FINAL CLINICAL STUDY REPORT

Study Title:	Study GS-US-196-0112: A Phase 2, Randomized, Open-Label Trial of GS-9256 plus GS-9190 alone and in Combination with Ribavirin for 28 Days in Treatment-Naive Subjects with Chronic Genotype 1 Hepatitis C Virus Infection
Name of Test Drugs:	GS-9256, Tegobuvir (TGV, GS-9190)
Dose and Formulation:	GS-9256 25-mg strength capsule Tegobuvir 40-mg strength capsule
Indication:	Hepatitis C Infection
Sponsor:	Gilead Sciences, Inc. (GSI) 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-196-0112
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	This was a non-IND study 2009-013690-18
Study Start Date: **Study End Date**	09 February 2010 (First Subject Screened) 30 January 2012 (Last Subject Observation, excluding long-term resistance follow-up, which will be reported separately)
Principal or Coordinating Investigator:	Name: Stefan Zeuzem, MD Affiliation: PPD PPD
GSI Responsible Medical Director:	Name: Mani Subramanian, MD, PhD Telephone: PPD Fax: PPD
Report Date:	17 January 2013

STUDY SYNOPSIS

Study GS-US-196-0112:

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

Title of Study: Study GS-US-196-0112: A Phase 2, Randomized, Open-Label Trial of GS-9256 plus GS-9190 alone and in Combination with Ribavirin for 28 Days in Treatment-Naive Subjects with Chronic Genotype 1 Hepatitis C Virus Infection

Investigators: Multicenter study

Study Centers: 11 enrolling sites in the European Union (EU)

Publications:

Zeuzem S, Buggisch P, Agarwal K, Manns M, Marcellin P, et al. Dual, triple, quadruple combination treatment with a protease inhibitor (GS-9256) and a polymerase inhibitor (TGV) alone and in combination with ribavirin (RBV) or PegIFN/RBV for up to 28 days in treatment naive genotype 1 HCV subjects. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Poster/Oral #LB-1. October 29–November 2, 2010 (Boston, MA).

Foster GR, Buggisch P, Marcellin P, Zeuzem S, Agarwal K et al. Four-week treatment with GS-9256 and tegobuvir (TGV), ± RBV ± PEG, results in enhanced viral suppression on follow-up PEG+RBV therapy, in genotype 1A/1B HCV patients. Abstract A-343-0028-00340. 46th Annual Meeting of the European Association for the Study of Liver Disease. Berlin, Germany, March 30–April 3, 2011.

Mo H, Hebner B, Han J et al. Characterization of viral resistance mutations In genotype 1 HCV patients receiving combination therapy with a protease inhibitor and a polymerase inhibitor with or without ribavirin. Poster 1138. 46th Annual Meeting of the European Association for the Study of Liver Disease. Berlin, Germany, March 30-April 3, 2011.

Study Period:

09 February 2010 (First subject screened)
18 October 2010 (Last subject observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To describe the antiviral efficacy of GS-9256 plus GS-9190 (tegobuvir [TGV]) alone and in combination with ribavirin (RBV) against genotype 1 hepatitis C virus (HCV), as measured by the percentage of subjects achieving rapid virologic response (RVR; ie, HCV ribonucleic acid [RNA] undetectable at Day 28)
- To evaluate the safety and tolerability of GS-9256+TGV alone and in combination with RBV for 28 days in subjects with chronic genotype 1 HCV infection

The secondary objective of this study was as follows:

- To characterize the pharmacokinetics (PK) of GS-9256 and TGV following administration of multiple oral doses of GS-9256+TGV alone, in combination with RBV, and in combination with pegylated interferon and RBV (PEG+RBV)

Exploratory objectives of this study included the following:

- To describe the antiviral efficacy of and to evaluate the safety and tolerability of GS-9256+TGV in combination with PEG+RBV against genotype 1 HCV
- To evaluate the emergence of viral resistance during and following treatment with GS-9256+TGV alone, in combination with RBV, and in combination with PEG+RBV for 28 days and for 72 weeks following discontinuation of study drugs (GS-9256+TGV)

