Janssen Research & Development

Clinical Study Report Synopsis
[TMC435-TiDP16-C206; Phase IIb]

TMC435 (Simeprevir)

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- 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

Trial Identification and Protocol Summary

Company: Janssen Research & Development* **Trade Name**: - **Indication**: Hepatitis C	**Drug Substance**: TMC435 **Trial no**.: TMC435-TiDP16-C206 **Clinical Phase**: IIb
Title: A Phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFNα-2a and ribavirin in HCV genotype 1 infected subjects who failed to respond or relapsed following at least 1 course of PegIFNα-2a/b and RBV therapy.	
Coordinating Investigator: [redacted] Dr. [redacted]	**Country**: International
Trial Period: Start: 24-Sep-2009 End: 17-Aug-2011	**No. of Investigators**: 89 **No. of Subjects**: 463

Objectives:

The primary objective of the trial was to evaluate the efficacy of 6 different regimens of TMC435 in combination with peginterferon alfa-2a (PegIFNα-2a) and ribavirin (RBV), defined as the proportion of subjects with < 25 IU/mL undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) 24 weeks after the planned end of treatment (SVR24), compared to the control group receiving PegIFNα-2a/RBV in combination with TMC435-matched placebo.

The secondary objectives were:

- To evaluate and compare the antiviral activity of TMC435 when administered in different regimens versus control (PegIFNα-2a/RBV) over the trial period.
- To evaluate and compare the antiviral activity of TMC435 when administered in different regimens versus control (PegIFNα-2a/RBV) over the trial period in the different subpopulations (prior null responders/partial responders/relapsers).
- To evaluate and compare the safety and tolerability of the TMC435-containing regimens versus PegIFNα-2a/RBV over the trial period.
- To determine the frequency/kinetics and viral genetics of virologic failures.
- To evaluate the pharmacokinetics and the pharmacokinetic/pharmacodynamic (PK/PD) relationship for efficacy and safety of TMC435.
- To collect Medical Resource Utilization (MRU) information, and to evaluate Quality of Life (QoL) and the level of fatigue over the trial period.

Design:

TMC435 is a HCV NS3/4A protease inhibitor (PI) under development for the treatment of chronic HCV infection.

This was a randomized, 7-arm, double-blind, placebo-controlled trial to compare the efficacy, tolerability and safety of different regimens of TMC435 plus PegIFNα-2a and RBV versus PegIFNα-2a and RBV alone in adult subjects with genotype 1 HCV infection who had failed at least one prior course of PegIFN/RBV therapy. In addition, the frequency, kinetics and genetics of virologic failures and the pharmacokinetics and PK/PD relationships of TMC435 were assessed.

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Design, Cont'd

A pharmacokinetic substudy was performed at selected sites. Patient reported outcomes (PROs) (EuroQol-5 dimensions [EQ-5D] and Fatigue Severity Scale [FSS] questionnaires) were also assessed. This trial was referred to as ASPIRE (i.e., Antiviral Stat-C Protease Inhibitor Regimen in Experienced subjects).

Approximately 455 subjects with a genotype 1 HCV infection who had at least one documented prior course of PegIFNα-2a/RBV or PegIFNα-2b/RBV therapy of at least 12 weeks and failed to respond or relapsed following treatment were planned to be included in the trial. Subjects had to have a screening 'plasma HCV RNA' (hereafter, referred to as 'HCV RNA') of > 10,000 IU/mL and no decompensated liver disease, liver disease of non-HCV etiology, co-infection with non genotype 1 HCV or human immunodeficiency virus (HIV) infection. All subjects were to be treated for 48 weeks and followed-up until Week 72.

Subjects were randomized in a 1:1:1:1:1:1:1 ratio to 1 of 7 different treatment arms. Treatment arms 1 and 2 consisted of 12 weeks triple therapy with 100 mg and 150 mg TMC435 once daily (q.d.), respectively, plus PegIFNα-2a/RBV followed by 36 weeks of PegIFNα-2a/RBV with TMC435-matched placebo, and 24 weeks of post-therapy follow up. Treatment arms 3 and 4 consisted of 24 weeks triple therapy with 100 mg and 150 mg TMC435 q.d., respectively, plus PegIFNα-2a/RBV followed by 24 weeks of PegIFNα-2a/RBV with TMC435 matched placebo and 24 weeks of post-therapy follow-up. Treatment arms 5 and 6 consisted of 48 weeks triple therapy with 100 mg and 150 mg TMC435 q.d., respectively, and 24 weeks of post-therapy follow-up. Treatment arm 7 (control arm) consisted of 48 weeks of TMC435-matched placebo plus PegIFNα-2a/RBV and 24 weeks of post-therapy follow up.

Subjects not achieving ≥ 1 $\log_{10}$ reduction from baseline in HCV RNA at Week 4, ≥ 2 $\log_{10}$ reduction from baseline in HCV RNA at Week 12 or subjects with detectable HCV RNA at Week 24 or Week 36 were to stop all study medication (TMC435/placebo, PegIFNα-2a, and RBV). The results of the HCV RNA measurements were reviewed on an ongoing basis by an external HCV RNA monitor who was unblinded to treatment. Investigators and subjects remained blinded. For all subjects, there was a post-treatment follow-up period for up to 72 weeks after treatment initiation.

Two unblinded interim analyses were performed. A first interim analysis was performed when all randomized subjects had received 24 weeks of treatment or discontinued earlier. The second interim analysis was performed after all subjects had received 48 weeks of treatment or discontinued earlier. Both interim analyses were done to support the dose selection and the further clinical development of TMC435 and to support regulatory submissions. This report describes the results of the final analysis, which was performed once all randomized subjects had completed the last trial-related visit or discontinued earlier**.**

Subject Selection

Inclusion Criteria:

1. Male or female subject aged between 18 and 70 years, extremes included.
2. Documented chronic HCV infection as evidenced by all of the following:
   - a liver biopsy demonstrating chronic viral hepatitis within 2 years of screening;
   - anti-HCV positive;
   - HCV RNA positive (if only inflammation was present on liver biopsy, HCV RNA presence had to be documented for at least 6 months prior to baseline).

   Note: If no biopsy was available, one was performed on a separate day during screening. For subjects with cirrhosis diagnosed by prior biopsy (evidence of which had to be available in the source documents) and no evidence of hepatocellular carcinoma (confirmed by alpha-fetoprotein [AFP] level < 50 ng/mL and ultrasound at screening), another biopsy was not required.
3. Genotype 1 HCV infection (confirmed at screening).
4. Plasma HCV RNA of > 10,000 IU/mL at screening (as assessed by standard quantitative in vitro nucleic acid amplification assay).
   Note: Retesting of HCV RNA to reassess eligibility was allowed only once using an unscheduled visit during the screening period.
5. At least 1 prior documented course of PegIFNα-2a/RBV or PegIFNα-2b/RBV therapy for at least 12 consecutive weeks which had not been discontinued due to intolerability to PegIFNα-2a/b and RBV therapy.
   Note: Subjects who were treated with (Peg)interferon (IFN) monotherapy were not allowed.
6. Body weight between 40 and 125 kg.

Inclusion Criteria, Cont'd

7. Subject (male with partner of childbearing potential or female of childbearing potential) agreed to use 2 separate forms of highly effective contraception methods (1 of the methods had to be a barrier method, e.g., condom or diaphragm) from screening throughout the duration of study treatment and for 7 months after the last dose of RBV, or was non-heterosexually active, vasectomized (male subject) or had a vasectomized partner (female subject), or was a female (subject or partner of male subject) of non-childbearing potential.
8. Informed consent signed voluntarily before the first trial-related activity.
9. Was able to comply with the protocol requirements.

