Janssen Research & Development

Clinical Study Report Synopsis
[TMC435-TiDP16-C205; Phase IIb]

TMC435 (Simeprevir)

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- 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

Study Identification and Protocol Summary

Company: Janssen Research & Development* **Trade Name**: - **Indication**: Hepatitis C	**Drug Substance**: TMC435 **Trial no**.: TMC435-TiDP16-C205 **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 peginterferon alfa 2a and ribavirin in treatment-naïve genotype 1 hepatitis C infected subjects.	
Coordinating Investigator: [redacted] M. D., [redacted] SA	**Country**: international
Study Period: Start: 12-May-2009 End: 27-Apr-2011	**No. of Investigators**: 79 **No. of Subjects**: 386

Objectives:

The primary objective of the study was to evaluate the efficacy of 4 different regimens of TMC435 in combination with peginterferon alfa-2a (PegIFNα-2a) and ribavirin (RBV), defined as the proportion of subjects with sustained virologic response at Week 72 (subjects with undetectable plasma HCV RNA [< 25 IU/mL undetectable] at the end of treatment and at Week 72), compared to the control group receiving PegIFN/RBV in combination with TMC435-matched placebo.

The secondary objectives of this study were:

- To evaluate and compare the antiviral activity of TMC435 with PegIFN/RBV when administered as different regimens versus control (PegIFN/RBV) over the study period;
- To evaluate and compare the safety and tolerability of the TMC435-containing regimens versus PegIFN/RBV over the study period;
- To determine the frequency, kinetics and viral genetics of virologic failures;
- To evaluate the pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship for efficacy and safety of TMC435;
- To collect Medical Resource Utilization information, and to evaluate Quality of Life (QoL) and the level of fatigue over the study period.

Design:

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

This was a randomized, 5-arm, double-blind, placebo-controlled study to compare the efficacy, tolerability and safety of different TMC435 regimens combined with PegIFNα-2a and RBV versus PegIFNα-2a plus RBV alone in adult treatment-naïve subjects with chronic genotype 1 HCV infection. This study was referred to as PILLAR (i.e., Protease Inhibitor TMC435 study assessing optimaL dose and duration as once daiLy Anti-viral Regimen).

Four hundred treatment-naïve subjects with documented genotype 1 HCV infection were planned to be included in the study. Subjects were to have a screening plasma HCV ribonucleic acid (RNA) level of > 100,000 IU/mL and no cirrhosis or human immunodeficiency virus (HIV)-infection. Subjects were randomized in a 1:1:1:1:1 fashion to one of five different arms. In treatment arms 1 and 2, subjects received 12 weeks of triple therapy with 75 or 150 mg TMC435 once daily (q.d.) plus PegIFNα-2a (Pegasys®) and RBV (Copegus®) followed by treatment with PegIFN/RBV plus TMC435-matched placebo. In treatment arms 3 and 4, subjects received 24 weeks of triple therapy with 75 or 150 mg TMC435 q.d. plus PegIFN/RBV.

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Design, Cont'd:

Total treatment duration with PegIFN/RBV in treatment arms 1-4 was response-guided 24 or 48 weeks. In subjects who achieved plasma HCV RNA levels < 25 IU/mL at Week 4 and had undetectable plasma HCV RNA levels at Weeks 12, 16, and 20 were to stop all study medication (TMC435/placebo plus PegIFN/RBV) at Week 24. All other subjects in those arms continued PegIFN/RBV until Week 48 (TMC435/placebo was completed at Week 24). In treatment arm 5 (control group), subjects were treated with PegIFN/RBV treatment for 48 weeks and TMC435-matched placebo for the first 24 weeks. No response-guided treatment was applied in treatment arm 5. An external HCV RNA monitor who was unblinded to treatment informed the investigator of the required treatment action while the investigator and subjects remained blinded to treatment and HCV RNA values: treatment was to be discontinued if subjects were eligible for shorter treatment duration of 24 weeks based on response-guided treatment (RGT) criteria or if they had met a stopping rule, or if PegIFN/RBV was to be administered until Week 48 if subjects were not eligible for shorter treatment. For all subjects, there was a post-treatment follow-up period up to 72 weeks after treatment initiation.

Two unblinded interim analyses were conducted. A first interim analysis was conducted when all randomized subjects had reached Week 24 or discontinued earlier. The second interim analysis was conducted when all subjects had reached Week 48 or discontinued earlier. Both interim analyses were conducted to support the dose selection and the further clinical development of TMC435 and to support regulatory submissions. This report presents the results of the final analysis, which was performed when all randomized subjects had completed the last study-related visit or discontinued earlier.

Subject Selection

Inclusion Criteria:

1. Male or female subject aged between 18 and 70 years, inclusive;
2. Documented chronic hepatitis C 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 liver biopsy was performed within 2 years prior to screening, this could be done on a separate day during the screening period;
3. Subject with genotype-1 HCV infection (confirmed at screening);
4. Subjects with plasma HCV RNA of > 100,000 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. Subject was not receiving and had never received (Peg)IFN, RBV or any other approved or investigational treatment for chronic HCV infection;
   Note: prior HCV treatment with herbal products or nutritional elements was allowed but should be stopped at screening.
6. Body weight between 40 and 125 kg;
7. Subject (male with partner of childbearing potential or female of childbearing potential) agreed to use 2 effective methods of contraception (one 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, or was vasectomized (male subject) or had a vasectomized partner (female subjects), or was a female (subject or partner of male subject) of non-childbearing potential;
8. Informed consent form signed voluntarily before the first study-related activity;
9. Subject was able to comply with the protocol requirements.

