SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: - **Indication**: HCV-infection	**Drug Substance**: TMC435350 **Trial no**.: TMC435350-TiDP16-C101 **Clinical Phase**: I
Title: Phase I, double blind, randomized, placebo-controlled trial in healthy subjects to examine the safety, tolerability and pharmacokinetics of increasing oral doses of TMC435350 after single and repeated dosing, followed by an open label repeated dosing session in 6 HCV-genotype 1 infected patients (non placebo-controlled).	
Investigator: Khalid Aboufarha, M.D.; PRA International EDS, Stationsweg 163, 9471 GP Zuidharen, The Netherlands; Phone: +31 50 4022 222; Mobile Phone: +31 6 510 861 80; Fax: +31 50 4022 622	**Country**: The Netherlands
Trial Period: Start: 23-Jan-2007 End: 04-Sep-2007	**No. of Investigators**: 2 **No. of Subjects**: 49 healthy subjects and 6 HCV-infected subjects

Objectives:

The objectives of this trial were:

- Under fed conditions, to determine the safety, tolerability, plasma and urine pharmacokinetics of TMC435350 after single oral doses from 50 mg up to 1200 mg or up to maximum tolerated dose (MTD) - whichever came first.
- Under fed conditions, to determine the safety, tolerability, plasma and urine pharmacokinetics of TMC435350 after 5 days of consecutive dosing in healthy subjects.
- Under fed conditions, to determine the safety, tolerability, plasma and urine pharmacokinetics of TMC435350 after 5 days of consecutive dosing in hepatitis C virus (HCV)-genotype 1 infected patients.
- To determine the effect of fasting on the safety, tolerability, plasma and urine pharmacokinetics of a single oral dose of TMC435350.
- Under fed conditions, to determine the safety, tolerability, plasma and urine pharmacokinetics of a single dose of TMC435350 when given in the presence of a low dose of ritonavir (100 mg b.i.d. for 2 days).

Design: This was a randomized, double blind, placebo-controlled trial to determine the safety, tolerability and pharmacokinetics of TMC435350 after single and multiple oral intakes in healthy non HCV-infected subjects, followed by an open label repeated dosing session in 6 HCV-genotype 1 infected patients (non placebo-controlled).

The single dose escalation part of the trial consisted of 6 sessions (Sessions Ia to VIa) and the trial population included 2 panels of 9 healthy non HCV-infected subjects each (Panels 1 and 2). The doses of the test drug were consecutively escalated, following interim data reviews for safety, tolerability, and pharmacokinetics. In each session, 6 subjects received active treatment and 3 subjects received placebo after a standardized breakfast. The treatment schedule ensured that over 3 sessions each subject received active treatment twice and placebo once. A washout period of at least 10 days was respected between consecutive TMC435350 or placebo dosings within each panel.

Subjects of Panel 1 had an additional session to investigate food effect: a single dose of TMC435350 was tested in fasted conditions (Session VIIa). A food effect was investigated for the 200 mg dose in Panel 1 using the same randomization scheme as for the prior dosing of 200 mg under fed conditions.

Subjects of Panel 2 were planned to have an additional session to investigate potential effects of twice daily (b.i.d.) dosing of 100 mg ritonavir on the pharmacokinetics, safety and tolerability of a single dose of TMC435350 (Session VIIIa). However, this session was cancelled as pharmacokinetic profiles demonstrated no need for pharmacokinetic enhancement with ritonavir (Norvir®).

Multiple dosing was started when Sessions Ia, IIa, and IIIa were found to be safe and tolerable. The multiple dose escalation part of the trial was planned to consist of 4 consecutive sessions (Sessions Ib to IVb) in 4 panels of

9 healthy non HCV-infected subjects each (Panels 3, 4, 5 and 6). In each session, 6 subjects were planned to receive active treatment and 3 subjects were planned to receive placebo. TMC435350 or placebo was administered during 5 consecutive days. Administration was after a standardized meal.

In all sessions, TMC435350 or placebo (vehicle) was formulated as an oral solution. The dosing was completed by drinking a glass of water after each oral intake of the formulation.

Full pharmacokinetic profiles of TMC435350 were determined up to 72 hours for each dose of TMC435350 in the single dose part of the trial (Sessions Ia to VIIa). In the multiple dose part of the trial (Sessions Ib to IVb), full pharmacokinetic profiles of TMC435350 were determined for the first intake, up to 24 hours after dosing, and up to 72 hours after the last dose. Safety and tolerability were evaluated continuously and documented (safety report), with 24-hours interim pharmacokinetic data after each single dose or after the last dose of each multiple dose regimen, before stepping up to the next dose and between each session. Dose escalation was continued only if the previous dose was found safe and tolerable by the investigator and sponsor and thereafter approved by the Medisch-Ethische Toetsingscommissie (METC).

After completion of the healthy subject sessions, an open label session (Ic) in HCV-genotype 1 infected patients was added. The trial population (Panel 7) included 6 male or female, interferon based treatment experienced (i.e., non-responders or relapsers to previous interferon/ribavirin therapy) HCV-genotype 1 infected patients with an HCV viral load of at least 50000 IU/mL. One dose regimen was selected which was shown to be safe in healthy subjects when administered for 5 days. In addition to drug safety and pharmacokinetic parameters, viral loads were determined in plasma and followed-up till 4 weeks after last drug intake.

