**Janssen Research & Development**

**Clinical Study Report Synopsis**
**[TMC435-TiDP16-C216; Phase 3]**

**TMC435 (Simeprevir)**

Redaction and Removal of Information in This Document

- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

## SYNOPSIS

| | |
|---|---|
| Name of Sponsor/Company | Janssen Research & Development* |
| Name of Finished Product | To be determined |
| Name of Active Ingredients | TMC435 (simeprevir) |

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**Status:** Approved

**Date:** 4 October 2013

**Prepared by:** Janssen Infectious Diseases - Diagnostics BVBA

**Protocol No.:** TMC435-TiDP16-C216

**Title of Study:** A Phase 3, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon α-2a (Pegasys®) and ribavirin (Copegus®) or peginterferon α-2b (PegIntron®) and ribavirin (Rebetol®) in treatment-naïve, genotype 1, hepatitis C-infected subjects

**Study Name:** TMC435-TiDP16-C216 (QUEST-2)

**EudraCT Number:** 2010-021174-11

**NCT No.:** NCT01290679

**Clinical Registry No.:** CR017380

**Coordinating Investigator:** [redacted] MD, [redacted] Germany

**Study Centers:** The study was conducted at 76 sites in 14 countries.

**Publication (Reference):**

Manns M, Marcellin P, Poordad Fred FP, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype-1 infection in treatment-naïve patients: Results from QUEST-2, a Phase 3 trial; Poster at The International Liver Congress 2013, April 24 - 28 2013, Amsterdam, The Netherlands; Journal of Hepatology 2013 Suppl 1(58) S568.

**Study Period:** 18 January 2011 to 5 February 2013

**Phase of Development:** Phase 3

**Objectives:** The primary objective was to demonstrate the superiority of TMC435 versus placebo as part of a treatment regimen including pegylated interferon alpha-2a (PegIFNα-2a)/ribavirin (RBV) or PegIFNα-2b/RBV, with respect to the proportion of treatment-naïve hepatitis C virus (HCV) genotype 1 infected subjects with sustained virologic response (SVR) 12 weeks after the planned end of treatment (SVR12).

The secondary objectives were:

- To demonstrate the superiority of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV, with respect to the proportion of subjects with SVR 24 weeks after the planned end of treatment (SVR24).
- To demonstrate the superiority of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV, with respect to the proportion of subjects with SVR at Week 72 (last study-related visit).
- To compare the antiviral activity of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV at all time points, with focus on Weeks 4, 12, 24, 36, 48, 60, and 72.
- To compare the incidence of on-treatment failure in the TMC435 and placebo treatment groups.
- To evaluate the incidence of viral breakthrough during the treatment period in the TMC435 and placebo treatment groups.
- To evaluate the relapse rate following treatment in the TMC435 and placebo treatment groups.
- To determine the viral NS3/4A sequence in subjects not achieving SVR in the TMC435 treatment group.
- To evaluate the pharmacokinetics of TMC435 and the relationship between TMC435 pharmacokinetics and efficacy and safety parameters.
- To determine the proportion of subjects in the TMC435 treatment group who were able to complete all treatment at Week 24.
- To compare the safety and tolerability of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV.
- To evaluate the antiviral activity, safety, tolerability, and pharmacokinetics of TMC435 as part of a treatment regimen in 2 subpopulations, ie, subjects receiving PegIFNα-2a/RBV and subjects receiving PegIFNα-2b/RBV.
- To compare the severity of fatigue as measured by the fatigue severity scale (FSS) between subjects treated with TMC435 versus subjects on placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV.
- To collect productivity data as measured by the Work Productivity and Activity Impairment: Hepatitis C (WPAI: Hepatitis C) questionnaire.

**Methodology:** This was a Phase 3, randomized, double-blind, placebo-controlled, 2-arm, multicenter study to compare the efficacy, tolerability and safety of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV in adult treatment-naïve subjects with HCV genotype 1 infection. In addition, the viral NS3/4A sequence in subjects not achieving SVR, pharmacokinetics of TMC435, patient-reported outcomes (PRO) and medical resource utilization (MRU) were assessed or explored.

The study consisted of a screening period with a maximum duration of 6 weeks, a response-guided 24- or 48-week (TMC435 treatment group) or 48-week (control group) treatment period, and a posttherapy follow-up period for up to 72 weeks after the start of treatment.

This report describes the final analysis including data up to the date of last patient last visit (LPLV), 5 February 2013 when all randomized subjects had completed the last study-related visit at Week 72 or discontinued earlier. The primary analysis (cut-off 22 October 2012) has been performed when all

randomized subjects had completed the Week 60 visit or discontinued earlier and the results have been provided in the Week 60 report.

Three hundred and seventy-five subjects with documented chronic HCV genotype 1 infection, who were treatment-naïve and had a screening plasma HCV ribonucleic acid (RNA) level of >10,000 IU/mL, were planned to be randomly assigned in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *interleukin-28B* (*IL28B*) genotype. Subjects had to have compensated liver disease to be considered eligible for this study. Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B virus coinfection were excluded.

In the first 24 weeks, subjects were to receive 12 weeks TMC435 150 mg or placebo once daily (qd) plus PegIFNα-2a/RBV or PegIFNα-2b/RBV, followed by 12 weeks of PegIFNα-2a/RBV or PegIFNα-2b/RBV alone. As part of a response-guided treatment (RGT) duration, HCV therapy had to be stopped at Week 24 in subjects in the TMC435 treatment group if they achieved HCV RNA levels <25 IU/mL (detectable or undetectable) at Week 4 and <25 IU/mL undetectable at Week 12. All other subjects had to continue PegIFN/RBV alone until Week 48. In the control group, all subjects had to continue PegIFN/RBV alone until Week 48.

The use of PegIFNα-2b was limited to a selected number of countries where subjects were randomized in a 1:1 ratio to PegIFNα-2a/RBV or PegIFNα-2b/RBV. A total of 123 subjects (31.5%) of the overall study population were randomized to the PegIFNα-2b containing regimen.

Virologic stopping rules were incorporated into the protocol design to ensure that subjects with suboptimal response discontinued. Subjects had to stop TMC435/placebo and continue with PegIFNα-2a/RBV or PegIFNα-2b/RBV if they had HCV RNA levels >1,000 IU/mL at Week 4. Subjects had to stop PegIFNα-2a/RBV or PegIFNα-2b/RBV if they had a <2 $\log_{10}$ IU/mL reduction in HCV RNA compared to baseline at Week 12, or if they had confirmed detectable and HCV RNA levels ≥25 IU/mL at Week 24 or Week 36. Detectable HCV RNA after previous undetectability had to be confirmed by repeated HCV RNA testing done within 2 weeks. These virologic stopping rules overruled RGT criteria at all times.

An external HCV RNA monitor who was unblinded to the treatment code monitored the HCV RNA results and had to inform the investigator if subjects needed to stop or change treatment in case RGT criteria or virologic stopping rules were met. The sponsor, investigators, site staff, and subjects remained blinded to the treatment code up to Week 60.

An independent Data Monitoring Committee (DMC) was commissioned for this study.

The total study duration for each subject was maximum 78 weeks (including the 6-week screening period). The study was considered completed with the last visit of the last subject participating in the study.

