ABBREVIATED CLINICAL STUDY REPORT

Study Title:	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating Response Guided Therapy with GS-5885 Alone or in Combination with GS-9451 with Peginterferon Alfa 2a and Ribavirin in Treatment Naive Subjects with Chronic Genotype 1 Hepatitis C Virus Infection
Name of Test Drug:	Ledipasvir (LDV, formerly GS-5885), Vedroprevir (VDV, formerly GS-9451)
Dose and Formulation:	LDV 30 mg (1 × 30-mg tablet) VDV 200 mg (2 × 100-mg tablet)
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-256-0148
Phase of Development:	Phase 2b
IND No.:	108,214
EudraCT No.:	2011-000456-42.
Study Start Date:	22 June 2011 (First Subject Screened)
Study End Date	14 June 2013 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Pr. Patrick Marcellin Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Bittoo Kanwar, MD Telephone: PPD Fax: PPD
Report Date:	11 October 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-256-0148
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: Study GS-US-256-0148: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating Response Guided Therapy with GS-5885 Alone or in Combination with GS-9451 with Peginterferon Alfa 2a and Ribavirin in Treatment Naive Subjects with Chronic Genotype 1 Hepatitis C Virus Infection

Investigators: Multicenter

Study Centers: A total of 70 clinical sites participated in this study including 38 in the United States, 12 in Australia, 6 in France, 4 in Poland, 3 in the Czech Republic, 2 in Germany, 2 in Italy, 2 in the United Kingdom, and 1 in Puerto Rico

Publications: None

Study Period:

22 June 2011 (First subject screened)
14 June 2013 (Last subject observation)

Phase of Development: Phase 2b

Objectives:

The primary objective of this study was as follows:

- To evaluate the antiviral efficacy as measured by sustained virologic response (SVR, defined as plasma hepatitis C virus [HCV] ribonucleic acid [RNA] < lower limit of quantification [LLOQ] at 24 weeks posttreatment) of response guided therapy (RGT) with ledipasvir (LDV, formerly GS-5885) + vedroprevir (VDV, formerly GS-9451) + pegylated interferon (PEG) + ribavirin (RBV), or LDV+PEG+RBV.

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of each regimen
- To characterize viral dynamics and steady state pharmacokinetics of LDV and VDV when administered with PEG and RBV
- To characterize the viral resistance to LDV and VDV when administered in combination with PEG and RBV

Exploratory objectives of this study were the following:

- Assess genetic variation in the human IL28B gene (IL28B) as a predictor of virologic response in each treatment arm.
- 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 (eg, pharmacogenomics), in subjects who provide their separate and specific consent

Methodology: This was a randomized, double-blind, placebo-controlled study that examined the antiviral efficacy, safety, and tolerability of RGT with LDV+VDV+PEG+RBV or LDV+PEG+RBV for up to 48 weeks in treatment-naive subjects with chronic genotype 1 HCV infection.

Arm 1:

RGT with LDV 30 mg once daily + VDV 200 mg once daily + PEG+RBV:

- Subjects who achieved very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2) and maintained HCV RNA < LLOQ through Week 8 were rerandomized (1:1) at Week 12 to either stop all therapy or to continue co-administration of LDV, VDV, and PEG+RBV through Week 24.
- Subjects without vRVR, but with extended rapid virologic response (eRVR, defined as HCV RNA < LLOQ at Week 4 and maintained HCV RNA < LLOQ through Week 20), continued co-administration of LDV, VDV, and PEG+RBV through Week 24.
- Subjects without vRVR or eRVR stopped treatment with LDV and VDV at Week 24 and continued PEG+RBV through Week 48.
- Subjects who were randomized to stop all treatment at Week 12, but then subsequently experienced a confirmed viral relapse through 24 weeks posttreatment follow-up, were eligible to re-initiate therapy in a Retreatment Substudy.
- Subjects who stopped treatment at Week 12 attended the Week 4 Posttreatment Follow-Up Visit as their next study visit.
- Subjects who stopped treatment at Week 24 attended the Week 4 Posttreatment Follow-Up Visit as their next study visit.

