FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	An Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 or 24 Weeks in Genotype 1 or 4 HCV Infected Subjects with Sickle Cell Disease
Name of Test Drug:	Ledipasvir/Sofosbuvir (LDV/SOF) fixed-dose combination (FDC)
Dose and Formulation:	LDV/SOF FDC (90/400 mg)
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-1405
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02301936
Study Start Date:	02 March 2015 (First Subject Screened)
Study End Date:	18 April 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Mark Sulkowski, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Theo Brandt-Sarif, MD Telephone: PPD Fax: PPD
Report Date:	01 August 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS
Study GS-US-337-1405
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: An Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 or 24 Weeks in Genotype 1 or 4 HCV Infected Subjects with Sickle Cell Disease

Investigators: Mark Sulkowski, MD

Study Centers: 1 site in the United States

Publications: There are no publications at the time of this clinical study report.

Study Period:

02 March 2015 (First Subject Screened)
18 April 2016 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of combination treatment with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of the treatment regimen 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 weeks after discontinuation of therapy (SVR4)
- 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
- To evaluate the effect of treatment on the health related quality of life

The exploratory objectives of this study are:

- To identify or validate genetic markers that may be predictive of the natural history of disease, response to therapy and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics), in subjects who provide their separate and specific consent

Methodology: This Phase 2, open-label study evaluated LDV/SOF for 12 or 24 weeks in subjects with sickle cell disease and chronic genotype 1 or 4 HCV infection.

Approximately 25 subjects were to be enrolled into 1 of the following 2 treatment groups:

Group 1 (Treatment-naive or treatment-experienced subjects without cirrhosis):

LDV/SOF FDC (90mg/400mg) tablet once daily for 12 weeks

Group 2 (Treatment-experienced subjects with cirrhosis):

LDV/SOF FDC (90mg/400mg) tablet once daily for 24 weeks

All subjects completed a screening assessment within 28 days prior to baseline/Day 1. Study visits occurred at screening, baseline/Day 1, and on-treatment Weeks 1, 2, 4, 6, 8, and 12 for all subjects and Weeks 16, 20, and 24 for treatment-experienced subjects with cirrhosis (Group 2). All subjects, including those who prematurely discontinued study drug, completed posttreatment follow-up visits at posttreatment Weeks 4 and 12.

All subjects were eligible to participate in the pharmacogenomic substudy to identify or validate genetic markers that may be predictive of the natural history of disease, virologic response to therapy, and/or the tolerability of medical therapies through genetic discovery research. Subjects provided additional, specific consent prior to participation in this substudy.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 25 subjects

Analyzed:

- 11 subjects Screened
- 10 subjects in the Full Analysis Set (9 subjects in the LDV/SOF 12-week treatment group [Group 1] and 1 subject in the LDV/SOF 24-week treatment group [Group 2])
- 10 subjects in the Safety Analysis Set (9 subjects in the 12-week treatment group [Group 1] and 1 subject in the 24-week treatment group [Group 2])

Diagnosis and Main Criteria for Inclusion: Eligible subjects were HCV treatment-naive (without cirrhosis) or treatment-experienced (with or without cirrhosis) males and nonpregnant/nonlactating females, aged 18 years of age or older, with sickle cell disease documented by hemoglobin electrophoresis or Hgb variant, hemoglobin value ≥ 6 g/dL, and with genotype 1 or 4 HCV infection.

Duration of Treatment: 12 weeks of treatment for treatment-naive or treatment-experienced subjects without cirrhosis or 24 weeks of treatment for treatment-experienced subjects with cirrhosis. All subjects were followed for 12 weeks after treatment was discontinued.