Methodology:

This study was a Phase 2, randomized, open-label study of GS-9256+TGV, 2 oral anti-HCV drugs, administered for 28 days alone or in combination with RBV or PEG+RBV in treatment-naive subjects infected with chronic genotype 1 HCV. In Part A, 30 subjects with genotype 1 were planned for randomization to GS-9256 75 mg taken twice daily (BID) plus TGV 40 mg BID, or GS-9256 75 mg BID plus TGV 40 mg BID plus RBV for 28 days. In Part B, 15 subjects with genotype 1 were to receive GS-9256 75 mg BID plus TGV 40 mg BID in combination with PEG+RBV. For both Parts A and B, after the 28-day treatment period, subjects received PEG+RBV alone (the combination of PEG+RBV was the standard of care [SOC] for the treatment of HCV infection at the time this study was designed and conducted; some of the posttext listings still use this terminology).

Part A: To provide an overlap of antiviral therapy prior to the discontinuation of GS-9256+TGV, subjects started PEG+RBV on Day 28, which was given in combination with GS-9256+TGV on Day 28. For any subjects meeting predefined, individual, virologic criteria in Part A, PEG+RBV was started prior to Day 28.

Part A: 31 subjects were randomized (1:1) to 1 of 2 treatment groups:

Group 1 (n=16): GS-9256 75 mg BID plus TGV 40 mg BID for 28 days. Starting on Day 28, subjects received PEG+RBV.

Group 2 (n=15): GS-9256 75 mg BID plus TGV 40 mg BID plus RBV for 28 days. Starting on Day 28, subjects started PEG+RBV.

In each group, RBV was initiated in a divided total daily oral dose of 1000 to 1200 mg (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg).

Part B: 15 subjects received the following treatment:

Group 3 (n=15): GS-9256 75 mg BID plus TGV 40 mg BID for 28 days in combination with PEG+RBV. Starting on Day 28, subjects changed to PEG+RBV treatment.

From Days 1 through 27, both PEG (supplied as open-label Pegasys®) and RBV (supplied as open-label Copegus®) were administered at their currently approved dose for chronic genotype 1 HCV infection. Subcutaneous injection of PEG 180 µg was given weekly. Ribavirin was administered in a divided total daily oral dose of 1000 to 1200 mg (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg).

Randomization was stratified by plasma HCV RNA level (< or ≥ 2,000,000 IU/mL) at screening for Part A (enrollment in Part B was not stratified by viral load).

Number of Subjects (Planned and Analyzed):

Planned: 30 subjects in Part A; Protocol Amendment 2 added Part B (15 subjects)

Randomized: 46 subjects (Full Analysis Set [FAS]; 16, 15, and 15 subjects in Groups 1, 2, and 3, respectively)

Evaluable: PK: 42 subjects (14, 13, and 15 in Groups 1, 2, and 3, respectively)

Efficacy: 42 subjects (15, 13, and 14 in Groups 1, 2, and 3, respectively)

Safety: 46 subjects (FAS)

Diagnosis and Main Criteria for Inclusion:

Subjects were required to meet the following key inclusion criteria in order to participate in the study:

- Adult subjects (18–70 years of age) with chronic HCV infection and baseline plasma HCV RNA ≥ 3 $\log_{10}$ IU/mL, but < 7.2 $\log_{10}$ IU/mL at screening
- Liver biopsy within 2 years prior to screening (or a FibroTest or FibroScan within 6 months prior to screening) with results indicating the absence of cirrhosis; and genotype 1 HCV infection
- Chronic HCV infection documented by a positive anti-HCV antibody test or evidence of HCV RNA (ie, viral load or genotype), a liver biopsy (or FibroTest or FibroScan results where appropriate) consistent with chronic HCV infection, or elevated alanine aminotransferase (ALT) values (ie, above the normal range) at any point within 1 year prior to screening
- HCV treatment naive, with body mass index (BMI) between 18 and 36 kg/m^2, and creatinine clearance ≥ 50 mL/min
- Female subjects of nonchildbearing potential and male subjects using highly effective contraception