Exclusion Criteria:

1. Decompensated liver disease defined as history or presence of ascites, hepatic encephalopathy, esophageal bleeding, or gastric varices.
2. Any other liver disease of non-HCV etiology; this could include but was not limited to hepatitis A or B, drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, non-alcoholic steatohepatitis (NASH) or primary biliary cirrhosis.
3. Infection/co-infection with non-genotype 1 HCV.
4. Co-infection with HIV type 1 or type 2 (HIV-1 or HIV-2) (positive HIV-1 or HIV-2 antibodies test at screening) or hepatitis B virus infection (hepatitis B surface antigen [HBsAg]).
5. History of invasive malignancy diagnosed or treated within 5 years prior to screening (locally treated non-invasive basal cell skin carcinoma was permitted; cervical carcinoma in situ was allowed if treated prior to screening).
6. Evidence of hepatocellular carcinoma (e.g., AFP > 50 ng/mL).
7. Medical conditions that were exclusion criteria for PegIFNα-2a or RBV treatment (please refer to the manufacturer's prescribing information for details):
   - Presence or history of psychiatric disorders including but not limited to severe depression, anxiety disorders, psychotic disorders, a history of hospitalization for any psychiatric disorder or a suicide attempt. *Note:* Transient and/or situational symptoms such as minor depression, mood disturbances or situational anxiety (e.g., prior to biopsy) did not exclude a subject from the trial. In general, an important consideration was the investigator's assessment of the clinical risk for the subject to start Pegasys®.
   - Uncontrolled/unstable cardiac disorders (e.g., congestive heart failure, supraventricular arrhythmias).
   - Uncontrolled/unstable chronic pulmonary disorders (e.g., chronic obstructive pulmonary disease).
   - Severe bacterial, viral or fungal infections including acute tuberculosis.
   - Uncontrolled/unstable thyroid disease (hypo- or hyperthyroidism).
   - Uncontrolled/unstable diabetes mellitus (e.g., glycosylated hemoglobin [HbA1c] ≥ 7%, diabetic retinopathy).
   - Renal impairment (e.g., serum creatinine > 1.5 x upper limit of laboratory normal range [ULN] or creatinine clearance [CLcr] < 50 mL/min).
   - Anti-nuclear antibody (ANA) titer ≥ 1:320.
   - Autoimmune disease (e.g., Graves' disease).
   - Hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
     Note: Subjects with thalassemia minor could be included if their hemoglobin level was normal at screening.
8. Any active clinically significant disease other than hepatitis C (e.g., chronic pancreatitis) or findings during screening of medical history, physical examination, laboratory testing or electrocardiogram (ECG) recordings that, in the investigator's opinion, could compromise the subject's safety or the outcome of the trial.
9. Having had an organ transplant (other than cornea or hair transplant or skin graft).

Exclusion Criteria, Cont'd

10. Having any of the following laboratory abnormalities:
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 10 x ULN.
    - Laboratory evidence of significantly decreased hepatic function or decompensation (i.e., international normalized ratio [INR] > 1.5, or albumin < 30 g/L, or bilirubin > 1.5 x ULN).
      Note: Subjects could be included if elevated bilirubin, elevated INR, or decreased albumin was assessed at the time of screening as not related to liver disease (e.g., elevated bilirubin due to Gilbert's disease).
    - Laboratory abnormalities that were exclusion criteria for PegIFNα-2a or RBV treatment (please refer to the manufacturer's prescribing information for details):
      a. Platelet count < 90,000/mm³.
      b. Absolute neutrophil count (ANC) < 1500 cells/mm³.
      c. Hemoglobin < 12 g/dL for females and < 13 g/dL for males.
    - Any other grade 3 or grade 4 laboratory abnormality according to the World Health Organization (WHO) Toxicity Grading Scale.

    Note: Retesting of abnormal screening values that led to exclusion were allowed once using an unscheduled visit during the screening period to reassess eligibility.
11. History or evidence of current use of alcohol, barbiturates, amphetamines, recreational or narcotic drug use, which in the investigator's opinion could compromise the subject's safety and/or compliance with the trial procedures (period of drug/alcohol misuse had to be at least 1 year before the first administration of study medication).
    Note: Urine was tested at screening to check the current use of amphetamines, cocaine, opioids, and barbiturates. Subjects with a positive urine drug test were not eligible.
12. Female subject who was pregnant, planning on becoming pregnant, or breast-feeding or partner of male subject who was pregnant or planning on becoming pregnant.
13. Concurrent participation in a clinical trial with another investigational drug or device within 30 days of the screening visit.
14. Known allergy or hypersensitivity to any of the components of the investigational medication or to any of the components of PegIFNα-2a subcutaneous (s.c.) solution or RBV tablets.
15. Having previously received treatment with TMC435 or any other direct-acting anti-HCV agent (e.g., NS5B polymerase, NS3/4A protease, or NS5A inhibitor).

Treatment	**TMC435**		**placebo**	**PegIFNα-2a (Pegasys®)**	**RBV (Copegus®)**
Concentration Dosage Form (F No.) Usage	100 mg/capsule F020 oral	75 mg/capsule F021 oral	- F022 capsules oral	180 µg solution injection s.c.	200 mg tablet oral
Batch Numbers	09D01/F020 09H22/F020 10A27/F020	09C09/F021 09H21/F021 10A26/F021	09C16/F022 09H20/F022 10A25/F022	B1131	97417, 115189 119822, 119986
Dose Regimen	**Treatment Arm 1 (TMC12/PR48 100 mg q.d.)** Triple therapy of 100 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (twice daily [b.i.d.] regimen) and PegIFNα-2a 180 µg/week for 12 weeks (Weeks 1 to 12) followed by 36 weeks of triple therapy with TMC435-matched placebo q.d. plus PegIFNα-2a/RBV (Weeks 13 to 48). **Treatment Arm 2 (TMC12/PR48 150 mg q.d.)** Triple therapy of 150 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (b.i.d. regimen) and PegIFNα-2a 180 µg/week for 12 weeks (Weeks 1 to 12) followed by 36 weeks of triple therapy with TMC435-matched placebo q.d. plus PegIFNα-2a/RBV (Weeks 13 to 48). **Treatment Arm 3 (TMC24/PR48 100 mg q.d.)** Triple therapy of 100 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (b.i.d. regimen) and PegIFNα-2a 180 µg/week for 24 weeks (Weeks 1 to 24) followed by 24 weeks of triple therapy with TMC435-matched placebo q.d. and PegIFNα-2a/RBV (Weeks 25 to 48).				