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

- **LDV/SOF FDC** was administered orally to subjects with genotype 1 or 4 HCV infection at a dose of 90/400 mg/day (1 tablet once daily)

The batch numbers of the study drug administered in this study were as follows:

- **LDV/SOF:** DK1208B1R, DK1303B1

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

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening, baseline/Day 1 (predose), Weeks 1, 2, 4, 8, and 12 during treatment (or upon early termination), and posttreatment Weeks 4 and 12. Additional blood samples to determine HCV RNA levels were collected at on-treatment Weeks 16, 20, and 24 from subjects in Group 2. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected starting at each on-treatment visit and at early termination (if applicable) for all subjects.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations.

Other: Quality of life was evaluated using the Short-Form (SF-36) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) surveys administered on Day 1, on treatment at Weeks 4, 8, 12 in Groups 1 and 2, and Weeks 16, 20, and 24 in Group 2, early termination, and posttreatment at Weeks 4 and 12.

Statistical Methods: All tables, figures, and listings produced for this study are provided in Section 15 and Appendix 16.2. Documentation of statistical methods is provided in Appendix 16.1.9.

Subject Disposition: Subject disposition was summarized by treatment group (LDV/SOF 12-week treatment group [Group 1] and LDV/SOF 24-week treatment group [Group 2]) and included the number of subjects screened, rescreened, enrolled, not enrolled, in the Full Analysis Set, in the Safety Analysis Set, the number and percentage of subjects who completed treatment, discontinued treatment (and the reasons for doing so), completed the study, and did not complete the study (and the reasons for doing so). Additionally, further categorization by available HCV RNA assessment at posttreatment Week 4 and posttreatment Week 12 was provided.

Subject Demographics: Subject demographics were summarized by treatment group and were summarized for subjects in the Safety Analysis Set. Subject demographics and baseline disease characteristics were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum) for continuous data and by number and percentage of subjects for categorical data.

Efficacy: Efficacy data were summarized by treatment group. The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of study treatment (SVR12) for the Full Analysis Set. The proportion of subjects who achieved SVR12 within each treatment group was calculated; exact 2-sided 95% confidence intervals (CIs) were constructed using the Clopper-Pearson method {Clopper et al 1934}. No statistical hypothesis testing was performed.

The secondary efficacy endpoints were the proportion of subjects who achieved SVR4, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through the end of treatment, and the proportion of subjects with virologic failure. Hepatitis C drug resistance-associated variants (RAVs) were characterized at baseline, and as applicable, during and after treatment.

A summary of the number and percentage of subjects with HCV RNA < LLOQ by on treatment study visit was provided; 95% Clopper-Pearson exact CIs were presented for the proportion of subjects with HCV RNA< LLOQ within each treatment group. Additionally, a summary table of the number and percentage of subjects with HCV RNA < LLOQ and ≥ LLOQ at each posttreatment follow-up visit (observed and imputed, with reasons for imputed) was provided; 95% Clopper-Pearson exact CIs were presented for the proportion of subjects with HCV RNA< LLOQ within each treatment group.

A summary of virologic outcomes was provided by treatment group that included the number and percentage of subjects with SVR12, virologic failure (with subgroups for on-treatment virologic failure and relapse), and other (those who did not achieve SVR12 and did not meet virologic failure criteria).

Exploratory efficacy endpoints were to include the identification or validation of genetic markers that may predict the natural history of disease, response to therapy, and/or tolerability of medical therapy through genetic discovery research (eg, pharmacogenomics). Exploratory endpoints were not evaluated in this final synoptic clinical study report (sCSR).

Pharmacokinetics: No statistical PK analyses were performed for this report.

Safety: Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations for subjects in the Safety Analysis Set. Safety data were summarized by treatment group and safety summaries included all data collected on or after the first dose of study drug through the date of the last dose of any study drug plus 30 days. All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs for the purposes of this report. Adverse events and laboratory abnormalities were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 16.1.1, Appendix 3). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.

