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Telaprevir Twice Daily Is Noninferior to Telaprevir Every 8 Hours for Patients With Chronic Hepatitis C

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BACKGROUND & AIMS: We performed an open-label, multicenter, phase 3 study of the safety and efficacy of twice-daily telaprevir in treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 infection, including those with cirrhosis. **METHODS:** Patients were randomly assigned to groups treated with telaprevir 1125 mg twice daily or 750 mg every 8 hours plus peginterferon alfa-2a and ribavirin for 12 weeks; patients were then treated with peginterferon alfa-2a and ribavirin alone for 12 weeks if their level of HCV RNA at week 4 was <25 IU/mL or for 36 weeks if their level was higher. The primary objective was to demonstrate noninferiority of telaprevir twice daily versus every 8 hours in producing a sustained virological response 12 weeks after the end of therapy (SVR12) (based on a −11% lower limit of the 95% lower confidence interval for the difference between groups). **RESULTS:** At baseline, of 740 patients, 85% had levels of HCV RNA ≥800,000 IU/mL, 28% had fibrosis (F3–F4), 14% had cirrhosis (F4), 57% were infected with HCV genotype 1a, and 71% had the non-CC *IL28B* genotype. Of patients who were treated with telaprevir twice daily, 74.3% achieved SVR12 compared with 72.8% of patients who were treated with telaprevir every 8 hours (difference in response, 1.5%; 95% confidence interval, −4.9% to 12.0%), so telaprevir twice daily is noninferior to telaprevir every 8 hours. All subgroups of patients who were treated with telaprevir twice daily versus those who were treated every 8 hours had similar rates of SVR12. The most frequent adverse events (AEs) in the telaprevir phase were fatigue (47%), pruritus (43%), anemia (42%), nausea (37%), rash (35%), and headache (26%); serious AEs were reported in 9% of patients. Rates of AEs and serious AEs were similar or slightly higher among patients treated with telaprevir every 8 hours. **CONCLUSIONS:** Based on a phase 3 trial, telaprevir twice daily is noninferior to every 8 hours in producing SVR12, with similar levels of safety and tolerability. These results support use of telaprevir twice daily in patients with chronic HCV genotype 1 infection, including those with cirrhosis. ClinicalTrials.gov, Number: NCT01241760.

Keywords: OPTIMIZE; Clinical Trial; Protease Inhibitor; DAA.

The NS3/4A protease inhibitor telaprevir (TVR), in combination with peginterferon (PEG-IFN) alfa-2a and ribavirin (RBV), is approved at a dose of 750 mg every 8 hours for the treatment of genotype 1 (G1) chronic hepatitis C virus (HCV) infection in adults with compensated liver disease who are treatment naive or have previously received interferon-based treatment.[1,2] Reducing the frequency of TVR dosing to twice daily to coincide with RBV dosing and to allow for easier coordination with mealtimes (to optimize absorption) may be beneficial for patient adherence and treatment success.

Twice-daily dosing of TVR was previously explored in the phase 2 C208 clinical study (NCT00528528), which evaluated the efficacy, safety, and pharmacokinetics (PK) of 12 weeks of treatment with TVR 1125 mg every 12 hours or TVR 750 mg every 8 hours in combination with a maximum of 48 weeks of treatment with PEG-IFN alfa-2a/RBV or PEG-IFN alfa-2b/RBV in 161 treatment-naive, predominantly noncirrhotic patients.[3] In this study, sustained virological response (SVR) rates were similar between groups, with >80% of patients achieving SVR regardless of the dosing frequency of TVR. Viral breakthrough and relapse were infrequent in all treatment groups, with no statistically significant differences observed between dosing of

Abbreviations used in this paper: **AE, adverse event; $AUC_{24,ss}$, area under the plasma concentration-time curve from time of administration up to 24 hours; CI, confidence interval; C_{max}, maximum concentration; $C_{max,ss}$, maximum steady-state concentration; $C_{trough,ss}$, predose steady-state concentration; e-diary, electronic diary; G1, genotype 1; HCV, hepatitis C virus; ITT, intent-to-treat; PEG-IFN, peginterferon; PK, pharmacokinetics; RBV, ribavirin; RVR, rapid virological response; SSC, special search category; SVR, sustained virological response; TVR, telaprevir.**

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TVR every 8 hours or every 12 hours. The PK analysis showed a higher maximum concentration (C_{max}) and lower predose concentration when TVR was given every 12 hours compared with every 8 hours, but this difference did not translate into any differences in clinical outcome. In addition, the safety profile was similar in both treatment groups. However, given the small number of patients per arm, confirmation of these results was warranted in a larger clinical trial.

OPTIMIZE is the first phase 3 trial to investigate the use of TVR twice daily versus every 8 hours in combination with PEG-IFN/RBV. Here we present findings on the efficacy and safety of the 2 dosing regimens in treatment-naive patients with G1 HCV, including patients with cirrhosis.

Patients and Methods

Patients

Patients were enrolled at 125 international sites. The study was initiated on November 15, 2010, and completed on November 28, 2012. Eligible patients were 18 to 70 years of age and treatment naive, with HCV RNA levels >1000 IU/mL and evidence of chronic HCV infection confirmed by detectable HCV RNA >6 months before the screening visit or by histological diagnosis based on liver biopsy. All patients had a documented liver biopsy <2 years before screening or had a biopsy performed within the screening period. Patients were excluded if they had an HCV genotype other than 1 or if they had received prior HCV treatment. Patients were not eligible if they had decompensated liver disease, hepatocellular carcinoma, or significant liver disease in addition to hepatitis C, including drug- or alcohol-related cirrhosis.

Study Design

OPTIMIZE was a randomized, open-label, multicenter, phase 3 study comparing the efficacy, safety, and tolerability of TVR 1125 mg twice daily versus TVR 750 mg every 8 hours, each in combination with PEG-IFN/RBV (NCT01241760). The study consisted of a screening period of approximately 4 weeks, a treatment phase of 24 or 48 weeks, and a follow-up period of at least 24 weeks. Written informed consent was obtained from all study participants. The study protocol was reviewed and approved by the appropriate review boards or institutional ethics committees and health authorities. The study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and applicable regulatory requirements.

The primary study objective was to establish noninferiority in SVR12 (defined as plasma HCV RNA levels <25 IU/mL 12 weeks after the last planned dose of study drug) with dosing of TVR twice daily compared with every 8 hours. The secondary objectives of the study were to evaluate the effect of *IL28B* genotype and liver fibrosis stage on viral response and to evaluate the tolerability and safety of TVR when administered twice daily or every 8 hours. Other secondary objectives included evaluating the PK of TVR, PEG-IFN, and RBV and to investigate PK-pharmacodynamic relationships for safety and efficacy. Changes from baseline in the amino acid sequence of the HCV NS3/4A region were also assessed.