**Number of Subjects (planned and analyzed):** Three hundred and seventy-five subjects with documented chronic HCV genotype 1 infection, who were treatment-naïve, were planned to be included. Subject disposition data are provided below. At the time of the final analysis, of the 391 randomized and treated subjects, 354 subjects (90.5%) had completed the study, and 37 subjects (9.5%) had discontinued prematurely.

| **Subjects Screened, Randomized, Treated; All Subjects** | |
|---|---|
| | Total |
| Screened | 474 |
| Not randomized | 81 |
| Randomized | 393 |
| Not treated | 2 |
| Treated[a] | 391 |
| Completed study[b] | 354 |
| Discontinued study | 37 |

[a] Received at least 1 dose of study drugs
[b] Completed last study-related visit at Week 72

**Diagnosis and Main Criteria for Inclusion:** Male or female, aged ≥18 years; liver biopsy within 3 years prior to the screening visit (or between the screening and baseline visit) with histology consistent with chronic HCV infection; subjects with bridging fibrosis (METAVIR score F3) or cirrhosis (METAVIR score F4) had to have an ultrasound taken within 6 months prior to the screening visit (or between the screening and baseline visit) with no findings suspicious for hepatocellular carcinoma (HCC); HCV genotype 1 infection (confirmed at screening); plasma HCV RNA of >10,000 IU/mL at screening; subjects with HCV/HIV coinfection or liver disease of non-HCV etiology were excluded; and prior treatment with any approved or investigational drug for the treatment of hepatitis C was not allowed.

**Test Product, Dose and Mode of Administration, Batch No.:** TMC435 oral capsules (G007; Batch No 10K03 and 11B03) at a dose of 150 mg qd. The TMC435 matching placebo was formulated as an oral capsule (G009; Batch No 10K02 and 11E18).

**Reference Therapy, Dose and Mode of Administration, Batch No.:** PegIFNα-2a in combination with RBV given as Pegasys and Copegus, respectively, and PegIFNα-2b in combination with RBV as PegIntron and Rebetol, respectively. Pegasys, PegIntron, Copegus, and Rebetol were to be administered according to the manufacturer's prescribing information. Pegasys (180 µg once weekly; Batch No B1181 and B1191) or PegIntron (prefilled pens per weight band; Batch No OIRA60242, OIRA60304, OIRG60420, OIRG60615, OIRB60440, OIRB60549, OIRJ60612, OIRJ60721, OIRJ60808, OIRC60420, and OIRC60632) were to be administered as weekly subcutaneous (SC) injections. The total daily dose of Copegus (1,000-1,200 mg/day) or Rebetol (800-1,400 mg/day) was based on body weight. RBV, Copegus as oral tablets (200 mg; Batch No 134977, 123650, 899759, 134978, 899761, 119987, and 899755) and Rebetol as oral capsules (200 mg; Batch No ORCJA26B01 and ORCJA60A01), were to be administered as a twice daily regimen (morning and evening).

**Criteria for Evaluation:**

**Efficacy evaluations**: Samples for the determination of HCV RNA were taken at predefined time points and processed in real-time. Plasma HCV RNA values were determined using Roche COBAS Taqman HCV/HPS v2.0 assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 15 IU/mL. Alanine aminotransferase levels were determined as part of the biochemistry panel of the clinical laboratory tests. Samples for biochemistry were taken at predefined time points and processed in real-time.

**Resistance determinations**: Samples for sequencing of HCV NS3/4A were collected at baseline, at scheduled visits during the treatment period, and at follow-up. Sequencing could be triggered by the external HCV RNA monitor throughout the study and by the sponsor virologist after unblinding at Week 60.

**Exploratory biomarker and pharmacogenomic analyses**: The study included the option for analyzing exploratory biomarkers at the RNA, protein, and cell level. The samples for these analyses were collected at predefined time points during the investigational treatment period from all subjects who consented to

participate in the study. The samples could be stored until biomarkers could be linked with treatment responses for meaningful comparisons.

One pharmacogenomic blood sample for host *IL28B* genotyping was taken at the screening visit and immediately analyzed for *IL28B* genotype. This sample could also be genotyped for genes involved in the metabolism of TMC435 (cytochrome P450 enzyme [CYP]3A5 and CYP2C19). In addition, drug transporter genes could be genotyped (organic anion-transporting polypeptide 1B1 [OATP1B1], adenosine triphosphate [ATP]-binding cassette transporter protein [ABC]G2, ABCB1, and multidrug resistance protein [MRP]2) to potentially help assess the relationship between drug metabolizing and transporter gene variants, and efficacy, safety, and pharmacokinetics. The sample for *IL28B*, CYP3A5, CYP2C19, and transporters was mandatory and was required to be collected from all subjects who consented to participate in the study.

One pharmacogenomic blood sample for exploratory host genotyping was taken, preferably at the baseline visit. This sample was optional and was only collected from subjects who consented separately to this pharmacogenomic component of the study (and where local regulations permitted).

**Pharmacokinetic evaluations:** Sparse blood sampling was performed in all subjects to determine the individual steady-state pharmacokinetics of TMC435 (apparent clearance [CL/F], area under concentration-time curve [AUC], predose plasma concentration [$C_{0h}$], and steady-state average concentration [$C_{ss,avg}$]). Relationships between TMC435 pharmacokinetics and efficacy and safety parameters were evaluated. A post hoc questionnaire was introduced to obtain an indication on the intake of TMC435 with or without food throughout the study.

**Safety evaluations**: Safety and tolerability were evaluated throughout the study. The evaluations of safety and tolerability included monitoring of adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examination.

The safety monitoring and toxicity management plan in the protocol took into account AEs of special interest based on toxicities of the protease inhibitor (PI) class, clinical safety data of TMC435 available at time of the protocol writing, target organs identified in nonclinical studies, and toxicities reported with PegIFNα-2a or 2b and RBV.

**Patient-reported outcomes**: Subjects completed 4 questionnaires during study visits at baseline, throughout treatment, and posttreatment follow-up. Subjects rated the severity of their fatigue using the FSS. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D). Three endpoints were based on subjects' responses to the WPAI: impairment in productivity (WPAI Productivity Score), question 6 of the WPAI regarding impairment in daily activities (WPAI Activity Impairment Score), and question 2 of the WPAI regarding hours missed from work for subjects in the laborforce (WPAI absenteeism score). Subjects also assessed their health status using the EuroQol 5-dimension questionnaire (EQ-5D). Three endpoints were evaluated based on EQ-5D scores: EQ-5D descriptive system scores, EQ-5D valuation index, and a summary measure of overall health-related quality of life, the EQ5D visual analog scale (EQ-5D VAS).

**Medical resource utilization**: MRU data were collected throughout the study.

**Statistical Methods:**

This report describes results of the final analysis including data up to the date of LPLV, 5 February 2013, performed when all randomized subjects had completed the last study-related visit at Week 72 or discontinued earlier. The primary analysis has been performed when all randomized subjects had completed the Week 60 visit or discontinued earlier and the results have been provided in the Week 60 report.

All analyses were performed on the intent-to-treat population, which was defined as those subjects who received at least 1 dose of investigational drug (TMC435/placebo). Subjects were analyzed according to their randomized treatment.

Sample size determination: Phase 3 data from telaprevir and boceprevir showed a strong correlation between SVR12 and SVR24. Similarly, a strong correlation was observed in the Phase 2b studies with TMC435 (Study C205 and C206). Therefore, sample size calculation that was based on the SVR24 response parameter was also regarded applicable for SVR12.

Based on published data, the SVR24 (assessed 24 weeks after the planned end of treatment) in the control group was expected to be approximately 45%. With a 5% significance level (2-sided), 125 subjects in the control group and 250 subjects in the TMC435 group, the power to detect a significant difference of at least 20% between the 2 treatment groups was >90%.

Primary endpoint: The primary efficacy parameter was the proportion of subjects in each treatment group achieving SVR12, defined as the proportion of subjects with undetectable HCV RNA (<25 IU/mL undetectable) at the actual end of treatment and HCV RNA <25 IU/mL detectable/undetectable 12 weeks after the planned end of treatment.