Adverse events were summarized (by system organ class and/or preferred term) by analysis group for the number and percentage of subjects who had (1) any AE, (2) Grade 3 or above AEs, (3) Grade 2 or above AEs, (3) all treatment-related AEs, (5) nonserious AEs occurring in at least 10% of subjects in any treatment group, (6) any Grade 3 or above treatment-related AE, (7) Grade 2 or above treatment-related AEs, (8) serious adverse events (SAEs),

(9) treatment-related SAEs, (10) AEs leading to permanent discontinuation from study drug, and (11) AEs leading to interruption of study drug. Data listings for all AEs, SAEs, deaths, Grade 3 or above AEs, and AEs leading to permanent discontinuation from LDV/SOF were provided.

Laboratory results were assigned toxicity grades of 0 to 4. Laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline time point to the date of the last dose of any study drug plus 30 days (ie, treatment emergent). The number and percentage of subjects by analysis group who had any graded laboratory abnormality or any Grade 3 or 4 laboratory abnormality were summarized. Laboratory data were summarized using descriptive statistics by treatment group with corresponding changes from baseline for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, white blood cell (WBC) counts, neutrophils, lymphocytes, platelets, International Normalized Ratio (INR), activated partial thromboplastin time (APTT), serum ferritin and iron concentration, transferrin-iron saturation, hemoglobin F concentration. Data listings of hematology, chemistry, coagulation, hemoglobin and iron assessments including Hgb variant, serum ferritin and iron concentration, transferrin-iron saturation, and hemoglobin F concentration laboratory values, Grade 3 or 4 laboratory abnormalities, and urinalysis results were provided.

Other: Other secondary endpoints included the absolute scores and the change from baseline through the end of treatment and through posttreatment Week 12 for the subject reported health-related quality of life surveys (SF-36 and FACIT-F).

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 10 subjects were enrolled in the study; 9 subjects were enrolled into the LDV/SOF 12-week treatment group (Group 1) and 1 subject was enrolled into the LDV/SOF 24-week treatment group (Group 2) (Section 15.1, Table 2). All subjects (100.0%) completed treatment (Appendix 16.2, Listing 3).

In Group 1, the mean (range) age of subjects was 43 years (22 to 62 years) and 66.7% (6 of 9) were male subjects (Section 15.1, Table 4). All subjects were black or African American, and not of Hispanic or Latino ethnicity. The mean (range) body mass index (BMI) was 22.5 kg/m^2 (18.7 to 27.7). No subject had cirrhosis and 77.8% (7 of 9) were treatment naive. Six subjects had genotype 1 HCV infection (5 subjects with genotype 1a and 1 subject with genotype 1b) and 88.9% (8 of 9) had a IL28B non-CC allele. The overall mean (SD) baseline HCV RNA value was 5.8 (0.74) log_{10} IU/mL, and 66.7% (6 of 9) subjects had baseline HCV RNA < 800,000 IU/mL. The single subject enrolled in Group 2 was female, 44 years of age, black or African American, and had a baseline BMI of 45.2 kg/m^2. The subject was infected with genotype 1a HCV, was treatment experienced with cirrhosis, had the IL28B CT allele, and a baseline HCV RNA value of 6.2 log_{10} IU/mL.

Analyses related to disposition, demographics, concomitant medications, and study drug exposure are presented in Section 15.1, Tables 1 to 7, Figure 1, and Appendix 16.2, Listings 1 to 8.

Efficacy Results: The primary endpoint was the proportion of subjects who achieved SVR12 in each LDV/SOF treatment group (Section 15.1, Table 8). The single subject in Group 2 who was treated with 24 weeks of LDV/SOF achieved SVR12. In Group 1, 88.9% (8 of 9) subjects

achieved SVR12 following 12 weeks of treatment with LDV/SOF (Table 1). One subject failed to achieve SVR12: Subject PPD who was treatment-experienced with genotype 4f HCV infection at baseline, had virologic failure (relapse) at posttreatment Week 4, and was then lost to follow-up (Appendix 16.2, Listings 3, 4, and Listing 10.1). (Table 1).