Patients were randomized (1:1) to receive TVR twice daily or every 8 hours and were stratified according to liver fibrosis stage and *IL28B* rs12979860 genotype CC, CT, or TT.[4–6] Randomization was performed using a central, computer-generated schedule prepared under supervision of the sponsor before the study. An interactive telephone or Internet system assigned a unique code that dictated the treatment assignment and matching study drug kit for the patient. Fibrosis stage was assessed by liver biopsy and graded locally as no/mild fibrosis and portal fibrosis (METAVIR F0–F2; Ishak score ≤3) or bridging fibrosis and cirrhosis (METAVIR F3–F4; Ishak score ≥4).[7]

All patients received 12 weeks of treatment with TVR twice daily or every 8 hours, each in combination with PEG-IFN/RBV. TVR was administered orally at a dose of either 750 mg every 8 hours or 1125 mg twice daily (with a time window of 10–14 hours between twice-daily drug intake). The dosage of PEG-IFN was 180 μg/wk, and the dosage of RBV was 1000 mg/day in patients weighing <75 kg or 1200 mg/day in patients weighing ≥75 kg. Patients assigned to the TVR twice daily group took RBV with their dose of TVR. Patients assigned to TVR every 8 hours could take RBV with 2 of the 3 daily doses of TVR, with the first dose always to be taken with the morning dose of TVR. At week 12, TVR dosing ended and patients continued on standard PEG-IFN/RBV treatment. If a patient achieved a rapid virological response (RVR; HCV RNA <25 IU/mL, target not detected at week 4 of treatment), the total treatment duration was 24 weeks; otherwise, the total treatment duration was 48 weeks. An electronic diary (e-diary), completed by the patients, captured the amount and timing of TVR dosing relative to the prescribed regimen.

Futility rules were applied to all patients to minimize the risk of viral resistance in patients without an adequate antiviral response. HCV RNA results were monitored, and all treatment was stopped if HCV RNA levels were >1000 IU/mL at week 4 or ≥25 IU/mL at weeks 12, 24, 32, or 40.

TVR was permanently discontinued for any grade 4 adverse event (AE) or toxicity that was considered at least possibly related to TVR or for any patient experiencing a severe skin reaction. TVR was not restarted once discontinued due to an AE or toxicity considered at least possibly related to TVR. RBV dosing, including modifications to manage anemia, followed local prescribing instructions. If RBV was permanently discontinued for the management of anemia, TVR was also permanently discontinued. RBV could be restarted as per the dosing modification guidelines.[8]

Study Evaluations and Statistical Methods

Efficacy assessments and end points. Blood samples for quantification of HCV RNA were obtained during screening; at day 1 predose (baseline); at weeks 4, 8, 12, 24, 32, 40, and 48 or time of discontinuation; and during follow-up. Plasma HCV RNA values were quantified using the COBAS TaqMan HCV test (version 2.0; lower limit of quantification, 25 IU/mL) using the high pure system method of extraction. Values below the lower limit of quantification were reported as <25 IU/mL detectable if a signal was detected or <25 IU/mL target not detected if no target was detected.

The intent-to-treat population (ITT) included all randomized patients who received at least one dose of TVR, irrespective of protocol compliance. The ITT population was the primary population for the efficacy analyses, including the evaluation of noninferiority. On-treatment virological failure was defined as patients who met a virological stopping rule or experienced viral breakthrough (>1-log increase in HCV RNA level from the nadir value or HCV RNA level >100 IU/mL in patients whose HCV RNA

level had previously become <25 IU/mL during treatment). Analysis of the primary end point was performed when patients had either completed the follow-up visit 12 weeks after the last planned dose of study drug or had discontinued earlier ($SVR12_{planned}$) and was conducted using a snapshot approach (SVR assessment based on the last HCV RNA value) in the week 12 follow-up visit window. Relapse was defined as all non-SVR12 patients who had an HCV RNA level <25 IU/mL at the end of treatment but whose HCV RNA levels were ≥25 IU/mL during follow-up. In addition to the ITT population, supportive efficacy analyses were also performed on the per-protocol population, which was all randomized patients who received at least one dose of study medication without any major protocol deviation that could significantly affect efficacy. Major protocol deviations included patients not meeting the selection criteria, wrong treatment or incorrect dose, and patients receiving disallowed concomitant medication.

Noninferiority assessment was conducted using a logistic regression model including *IL28B* genotype, baseline liver fibrosis stage, and their interaction and baseline HCV RNA level as covariates. Noninferiority was confirmed if the lower limit of the 95% confidence interval (CI) of the difference between TVR twice daily and every 8 hours was greater than −11%. The noninferiority margin was prespecified using available meta-analysis data and was determined based on both statistical and clinical considerations and followed standard methodology endorsed by regulatory agencies. The pooled SVR rate with TVR every 8 hours/PEG-IFN and RBV in 3 previous phase 2 and 3 randomized, placebo-controlled studies[9–11] was 72% and the overall effect size versus placebo was 28%, with a lower 95% CI of 23%. To be conservative, the lower CI was used and the margin was further reduced to account for potential loss of effect in this study. Only half of the statistical margin was retained using conservative clinical judgment, setting the clinical margin at 11.5%, and giving a final noninferiority margin of 11%. A sample size of 704 patients, including 352 patients in each treatment group, was considered sufficient for showing noninferiority of TVR twice-daily dosing. Assuming an expected SVR12 rate of 72% in each group and a noninferiority margin of −11%, this sample size provided 90% power to reject the inferiority hypothesis.

Secondary efficacy variables included the proportion of patients who achieved RVR, achieved SVR at week 24, experienced a relapse, and experienced on-treatment virological failure. For virological responses, data were analyzed without imputation ("observed" analyses) and using a noncompleter equals failure (NC = F) imputation. Intermittent missing values were imputed as a "response" if the immediate preceding and following visits showed a response and as "no response" otherwise. If any study drug was prematurely discontinued due to virological failure, "no response" was imputed. If any study drug was prematurely discontinued for another reason (ie, not related to virological failure), missing data were marked as "missing for another reason." However, missing HCV RNA assessments at the SVR12 visit were not imputed and were considered treatment failures (no SVR). Additional sensitivity analyses were also performed to compare virological response rates (Supplementary Methods).

Descriptive statistics of treatment adherence and the number of patients in each adherence category were reported for TVR dosing frequency, timing of intake, and intake based on the e-diary. This diary captured the amount and timing of TVR dosing relative to the prescribed regimen. Additionally, adherence to dosing of TVR and PEG-IFN/RBV was measured by dispensed versus returned medications (pill count). Adherence was expressed as the percentage of prescribed doses during the treatment period and categorized by defined thresholds. The e-diary analysis was performed using the ITT population, with missing entries considered 0% adherent. Observed data analyses were also performed.

The 95% CIs stated in the report were part of the prespecified statistical analysis and provided an informal comparison within the framework of noninferiority. *P* values stated in the report for the secondary efficacy variables and subgroup analyses were from post hoc statistical testing.

Virological, safety, and PK assessments. HCV NS3/4A population sequencing was performed on plasma samples at baseline and in the case of virological failure or relapse. The frequency of TVR-resistant variants is presented descriptively.

