The Protease Inhibitor GS-9256 and Non-Nucleoside Polymerase Inhibitor Tegobuvir Alone, With RBV or Peginterferon plus RBV in Hepatitis C

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BMI, body mass index; DAA, direct-acting antiviral agent; ECG, electrocardiogram; HCV, hepatitis C virus; PEG-IFN, peginterferon alfa; RBV, ribavirin; RVR, rapid virologic response; SNP, single nuclear polymorphism.

ABSTRACT

Tegobuvir (GS-9190), a non-nucleoside NS5B polymerase inhibitor, and GS-9256, an NS3 serine protease inhibitor, individually have activity against hepatitis C virus (HCV) genotype 1. The antiviral activity of tegobuvir and GS-9256 as oral combination therapy, or together with ribavirin (RBV) or peginterferon alfa-2a (PEG-IFN) and RBV, was assessed in a phase 2, randomized, open-label trial. Treatment-naïve patients with genotype 1 HCV were assigned 28 days of tegobuvir 40 mg twice daily and GS-9256 75 mg twice daily (n=16), tegobuvir and GS-9256 plus RBV 1000-1200 mg daily (n=15), or tegobuvir and GS-9256 plus PEG-IFN alfa-2a (180 mcg qw)/RBV (n=15). The primary efficacy endpoint was rapid virologic response (RVR), HCV RNA <25 IU/mL at Day 28. After 28 days, all patients received PEG-IFN/RBV. All patients with viral rebound or nonresponse, defined as >0.5-$\log_{10}$ increase in HCV RNA from nadir or <2-log decrease at Day 5, initiated PEG-IFN/RBV immediately. Median maximal reductions in HCV RNA were -4.1 $\log_{10}$ IU/mL for tegobuvir/GS-9256, -5.1 $\log_{10}$ IU/mL for tegobuvir/GS-9256/RBV, and -5.7 $\log_{10}$ IU/mL for tegobuvir/9256/PEG-IFN/RBV. RVR was observed in 7% (1/15) of patients receiving tegobuvir/GS-9256, 38% (5/13) receiving tegobuvir/GS-9256/RBV, and 100% (14/14) receiving tegobuvir/9256/PEG-IFN/RBV. The addition of PEG-IFN/RBV at Day 28 or earlier resulted in HCV RNA <25 IU/mL at Week 24 in 67% (10/15), 100% (13/13) and 94% (13/14) of patients in the 3 treatment groups. Transient elevations in serum bilirubin occurred in all treatment groups. *Conclusion:* In genotype 1 HCV, adding RBV or RBV with PEG-IFN provides additive antiviral activity to combination therapy with tegobuvir and GS-9256.

For the past decade, standard of care for patients with chronic infection with genotype 1 hepatitis C virus (HCV) has been 48 weeks of peginterferon alfa (PEG-IFN) and ribavirin (RBV). Observed rates of sustained virologic response with PEG-IFN and RBV therapy are 40-52% (1-4). However, the addition of the HCV NS3 serine protease inhibitors telaprevir or boceprevir results in higher rates of sustained virologic response (67-75%), leading to the recent approval of these two drugs in the United States and the European Union (5-10). Because triple therapy can result in higher rates of rapid virologic response (RVR, HCV RNA < lower limit of quantification at Week 4) in the range of 60% to 70% (5,6,9,10), shortened treatment duration from 48 to 24 weeks is possible in a significant proportion of patients.

Several novel inhibitors of viral replication, including those targeting the NS3 serine protease and NS5B RNA-dependent RNA polymerase, are in clinical development (11). Although many of these direct-acting antiviral agents (DAAs) can cause rapid and substantial reductions in viral load, their use as monotherapies has been limited by inadequate suppression of replication and/or the development of resistance (12,13). In the context of polymerase or protease inhibitor therapy, PEG-IFN and RBV have repeatedly demonstrated their importance in reducing viral load and suppressing viral breakthrough (14-16). In studies of regimens containing telaprevir or boceprevir, excluding RBV or using a reduced dose results in higher rates of viral breakthrough and relapse (5,7,17).

Several recent studies have explored combining two DAAs to enhance early antiviral activity and to theoretically minimize development of resistance. In a study of treatment-naïve patients with HCV genotype 1, 14 days of combination therapy with the nucleoside analog RG7128 and

the NS3 protease inhibitor danoprevir resulted in 5-$\log_{10}$ IU/mL HCV RNA reductions from baseline (18). More recently, the combination of the non-nucleoside NS5B polymerase inhibitor VX-222 with telaprevir improved early antiviral response but was associated with high rates of viral breakthrough (19).