Subject Selection

Inclusion Criteria

HEALTHY SUBJECTS

1. Subjects aged between 18 and 55 years, extremes included.
2. Non-smokers for at least 3 months prior to selection.
3. Normal weight as defined by a Quetelet Index (Body Mass Index [BMI], weight in kg divided by the square of height in meters) of 18.0 to 30.0 kg/m^2, extremes included.
4. Informed Consent Form (ICF) signed voluntarily before the first trial-related activity.
5. Able to comply with protocol requirements.
6. Normal 12-lead electrocardiogram (ECG, in triplicate) at screening including:
   a. normal sinus rhythm (heart rate [HR] between 40 and 100 beats per minute [bpm]);
   b. QTc interval ≤ 450 ms;
   c. QRS interval ≤ 120 ms;
   d. PR interval ≤ 220 ms.
7. Healthy on the basis of a medical evaluation that reveals the absence of any clinically relevant abnormality and includes a physical examination, medical history, ECG, echocardiogram (multiple dose panels only), vital signs, and the results of blood biochemistry, blood coagulation and hematology tests and a urinalysis carried out at screening.

HCV-INFECTED SUBJECTS

Note: The patient population was screened by Prof. Reesink of the Academisch Medisch Centrum (AMC) of the Universiteit van Amsterdam and the post-dose follow-up visits occurred at the AMC.

1. Subjects aged between 18 and 70 years, extremes included.
2. Normal weight as defined by a Quetelet Index (BMI, weight in kg divided by the square of height in meters) of 18.0 to 30.0 kg/m^2, extremes included.
3. Informed consent form signed voluntarily before the first trial-related activity.
4. Able to comply with protocol requirements and having good accessible veins.
5. Normal 12-lead ECG (in triplicate) at screening including:
   a. normal sinus rhythm (HR between 40 and 100 bpm);
   b. QTc interval ≤ 450 ms;
   c. QRS interval ≤ 120 ms;
   d. PR interval ≤ 220 ms.
6. Subjects with chronic genotype 1 HCV infection (line probe assay), non-responders or relapsers to previous treatment regimens (being interferon/ribavirin or pegylated interferon/ribavirin).
7. HCV viral load at least 50000 IU/mL plasma at screening.

Exclusion Criteria

HEALTHY SUBJECTS

1. Past history of heart arrhythmias (frequent extrasystoli, tachycardia at rest) or having baseline prolongation of QTc interval > 450 ms, history of risk factors for Torsade de Pointes syndrome (hypokalemia, hypomagnesemia, family history of long QT Syndrome) or echographically suspected cardiomyopathy as indicated by decrease in 2 or more of the assessed hemodynamic parameters below the cut off points determined in Table 1 of the protocol.
2. A positive human immunodeficiency virus type 1 or type 2 (HIV-1 or HIV-2) test at screening.
3. Female, except if postmenopausal since more than 2 years, or posthysterectomy, or post-tubal ligation (without reversal operation).
4. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the investigator's opinion would compromise subject's safety and/or compliance with the trial procedures (period of non-drug/alcohol misuse must at least be 1 month before the first admistration of study medication).
5. Hepatitis A, B, or C infection (confirmed by hepatitis A antibody immunoglobulin M (IgM), hepatitis B surface antigen, or hepatitis C virus antibody, respectively) at screening.
6. A positive urine drug test at screening. Urine was tested to check the current use of amphetamines, benzodiazepines, cocaine, and opioids.
7. Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory, or infectious disease.
8. Currently significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability.
9. Any history of significant skin disease such as, but not limited to, rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, or urticaria.
10. History of drug allergy such as, but not limited to, sulfonamides and penicillins, or drug allergy witnessed in previous trials with experimental drugs.
11. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication administered in this trial.
12. Use of concomitant medication, including herbal medications and dietary supplements and products containing *Hypericum perforatum* (St. John's wort), except for paracetamol (acetaminophen) or ibuprofen in a period of 14 days before the first study medication intake.
13. Participation in an investigational drug trial within 30 days prior to the first intake of study medication.
14. Donation of blood or plasma within 60 days preceding the first intake of study medication.
15. Subjects with at least one the following laboratory abnormalities as defined by the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table:
    - serum creatinine grade 1 or greater (> 1.0 x upper limit of laboratory normal range [ULN]);
    - pancreatic amylase or lipase grade 2 or greater (> 1.5 x ULN);
    - hemoglobin grade 1 or greater (≤ 10.5 g/dL);
    - platelet count grade 1 or greater (≤ 99,999/mm³);
    - absolute neutrophil count grade 1 or greater (≤ 1500/mm³);
    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) grade 1 or greater (> 1.24 x ULN);
    - total bilirubin grade 1 or greater (> 1.0 x ULN);
    - any other toxicity grade 2 or above including:
      - proteinuria (spot urine) > 1+,
      - gross hematuria (> 10 red blood cells [RBCs]/high power field [HPF]).