Individual empirical Bayesian estimates of TVR PK parameters were determined using a population PK modeling approach. Blood samples (sparse sampling) were taken at sites with the capabilities for PK sampling at weeks 2, 4, 6, and 8 to determine concentrations of TVR, PEG-IFN, and RBV for adherence assessments as well as for PK evaluations. An additional sample was collected for analysis of TVR if a patient discontinued TVR due to an AE and was to be taken as close as possible to the time of discontinuation. PK-pharmacodynamic relationships for both safety and efficacy were evaluated. No formal PK analysis was conducted for RBV and PEG-IFN, although descriptive statistics were calculated for each time point.

An independent data and safety monitoring board was used throughout the study. The ITT population was used for the safety analysis. Safety data were summarized for the TVR treatment phase (from the date of first intake of study drug to the date of last TVR intake plus 1 day) and for the overall treatment phase (from the date of first intake of study drug to the date of last intake of study drug plus 30 days). Special search categories (SSCs) were created by grouping AE terms representing similar medical concepts from the same or different body systems to ensure that each patient was counted only once. The grade and severity of rash events were assigned using criteria previously described.[1,2,12]

Anemia as an AE was graded by the investigator with guidance on grading hemoglobin levels using the Division of AIDS table for grading the severity of AEs. In addition, hemoglobin levels were measured throughout the trial, such that both hemoglobin levels and the AE of anemia were analyzed separately.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patient Disposition and Baseline Characteristics

A total of 884 patients were screened. Of these, 740 patients were randomized and treated with TVR twice daily (n = 369) or every 8 hours (n = 371) (Supplementary Figure 1). Overall, 90% of patients completed the study. Reasons for discontinuation were primarily loss to follow-up (5%) or withdrawal of consent (4%) (Supplementary Figure 1).

The demographic and baseline disease characteristics are shown in Table 1. The baseline characteristics were

Table 1. Baseline Demographics and Disease Characteristics

	TVR twice daily (n = 369)	TVR every 8 hours (n = 371)	All patients (N = 740)
Age (*y*), mean (SD)	48 (11)	48 (11)	48 (11)
Body mass index (kg/m^2), mean (SD)	26 (5)	27 (5)	27 (5)
Male sex	209 (57)	235 (63)	444 (60)
Race			
Asian	10 (3)	6 (2)	16 (2)
Black	20 (5)	15 (4)	35 (5)
Multiple	6 (2)	3 (0.8)	9 (1)
White	333 (90)	347 (94)	680 (92)
Region			
Europe	179 (49)	192 (52)	371 (50)
North America	137 (37)	126 (34)	263 (36)
Baseline $\log_{10}$ HCV RNA (*IU/mL*),[a] mean IU/mL (SD)	6.48 (0.7)	6.49 (0.7)	6.49 (0.7)
Baseline HCV RNA[a]			
<800,000 IU/mL	57 (15)	54 (15)	111 (15)
≥800,000 IU/mL	312 (85)	317 (85)	629 (85)
HCV genotype subtype[b]			
1a	210 (57)	209 (56)	419 (57)
1b	157 (43)	160 (43)	317 (43)
IL28B subtype[c]			
CC	105 (28)	106 (29)	211 (29)
CT	206 (56)	208 (56)	414 (56)
TT	58 (16)	57 (15)	115 (16)
Baseline fibrosis stage[c]			
No or minimal fibrosis (F0/1)	172 (47)	177 (48)	349 (47)
Portal fibrosis (F2)	95 (26)	85 (23)	180 (24)
Bridging fibrosis (F3)	48 (13)	59 (16)	107 (15)
Cirrhosis (F4)	54 (15)	49 (13)	103 (14)
Other[d]	0	1 (0.3)	1 (0.1)

NOTE. Values are expressed as n (%) unless otherwise noted.
SVR12, sustained virological response defined as plasma HCV RNA levels <25 IU/mL at 12 weeks after the last planned dose of study drug.
[a]HCV RNA levels were measured with the use of COBAS TaqMan HCV assay (version 2.0; Roche, Basel, Switzerland). Lower limit of quantification was 25 IU/mL.
[b]HCV genotype and subtype were determined using NS3 assay.
[c]Stratification factor. For fibrosis stage, stratification factors were F0–2 versus F3–4.
[d]One patient treated with TVR every 8 hours had no biopsy result available at baseline. This patient's fibrosis status was therefore recorded as "other" and excluded from the efficacy analyses.

similar between the treatment groups. Of the 740 patients treated, 28% had advanced fibrosis (METAVIR F3–F4); 14% had compensated cirrhosis, 57% had G1a, and 29% had *IL28B* CC genotype. The majority of patients (92%) were white, mean age was 48 years, and mean body mass index was 27 kg/m^2. At baseline, 85% of patients had an HCV RNA level ≥800,000 IU/mL. Baseline TVR-resistant variants were uncommon (2.4% T54S, 1.5% V36L, and <0.5% V36I/M, I132V, or R155K).

Efficacy

SVR12 was 74.3% with TVR twice daily and 72.8% with TVR every 8 hours (Figure 1*A*). The adjusted difference in response between groups was 1.5% (95% CI, −4.9% to 12.0%), with the lower 95% CI (−4.9%) exceeding the noninferiority margin of −11%. Thus, noninferiority of TVR twice daily compared with every 8 hours was established. Noninferiority was also confirmed in the per-protocol population. The treatment difference and 95% CI between TVR twice daily and every 8 hours was 1.3% (−4.8% to 11.8%) based on SVR12 estimates of 76.3% and 75.1%, respectively. Results obtained for the sensitivity analyses supported the ITT and per-protocol efficacy results. The secondary end point, SVR at week 24, was achieved in 74.8% of patients treated with TVR twice daily and 72.8% of patients treated with TVR every 8 hours (see Supplementary Results). Relapse rates were similar between those treated with TVR twice daily (7.7%) and every 8 hours (6.5%).

Virological response by *IL28B* genotype showed that the efficacy of TVR twice daily versus every 8 hours was similar regardless of *IL28B* genotype (Figure 1*B*). SVR12 was higher in patients with CC versus non-CC genotypes (90% vs 67%, respectively; $P < .0001$). In a post hoc analysis, *IL28B* genotype was strongly associated with SVR12 after adjustment for other baseline factors, including fibrosis stage (odds ratio, 5.00; 95% CI, 3.01–8.30; $P < .0001$). Virological response rates for TVR dosing twice daily and every 8 hours were also generally comparable across fibrosis stage subgroups (Figure 1*C*). In patients without cirrhosis, SVR12 rates were 78% (245/315) and 77% (246/321) for TVR twice daily and every 8 hours, respectively; in patients with cirrhosis,