Dose Regimen, Cont'd	**Treatment Arm 4 (TMC24/PR48 150 mg q.d.)** Triple therapy of 150 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (b.i.d. regimen) and PegIFNα-2a 180 µg/week for 24 weeks (Weeks 1 to 24) followed by 24 weeks of triple therapy with TMC435-matched placebo q.d. and PegIFNα-2a/RBV (Weeks 25 to 48). **Treatment Arm 5 (TMC48/PR48 100 mg q.d.)** Triple therapy of 100 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (b.i.d. regimen) and PegIFNα-2a 180 µg/week for 48 weeks (Weeks 1 to 48). **Treatment Arm 6 (TMC48/PR48 150 mg q.d.)** Triple therapy of 150 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (b.i.d. regimen) and PegIFNα-2a 180 µg/week for 48 weeks (Weeks 1 to 48). **Treatment Arm 7 (placebo)** Triple therapy of TMC435-matched placebo q.d. plus RBV 1000 or 1200 mg/day[a] (b.i.d. regimen) and PegIFNα-2a 180 µg/week for 48 weeks (Weeks 1 to 48). [a] RBV dosing was weight-based: < 75 kg = 1000 mg/day, ≥ 75 kg = 1200 mg/day
Duration of Treatment	48 weeks for all subjects
Duration of Study	Screening: approximately 6 weeks Treatment: up to 48 weeks Follow-up: up to 24 weeks Total participation in the study: 72 weeks after initiation of treatment
Disallowed Medication	The following medications were not allowed from screening onwards during the overall treatment period: - any other anti-HCV therapy other than TMC435, PegIFNα-2a and RBV; - all investigational drugs, except for TMC435; - immunomodulators (e.g., interleukins, systemic corticosteroids), except for PegIFNα-2a; - experimental vaccines; - erythropoiesis stimulating agents. Because of the interaction potential of TMC435 with medications that are substrates, inhibitors, or inducers of cytochrome P450 (CYP) 3A4/5, a list of currently marketed medications that could interact via these enzymes is presented in the protocol. These drugs were not to be used during the TMC435/placebo treatment period. CYP3A4 inducers were not to be used during the overall treatment period from screening onwards. For guidance on the use of medications concomitantly with PegIFNα-2a (Pegasys®), or RBV (Copegus®), the locally approved product information of these drugs were to be consulted.
Assessments	
Efficacy	Samples for the determination of HCV RNA were taken at every study visit. HCV RNA was measured using the Roche COBAS Taqman HCV/HPS v2.0 assay with a linear range from 25-300,000,000 IU/mL and a lower limit of quantification (LLOQ) of 25 IU/mL. In this synopsis, the term 'undetectable HCV RNA' is used when no HCV RNA was detected in the plasma samples.
Resistance Determinations	Samples for sequencing of the HCV NS3/4A protease domain were taken at every study visit after screening. Sequencing of additional samples could be triggered by the external viral load monitor before and by the Sponsor virologist after the first interim analysis.
Immunologic Response	Separate blood samples were collected to allow for the analysis of immune markers at the RNA, protein and cell level, on the premise that these markers could play a role in the level of treatment response. This sampling was performed on Days 1, 14, 21, 28 and at Weeks 12 and 24. Analytes could be investigated by RNA quantification through polymerase chain reaction (PCR) or microarray technology.

Pharmacokinetics	Blood samples for determination of TMC435 pharmacokinetics were obtained in all subjects on Weeks 2, 4, 8, 12, 16, 24 and 48. Blood samples for determination of RBV pharmacokinetics clearance and exposure were drawn at Weeks 12, 24 and 48 in all subjects. A pharmacokinetic substudy was conducted to assess full pharmacokinetic profiles for TMC435 between 4 and 6 weeks after initiation of TMC435 treatment in a subset of subjects from each dose group. This required additional assessments as specified in a subprotocol for pharmacokinetic sampling.
Exploratory DNA Analyses – *IL28B*	A sample was collected at the baseline visit (subject to informed consent) for genomic deoxyribonucleic acid (DNA) typing, providing an opportunity to explore the genetic basis of host factors that might or could influence subject response to therapy, pharmacokinetics and side effects. Recently, an association between a genetic polymorphism near the *interleukin (IL) 28B* gene, encoding IFN-lambda-3 and response to PegIFN/RBV therapy has been reported. The samples that were collected from the subjects who gave a separate informed consent in this study were analyzed for the genetic *IL28B* polymorphism (locus rs1297860).
Patient Reported Outcome (PRO)	The EQ-5D questionnaire was self-administered by the subject at baseline, Weeks 24, 48, 72 and at time of early discontinuation (if applicable). The FSS questionnaire was self-administered by the subject at baseline, Weeks 4, 12, 24, 36, 48, 60, and 72 and at time of early discontinuation (if applicable). MRU data were not collected in this study.
Safety	
Adverse Events	Adverse events (AEs) were monitored throughout the trial from signing of the Informed Consent Form (ICF) onwards until the last trial-related visit.
Clinical Laboratory	Samples for hematology (including coagulation testing) and biochemistry were taken at screening, on Days 1, 7, 14, 28 and at Weeks 6, 8, 12, 16, 20, 24, 28, 36, 42, 48, 52, 72, and at time of early discontinuation (if applicable). At screening, a serum pregnancy test for all female subjects was done and samples were taken for HIV-1 and -2 tests, hepatitis A, B, C tests (hepatitis A antibody immunoglobulin M [IgM], HBsAg, and HCV antibody, respectively), and follicle stimulating hormone (FSH), AFP, HbA1c, and ANA. Thyroid stimulating hormone (TSH) was measured at screening, and every 12 weeks after start of treatment until the end of treatment (EOT). Urinalysis was performed at screening (including urine drug screening test), on Days 1, 7, 14, 28 and at Weeks 6, 8, 12, 16, 20, 24, 28, 36, 42, 48, 52, 72, and at time of early discontinuation (if applicable). A urine pregnancy test was performed at baseline, Days 7, 14, and at every visit from Day 28 onwards.
Cardiovascular Safety	Vital signs and standard 12-lead ECGs were recorded at screening, on Days 1, 14, 28, and every 12 weeks from Week 12 onwards until EOT, at the follow-up visits 4 weeks and 24 weeks after EOT, and at time of early discontinuation (if applicable).
Physical Examination	Physical examinations were performed at screening (including eye examinations), on Days 1, 14, and 28, and every 12 weeks from Week 12 onwards until EOT, at the follow-up visits 4 weeks and 24 weeks after EOT, and at time of early discontinuation (if applicable).
Statistical Methods Performed	Intent-to-treat analysis, descriptive statistics, frequency tabulations, Kaplan-Meier plots, exploratory subgroup analyses, logistic regression, Wilcoxon's matched pairs signed ranks test, longitudinal mixed effects model, generalized additive model (GAM) analysis.

Main Features of the Subject Sample and Summary of the Results

Subject Disposition	TMC12 PR48 100 mg	TMC24 PR48 100 mg	TMC48 PR48 100 mg	TMC12 PR48 150 mg	TMC24 PR48 150 mg	TMC48 PR48 150 mg	Placebo	All Subjects
Number of subjects treated, N	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
Exposure (TMC435/PBO+PR, weeks), median [range]	48.0 [3; 49]	48.0 [3; 48]	48.0 [1; 49]	48.0 [3; 48]	48.0 [3; 49]	48.0 [1; 49]	27.3 [1; 49]	48.0 [1; 49]
***Study Discontinuation**, n (%)*								
Completed the study	**61 (92.4)**	**60 (92.3)**	**58 (87.9)**	**61 (92.4)**	**63 (92.6)**	**61 (93.8)**	**59 (89.4)**	**423 (91.6)**
Discontinued the study	**5 (7.6)**	**5 (7.7)**	**8 (12.1)**	**5 (7.6)**	**5 (7.4)**	**4 (6.2)**	**7 (10.6)**	**39 (8.4)**
- Adverse event	0	0	0	1 (1.5)	0	0	0	1 (0.2)
- Subject lost to follow-up	1 (1.5)	1 (1.5)	4 (6.1)	2 (3.0)	1 (1.5)	1 (1.5)	2 (3.0)	12 (2.6)
- Withdrawal of consent	2 (3.0)	4 (6.2)	4 (6.1)	1 (1.5)	3 (4.4)	2 (3.1)	5 (7.6)	21 (4.5)
- Other	2 (3.0)	0	0	1 (1.5)	1 (1.5)	1 (1.5)	0	5 (1.1)
***Treatment Discontinuation**, n (%)*								
Completed TMC435/PBO and PR	**49 (74.2)**	**46 (70.8)**	**47 (71.2)**	**49 (74.2)**	**52 (76.5)**	**50 (76.9)**	**26 (39.4)**	**319 (69.0)**
Discontinued at least 1 study medication	**17 (25.8)**	**19 (29.2)**	**19 (28.8)**	**17 (25.8)**	**16 (23.5)**	**15 (23.1)**	**40 (60.6)**	**143 (31.0)**
- Adverse event	7 (10.6)	4 (6.2)	6 (9.1)	5 (7.6)	7 (10.3)	7 (10.8)	2 (3.0)	38 (8.2)
- Lost to follow-up	0	0	2 (3.0)	0	0	1 (1.5)	0	3 (0.6)
- Subject non-compliant	0	2 (3.1)	1 (1.5)	0	0	0	0	3 (0.6)
- Subject reached a virologic endpoint[a]	10 (15.2)	11 (16.9)	11 (16.7)	11 (16.7)	8 (11.8)	6 (9.2)	35 (53.0)	92 (19.9)
- Withdrawal of consent	0	2 (3.1)	0	1 (1.5)	1 (1.5)	0	2 (3.0)	6 (1.3)
- Other	1 (1.5)	0	1 (1.5)	0	0	1 (1.5)	1 (1.5)	4 (0.9)
Discontinued TMC435/PBO only	**0**	**1 (1.5)**	**1 (1.5)**	**0**	**4 (5.9)**	**1 (1.5)**	**0**	**7 (1.5)**
Discontinued RBV only	**0**	**0**	**0**	**1 (1.5)**	**0**	**1 (1.5)**	**0**	**2 (0.4)**
Discontinued TMC435/PBO/PR[b]	**17 (25.8)**	**18 (27.7)**	**18 (27.3)**	**16 (24.2)**	**12 (17.6)**	**13 (20.0)**	**40 (60.6)**	**134 (29.0)**

