FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir + GS-5816 for 12 Weeks in Treatment-Naive Subjects with Chronic HCV Infection	
Name of Test Drug:	Sofosbuvir (SOF), GS-5816	
Dose and Formulation:	SOF 400-mg tablet GS-5816 25-mg or 100-mg tablet	
Indication:	Hepatitis C virus infection	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	
Study No.:	GS-US-342-0102	
Phase of Development:	Phase 2	
IND No.:	115670	
EudraCT No.:	Not applicable	
Study Start Date:	22 April 2013 (First Subject Screened)	
Study End Date	12 August 2014 (Last Subject Observation)	
Principal or Coordinating Investigator:	Name: Affiliation:	Greg Everson, MD, FACP PPD
Gilead Responsible Medical Monitor:	Name: Telephone: Fax:	Diana Brainard, MD PPD PPD
Report Date:	13 February 2015	

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-342-0102
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir + GS-5816 for 12 Weeks in Treatment-Naive Subjects with Chronic HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 48 sites in the United States (US).

Publications:

Everson GT, Tran TT, Towner WJ , Davis MN, Wyles D, Nahass R, McNally J, Brainard DM, Han L, Doehle B, Mogalian E, Symonds WT, McHutchison JG, Morgan T, Chung RT. Safety and Efficacy of Treatment with the Interferon-Free, Ribavirin-Free Combination of Sofosbuvir + GS-5816 for 12 Weeks in Treatment Naive Patients with Genotype 1–6 HCV Infection. Journal of Hepatology, Volume 60, Issue 1, Supplement, Page S46. April 2014 (EASL 2014).

Tran TT, Morgan TR, Thuluvath PJ, Etzkorn K, Hinestrosa F, Tong M, McNally J, Brainard DM, Han L, Doehle B, Mogalian E, McHutchison JG, Chung RT, Everson GT. Safety and Efficacy of Treatment with Sofosbuvir+ GS-5816±Ribavirin for 8 or 12 Weeks in Treatment Naïve Patients with Genotype 1-6 HCV Infection. Hepatology (2014), 60: 4 (suppl) 237A.

Doehle B, Gontcharova V, Chodavarapu1 RK, McNally J, Chung RT, Everson GT, McHutchison JG, Miller MD, Mo H. Resistance Analysis of Treatment-Naive HCV Genotype 1-6 Infected Patients Treated with Sofosbuvir in Combination with GS-5816 for 12 Weeks. Hepatology (2014), 60: 4 (suppl) 1138A.

Study Period:

22 April 2013 (First Subject Screened)
12 August 2014 (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 sofosbuvir (SOF) + GS-5816 with or without ribavirin (RBV) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after completion of treatment (SVR12)
- To evaluate the safety and tolerability of each 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 attained SVR at 4 and 24 weeks after completion of treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after completion of treatment
- To evaluate the emergence of viral resistance to SOF and GS-5816 during treatment and after completion of treatment
- To characterize the steady-state pharmacokinetics (PK) of study drugs

The exploratory objective of this study was as follows:

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

Methodology: This Phase 2, multicenter, randomized, open-label study assessed the safety, tolerability, and antiviral efficacy of SOF+GS-5816 with or without RBV administered for 8 or 12 weeks in treatment-naive, noncirrhotic subjects with chronic HCV infection. Approximately 340 subjects were randomized into 1 of 14 treatment groups as described below.

Approximately 50 subjects with genotype 1 HCV infection were randomized 1:1 to one of the following 2 treatment groups:

- Group 1: SOF 400 mg + GS-5816 25 mg once daily for 12 weeks
- Group 2: SOF 400 mg + GS-5816 100 mg once daily for 12 weeks

Approximately 50 subjects with genotype 3 HCV infection were randomized 1:1 to one of the following 2 treatment groups:

- Group 3: SOF 400 mg + GS-5816 25 mg once daily for 12 weeks
- Group 4: SOF 400 mg + GS-5816 100 mg once daily for 12 weeks

Approximately 40 subjects with genotype 2, 4, 5, or 6 HCV infection were randomized 1:1 to one of the following 2 treatment groups:

- Group 5: SOF 400 mg + GS-5816 25 mg once daily for 12 weeks
- Group 6: SOF 400 mg + GS-5816 100 mg once daily for 12 weeks