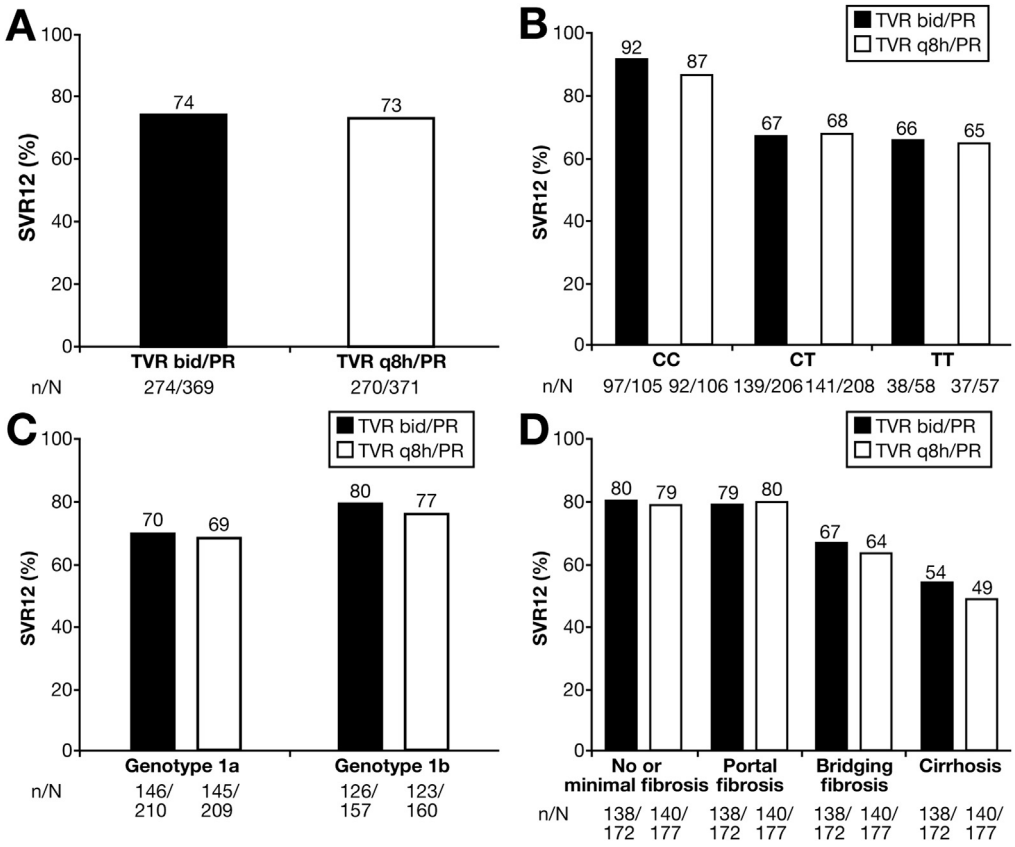
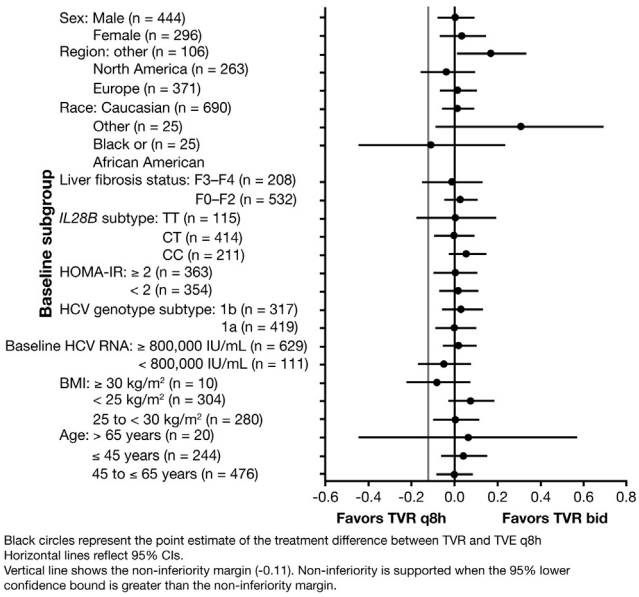


Figure 1. SVR12 in patients treated with TVR twice daily, TVR every 8 hours, and all patients (*A*) overall, (*B*) by *IL28B* genotype, (*C*) HCV genotype, and (*D*) by liver disease stage.

SVR12 rates were 54% (29/54) and 49% (24/49), respectively. Overall, SVR12 was lower in patients with cirrhosis versus those without (51% vs 77%, respectively; $P = .0001$). When *IL28B* genotype and fibrosis stage were considered together, the highest SVR12 rate (90%; 95% CI, 84%–94%) was observed in patients with CC genotype with F0 to F2 fibrosis stage and the lowest SVR12 rate (47%; 95% CI, 39%–55%) was observed in patients with non-CC genotype with advanced fibrosis or cirrhosis (F3–F4). Both *IL28B* genotype and fibrosis stage correlated strongly with SVR12 ($P < .0001$).

Subgroup analyses for baseline characteristics, including sex, region, body mass index, insulin resistance (as measured by homeostasis model assessment of insulin resistance), HCV RNA level, and HCV genotype (1a and 1b), showed similar SVR12 outcomes for TVR twice daily and every 8 hours (Figure 2). The low numbers of patients older than 65 years and who were Asian, black, or "other" race meant no reliable conclusions could be drawn on differences in SVR12 rate between the 2 TVR dosing regimens in these subgroups.

The total treatment duration was determined by RVR rates, which were similar with TVR twice daily (69.4%) and every 8 hours (67.4%). For patients who achieved RVR and were eligible for 24 weeks of treatment (68.4%), SVR rates were 86.3% and 85.2% for TVR twice daily and every 8 hours, respectively. In patients with cirrhosis who achieved RVR, SVR rates after 24 weeks of treatment were 67.9% for TVR twice daily and 58.6% for TVR every 8 hours. The SVR12 rate for the minority of patients who did not achieve RVR was 47% for both dosing regimens. Overall, the extended RVR rates (<25 IU/mL, target not detectable at weeks 4 and 12) were 66.1% and 63.1% for TVR twice daily and every 8 hours, respectively. The proportion of patients



Black circles represent the point estimate of the treatment difference between TVR and TVE q8h
Horizontal lines reflect 95% CIs.
Vertical line shows the non-inferiority margin (-0.11). Non-inferiority is supported when the 95% lower confidence bound is greater than the non-inferiority margin.

Figure 2. SVR12 in patients treated with TVR twice daily and TVR every 8 hours according to baseline subgroup.

with extended RVR rates who achieved SVR12 was 89.3% for both groups.

On-treatment virological failure was observed in 38 (10.3%) and 36 (9.7%) patients treated with TVR twice daily and every 8 hours, respectively. The proportion of patients meeting a virological stopping rule was similar in those treated with TVR twice daily (8.1%) and every 8 hours (9.2%). The proportion of patients with on-treatment virological failure during treatment with TVR was 4.3% in those treated twice daily and 6.2% in those treated every 8 hours. After treatment with TVR, the proportion of patients with on-treatment virological failure was 6.0% in those treated twice daily and 3.5% in those treated every 8 hours.

Overall, 54 of 369 patients (14.6%) treated with TVR twice daily and 62 of 371 patients (16.7%) treated with TVR every 8 hours had TVR-resistant variants at time of failure. TVR-resistant variants were present in the majority of non-SVR patients with available sequence data (70% in those treated twice daily and 72% in those treated every 8 hours). Variants V36M, R155K, and R155T (in G1a) and V36A, T54A, and A156S (in G1b) were identified as significantly enriched in non-SVR patients in both treatment groups. There was no notable difference in the type of variants between the groups.