N: number of subjects; n: number of subjects with that observation; PBO: placebo; PR: PegIFNα-2a/RBV

[a] Subjects who met a virologic stopping rule.

[b] TMC435/PBO/PR discontinuation did not necessarily occur at the same time.

Demographic and Baseline Characteristics	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
Demographic Characteristics								
Gender, n (%)								
Female	22 (33.3)	21 (32.3)	21 (31.8)	21 (31.8)	25 (36.8)	17 (26.2)	24 (36.4)	151 (32.7)
Male	44 (66.7)	44 (67.7)	45 (68.2)	45 (68.2)	43 (63.2)	48 (73.8)	42 (63.6)	311 (67.3)
Region, n (%)								
Europe	34 (51.5)	46 (70.8)	46 (69.7)	49 (74.2)	49 (72.1)	43 (66.2)	46 (69.7)	313 (67.7)
North America	28 (42.4)	14 (21.5)	16 (24.2)	13 (19.7)	18 (26.5)	18 (27.7)	13 (19.7)	120 (26.0)
Asia Pacific	4 (6.1)	5 (7.7)	4 (6.1)	4 (6.1)	1 (1.5)	4 (6.2)	7 (10.6)	29 (6.3)
Race, n (%)								
White	59 (89.4)	60 (92.3)	62 (93.9)	61 (92.4)	61 (89.7)	63 (96.9)	62 (93.9)	428 (92.6)
Black	5 (7.6)	2 (3.1)	3 (4.5)	3 (4.5)	5 (7.4)	2 (3.1)	1 (1.5)	21 (4.5)
Asian	1 (1.5)	3 (4.6)	1 (1.5)	1 (1.5)	0	0	2 (3.0)	8 (1.7)
Other	1 (1.5)	0	0	1 (1.5)	2 (2.9)	0	1 (1.5)	5 (1.1)
Age at screening, years								
Median	51.5	50.0	50.0	48.0	51.5	50.0	50.5	50.0
[range]	[20; 68]	[20; 68]	[22; 69]	[20; 63]	[25; 68]	[21; 69]	[22; 66]	[20; 69]
BMI, kg/m²								
Median	27.55	26.50	26.60	26.40	27.45	27.20	27.95	27.20
[range]	[19.5; 42.3]	[18.9; 42.9]	[18.5; 48.7]	[18.2; 43.2]	[19.7; 42.4]	[18.9; 44.1]	[18.5; 40.5]	[18.2; 48.7]
Baseline Disease Characteristics								
***IL28B* Genotype**[a], n (%)								
N	**43**	**46**	**47**	**43**	**50**	**49**	**50**	**328**
CC	7 (16.3)	8 (17.4)	8 (17.0)	5 (11.6)	9 (18.0)	10 (20.4)	11 (22.0)	58 (17.7)
CT	32 (74.4)	30 (65.2)	28 (59.6)	30 (69.8)	32 (64.0)	28 (57.1)	32 (64.0)	212 (64.6)
TT	4 (9.3)	8 (17.4)	11 (23.4)	8 (18.6)	9 (18.0)	11 (22.4)	7 (14.0)	58 (17.7)
HCV RNA (log_{10} IU/mL)								
Median	6.49	6.68	6.64	6.62	6.60	6.55	6.61	6.60
[range]	[4.2; 7.5]	[4.8; 7.5]	[5.2; 7.5]	[3.5; 7.5]	[5; 7.7]	[4.9; 7.5]	[5.2; 7.6]	[3.5; 7.7]
HCV RNA Category (IU/mL), n (%)								
< 400000	3 (4.5)	3 (4.6)	7 (10.6)	4 (6.1)	4 (5.9)	5 (7.7)	4 (6.1)	30 (6.5)
[400000; 800000]	5 (7.6)	3 (4.6)	1 (1.5)	5 (7.6)	6 (8.8)	6 (9.2)	7 (10.6)	33 (7.1)
> 800 000	58 (87.9)	59 (90.8)	58 (87.9)	57 (86.4)	58 (85.3)	54 (83.1)	55 (83.3)	399 (86.4)
Metavir Score, n (%)								
N'	**65**	**63**	**66**	**66**	**67**	**64**	**64**	**455**
Score F0	6 (9.2)	3 (4.8)	6 (9.1)	5 (7.6)	11 (16.4)	1 (1.6)	7 (10.9)	39 (8.6)
Score F1	17 (26.2)	14 (22.2)	23 (34.8)	19 (28.8)	11 (16.4)	27 (42.2)	18 (28.1)	129 (28.4)
Score F2	21 (32.3)	17 (27.0)	9 (13.6)	18 (27.3)	21 (31.3)	16 (25.0)	16 (25.0)	118 (25.9)
Score F3	14 (21.5)	16 (25.4)	14 (21.2)	11 (16.7)	11 (16.4)	7 (10.9)	13 (20.3)	86 (18.9)
Score F4	7 (10.8)	13 (20.6)	14 (21.2)	13 (19.7)	13 (19.4)	13 (20.3)	10 (15.6)	83 (18.2)

Demographic and Baseline Characteristics	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
HCV Geno/Subtype (NS5B)[b], n (%)								
N'	**66**	**63**	**65**	**66**	**65**	**64**	**66**	**455**
1a	26 (39.4)	28 (44.4)	25 (38.5)	30 (45.5)	29 (44.6)	23 (35.9)	27 (40.9)	188 (41.3)
1b	39 (59.1)	34 (54.0)	39 (60.0)	36 (54.5)	34 (52.3)	41 (64.1)	39 (59.1)	262 (57.6)
1d	0	1 (1.6)	0	0	1 (1.5)	0	0	2 (0.4)
1e	0	0	0	0	1 (1.5)	0	0	1 (0.2)
1i	0	0	1 (1.5)	0	0	0	0	1 (0.2)
6p	1 (1.5)	0	0	0	0	0	0	1 (0.2)
Response to Prior PegIFN/RBV Therapy, n (%)								
Null Responder	16 (24.2)	16 (24.6)	18 (27.3)	17 (25.8)	17 (25.0)	17 (26.2)	16 (24.2)	117 (25.3)
Partial Responder	23 (34.8)	23 (35.4)	22 (33.3)	23 (34.8)	24 (35.3)	22 (33.8)	23 (34.8)	160 (34.6)
Relapser	27 (40.9)	26 (40.0)	26 (39.4)	26 (39.4)	27 (39.7)	26 (40.0)	27 (40.9)	185 (40.0)
Baseline Q80K, n (%)	8 (12.1)	5 (7.7)	11 (16.9)	8 (12.1)	6 (9.0)	10 (15.6)	5 (7.6)	53 (11.5)

N: number of subjects from intent-to-treat (ITT) population; N': number of subjects with data; n: number of subjects with that observation; BMI: body mass index; HCV: hepatitis C virus; RNA: ribonucleic acid

[a] *IL28B* data were only available for subjects who signed the separate ICF.