Arm 2:

RGT with LDV 30 mg once daily + VDV placebo once daily + PEG+RBV

- Subjects who achieved eRVR stopped all treatment at Week 24. Subjects not achieving eRVR stopped treatment with LDV and VDV placebo at Week 24 and continued PEG+RBV only through Week 48.

Randomization was stratified by IL28B genotype (CC versus non-CC) and HCV RNA viral load at Screening (ie, ≤ or > 800,000 IU/mL). In order to achieve balanced enrollment across genotype 1, enrollment of genotype 1a or genotype 1b was not to exceed 70% of the total enrollment.

Rerandomization at Week 12 in Arm 1 was to be stratified by IL28B genotype.

Up to 20 subjects (10 per arm) were planned for participation in a Viral Dynamics Substudy with sampling on Days 1 (4, 6, 8 h postdose), 2 (24 h postdose), 3 (48 h postdose), 5 (or 6 or 7 based on scheduling preference), and 10.

Up to 24 subjects (12 per arm) were planned for participation in the Pharmacokinetic (PK) Substudy and had serial PK collection (samples obtained up to 24 hours after dosing) performed at Week 2 to determine the steady state pharmacokinetics of LDV and VDV.

A Retreatment Substudy was available to subjects in Arm 1 who were rerandomized to stop treatment at Week 12 and who relapsed through 24 weeks posttreatment. Subjects received their original assigned regimen for a 24- to 48-week RGT duration. Subjects achieving eRVR during retreatment stopped treatment at Week 24. Subjects without eRVR stopped treatment with LDV and VDV at Week 24 and continued PEG+RBV through Week 48.

Futility analyses were performed to determine if the relapse rates for subjects in Arm 1 who were randomized to stop treatment at Week 12 were unacceptably high, where an unacceptably high rate was considered to be > 20%. If the futility criteria were met, no additional subjects were to be rerandomized to stop treatment at Week 12.

Number of Subjects (Planned and Analyzed):

Planned: 300 (200 subjects planned for Arm 1; 100 subjects planned for Arm 2)

Analyzed: 348 (232 subjects in Arm 1; 116 subjects in Arm 2)

Diagnosis and Main Criteria for Inclusion: The study enrolled male and female subjects, aged 18 to 70 years (inclusive), with documented chronic genotype 1 HCV monoinfection (positive anti-HCV antibody test, positive HCV RNA genotyping test, or liver biopsy). The subjects must have had viral loads > 10^4 IU/mL, been HCV treatment-naive, and been candidates for PEG+RBV therapy. Eligible subjects must have had a body mass index (BMI) 18 to 36 kg/m^2, inclusive, and must not have exceeded defined thresholds for leukopenia, neutropenia, anemia, thrombocytopenia, thyroid stimulating hormone with laboratory parameters of alanine aminotransferase (ALT)/aspartate aminotransferase levels ≤ 10 × the upper limit of normal (ULN), hemoglobin ≥ 12 g/dL, white blood cell count ≥ 2500 cells/μL, absolute neutrophil count ≥ 1500 cells/mm^3, platelets ≥ 90,000/mm^3, prothrombin time ≤ 1.5 × ULN, albumin > 3 g/dL, direct bilirubin < ULN, and creatinine clearance ≥ 50 mL/min. Finally, the subjects must have presented with an absence of decompensated liver disease, poorly controlled diabetes mellitus, significant psychiatric illness, severe chronic obstructive pulmonary disease, human immunodeficiency virus, hepatitis B virus, hepatocellular carcinoma or other malignancy (with the exception of certain resolved skin cancers), hemoglobinopathy, retinal disease, and a diagnosis of autoimmune disease; the subjects must not have been immunosuppressed.

Duration of Treatment: Duration of therapy in this study was determined by the virologic response to therapy, as described in the Methodology section above.