Exclusion Criteria

1. Cirrhosis confirmed by biopsy taken within 2 years prior to enrollment;
2. Decompensated liver disease defined as history or presence of ascites, hepatic encephalopathy, bleeding esophageal, or gastric varices.
3. 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, or primary biliary cirrhosis.
4. Infection/co-infection with non-genotype 1 HCV;
5. Co-infection with human immunodeficiency virus type 1 or type 2 (HIV-1 or HIV-2) (positive HIV-1 or HIV-2 antibodies test), or hepatitis B virus infection (hepatitis B surface antigen [HBsAg]);
6. 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);
7. Evidence of hepatocellular carcinoma (e.g., alpha-fetoprotein [AFP] > 50 ng/mL);
8. *Note:* Subjects with AFP levels between 50 and 100 ng/mL could be included if they had a negative ultrasound or other abdominal imaging.
9. Medical conditions which 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 suicidal 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 study. 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., HbA1c ≥ 7%, diabetic retinopathy);
    - Renal impairment (e.g., serum creatinine > 1.5 x upper limit of laboratory normal range [ULN] or creatinine clearance < 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.
10. Any active clinically significant disease other than hepatitis C (e.g., chronic pancreatitis) or findings during screening of medical history or 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 study;
11. Subject with organ transplant (other than cornea or hair transplant or skin graft);

Exclusion Criteria, Cont'd

12. Subject with 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 which were exclusion criteria for PegIFNα-2a or RBV treatment (please refer to the manufacturer's prescribing information for details):
      - Platelet count < 90,000/mm^3;
      - Absolute neutrophil count < 1,500 cells/mm^3;
      - 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.
13. History, clinical suspicion or evidence of current misuse of alcohol, barbiturate, amphetamine, recreational or narcotic drugs, which in the investigator's opinion could compromise the subject's safety and/or compliance with the study procedures;
    Note:
    - Urine was tested at screening to check the current use of amphetamines, cocaine, opioids, and barbiturates. In case of history, clinical suspicion or evidence of current misuse, subjects with a positive urine drug test were not eligible.
    - Subjects with a positive history and for whom the period of drug/alcohol misuse had ended at least 1 year before the first administration of study medication could be included at the investigator's discretion.
14. Pregnant, planning on becoming pregnant, or breast feeding female subject or male subject whose partner was pregnant or planning on becoming pregnant;
15. Concurrent participation in a clinical study with another investigational drug or device within 30 days of the screening visit;
    Known allergy or hypersensitivity to any of the components of the investigational medication or to any of the components of PegIFNα-2a s.c. solution or RBV tablets.

Treatment	**TMC435**	**placebo**	**PegIFNα-2a (Pegasys®)**	**RBV (Copegus®)**
Concentration Dosage Form (F No.) Usage	75 mg/capsule F021 oral	- F022 capsules oral	180 µg solution injection s.c.	200 mg tablet oral
Batch Numbers	09C09/F021	09C16/F022	B1111, B1097, B1116	105873, 112532, 109219

Dose Regimen	**Treatment arm 1 (TMC12/PR 75 mg q.d.)** Triple therapy of 75 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (twice daily regimen) and PegIFNα-2a 180 µg/week for 12 weeks (Week 1 to Week 12) followed by 12 weeks of TMC435-matched placebo q.d. plus PegIFN/RBV (Week 13 to Week 24) **Treatment arm 2 (TMC12/PR 150 mg q.d.)** Triple therapy of 150 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (twice daily regimen) and PegIFNα-2a 180 µg/week) for 12 weeks (Week 1 to Week 12) followed by 12 weeks of TMC435-matched placebo q.d. and PegIFN/RBV (Week 13 to Week 24) **Treatment arm 3 (TMC24/PR 75 mg q.d.)** Triple therapy of 75 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (twice daily regimen) and PegIFNα-2a 180 µg/week for 24 weeks (Week 1 to Week 24) **Treatment arm 4 (TMC24/PR 150 mg q.d.)** Triple therapy of 150 mg TMC435 q.d. plus RBV 1000 or 1200 mg/day[a] (twice daily regimen) and PegIFNα-2a 180 µg/week for 24 weeks (Week 1 to Week 24) **Treatment arm 5 (placebo)** TMC435-matched placebo q.d. plus RBV 1000 or 1200 mg/day[a] (twice daily regimen) and PegIFNα-2a 180 µg/week for 24 weeks (Week 1 to Week 24) followed by PegIFN/RBV treatment for 24 weeks (Week 25 to Week 48) [a] RBV dosing was weight-based: < 75 kg = 1000 mg/day, ≥ 75 kg = 1200 mg/day. Subjects in treatment arms 1-4 who achieved plasma HCV RNA levels < 25 IU/mL at Week 4 and had undetectable plasma HCV RNA levels at Weeks 12, 16, and 20 were to stop all study medication (TMC435/placebo plus PegIFN/RBV) at Week 24. All other subjects in those arms continued PegIFN/RBV until Week 48 (TMC435/placebo was completed at Week 24).
Duration of Treatment	24 weeks for subjects in treatment arms 1-4 who achieved plasma HCV RNA levels < 25 IU/mL at Week 4 and had undetectable plasma HCV RNA levels at Weeks 12, 16, and 20 and 48 weeks for subjects who did not fulfill these criteria and subjects in treatment arm 5 (placebo group).
Duration of Study	Screening: approximately 6 weeks Treatment: up to 48 weeks Follow-up: up to 48 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 entire treatment period: - any other anti-HCV therapy other than TMC435, interferon and RBV; - all investigational drugs, except for TMC435; - immunomodulators (e.g. interleukins, systemic corticosteroids), except for Pegasys®. - experimental vaccines. - erythropoiesis stimulating agents. Because of the interaction potential of TMC435 with medications that are substrates, inhibitors, or inducers of cytochrome P450 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. Cytochrome P450 3A4 inducers were not to be used during the entire treatment period from screening onwards. For guidance on the use of medications concomitantly with PegIFNα-2a (Pegasys®), or RBV (Copegus®), the package inserts of these drugs were to be consulted.