Tegobuvir (GS-9190) is a novel, non-nucleoside inhibitor of the NS5B polymerase. Studies to elucidate tegobuvir's mechanism of action are ongoing; however, current data indicate the inhibitory effect may be exerted via an interaction with the β-hairpin in the NS5B thumb sub-domain (20). Tegobuvir and the NS3 protease inhibitor GS-9256 each have demonstrated antiviral activity in HCV-infected patients (21-23). Tegobuvir demonstrated median reductions in HCV RNA of 1.5 $\log_{10}$ IU/mL for individual patients with 8 days of monotherapy (21) and enhanced rates of RVR (HCV RNA <25 IU/mL at Week 4) when combined with PEG-IFN and RBV (22). At 200 mg twice daily for 3 days, GS-9256 monotherapy demonstrated a median HCV RNA reduction of 2.7 $\log_{10}$ IU/mL (22). Both tegobuvir and GS-9256 were well-tolerated in these short-term monotherapy studies. We therefore evaluated the antiviral activity of tegobuvir and GS-9256 dual therapy, tegobuvir and GS-9256 plus RBV, and tegobuvir and GS-9256 plus PEG-IFN and RBV for 28 days. After 28 days of treatment, patients then continued treatment with PEG-IFN and RBV for 48 weeks.

METHODS

Patients

Eligible patients were adults 18–70 years of age with chronic HCV infection who had not been previously treated. Patients had HCV genotype 1 infection and absence of cirrhosis as judged by liver biopsy within 2 years prior to screening or by FibroTest™ or FibroScan™ within the prior 6 months.

Patients were excluded from the study if they had any of the following conditions or characteristics: elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma glutamyl transferase levels to >5 times the upper limit of normal; autoimmune diseases; decompensated liver disease; cirrhosis; severe psychiatric illness; severe chronic obstructive pulmonary disease; coinfection with HIV or hepatitis B virus; history of clinically significant cardiac disease or relevant electrocardiogram (ECG) abnormalities during screening.

IL28B genotyping was retrospectively performed at the Duke Center for Human Genome Variation utilizing a custom Taqman assay (Applied Biosystems) for the rs12979860 *IL28B* single nuclear polymorphism (SNP) (24).

All patients provided written informed consent before undertaking any study-related procedures.

Study Design

This was a Phase 2, randomized, open-label trial of tegobuvir plus GS-9256, both administered orally in combination for 28 days, or both in combination with RBV, or both in combination with

PEG-IFN alfa-2a and RBV. Patients were randomly assigned (1:1) to 40 mg tegobuvir taken twice daily (BID) plus 75 mg GS-9256 BID or 40 mg tegobuvir BID plus 75 mg GS-9256 BID plus RBV for 28 days. RBV (Copegus®) was administered in a divided total daily oral dose of 1000 to 1200 mg (1000 mg for patients weighing < 75 kg and 1200 mg for patients weighing ≥ 75 kg). Randomization was stratified by plasma HCV RNA level (< or ≥ 2,000,000 IU/mL) at screening (15 blocks of size 2). The sponsor's Biometrics group generated the randomization schedule by using SAS® software (SAS Institute, Cary, North Carolina, USA). In assigning patients to treatment in this open-label study, individual study sites sent randomization worksheets to the sponsor, who assigned subject numbers on the basis of the randomization schedule.

After the first two treatment arms were completed, the protocol was amended and a third arm was added to the study to evaluate antiviral response with quadruple therapy. Patients received 40 mg tegobuvir BID plus 75 mg GS-9256 BID in combination with PEG-IFN alfa-2a (Pegasys®) and RBV for 28 days. Subcutaneous injections of 180 mcg PEG-IFN alfa-2a were given once weekly.

After the first 28 days of treatment, all patients received continued treatment with PEG-IFN and RBV and were asked to return for follow-up visits 12, 24, 48 and 72 weeks after the last study drug dose. The selection of the specific PEG-IFN (alfa-2a or alfa-2b) and RBV products and regimen during this phase of the study was at the discretion of the investigator. PEG-IFN and RBV standard of care was initiated earlier than 28 days in the following circumstances: lack of early response, as defined by a < 2-$\log_{10}$ IU/mL HCV RNA reduction from baseline by Day 5, or

rebound, as defined by an 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.

The study protocol (EudraCT identifier: 2009-013690-18) was approved by each institution's independent ethics committee prior to study initiation.

Efficacy Assessments

HCV RNA

The primary efficacy endpoint was viral load suppression at Day 28, as measured by the proportion of patients achieving RVR, defined as plasma HCV RNA < 25 IU/mL at Day 28. Plasma HCV RNA reduction from baseline was also evaluated. Plasma for HCV RNA measurements was collected at Screening, on Day 1 predose (Baseline), and on Days 3, 5, 7, 14, 21, and 28. HCV RNA levels were measured with the Roche COBAS TaqMan RT-PCR Assay, lower limit of quantification, 25 IU/mL.

Viral Resistance

The complete NS3/4A and NS5B genes from plasma samples were PCR amplified, and population sequencing was performed from samples with HCV RNA ≥1000 IU/mL by Virco BVA (Beerse, Belgium). The detection limit with this assay for detecting a drug resistant variant was approximately 25%. The viral sequence analysis was performed for Baseline (Day 1 predose) and Day 28 samples and in the events of viral plateau or rebound. Because results from the Baseline (Day 1) sample were not available at patient enrollment, HCV genotyping for study eligibility was performed in parallel according to Versant INNO-LiPA HCV 2.0 (Innogenetics, Gent, Belgium).