Approximately 100 subjects with genotype 1 HCV infection were randomized 1:1:1:1 to one of the following 4 treatment groups:

- Group 7: SOF 400 mg + GS-5816 25 mg once daily for 8 weeks
- Group 8: SOF 400 mg + GS-5816 25 mg once daily + RBV (1000 or 1200 mg/day divided twice daily [BID]) for 8 weeks

- Group 9: SOF 400 mg + GS-5816 100 mg once daily for 8 weeks
- Group 10: SOF 400 mg + GS-5816 100 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 8 weeks

Approximately 100 subjects with genotype 2 HCV infection were randomized 1:1:1:1 to one of the following 4 treatment groups:

- Group 11: SOF 400 mg + GS-5816 25 mg once daily for 8 weeks
- Group 12: SOF 400 mg + GS-5816 25 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 8 weeks
- Group 13: SOF 400 mg + GS-5816 100 mg once daily for 8 weeks
- Group 14: SOF 400 mg + GS-5816 100 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 8 weeks

Randomization was stratified by HCV genotype (genotype 1a or 1b for Groups 1, 2, and 7 through 10; genotype 2, 4, 5, or 6 for Groups 5 and 6). For stratification, mixed genotype 1a/1b or genotype 1 was considered genotype 1a.

All subjects were to complete posttreatment Week 4, 8, and 12 visits regardless of treatment duration. Subjects with HCV RNA < the lower limit of quantitation (LLOQ) at the posttreatment Week 12 visit were to complete a posttreatment Week 24 visit unless confirmed viral relapse occurred.

All subjects were eligible to participate in the PK substudy if written consent was obtained. An intensive 24-hour PK sample collection was performed at the on-treatment Week 2 or 4 visit to determine the steady-state PK of SOF, SOF metabolites GS-566500 and GS-331007, GS-5816, and RBV (if appropriate). Subjects providing separate and specific consent were eligible for participation in the pharmacogenomics substudy. A blood sample was drawn at the baseline/Day 1 visit or at any time during the study.

Subjects who did not achieve SVR were eligible for enrollment in the Sequence Registry Study (GS-US-248-0123) to monitor the persistence of resistance-associated mutations for up to 3 years. All subjects who achieved SVR24 were eligible for enrollment in the SVR Registry Study (GS-US-248-0122) to evaluate durability of SVR for up to 3 years posttreatment.

Number of Subjects (Planned and Analyzed):
Planned: 340 subjects

Analyzed:

- All randomized subjects: 379 subjects
- Full Analysis Set: 377 subjects
- Safety Analysis Set: 377 subjects
- PK Analysis Set: 208 subjects
- PK Substudy Analysis Set: 37 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age with chronic HCV infection, screening HCV RNA levels ≥ 10^4 IU/mL, body mass index (BMI) ≥ 18 kg/m^2, documentation of absence of cirrhosis, treatment naive to other HCV treatments, and otherwise in general good health as determined by the investigator at screening.

Duration of Treatment: Treatment duration was 12 weeks for Groups 1 through 6 and 8 weeks for Groups 7 through 14.

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

- SOF was administered orally to all subjects at a dose of 400 mg (1 × 400-mg tablet once daily).
- GS-5816 was administered orally to all subjects at a dose of either 25 mg (Groups 1, 3, 5, 7, 8, 11, 12) or 100 mg (Groups 2, 4, 6, 9, 10, 13, 14) (1 × 25-mg tablet or 1 × 100-mg tablet once daily).
- RBV was administered orally to subjects in Groups 8, 10, 12, and 14 at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided BID).

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

- **SOF**: DC1205B1
- **GS-5816**: DL1301C1 and DL1301D1
- **RBV**: AA2773Z

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

Criteria for Evaluation:

Efficacy: Blood samples to determine serum HCV RNA levels were collected from subjects at screening, Day 1 (predose), and at every subsequent on-treatment and posttreatment visit. The COBAS® TaqMan® HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study. The LLOQ of the assay was 25 IU/mL.

Pharmacokinetics: A single PK blood sample was collected from all subjects at each on-treatment visit. For a subset of subjects who consented to participate in the optional PK substudy, intensive serial PK blood samples were collected at the on-treatment Week 2 or 4 visit. The PK of SOF, GS-566500, GS-331007, GS-5816, and RBV (if appropriate) were assessed.