Assessments	
Antiviral Activity	Samples for the determination of plasma HCV RNA levels were taken at every study visit. Plasma HCV RNA levels were measured using the Roche COBAS TaqMan HCV test version 2.0 with a lower limit of quantification (LLOQ) of 25 IU/mL. Plasma HCV RNA below the LLOQ is either assigned as 'HCV RNA < 25 IU/mL detectable' if traces of HCV RNA were detected or' < 25 IU/mL undetectable' if no HCV RNA was detected. 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 HCV NS3/4A were taken at every study visit after screening. Sequencing at baseline was performed by default and sequencing of additional samples could be triggered by the external HCV RNA monitor before and by the sponsor virologist after the first interim analysis.
Pharmacokinetics	Blood samples for determination of TMC435 plasma pharmacokinetics were obtained in all subjects on Weeks 2, 4, 8, 12, 16, and 24. Blood samples for optional determination of RBV and PegIFNα-2a concentrations were drawn at Weeks 12 and 24 in all subjects. Ribavirin and PegIFNα-2a concentrations were not analyzed in this study. A pharmacokinetic substudy was conducted to assess full pharmacokinetic profiles for TMC435 between 4 and 6 weeks after initiation of a treatment regimen 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 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 interferon-lambda-3 (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 EuroQol – 5 dimensions (EQ-5D) questionnaire was self-administered by the subject at baseline, Weeks 24, 48, 72 and at time of early discontinuation. The Fatigue Severity Scale (FSS) questionnaire self-administered by the subject at baseline, Weeks 4, 12, 24, 36, 48, 60, and 72 and at time of early discontinuation. Medical resource utilization data were not collected in this study.
Safety	
Adverse Events	Adverse events (AEs) were monitored throughout the study from signing of the Informed Consent Form (ICF) onwards until the last study-related visit.
Clinical Laboratory	Samples for hematology, biochemistry (fasted for at least 10 hours), and coagulation were taken at screening, on Days 1, 7, 14, 28 and at Weeks 6, 8, 12, 16, 20, 24, 28 (only for subjects who stopped treatment at Week 24), 36 and 42 (only for subject continuing PegIFN/RBV until Week 48), 48, 52 (only for subject continuing PegIFN/RBV until Week 48), 72, and at time of dropout (if applicable). At screening, samples were taken for HIV-1 and -2 tests, hepatitis A, B, C tests (hepatitis A antibody IgM, HBsAg, and HCV antibody, respectively), and testing follicle stimulating hormone and AFP. Urinalysis was performed at screening, Days 1, 7, 14, 28 and at Weeks 6, 8, 12, 16, 20, 24, 28, 36, 42 (only for subject continuing PegIFN/RBV until Week 48), 48, 60 (only for subjects continuing PegIFN/RBV until Week 48), 72, and at time of dropout (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 end of treatment, at the follow-up visits 4 weeks and 24 weeks after EOT, and at time of dropout (if applicable).

Physical Examination	Physical examinations were performed at screening (including eye examinations), Days 1 14, and 28, and every 12 weeks from Week 12 onwards until end of treatment, at the follow-up visits 4 weeks and 24 weeks after EOT, and at time of dropout (if applicable).
Statistical Methods Performed	Intent-to-Treat analysis, descriptive statistics, frequency tabulations, Wilcoxon's matched pairs signed ranks test, logistic regression, longitudinal mixed effects model, generalized additive model (GAM) analysis.

Main Features of the Subject Sample and Summary of the Results

Subject Disposition, n (%)	**TMC12/PR 75 mg q.d.**	**TMC24/PR 75 mg q.d.**	**TMC12/PR 150 mg q.d.**	**TMC24/PR 150 mg q.d.**	**Placebo**	**All Subjects**
Number of subjects treated	78	75	77	79	77	386
Exposure (overall treatment period, weeks), median (range)	24.00 (11.9, 48.3)	24.00 (4.0, 48.1)	24.00 (12.0, 48.0)	24.00 (1.9, 48.1)	47.86 (3.7, 49.0)	24.00 (1.9, 49.0)
Study Discontinuation						
Number of subjects who:						
- Completed the study, n (%)	75 (96.2)	69 (92.0)	70 (90.9)	72 (91.1)	71 (92.2)	357 (92.5)
- Discontinued the study, n (%)	3 (3.8)	6 (8.0)	7 (9.1)	7 (8.9)	6 (7.8)	29 (7.5)
Adverse event	0	0	1 (1.3)	0	1 (1.3)	2 (0.5)
Subject lost to follow-up	3 (3.8)	5 (6.7)	3 (3.9)	1 (1.3)	2 (2.6)	14 (3.6)
Subject noncompliant	0	1 (1.3)	0	0	0	1 (0.3)
Subject reached a virologic endpoint[a]	0	0	0	0	1 (1.3)	1 (0.3)
Subject withdrew consent	0	0	3 (3.9)	5 (6.3)	2 (2.6)	10 (2.6)
Study terminated in error	0	0	0	1 (1.3)[a]	0	1 (0.3)

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Main Features of the Subject Sample and Summary of the Results, Cont'd

Subject Disposition, n (%)	**TMC12/PR 75 mg q.d.**	**TMC24/PR 75 mg q.d.**	**TMC12/PR 150 mg q.d.**	**TMC24/PR 150 mg q.d.**	**Placebo**	**All Subjects**
Treatment Discontinuation						
Number of subjects who:						
- Completed TMC435/placebo and PR, n (%)	66 (84.6)	67 (89.3)	61 (79.2)	67 (84.8)	55 (71.4)	316 (81.9)
- Completed intake of study medication at Week 24 due to meeting response-guided criteria[b], n (%)	64 (82.1)	61 (81.3)	61 (79.2)	68 (86.1)	NA	254 (65.8)
- Discontinued TMC435/placebo only, n (%)	3 (3.8)	1 (1.3)	2 (2.6)	2 (2.5)	2 (2.6)	10 (2.6)
- Discontinued TMC435/placebo and PR, n (%)	9 (11.5)	6 (8.0)	12 (15.6)	10 (12.7)	10 (13.0)	47 (12.2)
- Discontinued PR only[c], n (%)	0	1 (1.3)	2 (2.6)	0	10 (13.0)	13 (3.4)
- Discontinued at least 1 study drug, n (%)	12 (15.4)	8 (10.7)	16 (20.8)	12 (15.2)	22 (28.6)	70 (18.1)
Adverse event	7 (9.0)	3 (4.0)	8 (10.4)	6 (7.6)	10 (13.0)	34 (8.8)
Subject noncompliant	0	1 (1.3)	1 (1.3)	2 (2.5)	0	4 (1.0)
Subject reached a virologic endpoint[d]	5 (6.4)	2 (2.7)	6 (7.8)	2 (2.5)	11 (14.3)	26 (6.7)
Subject withdrew consent	0	2 (2.7)	1 (1.3)	2 (2.5)	2 (2.6)	7 (1.8)
Subject was randomized due to error	0	0	0	1 (1.3)[e]	0	1 (0.3)

