on posttreatment Day 156). Narratives for all subjects in the reanalysis population with SAEs from the first dose of study drug through the end of the study (ie, the SVR24 visit) and those who prematurely discontinued LDV/SOF due to an AE are provided in Section 15.2.

One subject died during the study (Appendix 16.2, Listing 16). Subject PPD in the LDV/SOF+RBV 12 Week treatment-naive group, died as a result of cardiac arrest. Full details can be found in Section 11.3 of the second interim CSR and a narrative is provided in Section 15.2.

No subject pregnancies were reported in this study (Appendix 16.2, Listing 15).

Removal of 23 subjects from the original safety analyses did not impact the safety profile of LDV/SOF±RBV in this study population.

All AE results are provided in Section 15.1, Tables 15 through 30, and Appendix 16.2, Listings 10 through 16.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were not collected at the posttreatment Week 24 visit.

All laboratory results are provided in Section 15.1, Tables 31.1 through 33, Figures 5.1 through 5.11, and Appendix 16.2, Listings 19 through 22.2.

Vital Sign Measurements and ECGs

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) and weight were collected at the posttreatment Week 24 visit. No notable changes were observed (Appendix 16.2, Listings 24.1 and 24.2).

All vital sign measurements and ECG results are provided in Section 15.1, Tables 34 through 35.4, and Appendix 16.2, Listings 23 through 24.2.

Special Situations

Special situations, including pregnancy reports, reports of medication error, abuse, misuse, or overdose, reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints, were collected during the study; no new safety concerns were identified from evaluation of reports of special situation events (Appendix 16.2, Special Situations Listing).

**Quality of Life:**

Complete details on the quality of life survey (SF-36) are reported in Section 12 of the second interim CSR. There are no additional data or changes to data that were previously reported in the second interim CSR. Quality of life surveys (SF-36) were not collected during the posttreatment Week 24 visit.

Quality of life analyses are provided in Section 15.1, Table 36, Figure 6, and Appendix 16.2, Listing 9

**CONCLUSIONS:**

The conclusions from the study are as follows:

- The LDV/SOF FDC regimen administered orally, once daily for 12 weeks in treatment-naive and treatment-experienced Japanese subjects with chronic genotype 1 HCV infection achieved an SVR12 rate of 100%.
- Concordance between SVR12 and SVR24 was 100%.
- Concomitant RBV increased toxicity, offered no efficacy advantage, and is not required as part of this regimen.
- The LDV/SOF FDC regimen administered once daily for 12 weeks was safe and well-tolerated. No subjects (0 of 157) prematurely discontinued this regimen.
- All subjects with baseline NS5A RAVs achieved SVR12 and SVR24 after 12 weeks of treatment with LDV/SOF.
- NS5A RAV, but no SOF RAV, was detected in the single subject who relapsed after taking LDV/SOF+RBV.

- Following administration of the LDV/SOF FDC tablet, the PK of SOF, GS-331007, and LDV in Japanese subjects with chronic genotype 1 HCV infection were comparable to those observed in overseas studies.
- The IFN- and RBV-free, LDV/SOF FDC tablet administered orally, once daily for 12 weeks provides high efficacy coupled with a favorable safety and tolerability profile in treatment-naive and treatment-experienced Japanese subjects in most urgent need of treatment. These data support the use of the LDV/SOF FDC tablet in Japanese patients with chronic genotype 1 HCV infection, including those with compensated cirrhosis.
- Removal of 23 subjects from the original analyses did not impact the efficacy, PK, or safety profiles of LDV/SOF±RBV in this population.