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

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the Full Analysis Set. The 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method was provided for the SVR12 rates in each efficacy analysis group. Secondary efficacy endpoints included SVR4, SVR24, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through Week 12 or Week 8, and the proportion of subjects with virologic failure.

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

Pharmacokinetics: Steady-state PK over a 24-hour dosing interval was determined in subjects who participated in the PK substudy at the on-treatment Week 2 or 4 visit. Concentrations of SOF (and its metabolites GS-566500 and GS-331007), GS-5816, and RBV (if appropriate) in plasma were determined using validated bioanalytical assays. The PK parameters for these analytes were computed for all subjects with evaluable PK profiles. Descriptive statistics (sample size, mean, SD, coefficient of variation [CV], median, Q1, Q3, minimum, maximum, and geometric mean and its 95% CI) were presented for PK concentration data and PK parameter data.

Safety: All randomized subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital sign measurements, ECGs, and physical examinations. Safety data included all data collected on or after the date of the first dose of any study drug through the date of the last dose of study drug plus 30 days. Safety endpoints were analyzed by the number and percentage of subjects with events or abnormalities for categorical values or descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data by GS-5816 dose, treatment duration, and with or without RBV. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 379 subjects were randomized in the study (2 subjects were randomized and not treated). All randomized and treated subjects were enrolled at 1 of 48 sites in the US. Of these randomized subjects, 377 received at least 1 dose of study drug and were included in the Safety and Full Analysis Sets. Two subjects were randomized in the study but did not receive study drug resulting in a protocol deviation, and were excluded from both the Safety and Full Analysis Sets.

The majority of subjects (99.2%, 374 of 377 subjects) completed study treatment. Of the 377 enrolled subjects, 3 (0.8%) prematurely discontinued study treatment: 1 of 27 subjects (3.7%) with genotype 3 HCV infection in the SOF + GS-5816 25 mg 12 Week group, 1 of 30 subjects (3.3%) with genotype 1 HCV infection in the SOF + GS-5816 25 mg 8 Week group, and 1 of 31 subjects (3.2%) with genotype 1 HCV infection in the SOF + GS-5816 100 mg + RBV 8 Week group. The reasons for premature discontinuation of study treatment were lack of

efficacy (virologic failure), AEs (abdominal pain, palpitations, and dizziness on Day 6), and noncompliance with study drug.

Across all treatment groups, the majority of subjects were male (57.8%), white (86.5%), and non-Hispanic/Latino (89.7%), with a mean age of 52 years (range: 18 to 78 years). The mean (SD) baseline BMI was 28.0 (5.92) kg/m^2, and 30.2% of subjects had a BMI ≥ 30 kg/m^2.

Of the 377 subjects across all treatment groups, 175 subjects had genotype 1 HCV infection (142 subjects [37.7%] were infected with HCV genotype 1a subtype, 32 subjects [8.5%] with the genotype 1b subtype, and 1 subject [0.3%] with the genotype 1g subtype), 124 subjects (32.9%) had genotype 2 HCV infection, 54 subjects (14.3%) had genotype 3 HCV infection, 14 subjects (3.7%) had genotype 4 HCV infection, 1 subject (0.3%) had genotype 5 HCV infection, and 9 subjects (2.4%) had genotype 6 HCV infection. The majority of subjects did not have cirrhosis (99.5%) and 35.8% had IL28B CC alleles. The overall mean (SD) baseline HCV RNA was 6.5 (0.75) log_{10} IU/mL, and most subjects (80.4%) had baseline HCV RNA ≥ 800,000 IU/mL and baseline alanine aminotransferase (ALT) values > 1.5 × upper limit of normal (ULN) (51.2%). The overall mean (SD) baseline estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation was 108.3 (35.56) mL/min.