n: number of subjects with that observation; PR: PegIFN/RBV; NA = not applicable.

[a] Subject [redacted] discontinued treatment due to AEs on Day 13 and should have been followed-up further off-treatment. However, study participation was terminated in error as there was no withdrawal of consent.

[b] Response-guided treatment duration criteria: subjects in treatment arms 1-4 who achieved plasma HCV RNA levels < 25 IU/mL at Week 4 and had undetectable (< 25 IU/mL undetectable) plasma HCV RNA levels at Weeks 12, 16, and 20 were to stop all study medication (TMC435/placebo plus PegIFN/RBV) at Week 24. All other subjects in those arms continued PegIFN/RBV until Week 48 (TMC435/placebo was completed at Week 24).

[c] Discontinuation of PR during PR only treatment phase after treatment completion of TMC435/placebo (TMC435 monotherapy was not allowed).

[d] Subject met a virologic stopping rule.

[e] Subject [redacted] was randomized and assigned to treatment by error: the subject had Metavir score F4 (cirrhosis) confirmed by biopsy within 2 years of enrollment. This was initially classified as a minor protocol deviation. However, as the enrollment of this subject violated the study inclusion criteria, this case was re-assessed and considered as being a major deviation. The subject was withdrawn from treatment 13 days after treatment start and discontinued the trial.

	TMC12/PR 75 mg q.d. N = 78	TMC24/PR 75 mg q.d. N = 75	TMC12/PR 150 mg q.d. N = 77	TMC24/PR 150 mg q.d. N = 79	Placebo N = 77	All Subjects N = 386
Demographic Characteristics						
Gender, n (%)						
Female	38 (48.7)	28 (37.3)	34 (44.2)	35 (44.3)	38 (49.4)	173 (44.8)
Male	40 (51.3)	47 (62.7)	43 (55.8)	44 (55.7)	39 (50.6)	213 (55.2)
Region, n (%)						
Asia pacific	9 (11.5)	9 (12.0)	7 (9.1)	13 (16.5)	4 (5.2)	42 (10.9)
Europe	52 (66.7)	52 (69.3)	56 (72.7)	44 (55.7)	58 (75.3)	262 (67.9)
North-America	17 (21.8)	14 (18.7)	14 (18.2)	22 (27.8)	15 (19.5)	82 (21.2)
Race, n (%)						
White	70 (89.7)	71 (94.7)	74 (96.1)	73 (92.4)	74 (96.1)	362 (93.8)
Black or African American	3 (3.8)	2 (2.7)	3 (3.9)	3 (3.8)	2 (2.6)	13 (3.4)
Asian	5 (6.4)	1 (1.3)	0	2 (2.5)	0	8 (2.1)
Native Hawaiian or Other Pacific Islander	0	1 (1.3)	0	1 (1.3)	1 (1.3)	3 (0.8)
Age, years						
Median (range)	47.0 (19, 66)	46.0 (18, 67)	47.0 (18, 69)	47.0 (18, 69)	45.0 (21, 67)	46.5 (18, 69)
Body Mass Index, kg/m²						
Median (range)	25.85 (16.8, 39.6)	24.20 (17.4, 37.8)	24.70 (18.1, 38.2)	24.90 (17.6, 37.3)	25.60 (17.5, 42.2)	25.00 (16.8, 42.2)
Baseline *IL28B* genotype[a], n (%)						
N	58	51	55	52	46	262
CC	13 (22.4)	18 (35.3)	22 (40.0)	13 (25.0)	12 (26.1)	78 (29.8)
CT	36 (62.1)	28 (54.9)	27 (49.1)	33 (63.5)	28 (60.9)	152 (58.0)
TT	9 (15.5)	5 (9.8)	6 (10.9)	6 (11.5)	6 (13.0)	32 (12.2)
Baseline Disease Characteristics						
Plasma HCV RNA (log_{10} IU/mL)						
Median (range)	6.57 (3.5, 7.6)	6.59 (5.3, 7.6)	6.60 (4.9, 7.5)	6.57 (4.7, 8.1)	6.57 (4.3, 7.5)	6.58 (3.5, 8.1)
Plasma HCV RNA category (IU/mL), n (%)						
< 400,000	6 (7.7)	8 (10.7)	4 (5.2)	5 (6.3)	9 (11.7)	32 (8.3)
≥ 400,000 ≤ 800,000	8 (10.3)	4 (5.3)	4 (5.2)	2 (2.5)	5 (6.5)	23 (6.0)
> 800,000	64 (82.1)	63 (84.0)	69 (89.6)	72 (91.1)	63 (81.8)	331 (85.8)
Metavir score, n (%)						
Score F0	9 (11.5)	7 (9.3)	12 (15.6)	8 (10.1)	9 (11.7)	45 (11.7)
Score F1	33 (42.3)	25 (33.3)	32 (41.6)	33 (41.8)	35 (45.5)	158 (40.9)
Score F2	26 (33.3)	26 (34.7)	26 (33.8)	25 (31.6)	26 (33.8)	129 (33.4)
Score F3	10 (12.8)	17 (22.7)	7 (9.1)	12 (15.2)	7 (9.1)	53 (13.7)
Score F4	0	0	0	1 (1.3)[b]	0	1 (0.3)