Subjects were excluded from participation if they met the following key criteria:

- Exceeded defined thresholds for leukopenia, neutropenia, anemia, thrombocytopenia, hypokalemia, hypomagnesemia, thyroid-stimulating hormone (TSH), total bilirubin, or had autoimmune disease; decompensated liver disease; non-HCV chronic liver disease; history of sarcoidosis or porphyria
- Grade 3 or higher ALT, aspartate aminotransferase (AST), or gamma-glutamyltransferase (GGT); cirrhosis; poorly controlled diabetes mellitus; severe psychiatric illness; or severe chronic obstructive pulmonary disease (COPD)
- Serological evidence of coinfection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or another HCV genotype; suspicion of hepatocellular carcinoma or other malignancy (with exception of certain skin cancers); history of hemoglobinopathy or known retinal disease; or immunosuppression
- Known, current use of amphetamines, cocaine, opiates (ie, morphine, heroin), methadone, or ongoing alcohol abuse
- Current or anticipated use of potent cytochrome (CYP)3A4 and/or P-glycoprotein (Pgp) inhibitors or QT-prolonging medications within 2 weeks of study baseline (Day 1) or during the study
- History of clinically significant cardiac disease, including a family history of long QT syndrome or relevant electrocardiogram (ECG) abnormalities at screening

Duration of Treatment: In Part A, each subject received GS-9256 75 mg BID plus TGV 40 mg BID with or without RBV for up to 28 days. In Part B, each subject received GS-9256 75 mg BID plus TGV 40 mg BID in combination with PEG+RBV for 28 days. For both Parts A and B, subjects discontinued GS-9256+TGV after the last doses on Day 28, and all subjects received PEG+RBV starting on Day 28 and continuing thereafter.

Follow-up evaluation occurred approximately 14 days after the last doses of GS-9256+TGV. Additional resistance surveillance follow-up occurred at Weeks 6, 12, 24, 48, and 72 after discontinuation of study drugs.

<u>Part A, Group 1:</u>

- GS-9256 in the form of 25-mg capsules for oral administration. Subjects received GS-9256 75 mg, taken BID for 28 days.
- TGV in the form of 40-mg capsules for oral administration. Subjects received TGV 40 mg, taken BID for 28 days.

<u>Part A, Group 2:</u>

- The same GS-9256 and TGV regimen as that received in Part A, Group 1

AND

- Initially, RBV taken orally with food BID in a divided total daily oral dose of 1000 to 1200 mg (1000 mg for subjects weighing < 75 kg, and 1200 mg for subjects weighing

≥ 75 kg) for 27 days. RBV was dosed with food at least 2 hours after dosing with GS-9256+TGV. RBV doses could be adjusted if subjects were anemic.

Part B, Group 3:

- The same GS-9256, TGV, and RBV regimen as that received in Part A, Group 2

AND

- Initially, PEG at a dose of 180 µg given weekly by subcutaneous injection on Days 1, 7, 14, and 21. PEG doses could be adjusted in accordance with the product label for toxicity.

GS-9256+TGV were coadministered under fasting conditions (at least 2 hours before or at least 2 hours after the consumption of food, where practicable to do so).

Virologic Criteria for PEG+RBV Initiation in Part A:

The following individual virologic criteria were used for early initiation of PEG+RBV:

- Lack of early response: < 2 $\log_{10}$ IU/mL reduction from baseline HCV RNA by Day 5
- Rebound: HCV RNA increase of > 0.5 $\log_{10}$ IU/mL from nadir confirmed over 2 time points occurring after Day 5 with an absolute value > 1000 IU/mL

If necessary investigators could, with the approval of the medical monitor on a case-by-case basis, initiate PEG+RBV prior to meeting these criteria.

For Part A subjects (Groups 1 and 2) who met early PEG+RBV initiation criteria, PEG+RBV was started. Treatment with GS-9256+TGV could have been continued at the discretion of the investigator, but the treatment duration of GS-9256+TGV could not exceed 28 days of dosing. Subjects meeting early PEG+RBV initiation criteria continued with all subsequent study visits and procedures after initiating early PEG+RBV. For expediency, HCV RNA results in Part A of the study were obtained from central and local laboratories through Week 6; for Part B, HCV RNA results were obtained from a central laboratory through Week 6; and for both Parts A and B, data after Week 6 were collected at a local laboratory or a central laboratory when a sample was not available from a local laboratory.