Efficacy Results: All subjects achieved HCV RNA < LLOQ on treatment in the 12-week treatment groups, except for 1 subject with genotype 3 HCV infection who received SOF + GS-5816 25 mg for 12 weeks who met virologic stopping criteria at Week 8 of treatment. Subjects with genotype 1 HCV infection who received SOF + GS-5816 25 mg or 100 mg for 12 weeks had SVR12 rates of 96.3% and 100.0%, respectively. Subjects with genotype 2 HCV infection who received SOF + GS-5816 25 mg or 100 mg for 12 weeks had SVR12 rates of 90.9% and 100.0%, respectively. Subjects with genotype 3 HCV infection who received SOF + GS-5816 25 mg or 100 mg for 12 weeks had SVR12 rates of 92.6% and 92.6%, respectively. All subjects with genotype 4, 5, and 6 HCV infection who received SOF + GS-5816 25 mg or 100 mg for 12 weeks and completed posttreatment assessments, achieved SVR12. One subject with genotype 4 HCV infection who received SOF + GS-5816 100 mg for 12 weeks did not return for posttreatment assessments and was considered lost to follow-up.

All subjects achieved HCV RNA < LLOQ on treatment in the 8-week treatment groups. A total of 190 of 223 subjects (85.2%) with genotype 1 or 2 HCV infection achieved SVR12 across all 8-week treatment groups. Within individual treatment groups, proportions of subjects with genotype 1 HCV infection who achieved SVR12 ranged from 83.3% to 86.7% in the SOF + GS-5816 25 mg ± RBV 8-week treatment groups and 80.6% to 89.7% in the SOF + GS-5816 100 mg ± RBV 8-week treatment groups. Within individual treatment groups, proportions of subjects with genotype 2 HCV infection who achieved SVR12 ranged from 76.9% to 88.0% in the SOF + GS-5816 25 mg ± RBV 8-week treatment groups and 88.5% (each treatment group) in the SOF + GS-5816 100 mg ± RBV 8-week treatment groups.

Most subjects who experienced virologic relapse did so by the posttreatment Week 4 visit. In the 12-week treatment groups, 2 of 4 subjects (50.0%) with virologic relapse had relapsed by the posttreatment Week 4 visit. In the 8-week treatment groups, 24 of 30 subjects (80.0%) with virologic relapse had relapsed by the posttreatment Week 4 visit. Relapse after achieving SVR12 was rare. Only 1 subject with genotype 1 HCV infection in the SOF + GS-5816 25 mg 12 Week treatment group achieved SVR12, but had HCV RNA > LLOQ at posttreatment Week 24. This subject had virologic evidence of reinfection.

Potent and rapid suppression of HCV RNA while on treatment was observed in all subjects who received SOF + GS-5816 25 mg or 100 mg for 12 weeks or SOF + GS-5816 25 mg or 100 mg ± RBV for 8 weeks. All subjects achieved HCV RNA < LLOQ on treatment, except for 1 subject with genotype 3 HCV infection who received SOF + GS-5816 25 mg. This subject (PPD had an approximately 5 $\log_{10}$ reduction in HCV RNA at Week 2 of treatment but remained viremic though Week 8 and was discontinued from treatment per the virologic stopping criteria.

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly in subjects with genotype 1, 2, 3, 4, or 6 HCV infection who received SOF + GS-5816 25 mg or 100 mg for 12 weeks. Overall, there was no difference between genotypes in HCV RNA decline when subjects were treated with SOF + GS-5816 25 mg or 100 mg. After 1 week of treatment, mean (SD) changes from baseline ranged from −4.71 (0.892) to −4.45 (0.770) $\log_{10}$ IU/mL across all 25-mg treatment groups and −4.84 (0.659) to −4.25 (0.537) $\log_{10}$ IU/mL across all 100-mg treatment groups. The decreases in HCV RNA were maintained from Week 2 through Week 12.

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly in subjects with genotype 1 or 2 HCV infection who received SOF + GS-5816 25 mg or 100 mg ± RBV for 8 weeks. After 1 week of treatment, mean (SD) changes from baseline ranged from −4.99 (0.564) to −4.45 (0.708) $\log_{10}$ IU/mL across all 25-mg and 100-mg treatment groups, demonstrating that similar decreases in HCV RNA were observed in all treatment groups, irrespective of inclusion of RBV in the treatment regimen.

The high SVR12 rates observed across all treatment groups preclude meaningful interpretation of subgroup analyses.