All subjects who achieved HCV RNA < LLOQ by Week 4 achieved SVR12.
Subject PPD in Group 1, the only subject who did not achieve HCV RNA < LLOQ by Week 4, did not achieve HCV RNA < LLOQ until an unscheduled visit on Day 70 and subsequently relapsed at posttreatment Week 4.

Although drug accountability records for the subject who had virologic relapse indicated 97.6% compliance to study drug, there was no initial decline in HCV RNA; at Week 4 HCV RNA increased from a baseline value of 6.66 $\log_{10}$ IU/mL to 6.85 $\log_{10}$ IU/mL (Appendix 16.2, Listings 7.1 and 10.1). Drug level concentrations of SOF (and its metabolites GS-566500, GS-331007) and LDV measured at Weeks 2 and 4 were consistent with noncompliance to study drug (ie, below the level of quantification [BLQ]).

In both treatment groups, HCV RNA levels declined rapidly (Section 15.1, Table 13). At Week 1 the mean (SD) change from baseline was −4.20 (0.543) $\log_{10}$ IU/mL in Group 1 and −3.86 $\log_{10}$ IU/mL for the single subject in Group 2.

All efficacy analyses are provided in Section 15.1, Tables 8 to 13, Figures 2 to 3.4, and in Appendix 16.2, Listings 10 to 10.2.

Table 1. GS-US-337-1405: Proportion of Subjects with SVR4, SVR12, and Virologic Outcomes (Full Analysis Set)

	Group 1 LDV/SOF 12 Weeks N = 9	Group 2 LDV/SOF 24 Weeks N = 1
SVR4	8/9 (88.9%)	1/1 (100.0%)
95% CI	51.8% to 99.7%	2.5% to 100.0%
SVR12	8/9 (88.9%)	1/1 (100.0%)
95% CI	51.8% to 99.7%	2.5% to 100.0%
Overall Virologic Failure	1/9 (11.1%)	0/1
Relapse	1/9 (11.1%)	0/1
On Treatment Virologic Failure	0/9	0/1
Other	0/9	0/1

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with a limit of quantitation of 15 IU/mL.
SVRx was sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.
A missing SVR value was imputed as a success if it was bracketed by values that were termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR value was imputed as a failure.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Section 15.1, Tables 8 to 10

Virologic Resistance Analysis:

Virology listings are provided in Appendix 16.2, Virology Listings 1 to 5.

The full-length nonstructural protein NS5A and NS5B coding regions were successfully deep sequenced at pretreatment (baseline) for all 10 patients including the 1 subject who had virologic failure. Baseline and posttreatment analyses were conducted with a 1% cutoff.

Among the 10 subjects, 7 subjects had genotype 1 HCV infection; 6 subjects had subtype 1a and 1 subject had subtype 1b. The remaining 3 subjects had genotype 4 HCV infection. One subject (Subject PPD had no subtype definition at screening and was later found to be infected with genotype 4a by BLAST analysis using the NS5A and NS5B sequences (Appendix 16.2, Virology Listing 5). Another subject with genotype 4 HCV infection was found to have subtype 4h at screening, but later through BLAST analysis the subject was found to have subtype 4k (Appendix 16.2, Virology Listing 5).

Overall, 4 of 10 subjects (40.0%) (1 subject with genotype 1 HCV infection and 3 subjects with genotype 4 HCV infection) had NS5A RAVs at baseline and 3 of the 4 subjects (75.0%) achieved SVR12, compared with 6 of 6 subjects (100.0%) without NS5A RAVs who achieved SVR12 (Appendix 16.2, Virology Listing 1). The subject who failed to achieve SVR12 was treatment-experienced, and had genotype 4f HCV infection and L30R (> 99%) at baseline and at time of virologic failure. The other subjects with genotype 4 HCV infection were treatment-naive, had L30R (> 99%) at baseline, and achieved SVR12. One of the 10 subjects (10.0%) had NS5B RAVs at baseline at low frequencies (L159F [1.3%] and F289L [1.4%]) and achieved SVR12 (Appendix 16.2, Virology Listing 2).