HCV-INFECTED SUBJECTS

1. Past history of heart arrhythmias (frequent extrasystoli, tachycardia at rest) or having baseline prolongation of QTc interval > 450 ms, history of risk factors for Torsade de Pointes syndrome (hypokalemia, hypomagnesemia, family history of long QT Syndrome) or echographically suspected cardiomyopathy as indicated by decrease in 2 or more of the assessed cardiac hemodynamic parameters below the cut off points determined in Table 1 of the protocol.
2. Subjects co-infected with HIV-1, HIV-2 or any hepatitis infection other than HCV.
3. Women of childbearing potential.
4. Male subjects with female partners of childbearing potential not agreeing to use a reliable birth control method for 90 days after the last dosing in the trial.
5. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the investigator's opinion could compromise subject's safety and/or compliance with the trial procedures (period of non-drug/alcohol misuse must at least be 1 month before the first admistration of study medication).
6. A positive urine drug test at screening. Urine was tested to check the current use of amphetamines, benzodiazepines, cocaine, cannabinoids, and opioids.
7. Subjects with any cardiovascular, hepatic or renal disease of clinical significance
8. Subjects having uncontrolled/unstable diabetes, epilepsy or psychiatric disease.
9. Subjects on non stable methadone use, on non stable anti-hypertensive treatment or on non stable antidepressant treatment.
10. Any history of significant skin disease such as, but not limited to, rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, or urticaria.
11. History of drug allergy such as, but not limited to, sulfonamides and penicillins, or drug allergy witnessed in previous trials with experimental drugs.
12. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication administered in this trial.
13. Use of concomitant medication, including herbal medications and dietary supplements and products containing *Hypericum perforatum* (e.g. St. John's wort), except for paracetamol (acetaminophen) or ibuprofen in a period of 14 days before the first study medication intake.
14. Subjects enrolled in another clinical trial for 90 days prior to screening.
15. Evidence of Child Pugh B or C liver disease at screening.
16. Subjects receiving or having received polymerase inhibitor or protease inhibitor treatment for HCV during the last 6 months.
17. Subjects with at least one of the following laboratory abnormalities at screening:
    - ALT level > 5 x ULN,
    - Bilirubin ≥ 1.5 x ULN,
    - Platelet count < 80,000/mm^3,
    - WBC count < 2,000 cells/mm^3,
    - Any other lab toxicity found to be clinically significant by the investigator.
18. Subjects having other diseases than the aforementioned ones, having no stable disease or treatment regimen.

Treatment	TMC435350	Placebo
Concentration	100 mg/mL	
Dosage Form (TF No.)	PEG400 solution	PEG400 solution
Usage	oral	oral
Batch Number	07A08/F002	07A08/F003

Dose Regimen	In Part I, doses of 50 mg, 100 mg, 200 mg, 400 mg, 800 mg and 1200 mg of TMC435350 or placebo were planned to be administered as a single oral administration alternating over the 2 panels. As a result of the observed more than dose-proportional increase in plasma concentrations, doses were adapted to 50 mg, 100 mg, 200 mg, 300 mg, 450 mg, and 600 mg of TMC435350 or placebo administered as a single oral administration. In Part II, treatment was anticipated to be a b.i.d. regimen with doses of 50 mg, 100 mg, 200 mg and 400 mg. However these dose regimens were adapted to 100 mg q.d., 200 mg q.d., 200 mg b.i.d., and 400 mg q.d. as safety, tolerability and/or pharmacokinetic data from the single dose part of the trial supported a change in the predetermined regimens for multiple dosing. Subjects of Panel 2 were planned to have an additional session to investigate potential effects of twice daily dosing of 100 mg ritonavir on the pharmacokinetics, safety and tolerability of a single dose of TMC435350 (Session VIIIa). However, this session was cancelled as pharmacokinetic profiles demonstrated no need for pharmacokinetic enhancement with ritonavir (Norvir®). In addition, the number of subjects participating in Part II of the trial was adapted due to low recruitment and after review. From this point onwards, actual used doses and number of subjects are displayed. IN HEALTHY SUBJECTS PART I: – Panel 1, Session Ia: A single oral dose of 50 mg TMC435350 (n=6) or placebo (n=3); fed conditions. – Panel 2, Session IIa: A single oral dose of 100 mg TMC435350 (n=6) or placebo (n=3); fed conditions. – Panel 1, Session IIIa: A single oral dose of 200 mg TMC435350 (n=6) or placebo (n=3); fed conditions. – Panel 2, Session IVa: A single oral dose of 300 mg TMC435350 (n=6) or placebo (n=3); fed conditions. – Panel 1, Session Va: A single oral dose of 450 mg TMC435350 (n=6) or placebo (n=3); fed conditions. – Panel 2, Session VIa: A single oral dose of 600 mg TMC435350 (n=6) or placebo (n=3); fed conditions. – Panel 1, Session VIIa: A single oral dose of 200 mg TMC435350 (n=5) or placebo (n=3); fasted conditions. PART II: – Panel 3, Session Ib: Once daily oral doses of 100 mg TMC435350 (n=4) or placebo (n=2) during 5 days; fed conditions. – Panel 4, Session IIb: Once daily oral doses of 200 mg TMC435350 (n=5) or placebo (n=2) during 5 days; fed conditions. – Panel 5, Session IIIb: Twice daily oral doses of 200 mg TMC435350 (n=6) or placebo (n=3) during 5 days; fed conditions. – Panel 6, Session IVb: Once daily oral doses of 400 mg TMC435350 (n=6) or placebo (n=3) during 5 days; fed conditions. IN HCV-INFECTED SUBJECTS PART III: – Panel 7, Session Ic: Once daily oral dose of 200 mg TMC435350 (n=6) during 5 days; fed conditions.