Safety Assessments

Safety was evaluated on the basis of adverse events, vital signs, ECG findings, and laboratory abnormalities. Concomitant medication intake was also recorded. Prohibited medications included atypical antipsychotic agents, systemic chemotherapeutics, immunosuppressants, immunomodulators, H_2-receptor antagonists, agents potentially causing QT prolongation, and alternative medicines (e.g., St. John's Wort and milk thistle).

Endpoints and Statistical Analyses

A sample size of 15 patients per treatment arm was determined on the basis of experience with other proof-of-concept studies; no formal power or sample-size calculations were planned or undertaken.

The full efficacy analysis set included patients who had HCV genotype 1a or 1b as evaluated by NS5B sequencing/phylogenetic analysis, not Versant INNO-LiPA HCV 2.0 (Innogenetics, Gent, Belgium) alone. The primary endpoint was the proportion of patients achieving an RVR. Patients who added or switched to standard of care early were counted as failures and characterized as censored patients. The analysis set for safety included all patients who received at least one dose of study drug.

All statistical summaries and analyses were performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient Population

Between February and October of 2010, a total of 46 patients were randomized and treated in 4 European countries (Belgium, France, Germany, United Kingdom). Among the treatment arms, patients were predominately male (73% to 88%) and white (80% to 93%), and mean age ranged from 45 to 54 years (Table 1). Of the 46 patients treated, 45 patients completed Week 6 of the study (Table 2), and 42 were still on PEG-IFN/RBV at Week 24. Treatment with PEG-IFN/RBV is ongoing at the time of this report. As evaluated at Baseline with the LiPA 2.0 assay, 15 (33%) patients were HCV genotype 1a, 30 (65%) were genotype 1b, and 1 (2%) was unable to be genotyped. Upon subsequent NS5B sequencing/phylogenetic analysis, 4 patients were identified as having HCV genotypes 1e, 1l, 1e/m, and 4r (refer to supplementary table for virologic outcomes). These patients were therefore excluded from the primary efficacy analysis.

The majority of patients were genotype CT (ranging from 53% to 63%) at the *IL28B* polymorphism rs12979860. A higher percentage of patients were *IL28B* genotype CC in the tegobuvir/GS-9256/RBV arm (40%) versus the tegobuvir/GS-9256 arm (12.5%) or tegobuvir/GS-9256/PEG-IFN/RBV arm (26.7%).

Efficacy Assessments

HCV RNA

Patients in all treatment arms had an initial sharp decline in plasma HCV RNA levels during the first 48 hours of therapy (Figure 1). In the tegobuvir/GS-9256 arm, this decrease was generally maintained through Day 7, after which HCV RNA levels began to rebound, associated with the

emergence (detection) of resistance-associated variants. The addition of ribavirin to the treatment regimen increased the magnitude, extent, and duration of viral reduction; in the tegobuvir/GS-9256/RBV arm, reductions in HCV RNA levels were observed through Day 14 and were generally maintained through Day 28. The addition of PEG-IFN alfa-2a had a similar additive effect; in the tegobuvir/GS-9256/PEG-IFN/RBV arm, reductions in HCV RNA levels were observed through Day 28. The association of *IL28B* genotype and initial antiviral response was variable, with a trend towards a greater magnitude of HCV RNA reductions in *IL28B*-CC patients. No differences in mean maximal HCV RNA reduction by HCV subtype (1a or 1b) were observed. Virologic responses in the four patients infected with other HCV-1-subtypes are presented in the Supplementary table. In each case, HCV RNA reductions from Baseline during randomized therapy ranged from -0.75 to -2.84 $\log_{10}$ IU/mL. Following the switch to PEG-IFN/RBV, continued viral load reductions were observed ranging from -2.98 to -5.23 $\log_{10}$ IU/mL from Baseline by Week 6.

In the primary efficacy analysis, a greater percentage of patients achieved RVR after receiving tegobuvir/GS-9256 in combination with RBV (38%) compared with tegobuvir/GS-9256 alone (7%) (Table 3). All patients (14/14) receiving tegobuvir/GS-9256 in combination with PEG-IFN/RBV achieved RVR.

Excluding datapoints following the early introduction of PEG-IFN/RBV, the median (Q1, Q3) maximal reduction in HCV RNA was highest for patients receiving tegobuvir/GS-9256/PEG-IFN/RBV, -5.7 (-5.9, -5.5) $\log_{10}$ IU/mL, versus -5.1 (-5.3, -4.4) for tegobuvir/GS-9256/RBV, and -4.1 (-4.4, -2.9) for tegobuvir/GS-9256 alone.