One of the 10 subjects failed to achieve SVR12. The subject was treatment-experienced with genotype 4f HCV infection, and relapsed at posttreatment Week 4. The subject had NS5A RAVs at baseline and at the time of relapse. The subject did not have any treatment-emergent NS5A or NS5B RAVs.

Table 2. GS-US-337-1405: Baseline and Postbaseline NS5A, and NS5B RAVs in Subjects with Virologic Failure

Subject ID	Genotype	Treatment	NS5A RAVs		NS5B RAVs	
			Baseline	Post treatment	Baseline	Post treatment
PPD	4f	LDV/SOF 12 Weeks	L30R (> 99%)	L30R (> 99%)	None	None

Source: Appendix 16.2, Virology Listings 3 and 4

Pharmacokinetic Results: Plasma concentrations of LDV and SOF and its metabolites GS-566500 and GS-331007 were determined to assess adherence to study drug for Subject PPD who relapsed at posttreatment Week 4. No measurable drug was detectable through the Week 4 on-treatment study visit suggesting nonadherence to study drug (Appendix 16.1.10, Sample Analysis Reports QPS 60N-1563A and QPS 60N-1563B).

Safety Results: The median (range) duration of exposure to study regimen was 12.1 (11.1–12.3) weeks in Group 1 and in Group 2, duration of exposure for the single subject was 23.1 weeks. (Section 15.1, Table 5).

Adverse Events and Serious Adverse Events

The majority of subjects experienced at least 1 AE: 66.7% (6 of 9) of subjects treated with LDV/SOF for 12 weeks in Group 1 and 100% (1 of 1) subjects treated for 24 weeks in Group 2.

In Group 1, AEs occurring in ≥ 2 subjects were headache (66.7%; 6 of 9), nausea (22.2%; 2 of 9), and sickle cell anemia crisis (22.2%; 2 of 9) (Section 15.1, Table 15). Adverse events experienced by the single subject enrolled Group 2 included eye discharge, fatigue, pneumonia, musculoskeletal chest pain, and insomnia. The only AEs considered by the investigator as related to study drug included headache (55.6%; 5 of 9) and nausea (22.2%; 2 of 9).

Most AEs reported in the study were Grade 1 or Grade 2 in severity (Appendix 16.2, Listing 12 and Listing 15). No subject experienced a Grade 4 AE, and overall, 2 subjects treated for 12 weeks in Group 1 experienced Grade 3 AEs. Subject PPD experienced a Grade 3 AE of sickle cell anemia crisis beginning on Day 6. The AE was considered not related to study drug and resolved within 2 days following treatment, with no changes to study drug. Subject PPD experienced Grade 3 AEs of sickle cell anemia crisis (also an SAE), pyrexia, and anemia beginning on Day 8. The events were resolved on Day 16 following treatment. Study drug continued uninterrupted and the AEs were considered not related to study drug.

One SAE occurred during the study. As noted above, Subject PPD experienced the SAE sickle cell anemia crisis (Appendix 16.2, Listing 15). A subject narrative is provided in Section 15.2.

No subject experienced an AE leading to the interruption or discontinuation of treatment (Section 15.1, Tables 21, 25.1, and 26.1). There were no subject deaths or pregnancies reported during the study (Appendix 16.2, Listing 16 and 17).

Clinical Laboratory Results

Overall, 3 subjects (all in Group 1) experienced a Grade 3 or 4 laboratory abnormality.

Subject PPD experienced a single Grade 3 lipase value postbaseline. At screening and baseline, lipase values were 311 U/L (Grade 3) and 193 U/L (Grade 2), respectively. At Week 2 lipase had increased to 351 U/L. At the next visit lipase had declined to 105 U/L. At the time of the laboratory abnormality, the subject was asymptomatic (Appendix 16.2, Listing 19 and Listing 21).