	TMC12/PR 75 mg q.d. N = 78	**TMC24/PR 75 mg q.d. N = 75**	**TMC12/PR 150 mg q.d. N = 77**	**TMC24/PR 150 mg q.d. N = 79**	**Placebo N = 77**	**All Subjects N = 386**
HCV genotype (NS5B), n (%)						
N	77	75	76	79	76	383
1a	36 (46.8)	34 (45.3)	37 (48.7)	37 (46.8)	29 (38.2)	173 (45.2)
1b	41 (53.2)	40 (53.3)	38 (50.0)	42 (53.2)	47 (61.8)	208 (54.3)
1e	0	0	1 (1.3)	0	0	1 (0.3)
6e	0	1 (1.3)[c]	0	0	0	1 (0.3)
Baseline Q80K, n (%)	13 (16.7)	8 (10.7)	6 (7.8)	6 (7.6)	7 (9.2)	40 (10.4)

N: number of subjects with data; n: number of subjects with that observation

[a] Information only available for subjects who signed the separate Informed Consent Form.

[b] Subject [redacted] was randomized and assigned to treatment by error: the subject had Metavir score F4 (cirrhosis) confirmed by biopsy within 2 years of enrollment. This was initially classified as a minor protocol deviation. However, as the enrollment of this subject violated the study inclusion criteria, this case was re-assessed and considered as being a major deviation. The subject was withdrawn from treatment 13 days after treatment start and discontinued the trial.

[c] Subject [redacted] had HCV genotype 1b using the Trugene® assay at screening.

Efficacy

Virologic Response, n (%)	TMC12/PR 75 mg q.d. N = 78	TMC24/PR 75 mg q.d. N = 75	TMC12/PR 150 mg q.d. N = 77	TMC24/PR 150 mg q.d. N = 79	Placebo N = 77
Primary Efficacy Endpoint					
SVRW72	63 (80.8)	53 (70.7)	60 (77.9)	67 (84.8)	50 (64.9)
Secondary Efficacy Endpoints					
Week 4					
< 25 IU/mL undetectable (i.e., RVR)	59 (75.6)	51 (68.0)	58 (75.3)	59 (74.7)	4 (5.2)
< 25 IU/mL detectable or undetectable	67 (85.9)	66 (88.0)	70 (90.9)	72 (91.1)	12 (15.6)
cEVR	71 (91.0)	70 (93.3)	72 (93.5)	75 (94.9)	43 (55.8)
EOTR	72 (92.3)	73 (97.3)	71 (92.2)	74 (93.7)	61 (79.2)
Viral breakthrough	5 (6.4)	2 (2.7)	6 (7.8)	2 (2.5)	4 (5.2)
SVR12	65 (83.3)	57 (76.0)	62 (80.5)	68 (86.1)	51 (66.2)
SVR24	64 (82.1)	56 (74.7)	62 (80.5)	68 (86.1)	50 (64.9)
Viral relapse, n/N (%)[a]	8/72 (11.1)	14/72 (19.4)	6/69 (8.7)	6/75 (8.0)	11/62 (17.7)

N: number of subjects; n: number of subjects with that observation

RVR: rapid virologic response (undetectable plasma HCV RNA at Week 4); cEVR: complete EVR (undetectable plasma HCV RNA at Week 12); EOTR: virologic response at actual end of treatment (undetectable plasma HCV RNA); SVR12: sustained virologic response 12 weeks after the planned end of treatment; SVR24: sustained virologic response 24 weeks after the planned end of treatment; SVRW72: sustained virologic response at Week 72; viral breakthrough: a confirmed increase of > 1 $\log_{10}$ IU/mL in plasma HCV RNA level from the lowest level reached, or a confirmed plasma HCV RNA level of > 100 IU/mL in subjects whose plasma HCV RNA had previously been below the lower limit of quantification (25 IU/mL) or undetectable (< 25 IU/mL undetectable); viral relapse: confirmed detectable plasma HCV RNA during follow-up in subjects who had undetectable plasma HCV RNA (< 25 IU/mL) at end of treatment.

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

Statistical Comparison (Logistic Regression)	N	SVR, n (%)	(95% CI)[a]	Comparison Versus Placebo	
				Difference in proportions (97.5% CI)[a]	p-value
SVR24					
Placebo	77	50 (63.4)	(52.3; 74.5)	-	-
TMC12/PR 75 mg q.d.	78	64 (82.4)	(73.9; 90.9)	19.1 (3.0; 35.1)	0.008*
TMC24/PR 75 mg q.d.	75	56 (74.9)	(65.0; 84.8)	11.5 (-5.5; 28.6)	0.129
TMC12/PR 150 mg q.d.	77	62 (81.3)	(72.6; 90.0)	17.9 (1.7; 34.1)	0.013*
TMC24/PR 150 mg q.d.	79	68 (86.6)	(79.1; 94.1)	23.2 (7.9; 38.6)	<0.001*
TMC435 75 mg	153	120 (78.9)	(72.3; 85.5)	15.5 (0.7; 30.3)	0.019*
TMC435 150 mg	156	130 (84.1)	(78.3; 89.9)	20.7 (6.4; 35.1)	0.001*
SVRW72					
Placebo	77	50 (63.3)	(52.2; 74.4)	-	-
TMC12/PR 75 mg q.d.	78	63 (81.1)	(72.4; 89.9)	17.8 (1.6; 34.0)	-
TMC24/PR 75 mg q.d.	75	53 (70.8)	(60.4; 81.3)	7.5 (-9.9; 25.0)	-
TMC12/PR 150 mg q.d.	77	60 (78.7)	(69.5; 87.9)	15.4 (-1.1; 32.0)	0.037
TMC24/PR 150 mg q.d.	79	67 (85.3)	(77.5; 93.1)	22.0 (6.4; 37.6)	0.002*
TMC435 75 mg	153	116 (76.4)	(69.5; 83.3)	13.0 (-1.9; 28.0)	0.051
TMC435 150 mg	156	127 (82.3)	(76.2; 88.4)	18.9 (4.4; 33.5)	0.004*