Viral breakthrough was most common in the tegobuvir/GS-9256 arm, where the majority of patients (80%) started standard of care with PEG-IFN and RBV prior to Day 28. Although RBV decreased and delayed breakthrough, in the tegobuvir/GS-9256/RBV arm, 31% started standard of care early because of the observed increases in HCV RNA at or prior to Day 28. None of the patients receiving tegobuvir/GS-9256/PEG-IFN/RBV experienced viral plateau or rebound through Day 28. For patients in the tegobuvir/GS-9256 arm who had an increase in HCV RNA levels observed at Day 14 or Day 21, HCV RNA levels declined again by Day 28 after initiating PEG-IFN and RBV.

Among the patients who either did not experience early response or had viral rebound, several achieved RVR after starting either PEG-IFN or PEG-IFN and RBV early. Two patients in the tegobuvir/GS-9256 arm who started PEG-IFN and RBV early achieved RVR, as did 3 patients in the tegobuvir/GS-9256/RBV arm who started PEG-IFN early (Table 3).

Viral suppression continued through 24 weeks for many patients, especially those initially assigned to therapy with RBV (arm 2) or PEG-IFN/RBV (arm 3). All patients (13/13) receiving tegobuvir/GS-9256/RBV initially and continuing on PEG-IFN/RBV had HCV RNA <25 IU/mL at Week 24; 13 of 14 (94%) of patients assigned to tegobuvir/GS-9256/PEG-IFN/RBV and continuing on PEG-IFN/RBV maintained HCV RNA <25 IU/mL at Week 24.

Resistance Mutants

Population sequence analysis was performed in 15 rebound patients whose HCV RNA was

≥1000 IU/mL at the time of rebound. In 14/15 of these patients, mutations were detected in both the NS3 and NS5B genes (Table 4), and the mutations are known to cause lowered antiviral susceptibility to GS-9256 and tegobuvir in vitro. The remaining patient had only the NS3 R155K mutation detected. The dual therapy arm with tegobuvir/GS-9256 had the highest rate of detected mutations. In HCV genotype 1a patients, NS3 R155K and NS5B Y448H were the most common mutations selected; in HCV genotype 1b patients, NS3 D168E/V and NS5B Y448H were most common. In 4 of 5 patients with HCV genotype 1b with either NS5B C316N or C445F at Baseline, the viral rebound was associated with the emergence of NS3 D168E/V/H/L mutations without the selection of additional NS5B mutations.

Safety Assessments

Tegobuvir/GS-9256 was well tolerated, and most adverse events were mild to moderate in severity. Adverse events were more common in the tegobuvir/GS-9256/PEG-IFN/RBV treatment arm, with events consistent with those reported for IFNs (Table 5). Two serious adverse events were reported during the study: infective bursitis and vasovagal collapse. Both were considered by the investigator to be unrelated to study drug. One patient, in the tegobuvir/GS-9256 arm, discontinued tegobuvir and GS-9256 on Day 22 because of fatigue. This patient had initiated PEG-IFN and RBV on Day 19 but continued with PEG-IFN/RBV after discontinuing tegobuvir and GS-9256. The patient completed study participation to Week 6 but was later lost to follow-up.

No Grade 4 adverse events or lab abnormalities were observed. Reductions in hemoglobin and neutrophils were consistent with those associated with RBV and PEG-IFN alfa-2a

administration. Transient bilirubin elevations, primarily Grades 1 and 2, occurred in all treatment groups but were generally indirect and not associated with elevations in ALT or AST. Overall, while taking assigned therapy, 9 patients experienced Grade 1 elevations in total bilirubin, 4 had Grade 2 elevations, and 2 had Grade 3 elevations (3.2 mg/dL maximum). The overall incidence of hyperbilirubinemia (Grade 1 and above) in treated patients was 4/16 (25%), 5/15 (33%) and 6/15 (40%) in the tegobuvir/GS-9256, tegobuvir/GS-9256/RBV, and tegobuvir/GS-9256/PEG-IFN/RBV arms, respectively.

No clinically significant impact on cardiac repolarization (prolongation of the QTcF interval >60 msec change from Baseline or increase to >500 msec) was observed for the tegobuvir/GS-9256 combination following multiple dosing.

DISCUSSION

This study of tegobuvir plus GS-9256 is the first to explore the additional contribution of RBV to a 2-drug oral DAA regimen during a limited 4-week dosing period. The two oral DAAs exhibited additive antiviral activity: tegobuvir 40 mg BID monotherapy induces median HCV RNA reductions of 1.5 $\log_{10}$ (21), whereas GS-9256 monotherapy induces median HCV RNA reductions of 2.7 $\log_{10}$ (22), and in this study, the combination of the two drugs resulted in median HCV RNA reductions of 4.1 $\log_{10}$. The additive antiviral effect we observed is consistent with the additive interaction of tegobuvir and GS-9256 in the replicon system (Gilead Sciences, unpublished data). Even with the additive antiviral activity of these 2 classes of HCV inhibitors, viral breakthrough was common, especially in patients with genotype 1a HCV infection. The addition of RBV enhanced antiviral activity, delayed the emergence/selection of resistance, and resulted in a greater proportion of patients achieving an RVR. Adding PEG-IFN plus RBV to the 2 antiviral agents further enhanced viral suppression, with 100% of patients reaching RVR. In the majority of patients, treatment with PEG-IFN plus RBV after 28 days maintained HCV RNA suppression to <25 IU/mL up to Week 24. Virologic response data beyond Week 24 is awaited. Four patients with non-1 HCV genotype were treated in the study. The virologic responses in these patients were sub-optimal. Three patients discontinued randomized treatment and initiated PEG-IFN/RBV. The fourth patient, assigned to tegobuvir/GS-9256/RBV/PEG-IFN, remained on assigned therapy for 28 days per protocol. The virologic response rates observed in these patients are consistent with the specificity of tegobuvir and GS-9256 for HCV genotypes 1a and 1b.