Duration of Treatment	Panels 1 - 2: a maximum of respectively 4 and 3 single intakes with 72 hours follow-up after each intake Panels 3 – 6: 5 days of dosing with 72 hours follow-up after the last intake Panel 7: 5 days of dosing with 72 hours follow-up after the last intake
Duration of Trial	Screening: maximum of 3 weeks Panel 1 - 2: approximately 7 and 6 weeks, respectively Panels 3 – 6: 2 weeks Panel 7: 8 days Follow-up: 4 weeks
Disallowed Medication	During the entire trial, subjects were not allowed to use any medication other than the study medication. All medication had to be discontinued at least 14 days before first drug administration, except for paracetamol (acetaminophen) or ibuprofen. Subjects were not allowed to use any herbal medications or dietary supplements including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the start of the trial and throughout the duration of the trial. Paracetamol could be used up to 3 days before the first administration of study medication. After that, the investigator could permit the use of paracetamol from 3 days before the first administration of study medication in each session until the last pharmacokinetic blood sample had been taken in each session at no more than 3 x 500 mg per day and no more than 3 grams per week. Ibuprofen could be used up to 3 days before the first administration of study medication. After that, the investigator could permit the use of ibuprofen from 3 days before the first administration of study medication in each session until the last pharmacokinetic blood sample had been taken in each session at no more than 1 x 400 mg per day. Comedication was allowed in the following cases: - In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine (Zyrtec®), levocetirizine (Xyzal®), topical corticosteroids, or antipruritic agents in the recommended dosing scheme was permitted. - In case of nausea, the use of antiemetics known not to affect QTc prolongation (i.e, diphenhydramine or others) was permitted. - In case of diarrhea, the use of loperamide was permitted. HCV-genotype 1 infected patients in Session Ic also had following additional restrictions: - Subjects could not use any polymerase inhibitor nor protease inhibitor treatment for HCV nor have used any during the last 6 months. - Any vaccine nor immunomodulator other than the study medications during the trial period. For all concomitant medication used, the indication, the dose and dose regimen was recorded in the Concomitant Therapy section of the CRF. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition was documented in the Adverse Event (AE) section of the CRF.

Assessments	
Pharmacokinetics	In the single dose part (in fed and fasted conditions) of the trial, blood samples were taken: - at Day 1 (predose, at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 11h30, 12h, and 16h postdose); - at Day 2 (24h and 36h postdose), Day 3 (48h postdose), and Day 4 (72h postdose); - at time of dropout or the following morning. In the multiple dose part (in healthy subjects and HCV-infected subjects) of the trial, blood samples were taken: - at Day 1 (predose, at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h[a], and 16h[b] postdose); - at Days 2, 3, and 4 (predose); - at Day 5 (predose, at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, and 16h postdose); - at Day 6 (24h and 36h postdose), Day 7 (48h postdose), and Day 8 (72h postdose); - at time of dropout or the following morning. [a] In case of a b.i.d. regimen just before drug intake. [b] Only in case of a q.d. regimen.
Safety Adverse Events	Adverse events and concomitant therapy were monitored continuously from signing of informed consent onwards until last trial-related activity.
Clinical Laboratory	In the single dose part (in fed and fasted conditions) of the trial, blood and urine samples were taken: - at screening[a]; - at Day 1 (predose[b], at 4h and 8h [urine sample only] postdose); - at Day 2 (24h postdose[b]) and Day 4 (72h postdose [b]); - at time of dropout or the following morning and at 7 and 30-32 days after dropout[c]; - at follow-up (i.e., 10-14 and 30-35 days postdose)[a]. In the multiple dose part (in healthy subjects and HCV-infected subjects) of the trial, blood and urine samples were taken: - at screening[a]; - at Days 1 and 5 (predose[b], and 4h postdose); - at Day 3 (predose[b]); - at Day 8 (72h postdose[b]); - at time of dropout or the following morning and at 7 and 30-32 days after dropout[c]; - at follow-up (i.e., 10-14 and 30-35 days postdose)[a]. Safety sampling at screening also included coagulation. In Sessions Ib to IVb and Ic (multiple dose panels) only, Pro-ANP, Pro-BNP, and BNP levels were measured in each separate safety sample taken (including screening). Troponin-I levels were determined in blood samples taken at screening and predose and 2 hours postdose on Days 1, 3 and 5. Safety samples taken at the follow-up visits did not include Pro-ANP, Pro-BNP, and BNP levels if no effects were seen on Day 5 (± 1 day) or at dropout. [a] Biochemistry samples had be taken fasted for at least 4 hours. [b] Biochemistry samples had to be taken fasted for at least 10 hours. On Day 2 (single dose part) and Day 8 (multiple dose part) coagulation was included. [c] Biochemistry samples had to be taken fasted for at least 4 hours, if possible.