N: number of subjects with data; n: number of subjects with SVR; SVR24: sustained virologic response 24 weeks after the planned end of treatment; SVRW72: sustained virologic response at Week 72.
[a] derived from a logistic regression model including baseline HCV RNA (continuous) and the stratification factor (genotype 1b subtype versus others based on NS5B sequencing).
* To adjust for multiple comparisons, a closed testing procedure was used to control the overall significance level of 5% (2-sided). First, the TMC435 groups of the same dose (different duration of triple therapy) were compared together versus the control group at the 2.5% significance level (2-sided). Only if the difference versus control was significant, the 2 groups (with the same dose but different duration of triple therapy) were compared individually versus the control group at the 2.5% significance level (2-sided). Statistically significant difference (p value < 0.025).

The primary endpoint of this study was the proportion of subjects in each treatment group achieving sustained virologic response at Week 72 (SVRW72), defined as having undetectable plasma HCV RNA levels at the end of treatment and at Week 72.

The majority of subjects achieved SVRW72 and a larger proportion of subjects with SVRW72 were observed in the TMC435 treatment groups compared to the placebo group. SVR12 and SVR24 rates were similar to SVRW72 rates. Differences between SVR24 and SVRW72 rates were due to 7 subjects with missing follow-up data and differences between SVR12 and SVR24 rates were due to 3 subjects with a viral relapse.

In the overall population, similar SVR24 rates were observed between the different TMC435 doses (150 mg q.d. and 75 mg q.d.) and different TMC435 treatment duration groups (i.e., 12 weeks or 24 weeks).

Subgroup analyses of SVR showed a trend for lower SVR24 rates in TMC435-treated subjects infected with HCV genotype 1a compared to subjects infected with HCV genotype 1b (only in 75 mg q.d. dose groups), in subjects with Q80K at baseline compared to subjects without Q80K at baseline, and in subjects with a Metavir score F3* compared to subjects with Metavir score F0-F2. A trend for higher SVR24 rates was observed in the TMC435 150 mg q.d. dose groups compared to the 75 mg q.d. dose groups among subjects infected with HCV genotype 1a either with (66.7% versus 55.0%) or without (85.5% versus 70.6%) Q80K at baseline, among subjects with Metavir score F3* (75.0% versus 63.0%), among subjects aged > 45 years (82.1% versus 70.4%), among subjects with Body Mass Index (BMI) ≥ 30 kg/m² (90.0% versus 66.7%), among male subjects (86.2% versus 75.9%), and among Black subjects (100.0% versus 60.0%). In addition, a higher SVR24 rate was observed in the 150 mg q.d. dose groups compared to the 75 mg q.d. dose groups (81.8% versus 54.5%) in subjects with < 25 IU/mL HCV RNA detectable at Week 4 who met the RGT criteria and subsequently completed their planned 24-week treatment period.

* One subject had Metavir score 4 (cirrhosis). This subject (CRF ID [redacted] TMC24/PR 150 mg q.d. group) was randomized and assigned to treatment by error. The subject discontinued treatment 13 days after treatment start and discontinued the trial.

Efficacy, Cont'd

Note that the subject numbers were low for some subgroups. No relevant differences were observed in response rates between the 12 weeks and 24 weeks TMC435 treatment duration groups.

The majority of subjects in the TMC435 treatment groups (82.1%, 81.3%, 79.2%, and 86.1% in the TMC12/PR 75 mg q.d., TMC24/PR 75 mg q.d., TMC12/PR 150 mg q.d., and TMC24/PR 150 mg q.d. group, respectively) met the RGT criteria for shorter treatment duration and completed treatment with RBV and PegIFNα-2a at Week 24. In total, 91.3% of the TMC435-treated subjects who met the RGT criteria and subsequently completed their planned 24-week treatment period achieved SVR24 (90.6%, 85.2%, 93.4%, and 95.6% in the TMC12/PR 75 mg q.d., TMC24/PR 75 mg q.d., TMC12/PR 150 mg q.d., and TMC24/PR 150 mg q.d. group, respectively), whereas 50.0% of the TMC435-treated subjects who required 48 weeks of treatment according to the RGT criteria and completed treatment had SVR24.

Viral breakthrough, defined as a confirmed increase of > 1 $\log_{10}$ IU/mL in plasma HCV RNA level from the lowest level reached, or a confirmed plasma HCV RNA level of > 100 IU/mL in subjects whose plasma HCV RNA had previously been below the lower limit of quantification (25 IU/mL) or undetectable (< 25 IU/mL undetectable), was observed in 15 (4.9%) TMC435-treated subjects. No relevant difference was observed in the viral breakthrough rate between the TMC435 75 mg q.d. and 150 mg q.d. dose groups. The majority of viral breakthroughs in TMC435-treated subjects occurred at or before Week 12 (9/15) and occurred in HCV genotype 1a infected subjects (11/15). Emerging mutations in the NS3 protease domain, known to confer reduced susceptibility to TMC435 in vitro, were detected in all 15 TMC435-treated subjects with viral breakthrough (mostly D168E, D168V, and/or R155K). Viral breakthrough did occur in 4 (5.2%) subjects in the placebo group.

Viral relapse was observed in 34 out of 288 (11.8%) TMC435-treated subjects with undetectable plasma HCV RNA at EOT and available follow-up data. Viral relapse rates were comparable between the 12 weeks and 24 weeks TMC435 treatment duration groups and were lower in the 150 mg q.d. dose groups compared to the 75 mg q.d. dose groups among subjects infected with HCV genotype 1a. The majority of the TMC435-treated subjects with viral relapse (88.2%; 30/34 subjects) experienced viral relapse within 12 weeks after actual EOT. In 29 out of 33 (87.9%) TMC435-treated subjects with viral relapse and available NS3 sequence information, emerging mutations in the NS3 protease domain (mostly R155K or D168V) were detected at time of viral relapse. Two out of the 4 subjects without emerging mutations in the NS3 protease domain at time of viral relapse had a baseline polymorphism in the NS3 protease domain known to confer reduced susceptibility to TMC435 in vitro (1 subject with Q80K and 1 subject with R155K).