The primary analysis method for comparing the SVR12 rate between the 2 treatment groups was the Cochran-Mantel-Haenszel (CMH) test controlling for type of PegIFN and the stratification factors HCV genotype 1 subtype and *IL28B* genotype. A Breslow-Day test for homogeneity of odds ratios based on this model was also performed. In addition, the 95% confidence interval (CI) was constructed around the response rate in each treatment group. A sensitivity analysis with respect to the model, the SVR12 rate in the TMC435 treatment group was compared with the SVR12 rate in the control group using a logistic regression model including baseline $\log_{10}$ HCV RNA (included as continuous parameter), type of PegIFN and the stratification factors HCV genotype 1 subtype and *IL28B* genotype. The 95% CI around the difference in proportions of response was constructed based on this model. Additional sensitivity analyses were done by applying different imputation rules for missing data. Missing data patterns were analyzed and described in detail.

Secondary endpoints: The following null hypotheses were tested to address some of the secondary objectives.

- There is no statistically significant difference between the active treatment arm and the control group for SVR24.
- There is no statistically significant difference between the treatment arms in the area under the curve ($AUC_{72}$) for the change from baseline to Week 72 in FSS score.
- There is no statistically significant difference between treatment arms in the $AUC_{72}$ for the change from baseline in WPAI Productivity Score.
- There is no statistically significant difference between treatment arms in the $AUC_{72}$ for the change from baseline in WPAI score, based on the 6$^{th}$ question (activity impairment score) only.
- There is no statistically significant difference between treatment arms in the $AUC_{72}$ for the change from baseline in WPAI score, based on the 2$^{nd}$ question (absenteeism score) only.

The null hypotheses were tested in the order as presented above as part of a closed testing procedure, ie, the first secondary endpoint was only planned to be tested if the null hypothesis for the primary efficacy endpoint was rejected at the 5% significance level etc. This allowed the significance level for the comparison between treatment groups to be 5% in each test, given that the previous comparison was significant.

Other efficacy parameters, and virology, safety, PRO, and MRU data were analyzed, as appropriate, by means of descriptive statistics, frequency tabulations, crosstabulations, Kaplan-Meier estimates, analysis

of covariance, logistic regression, piecewise-linear linear mixed models, and generalized additive model analysis. Patient-reported outcomes endpoints were evaluated using closed testing to control for multiple comparisons.

**RESULTS:**

STUDY POPULATION

| | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 | Total |
|---|---|---|---|
| Analysis Set: Intent-to-treat | 134 | 257 | 391 |
| TMC435/PBO Exposure (weeks), median (range) | 6.20 (4.7; 12.6) | 12.00 (2.0; 12.6) | 12.00 (2.0; 12.6) |
| **Study Completion/Discontinuation** | | | |
| Number of subjects who: | | | |
| Completed | 113 (84.3%) | 241 (93.8%) | 354 (90.5%) |
| Discontinued | 21 (15.7%) | 16 (6.2%) | 37 (9.5%) |
| Adverse event | 0 | 2 (0.8%) | 2 (0.5%) |
| Withdrawal by subject | 5 (3.7%) | 6 (2.3%) | 11 (2.8%) |
| Subject non-compliant | 1 (0.7%) | 0 | 1 (0.3%) |
| Lost to follow-up | 10 (7.5%) | 8 (3.1%) | 18 (4.6%) |
| Subject entered another investigational study | 5 (3.7%) | 0 | 5 (1.3%) |
| **Treatment Completion/Discontinuation[a]** | | | |
| Number of subjects who: | | | |
| Completed all study therapy | 47 (35.1%) | 235 (91.4%) | 282 (72.1%) |
| Completed PR[b] | 81 (60.4%) | 237 (92.2%) | 318 (81.3%) |
| During the TMC435/PBO + PR phase[c] | | | |
| Discontinued TMC435/PBO only | 83 (61.9%) | 5 (1.9%) | 88 (22.5%) |
| Discontinued all study therapy | 0 | 5 (1.9%) | 5 (1.3%) |
| TMC435/PBO | | | |
| Completed | 51 (38.1%) | 247 (96.1%) | 298 (76.2%) |
| Discontinued | 83 (61.9%) | 10 (3.9%) | 93 (23.8%) |
| Adverse event[d] | 1 (0.7%) | 4 (1.6%) | 5 (1.3%) |
| Withdrawal by subject | 0 | 2 (0.8%) | 2 (0.5%) |
| Subject non-compliant | 0 | 1 (0.4%) | 1 (0.3%) |
| Subject reached a virologic endpoint[e] | 82 (61.2%) | 3 (1.2%) | 85 (21.7%) |

[a] Subjects who prematurely discontinued treatment could continue the study.
[b] Subjects who completed at least one study drug (RBV or PegIFN) at Week 24 (for subjects in the TMC435 arm who met the RGT criteria) or at Week 48 (all other subjects).
[c] In case the stopping rule at Week 12 was met, it is possible that the actual discontinuation of PR occurred during the PR only phase, and not during the TMC435/PBO + PR phase.
[d] May include subjects who stop TMC435 because they have to stop RBV and/or PegIFN due to an AE.
[e] Subject met a virologic stopping rule at Week 4.
Note: subjects can be counted in more than one category.
Information presented in the table is based upon the Trial and Treatment Termination CRF pages (investigator evaluation).

| | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 | Total |
|---|---|---|---|
| Analysis Set: Intent-to-treat | 134 | 257 | 391 |
| **Demographic Characteristics** | | | |
| Gender | | | |
| Female | 57 (42.5%) | 117 (45.5%) | 174 (44.5%) |
| Male | 77 (57.5%) | 140 (54.5%) | 217 (55.5%) |
| Region | | | |
| Europe | 90 (67.2%) | 162 (63.0%) | 252 (64.5%) |
| North-America | 25 (18.7%) | 54 (21.0%) | 79 (20.2%) |
| South-America | 19 (14.2%) | 41 (16.0%) | 60 (15.3%) |
| Race | | | |
| White | 123 (91.8%) | 237 (92.2%) | 360 (92.1%) |
| Black or African American | 10 (7.5%) | 16 (6.2%) | 26 (6.6%) |
| American Indian or Alaska Native | 0 | 1 (0.4%) | 1 (0.3%) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Asian | 1 (0.7%) | 2 (0.8%) | 3 (0.8%) |
| Multiple | 0 | 1 (0.4%) | 1 (0.3%) |
| Ethnicity | | | |
| Hispanic or Latino | 25 (18.7%) | 60 (23.3%) | 85 (21.7%) |
| Not Hispanic or Latino | 109 (81.3%) | 197 (76.7%) | 306 (78.3%) |
| Age (years) | | | |
| Median | 47.0 | 46.0 | 47.0 |
| Range | (18; 73) | (18; 73) | (18; 73) |
| Body Mass Index ($kg/m^2$) | | | |
| Median | 26.20 | 25.80 | 26.00 |
| Range | (18.1; 51.6) | (17.5; 53.5) | (17.5; 53.5) |
| *IL28B* Genotype[a] | | | |
| CC | 42 (31.3%) | 75 (29.2%) | 117 (29.9%) |
| CT | 71 (53.0%) | 142 (55.3%) | 213 (54.5%) |
| TT | 21 (15.7%) | 40 (15.6%) | 61 (15.6%) |
| **Baseline Disease Characteristics** | | | |
| Baseline HCV RNA ($log_{10}$ IU/mL) | | | |
| Median | 6.50 | 6.51 | 6.51 |
| Range | (4.4; 7.5) | (4.0; 7.6) | (4.0; 7.6) |
| Baseline HCV RNA category (IU/mL) | | | |
| <400,000 | 19 (14.2%) | 31 (12.1%) | 50 (12.8%) |
| ≥400,000 - ≤800,000 | 17 (12.7%) | 27 (10.5%) | 44 (11.3%) |
| >800,000 | 98 (73.1%) | 199 (77.4%) | 297 (76.0%) |
| METAVIR fibrosis score[b] | | | |
| Subjects with METAVIR score available | 134 | 248 | 382 |
| Score F0-F1 | 60 (44.8%) | 130 (52.4%) | 190 (49.7%) |
| Score F2 | 42 (31.3%) | 65 (26.2%) | 107 (28.0%) |
| Score F3 | 17 (12.7%) | 36 (14.5%) | 53 (13.9%) |
| Score F4 | 15 (11.2%) | 17 (6.9%) | 32 (8.4%) |
| HCV geno/subtype (NS5B)[c] | | | |
| 1 | 1 (0.7%) | 0 | 1 (0.3%) |
| 1a | 54 (40.3%) | 105 (40.9%) | 159 (40.7%) |
| 1b | 77 (57.5%) | 150 (58.4%) | 227 (58.1%) |
| 1e | 1 (0.7%) | 1 (0.4%) | 2 (0.5%) |
| 1g | 1 (0.7%) | 0 | 1 (0.3%) |
| 1l | 0 | 1 (0.4%) | 1 (0.3%) |

| | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 | Total |
|---|---|---|---|
| Analysis Set: Intent-to-treat | 134 | 257 | 391 |
| Baseline Q80K | | | |
| Subjects with sequencing data | 130 | 255 | 385 |
| Q80K | 14 (10.8%) | 26 (10.2%) | 40 (10.4%)[d] |
| No Q80K | 116 (89.2%) | 229 (89.8%) | 345 (89.6%) |

[a] Results obtained from the central laboratory: may not be the same as stratified.
[b] Limited to results from METAVIR scoring system.
[c] HCV geno/subtype is based on the NS5B assay, and if not available is based on LiPA HCV II or Trugene results.
[d] Of the 40 subjects with a Q80K polymorphism at baseline, only 1 subject was infected with HCV genotype 1b (enrolled in the TMC435 + PegIFN/RBV arm). The prevalence of Q80K at baseline in subjects infected with HCV genotype 1a/other was 24.5% (39 of 159 HCV genotype 1a/other infected subjects with sequencing data.

| | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 | Total |
|---|---|---|---|
| Analysis Set: Intent-to-treat | 134 | 257 | 391 |
| **PegIFNα-2a vs PegIFNα-2b** | | | |
| PegIFNα-2a/RBV, not randomized [a] | 46 (34.3%) | 100 (38.9%) | 146 (37.3%) |
| Randomized to PegIFNα-2a/RBV | 45 (33.6%) | 77 (30.0%) | 122 (31.2%) |
| Randomized to PegIFNα-2b/RBV | 43 (32.1%) | 80 (31.1%) | 123 (31.5%) |

[a] Subjects in the following EMA countries (Austria, Belgium, Bulgaria, Germany, Spain, France, The Netherlands, Poland, Portugal, Slovakia) were randomized to either PegIFNα-2a or 2b.
Subjects outside EMA all received PegIFNα-2a.

EFFICACY RESULTS:

**Primary Efficacy Endpoint**

The proportion of subjects with SVR12 was higher in the TMC435 + PegIFN/RBV arm than in the placebo + PegIFN/RBV arm (81.3% versus 50.0%), resulting in a significant p-value for the CMH test controlling for the type of PegIFN/RBV and the stratification factors ($p < 0.001$). The adjusted difference (95% CI) between treatment arms was 32.2% (23.3%; 41.2%).

| **Number (%) of Subjects With SVR12** | | | | |
|---|---|---|---|---|
| | Observed | Stratum Adjusted | Comparison versus Placebo | |
| | n/N (%) | % (95% CI)[c] | Difference in proportions (95% CI)[b] | p-value[a] |
| PBO 12 Wks PR48 | 67/134 (50.0) | 49.7 (42.0;57.3) | | |
| TMC435 150 mg 12 Wks PR24/48 | 209/257 (81.3) | 81.9 (77.2;86.6) | 32.2 (23.3;41.2) | <0.001 |

[a] Based on the CMH test controlling for PegIFN/RBV type and stratification factors.
[b] Difference in proportions (active – placebo) adjusted for PegIFN/RBV type and stratification factors and the corresponding 95% CI based on the normal approximation.
[c] Proportions adjusted for the PegIFN/RBV type and the stratification factors with corresponding 95% CIs based on the normal approximation.
Stratification factors are *IL28B* and HCV geno/subtype. HCV geno/subtype is based on the NS5B assay (if not available, LiPA II or Trugene result is used) and categorized as 1b versus any other geno/subtype (1a/other).

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.954.

Statistically significantly higher SVR12 rates were achieved in the TMC435 + PegIFN/RBV arm compared to the placebo + PegIFN/RBV arm irrespective of the type of PegIFN/RBV used. Within the TMC435 + PegIFN/RBV treatment arm, a trend for lower virologic response rates and higher on-treatment failure, viral breakthrough, and viral relapse rates was noted in subjects randomized to PegIFNα-2b/RBV compared to subjects randomized to PegIFNα-2a/RBV. The RGT criteria were met by 87.5% of the subjects randomized to PegIFNα-2b/RBV and 97.4% of the subjects randomized to PegIFNα-2a/RBV.

Statistically significantly higher SVR12 rates were achieved in the TMC435 + PegIFN/RBV arm compared to the placebo + PegIFN/RBV arm irrespective of the *IL28B* genotype. In the TMC435 + PegIFN/RBV arm, higher SVR12 rates were observed in subjects with *IL28B* genotype CC compared to CT and with CT compared to TT.

Statistically significantly higher SVR12 rates were achieved in the TMC435 + PegIFN/RBV arm compared to the placebo + PegIFN/RBV arm irrespective of the HCV geno/subtype. In the TMC435 + PegIFN/RBV arm, similar SVR12 rates were observed in subjects with HCV genotype 1a/other and subjects with HCV genotype 1b.

SVR12 rates were higher in the TMC435 + PegIFN/RBV arm than in the placebo + PegIFN/RBV arm in subjects with HCV genotype 1a/other with Q80K (72.0% versus 50.0%) and without Q80K (82.5% versus 42.5%), although the difference between treatments was not statistically significant in subjects with Q80K. A statistically significant difference was observed when the SVR12 rate in subjects with HCV genotype 1a/other and Q80K in the TMC435 + PegIFN/RBV arm (72.0%) was compared with the SVR12 rate in all subjects from the placebo + PegIFN/RBV arm with genotype 1a/other (with and without Q80K combined) (45.6%).