Cardiovascular Safety	In the single dose part (in fed and fasted conditions) of the trial, ECG and vital signs were measured: - at screening; - at Day –1[a]; - at Day 1 (predose[b], at 1h, 2h, 3h [ECG only], 4h, 8h, and 12h [vital signs only] postdose); - at Day 2 (24h postdose), Day 3 (48h postdose), and Day 4 (72h postdose); - at time of dropout or the following morning and at 7[c] and 30-32[d] days after dropout; - at follow-up (i.e., 10-14 and 30-35 days postdose). In the multiple dose part (in healthy subjects and HCV-infected subjects): - ECG and vital signs were measured: - at screening; - at Day –1[a]; - at Days 1 and 5 (predose [b], at 1h [ECG only], 2h [ECG only], 3h [ECG only], 4h, 8h [ECG only], and 12h postdose); - at Day 3 (predose[b]); - at Day 6 (24h postdose)[f]; - at Day 8 (72h postdose); - at time of dropout or the following morning and at 7[c] and 30-32[d] days after dropout; - at follow-up (i.e., 10-14 and 30-35 days postdose)[e]. In the multiple dose part (in healthy subjects and HCV-infected subjects): - chest echocardiography was measured: - at screening; - at Day –1[f]; - at Day 6 (24h postdose) and Day 8 (72h postdose)[g]; - at time of dropout or the following morning and at 7[c] and 30-32[d] days after dropout; - at follow-up (i.e., 10-14 and 30-35 days postdose)[e]. [a] Twelve lead ECG (triplicate) was made at the same timings as on Day 1 (single dose part) or Day 5 (multiple dose part) in order to document diurnal variation of baseline QT values within the same subject. [b] Within 2 hours before drug intake and before breakfast. [c] Only if effects were seen at dropout. [d] Only if effects were seen at previous assessments. [e].Only if effects were seen during treatment. [f] Only for Session Ic (in HCV-infected subjects). [g] Only if effects were noted on Day 6.
Physical Examination	In the single dose part (in fed and fasted conditions) of the trial, physical examination was performed: - at screening; - at time of dropout or the following morning and at 7 and 30-32 days after dropout; - at follow-up (i.e., 10-14 and 30-35 days postdose). In the multiple dose part (in healthy subjects and HCV-infected subjects), physical examination was performed: - at screening; - at Day 5; - at time of dropout or the following morning and at 7 and 30-32 days after dropout; - at follow-up (i.e., 10-14 and 30-35 days postdose).

Staging for Fibrosis	In the multiple dose part in HCV-infected subjects, staging for fibrosis was performed at screening.
Antiviral Activity Viral Load	In the multiple dose part in HCV-infected subjects, a blood sample for viral load was taken: - at screening; - at Day 1 (predose[a], at 8h and 16h postdose); - at Day 2 (predose[a], and at 12h postdose); - at Day 3 (Predose)[a], Day 4 (predose)[a], and Day 5 (predose)[a]; - at Day 6 (24h postdose)[a], Day 7 (48h postdose)[a], and Day 8 (72h postdose)[a]; - at time of dropout or the following morning and at 7 and 30-32 days after dropout[a]; - at follow-up (i.e., 10-14 and 30-35 days after last drug intake)[a]. [a] Including a sample for viral genome sequencing .
Statistical Methods	Intent-to-treat analysis, descriptive statistics, frequency tabulations, linear mixed effects modeling.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition in Part I (Single Dose Escalation Part) **Healthy Subjects**	**Panel 1** (50, 200, and 450 mg fed + 200 mg fasted)	**Panel 2** (100, 300, and 600 mg fed)	**Part I**
Number of Subjects Entered (M/F)	8/1	9/0	17/1
Age: median (range), years	37.0 (21-55)	38.0 (23-55)	37.5 (21-55)
Drop-Outs - Reason			
Subject withdrew consent	1	0	1

M: male, F: female

Baseline Characteristics - Subject Disposition in Part II (Multiple Dose Escalation Part) **Healthy Subjects**	**Panel 3** 100 mg q.d.	**Panel 4** 200 mg q.d.	**Panel 5** 200 mg b.i.d.	**Panel 6** 400 mg q.d.	**Part II**
Number of Subjects Entered (M/F)	3/3	7/0	8/1	8/1	26/5
Age: median (range), years	40.5 (22-53)	25.0 (23-51)	38.0 (25-54)	24.0 (20-44)	27.0 (20-54)
Drop-Outs	0	0	0	0	0

M: male, F: female

Baseline Characteristics - Subject Disposition in Part III (Multiple Dose Part) **HCV-Infected Subjects**	**Panel 7** 200 mg q.d.
Number of Subjects Entered (M/F)	6/0
Age: median (range), yrs	56.5 (32-67)
Drop-Outs	0
Child-Pugh Class	
A	6
Viral Subtype	
1a	4
1b	2
Baseline Log_{10} Viral Load	
Median (range)	6.73 (6.47-7.03)

M: male, F: female

Pharmacokinetics of single dose TMC435350 (mean ± SD, t_{max}: median [range])	**50 mg TMC435350**	**100 mg TMC435350**	**200 mg TMC435350**
n	6	6	6
t_{max}, h	5.0 (3.0 - 6.0)	5.0 (4.0 - 6.0)	6.0 (4.0 - 6.0)
C_{max}, ng/mL	293.5 ± 96.06	582.0 ± 86.15	2957 ± 1022
AUC_{last}, ng.h/mL	4209 ± 2139	7550 ± 1630	37550 ± 14820
AUC_{∞}, ng.h/mL	4283 ± 2218	7621 ± 1630	38150 ± 15500
$t_{1/2term}$, h	9.844 ± 2.720	9.541 ± 1.261	10.85 ± 2.824
$Ae_{total,}$ mg	0	0	0.001399 ± 0.001705
$D_{urine,total}$, %	0	0	0.0006997 ± 0.0008523
	300 mg TMC435350	**450 mg TMC435350**	**600 mg TMC435350**
n	6	6	6
t_{max}, h	6.0 (4.0 - 6.0)	6.0 (4.0 - 6.0)	6.0 (4.0 - 6.0)
C_{max}, ng/mL	5092 ± 786.1	10460 ± 2458	13550 ± 1787
AUC_{last}, ng.h/mL	54720 ± 15890	175500 ± 69210	225000 ± 42670
AUC_{∞}, ng.h/mL	55060 ± 16180	182400 ± 78910	229100 ± 46350
$t_{1/2term}$, h	9.822 ± 1.422	13.31 ± 4.138	11.74 ± 2.018
$Ae_{total,}$ mg	0.005482 ± 0.003655	0.01098 ± 0.01235	0.03695 ± 0.01874
$D_{urine,total}$, %	0.001827 ± 0.001218	0.002439 ± 0.002744	0.006158 ± 0.003123