Adherence

E-diary and pill count adherence data were available for 700 patients (95%). Mean adherence rates to treatment with TVR calculated using a pill count was high in patients treated with TVR twice daily and every 8 hours (Table 2). Mean adherence rates to treatment with TVR reported using the e-diary were also high for TVR twice daily compared with every 8 hours for both the imputed (where missing e-diary entries were included and designated as 0% adherent) and observed data sets. Two patients (0.5%) in the group treated every 8 hours discontinued TVR because of noncompliance. No patients in the group treated twice daily discontinued TVR for this reason.

Safety

During the TVR treatment phase, those treated with TVR twice daily had a similar safety profile to that of those treated every 8 hours (Table 3). This was also true for safety assessments during the overall treatment phase (from the date of first intake of study drug to the last intake of study drug plus 30 days) (see Supplementary Results). Fatigue, pruritus, anemia, nausea, rash, and headache were the most frequent AEs, occurring in >25.0% of patients in both groups during the TVR (Table 3) and overall treatment phases. Anemia, rash, pruritus, anorectal signs and symptoms, and injection site reaction SSC events were observed in a similar proportion of patients treated with TVR twice daily and every 8 hours. Serious AEs, mainly anemia, were reported in 8% of patients treated with TVR twice daily versus 9% of patients treated every 8 hours. AEs leading to discontinuation of TVR occurred in 15% versus 19% of patients treated with TVR twice daily and every 8 hours, respectively (mainly due to rash, anemia, and pruritus). Serious AEs and discontinuations of TVR due to AEs occurred in 14% and 21% of patients with cirrhosis treated with TVR twice daily or every 8 hours, respectively, and 8% and 16% of those without cirrhosis, respectively. One patient in the group treated every 8 hours died during treatment; this patient had a brain neoplasm that was not considered related to treatment.

Subgroup analyses, including liver fibrosis stage, showed no relevant differences within each SSC between those treated with TVR twice daily and those treated every 8 hours during the TVR treatment phase (data not shown) in serious AEs and AEs leading to permanent discontinuation of TVR.

No differences were observed in the incidence of rash SSC between the 2 treatment groups: 51% (twice daily) versus 54% (every 8 hours). During the TVR treatment phase, drug rash with eosinophilia and systemic symptoms was reported in 1 patient treated with TVR twice daily. One patient treated with TVR every 8 hours was reported to have drug rash with eosinophilia and systemic symptoms during the overall treatment phase.

The incidence of grade ≥3 AEs was 42% for TVR twice daily and 38% for TVR every 8 hours (Table 3). AEs of at least grade 3 severity that were most frequently considered at least possibly related to TVR were anemia and rash SSC events.

The total incidence of anemia SSC events was 45% for TVR twice daily versus 44% for TVR every 8 hours. The incidence of grade ≥3 anemia SSC was higher for TVR twice daily versus every 8 hours (26% [95% CI, 21.4%–30.5%] vs 19% [15.0%–23.2%]). The kinetics of anemia appeared similar between the treatment groups. The incidence of SSC events reached its highest value during weeks 5 to 8 in both treatment groups and decreased thereafter. In those treated with TVR twice daily and every 8 hours, respectively, the prevalence of anemia SSC events in patients on treatment was 46.6% and 46.6% during weeks 0 to 16, 39.7% and 39.9% during weeks 17 to 32, and 25.4% and 24.6% during weeks 33 to 48. Subgroup analyses by age, race, body mass index, fibrosis stage, and IL28B genotype showed that there were no relevant differences between those treated with TVR twice daily and those treated every 8 hours in the incidence of anemia SSC events during the TVR treatment phase.

Although the incidence of grade ≥3 anemia was higher in those treated with TVR twice daily compared with those treated every 8 hours, changes in hemoglobin level from baseline over time were similar between treatment groups (4.7 g/dL for each arm). During the TVR treatment phase, a decrease in hemoglobin level of grade ≥3 (<9.0 g/dL [<5.4 mmol/L] or any decrease ≥4.5 g/dL [≥2.7 mmol/L] from baseline) was observed in a similar proportion of patients in each treatment group: 59% of patients treated with TVR twice daily and 55% of patients treated every 8 hours.

Grade 3/4 anemia SSC events occurred in 27% of patients with cirrhosis and 21% of patients without cirrhosis. There were no relevant differences in the incidence of grade ≥3 hemoglobin abnormalities between patients with and without cirrhosis. Treatment with TVR twice daily was associated with a higher incidence of grade ≥3 anemia over TVR every 8 hours in patients with cirrhosis (35% vs 18%, respectively), but the

Table 2. Adherence to Treatment With TVR by Treatment Arm, Based on E-Diary and Pill Count Methods

Adherence method	Statistic	TVR twice daily (n = 369)[a]	TVR every 8 hours (n = 371)[a]
Pill count (imputed)	Mean (SE)	99 (0.2)	98 (0.3)
	Median	100	100
	Range	75–100	32–100
e-diary (imputed)[b]	Mean (SE)	87 (1.1)	85 (1.2)
	Median	95	94
	Range	0–100	0–100
e-diary (observed data)	Mean (SE)	95 (0.5)	92 (0.7)
	Median	99	97
	Range	0–100	0–100

[a]E-diary for patients treated with TVR every 8 hours, n = 353; e-diary for patients treated with TVR twice daily, n = 347.
[b]Imputation method in which missing e-diary entries were included and designated as 0% adherent.

mean change in hemoglobin level from baseline over time was similar between those treated with TVR twice daily and those treated every 8 hours by fibrosis stage.

In an exploratory, multivariable logistic regression analysis (n = 731), baseline factors significantly associated with the development of anemia (as reported by the investigator) during treatment with TVR were low baseline hemoglobin level, high dose of RBV, age, and cirrhosis ($P < .05$). There was no effect of treatment arm on overall occurrence of anemia ($P = .9194$) and the effects of prognostic factors were similar between the TVR groups, with the exception that the effect of cirrhosis on anemia was not observed with TVR twice daily. It should be noted that the study was not designed or powered to identify factors associated with the development of anemia per se.

The dose of RBV was reduced in 23% of patients treated with TVR twice daily and in 25% of patients treated every 8 hours at a median of 9 weeks from initiation of TVR. Temporary discontinuations of RBV due to anemia occurred in 14% of patients treated with TVR twice daily and in 9% of

Table 3. Summary of AEs During the TVR Treatment Phase

	TVR twice daily (n = 369)	TVR every 8 hours (n = 371)	All patients (N = 740)
Any AE	360 (98)	367 (99)	727 (98)
Serious AE	28 (8)	35 (9)	63 (9)
Death[a]	0	1 (0.3)	1 (0.1)
Grade ≥3 AE	156 (42)	139 (38)	295 (40)
Grade 4 AE	23 (6)	24 (7)	47 (6)
Any AE leading to permanent discontinuation of TVR	57 (15)	69 (19)	126 (17)
Any treatment-related AE considered possibly related to TVR[b]	344 (93)	335 (90)	679 (92)
Most frequent AEs[c]			
Fatigue	173 (47)	177 (48)	350 (47)
Pruritus	159 (43)	157 (42)	316 (43)
Anemia	157 (43)	151 (41)	308 (42)
Nausea	128 (35)	142 (38)	270 (37)
Rash	129 (35)	132 (36)	261 (35)
Headache	87 (24)	107 (29)	194 (26)
Anemia SSC events	167 (45)	162 (44)	329 (45)
Grade ≥3 anemia	95 (26)	70 (19)	165 (22)
Rash SSC events	189 (51)	199 (54)	388 (52)
Grade ≥3 rash	18 (5)	22 (6)	40 (5)
Pruritus SSC events	170 (46)	171 (46)	341 (46)
Electrocardiography/QT SSC events	12 (3)	11 (3)	23 (3)
Anorectal signs and symptoms SSC events	99 (27)	116 (31)	215 (29)
Injection site reaction SSC events	39 (11)	46 (12)	85 (12)