A small imbalance in the proportion of *IL28B*-CC patients was observed across groups (Figure 1). The small sample size limits interpretation; however, it is possible that the apparent impact of

ribavirin in reducing viral load and suppressing resistance could be partially related to a relatively high proportion of *IL28B*-CC patients in the tegobuvir/GS-9256/RBV arm.

Most adverse events occurring in the tegobuvir/GS-9256 arm were mild to moderate in severity. Although the number of adverse events was highest in the tegobuvir/GS-9256/PEG-IFN/RBV treatment arm, these events were consistent with those associated with IFNs. Transient bilirubin elevations were also observed, consistent with the known class effects of NS3 serine protease inhibitors on bilirubin transporters, such as organic anion transporting polypeptide 1B1 (OATPB1), with resulting increase in unconjugated bilirubin (25,26).

The emergence of resistance-associated variants with non-nucleoside NS5B or NS3 inhibitors has been described in other studies and is consistent with the lower genetic barrier against resistance for non-nucleoside analogs and NS3 protease inhibitors (for review see [13]). The high rate of emergence of the protease resistant variant R155K in genotype 1a, but not in genotype 1b infected patients has also been described previously with this class of agents, and is reflective of single-nucleotide change that is required for the development of resistance in genotype 1a patients, but two-nucleotide changes in the majority of genotype 1b patients (27). It is of note that single-nucleotide change is required for both mutations at NS3 R155 and D168 in genotype 1a patients; however, a mutation at only R155, and not D168, was identified in genotype 1a patients by population sequencing. The R155 nucleotide sequence may be more susceptible to change than D168, or the R155K may be more fit than mutations at D168 in this genotype. Mutations at D168 were commonly selected in genotype 1b–infected patients, consistent with genotype 1b replicon data.

The Y448H mutation observed with tegobuvir has been observed frequently in monotherapy studies and is consistent with in vitro mutational data indicating the tegobuvir interaction likely involves the β-hairpin in the thumb sub-domain of the NS5B polymerase (20). In the present study, 7/8 genotype 1a patients developed dual-class resistance: R155K against the NS3 protease inhibitor and Y448H for the NS5B polymerase inhibitor. However, with the addition of RBV, the incidence of resistance was significantly reduced, with none of genotype 1a patients (n=3) exhibiting drug resistant variants. While RBV has been shown to have modest antiviral activity (28), its ability to significantly reduce development of resistance highlights a distinct mechanism of action. This may indicate a broader mutational effect of RBV on viral fitness, which renders a proportion of virus non-infectious, regardless of oral antiviral resistance mutations. Although similar trials have been reported (29), the present study is the first report of an interferon-free NS5B polymerase/NS3 protease combination both with and without RBV, thus allowing for prospective evaluation of the contribution of RBV to the antiviral effect of the regimen.

The emergence of various classes of DAAs for treating chronic HCV infection has enabled evaluation of multiple combination approaches either with or without PEG-IFN and RBV (19,30,31). Specifically, the strategy of quadruple therapy with a non-nucleoside analog, a protease inhibitor, and PEG-IFN and RBV has been supported by results from a recently reported study in which the non-nucleoside NS5B polymerase inhibitor VX-222, telaprevir, and PEG-IFN/RBV resulted in RVR in 51/59 (86%) of treatment-naïve patients (19), which is higher than those reported with telaprevir and PEG-IFN/RBV (6,9). In this study, 100% of patients receiving quadruple therapy achieved RVR at Week 4, and a high proportion of patients (71%)

had HCV RNA below 25 IU/mL at Week 2. The rapidity of viral clearance in patients with quadruple therapy provides a basis for examining response-guided therapy in which total duration of treatment could be fewer than 24 weeks. To explore this possibility, phase 2 combination studies of tegobuvir plus GS-9256 with PEG-IFN and RBV are underway.