**SVR12 by Type of PegIFN/RBV and Stratification Factors**

| | PBO 12 Wks PR 48 | | TMC435 150 mg 12 Wks PR 24/48 | | Difference between Treatment Groups (TMC435 - PBO) |
|---|---|---|---|---|---|
| | n/N (%) | % (95% CI)[a] | n/N (%) | % (95% CI)[a] | 95% CI[a] |
| Type of PegIFN/RBV | | | | | |
| Randomized to PegIFNα-2a/ RBV | 28/45 (62.2) | 57.6 (42.5;72.6) | 68/77 (88.3) | 91.5 (86.4;96.6) | 33.9 (21.0;46.8) |
| Randomized to PegIFNα-2b/ RBV | 18/43 (41.9) | 34.9 (21.1;48.8) | 62/80 (77.5) | 81.0 (72.2;89.8) | 46.1 (33.9;58.3) |
| PegIFNα-2a/ RBV, not randomized | 21/46 (45.7) | 45.5 (31.2;59.8) | 79/100 (79.0) | 86.9 (80.6;93.2) | 41.4 (28.6;54.2) |
| HCV geno/subtype | | | | | |
| 1a/other | 26/57 (45.6) | 38.9 (22.6;55.2) | 86/107 (80.4) | 84.2 (76.4;92.1) | 45.3 (27.6;63.0) |
| 1b | 41/77 (53.2) | 52.8 (38.3;67.3) | 123/150 (82.0) | 89.5 (84.3;94.8) | 36.7 (21.9;51.6) |
| *IL28B* | | | | | |
| CC | 34/42 (81.0) | 87.8 (79.8;95.8) | 72/75 (96.0) | 98.3 (96.8;99.8) | 10.5 (3.6;17.4) |
| CT | 29/71 (40.8) | 36.5 (25.1;47.8) | 114/142 (80.3) | 82.0 (75.7;88.3) | 45.5 (33.5;57.6) |
| TT | 4/21 (19.0) | 12.9 (4.3;21.5) | 23/40 (57.5) | 54.0 (38.5;69.5) | 41.1 (29.3;52.9) |

[a] The proportions, difference in proportions and their respective CI are derived from a logistic regression model with factors for treatment group, baseline HCV RNA ($log_{10}$ IU/mL), HCV geno/subtype, *IL28B* and type of PegIFN/RBV. For the logistic regression model on subgroup HCV geno/subtype, also an interaction term between treatment and geno/subtype has been added to the model.
HCV geno/subtype is based on the NS5B assay (and if not available based on LiPA II or Trugene results).

SVR12 rates were statistically significantly higher in the TMC435 + PegIFN/RBV arm than in the placebo + PegIFN/RBV arm irrespective of the METAVIR score at baseline. Among subjects with cirrhosis (METAVIR score F4), SVR12 rates were 64.7% (11 of 17 subjects) and 40.0% (6 of 15 subjects) in the TMC435 + PegIFN/RBV and placebo + PegIFN/RBV arms, respectively.

For all other baseline characteristics analyzed, SVR12 rates were also statistically significantly higher in the TMC435 + PegIFN/RBV arm than the placebo + PegIFN/RBV arm.

**Secondary Efficacy Endpoints**

The majority (91.4%) of TMC435-treated subjects met the RGT criteria of whom 86.0% achieved SVR12.

Most (98.3%) of the subjects in the TMC435 + PegIFN/RBV arm who met the RGT criteria completed treatment with PegIFN and/or RBV. The SVR12 rate in this group of completers was 86.6%. SVR12 rates were higher in the completers with undetectable HCV RNA at Week 4 (91.7%) than in the completers with HCV RNA <25 IU/mL detectable at Week 4 (61.5%). Viral relapse rates were lower in the completers with undetectable HCV RNA at Week 4 (8.9%) than in the completers with HCV RNA <25 IU/mL detectable at Week 4 (29.4%).

Sixteen subjects (6.2%) in the TMC435 + PegIFN/RBV arm did not meet the RGT criteria. Amongst these, SVR12 was achieved by 4 of the 6 subjects (66.7%) who completed treatment with PegIFN and/or RBV at Week 48.

**SVR12 by RGT in the TMC435 + PegIFN/RBV arm**

| | | SVR12 |
|---|---|---|
| | n/N | n/N |
| Met RGT criteria | 235/257 (91.4 %) | 202/235 (86.0 %) |
| Completed PegIFN and/or RBV[a] | 231/235 (98.3 %) | 200/231 (86.6 %) |
| HCV RNA <25 IU/mL undetectable at Week 4 (eRVR) | 192/231 (83.1 %) | 176/192 (91.7 %) |
| HCV RNA <25 IU/mL detectable at Week 4 | 39/231 (16.9 %) | 24/39 (61.5 %) |
| Discontinued PegIFN and RBV | 4/235 (1.7 %) | 2/4 (50.0 %) |
| Did not meet RGT criteria | 16/257 (6.2 %) | 5/16 (31.3 %) |
| Completed PegIFN and/or RBV[a] | 6/16 (37.5 %) | 4/6 (66.7 %) |
| Discontinued PegIFN and RBV | 10/16 (62.5 %) | 1/10 (10.0 %) |
| Not classifiable[b] | 6/257 (2.3 %) | 2/6 (33.3 %) |

RGT criteria: TMC435-treated subjects with on-treatment HCV RNA <25 IU/mL detectable/undetectable at Week 4 and <25 IU/mL undetectable at Week 12. Subjects who meet the RGT criteria have a planned treatment duration of 24 weeks, whereas subjects who do not meet these criteria have a planned treatment duration of 48 weeks. Subjects in the placebo group have a planned treatment duration of 48 weeks.
[a] Completed treatment with PegIFN and/or RBV at Week 24/48 in line with meeting RGT criteria; Subjects who stopped study therapy because they met a stopping rule are not considered subjects who completed study therapy.
[b] Subject discontinued study therapy prior to assessment of the RGT criteria, ie subjects who discontinued prior to the HCV measurement at Week 4, or subjects who discontinued prior to their measurement at Week 12 for subjects with HCV RNA <25 IU/mL detectable/undetectable at Week 4.

Note: there was 1 subject who met RGT criteria based on [redacted] HCV RNA data, but continued and completed treatment at Week 48.

The proportion of subjects with SVR24 was 80.5% in the TMC435 + PegIFN/RBV arm versus 50.0% in the placebo + PegIFN/RBV arm, resulting in a significant p-value for the CMH test controlling for the type of PegIFN/RBV and the stratification factors ($p < 0.001$). The adjusted difference (95% CI) between treatment arms was 31.5% (22.5%; 40.5%).

In the TMC435 + PegIFN/RBV arm, SVR24 was achieved by all but 2 subjects with SVR12 (99.0%). The 2 subjects who did not achieve SVR24 had viral relapse after having achieved SVR12. In the placebo + PegIFN/RBV arm, all subjects with SVR12 achieved SVR24.

Treatment failure occurred less frequently in the TMC435 + PegIFN/RBV arm than in the placebo + PegIFN/RBV arm. In the TMC435 + PegIFN/RBV arm, 19.8% of the subjects experienced treatment failure (on-treatment failure in 7.0% and post-treatment failure in 12.8% of the subjects). In the placebo + PegIFN/RBV arm, treatment failure was observed in 50.0% of the subjects (on-treatment failure in 32.1% and post-treatment failure in 17.9% of the subjects).

**On- and Post-Treatment Failure**

| | PBO<br><br>12 Wks<br>PR 48 | TMC435<br>150 mg<br>12 Wks<br>PR 24/48 |
|---|---|---|
| Analysis Set: Intent-to-treat | 134 | 257 |
| Failure[a] | 67 (50.0%) | 51 (19.8%) |
| On-treatment Failure[b] | 43 (32.1%) | 18 (7.0%) |
| Did not complete treatment at week 24/48[c] | 42 (31.3%) | 10 (3.9%) |
| Met stopping rule at Week 12/24/36[d] | 38 (28.4%) | 7 (2.7%) |
| Other (detectable at EOT) | 4 (3.0%) | 3 (1.2%) |
| Completed at least one study drug at week 24/48[c] | 1 (0.7%) | 8 (3.1%) |
| Met stopping rule at Week 4[e] | 1 (0.7%) | 0 |
| Viral breakthrough[f] | 0 | 5 (1.9%) |
| Other (detectable at EOT) | 0 | 3 (1.2%) |
| Post-treatment Failure[g] | 24 (17.9%) | 33 (12.8%) |
| Viral Relapse[h] | 21 (15.7%) | 29 (11.3%) |
| Discontinued PegIFN and RBV | 5 (3.7%) | 1 (0.4%) |
| Completed PegIFN and/or RBV[c] | 16 (11.9%) | 28 (10.9%) |
| Missing at time point of SVR12[i] | 3 (2.2%) | 4 (1.6%) |

Note: A subject can occur in only one category.
EOT: end of treatment

[a] A subject with treatment failure refers to a subject who did not achieve SVR12 or who achieved SVR12 and had a relapse thereafter.
[b] Confirmed detectable HCV RNA levels at actual EOT
[c] Completed treatment with PegIFN and/or RBV at Week 24/48 in line with meeting RGT criteria; Subjects who stopped PR because they met a stopping rule are not considered subjects who completed study therapy.
[d] Stopping rules at Weeks 12, 24 and 36, respectively: <2 log reduction from baseline in HCV RNA at Week 12, detectable HCV RNA at Week 24 or Week 36.
[e] Subjects who met the stopping rule at Week 4 (>1000 IU/mL) had to discontinue treatment with TMC435/PBO but continue with PR.
[f] Viral breakthrough but did not meet any stopping rule for subjects who completed treatment with PR.
[g] Failure but with undetectable (or unconfirmed detectable) HCV RNA levels at EOT
[h] Calculated for all ITT subjects
[i] Subjects with on-treatment response, without viral relapse, but who fail solely because of missing data at the time point of SVR12 (and thereafter).

Viral breakthrough was observed in 4.7% (12 of the 256 subjects) in the TMC435 + PegIFN/RBV arm and 10.4% (14 of the 134 subjects) in the placebo + PegIFN/RBV arm. In the TMC435 + PegIFN/RBV arm, viral breakthrough mainly occurred during treatment with PegIFN/RBV, after stopping TMC435 (in 10 of the 12 subjects with viral breakthrough).

Ten of the 12 subjects with viral breakthrough in the TMC435 + PegIFN/RBV arm met a virologic stopping rule. Viral breakthrough was not a stopping rule in this study.

Viral relapse was observed less frequently in the TMC435 + PegIFN/RBV arm than in the placebo + PegIFN/RBV arm (12.3% versus 23.9% [or 29 of 236 versus 21 of 88 subjects with undetectable HCV RNA at end of treatment]). One subject in the TMC435 + PegIFN/RBV arm (CRF ID [redacted]) was classified as a relapser in the primary analysis, but is no longer considered to be a relapser in the final analysis. This subject had unconfirmed viral relapse at the cut-off date for the primary analysis (HCV RNA: 34 IU/mL). At the confirmation visit after this cut-off date and at the last study visit (Week 72), HCV RNA was undetectable.

Of the 4 subjects in the TMC435 + PegIFN/RBV arm with viral relapse more than 12 weeks after end of treatment, 1 subject experienced viral relapse at the SVR12 assessment time point, 2 subjects after achieving SVR12, and 1 subject after achieving SVR12 and SVR24.

| **Number (%) of Subjects With Viral Relapse** | | |
|---|---|---|
| | PBO<br><br>12 Wks<br>PR 48 | TMC435<br>150 mg<br>12 Wks<br>PR 24/48 |
| Analysis Set: Intent-to-treat | 134 | 257 |
| All Subjects | 21/88 (23.9 %) | 29/236 (12.3 %) |
| Over time[a] | | |
| ≤4 weeks | 11/88 (12.5 %) | 12/236 (5.1 %) |
| >4 - ≤12 weeks | 10/77 (13.0 %) | 13/223 (5.8 %) |
| >12 - ≤24 weeks | 0/66 | 3/208 (1.4 %) |
| >24 weeks | 0/9 | 1/199 (0.5 %) |

Note: the incidence of viral relapse is only calculated for subjects with undetectable HCV RNA levels (or unconfirmed detectable) at EOT and with at least one follow-up HCV RNA measurement.
[a] Time to relapse is calculated versus the actual end of treatment date.

Paired baseline and failure NS3 sequencing information was available for 46 of the 51 subjects with failure in the TMC435 + PegIFN/RBV treatment arm. The majority of subjects (97.8% or 45 of 46 subjects) with failure and sequencing data available had emerging mutations at time of failure: mainly R155K alone or in combination with other mutations at NS3 positions 80, 168, and/or 170 in subjects with HCV genotype 1a, and D168V or Q80R+D168E in subjects with HCV genotype 1b. In 27 of the 45 (60.0%) TMC435-treated subjects with emerging mutations at time of failure, the emerging mutations were no longer detected at the last available time point of the study (EOS). The median follow-up time after failure was 42.64 weeks, ranging from 0.0 to 68.7 weeks, in subjects with failure and sequencing information available.

PHARMACOKINETIC RESULTS:

| **Pharmacokinetic parameter** | TMC435<br>150 mg<br>12 Wks<br>PR 24/48 |
|---|---|
| Analysis Set: Intent-to-treat | 257 |
| $AUC_{24h}$ (ng.h/mL) | |
| N | 255 |
| Mean (SD) | 56611 (66935.4) |
| Median | 33285 |
| Range | (4868; 393225) |
| $C_{0h}$ (ng/mL) | |
| N | 255 |
| Mean (SD) | 1902 (2781.1) |
| Median | 912 |
| Range | (19.3; 16004) |
| CL (L/h) | |
| N | 255 |
| Mean (SD) | 5.23 (3.767) |
| Median | 4.51 |
| Range | (0.41; 30.8) |

There was no difference in the pharmacokinetics of TMC435 by genotype 1 subtype, gender, or presence of Q80K at baseline, although the number of subjects in some of these subgroups was small. There was a trend for increase in TMC435 exposure ($AUC_{24h}$ and $C_{0h}$) and decrease in clearance (CL/F) with increasing METAVIR fibrosis score. There were no differences in exposure with race, although no conclusions could be made for Asians, as there were only 2 subjects treated with TMC435.

No relationship between food intake and TMC435 plasma exposure was observed based on the results of the Food Intake questionnaire, although numbers of subjects reporting never or sometimes taking TMC435 with food were small.

SAFETY RESULTS:

**Adverse Events**

During the first 12 weeks, the most frequent AEs in the TMC435 + PegIFN/RBV treatment arm (in >25% of the subjects) were headache, fatigue, pyrexia, and influenza-like illness which occurred at a similar frequency in the placebo + PegIFN/RBV treatment arm. The majority of AEs was grade 1 or 2 in severity. Grade 3 or 4 AEs were reported in 25.7% of the subjects in the TMC435 + PegIFN/RBV treatment arm and in 23.9% of the subjects in the placebo + PegIFN/RBV treatment arm. Except from neutropenia (10.9% of the subjects in the TMC435 + PegIFN/RBV treatment arm and in 8.2% of the subjects in the placebo + PegIFN/RBV treatment arm), all grade 3 or 4 AEs by preferred term (PT) were reported in <2% of the subjects in the TMC435 + PegIFN/RBV treatment arm. Serious adverse events (SAEs) occurred in 2.3% of the subjects in TMC435 + PegIFN/RBV treatment arm and in 1.5% of the subjects in the placebo + PegIFN/RBV treatment arm. In the TMC435 + PegIFN/RBV arm, all SAEs by PT occurred in at most 1 subject and were considered not or doubtfully related to TMC435/placebo. AEs that led to permanent discontinuation of TMC435/placebo were reported in 1.6% of the subjects in the TMC435 + PegIFN/RBV treatment arm and in 1 subject (0.7%) in the placebo + PegIFN/RBV treatment arm. By PT, all AEs leading to discontinuation of TMC435/placebo occurred in at most 1 subject.