ECG Criteria for Study Drug Discontinuation:

Both GS-9256 and TGV were to be discontinued for any subject with a confirmed QTcF value of > 500 msec or a confirmed increase of > 60 msec from baseline after consultation with the GSI medical monitor and/or cardiologist from the core cardiology laboratory.

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

GS-9256, 25-mg strength oral capsules: Lot Nos. BU0904A1-A and BU0904A1
TGV, 40-mg strength oral capsules: Lot No. AL0910A1
RBV, 200-mg strength oral tablets: Lot No. U8040
PEG, 180-µg/0.5-mL strength subcutaneous injection: Lot No. B1111

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

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was viral load suppression at Day 28, as measured by the proportion of subjects achieving RVR (ie, HCV RNA below the lower limit of quantitation [BLQ] at Day 28). Plasma HCV RNA reduction from baseline was evaluated. Resistance surveillance was conducted to characterize the development of resistance mutations to GS-9256 and TGV.

Central laboratory measurements of HCV RNA were conducted by Covance using the COBAS® TaqMan® HCV assay (lower limit of quantitation [LLOQ]=25 IU/mL; limit of detection [LOD]=20 IU/mL).

Pharmacokinetics: Steady-state PK parameters of GS-9256 and TGV were summarized.

Safety: Adverse events (AEs), clinical laboratory test results, vital signs, physical examination findings, and ECG results were summarized through the Week 6 follow-up assessment.

Statistical Methods:

Efficacy: Antiviral activity data were assessed for the percentage of subjects with RVR (HCV RNA BLQ [< 25 IU/mL] at Day 28. Additionally, the proportion of subjects who had HCV RNA BLQ was assessed at each postbaseline measurement. Other endpoints included change from baseline in HCV RNA, as a continuous variable, and as categorical reductions from baseline (reductions of < 1, ≥ 1 to < 2, ≥ 2 to < 3, or ≥ 3 $\log_{10}$ IU/mL). HCV RNA data were listed by subject and summarized by treatment group (including and excluding data after initiation of PEG+RBV) using descriptive statistics, as well as a 95% confidence interval (CI) around the percent RVR at Day 28. HCV RNA absolute and change-from-baseline values were also evaluated by treatment group and HCV genotype (1a and 1b), and by treatment group and IL28B genotype ([CC, CT and TT] and [CC and non-CC] for central laboratory data only, including and excluding data after initiation of PEG+RBV).

Pharmacokinetics: Plasma GS-9256 and TGV concentration data were summarized by treatment group using descriptive statistics and listed by subject. GS-9256 and TGV PK parameters were summarized by treatment group. No formal statistical testing was performed. For concentration values BLQ, the number of subjects with values of BLQ was presented. GS-9256 and TGV concentrations (full profile day) were plotted by treatment group on linear and semi-log scales. Additionally, individual subject plots of GS-9256 and TGV concentrations (full profile day) were presented on linear and semi-log scales.

Safety: All safety data were summarized by treatment group using the frequency of events/abnormalities for categorical data and using descriptive statistics appropriate for continuous data. AEs, laboratory data, laboratory abnormalities, 12-lead ECGs, and vital sign measurements were summarized by treatment group; these data and physical examination findings were listed by subject. All ECG-derived QT intervals were corrected using the Fridericia (QTcF) formula. QTcF values (absolute and change from baseline) were listed for each subject at each postbaseline time point along with maximum change values. Changes from baseline in 12-lead ECG findings were summarized by treatment group using descriptive statistics and pre-determined, clinically relevant threshold categories. All

laboratory, vital sign, and ECG data were summarized including data after initiation of PEG+RBV; the QTcF analyses were summarized including and excluding these data.