[b] Based on Virco NS5B assay. If the NS5B assay failed, the results from the Trugene assay (used for stratification) were used.

Efficacy Virologic Response, n/N (%)	**TMC12 PR48 100 mg**	**TMC24 PR48 100 mg**	**TMC48 PR48 100 mg**	**TMC12 PR48 150 mg**	**TMC24 PR48 150 mg**	**TMC48 PR48 150 mg**	**Placebo**
OVERALL POPULATION							
Primary Efficacy Endpoint							
SVR24	46/66 (69.7)	43/65 (66.2)	40/66 (60.6)	44/66 (66.7)	49/68 (72.1)	52/65 (80.0)	15/66 (22.7)
Secondary Efficacy Endpoints							
SVR12	46/66 (69.7)	44/65 (67.7)	40/66 (60.6)	44/66 (66.7)	49/68 (72.1)	52/65 (80.0)	15/66 (22.7)
Week 4 HCV RNA < 25 IU/mL undetectable (RVR)	44/66 (66.7)	38/65 (58.5)	35/66 (53.0)	41/66 (62.1)	46/68 (67.6)	43/65 (66.2)	1/66 (1.5)
HCV RNA < 25 IU/mL detectable or undetectable	52/66 (78.8)	47/65 (72.3)	54/66 (81.8)	57/66 (86.4)	56/68 (82.4)	56/65 (86.2)	2/66 (3.0)
cEVR[a]	54/66 (81.8)	48/65 (73.8)	48/66 (72.7)	53/66 (80.3)	58/68 (85.3)	54/65 (83.1)	13/66 (19.7)
EOTR[b]	53/66 (80.3)	51/65 (78.5)	53/66 (80.3)	53/66 (80.3)	57/68 (83.8)	56/65 (86.2)	27/66 (40.9)
Viral breakthrough	7/66 (10.6)	9/65 (13.8)	9/66 (13.6)	6/66 (9.1)	7/68 (10.3)	5/65 (7.7)	1/66 (1.5)
Viral relapse[c]	5/54 (9.3)	7/51 (13.7)	9/50 (18.0)	6/51 (11.8)	8/57 (14.0)	3/55 (5.5)	12/27 (44.4)
Stopping rule met[d]	4/66 (6.1)	3/65 (4.6)	2/66 (3.0)	5/66 (7.6)	2/68 (2.9)	2/65 (3.1)	34/66 (51.5)
NULL RESPONDERS							
Primary Efficacy Endpoint							
SVR24	6/16 (37.5)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	7/17 (41.2)	10/17 (58.8)	3/16 (18.8)
Secondary Efficacy Endpoints							
SVR12	6/16 (37.5)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	7/17 (41.2)	10/17 (58.8)	3/16 (18.8)
Week 4 HCV RNA < 25 IU/mL undetectable (RVR)	5/16 (31.3)	8/16 (50.0)	4/18 (22.2)	6/17 (35.3)	7/17 (41.2)	7/17 (41.2)	0/16 (0.0)
HCV RNA < 25 IU/mL detectable or undetectable	7/16 (43.8)	10/16 (62.5)	11/18 (61.1)	12/17 (70.6)	13/17 (76.5)	13/17 (76.5)	0/16 (0.0)
cEVR[a]	9/16 (56.3)	11/16 (68.8)	9/18 (50.0)	10/17 (58.8)	11/17 (64.7)	11/17 (64.7)	3/16 (18.8)
EOTR[b]	9/16 (56.3)	11/16 (68.8)	11/18 (61.1)	11/17 (64.7)	12/17 (70.6)	13/17 (76.5)	4/16 (25.0)
Viral breakthrough	4/16 (25.0)	5/16 (31.3)	4/18 (22.2)	2/17 (11.8)	4/17 (23.5)	4/17 (23.5)	0/16 (0.0)
Viral relapse[c]	2/9 (22.2)	1/11 (9.1)	3/11 (27.3)	2/11 (18.2)	5/12 (41.7)	3/13 (23.1)	1/4 (25.0)
Stopping rule met[d]	2/16 (12.5)	0/16 (0.0)	2/18 (11.1)	3/17 (17.6)	1/17 (5.9)	0/17 (0.0)	12/16 (75.0)

Efficacy Virologic Response, n/N (%)	**TMC12 PR48 100 mg**	**TMC24 PR48 100 mg**	**TMC48 PR48 100 mg**	**TMC12 PR48 150 mg**	**TMC24 PR48 150 mg**	**TMC48 PR48 150 mg**	**Placebo**
PARTIAL RESPONDERS							
Primary Efficacy Endpoint							
SVR24	16/23 (69.6)	11/23 (47.8)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
Secondary Efficacy Endpoints							
SVR12	16/23 (69.6)	12/23 (52.2)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
Week 4 HCV RNA < 25 IU/mL undetectable (RVR)	15/23 (65.2)	9/23 (39.1)	14/22 (63.6)	15/23 (65.2)	16/24 (66.7)	15/22 (68.2)	0/23 (0.0)
HCV RNA < 25 IU/mL detectable or undetectable	18/23 (78.3)	13/23 (56.5)	19/22 (86.4)	21/23 (91.3)	19/24 (79.2)	19/22 (86.4)	0/23 (0.0)
cEVR[a]	20/23 (87.0)	14/23 (60.9)	17/22 (77.3)	20/23 (87.0)	21/24 (87.5)	19/22 (86.4)	2/23 (8.7)
EOTR[b]	18/23 (78.3)	16/23 (69.6)	19/22 (86.4)	18/23 (78.3)	20/24 (83.3)	19/22 (86.4)	4/23 (17.4)
Viral breakthrough	3/23 (13.0)	3/23 (13.0)	3/22 (13.6)	4/23 (17.4)	2/24 (8.3)	1/22 (4.5)	1/23 (4.3)
Viral relapse[c]	2/19 (10.5)	5/16 (31.3)	5/18 (27.8)	1/17 (5.9)	2/20 (10.0)	0/19 (0.0)	2/4 (50.0)
Stopping rule met[d]	1/23 (4.3)	2/23 (8.7)	0/22 (0.0)	0/23 (0.0)	1/24 (4.2)	2/22 (9.1)	16/23 (69.6)
RELAPSERS							
Primary Efficacy Endpoint							
SVR24	24/27 (88.9)	23/26 (88.5)	20/26 (76.9)	20/26 (76.9)	24/27 (88.9)	23/26 (88.5)	10/27 (37.0)
Secondary Efficacy Endpoints							
SVR12	24/27 (88.9)	23/26 (88.5)	20/26 (76.9)	20/26 (76.9)	24/27 (88.9)	23/26 (88.5)	10/27 (37.0)
Week 4 HCV RNA < 25 IU/mL undetectable (RVR)	24/27 (88.9)	21/26 (80.8)	17/26 (65.4)	20/26 (76.9)	23/27 (85.2)	21/26 (80.8)	1/27 (3.7)
HCV RNA < 25 IU/mL detectable or undetectable	27/27 (100)	24/26 (92.3)	24/26 (92.3)	24/26 (92.3)	24/27 (88.9)	24/26 (92.3)	2/27 (7.4)
cEVR[a]	25/27 (92.6)	23/26 (88.5)	22/26 (84.6)	23/26 (88.5)	26/27 (96.3)	24/26 (92.3)	8/27 (29.6)
EOTR[b]	26/27 (96.3)	24/26 (92.3)	23/26 (88.5)	24/26 (92.3)	25/27 (92.6)	24/26 (92.3)	19/27 (70.4)
Viral breakthrough	0/27 (0.0)	1/26 (3.8)	2/26 (7.7)	0/26 (0.0)	1/27 (3.7)	0/26 (0.0)	0/27 (0.0)
Viral relapse[c]	1/26 (3.8)	1/24 (4.2)	1/21 (4.8)	3/23 (13.0)	1/25 (4.0)	0/23 (0.0)	9/19 (47.4)
Stopping rule met[d]	1/27 (3.7)	1/26 (3.8)	0/26 (0.0)	2/26 (7.7)	0/27 (0.0)	0/26 (0.0)	6/27 (22.2)