Virologic Resistance Results: Of the 377 subjects enrolled, 375 and 372 had sequencing data for HCV nonstructural protein (NS)5A and NS5B, respectively. The prevalence of pretreatment NS5A resistance-associated polymorphisms (RAPs) was 38.1% (143 of 375 subjects) overall, and 22.5% (32 of 142 subjects), 29.0% (9 of 31 subjects), 50.8% (62 of 122 subjects), and 27.8% (15 of 54 subjects) in subjects with genotype 1a, 1b, 2, and 3 HCV infection, respectively.

The SVR12 was similar in subjects with genotype 1 to 6 HCV infection with pretreatment RAPs compared with subjects without pretreatment RAPs who received SOF + GS-5816 25 mg or 100 mg for 12 weeks. Among the 6 subjects treated for 12 weeks who had virologic failure, 1 had nonresponse, 3 relapsed, and 2 had HCV reinfection. Excluding the subjects with reinfection, all 4 subjects with virologic failure (3 subjects who received SOF + GS-5816 25 mg for 12 weeks and 1 subject who received SOF + GS-5816 100 mg for 12 weeks) had pretreatment and posttreatment NS5A RAPs and 1 subject had NS5B N142T at pretreatment and posttreatment. Given the high prevalence of RAPs in the study population, the single virologic failure among subjects who received SOF + GS-5816 100 mg for 12 weeks suggest that this regimen has a high barrier to resistance.

Among subjects with genotype 1 HCV infection who received SOF + GS-5816 25 mg or 100 mg ± RBV for 8 weeks, the SVR12 was similar in subjects with pretreatment RAPs compared with those without pretreatment RAPs. Of the 16 subjects with genotype 1 HCV infection treated for 8 weeks with SOF + GS-5816 25 mg or 100 mg ± RBV with virologic failure, 7 subjects had pretreatment RAPs, 4 subjects had treatment-emergent NS5A RAPs, and 1 subject had NS5B S282G (18.2%) that emerged posttreatment.

Among subjects with genotype 2 HCV infection who received SOF + GS-5816 25 mg ± RBV for 8 weeks, the SVR12 trended lower in subjects with pretreatment RAPs compared with those

without pretreatment RAVs. However, among subjects with genotype 2 HCV infection who received SOF + GS-5816 100 mg ± RBV for 8 weeks, the SVR12 was similar in subjects with pretreatment RAPs compared with those without pretreatment RAPs. None of the 14 subjects with genotype 2 HCV infection treated for 8 weeks with SOF + GS-5816 25 mg or 100 mg ± RBV with virologic failure had treatment emergent NS5A RAPs and 2 subjects had low levels (1.7% and 2.5%) of NS5B V321A that emerged at relapse.

Seventeen of 372 subjects (4.6%) had pretreatment NS5B RAPs, of which, 15 subjects achieved SVR12. No S282T was observed in any subject in this study.

Pharmacokinetics Results: Administration of SOF + GS-5816 100 mg ± RBV resulted in an approximate 50% higher SOF and GS-566500 exposures compared with administration of SOF + GS-5816 25 mg ± RBV. No notable difference in GS-331007 exposure was observed following administration of SOF with GS-5816 25 mg or 100 mg. GS-5816 exposure was not dose-proportional between GS-5816 25 mg and 100 mg, with a 6- to 8-fold exposure range observed.

Safety Results: Overall, the highest percentage of subjects with any AE was observed in RBV-containing treatment groups (SOF + GS-5816 25 mg + RBV 8 Week group, 81.8% and SOF + GS-5816 100 mg + RBV 8 Week group, 73.7%) as compared with RBV-free treatment groups where 60.0% to 70.1% of subjects experienced any AE. This difference was largely accounted for by higher incidences in AEs associated with RBV treatment such as fatigue, headache, insomnia, and rash. Additionally, AEs leading to modification or interruption of any study drug were only reported in RBV-containing treatment groups (SOF + GS-5816 25 mg + RBV 8 Week group, 5.5% and SOF + GS-5816 100 mg + RBV 8 Week group, 8.8%).

Headache was the only AE occurring with > 10% incidence across all treatment groups. Types and percentages of AEs were similar in subjects receiving GS-5816 25 mg versus 100 mg with no discernible dose-related toxicity.