SUMMARY – RESULTS:

Subject Disposition and Demographics: A total of 46 subjects were randomized and treated in the study (16 subjects received GS-9256+TGV and 15 subjects each received GS-9256+TGV+RBV and GS-9256+TGV+PEG+RBV). Of these 46 subjects, 45 subjects (97.8%) completed Week 6 and 41 subjects (89.1%) completed Week 72. Of the 5 subjects who did not complete Week 72, 1 subject in the GS-9256+TGV+PEG+RBV group discontinued because of efficacy (HCV RNA was below the lower limit of quantitation [BLQ] at Day 28 and Week 6) and 4 subjects were lost to follow-up, 3 subjects in the GS-9256+TGV group and 1 subject in the GS-9256+TGV+RBV group.

Overall, subjects were predominately male (73.3%–87.5% across treatment groups), and the majority of subjects were white (80.0%–93.3%). Mean age ranged from 45 to 54 years, and mean BMI ranged from 25.6 to 27.1 kg/m^2. The median baseline HCV RNA level was similar across the treatment groups (overall median was 6.38 log_{10} IU/mL; Q1, Q3 of 5.96, 6.83).

Using the LiPA 2.0 HCV genotyping assay, a greater number of subjects with HCV genotype 1b were detected in the GS-9256+TGV+RBV and GS-9256+TGV+PEG+RBV groups compared with the GS-9256+TGV group (FAS). Of note, when more sensitive methods of HCV genotyping were used, 4 subjects who were identified as genotype 1 by LiPA 2.0 at screening were found to be a genotype other than genotype 1a or 1b. These 4 subjects are included in safety and tolerability analyses, but were not included in efficacy analyses.

The majority of subjects were IL28B genotype CT (53.3–62.5% in the treatment groups). However, a higher percentage of subjects were IL28B genotype CC (the more favorable genotype for PEG+RBV treatment) in the GS-9256+TGV+RBV group (40%) compared with 12.5% in the GS-9256+TGV group, and 26.7% in the GS-9256+TGV+PEG+RBV group.

Efficacy Results: The primary efficacy endpoint was viral load suppression at Day 28, as measured by the proportion of subjects achieving RVR (HCV RNA < 25 IU/mL) after multiple, oral doses of GS-9256+TGV alone and in combination with RBV. One of 15 subjects (6.7%) receiving GS-9256+TGV alone and 5 of 13 subjects (38.5%) receiving GS-9256+TGV+RBV achieved RVR at Day 28. As an exploratory objective, RVR was also evaluated in the GS-9256+TGV+PEG+RBV group: All 14 subjects (100%) in this group achieved RVR at Day 28. Subjects who had missing data at Day 28 or who switched to or added PEG+RBV to their treatment regimen prior to Day 28 were considered failures in these analyses; these comprised 80.0%, 30.8%, and 0% of the GS-9256+TGV, GS-9256+TGV+RBV, and GS-9256+TGV+PEG+RBV groups, respectively.

Subjects in all 3 treatment groups had an initial sharp decline in plasma HCV RNA levels over the first 72 hours after the first dose. In the GS-9256+TGV group, decreases in HCV RNA levels were generally maintained through Days 5 to 7; then HCV RNA levels began to increase, associated with the detection of antiviral resistance mutations. In the

GS-9256+TGV+RBV group, additional smaller reductions in HCV RNA levels were observed through Day 21 and maintained through Day 28. In the GS-9256+TGV+PEG+RBV group, additional smaller reductions in HCV RNA levels were observed through Day 28. The median maximum reductions in HCV RNA were −4.08, −5.12, and −5.71 $\log_{10}$ IU/mL in subjects who received GS-9256+TGV alone, GS-9256+TGV+RBV, and GS-9256+TGV+PEG+RBV, respectively, excluding data after initiation of/switch to PEG+RBV.

When subjects who added/switched to PEG+RBV prior to Day 28 were counted as failures, higher percentages of subjects receiving combination treatment with GS-9256+TGV plus RBV or PEG+RBV had a reduction in HCV RNA levels ≥ 3-$\log_{10}$ IU/mL at Day 28 (61.5% and 100%, respectively) compared with subjects receiving GS-9256+TGV alone (13.3%).