N: number of subjects; n: number of subjects with that observation
RVR: rapid virologic response (HCV RNA < 25 IU/mL undetectable at Week 4); SVR12: sustained virologic response 12 weeks after the planned EOT; SVR24: sustained virologic response 24 weeks after the planned EOT; viral breakthrough: confirmed increase of > 1 $\log_{10}$ IU/mL in HCV RNA from the lowest level reached or a confirmed HCV RNA of > 100 IU/mL in subjects whose HCV RNA had previously been below the LLOQ (i.e., < 25 IU/mL detectable or < 25 IU/mL undetectable); viral relapse: confirmed detectable HCV RNA during the follow-up period in subjects with HCV RNA < 25 IU/mL undetectable at EOT

[a] cEVR: complete EVR (HCV RNA < 25 IU/mL undetectable at Week 12)

[b] EOTR: virologic response at actual end of treatment (HCV RNA < 25 IU/mL undetectable)

[c] Percentages calculated relative to the number of subjects with undetectable HCV RNA at EOT and follow-up data available (N).

[d] Meeting virologic stopping rule at Week 4 (< 1 $\log_{10}$ IU/mL reduction in HCV RNA from baseline), Week 12 (< 2 $\log_{10}$ IU/mL reduction in HCV RNA from baseline), confirmed detectable (HCV RNA ≥ 25 IU/mL) at Weeks 24 or 36.

SVR24 Statistical Comparison (Logistic Regression)	N	SVR, n (%)	(95% CI)[a]	Comparison Versus Placebo	
				Difference in proportions (97.5% CI)[a]	p-value
Placebo	66	15 (16.8)	(8.0;25.5)		
TMC12PR48 100 mg	66	46 (68.2)	(55.9;80.5)	51.4 (33.0;69.9)	< 0.001*
TMC24PR48 100 mg	65	43 (65.6)	(53.0;78.2)	48.8 (30.1;67.6)	< 0.001*
TMC48PR48 100 mg	66	40 (58.4)	(45.3;71.4)	41.6 (22.5;60.7)	< 0.001*
TMC12PR48 150 mg	66	44 (66.2)	(53.7;78.6)	49.4 (30.7;68.1)	< 0.001*
TMC24PR48 150 mg	68	49 (72.4)	(61.1;83.7)	55.6 (38.0;73.3)	< 0.001*
TMC48PR48 150 mg	65	52 (79.9)	(69.4;90.3)	63.1 (46.3;80.0)	< 0.001*
TMC 100 mg	197	129 (64.2)	(56.8;71.5)	47.4 (34.3;60.5)	< 0.001*
TMC 150 mg	199	145 (73.2)	(66.4;80.0)	56.4 (43.6;69.3)	< 0.001*

N: number of subjects with data; n: number of subjects with SVR; CI: confidence interval; SVR24: sustained virologic response 24 weeks after the planned EOT.

[a] Proportions, differences in proportions and their respective CIs are derived from a logistic regression model with factors for treatment group, baseline $\log_{10}$ HCV RNA, the stratification factors genotype (1b, 1a/other) and prior response (null responder, partial responder, or relapser).

* Statistically significant difference; for the pooled TMC435 dose groups [100- or 150-mg dose] the p-value threshold was < 0.025 and for the individual treatment groups the p-value threshold was < 0.0167.

In the overall population, the majority of TMC435-treated subjects achieved SVR24 (primary endpoint) and a larger proportion of subjects with SVR24 were observed across the TMC435 treatment groups (range 60.6% to 80.0%) compared to the placebo group (22.7%). In the overall population, comparable sustained virologic response (SVR) rates were observed between the different TMC435 doses (100- and 150-mg q.d.) and different TMC435 duration groups (i.e., 12, 24 or 48 weeks). In each of the 3 subpopulations (null responders, partial responders and relapsers), a higher proportion of subjects in all TMC435 treatment groups achieved SVR24 compared to placebo.

The differences in SVR24 rate between the pooled TMC435 groups (100- or 150-mg dose) and the placebo group were each statistically significant (p-value threshold < 0.025). The difference in SVR24 rate between all TMC435 treatment groups individually and the placebo group were also statistically significant (p-value threshold < 0.0167). There was a good correlation observed between SVR12 and SVR24: 274 out of the 275 subjects with SVR12 also had SVR24.

A trend for higher SVR24 was observed in the prior null and partial responder population treated with TMC435 150 mg compared to 100 mg, while SVR24 rates were similar between the 2 TMC435 dose groups in prior relapsers. There were no consistent differences between the different TMC435 treatment durations across the TMC435 doses and subpopulations.

In the overall population and each of the 3 subpopulations, higher proportions of subjects achieved on treatment virologic responses (e.g., rapid virologic response [RVR] and EOTR) in the TMC435 treatment groups compared to the placebo group.

Overall, virologic failure was observed in 13.8% to 30.3% TMC435-treated subjects across the TMC435 treatment groups and in 72.7% placebo-treated subjects. For TMC435-treated subjects; the main reason for virologic failure was meeting a viral breakthrough stopping rule and viral relapse, and for placebo-treated subjects the main reason was meeting a virologic stopping rule at Weeks 4, 12, 24 or 36.

In the overall population, more subjects in the TMC435 treatment groups (range 70.8 to 76.9%) completed their assigned treatment regimen than in the placebo group (39.4%). The main reason for treatment discontinuation was meeting a virologic stopping rule (including a viral breakthrough stopping rule) which was reported more frequently in placebo-treated subjects (53.0%) compared to TMC435-treated subjects (range 9.2% to 16.9%).

Overall, viral breakthrough was observed in 7.7% to 13.8% TMC435-treated subjects across the TMC435 treatment groups and in 1.5% of the placebo-treated subjects. There was a trend for lower viral breakthrough rates for subjects in the 150-mg TMC435 dose groups compared to subjects in the 100-mg TMC435 dose groups. Viral breakthrough mostly occurred before or at Week 12 for all TMC435-treated subjects. Emerging mutations in the HCV NS3 protease domain, known to confer reduced susceptibility to TMC435 in vitro, were detected in 41 out of 42 TMC435-treated subjects with viral breakthrough and available NS3 sequencing information (mostly D168V or R155K alone or combination sof mutations Q80K or R, R155K and/or D168E).

Amongst TMC435-treated subjects, viral breakthrough was observed most frequently amongst null responders (range 11.8% to 31.3%) compared to partial responders (range 4.5% to 17.4%) and relapsers (range 0.0% to 7.7%).