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Table 1. Patient Demographic and Baseline Disease Characteristics

	Tegobuvir/ GS-9256 (n = 16)	Tegobuvir/ GS-9256/RBV (n = 15)	Tegobuvir/ GS-9256/ PEG-IFN/RBV (n = 15)
Age, mean (SD) yr	48 (10.0)	45 (12.7)	54 (9.0)
Male sex	14 (87.5%)	11 (73.3%)	12 (80.0%)
Race			
White	13 (81.3%)	12 (80.0%)	14 (93.3%)
Black	2 (12.5%)	2 (13.3%)	1 (6.7%)
Asian	1 (6.3%)	0	0
Other	0	1 (6.7%)	0
Body Mass Index (kg/m^2)			
Mean (SD)	27.0 (3.13)	26.3 (4.58)	25.6 (3.42)
Baseline HCV RNA			
Mean (SD) $\log_{10}$ IU/mL	6.18 (0.685)	6.29 (0.440)	6.50 (0.779)
Median (Q1, Q3) $\log_{10}$ IU/mL	6.17 (5.57, 6.71)	6.34 (5.96, 6.50)	6.68 (6.45, 6.88)
≥ 800,000 IU/mL, n (%)	10 (62.5%)	13 (86.7%)	13 (86.7%)
Baseline HCV genotype (LipA 2.0)[a]			
1a	8 (50.0%)	3 (20.0%)	4 (26.7%)
1b	8 (50.0%)	12 (80.0%)	10 (66.7%)
Unable to genotype	0	0	1 (6.7%)
IL28B genotype			
CC	2 (12.5%)	6 (40.0%)	4 (26.7%)
CT	10 (62.5%)	8 (53.3%)	9 (60.0%)
TT	4 (25.0%)	1 (6.7%)	2 (13.3%)
ALT IU/mL			
Mean (SD)	88.4 (51.13)	66.7 (25.11)	73.1 (38.28)
Metavir Fibrosis Score, n (%)			
F0	0 (0)	2 (13.3)	0 (0)
F1	9 (56.3)	6 (40)	7 (46.7)
F2	3 (18.8)	5 (33.3)	6 (40)
F3	4 (25)	2 (13.3)	2 (13.3)

[a]Four patients were later identified by NS5B sequencing as having HCV genotypes 1e, 1l, 1e/m and 4r.

Table 2. Patient Disposition Throughout the Study

	Randomized (n=46)		
	Treated (n=46)		
	Tegobuvir/ GS-9256 (n=16)	**Tegobuvir/ GS-9256/RBV (n=15)**	**Tegobuvir/ GS-9256/ PEG-IFN/RBV (n=15)**
Day 28			
Completed assigned treatment	3	9	15
Completed assigned treatment with overlapping PEG-IFN/RBV or PEG-IFN	9	4	0
Discontinued tegobuvir and GS-9256 early	4	2	0
Week 6			
Completed PEG-IFN/RBV	15	15	15
Discontinued PEG-IFN/RBV	1	0	0
Week 12			
Completed PEG-IFN/RBV	15	15	15
Discontinued PEG-IFN/RBV	1	0	0
Week 24			
Completed PEG-IFN/RBV	13	15	14
Discontinued PEG-IFN/RBV	3	0	1

Table 3. Virologic Response Among Patients With HCV Genotype 1a or 1b

	Tegobuvir/ GS-9256 (n = 15)	Tegobuvir/ GS-9256/RBV (n = 13)	Tegobuvir/GS-9256/ PEG-IFN/RBV (n = 14)
HCV RNA, IU/mL			
Day 14			
< 25	1/15 (7%)	6/13 (46%)	10/14 (71%)
Day 28 (RVR)			
< 25	1/15 (7%)	5/13 (38%)	14/14 (100%)
< 25 (uncensored population[a])	3/15 (20%)	8/13 (62%)	14/14 (100%)
Week 12			
< 25	12/15 (80%)	13/13 (100%)	14/14 (100%)
Week 24			
< 25	10/15 (67%)	13/13 (100%)	13/14[b] (94%)
Median (Q1,Q3) maximal HCV RNA change from baseline, $\log_{10}$ IU/mL	-4.1 (-4.4, -2.9)	-5.1 (-5.3, -4.4)	-5.7 (-5.9, -5.5)

[a]Includes patients who initiated standard of care with PEG-IFN/RBV prior to 28 days.
[b]One patient experienced breakthrough after Week 12.
RBV, ribavirin; PEG-IFN, peginterferon; RVR, rapid virologic response.

Table 4. Resistance Mutation Detection

	Tegobuvir/ GS-9256		Tegobuvir/GS-9256/ RBV	
HCV genotype	1a (n=8)	1b (n=7)	1a (n=3)	1b (n=10)
Mutations in NS3[a] + NS5B[b]				
R155K + Y448H	7			
R155K	1			
D168E/V + Y448H		2		
D168H/L/V + C/F445F		1		
R155K/Q, D168E/D + Y448H, C316N (BL)				1
D168E/V + C316N (BL)[c]		2		1
Total, n (%)	8 (100)	5 (71)	0	2 (20)

[a]NS3 mutations: R155K/Q, D168H/L/E/V
[b]NS5B mutations: Y448H, C316N, C/F445F
[c]C316N (BL): C316N mutation in NS5B that occurred at Baseline and during treatment.