Median time to virologic failure (VF) was 15.0 days in Group 1 (GS-9256+TGV) and was not reached in Group 2 (GS-9256+TGV+RBV) or Group 3 (GS-9256+TGV+PEG+RBV). The majority of subjects in the GS-9256+TGV group initiated PEG+RBV between Days 8 and 21, inclusive. When data after the initiation of PEG+RBV were included, results demonstrated that subjects in the GS-9256+TGV group, who had increased HCV RNA levels observed at Day 14 and/or Day 21, experienced declines in mean HCV RNA levels at Day 28 and Week 6; after Week 6, mean values were approximately 1 $\log_{10}$ IU/mL through Week 48. This finding indicates the sensitivity of GS-9256 and TGV resistance-associated mutations (RAMs) to PEG+RBV.

Treatment responses among HCV genotype 1a and 1b subjects and among IL28B genotype CC or non-CC were generally similar in each of the 3 treatment groups. When individual IL28B genotypes were compared, reductions in HCV RNA in subjects differed by IL28B genotype (CC > CT > TT) for only the GS-9256+TGV group, but small sample sizes in the subgroups (n=2, 10, and 3, respectively) limit the significance of this finding.

Pharmacokinetic Results: The PK of GS-9256 and TGV (assessed by AUC_{tau}, C_{max}, and C_{tau}) in HCV-infected subjects exhibited high variability. Across the 3 treatment groups, oral administration of TGV and GS-9256 provided mean steady-state plasma trough exposures 1.5- to 15-fold (GS-9256) higher and 9- to 21-fold (TGV) higher than the protein-adjusted EC_{50}.

Safety Results: Of the 46 subjects randomized and treated in this study, the majority in each randomized treatment group completed at least 28 days on randomized study drug (75%, 87%, and 100% in Groups 1, 2, and 3, respectively). Mean durations of randomized treatment were 25, 25, and 28 days for Groups 1, 2, and 3, respectively. Early initiation of PEG+RBV was implemented before Day 28 in 81.3% and 40.0% of subjects in Groups 1 and 2, respectively. The mean duration of PEG+RBV treatment throughout the study was 296, 302, and 272 days for Groups 1, 2, and 3, respectively.

The overall frequency of treatment-emergent AEs during randomized treatment was lowest in Group 1 (50.0%, 93.3%, and 100% of subjects with randomized treatment in Groups 1, 2, and 3, respectively). After adding PEG+RBV, 71% of subjects in Groups 1 and 2 combined reported AEs, and 38.7% reported AEs after switching from randomized treatment to PEG+RBV. In Group 3, 40% of subjects reported AEs after switching from randomized

treatment to PEG+RBV.

Across all treatments, the most common AEs were influenza-like illness, headache, diarrhea, fatigue, and nausea. In Groups 1 and 2, all AEs during randomized treatment were Grade 1 or 2. Grade 3 AEs were reported in 2 subjects in Group 1 after adding PEG+RBV (fatigue) or replacing their randomized treatment with PEG+RBV (infective bursitis), in 2 subjects in Group 3 (syncope and neutropenia), and in 1 subject in Group 3 after switching to PEG+RBV treatment (decreased neutrophil count).

The profile of AEs considered to be related to study drug was similar to the profile of AEs overall. The majority of AEs in all randomized groups were judged by the investigator to be treatment related. The most common treatment-related AEs were headache, influenza-like illness, nausea, diarrhea, and fatigue.

In this study, Grade 3 neutropenia and Grade 2 hyperbilirubinemia were each reported in a single subject, and anemia was reported in 4 subjects (2 Grade 2, 2 Grade 1) One subject had an AE of abnormal ECG (Grade 1) after adding PEG+RBV to the treatment regimen. All reported psychiatric disorder AEs were mild or moderate; preferred terms included insomnia, agitation, depressed mood, emotional disorder, mood altered, nervousness, panic attack, anxiety, and sleep disorder.