Overall, viral relapse was observed in 5.5% (3/55) to 18.0% (9/50) TMC435-treated subjects across the TMC435 treatment groups compared to 44.4% (12/27) placebo-treated subjects. All but 2 TMC435-treated subjects with viral relapse experienced viral relapse within 12 weeks after actual EOT. In 34 out of 35 (97.1%) TMC435-treated subjects with viral relapse and available NS3 sequence information, emerging mutations in the HCV NS3 protease domain (mostly R155K or D168V alone or combinations of mutations Q80K or R, R155K and/or D168E) were detected at the time of viral relapse.

Overall, a trend for higher relapse in TMC435-treated subjects was observed in null responders (range 9.1% to 41.7%) compared to partial responders (range 0.0% to 31.3%) and relapsers (range 0.0% to 13.0%).

Subgroup analyses showed that SVR rates and on treatment virologic response rates were generally higher and on treatment virologic failure and viral relapse were generally lower in TMC435-treated subjects compared to subjects in the placebo group, independent of the HCV genotype, Metavir score and the presence of Q80K at baseline. Amongst TMC435 treated subjects in both 100-mg and 150-mg dose groups there was a trend for lower virologic response rates including SVR, and a trend for higher viral breakthrough, on treatment virologic failure and viral relapse rates in subjects infected with HCV genotype 1a compared to subjects infected with HCV genotype 1b.

Among the TMC435 150 mg treated subjects infected with HCV genotype 1a, SVR, viral breakthrough and relapse rates were similar between subjects with and without Q80K at baseline, while for some on treatment virologic response parameters (e.g., RVR) a trend for lower responses were seen for subjects harboring Q80K at baseline.

A trend for higher SVR rates were noted with the 150-mg TMC435 dose group compared to the 100-mg dose group across most subgroups, including in subjects with Metavir score F3-F4 and F4, in subjects infected with subtype 1a, in the presence of Q80K polymorphisms at baseline and in subjects with a higher body mass index (BMI).

None of the TMC435-treated subjects with HCV RNA > 1000 IU/mL at Week 4 achieved SVR24. SVR24 rates were higher in TMC435-treated subjects with HCV RNA < 25 IU/mL undetectable compared to subjects with HCV RNA < 25 IU/mL detectable at Week 4. This trend was less apparent in the TMC435 150-mg dose group.

Within each *IL28B* genotype, higher response rates and lower relapse and virologic failure rates were observed in TMC435-treated subjects compared to placebo-treated subjects. In both TMC435 dose groups, a trend for higher virologic response rates were noted in subjects with the *IL28B* CC genotype compared to the *IL28B* CT and TT genotypes.

As measured by the PRO tools used in this study (EQ-5D and FSS), fatigue and other health-related dimensions appeared to worsen during therapy in all treatment groups. The addition of TMC435 to PegIFNα-2a/RBV treatment did not impact fatigue and other health-related dimensions negatively as evidenced by the absence of major differences between the treatment groups. After the end of therapy, fatigue and other health-related dimensions returned to baseline values in all treatment groups.

Pharmacokinetics (Substudy)

TMC435 Pharmacokinetic Parameter	100 mg TMC435 q.d. + PegIFNα-2a/RBV		150 mg TMC435 q.d. + PegIFNα-2a/RBV	
	Geometric Mean	mean ± SD, t_{max}: median [range]	Geometric Mean	mean ± SD, t_{max}: median [range]
n	33[a]	33[a]	26	26
C_{0h}, ng/mL	517.5	1103 ± 1488	889.1	1440 ± 1864
C_{min}, ng/mL	438.6	986.7 ± 1407	818.3	1345 ± 1795
C_{max}, ng/mL	1943	2626 ± 2192	3218	3953 ± 2893
t_{max}, h	-	6.0 [4.0 - 12.0]	-	6.0 [4.0 - 8.0]
AUC_{24h}, ng.h/mL	26010	39720 ± 41790	45580	59810 ± 55650
$C_{ss,av}$, ng/mL	1084	1655 ± 1741	1899	2492 ± 2319
FI, %	123.4	134.3 ± 49.57	120.5	125.9 ± 34.77

AUC_{24h}: area under the plasma concentration-time curve from time of administration to 24 hours after dosing; C_{0h}: predose plasma concentration; C_{min}: minimum plasma concentration; C_{max}: maximum plasma concentration; $C_{ss,av}$: average steady-state plasma concentration; FI: fluctuation index; SD: standard deviation; t_{max}: time to reach the maximum plasma concentration

[a] n = 32 for AUC_{24h}, $C_{ss,av}$ and FI

After intake of TMC435 at 150 mg q.d., geometric mean values for minimum plasma concentration (C_{min}), maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time of administration to 24 hours after dosing (AUC_{24h}) at steady-state were about 1.8 times higher compared to after intake of TMC435 at 100 mg q.d., both in combination with PegIFNα-2a and RBV. The increase in systemic exposure to TMC435 for the 100- to 150-mg q.d. dose increase was more than dose proportional.
The median time to reach maximum plasma concentrations of TMC435 was about 6 hours after dosing for both dose groups, with comparable ranges.

Population Pharmacokinetics (Main Study)

TMC435 Pharmacokinetic Parameter Median [range]	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 65	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 64
AUC_{24h}, ng.h/mL	16587.0 [4897; 95030]	18492.5 [8252; 173240]	21409.0 [6949; 109920]	47061.8 [7301; 313135]	43015.0 [12777; 357415]	38564.5 [15233; 538010]
C_{0h}, ng/mL	380.5 [34; 3599]	411.3 [101; 6943]	529.8 [62; 4219]	1323.5 [37; 12478]	1074.0 [110; 14303]	886.1 [150; 21825]
CL/F, L/h	7.8 [1; 26]	7.0 [1; 16]	5.9 [1; 19]	3.8 [0; 27]	4.4 [0; 16]	5.1 [0; 14]
$C_{ss,av}$, ng/mL	691.1 [204; 3960]	770.5 [344; 7218]	892.0 [290; 4580]	1960.9 [304; 13047]	1792.3 [532; 14892]	1606.9 [635; 22417]

N: number of subjects; AUC_{24h}: area under the plasma concentration-time curve from time of administration to 24 hours after dosing; C_{0h}: predose plasma concentration; CL/F: clearance/fraction of drug; $C_{ss,av}$: average steady-state plasma concentration;

TMC435 exposure following 100 and 150 mg q.d. increased in a more than dose proportional manner consistent with previous findings. Despite this increase, a significant overlap in TMC435 exposures was observed following TMC435 doses of 100 and 150 mg q.d. TMC435 exposure in the different groups at the same dose was comparable. There was no difference in the pharmacokinetics of TMC435 by genotype 1 subtype, Metavir score, race, or gender, response to prior PegIFN/RBV therapy and presence of Q80K at baseline, although the number of subjects in some of these subgroups was small.