Table 5. Most Common Adverse Events in 28 Days of Therapy[a]

	Part A			Part B
	Tegobuvir/ GS-9256 (n = 16)	**Tegobuvir/ GS-9256/ RBV (n = 15)**	**Tegobuvir/ GS-9256/ PEG-IFN/RBV[b] (n = 16)**	**Tegobuvir/ GS-9256/ PEG-IFN/RBV (n = 15)**
Number of Patients Experiencing any Treatment Emergent Adverse Event	8 (50%)	14 (93%)	13 (81%)	15 (100%)
Blood and lymphatic system disorders				
Anaemia	0	0	0	2 (13%)
Eye disorders				
Eye pain	0	0	0	2 (13%)
Gastrointestinal disorders				
Diarrhea	3 (19%)	3 (20%)	1 (6%)	6 (40%)
Nausea	2 (13%)	3 (20%)	1 (6%)	6 (40%)
Abdominal pain	0	1 (7%)	0	2 (13%)
Vomiting	0	0	0	2 (13%)
General disorders				
Influenza-like illness	0	0	7 (44%)	12 (80%)
Fatigue	1 (6%)	5 (33%)	2 (13%)	5 (33%)
Asthenia	0	2 (13%)	2 (13%)	2 (13%)
Chills	0	1 (7%)	2 (13%)	1 (7%)
Irritability	0	0	2 (13%)	0
Metabolism and nutrition disorders				
Anorexia	0	0	0	2 (13%)
Decreased appetite	0	1 (7%)	0	2 (13%)
Musculoskeletal and connective tissue disorders				
Myalgia	0	1 (7%)	6 (38%)	3 (20%)
Nervous system disorders				
Headache	5 (31%)	7 (47%)	2 (13%)	6 (40%)
Disturbance in attention	1 (6%)	2 (13%)	1 (6%)	0
Psychiatric disorders				
Insomnia	0	3 (20%)	1 (6%)	2 (13%)
Sleep disorder	0	0	0	2 (13%)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	0	1 (7%)	2 (13%)	2 (13%)
Cough	0	0	0	3 (20%)
Skin and subcutaneous tissue disorders				
Dry skin	0	2 (13%)	0	0
Pruritus	1 (6%)	3 (20%)	0	1 (7%)
Erythema	1 (6%)	0	0	2 (13%)

[a]Events occurred in at least 2 patients per treatment regimen.
[b]Patients who initiated PEG-IFN and RBV prior to 28 days of assigned therapy.

SUPPLEMENTARY TABLE: HCV RNA BY VISIT FOR NON-1 GENOTYPES

HCV Genotype	Arm[a]	HCV RNA (log_{10} IU/mL)											
				Study Day									Study Week
		Screen	Baseline	1	3	5	7	11	14	18	21	28	6
1e	1	5.47	5.58	5.79	5.17	5.17	4.83	-	-	-	-	-	2.15[b]
1l	2	5.44	5.41	5.20	3.26	3.31	3.58	-	-	-	-	-	2.43[b]
1e/m	2	6.42	6.36	6.22	4.83	4.03	4.04	-	-	-	-	-	1.38[b]
4r	3	-	6.61	6.49	5.80	5.56	5.26	5.28	5.35	4.58	4.31	3.77	1.38[b]

[a]Arm 1 = tegobuvir/GS-9256; Arm 2 = tegobuvir/GS-9256/RBV; Arm 3 = tegobuvir/GS-9256/RBV/PEG-IFN
[b]Denotes first HCV RNA during standard of care (PEG-IFN/RBV)

FIGURE LEGENDS

Figure 1. **HCV RNA Levels in Individual Patients With Confirmed Genotype 1a or 1b HCV Through Day 28.** (A) Tegobuvir 40 mg BID and GS-9256 75 mg BID. (B) Tegobuvir 40 mg BID and GS-9256 75 mg BID plus RBV. (C) Tegobuvir 40 mg BID and GS-9256 75 mg BID plus PEG-IFN and RBV. Antiviral activity was expressed as the $\log_{10}$ change from baseline in HCV RNA. Plots ending prior to 28 days indicate early addition of peginterferon alfa-2a (PEG-IFN) or ribavirin (RBV) therapy or early cessation of GS-9256 and tegobuvir. Color indicates *IL28B* genotype: red is CC, black is CT, and blue is TT. Dotted line indicates HCV RNA 25 IU/mL.