For subjects with available *IL28B* data, the SVR24 rates were 83.9%, 78.1%, and 50.0% for subjects with the *IL28B* CC, CT, and TT genotype in the pooled TMC435 75 mg q.d. group, respectively. In the pooled TMC435 150 mg q.d. treatment group, the SVR24 rates were 97.1%, 80.0%, and 66.7%, for the CC, CT, and TT genotype, respectively. In the placebo group, highest SVR24 rates were observed in subjects with the CC genotype (100.0%) followed by the CT and TT genotypes (both 50.0%). Overall, viral breakthrough and viral relapse occurred less frequently when subjects had the *IL28B* CC genotype compared to subjects with the *IL28B* CT or TT genotypes. Results of these subgroup analyses should be interpreted with caution due to the small sample size of some subgroups.

As measured by the PRO tools used in this study (EQ-5D and FSS), fatigue and other health-related dimensions appeared to worsen during triple 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 similar scores between all treatment groups until Week 24. After the end of therapy, fatigue and other health-related dimensions returned to baseline values in all treatment groups underscoring the benefit of shorter overall treatments.

TMC435 Pharmacokinetics (Substudy)

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	**75 mg TMC435 q.d. + PegIFNα-2a and RBV**		**150 mg TMC435 q.d. + PegIFNα-2a and RBV**	
	Geometric Mean	mean ± SD, t_{max}: median [range]	Geometric Mean	mean ± SD, t_{max}: median [range]
n	21[a]	21[a]	23[b]	23[b]
C_{0h}, ng/mL	170.4	213.3 ± 176.5	834.4	1796 ± 3116
C_{min}, ng/mL	153.7	190.2 ± 148.4	631.3	1579 ± 3096
C_{max}, ng/mL	932.3	1035 ± 522.4	3255	4394 ± 4430
t_{max}, h	-	6.0 (2.0 - 8.0)	-	6.0 (2.0 - 12.0)
$AUC_{24h,}$ ng.h/mL	11810	13200 ± 6772	44760	70090 ± 93390
$C_{ss,av}$, ng/mL	492.7	550.3 ± 282.1	1863	2919 ± 3892
Fluctuation index, %	154.9	158.0 ± 31.84	126.2	135.7 ± 47.89

[a] n=20 for AUC_{24h}, $C_{ss,av}$ and fluctuation index
[b] n=22 for AUC_{24h}, $C_{ss,av}$ and fluctuation index

After intake of TMC435 at 150 mg q.d., mean C_{min}, C_{max}, and AUC_{24h} values were considerably higher compared to after intake at 75 mg q.d., both in combination with PegIFNα-2a and RBV, in adult treatment-naïve subjects with chronic genotype 1 hepatitis C virus infection. The increase in systemic exposure to TMC435 for the 75 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 levels, with comparable ranges.

TMC435 Population Pharmacokinetics

Pharmacokinetic parameter Median (range)	**TMC12/PR 75 mg q.d. N = 77**	**TMC24/PR 75 mg q.d. N = 75**	**TMC12/PR 150 mg q.d. N = 77**	**TMC24/PR 150 mg q.d. N = 78**
AUC_{24h}, ng.h/mL	9926.4 (138, 50179)	8976.8 (3615, 57243)	39884.0 (2948, 380830)	36038.8 (1134, 279550)
C_{0h}, ng/mL	240.9 (0, 1927)	213.6 (40, 2124)	1123.3 (91, 13771)	1176.7 (0, 9875)
CL/F, L/h	9.9 (1, 545)	10.7 (2, 30)	5.1 (0, 27)	5.2 (1, 141)
$C_{ss,av}$, ng/mL	413.6 (6, 2091)	374.0 (151, 2385)	1661.8 (123, 15868)	1501.6 (47, 11648)

N: number of subjects

TMC435 exposure following 75 mg q.d. and 150 mg q.d. increased in a more than dose proportional manner consistent with previous findings. A 2-fold increase in TMC435 dose resulted in approximately 4-fold increase in TMC435 AUC. TMC435 exposure following 12 or 24 weeks of treatment was comparable. There was no difference in the pharmacokinetics of TMC435 by genotype 1 subtype, Metavir score, race, or gender although the number of subjects in some of these subgroups was small.

Safety

Adverse Events

Overall treatment period[a]	**TMC12/ PR 75 mg q.d. N = 78**	**TMC24/ PR 75 mg q.d. N = 75**	**TMC12/ PR 150 mg q.d. N = 77**	**TMC24/ PR 150 mg q.d. N = 79**	**All TMC435 N = 309**	**Placebo N = 77**
Any AE, n (%)	77 (98.7)	75 (100.0)	76 (98.7)	79 (100.0)	307 (99.4)	75 (97.4)
Most frequently reported AEs by preferred term (i.e., in > 25% of all TMC435-treated subjects), n (%)						
Headache	41 (52.6)	34 (45.3)	35 (45.5)	32 (40.5)	142 (46.0)	40 (51.9)
Fatigue	26 (33.3)	35 (46.7)	32 (41.6)	38 (48.1)	131 (42.4)	37 (48.1)
Influenza-like illness	21 (26.9)	32 (42.7)	18 (23.4)	27 (34.2)	98 (31.7)	29 (37.7)
Pruritus	25 (32.1)	17 (22.7)	30 (39.0)	24 (30.4)	96 (31.1)	35 (45.5)
Nausea	26 (33.3)	16 (21.3)	20 (26.0)	24 (30.4)	86 (27.8)	21 (27.3)
Any grade 3 or 4 AE, n (%)	21 (26.9)	22 (29.3)	28 (36.4)	28 (35.4)	99 (32.0)	27 (35.1)
Deaths, n (%)	0	0	0	0	0	0
Any serious AEs, n (%)	9 (11.5)	4 (5.3)	4 (5.2)	3 (3.8)	20 (6.5)	10 (13.0)
Any AE leading to permanent stop of:						
TMC435/placebo and PegIFNα-2a and RBV	4 (5.1)	1 (1.3)	4 (5.2)	2 (2.5)	11 (3.6)	4 (5.2)
TMC435/placebo only	3 (3.8)	1 (1.3)	3 (3.9)	4 (5.1)	11 (3.6)	2 (2.6)
PegIFNα-2a and RBV only	0	1 (1.3)	1 (1.3)	1 (1.3)	3 (1.0)	4 (5.2)

N: number of subjects; n: number of subjects with that observation

[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).