NOTE. All values are expressed as n (%).
SSC, grouped AE terms representing similar medical concepts used to ensure that each patient with an event included in a predefined special search category was counted but counted only once.
[a]One patient died during the study of a brain neoplasm that was considered not related to TVR, PEG-IFN alfa-2a, and RBV by the investigator.
[b]Considered at least possibly related to TVR by an investigator.
[c]Preferred terms (in >25% of the patients in any treatment group).

Table 4. Population PK Parameter Estimates of TVR at Steady State After Administration of TVR Twice Daily or TVR Every 8 Hours in Combination With PEG-IFN/RBV

PK parameter estimate, mean ± SD	TVR bid n = 369 (n = 203*)	TVR q8h n = 371 (n = 199*)
$AUC_{\tau,ss}$ (*h · ng/mL*), mean ± SD	43,539 ± 12,478	27,749 ± 8640
$AUC_{24,ss}$ (*h · ng/mL*), mean ± SD	87,072 ± 24,960	83,256 ± 25,920
$C_{avg,ss}$ (*ng/mL*), mean ± SD	3628 ± 1040	3469 ± 1080
$C_{trough,ss}$ (*ng/mL*), mean ± SD	2537 ± 797	2987 ± 987
$C_{max,ss}$ (*ng/mL*), mean ± SD	4307 ± 1233	3732 ± 1133
Least-square mean ratio[a] (90% CI)		
$AUC_{24,ss}$ (*h · ng/mL*)	1.08 (1.02–1.13)[b]	
$C_{trough,ss}$ (*ng/mL*)	0.878 (0.827–0.930)	
$C_{max,ss}$ (*ng/mL*)	1.18 (1.12–1.24)	

NOTE. The PK analysis was performed in a subset of patients.
[a]TVR twice daily/PR (test) versus TVR every 8 hours/PEG-IFN and RBV (reference).
[b]Empirical Bayesian estimates determined using a population PK modeling approach showed the ratio of telaprevir AUC_{24} between treatment arms falls within the limits of bioequivalence (0.80–1.25).

patients treated every 8 hours. Blood transfusions and/or erythropoietin-stimulating agents were received by 17% of those treated with TVR twice daily (blood transfusions, 8.4%; erythropoietin-stimulating agents, 10.6%) and 13.5% of those treated every 8 hours (blood transfusions, 8.6%; erythropoietin-stimulating agents, 7.8%) during the overall treatment phase ($P > .05$). Anemia events leading to permanent discontinuation of TVR occurred in 5% of patients treated with TVR twice daily and every 8 hours.

Increases in creatinine levels occurred in 6.8% of patients during the TVR treatment phase. All but one of these abnormalities was grade 1 or 2 in severity. One patient treated with TVR every 8 hours had a grade 3 increase in creatinine level and renal failure (grade 3 AE). Hyperuricemia was reported as a grade 3/4 AE for 5 patients treated with TVR every 8 hours and for 7 patients treated with TVR twice daily. Any other changes in creatinine levels were small. In a post hoc exploratory analysis, 41 of 365 patients (11.2%) treated with TVR twice daily and 40 of 368 patients (10.9%) treated every 8 hours had a glomerular filtration rate of <60 mL/min/1.73 m^2 during therapy.

Infections occurred in a similar proportion of patients in each treatment arm: 68 (18.3%) and 64 (17.3%) patients treated with TVR every 8 hours and twice daily, respectively. No grade 3/4 infections were reported.

Electrocardiogram parameters were generally similar between those treated with TVR twice daily and every 8 hours. None of the patients had a QTcF value >500 milliseconds or an increase from baseline >60 milliseconds.

PK

A total of 402 patients provided sparse plasma samples: 203 treated with TVR twice daily and 199 treated with TVR every 8 hours. Therefore, the PK data represent estimates derived from approximately 55% of all study participants.

As expected, maximum steady-state concentration ($C_{max,ss}$) was higher and predose steady-state concentration ($C_{trough,ss}$) was lower in those treated with TVR twice daily than in those treated with TVR every 8 hours (Table 4). Total exposure to TVR (measured as area under the plasma concentration-time curve from time of administration up to 24 hours [$AUC_{24,ss}$]) was similar across treatment groups. The mean (SD) model-predicted TVR $AUC_{24,ss}$ values were similar in patients regardless of RVR but were slightly higher in patients who achieved SVR12 (89,787 ± 25,531 h · ng/mL [twice daily] and 84,931 ± 26,739 h · ng/mL [every 8 hours]) compared with those patients not achieving SVR12 (79,001 ± 21,419 h · ng/mL [twice daily] and 76,559 ± 21,375 h · ng/mL [every 8 hours]). For both population estimates, all mean parameters in those treated with TVR twice daily were within 15% of those treated every 8 hours. TVR exposures were analyzed by subgroups, including *IL28B* genotype and cirrhosis status. Similar mean exposures were noted for all *IL28B* genotypes. The mean $C_{max,ss}$ (±SD) was lower in patients with cirrhosis compared with noncirrhotic patients (3569 ± 1181 ng/mL and 4100 ± 1218 ng/mL, respectively). Mean $AUC_{24,ss}$ exposures in patients with cirrhosis treated with TVR every 8 hours were lower than those in patients with cirrhosis treated with TVR twice daily (64,493 ± 17,407 ng · h/mL and 84,404 ± 23,559 ng · h/mL, respectively) or patients without cirrhosis treated with either regimen (86,176 ± 25,834 ng · h/mL and 87,577 ± 25,075 ng · h/mL, respectively). Mean $C_{trough,ss}$ levels were lower for patients with cirrhosis treated with TVR every 8 hours compared with those without cirrhosis (2309 ± 656 ng/mL and 2476 ± 818 ng/mL, respectively); no apparent difference was observed for mean $C_{trough,ss}$ values in patients with or without cirrhosis treated with TVR twice daily (3094 ± 990 ng/mL and 2549 ± 794 ng/mL, respectively).

The mean exposure to TVR was similar in patients with or without rash, irrespective of severity. No differences were apparent in relative exposure between the 2 groups with regard to hemoglobin toxicities.

Regardless of TVR regimen, observed mean PEG-IFN and RBV concentrations at weeks 4 and 8 were similar. There were no apparent differences between the treatment groups in predicted TVR exposures for patients experiencing an AE leading to permanent discontinuation. Furthermore, there were no

clinically relevant differences between treatment groups in the pattern of individual worst QTcF interval values or changes from baseline and $C_{max,ss}$ values of TVR (data not shown).