Subject PPD experienced Grade 4 hemoglobin values. At baseline, hemoglobin was 7.0 g/dL (Grade 3) and at Weeks 1 and 2, hemoglobin had declined to 6.6 g/dL and 6.8 g/dL, respectively. At subsequent on-treatment visits, hemoglobin had returned to baseline. The final posttreatment hemoglobin value was 7.7 g/dL. The subject also experienced a Grade 3 total bilirubin elevation. At baseline, total bilirubin was 2.7 mg/dL, that increased to 3.4 mg/dL at Week 2. At subsequent on-treatment visits, total bilirubin had returned to at least the baseline value, and at the final posttreatment visit total bilirubin was 2.3 mg/dL. At the time of the laboratory abnormalities, the subject was asymptomatic.

Subject PPD experienced a single Grade 3 hemoglobin value. At baseline, hemoglobin was 9.2 g/dL (Grade 2) and at Week 2, hemoglobin had declined to 8.9 g/dL. At subsequent visits, hemoglobin had increased to at least the baseline value, and at the final posttreatment visit

the hemoglobin value was 9.4 g/dL. Aside from a mild headache, the subject was asymptomatic at the time of the laboratory abnormality.

In both cases, the change from baseline in hemoglobin values were small, and the Grade 3 or 4 anemia simply reflects baseline sickle cell disease.

Overall, the median (range) baseline hemoglobin value for Group 1 was 8.8 (6.8–11.7) g/dL and the median (range) change from baseline at posttreatment Week 4 was 0.0 (−1.1–1.3) g/dL (Section 15.1, Table 27.2.1). For the single subject in Group 2, the baseline hemoglobin value was 11.1 g/dL and the change from baseline at posttreatment Week 4 was −0.1 g/dL.

At baseline, the proportion of subjects in Group 1 with hemoglobin values < 10 g/dL and < 8.5 g/dL was 7 of 9 subjects and 4 of 9 subjects, respectively. During posttreatment follow-up, the proportion of subjects with any posttreatment value < 10 g/dL remained the same; however, the proportion of subjects with hemoglobin values < 8.5 g/dL declined to 3 of 9 subjects.

There were no notable changes in serum ferritin, serum iron levels, hemoglobin F percent concentration, and transferrin-iron percent saturation (Section 15.1, Tables 27.3.1 – 27.3.4).

All laboratory results are provided in Section 15.1, Tables 27.1.1 to Table 28.1, Figures 4.1.1 to 4.2.6, and Appendix 16.2, Listing 11, Listings 19 to 25.2.

Vital Signs Measurements

No clinically relevant changes in vital signs measurements were reported (Section 15.1, Tables 29.1 to 29.3 and Appendix 16.2, Listing 28).

Other Results: Health-related, quality of life questionnaires (ie, SF-36 and FACIT-F) are summarized in Section 15.1, Tables 31.1 and Table 31.2 and subject data are listed in Appendix 16.2, Listings 26.1 and 26.2.

CONCLUSIONS: The conclusions of this Phase 2 study were as follows:

- In subjects with sickle cell disease and genotype 1 or 4 HCV infection, treatment with LDV/SOF provided high virologic response rates; 8 of 9 treatment-naive or treatment experienced subjects without cirrhosis who received LDV/SOF for 12 weeks and 1 of 1 treatment-experienced subject with cirrhosis who received LDV/SOF for 24 weeks achieved SVR12.
  - One subject had posttreatment virologic failure. At Week 4, this subject had evidence of study drug nonadherence by pharmacologic analysis and no change in HCV RNA at that time point.
- Treatment with LDV/SOF resulted in rapid and sustained viral suppression. No subjects experienced on-treatment virologic failure.
- Treatment with LDV/SOF was well tolerated in this study. The safety profile was consistent with that of LDV/SOF in subjects without cirrhosis or with compensated cirrhosis, and the sickle cell crisis in 2 subjects is consistent with what would be expected in this patient population. There were no new safety signals or toxicity observed in this study of subjects with sickle cell disease and HCV infection.