0 = NQ = Not Quantifiable

Pharmacokinetics of single dose TMC435350 (mean ± SD, t_{max}: median [range])	**200 mg TMC435350 – fed (ref)**	**200 mg TMC435350 – fasted (test)**
n	6	5
t_{max}, h	6.0 (4.0 - 6.0)	4.0 (3.0 - 6.0)
C_{max}, ng/mL	2957 ± 1022	2944 ± 1767
AUC_{last}, ng.h/mL	37550 ± 14820	35400 ± 19970
AUC_{∞}, ng.h/mL	38150 ± 15500	35740 ± 20090
$t_{1/2term}$, h	10.85 ± 2.824	10.47 ± 2.432
$Ae_{total,}$ mg	0.001399 ± 0.001705	0
$D_{urine,total}$, %	0.0006997 ± 0.0008523	0
LSmean ratio (90% CI), %		
		Test vs reference
n		5 vs 6
C_{max}	-	85.00 (44.88 - 161.0)
AUC_{last}	-	83.89 (48.11 - 146.3)
AUC_{∞}	-	83.66 (47.81 - 146.4)

0 = NQ = Not Quantifiable

Pharmacokinetics of multiple dose TMC435350 (mean ± SD, t_{max}: median [range])	**100 mg TMC435350 q.d. for 5 days**	**200 mg TMC435350 q.d. for 5 days**	**200 mg TMC435350 b.i.d. for 5 days**	**400 mg TMC435350 q.d. for 5 days**
n	4	5	6	6
Day 1				
t_{max}, h	5.0 (3.0 - 6.0)	4.0 (3.0 - 6.0)	6.0 (6.0 - 6.0)	6.0 (4.0 - 8.0)
C_{max}, ng/mL	679.8 ± 174.3	2304 ± 917.8	2790 ± 622.0	7088 ± 1350
AUC_{24h}, ng.h/mL[a]	6353 ± 1605	24630 ± 7331	20230 ± 4377	75700 ± 15510
Day 3				
C_{0h}, ng/mL	81.65 ± 30.74	749.0 ± 373.7	7663 ± 3696	3073 ± 1497
Day 4				
C_{0h}, ng/mL	77.55 ± 30.92	1005 ± 560.0	11280 ± 4672	6342 ± 3282
Day 5				
t_{max}, h	4.0 (4.0 - 6.0)	4.0 (3.93 - 8.0)	4.0 (3.0 - 6.0)	4.0 (3.0 - 6.0)
C_{0h}, ng/mL	97.05 ± 38.93	1482 ± 791.3	15590 ± 5326	8560 ± 4301
C_{min}, ng/mL	88.33 ± 32.20	1445 ± 767.3	13460 ± 4725	7795 ± 4015
C_{max}, ng/mL	758.3 ± 208.2	6172 ± 2859	21830 ± 5339	19380 ± 6251
AUC_{24h}, ng.h/mL[a]	7620 ± 1912	79710 ± 37230	216800 ± 62690	332100 ± 120300
$t_{1/2term}$, h[b]	7.708 ± 0.7297	16.04 ± 5.114	37.60 ± 27.69	21.51 ± 11.87
$C_{ss,av}$, ng/mL	317.5 ± 79.68	3324 ± 1554	18060 ± 5224	13840 ± 5013
FI, %	213.2 ± 40.28	144.7 ± 25.13	48.42 ± 9.821	88.30 ± 26.15
Ratio $AUC_{24h,\ Day\ 5/Day\ 1}$ (%)	120.1 ± 5.272	316.0 ± 101.2	1073 ± 196.4	431.8 ± 82.59
$Ae_{total,}$ mg	0	0.01037 ± 0.003033	0.02441 ± 0.02335	0.08475 ± 0.07094
$D_{urine,total}$, %	0	0.005186 ± 0.001516	0.01220 ± 0.01167	0.02119 ± 0.01774

[a] For the 200 mg b.i.d. dose group AUC_{12h} is reported instead of AUC_{24h}.
[b] Accurate determination not possible. For the 200 mg b.i.d. dose group, the individual data suggest a delayed start of the terminal phase, up to 48 hours from dosing. This mean value is also influenced by one high individual value (overall range: 14 - 92 hours).
0 = NQ = Not Quantifiable