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

LDV (1 × 30-mg tablet), orally administered; lot numbers CF1103B1, CF1105B1, and CF1106B1

VDV (2 × 100-mg tablets), orally administered; lot numbers BN1101B1, BN1102B1, BN1104B1, BN1105B1, BN1106B1, and BN1107B1

PEG (Pegasys®, 180 μg/0.5 mL prefilled syringes), subcutaneously administered; lot numbers B1151, B1191, B1205, B1223, and B1233

RBV (Copegus®, 5 or 6 × 200-mg tablets), orally administered, lot numbers 119016, 899760, 899764, 913114, 914594, and 914595

Reference Therapy, Dose, Mode of Administration, and Batch No.:

Placebo to match VDV (2 × tablets), orally administered; lot number BN1103B1

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint

- The primary efficacy endpoint was SVR in all randomized and treated subjects, defined as HCV RNA < LLOQ at 24 weeks posttreatment

Additional Efficacy Endpoints

- Proportion of subjects with HCV RNA < LLOQ at 4 and 12 weeks after discontinuation of therapy

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 and VDV.

Safety: Safety was evaluated by assessment of adverse events (AEs), clinical laboratory test results, physical examination findings, vital sign measurements, and electrocardiogram (ECG) readings at various time points during the study. All safety data collected while "on treatment" (ie, on or after the first dose of study drug administration up to 30 days after the last dose of study drug) was summarized by treatment group according to the study drug received.

Other: Pharmacogenomic markers were assessed, including genetic variation of gene IL28B, as possible predictors of the natural history of disease, virologic response to therapy, and/or the tolerability of medical therapies through genetic discovery research in subjects who provided separate and specific consent.

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR in all randomized and treated subjects, defined as HCV RNA < LLOQ at 24 weeks posttreatment. The differences in SVR rates between Arm 1 and Arm 2 were tested using the Cochran-Mantel-Haenszel test, stratified by randomization stratification factors. This primary analysis was based on the full analysis set.

For Arm 1, a 90% confidence interval (CI) on the difference in SVR rates between 12-week therapy and 24-week therapy was constructed to estimate the difference in SVR rates between the 2 treatment durations in subjects achieving vRVR.

If differential SVR rates were observed between 12 and 24 weeks of treatment in Arm 1, separate comparisons to Arm 2 were performed by treatment and duration, with adjustment for the rerandomization.

Pharmacokinetics: Steady state PK of LDV and VDV over a 24-hour dosing interval was determined using validated bioanalytical assays. The PK parameters of C_{max}, T_{max}, C_{tau}, λ_z, $AUC_{tau,}$ and $t_{1/2}$ were calculated for all subjects with evaluable PK profiles. The PK parameters were estimated by application of a nonlinear model using standard noncompartmental methods (WinNonlin® software v6.3). Descriptive statistics (sample size [N], mean, standard deviation [SD], coefficient of variation, median, first quartile, third quartile, minimum, maximum, and geometric mean and the 95% CI) were presented for PK concentration data and PK parameter data. For concentration values below the limit of quantitation (BLQ), the number of subjects with values of BLQ was presented.

Safety: Safety data were summarized for subjects included in the safety analysis set. Summaries of safety data (AEs, clinical laboratory tests, vital signs, physical examination parameters, ECG readings, and concomitant medications) included all data collected on or after the first dose date of study regimen through the last dose date of any study drug plus 30 days.

SUMMARY – RESULTS:

On 19 September 2012, Gilead Sciences issued a safety notification to the investigational centers regarding concerns of pancytopenia. The emerging safety data from Gilead-sponsored clinical studies indicated that the incidence of pancytopenia associated with a 4-drug regimen of PEG+RBV combined with 2 other direct acting antivirals was approximately 0.3%, which was higher than previously reported with PEG+RBV alone. In this letter, it was indicated that subjects currently on primary study treatment or retreatment with LDV+VDV+PEG+RBV were to stop all study drugs immediately. These subjects were to be brought into the investigational center to initiate early termination and follow-up visits as per the protocol. Also, subjects who met protocol-defined criteria for retreatment were not to initiate retreatment with the LDV+VDV+PEG+RBV regimen.

Subject Disposition and Demographics: A total of 348 subjects were randomized and received study drug: 232 subjects received LDV+VDV+PEG+RBV (Arm 1) and 116 subjects received LDV+PEG+RBV (Arm 2). In the safety analysis set, the majority of subjects were white (84.5%) and the majority of subjects were male (58.3%) . The subjects ranged in age from 19 to 69 years, with a mean (SD) age of 47 (11.3) years. The overall mean (SD) baseline body mass index value for subjects was 26.1 (4.09) kg/m^2. A greater percentage of subjects had HCV infection of genotype 1a (64.4%) than genotype 1b (35.6%) and most subjects had HCV RNA load > 800,000 IU/mL (76.7%). Most of the subjects (72.1%) had non-CC IL28B alleles and none of the subjects had cirrhosis. Overall, the demographic and baseline characteristics were balanced between treatment arms.

Initial Treatment Period

In Arm 1, 232 subjects were randomized and treated with study drug. At Week 12, 88 subjects were rerandomized to stop all therapy, while an additional 88 subjects were rerandomized to continue treatment with LDV+VDV+PEG+RBV through Week 24; 56 subjects were not rerandomized. Among the subjects who were rerandomized to stop treatment at Week 12, 87 (98.9%) completed treatment and 1 (1.1%) discontinued treatment due to a protocol violation. Among the subjects who were rerandomized to continue treatment through Week 24, 77 (87.5%) completed treatment and 11 (12.5%) discontinued treatment due to AEs (6 subjects [6.8%]), consent withdrawal (2 subjects [2.3%]), being lost to follow-up (2 subjects [2.3%]), or physician decision (1 subject [1.1%]).

In Arm 2, 116 subjects were randomized and treated with study drug. At Week 24, 82 subjects stopped all treatment as expected (ie, completed the planned treatment period). The 34 subjects who discontinued did so primarily due to lack of efficacy (16 subjects [13.8%]), AEs (10 subjects [8.6%]), withdrawal of consent (4 subjects [3.4%]), or physician decision (2 subjects [1.7%]). All other reasons for discontinuation occurred in less than 1% of the subjects.

Retreatment Substudy

In Arm 1, 7 subjects who were rerandomized to stop treatment at Week 12 relapsed through 24 weeks posttreatment and were included in the Retreatment Substudy. Of these subjects, 2 completed retreatment and 5 discontinued retreatment due to either lack of efficacy (3 subjects [42.9%]) or study termination by the sponsor (2 subjects [28.6%]).

Study Completion

Of the 348 randomized and treated subjects, 262 (75.3%) completed the study (ie, completed posttreatment follow-up Week 24) (Arm 1: 192 subjects [82.8%]; Arm 2: 70 subjects [60.3%]). In Arm 1, 76 of 88 subjects (86.4%) in the 12-week treatment group and 79 of 88 subjects (89.8%) in the 24-week treatment group completed the study.

The most common reason for premature discontinuation from the study was lack of efficacy (Arm 1: 19 subjects [8.2%]; Arm 2: 28 subjects [24.1%]), followed by being lost to follow-up (Arm 1: 12 subjects [5.2%]; Arm 2: 5 subjects [4.3%]), withdrawal by subject (Arm 1: 3 subjects [1.3%]; Arm 2: 7 subjects [6.0%]), and AEs (Arm 1: 3 subject [1.3%]; Arm 2: 6 subjects [5.2%]). All other reasons for discontinuation occurred in Arm 1, and included 1 subject (0.4%) each.

Efficacy Results: Although partial efficacy results of this study have been presented and summarized, it should be noted that Gilead Sciences has discontinued the development of the therapeutic regimen containing LDV+VDV in combination with PEG+RBV.

Overall, 192 of 232 subjects (82.8%) in Arm 1 and 70 of 116 subjects (60.3%) in Arm 2 achieved an SVR at 24 weeks after stopping initial treatment (SVR24). The difference in the percentage of subjects who achieved SVR24 between the 2 treatment arms (Arm 1 – Arm 2) was 22.4% (95% CI: 12.9% to 32.0%; $p < 0.001$). For rerandomized subjects in Arm 1, the difference in SVR24 between subjects treated with LDV+VDV+PEG+RBV for 12 weeks relative to subjects treated with LDV+VDV+PEG+RBV for 24 weeks was -8.0%; this difference was not statistically significant (84.1% vs 92.0%, respectively; difference between groups = -8.0%; 95% CI: -17.8% to 1.8%; $p = 0.11$).

In general, the trends observed for the proportion of subjects in each arm who achieved an SVR at 24 weeks posttreatment were also observed at 4 and 12 weeks posttreatment. Greater proportions of subjects in Arm 1 with genotype 1b HCV infection had an SVR at 4, 12, and 24 weeks posttreatment relative to subjects in the same arm at the same timepoints with genotype 1a HCV infection. Overall, while the numbers of subjects in Arm 2 with each HCV and IL28B genotype were markedly smaller than in Arm 1, similar trends were observed in Arm 2. The proportions of subjects in Arm 2 with an SVR at each timepoint by HCV and IL28B genotype were generally similar to or smaller than the proportions of subjects in Arm 1 with an SVR at the same timepoint within the same HCV and IL28B genotype subgroups.

Pharmacokinetic Results: In the PK Substudy, LDV and VDV PK parameters were generally consistent with results from Phase 1 and 2 studies that included similar treatment regimens (Studies GS-US-248-0102, GS-US-248-0120, GS-US-248-0125, GS-US-248-0132, and GS-US-256-0124).

Safety Results:

Initial Treatment Period

The majority of subjects in Arm 1 and Arm 2 experienced at least 1 AE during the initial treatment period. Most of the AEs that occurred during the initial treatment period were assessed by the investigators as treatment-related.

The most commonly reported AEs (ie, events reported for more than 20% of the subjects) in treatment Arm 1 and 2 included: fatigue (46.1% and 45.7%, respectively), headache (38.4% and 37.1%, respectively), nausea (27.2% and 33.6%, respectively), influenza-like illness (23.7% and 24.1%, respectively), insomnia (23.7% and 22.4%, respectively), pruritus (22.0% and 23.3%, respectively), rash (22.4% in both arms), cough (24.6% and 17.2%, respectively), myalgia (19.8% and 23.3%, respectively), anaemia (19.4% and 23.3%, respectively), and pyrexia (21.1% and 19.8%, respectively).

The most commonly reported AEs assessed as related to treatment (ie, treatment-related events occurring in 20% or more of the subjects in either treatment arm) included fatigue, headache, nausea, influenza-like illness, rash, pruritus, insomnia, cough, pyrexia, anaemia, and myalgia. Generally similar percentages of subjects in Arm 1 and Arm 2 experienced each of these individual AEs.

A total of 52 subjects (22.4%) in Arm 1 and 24 subjects (20.7%) in Arm 2 experienced Grade 3 or 4 AEs; all but 1 of these events was Grade 3. Most of the Grade 3 or 4 events occurred in 1 subject each and were assessed by the investigator as treatment-related.

The single Grade 4 AE was haemorrhagic stroke (Arm 1, [redacted]), which led to subject death. The subject died during the initial treatment period. The cause of death was respiratory failure with an associated serious adverse event (SAE) of haemorrhagic stroke, which was assessed by the investigator as related to the study drugs.

Overall, 15 subjects (6.5%) in Arm 1 and 9 subjects (7.8%) in Arm 2 experienced at least 1 SAE. In Arms 1 and 2, 10 subjects (4.3%) and 2 subjects (1.7%), respectively, experienced SAEs that were assessed by the investigator as treatment-related. With 2 exceptions, no more than 1 subject experienced any single treatment-related SAE. The exceptions, which occurred in 2 subjects each in Arm 1, were neutropenia and dyspnoea. Both events of neutropenia were Grade 2, resulted in hospitalization, and resolved. Both events of dyspnoea were Grade 3, resulted in hospitalization, and resolved.