Most AEs reported in the study were Grade 1 or 2 in severity. A total of 1 subject (1.3%) in the SOF + GS-5816 25 mg 12 Week group, 3 subjects (5.4%) in the SOF + GS-5816 25 mg 8 Week group, and 1 subject (1.8%) in the SOF + GS-5816 25 mg + RBV 8 Week group had a Grade 3 AE. No Grade 3 or 4 AEs occurred in > 1 subject in any treatment group. One subject death (Grade 4 AE of completed suicide) was reported in the SOF + GS-5816 25 mg 12 Week group, which was reported as serious and considered not related to study drug by the investigator. This subject had an extensive psychiatric history and experienced a significant life stressor during the posttreatment follow-up period that was thought to have triggered the event of suicide.

One pregnancy was reported in a female subject during the posttreatment follow up period (SOF + GS-5816 100 mg 12 Week group). The subject delivered a full-term healthy infant female on posttreatment Day 351.

Overall, serious adverse events (SAEs) were rare (1.9%, 7 of 377 subjects) and occurred with similar frequency across all treatment groups. No trends in SAE type or onset time were observed, as no SAE was reported in > 1 subject. All SAEs were considered by the investigator to be not related to study drug and no SAEs led to treatment discontinuation.

Only 1 subject in the SOF + GS-5816 25 mg 8 Week group permanently discontinued all study

drugs due to AEs. This subject reported Grade 1 abdominal pain, Grade 1 palpitations, and Grade 2 dizziness on treatment Day 6. The subject discontinued study drugs on treatment Day 7. A physical exam and ECG were performed on treatment Day 7 and were both normal. The palpitations and dizziness resolved on posttreatment Day 2. The investigator assessed the events as related to study drug.

Most subjects had at least 1 laboratory abnormality reported with the majority being Grade 1 (164 of 377 subjects, 43.5%) or Grade 2 (65 of 377 subjects, 17.2%) in severity. Higher percentages of subjects had Grade 3 laboratory abnormalities in the RBV-containing groups (SOF + GS-5816 25 mg + RBV 8 Week group, 10.9% and SOF + GS-5816 100 mg + RBV 8 Week group, 15.8%) as compared with the RBV-free treatment groups (1.8% to 5.2%). This difference was accounted for primarily by the expected decreases in hemoglobin observed with RBV therapy. All Grade 3 decreases in hemoglobin were observed in the RBV-containing groups (SOF + GS-5816 25 mg + RBV 8 Week group, 10.9% and SOF + GS-5816 100 mg + RBV 8 Week group, 12.3%). Grade 3 chemistry laboratory abnormalities were reported for lipase (all asymptomatic), creatinine, serum glucose (hyperglycemia), and total bilirubin (hyperbilirubinemia). Grade 3 hyperbilirubinemia was only observed in RBV-containing treatment groups and was consistent with RBV-associated hemolysis. One subject (0.3%) experienced an asymptomatic and transient Grade 4 laboratory abnormality of increased lipase.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study. No clinically significant abnormal 12-lead ECGs were captured.

CONCLUSIONS: The conclusions for Study GS-US-342-0102 are as follows:

- Treatment with SOF + GS-5816 25 mg or 100 mg for 12 weeks resulted in high SVR12 rates in treatment-naive subjects with genotype 1 to 6 HCV infection without cirrhosis.
- Treatment with SOF + GS-5816 25 mg or 100 mg ± RBV for 8 weeks resulted in lower SVR12 rates than treatment with SOF + GS-5816 25 mg or 100 mg for 12 weeks in treatment-naive subjects with genotype 1 or 2 HCV infection without cirrhosis.
- Administration of SOF + GS-5816 100 mg ± RBV resulted in approximately 50% higher SOF and GS-566500 exposures and 6- to 8-fold higher GS-5816 exposures compared with administration of SOF + GS-5816 25 mg ± RBV. GS-331007 exposure was similar regardless of GS-5816 dose.
- Among subjects treated for 12 weeks with SOF+GS-5816, high rates of SVR12 were observed in subjects with or without baseline NS5A RAPs; all subjects treated for 12 weeks who experienced virologic failure had NS5A RAPs detected at failure.
- SOF+GS-5816 for 8 or 12 weeks was generally well tolerated. The addition of RBV to the regimen increased the incidence of AEs and laboratory abnormalities, but did not affect the overall high rates of treatment completion.