Pharmacokinetics of multiple dose TMC435350 (mean ± SD, t_{max}: median [range])	**200 mg TMC435350 q.d. for 5 days - healthy subjects**	**200 mg TMC435350 q.d. for 5 days – HCV-infected subjects**
n	5	6
Day 1		
t_{max}, h	4.0 (3.0 - 6.0)	6.0 (4.0 - 8.0)
C_{max}, ng/mL	2304 ± 917.8	4067 ± 1479
AUC_{24h}, ng.h/mL	24630 ± 7331	56430 ± 22470
Day 3		
C_{0h}, ng/mL	749.0 ± 373.7	3015 ± 1971
Day 4		
C_{0h}, ng/mL	1005 ± 560.0	4610 ± 3205
Day 5		
t_{max}, h	4.0 (3.93 - 8.0)	4.0 (4.0 - 8.0)
C_{0h}, ng/mL	1482 ± 791.3	6057 ± 4213
C_{min}, ng/mL	1445 ± 767.3	5743 ± 4089
C_{max}, ng/mL	6172 ± 2859	11470 ± 5337
AUC_{24h}, ng.h/mL	79710 ± 37230	206000 ± 113600
$t_{1/2term}$, h	16.04 ± 5.114	41.32 ± 32.99
$C_{ss,av}$, ng/mL	3324 ± 1554	8584 ± 4732
FI, %	144.7 ± 25.13	80.84 ± 33.88
Ratio $AUC_{24h,\ Day\ 5/Day\ 1}$ (%)	316.0 ± 101.2	344.8 ± 67.16
$Ae_{total,}$ mg	0.01037 ± 0.003033	0.03123 ± 0.01902
$D_{urine,total}$, %	0.005186 ± 0.001516	0.01561 ± 0.009512

Safety Part I (Single Dose Escalation Part)	**Fed Conditions**								**Fasted Conditions**	
	TMC435350						**Placebo**		**TMC435350**	**Placebo**
Healthy Subjects	**50 mg (Panel 1)**	**100 mg (Panel 2)**	**200 mg (Panel 1)**	**300 mg (Panel 2)**	**450 mg (Panel 1)**	**600 mg (Panel 2)**	**Pooled Panel 1**	**Pooled Panel 2**	**200 mg (Panel 1)**	**200 mg (Panel 1)**
(N = number of subjects with data)	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=9)**	**(N=8)**	**(N=5)**	**(N=3)**
Adverse Events										
Most frequently reported AEs (reported in > 1 subject), n (%)										
Catheter site related reaction	0	1 (16.7)	0	0	0	1 (16.7)	0	2 (25.0)	0	0
Headache	1 (16.7)	2 (33.3)	0	0	1 (16.7)	0	0	0	0	0
Fatigue	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	0	0	0
Nasopharyngitis	0	0	0	0	2 (33.3)	0	0	0	0	0
n (%) with 1 or more AEs	2 (33.3)	3 (50.0)	3 (50.0)	4 (66.7)	5 (83.3)	2 (33.3)	1 (11.1)	2 (25.0)	0	1 (33.3)
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0	0	0	0	0	0	0
n (%) of deaths	0	0	0	0	0	0	0	0	0	0
n (%) with 1 or more other serious AEs	0	0	0	0	0	0	0	0	0	0
n (%) of treatment stopped due to AEs	0	0	0	0	0	0	0	0	0	0
n (%) with 1 or more AEs considered at least possibly related to TMC435350	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (16.7)	1 (11.1)	1 (12.5)	0	0

In general, no relevant differences in the incidence of AEs between the different doses of TMC435350 were found. In addition, no subjects developed an AE following TMC435350 administration under fasted conditions.

There were no subjects with an AE that was considered probably or very likely related to TMC435350. The number of subjects reporting 1 or more AEs that were considered possibly related to TMC435350 during Part I of the trial was 1 (16.7%), 1 (16.7%), 2 (33.3%), and 1 (16.7%) subjects following TMC435350 100 mg, 200 mg, 300 mg, and 600 mg administration, respectively. None of these events were reported in more than 1 subject following treatment with TMC435350. No grade 3 or 4 AEs were reported during Part I of the trial. Apart from 2 grade 2 AEs (i.e., increased ALT and increased AST) reported following TMC435350 200 mg and TMC435350 450 mg administration, respectively; all AEs were grade 1.

Safety Part II (Multiple Dose Escalation Part)	**100 mg q.d. (Panel 3)**		**200 mg q.d. (Panel 4)**		**200 mg b.i.d. (Panel 5)**		**400 mg q.d. (Panel 6)**	
Healthy Subjects	**TMC435350**	**placebo**	**TMC435350**	**placebo**	**TMC435350**	**placebo**	**TMC435350**	**placebo**
(N = number of subjects with data)	(N=4)	(N=2)	(N=5)	(N=2)	(N=6)	(N=3)	(N=6)	(N=3)
Adverse Events								
Most frequently reported AEs (reported in > 1 subject), n (%)								
Headache	1 (25.0)	0	3 (60.0)	1 (50.0)	0	0	0	0
Photosensitivity reaction	0	0	0	0	3 (50.0)	0	0	0
Diarrhea	0	0	0	0	2 (33.3)	0	0	0
Abdominal pain upper	0	0	0	0	2 (33.3)	0	0	0
Abdominal distension	1 (25.0)	0	0	0	1 (16.7)	0	0	0
n (%) with 1 or more AEs	3 (75.0)	1 (50.0)	4 (80.0)	1 (50.0)	6 (100)	1 (33.3)	4 (66.7)	1 (33.3)
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0	0	0	0	0
n (%) of deaths	0	0	0	0	0	0	0	0
n (%) with 1 or more other serious AEs	0	0	0	0	0	0	0	0
n (%) of treatment stopped due to AEs	0	0	0	0	0	0	0	0
n (%) with 1 or more AEs considered at least possibly related to TMC435350	1 (25.0)	0	0	0	5 (83.3)	1 (33.3)	1 (16.7)	0
Most frequently reported AEs possibly related to TMC435350 (reported in > 1 subject), n (%)								
Photosensitivity reaction	0	0	0	0	3 (50.0)	0	0	0
Diarrhea	0	0	0	0	2 (33.3)	0	0	0
Abdominal pain upper	0	0	0	0	2 (33.3)	0	0	0