Overall, no relevant differences in incidence of AEs were observed between the different treatment groups.

During the overall treatment period, the most frequently reported AEs in pooled TMC435-treated subjects (in > 25% of the subjects) were headache, fatigue, influenza-like illness, pruritus, and nausea, which occurred at comparable frequency than in the placebo group and are well-known to occur with PegIFNα-2a/RBV treatment. The majority of AEs were grade 1 or 2 in severity. Serious adverse events (SAEs) occurred in 20 (6.5%) TMC435-treated subjects and in 10 (13.0%) subjects in the placebo group. By preferred term, all SAEs were reported in at most 1 subject across all TMC435 treatment groups. TMC435/placebo was permanently discontinued due to an AE in 22 (7.1%) TMC435-treated subjects and in 6 (7.8%) subjects in the placebo group. There were no relevant differences in the incidence of grade 3 or 4 AEs between the different treatment groups.

Similar observations were made for the TMC435/placebo treatment period.

Special attention was given to the following AEs: hepatobiliary, rash (any type), pruritus (any type), jaundice, anemia, cardiac, gastrointestinal, and photosensitivity AEs. The incidence of these AEs in the TMC435 treatment groups was lower or similar to the incidence in the placebo group, except for hepatobiliary AEs (mainly hyperbilirubinemia) which was reported more frequently in TMC435-treated subjects (4.2%) compared to the subjects in the placebo group (2.6%).

Clinical Laboratory Tests

Comparable changes over time were observed between the TMC435 and placebo treatment groups for hematology (hemoglobin, hematocrit, red blood cell [RBC], white blood cell [WBC], neutrophil, and platelet count) parameters, amylase, hypocalcemia, and hypophosphatemia. Mean values for these parameters returned to baseline values after the end of treatment.

Mild increases in mean bilirubin (direct, indirect, and total) and alkaline phosphatase (ALP) levels were seen specifically in the TMC435 150 mg q.d. dose groups during the first 2 weeks of treatment. Mean bilirubin and ALP levels stabilized or decreased during continued treatment and returned to baseline values after completion of TMC435 dosing.

Clinical Laboratory Tests, Cont'd

Bilirubin abnormalities (increased total bilirubin, direct and indirect bilirubin above normal limits) were observed more frequently in the TMC435 150 mg q.d. dose groups than in the TMC435 75 mg q.d. groups and placebo group (total bilirubin: 41.3% versus 17.0% and 19.5%, direct bilirubin: 29.0% versus 5.2% and 6.5%, indirect bilirubin: 21.3% versus 9.2% and 11.7%, respectively).

Incidences of grade 3 or 4 laboratory abnormalities were low (i.e., < 5 % of all TMC435-treated subjects), except for decreases in absolute neutrophil count, and no consistent trends or relevant differences between the treatment groups were observed.

Cardiovascular Safety

Mean changes from baseline in vital signs and ECG parameters were generally small and not considered clinically relevant.

During the overall treatment period, none of the subjects had a treatment-emergent QTcF or QTcB value above 500 ms. Treatment-emergent QTcF and QTcB values between 480 and 500 ms were observed in 1 (0.3%) and 4 (1.3%) TMC435-treated subjects, respectively. QTcF and QTcB increases versus baseline of > 60 ms were observed in no and 3 (1.0%) TMC435-treated subjects, respectively, and in 1 (1.3%) and 2 (2.6%) subjects in the placebo group, respectively. None of the QTcF and QTcB increases versus baseline of > 60 ms corresponded to QTcF or QTcB values above 500 ms.

ECG-related AEs were reported during the overall treatment period in < 2% of the TMC435-treated subjects. The incidence was similar in the placebo group.

No relevant differences in incidences of vital signs and ECG abnormalities between the different treatment groups were observed.

Pharmacokinetic/Pharmacodynamic Relationships

There was a trend for lower plasma HCV RNA levels with higher TMC435 exposure (driven primarily by subjects with a baseline Q80K) at Day 7. However, no relationship was observed between TMC435 plasma pharmacokinetics and actual HCV RNA or change in HCV RNA from baseline at Weeks 12 and 24 or for any of the virologic response parameters including SVR12 and SVR24.

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

Conclusions

TMC435 in combination with PegIFNα-2a/RBV showed potent antiviral activity with no major differences between TMC435 doses 75 mg q.d. and 150 mg q.d. or length of therapy (i.e., 12 weeks or 24 weeks) in the overall population. In some subgroups (e.g., subjects infected with HCV genotype 1a, subjects with a baseline Q80K polymorphism, and subjects with Metavir score F3), a trend for better virologic response (e.g., SVR24) was observed with the 150 mg q.d. dose compared to 75 mg q.d. The majority of subjects in each TMC435 treatment group achieved SVR12, SVR24, and SVRW72.

Treatment with TMC435 at doses of 75 mg q.d. or 150 mg q.d. was generally safe and well tolerated in subjects infected with genotype 1 HCV. Mild elevations in bilirubin were observed specifically with the 150 mg TMC435 q.d. dose, which 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 PegIFN/RBV as the dose and duration of TMC435 therapy with a response-guided overall PegIFN/RBV treatment duration of 24 or 48 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection.