FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2 Randomized, Open-Label Study of GS-5885 Administered Concomitantly with GS-9451, Tegobuvir and Ribavirin (RBV) to Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir (LDV; GS-5885), Tegobuvir (TGV; GS-9190), Vedroprevir (VDV; GS-9451), and Ribavirin (RBV)
Dose and Formulation:	LDV 30 or 90 mg (1 or 3 × 30-mg tablets) once daily, TGV 30 mg (1 × 30-mg capsule) twice daily, and VDV 200 mg (2 × 100-mg tablets) once daily
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-248-0120
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	108,214 2011-000944-43
Study Start Date: **Study End Date**	23 May 2011 (First Subject Screened) 11 March 2013 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: David L. Wyles, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Benedetta Massetto, MD, PhD Telephone: PPD Fax: PPD
Report Date:	13 August 2013

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-248-0120:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404,
USA

Title of Study: Study GS-US-248-0120: A Phase 2 Randomized, Open-Label Study of GS-5885 Administered Concomitantly with GS-9451, Tegobuvir and Ribavirin (RBV) to Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled at a total of 34 sites: 30 in the United States (including Puerto Rico), 2 in Germany, and 2 in France.

Publications: Sulkowski M, Rodriguez-Torres M, Lawitz E, Shiffman M, Pol S, Herring R, et al. SVR12 Rates in Treatment-Naïve HCV Genotype 1a and 1b Patients Treated with an Interferon-Free All-Oral Regimen [Oral Presentation 212]. AASLD; 2012; Boston, MA.

Sulkowski M, Rodriguez-Torres M, Lawitz E, Shiffman M, Pol S, Herring R, et al. Interim Sustained Virologic Response Rates in Treatment-Naïve HCV Genotype 1a and 1b Patients Treated for 12 or 24 Weeks with an Interferon-Free All-Oral Quad Regimen [Poster 1421]. 47th Annual Meeting of the European Association for the Study of the Liver (EASL); 2012 April 18-22; Barcelona, Spain.

Study Period:

23 May 2011 (First subject screened)
02 October 2012 (Last subject observation in Main Study)
11 March 2013 (Last subject observation in Rescue Therapy Substudy)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy as measured by sustained virologic response (SVR; defined as hepatitis C virus [HCV] ribonucleic acid [RNA] < lower limit of quantitation [LLOQ] 24 weeks posttreatment) of ledipasvir (LDV; GS-5885) 30 mg or 90 mg when given with vedroprevir (VDV; GS-9451), tegobuvir (TGV), and ribavirin (RBV) for 12 or 24 weeks
- To evaluate the safety and tolerability of LDV 30 mg or 90 mg when given with TGV, VDV, and RBV for 12 or 24 weeks

The secondary objectives of this study were as follows:

- To evaluate the antiviral efficacy at Weeks 1, 2, 4, 12, and 24, as measured by the rates of HCV RNA < LLOQ and viral breakthrough and relapse
- To evaluate the antiviral efficacy (as defined by SVR) of the addition of pegylated interferon (PEG) for 24 weeks to LDV, VDV, and RBV in subjects who experience viral breakthrough on treatment (Rescue Therapy Substudy)
- To evaluate the emergence of viral resistance during treatment with TGV, VDV, and RBV when given with LDV 30 mg or 90 mg for 12 or 24 weeks
- To characterize viral dynamics and steady state pharmacokinetics (PK) of LDV, TGV, and VDV when coadministered with RBV

The exploratory objectives of this study were as follows:

- To assess genetic variation in the human IL28B gene (IL28B) as a predictor of virologic response in each treatment group
- To identify or validate 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) in subjects who provided additional consent

Methodology: This was a Phase 2, randomized, open-label, multicenter study. This study was designed to evaluate the safety, tolerability, and efficacy of LDV 30 mg or 90 mg when given with TGV+VDV+RBV for 12 or 24 weeks in subjects with chronic genotype 1a or 1b HCV infection. A total of 120 eligible subjects were to be initially randomized in a 1:2 ratio to one of the following treatment groups:

- Group 1 (n = 40): LDV 30 mg+TGV+VDV+RBV, which consisted of LDV 30 mg once daily + TGV 30 mg twice daily + VDV 200 mg once daily + weight-based RBV twice daily for 24 weeks.
- Group 2 (n = 80): LDV 90 mg+TGV+VDV+RBV, which consisted of LDV 90 mg once daily + TGV 30 mg twice daily + VDV 200 mg once daily + weight-based RBV twice daily for 12 or 24 weeks. Subjects with very rapid virologic response (vRVR; HCV RNA < LLOQ at Week 2) and HCV RNA < LLOQ maintained through Week 10 were rerandomized (1:1) at Week 12 to stop initial treatment or continue therapy to Week 24

For the purpose of analysis, Group 2 subjects who were rerandomized and actually did stop the initial treatment at Week 12 are included in the Group 2 12-Week subgroup; Group 2 subjects who were rerandomized to continue the initial treatment through Week 24 are included in the Group 2 24-Week subgroup.