Two subjects experienced serious AEs (SAEs) during the study: infective bursitis and syncope; both events were considered unrelated to study drug and both resolved. One subject discontinued study drug (GS-9256+TGV) because of severe fatigue; PEG+RBV were continued, and the event did not resolve before the subject was lost to follow up.

The majority of subjects in each treatment group had graded laboratory abnormalities, and the majority of these were Grade 1 (mild) (except in Group 3 after switching to PEG+RBV). The most common laboratory abnormalities (occurring in at least 2 subjects in a treatment group) were with serum glucose, neutrophils, white blood cell (WBC) count, total bilirubin, hemoglobin, platelets, serum uric acid, and phosphorus. During randomized treatment, Group 3 subjects tended to have more laboratory abnormalities than did Groups 1 or 2, notably neutrophils, WBC, platelets, and phosphorus. A Grade 4 laboratory abnormality of low neutrophil count was reported in 1 subject, and Grade 3 laboratory abnormalities in neutrophils (7 subjects) and WBC and hemoglobin (2 subjects each) were reported. Most bilirubin values remained in the normal range at all measurements; increases that were seen were transient, and concentrations returned to within the normal range by Week 6. All treatment-emergent bilirubin abnormalities during randomized treatment were Grade 1 (4, 5, and 5 subjects in Groups 1, 2, and 3, respectively). In addition, 2 subjects from Groups 1 or 2 who had added PEG+RBV also had Grade 1 bilirubin abnormalities.

Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values remained steady in all treatment groups through the study, with the maximal mean changes at any time point within approximately 10 mm Hg of the baseline value. Mean heart rate (HR) values tended to increase in the treatment groups over time (maximum mean increase from baseline of 10 bpm). Mean HR values were within 60 to 80 bpm at all time points. One subject in Group 3 had an AE of mild unrelated blood pressure (BP) increased.

Median QTcF values were not significantly changed from baseline in any of the 3 treatment

groups, whether including or excluding data after initiation of PEG+RBV. No subject had an observed QTcF value > 500 msec or a change from baseline > 60 msec during the study. One subject had an AE of mild drug-related abnormal ECG (ECG with occasional ventricular premature complexes) after adding PEG+RBV to his GS-9256+TGV regimen.

One partner pregnancy was reported during the study. There were no deaths or study drug overdoses reported during the study.

CONCLUSIONS: From the overall results of this study, the following conclusions were made:

- A greater percentage of subjects achieved RVR (ie, HCV RNA below the < 25 IU/mL LLOQ at Day 28) after receiving GS-9256+TGV in combination with RBV or PEG+RBV (38.5% and 100%, respectively) compared with GS-9256+TGV alone (6.7%).
- When viral rebound occurred with GS-9256+TGV alone or in combination with RBV, the addition of PEG+RBV or PEG to the regimen led to viral RNA suppression in the majority of subjects.
- The median (Q1, Q3) maximum reduction in HCV RNA was −4.08 (−4.42, −2.93), -5.12 (−5.32, −4.41), and −5.71 (−5.88, −5.50) $\log_{10}$ IU/mL in subjects who received GS-9256+TGV, GS-9256+TGV+RBV, and GS-9256+TGV+PEG+RBV, respectively, excluding data after initiation of PEG+RBV.
- The PK of GS-9256 and TGV (assessed by AUC_{tau}, C_{max}, and C_{tau}) in HCV-infected subjects exhibited high variability between treatment groups. Across the 3 treatment groups, oral administration of GS-9256+TGV provided mean steady-state plasma trough exposures 1.5- to 15-fold (GS-9256) higher and 9- to 21-fold (TGV) higher than the protein-adjusted EC_{50}.
- The combination of GS-9256 (75 mg) plus TGV (40 mg) was generally well tolerated in terms of AEs and graded laboratory abnormalities. Headache, influenza-like illness, nausea, diarrhea, and fatigue were the most common study drug-related AEs.
- No impact on cardiac repolarization (ie, prolongation of the QTcF interval from baseline) was observed for the GS-9256+TGV group following multiple doses. No subject had an observed QTcF value > 500 msec or a change from baseline > 60 msec during the study.