Two subjects in the TMC435 + PegIFN/RBV treatment arm died due to SAEs (colon cancer and death of unknown cause) reported during treatment with PegIFN/RBV alone. The death of unknown cause was considered by the investigator as likely due to sudden cardiac death, no autopsy was done as per the wish of the subject's relatives. Both SAEs were considered not related to TMC435/placebo, PegIFNα-2a/2b, or RBV by the investigator.

No major differences in the overall incidence of AEs, SAEs, and AEs leading to permanent discontinuation of study drugs were noted between subjects receiving PegIFNα-2a/RBV or PegIFNα-2b/RBV during the entire treatment phase. Grade 3 or 4 AEs were slightly more frequent in TMC435-treated subjects receiving PegIFNα-2a/RBV compared to subjects receiving PegIFNα-2b/RBV: 33.0% of the subjects on PegIFNα-2a/RBV without randomization, 36.4% of the subjects randomized to PegIFNα-2a/RBV, and 28.8% of the subjects randomized to PegIFNα-2b/RBV. Similar trends were observed in the placebo + PegIFN/RBV treatment arm.

| | First 12 weeks | | Entire Treatment Phase | |
|---|---|---|---|---|
| | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 |
| Analysis set: Intent-to-treat | 134 | 257 | 134 | 257 |
| Any AE | 130 (97.0%) | 246 (95.7%) | 132 (98.5%) | 249 (96.9%) |
| Most frequent AEs by PT during the first 12 weeks (ie, in >25.0% of TMC435-treated subjects), n (%) | | | | |
| Headache | 45 (33.6%) | 95 (37.0%) | 49 (36.6%) | 101 (39.3%) |
| Fatigue | 52 (38.8%) | 90 (35.0%) | 56 (41.8%) | 95 (37.0%) |
| Pyrexia | 48 (35.8%) | 78 (30.4%) | 53 (39.6%) | 80 (31.1%) |
| Influenza like illness | 34 (25.4%) | 66 (25.7%) | 35 (26.1%) | 66 (25.7%) |
| Any AE with fatal outcome | 0 | 0 | 0 | 2 (0.8%) |
| Any SAE | 2 (1.5%) | 6 (2.3%) | 10 (7.5%) | 16 (6.2%) |
| Worst grade 3 or 4 AE | 32 (23.9%) | 66 (25.7%) | 46 (34.3%) | 84 (32.7%) |
| AE leading to permanent stop[a] | 6 (4.5%) | 6 (2.3%) | 11 (8.2%) | 8 (3.1%) |
| TMC435/placebo[b] | 1 (0.7%) | 4 (1.6%) | 1 (0.7%) | 4 (1.6%) |
| TMC435/ placebo only | 1 (0.7%) | 2 (0.8%) | 1 (0.7%) | 2 (0.8%) |
| TMC435/ placebo, PegIFN and RBV | 0 | 2 (0.8%) | 0 | 2 (0.8%) |

[a] Permanent stop of at least one drug.
[b] Without regard to PegIFN and RBV.

Some AEs were of special interest (increased bilirubin) or of clinical interest (rash [any type], pruritus, anemia, neutropenia, and photosensitivity conditions). The majority of these events was grade 1 or 2 in severity and none were considered serious in the TMC435 + PegIFN/RBV arm. Only a few of these events led to permanent discontinuation of TMC435/placebo (<1% of the subjects in the TMC435 + PegIFN/RBV arm). The incidence of these events of special/clinical interest in the TMC435 + PegIFN/RBV treatment arm was similar to the incidence in the placebo + PegIFN/RBV treatment arm during the first 12 weeks, except for increased bilirubin (8.9% vs 2.2%), rash (any type) (23.7% vs 11.2%), and photosensitivity conditions (3.9% vs 0.7%). The majority of these events was grade 1 or 2 in severity. Incidence of dyspnea AEs was similar in both arms.

| | First 12 weeks | | Entire Treatment Phase | |
|---|---|---|---|---|
| | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 | PBO 12 Wks PR 48 | TMC435 150 mg 12 Wks PR 24/48 |
| Analysis set: Intent-to-treat | 134 | 257 | 134 | 257 |
| Events of special interest | 3 (2.2%) | 23 (8.9%) | 3 (2.2%) | 24 (9.3%) |
| Increased bilirubin | 3 (2.2%) | 23 (8.9%) | 3 (2.2%) | 24 (9.3%) |
| Events of clinical interest | 55 (41.0%) | 135 (52.5%) | 82 (61.2%) | 166 (64.6%) |
| Rash (any type) | 15 (11.2%) | 61 (23.7%) | 27 (20.1%) | 69 (26.8%) |
| Pruritus | 20 (14.9%) | 48 (18.7%) | 36 (26.9%) | 66 (25.7%) |
| Photosensitivity conditions | 1 (0.7%) | 10 (3.9%) | 1 (0.7%) | 10 (3.9%) |
| Neutropenia | 24 (17.9%) | 42 (16.3%) | 36 (26.9%) | 54 (21.0%) |
| Anemia | 21 (15.7%) | 35 (13.6%) | 37 (27.6%) | 53 (20.6%) |
| Dyspnea | 11 (8.2%) | 22 (8.6%) | 12 (9.0%) | 25 (9.7%) |

Adverse events are coded using MedDRA version 14.0 using the following generally defined grouped terms.
Increased bilirubin includes MedDRA PT: "Bilirubin conjugated abnormal", "Bilirubin conjugated increased", "Bilirubin excretion disorder", "Bilirubinuria", "Blood bilirubin abnormal", "Blood bilirubin increased", "Blood bilirubin unconjugated increased", "Hyperbilirubinaemia", "Jaundice", "Jaundice cholestatic", " Icterus index increased", "Jaundice extrahepatic obstructive", "Jaundice hepatocellular", "Ocular icterus", "Urine bilirubin increased", "Yellow skin".
Rash includes MedDRA HLTs: "Erythemas", "Papulosquamous conditions", "Rashes, eruptions and exanthems NEC", "Photosensitivity conditions", MedDRA SMQ "Severe cutaneous adverse reaction": narrow scope and selected terms of the broad scope.
Pruritus includes MedDRA HLT "Pruritus NEC".
Photosensitivity conditions include MedDRA HLT "Photosensitivity conditions".
Neutropenia includes MedDRA PT "Neutropenia", "Neutrophil count decreased".
Anemia includes MedDRA PT "Anaemia", "Haemoglobin decreased", "Haemolytic anemia".
Dyspnea includes MedDRA PT: "Acute respiratory distress syndrome", "Dyspnoea", "Dyspnoea exertional", "Dyspnoea at rest", "Hyperventilation", "Orthopnoea".

### Clinical Laboratory Tests

Reversible increases in mean bilirubin (direct, indirect, and total) were seen in the TMC435 + PegIFN/RBV treatment arm, mainly during the first 2 weeks of treatment. In general, bilirubin levels returned to baseline values after TMC435 dosing was complete. During the first 12 weeks, treatment-emergent bilirubin increases (hyperbilirubinemia, direct and indirect bilirubin above normal limits) were more frequent in the TMC435 + PegIFN/RBV treatment arm than in the placebo + PegIFN/RBV treatment arm. Incidences of grade 3 hyperbilirubinemia were low (3.1% of the subjects in the TMC435 + PegIFN/RBV treatment arm and 1 subject [0.7%] in the placebo + PegIFN/RBV treatment arm). The bilirubin elevations were not associated with elevation of transaminases and are attributed to a decrease in the bilirubin uptake related to inhibition of the hepatocyte transporters OATP1B1 and MRP2 in the context of RBV-induced hemolysis. No relevant differences between the treatment arms were observed for any of the other laboratory abnormalities.