Randomization and rerandomization were stratified by HCV RNA load (≤ or > 800,000 IU/mL) and genotype (1a or 1b) at screening.

The current study included 3 substudies. The first substudy was the Rescue Therapy Substudy, in which subjects received LDV (at the original assigned dose), VDV, RBV, and PEG for an additional 24 to 48 weeks of treatment. Subjects were eligible for the Rescue Therapy Substudy if they did not achieve vRVR, demonstrated confirmed virologic breakthrough on treatment, or were rerandomized to stop treatment at Week 12 and

demonstrated virologic relapse during the 24-week follow-up period. Subjects in the Rescue Therapy Substudy with eRVR (extended rapid virologic response; HCV RNA < LLOQ at Week 4 maintained through Week 20) stopped all treatment at Week 24 whereas those without eRVR stopped LDV and VDV at Week 24 and continued PEG+RBV through Week 48. Initially, the treatment regimen in the Rescue Therapy Substudy included TGV (ie, LDV+VDV+TGV+RBV+PEG). Protocol Amendment 2 removed TGV from the treatment regimen; prior to this, 7 subjects received TGV for a median duration of 28 days.

In the second substudy, the PK Substudy, up to 15 subjects in each group could participate and have intensive PK sample collection performed. In the third substudy, the Viral Dynamics Substudy, up to 15 subjects in each group could participate and have additional sampling. The same subjects were permitted, but not required, to participate in both the PK and Viral Dynamics Substudies.

The treatment period duration was dependent on the rerandomization at Week 12 as well as the subject's treatment response. All subjects were to complete a posttreatment Week 4 visit regardless of their treatment duration. Subjects who had HCV RNA < LLOQ at the posttreatment Week 4 visit were to complete posttreatment Week 12 and 24 visits unless a confirmed viral relapse had occurred.

After completing the current study, eligible subjects could have enrolled into 1 of 2 follow-on studies: the SVR Registry Study (GS-US-248-0122) or the Sequence Registry Study (GS-US-248-0123). All subjects who achieved SVR were eligible for enrollment in the SVR Registry Study, which is evaluating the durability of SVR for up to 3 years posttreatment. Subjects not achieving SVR were eligible for enrollment in the Sequence Registry Study, which is monitoring the persistence of resistance mutations for up to 3 years.

Number of Subjects (Planned and Analyzed):
Planned: 120 subjects (40 subjects in Group 1 and 80 subjects in Group 2).

Analyzed:

- Full analysis set: 140 subjects (46 in Group 1 and 94 in Group 2)
- Safety analysis set: 140 subjects (46 in Group 1 and 94 in Group 2)
- Rescue analysis set: 50 subjects (20 in Rescue Group 1 and 30 in Rescue Group 2)
- Rescue safety analysis set: 50 subjects (20 in Rescue Group 1 and 30 in Rescue Group 2)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant females who were 18 to 70 years of age, inclusive; had chronic genotype 1a or 1b HCV infection, a screening HCV RNA level of > 10^4 IU/mL, no prior treatment for HCV; and a body mass index of 18 to 36 kg/m^2, inclusive.

Duration of Treatment: In the Main Study, the duration of treatment was 12 weeks for Group 2 (rerandomized to stop at Week 12) and 24 weeks for Group 1 and for Group 2 (rerandomized to continue therapy through Week 24). In the Rescue Therapy Substudy, the duration of treatment was 24 to 48 weeks.

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

- Ledipasvir was administered orally at a dose of 30-mg or 90-mg once daily (1 × 30-mg tablet or 3 × 30-mg tablets).
- Tegobuvir was administered orally at a total daily dose of 60-mg (1 × 30-mg capsule twice daily).
- Vedroprevir was administered orally at a dose of 200-mg once daily (2 × 100-mg tablets).
- Weight-based RBV was administered orally at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets in a divided daily dose based on baseline body weight).
- In the Rescue Therapy Substudy, pegylated interferon (PEG) was administered subcutaneously at a fixed dose of 180 µg once weekly from a prefilled syringe.