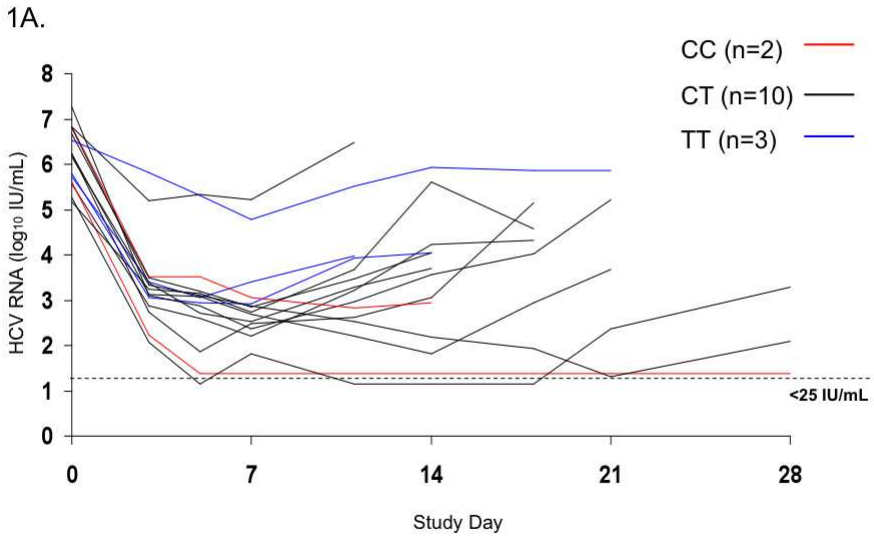

Figure 1. HCV RNA Levels in Individual Patients Through Day 28. Individual patient data for patients with confirmed genotype 1a or 1b virus was plotted for assigned therapy; data was censored after early addition of peginterferon alfa-2a (PEG-IFN) or ribavirin (RBV) therapy or early cessation of GS-9256 and tegobuvir. Color indicates IL28B genotype: red is CC, black is CT, and blue is TT. Dotted line indicates HCV RNA 25 IU/mL. (A) Tegobuvir 40 mg BID and GS-9256 75 mg BID. (B) Tegobuvir 40 mg BID and GS-9256 75 mg BID plus RBV. (C) Tegobuvir 40 mg BID and GS-9256 75 mg BID plus PEG-IFN and RBV. Antiviral activity was expressed as the log10 change from baseline in HCV RNA.
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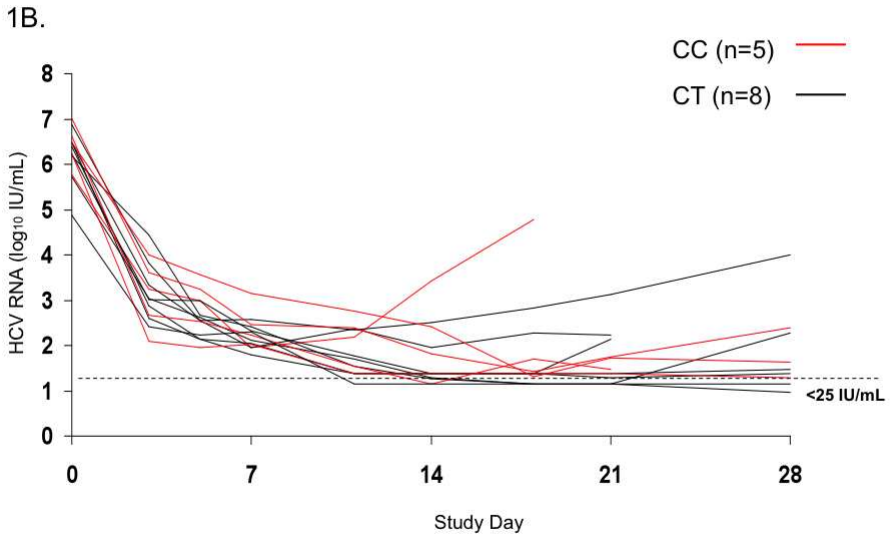

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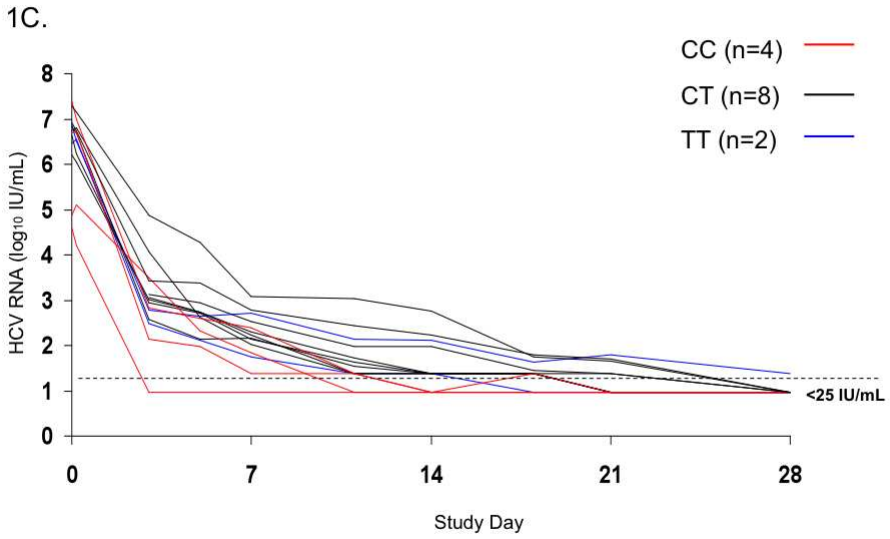

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