Generally similar percentages of subjects in Arm 1 and Arm 2 experienced AEs that led to permanent discontinuation of the study drugs (6.9% and 8.6% of the subjects in each arm, respectively). None of the events that led to study drug discontinuation were experienced by more than 2 subjects each.

Nearly all of the subjects in the initial treatment period (231 of 232 subjects in Arm 1 and 116 of 116 subjects in Arm 2) experienced at least 1 laboratory abnormality. The percentages of subjects in each arm who experienced at least 1 Grade 3 abnormality were similar (47.2% and 50.9% in Arms 1 and 2, respectively). Few subjects in either arm experienced any Grade 4 abnormality (15 subjects [6.5%] in Arm 1 and 5 subjects [4.3%] in Arm 2).

The most frequently reported Grade 3 abnormalities were increased bilirubin (Arm 1: 5.6%; Arm 2: 0.9%), decreased hemoglobin (Arm 1: 29.4%; Arm 2: 26.7%), decreased lymphocytes (Arm 1: 5.2%; Arm 2: 8.6%), decreased neutrophils (Arm 1: 18.6%; Arm 2: 20.7%), and decreased white blood cell counts (Arm 1: 8.2%; Arm 2: 6.9%). The only Grade 4 abnormalities experienced by more than 1 subject in any treatment arm were decreased lymphocytes (Arm 1: 1.7%; Arm 2: 1.7%), decreased neutrophils (Arm 1: 4.3%; Arm 2: 1.7%), and decreased white blood cell counts (Arm 1: 0.9% only).

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

Retreatment Substudy

No subject in the Retreatment Substudy experienced an SAE (fatal or nonfatal) or experienced an AE that led to permanent discontinuation of the study drugs. Of the 7 subjects who received retreatment, all 7 experienced at least 1 AE. The most commonly reported AEs were cough, fatigue, and headache, which were each reported by 3 subjects (42.9%; not necessarily the same 3 subjects). The most reported treatment-related AEs were fatigue, headache, and cough; each of these events was reported by a total of 3 subjects (42.9%). No subject in the Retreatment Substudy experienced a Grade 3 or 4 AE, and only 1 subject experienced a Grade 2 AE (headache, which was assessed by the investigator as treatment-related).

All 7 subjects experienced at least 1 laboratory abnormality. Overall, 3 subjects (42.9%) experienced at least 1 Grade 3 abnormality; no subject experienced any Grade 4 abnormality. The most common laboratory abnormality was a Grade 1 increase in glucose (4 subjects [57.1%]). One subject each experienced a Grade 3 decrease in hemoglobin, lymphocytes, and neutrophils.

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

CONCLUSIONS:

- A significantly greater percentage of subjects treated with LDV+VDV+PEG+RBV relative to subjects treated with LDV+PEG+RBV achieved an SVR24 (82.8% vs 60.3%, respectively; difference between groups = 22.4%; 95% CI: 12.9% to 32.0%; $p < 0.001$).
- In Arm 1, treatment with LDV+VDV+PEG+RBV for 12 weeks resulted in an SVR24 rate that was comparable to that achieved after treatment with LDV+VDV+PEG+RBV for 24 weeks (84.1% vs 92.0%, respectively; difference between groups = -8.0%; 95% CI: -17.8% to 1.8%; $p = 0.11$).
- In the PK Substudy, LDV and VDV PK parameters were generally consistent with results from Phase 1 and 2 studies that included similar treatment regimens.
- The incidences of AEs and the overall safety profiles of LDV+VDV+PEG+RBV and LDV+PEG+RBV were generally similar.
- Treatment of subjects taking 4-drug therapy (LDV+VDV+PEG+RBV) was discontinued due to concerns of pancytopenia in 3 subjects participating in other 4-drug combination studies sponsored by Gilead. The emerging safety data from Gilead-sponsored clinical studies indicated that the incidence of pancytopenia associated with a 4-drug regimen of PEG+RBV combined with 2 other direct acting antivirals was approximately 0.3%, which was higher than previously reported with PEG+RBV alone.