The lot numbers of study drugs administered in this study were CF1103B1, CF1105B1, CF1106B1 (LDV); BN1101B1, BN1104B1, BN1105B1 (VDV); CT1103A1, CT1105A1 (TGV); 899760, 899764, 913114, 914594 (RBV); and B1151, B1191, B1205, B1221, B1240 (PEG).

Criteria for Evaluation:

Efficacy: Efficacy was evaluated using scheduled assessments of HCV RNA performed using COBAS® TaqMan® HCV Test v2.0 for Use with the High Pure System .

Pharmacokinetics: For subjects who participated in the PK substudy, intensive PK sample collection was performed during Week 2 to determine the steady state PK of LDV, TGV, VDV, and RBV (if appropriate).

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medication, clinical laboratory analyses, vital sign measurements, 12-lead electrocardiograms (ECGs), and physical examinations at prespecified intervals throughout the study.

Statistical Methods:

Efficacy: The primary efficacy endpoint was the proportion of subjects with SVR 24 weeks after stopping all study drugs (SVR24), defined as HCV RNA < LLOQ 24 weeks after study drug cessation in the full analysis set. A Cochran-Mantel-Haenszel (CMH) test statistic for stratified proportions was used to test for superiority of the Group 1 (ie, LDV 30 mg+TGV+VDV+RBV) versus Group 2 (ie, LDV 90 mg+TGV+VDV+RBV). The 2-sided 95% confidence intervals (CIs) for the proportion difference between Group 1 and Group 2 was constructed based on stratum-adjusted Mantel-Haenszel proportions.

In the Main Study, secondary efficacy endpoints and endpoints of interest included the proportion of subjects with SVR4 and SVR12, virologic outcomes, the proportion of subjects with alanine aminotransferase (ALT) normalization, and the proportion of subjects with HCV RNA < LLOQ by study visit and at the end of initial treatment. Point estimates and 2-sided 95% exact CIs based on the Clopper-Pearson method were constructed for the proportion within each treatment group for these secondary endpoints (Group 1, Group 2, Group 2 [12-week subgroup], Group 2 [24-week subgroup], and Group 2 [not rerandomized

subgroup]). In addition, to compare Group 1 and Group 2, the 2-sided 95% CIs of the difference in SVR4 and SVR12 rates were constructed based on stratum-adjusted Mantel-Haenszel proportions, and the 95% CIs of the difference in proportions of subjects with virologic failure were constructed based on the exact method (standardized statistic and inverting two 1-sided tests).

In the Rescue Therapy Substudy, the proportion of subjects with SVR4, SVR12, and SVR24 after stopping rescue therapy (defined as HCV RNA < LLOQ 4, 12, and 24 weeks after stopping rescue therapy) was summarized by Rescue Group 1 and Rescue Group 2.

Pharmacokinetics: To determine the steady state PK of LDV, TGV, VDV, and RBV (if appropriate), the PK parameters for analytes LDV, VDV, TGV, and RBV were computed for all subjects with evaluable PK profiles. For each subject, the following PK parameters were calculated, as appropriate: AUC_{tau}, C_{max}, C_{tau}, $t_{1/2}$, T_{max}, and λ_z.

Safety: Safety data were summarized by treatment group for subjects included in the safety analysis set and the rescue safety analysis set separately. Summaries included AEs, laboratory abnormalities, and changes from baseline in ECGs, laboratory tests, and vital signs for all data collected on or after the date of the first dose of study drugs that were treatment emergent. Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.1. Laboratory abnormalities were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Version 18 June 2012). Laboratory test values were summarized using descriptive statistics.

SUMMARY – RESULTS:

Subject Disposition and Demographics: A total of 140 subjects were randomized and received study drug: 46 subjects received LDV 30 mg+TGV+VDV+RBV (Group 1) and 94 subjects received LDV 90 mg+TGV+VDV+RBV (Group 2). In Group 2, 2 subjects who were rerandomized to continue the initial treatment through Week 24 were included in the 12-week subgroup because they discontinued treatment at Week 12. Therefore, 33 subjects were analyzed in the Group 2 12-week subgroup and 31 subjects were analyzed in the Group 2 24-week subgroup.