Discussion

OPTIMIZE is the first randomized, phase 3 clinical study to investigate the use of TVR twice daily versus every 8 hours in combination with PEG-IFN/RBV in treatment-naive patients with G1 chronic HCV infection. At baseline, the majority of patients had a high viral load (≥800,000 IU/mL) and almost one-third (28%) had fibrosis stage F3 to F4, including 14% with cirrhosis; 57% of patients had G1a subtype, and 71% of patients had a non-CC *IL28B* genotype. Therefore, data from OPTIMIZE may apply to a relatively difficult-to-treat population.

The results from this study show that TVR twice daily is noninferior to dosing every 8 hours with regard to SVR. These findings are consistent with the phase 2 C208 study in which SVR rates were similar between groups; >80% of patients in the C208 study achieved SVR regardless of the dosing frequency of TVR.[3] However, the phase 2 study included only 4 cirrhotic patients, which may have contributed to the observed difference in SVR rates between the 2 studies.

In OPTIMIZE, subgroup analyses for a spectrum of baseline characteristics, including those typical of patients more challenging to treat, showed strikingly similar SVR12 outcomes for treatment with TVR twice daily and every 8 hours. The number and type of TVR-resistant variants detected in patients who did not achieve SVR12 were similar for TVR twice daily and every 8 hours. Evaluation of the data by *IL28B* genotype and liver fibrosis stage showed numerically higher response rates in patients with *IL28B* CC genotype and F0 to F2 liver fibrosis stage than patients with non-CC genotypes with advanced fibrosis (F3–F4).

There were no new clinically relevant findings with TVR administered either twice daily or every 8 hours compared with the known safety profile.[12–14] Anemia SSC was reported more frequently in this open-label study than in previous studies, possibly related to greater recognition of TVR-related anemia. The overall incidence of grade ≥3 anemia was higher for TVR twice daily vs every 8 hours (26% vs 19%). However, the mean change in hemoglobin level and the incidence of treatment-emergent hemoglobin abnormalities were similar in both groups.

Comparing the PK-pharmacodynamic relationships, there were no relevant differences in virological responses for those treated with TVR twice daily and every 8 hours.

Although some variability was seen between different adherence measures, mean adherence was high by all analysis methods for TVR twice daily and every 8 hours. In OPTIMIZE, a multivariate analysis showed that higher adherence was associated with a greater probability of achieving SVR12, irrespective of adherence measure.[15]

Although the sample size of the overall study was well powered to show noninferiority and to meet the study objectives, it was not large enough to allow meaningful, multifactor subgroup analyses on the combination of HCV genotype (1a/1b), *IL28B* genotype, and liver fibrosis stage. The population recruited was predominantly white, and the low number of Asian and black patients means that no reliable conclusions can be drawn from the analysis for these subgroups. A further limitation of the study is that PK blood samples (sparse sampling) were obtained from only 55% of participants.

In conclusion, both TVR 1125 mg twice daily and 750 mg every 8 hours were shown to have high rates of SVR12, a low incidence of virological failure, and a comparable safety and tolerability profile when administered in combination with PEG-IFN/RBV. The findings of this study support the use of TVR twice daily regardless of fibrosis stage or *IL28B* genotype, thus offering the potential of simplified TVR dosing to G1 HCV-infected patients, including those with advanced fibrosis or cirrhosis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.11.047.

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Conflicts of interest
The authors disclose the following: M.B. has served as a clinical investigator, speaker, and/or consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, Novartis, and Vertex Pharmaceuticals. K.A. has received grant support from Astellas, Gilead Sciences, and Roche and has served as a consultant/speaker for Abbott Laboratories, Astellas, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Merck Sharp & Dohme, Novartis, and Roche. Y.H. has served as a clinical investigator and/or consultant for Janssen Pharmaceuticals, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Gilead Sciences, Abbott Laboratories, and Boehringer Ingelheim. W.S. has served a clinical investigator and/or consultant for Janssen Pharmaceuticals, Roche, Merck Sharp & Dohme, Abbott Laboratories, Gilead Sciences, and Boehringer Ingelheim. E.J. has served as a clinical investigator and/or consultant for Janssen Pharmaceuticals, Merck Sharp & Dohme, Gilead Sciences, Bristol-Myers Squibb, AbbVie, Vertex Pharmaceuticals, and Roche. S.Z. has served as a clinical investigator and/or consultant for Abbott Laboratories, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, iTherX, Merck & Co, Novartis, Pharmasset, Roche/Genentech, Santaris Pharma A/S, Tibotec, Transgene, and Vertex Pharmaceuticals. L.N. has served as a clinical investigator and/or consultant for Janssen Pharmaceuticals, Gilead Sciences, Pharmasset, Abbott Laboratories, Roche/Genentech, Merck & Co, and Anadys Pharmaceuticals. R.S.B. has served as a clinical investigator and/or consultant for Janssen Pharmaceuticals. C.H. has served as a clinical investigator and/or consultant for Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharpe & Dohme, and Roche. M.R. has served as a clinical investigator and/or consultant for Janssen Pharmaceuticals. R.P. has served as a clinical investigator for Roche, Bristol-Myers Squibb, and Boehringer Ingelheim. S.D., R.D., D.L., K.B. and J.W. are employees of Janssen Pharmaceuticals and may be Johnson & Johnson stockholders.

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Supplementary Methods

The primary end point of this study was the proportion of patients in each treatment group who achieved $SVR12_{planned}$, defined as having plasma HCV RNA levels <25 IU/mL using the last available HCV RNA assessment 12 weeks after the last planned dose of HCV study drug. In this analysis, the virological outcome was based only on the HCV RNA assessment in the week 12 follow-up visit window (snapshot approach).