### Other Safety Observations

There were no clinically relevant changes over time in vital signs or ECG parameters, and no meaningful differences between the treatment arms regarding the incidence of treatment-emergent abnormalities in cardiovascular parameters. Adverse events related to cardiovascular abnormalities were infrequent in both arms.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

In general, pharmacokinetic/pharmacodynamic analyses relating TMC435 plasma exposures to virologic response parameters showed no consistent relationship. However, there was a trend for a longer time to undetectable HCV RNA in the subjects with low exposure to TMC435. There was a trend towards a decreasing number of subjects experiencing on-treatment failure with increasing $AUC_{24h}$, although the numbers in subgroups were small. However, a relationship between exposure and achieving SVR12 and relapse could not be identified.

No trends were observed when exploring the relationship between TMC435 exposure and the incidence or severity of AEs or treatment discontinuations due to AEs. There was also no relationship observed between the incidence of selected events (ie, events of special and clinical interest and dyspnea AEs) and TMC435 exposure.

A trend for mild increases from baseline in direct, indirect and total bilirubin was observed with higher exposure to TMC435. No trend was observed between TMC435 exposures and changes from baseline in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and neutrophils.

PATIENT-REPORTED OUTCOMES RESULTS:

Patient-reported outcomes endpoints were evaluated using closed testing to control for multiple comparisons. Adding TMC435 did not increase patient-reported severity of fatigue or depressive symptoms, nor were there greater impairments in productivity or daily activities beyond what was observed with PegIFN/RBV. Mean scores worsened by similar amounts in both treatment arms when treatment was initiated and remained elevated as long as the majority of subjects were on treatment (ie, through Week 24 for the TMC435 + PegIFN/RBV arm and through Week 48 for the placebo + PegIFN/RBV arm). Once the majority of subjects in the TMC435 + PegIFN/RBV arm was no longer receiving treatment (Week 36) the mean PRO score for most outcomes returned to values at or below baseline. The same was observed once subjects in the placebo + PegIFN/RBV arm were no longer receiving treatment (Week 60).

Where treatments differed was in the timing of improvements in PRO scores. Most subjects in the TMC435 + PegIFN/RBV arm met RGT criteria and were able to complete PegIFN/RBV treatment after 24 weeks compared with 48 weeks in the placebo + PegIFN/RBV arm. As a result, the TMC435 + PegIFN/RBV arm reported statistically significantly less fatigue or impairments in most other health outcomes over the total study period: $AUC_{72}$ for fatigue severity (FSS total score: $p = 0.012$), productivity (WPAI Productivity Score: $p = 0.009$), and daily activity impairment (WPAI question 6, $p = 0.008$). $AUC_{72}$ for time missed from work for subjects in the laborforce (WPAI question 2) were not statistically significantly different between treatments ($p = 0.183$). Results for PRO measuring health-related quality of life were consistent with the FSS results. Results for PRO measuring depressive symptoms did not show a statistically significant difference between treatment arms, but showed a trend over time similar to the FSS results.

Achievement of SVR12 in the TMC435 + PegIFN/RBV arm was associated with return to baseline or improvement from baseline for FSS total score, WPAI productivity and activity impairment scores.

MEDICAL RESOURCE UTILIZATION:

The addition of TMC435 to PegIFN/RBV treatment was not associated with an increase in the proportion of subjects requiring outpatient or inpatient medical resource use, compared to the placebo + PegIFN/RBV treatment arm. Overall, the proportion of subjects with outpatient MRU was 66.9% and the proportion of subjects with hospitalizations was 9.2%, with no statistically significant difference between the two treatment arms, over the 72-week period. The proportion of subjects with outpatient MRU during the first 24 weeks of treatment was similar between the TMC435 + PegIFN/RBV treatment arm (52.3%) and the placebo + PegIFN/RBV treatment arm (53.7%). There was a trend towards a lower proportion of

subjects with outpatient MRU after Week 24 of treatment in the TMC435 + PegIFN/RBV treatment arm (48.8%) versus the placebo + PegIFN/RBV arm (54.6%).

For the whole ITT population (TMC435 + PegIFN/RBV arm and placebo + PegIFN/RBV arm combined), a higher proportion of subjects with outpatient MRU was observed among subjects who experienced anemia (81.1%) compared to subjects for whom no anemia was reported (62.7%), and a higher proportion of subjects with outpatient MRU was observed among subjects who experienced rash (77.3%) compared to subjects for whom no rash was reported (63.5%).

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSION(S):

In this study with treatment-naïve chronic HCV genotype 1 infected subjects, TMC435 150 mg qd in combination with PegIFN/RBV demonstrated significantly higher SVR12 rates over PegIFN/RBV alone (81.3% in the TMC435 + PegIFN/RBV treatment arm versus 50.0% in the placebo + PegIFN/RBV treatment arm). All but 2 subjects in the TMC435 + PegIFN/RBV arm with SVR12 achieved SVR24 (99.0%). These 2 subjects had viral relapse after achieving SVR12. SVR24 was achieved by all subjects with SVR12 in the placebo + PegIFN/RBV arm. One subject in the TMC435 + PegIFN/RBV arm had viral relapse after having achieved SVR12 and SVR24. The majority of subjects in the TMC435 + PegIFN/RBV treatment arm (91.4%) met the RGT criteria, with 86.0% of these achieving SVR12.

Statistically significantly higher SVR12 rates were achieved in subjects treated with TMC435 compared to subjects in the placebo + PegIFN/RBV arm irrespective of the type of PegIFN/RBV used (PegIFNα-2a or PegIFNα-2b). SVR12 rates were also statistically significantly higher in the TMC435 + PegIFN/RBV arm compared to the placebo + PegIFN/RBV arm for all HCV genotypes (1a/other and 1b), *IL28B* genotypes (CC, CT, and TT), and METAVIR scores. Subjects infected with HCV genotype 1a/other with baseline Q80K polymorphism and those without Q80K in the TMC435 + PegIFN/RBV arm had statistically significantly higher SVR12 rates than all placebo subjects infected with HCV genotype 1a/other (with and without Q80K combined).
In the TMC435 + PegIFN/RBV treatment arm, SVR12 rates were similar in HCV genotype 1a and 1b infected subjects.

Treatment with TMC435 150 mg qd was generally safe and well tolerated. There were 2 death cases (both in the TMC435 + PegIFN/RBV treatment arm) which were both not considered related to TMC435/placebo by the investigator. The safety and tolerability profile of TMC435 + PegIFN/RBV was generally similar to placebo + PegIFN/RBV except for the events of increased bilirubin, rash (any type) and photosensitivity conditions, where a trend for an increased frequency was observed in the TMC435 + PegIFN/RBV group. Most of these events were grade 1 or 2 in severity. There were no permanent discontinuations of TMC435 treatment for increased bilirubin or photosensitivity conditions and <1% of subjects had to stop TMC435 treatment due to rash (any type). Patient-reported outcome measures are in line with these conclusions and show that duration of treatment-related symptoms and impairments could be significantly reduced by adding TMC435 to PegIFN/RBV.

In conclusion, the results of this study demonstrated that TMC435 150 mg qd administered for 12 weeks in combination with either PegIFNα-2a or PegIFNα-2b plus RBV with a response-guided overall PegIFN/RBV treatment duration of 24 or 48 weeks was superior to 48 weeks of treatment with PegIFN/RBV in treatment-naïve subjects with chronic genotype 1 HCV infection and TMC435 was generally safe and well tolerated.