The majority of subjects in the safety analysis set were white (85.7%), and non-Hispanic/Latino (87.9%), with a mean age of 48 years (ranging from 18 to 67 years) and similar numbers of males (57.1%) and females (42.9%). The overall mean (SD) baseline body mass index (BMI) value for subjects was 26.8 (4.53) kg/m^2.

A greater proportion of subjects had genotype 1a (73.6%) compared with genotype 1b (26.4%) HCV infection and most subjects had HCV RNA load > 800,000 IU/mL (81.4%) compared with ≤ 800,000 IU/mL (18.6%). The majority of subjects (62.1%) had non-CC (CT or TT) IL28B genotype, while 37.9% of subjects had the IL28B CC genotype.

Efficacy Results: A total of 140 subjects were randomized and received study drug: 46 subjects received LDV 30 mg+TGV+VDV+RBV (Group 1) and 94 subjects received LDV 90 mg+TGV+VDV+RBV (Group 2). Treatment with LDV 30 mg + TGV+VDV+RBV for 24 weeks (Group 1) resulted in an SVR24 rate that was lower, though not statistically

different (p-value = 0.18), compared with LDV 90 mg + TGV+VDV+RBV for 12 or 24 weeks (Group 2) (47.8% and 58.5% of subjects, respectively); the main difference between the groups was a higher rate of virologic breakthrough in Group 1 than Group 2 (19.6% and 10.6%, respectively). Prespecified subgroup analyses indicated that point estimates of the difference in SVR24 rates between Group 1 and Group 2 were generally consistent with those observed in the overall population.

Among the 94 subjects in Group 2, 64 subjects who had vRVR and HCV RNA < LLOQ maintained through Week 10 were rerandomized at Week 12 to stop treatment (n = 33; Group 2 [12-week subgroup]) or continue therapy to Week 24 (n = 31; Group 2 [24-week subgroup]). Lower SVR24 rates were observed for the Group 2 subjects rerandomized to 12 weeks of treatment than those rerandomized to 24 weeks of treatment (78.8% and 93.5% of subjects, respectively); the difference in the percentage of subjects who achieved SVR24 (12-week subgroup − 24-week subgroup) was −14.2% (80% CI: −26.2% to –2.1%).

Rapid suppression of HCV RNA was observed in both treatment groups. A total of 71.7% and 78.7% of subjects (33 of 46 subjects and 74 of 94 subjects) achieved vRVR in Groups 1 and 2, respectively; however proportionally more subjects experienced virologic breakthrough in Group 1 than in Group 2 (19.6% [9 of 46] and 10.6% [10 of 94], respectively). By the end of treatment in the Main Study, 54.3% of subjects (25 of 46) in Group 1 and 70.2% of subjects (66 of 94) in Group 2 had HCV RNA < LLOQ.

Similar proportions of subjects had ALT > upper limit of normal (ULN) at baseline in Group 1 and Group 2. In both treatment groups, normalization of ALT was observed in the majority of subjects during treatment with LDV+TGV+VDV+RBV, coincident with decreases in HCV RNA.

Of the 140 subjects who were randomized and treated, 31 subjects (22.1%) experienced virologic breakthrough (19 subjects) or virologic relapse (12 subjects) and qualified for population sequencing. All subjects who experienced virologic breakthrough on treatment in the Main Study had resistance-associated variants (RAVs) detected in 2 or more regions sequenced, with all subjects having a RAV in nonstructural protein 5A (NS5A). A total of 11 of 12 subjects (91.7%) with virologic relapse had 1 or more RAVs detected postbaseline in the NS3, NS5A, and/or NS5B regions, with all 11 subjects having an RAV in the NS5A region. For both subjects with viral breakthrough and virologic relapse, the VDV-associated, LDV-associated, or TGV-associated RAVs detected in the Main Study have been previously demonstrated to confer reduced susceptibility to VDV, LDV, or TGV, respectively.

Rescue Therapy Substudy

A total of 50 subjects experienced virologic failure (ie, failure to achieve vRVR, breakthrough, or relapse among Group 2 rerandomized subjects who stopped therapy at Week 12) in the Main Study and participated in the Rescue Therapy Substudy, which evaluated the antiviral efficacy of the addition of PEG to LDV (at the original assigned dose), VDV, and RBV for an additional 24 to 48 weeks of treatment.