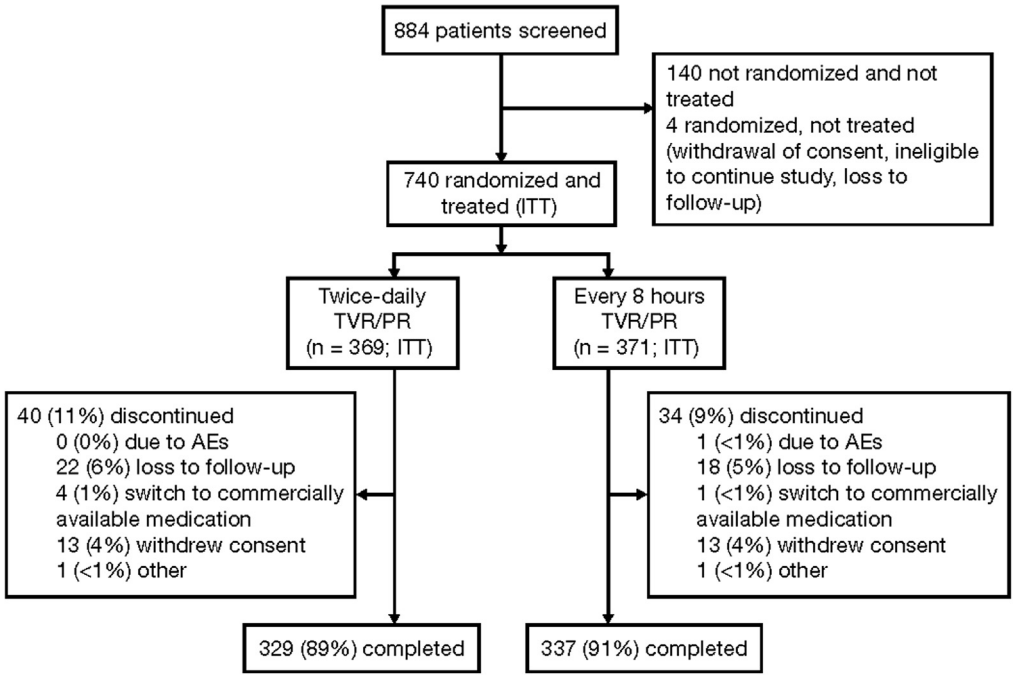
Sensitivity analyses were used to compare virological response rates of treatment with TVR every 8 hours and TVR twice daily. The sensitivity analyses used slightly different "definitions" of SVR12 relating to the assay cutoff and data point(s) used. $SVR12_{planned}$ (snapshot, target not detected) used the lower limit of detection of the HCV RNA assay rather than the lower limit of quantification (25 IU/mL). $SVR12_{planned}$ (classic, target not detected) also used the lower limit of the detection of the HCV RNA assay, but this threshold had to be met at the end of treatment and up to 12 weeks after the last planned dose of HCV study drug. These data are summarized in Supplementary Table 1.

Supplementary Results

A summary of AEs for the TVR treatment phases is provided in Table 3. Supplementary Table 2 summarizes the AEs for the overall treatment phase.

RVR (week 4) and eRVR (week 12) data presented in the report were analyzed as "HCV RNA <25 IU/mL, target not detected," because this assay cutoff (lower limit of detection) was used to determine treatment duration in this study, in accordance with the approved European and US labeling.

Data on the number of patients at weeks 4 and 12 with virological response using HCV RNA <25 IU/mL, target not detected, or alternatively using HCV RNA <25 IU/mL are shown in Supplementary Table 3.



Supplementary Figure 1. Patient disposition.

Supplementary Table 1. Comparison of Virological Response After Administration of TVR Twice Daily or TVR Every 8 Hours in Combination With PEG-IFN/RBV

Sensitivity analysis	TVR every 8 hours (n = 371)	TVR twice daily (n = 369)	All patients (N = 740)
$SVR12_{planned}$ (snapshot, target not detected)			
SVR12, n (%)	269 (72.5)	274 (74.3)	543 (73.4)
Difference[a] (%) (95% CI[b])		1.7 (−4.8 to 12.1)	
$SVR12_{planned}$ (classic, target not detected)			
SVR12, n (%)	271 (73.0)	268 (72.6)	539 (72.8)
Difference[a] (%) (95% CI[b])		−0.4 (−8.5 to 8.4)	

[a]Observed difference.
[b]From logistic regression model.

Supplementary Table 2. Summary of AEs During the Overall Treatment Phase

	TVR twice daily (n = 369)	TVR every 8 hours (n = 371)	All patients (N = 740)
Any AE	361 (98)	368 (99)	729 (99)
Serious AE	42 (11)	48 (13)	90 (12)
Death[a]	0	1 (0.3%)	1 (0.1%)
Grade ≥3 AE	180 (49)	160 (43)	340 (46)
Grade 4 AE	36 (10)	35 (9)	71 (10)
Any AE leading to permanent discontinuation of TVR	57 (15)	70 (19)	127 (17)
Any treatment-related AE considered possibly related to TVR[b]	347 (94)	359 (97)	706 (96)
Most frequent AEs[c]			
Fatigue	185 (50.1)	181 (48.8)	366 (49.5)
Pruritus	172 (46.6)	170 (45.8)	342 (46.2)
Anemia	174 (47.2)	166 (44.7)	340 (45.9)
Nausea	136 (36.9)	145 (39.1)	281 (38.0)
Rash	139 (37.7)	139 (37.5)	278 (37.6)
Headache	93 (25.2)	122 (32.9)	215 (29.1)
Anemia SSC events	184 (49.9)	178 (48.0)	362 (48.9)
Rash SSC events	201 (54.5)	210 (56.6)	411 (55.5)
Pruritus SSC events	183 (49.6)	185 (49.9)	368 (49.7)
Electrocardiogram/QT SSC events	14 (3.8)	14 (3.8)	28 (3.8)
Anorectal signs and symptoms SSC events	106 (28.7)	119 (32.1)	225 (30.4)
Injection site reaction SSC events	42 (11.4)	47 (12.7)	89 (12.0)

NOTE. All values are expressed as n (%).
SSC, grouped AE terms representing similar medical concepts used to ensure that each patient with an event included within a predefined special search category was counted but counted only once.
[a]One patient died during the study of a brain neoplasm that was considered not related to TVR, PEG-IFN alfa-2a, and RBV by the investigator.
[b]Considered at least possibly related to TVR by an investigator.
[c]Preferred terms (in >25% of the patients in any treatment group).

Supplementary Table 3. Virological Response at Weeks 4 and 12 During Administration of TVR Twice Daily or TVR Every 8 Hours in Combination With PEG-IFN/RBV

Parameter	Time point	Value	TVR every 8 hours (n = 371)			TVR twice daily (n = 369)		
			n	%	CI	n	%	CI
Virological response (<25 IU/mL target not detected) NC = F (non-VF)	Week 4	Nonresponder	109	29.4	(24.8–34.3)	101	27.4	(22.9–32.2)
		Responder (RVR)	250	67.4	(62.4–72.1)	256	69.4	(64.4–74.0)
		Missing: dropout unrelated to VF	12	3.2	(1.7–5.6)	12	3.3	(1.7–5.6)
	Week 12	Nonresponder	30	8.1	(5.5–11.3)	28	7.6	(5.1–10.8)
		Responder (complete early virological response)	306	82.5	(78.2–86.2)	313	84.8	(80.7–88.3)
		Missing: dropout unrelated to VF	35	9.4	(6.7–12.9)	28	7.6	(5.1–10.8)
Virological response (<25 IU/mL) NC = F (non-VF)	Week 4	Nonresponder	31	8.4	(5.7–11.7)	27	7.3	(4.9–10.5)
		Responder (RVR)	328	88.4	(84.7–91.5)	330	89.4	(85.8–92.4)
		Missing: dropout unrelated to VF	12	3.2	(1.7–5.6)	12	3.3	(1.7–5.6)
	Week 12	Nonresponder	24	6.5	(4.2–9.5)	18	4.9	(2.9–7.6)
		Responder (complete early virological response)	312	84.1	(80.0–87.7)	323	87.5	(83.7–90.7)
		Missing: dropout unrelated to VF	35	9.4	(6.7–12.9)	28	7.6	(5.1–10.8)

NC = F, noncompleter equals failure; non-VF, nonvirological failure; VF, virological failure; HCV RNA <25 IU/mL, target not detected at week 4 of treatment; HCV RNA <25 IU/mL, target not detected at week 12 of treatment.