Safety

Adverse Events Overall treatment period[a]	**TMC12 PR48 100 mg N = 66**	**TMC24 PR48 100 mg N = 65**	**TMC48 PR48 100 mg N = 66**	**TMC12 PR48 150 mg N = 66**	**TMC24 PR48 150 mg N = 68**	**TMC48 PR48 150 mg N = 65**	**All TMC435 N = 396**	**Placebo N = 66**
Median exposure to TMC435/PBO/PR (weeks), median [range]	48.0 [3, 49]	48.0 [3, 48]	48.0 [1, 49]	48.0 [3, 48]	48.0 [3, 49]	48.0 [1, 49]	48.0 [1; 49]	27.3 [1; 49]
Any AE, n (%)	**64 (97.0)**	**62 (95.4)**	**65 (98.5)**	**65 (98.5)**	**66 (97.1)**	**64 (98.5)**	**386 (97.5)**	**64 (97.0)**
Most frequently reported AEs by preferred term (i.e., in > 25% of TMC435-treated subjects)								
Fatigue	30 (45.5)	28 (43.1)	34 (51.5)	26 (39.4)	28 (41.2)	28 (43.1)	174 (43.9)	29 (43.9)
Headache	18 (27.3)	19 (29.2)	23 (34.8)	29 (43.9)	26 (38.2)	24 (36.9)	139 (35.1)	24 (36.4)
Pruritus	19 (28.8)	26 (40.0)	21 (31.8)	20 (30.3)	25 (36.8)	24 (36.9)	135 (34.1)	11 (16.7)
Influenza-like Illness	23 (34.8)	24 (36.9)	21 (31.8)	16 (24.2)	18 (26.5)	14 (21.5)	116 (29.3)	13 (19.7)
Neutropenia	16 (24.2)	15 (23.1)	15 (22.7)	18 (27.3)	18 (26.5)	20 (30.8)	102 (25.8)	11 (16.7)
Any grade 3 or 4 AE	21 (31.8)	21 (32.3)	13 (19.7)	24 (36.4)	24 (35.3)	25 (38.5)	128 (32.3)	17 (25.8)
TMC435/PBO-related AE[b]	56 (84.8)	49 (75.4)	50 (75.8)	51 (77.3)	53 (77.9)	52 (80.0)	311 (78.5)	43 (65.2)
Any AE with fatal outcome	0	0	0	1 (1.5)	0	0	1 (0.3)	0
Any SAE	3 (4.5)	5 (7.7)	3 (4.5)	7 (10.6)	5 (7.4)	8 (12.3)	31 (7.8)	4 (6.1)
Any AE leading to permanent stop	7 (10.6)	4 (6.2)	5 (7.6)	5 (7.6)	7 (10.3)	7 (10.8)	35 (8.8)	3 (4.5)
TMC435/PBO only	0	1 (1.5)	2 (3.0)	0	5 (7.4)	1 (1.5)	9 (2.3)	0
TMC435/PBO and PR	6 (9.1)	3 (4.6)	2 (3.0)	3 (4.5)	2 (2.9)	5 (7.7)	21 (5.3)	3 (4.5)
PR only	1 (1.5)	0	0	0	1 (1.5)	0	2 (0.5)	0

N: number of subjects; n: number of subjects with that observation; AE: adverse event; PBO: placebo;
PR: PegIFNα-2a/RBV; SAE: serious adverse event

[a] From the date of first intake of study medication (TMC435/placebo or PegIFNα-2a or RBV) until the date of last intake of PegIFNα-2a or RBV + 4 weeks).

[b] Treatment-related is defined as possibly, probably, or very likely related to TMC435/PBO by the investigator.

The majority of AEs were grade 1 or 2 in severity. Serious adverse events (SAEs) occurred in a comparable proportion of subjects across groups: in 31 (7.8%) TMC435-treated subjects and in 4 (6.1%) subjects in the placebo group. By preferred term, all SAEs were reported in at most 3 subjects across all TMC435 treatment groups. AEs that led to permanent discontinuation of at least one study medication were reported in 35 (8.8%) TMC435-treated subjects and in 3 (4.5%) subjects in the placebo group. One [redacted] subject in the TMC12PR48 150 mg group died due to the SAEs of bacterial meningitis, brain injury (onset date at Week 32, not related to TMC435 and RBV, but probably related to PegIFNα-2a) and cerebral hemorrhage (onset date at Week 33, not related to TMC435, RBV and PegIFNα-2a).

Special attention was given to the following AEs: hepatobiliary, rash (all types), anemia, neutropenia and photosensitivity AEs. The majority of these events were of grade 1 or 2. A benign, isolated and reversible increase in plasma bilirubin levels was observed in TMC435-treated subjects, but these bilirubin elevations were not associated with elevation of liver enzyms. Hepatobiliary events (mainly of hyperbilirubinemia type) were reported at a frequency of 7.3% in TMC435 subjects vs. 4.5% in the placebo group. Anemia occurred in 19.4% TMC435-treated subjects vs. 19.7% placebo-treated subjects.

Rash (all types) and pruritus were reported with higher frequency during the overall treatment period in the TMC435 groups than in the placebo group (26.5% vs. 18.2% for rash, 34.1% vs. 16.7% for pruritus); photosensitivity was reported in 3.5% of the TMC435 subjects vs. 1.5% in the placebo group. Neutropenia AEs (reported as preferred terms 'neutropenia' and 'neutrophil count decreased' combined) were also reported more frequently in the TMC435 groups (28.0% vs. 18.2%), however no difference was observed when objective laboratory neutrophil count shifts from baseline were compared across groups. It is possible that the difference in overall treatment exposure between TMC435 and the control group (median duration of 48.0 weeks vs. 27.3 weeks) influenced the frequency with which some AEs known to occur with PR were reported during the overall treatment period.

Clinical Laboratory Tests

Apart from bilirubin-related abnormalities (hyperbilirubinemia, direct and indirect bilirubin above normal limits), which were more commonly seen in the TMC435 treatment groups than in the placebo group, there were no substantial differences between treatment groups for any of the laboratory abnormalities. Overall, incidences of grade 3 or 4 laboratory abnormalities and laboratory-related AEs were low.

Changes over time in the clinical laboratory parameters, if any, returned to baseline values after EOT. Mild increases in mean bilirubin (direct, indirect, and total) were seen in all treatment groups during the first 2 weeks of treatment. Bilirubin levels were higher in subjects dosed with 150 mg of TMC435, and stabilized or decreased during further TMC435 dosing. Bilirubin levels returned to baseline values after TMC435 dosing was complete.

Cardiovascular Safety

There were no clinically relevant changes over time in vital signs or ECG parameters, and no meaningful differences between the treatment groups regarding the incidence of treatment-emergent abnormalities in cardiovascular parameters.

Pharmacokinetic/Pharmacodynamic Relationships

In general, PK/PD analyses relating TMC435 exposures to virologic response parameters showed no consistent relationship. However, there was a trend for a shorter time to undetectable HCV RNA in the subjects with higher exposure to TMC435 in partial and null responders.

No trends were observed when exploring the relationship between TMC435 exposure (AUC_{24h} quartiles) and the incidence or severity of AEs or treatment discontinuations due to AEs. A trend for mild increases from baseline in direct and total bilirubin and alkaline phosphatase (ALP) was observed with higher exposure to TMC435. No consistent trend was observed between TMC435 exposures and changes from baseline in ALT, AST and indirect bilirubin.

Conclusions

TMC435 in combination with PegIFNα-2a/RBV showed significantly higher SVR rates in the overall population of treatment-experienced subjects across all TMC435 treatment groups compared to the placebo group. In addition, substantially higher SVR rates were seen in all TMC435 treatment groups compared to placebo in all 3 subpopulations (previous null and partial responders, and relapsers). A trend for higher SVR rates was observed in the TMC435 150-mg dose group compared to the 100-mg dose group in null and partial responders, as well as across multiple subgroups (including subjects with Q80K, higher body mass index [BMI] and advanced fibrosis).

Treatment with TMC435 at doses of 100 or 150 mg q.d. was generally safe and well tolerated in treatment-experienced subjects infected with genotype 1 HCV. Mild elevations in bilirubin mainly seen in the 150-mg TMC435 q.d. dose were reversible and not associated with concomitant increases in transaminases.

The results of this study support the selection of TMC435 150 mg q.d. administered for 12 weeks in combination with 48 weeks of PegIFN/RBV, as the dose and duration of TMC435 therapy in null and partial responders to previous PR regimens with chronic genotype 1 HCV infection. High SVR rates observed in previous relapsers support assessment/evaluation of 12 weeks TMC435 150 mg q.d. in combination with a response-guided 24 or 48 weeks total treatment duration of PegIFN/RBV in this population.