Throughout the Rescue Therapy Substudy, a higher proportion of subjects in Rescue Group 2 achieved SVR. At Rescue Therapy Substudy posttreatment Week 4, SVR4 was achieved by 65.0% of subjects in Rescue Group 1 and 70.0% of subjects in Rescue Group 2. By Rescue

Therapy Substudy posttreatment Week 24, SVR rate had decreased over time to 35.0% and 56.7% of subjects in Rescue Group 1 and Rescue Group 2, respectively.

Of the 50 subjects who participated in the Rescue Therapy Substudy, 19 qualified for population sequencing, with 18 experiencing virologic relapse and 1 experiencing virologic breakthrough. All of the VDV-associated, LDV-associated, or TGV-associated RAVs detected in the Rescue Therapy Study have been previously demonstrated to confer reduced susceptibility to VDV, LDV, or TGV, respectively.

Pharmacokinetic Results: In the PK substudy, LDV, VDV, and TGV PK parameters were comparable across study groups and were generally consistent with results from Phase 1 and Phase 2 studies that included similar treatment regimens (Studies GS-US-248-0102, GS-US-248-0125, GS-US-256-0124). Likewise, RBV PK parameters were comparable across study groups and were consistent with previously reported clinical data.

Safety Results: In the Main Study, the majority of subjects in both Group 1 and Group 2 reported at least 1 AE. Similar percentages of subjects in each treatment group reported any AE, Grade 3 AEs, and any treatment-related AE. No subjects had a Grade 4 AE.

The most frequently reported overall AEs in both Group 1 and Group 2 were fatigue and headache. The most frequently reported treatment-related AEs in Group 1 were fatigue, headache, nausea, and anemia and in Group 2 were fatigue, headache, and diarrhea. Most AEs were Grade 1 or Grade 2 in severity. Grade 3 AEs were reported for 3 subjects (6.5%) in Group 1 and for 2 subjects (2.1%) in Group 2. Grade 2 AEs were reported for 39.1% and 28.7% of subjects in Group 1 and Group 2, respectively. No Grade 3 AEs were reported in > 1 subject.

No deaths were reported. Two serious adverse events (SAEs; viral gastroenteritis and pancreatitis) were reported for 1 subject in Group 1; the viral gastroenteritis event led to interruption of study drugs and the pancreatitis event, which was considered by the investigator to be related to study drugs, did not cause interruption or discontinuation of study drugs. Similar percentages of subjects in each treatment group reported AEs leading to permanent discontinuation of any study drug (Group 1: 2.2%; Group 2: 2.1%); none of the 7 AEs leading to permanent discontinuation of any study drug occurred in more than 1 subject.

Similar proportions of subjects in Group 1 (19.6%) and in Group 2 (17.0%) had Grade 3 laboratory abnormalities. The most frequently reported Grade 3 abnormalities were increased bilirubin (Group 1: 17.4%; Group 2: 4.3%) and decreased hemoglobin (Group 1: 8.7%; Group 2: 8.5%).

Few subjects had Grade 4 laboratory abnormalities, with similar proportions of subjects in Group 1 (2.2%) and in Group 2 (2.1%). Three Grade 4 laboratory abnormalities were reported: creatine kinase (1 subject in Group 1), urate hyper (1 subject in Group 2), and triacylglycerol lipase (1 subject in Group 2). All Grade 4 laboratory abnormalities were transient and returned towards baseline levels before or by the Week 24 visit.

Few subjects had liver-related laboratory events. No subjects in Group 1 and 2 subjects in Group 2 (12-week subgroup) had aspartate aminotransferase (AST) or ALT > 3 × ULN and

total bilirubin > 2 × ULN. Similarly, no subjects in Group 1 and 3 subjects in Group 2 (1 subject in each subgroup) had ALT > 5 × ULN. Ten subjects (21.7%) in Group 1 and 11 subjects (11.7%) in Group 2 had total bilirubin > 2 × ULN.

There were no notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) or ECG parameters reported during the Main Study.

Rescue Therapy Substudy

In the Rescue Therapy Substudy, the majority of subjects in both Rescue Group 1 and Rescue Group 2 reported at least 1 AE. Similar percentages of subjects in each treatment group reported any AE, Grade 3 AEs, and any treatment-related AE. No subjects had a Grade 4 AE.

The most frequently reported overall and treatment-related AEs in Rescue Group 1 were influenza-like illness, fatigue, and insomnia. The most frequently reported overall and treatment-related AEs in Rescue Group 2 were rash, fatigue, neutropenia, and anemia. Most AEs were Grade 1 or Grade 2 in severity. Grade 2 AEs were reported for 60.0% and 50.0% of subjects in Rescue Group 1 and Rescue Group 2, respectively. Grade 3 AEs were reported for 20.0% and 23.3% of subjects in Rescue Group 1 and Rescue Group 2, respectively. Grade 3 neutropenia and fatigue were the only Grade 3 AEs reported in > 1 subject (neutropenia for 2 subjects and 5 subjects, and fatigue for 2 subjects and 1 subject in Rescue Groups 1 and 2, respectively).

No deaths were reported. One subject (5.0%) in Rescue Group 1 and 2 subjects (6.7%) in Rescue Group 2 reported an SAE. No SAEs were reported in > 1 subject. Two subjects reported SAEs that were considered by the investigator to be related to study drug: Crohn's Disease in Rescue Group 1 and sepsis and urinary tract infection in Rescue Group 2. Similar percentages of subjects in each treatment group reported AEs leading to permanent discontinuation of any study drug in the Rescue Therapy Substudy (Rescue Group 1: 15.0%; Rescue Group 2: 13.3%).

Compared with the Main Study, a higher proportion of subjects who continued to the Rescue Therapy Substudy reported a Grade 3 or 4 laboratory abnormality. The proportion of subjects with a Grade 3 laboratory abnormality was 35.0% in Rescue Group 1 and 43.3% in Rescue Group 2. The most frequently reported Grade 3 abnormalities were decreased hemoglobin (Rescue Group 1: 30.0% and Rescue Group 2: 43.3%) and decreased neutrophils (Rescue Group 1: 25.0% and Rescue Group 2: 16.7%). Few subjects had Grade 4 laboratory abnormalities, with similar proportions of subjects in Rescue Group 1 (10.0%) and in Rescue Group 2 (13.3%).

A total of 4 subjects in the Rescue Therapy Substudy had liver-related laboratory events. No subjects had AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and no subjects in Rescue Group 1 and 1 subject (3.3%) in Rescue Group 2 had ALT > 5 × ULN. Three subjects (15.0%) in Rescue Group 1 and no subjects in Rescue Group 2 had total bilirubin > 2 × ULN.

There were no notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) or ECG parameters reported during the Rescue Therapy Substudy.

CONCLUSIONS:

The conclusions of the Main Study portion of Study GS-US-248-0120 are as follows:

- Treatment with LDV 90 mg + TGV+VDV+RBV for 12 or 24 weeks (Group 2) resulted in SVR24 rates that were higher compared with LDV 30 mg + TGV+VDV+RBV for 24 weeks (Group 1).
- Rapid suppression of HCV RNA was observed with LDV+TGV+VDV+RBV treatment, though proportionally more subjects experienced virologic breakthrough in Group 1 than in Group 2.
- Treatment with LDV 90 mg + TGV+VDV+RBV for 12 or 24 weeks (Group 2) resulted in overall virologic failure rates that were lower compared with LDV 30 mg + TGV+VDV+RBV for 24 weeks (Group 1), largely due to a lower breakthrough rate in Group 2.
- The viral breakthrough and relapse were associated with the detection of the VDV-, LDV-, and/or TGV-associated RAVs.
- Treatment with LDV+TGV+VDV+RBV was generally well tolerated in this study, with no deaths, few discontinuations during treatment, few SAEs, and few Grade 3 or 4 AEs or laboratory abnormalities. Increasing the LDV dose did not alter the safety profile of the regimen in terms of overall frequency or severity of AEs or laboratory abnormalities.

The conclusions of the Rescue Therapy Substudy are as follows:

- In the Rescue Therapy Substudy, higher SVR rates were observed for LDV 90 mg +VDV+RBV+PEG (Rescue Group 2) than for LDV 30 mg + VDV+RBV+PEG (Rescue Group 1).
- In the Rescue Therapy Substudy, the proportion of subjects reporting any AE, Grade 3 AEs, any treatment-related AE, and Grade 3 or 4 AEs, or laboratory abnormalities was generally balanced between the treatment groups.
- All of the VDV-associated, LDV-associated, or TGV-associated RAVs detected in the Rescue Therapy Substudy have been previously demonstrated to confer reduced susceptibility to VDV, LDV, or TGV, respectively.