In general, no relevant differences in the incidence of AEs between the different doses of TMC435350 were found.
The number of subjects reporting 1 or more AEs that were considered at least possibly related to TMC435350 was 5 (83.3%) subjects during 200 mg b.i.d. administration compared to 1 subject (25.0% and 16.7%, respectively) during both 100 mg q.d. and 400 mg q.d. administration. The most common AEs that were considered possibly related to the study medication were photosensitivity reaction, diarrhea, and abdominal pain upper reported in 3 (50.0%), 2 (33.3%), and 2 (33.3%) subjects, respectively during TMC435350 200 mg b.i.d. administration. No subjects reported an AE considered very likely related to study medication by the investigator. One subject reported an AE, i.e., abdominal distension (following intake of TMC435350 200 mg b.i.d.) that was considered probably related to TMC435350. In the multiple dose part of the trial, all AEs were grade 1.

Safety Part III (Multiple Dose Part) **HCV-Infected Subjects**	**200 mg q.d. TMC435350** **(Panel 7)**
(N = number of subjects with data)	(N=6)
Adverse Events	
Most frequently reported AEs (reported in > 1 subject), n (%)	
Headache	3 (50.0)
Fatigue	2 (33.3)
n (%) with 1 or more AEs	5 (83.3)
n (%) with 1 or more grade 3 or 4 AEs	0
n (%) of deaths	0
n (%) with 1 or more other serious AEs	0
n (%) of treatment stopped due to AEs	0
n (%) with 1 or more AEs considered at least possibly related to TMC435350	1 (16.7)
In the multiple dose part in HCV-infected subjects (Panel 7) of the trial, 5 (83.3%) subjects developed at least one AE. All events were considered not related to the hepatitis C infection. No events were considered probably or very likely related to study medication. One (16.7%) subject reported an AE considered possibly related to TMC435350 (i.e., rash). All AEs reported for HCV-infected subjects were grade 1.	
Clinical Laboratory Tests	During the single and multiple dose parts of the trial in healthy subjects (Part I and Part II), no consistent or clinically relevant changes over time in laboratory parameters were observed. During Part III (TMC435350 200 mg q.d.) in HCV-infected subjects, no consistent or clinically relevant changes over time in laboratory parameters were observed. No treatment-emergent grade 4 laboratory abnormalities were observed in the trial. One HCV-infected subject (Panel 7) was observed with a grade 3 increase in lipase levels after TMC435350 200 mg q.d. administration. Two healthy subjects were observed with grade 2 laboratory abnormalities, 1 subject was observed with grade 2 hyperkalemia following TMC435350 200 mg administration and 1 subject was observed with grade 2 increased ALT and increased AST following TMC435350 200 mg and 450 mg administration, respectively. The latter subject had a grade 2 increased ALT from Day 1 predose to Day 2 of TMC435350 450 mg administration. This laboratory abnormality was reported as a grade 2 AE judged as not related by the investigator. ALT levels returned to normal at an uscheduled visit 17 days after the start of TMC435350 administration; when the AE was considered resolved. In addition, on Day 1 predose of TMC435350 450 mg administration, AST levels were grade 1 increased; this abnormality was reported as grade 1 AE. On the same day (4 hours postdose and at an unscheduled time), AST levels were grade 2 increased and this was reported as grade 2 AE. AST levels returned to normal at an unscheduled visit on Day 8 of the treatment phase. Note that ALT and AST levels were normal at baseline. All other laboratory abnormalities were grade 1. In both healthy (Part I and Part II) and HCV-infected subjects (Part III), there were no consistent or clinically relevant changes over time in urinalysis.

Cardiovascular Safety	During the single dose and multiple dose parts of the trial in healthy subjects, i.e., Part I and Part II, median changes in vital signs and ECG parameters were generally minor, and none of the changes were considered clinically relevant. Also during the multiple dose part in HCV-infected subjects, i.e., Part III, median changes in vital signs and ECG parameters were generally minor and not considered clinically relevant. During the multiple dose parts of the trial, i.e., Part II (in healthy subjects) and Part III (in HCV-infected subjects), fluctuations in changes of all the chest echocardiography parameters were generally minor and not clinically significant. Except for abnormalities in BNP, no abnormalities related to cardiac markers were observed.
Physical Examination	No abnormal findings were observed in healthy subjects following TMC435350 administration in Part I of the trial. During Part II of the trial, abnormal findings in physical examination were observed in 2 subjects during TMC435350 200 mg b.i.d. administration; 1 subject developed macular rashes (face and neck) and photosensitivity and 1 subject developed macular rashes (face and neck) and phototoxicity. During TMC435350 administration in HCV-infected subjects (Part III), no abnormal findings were observed.
Antiviral Activity Viral Load (Panel 7 only)	Median $\log_{10}$ viral load was 6.75 $\log_{10}$ IU/mL at baseline. Sixteen hours after first intake viral load values had dropped with 2.23 $\log_{10}$ IU/mL to 4.43 $\log_{10}$ IU/mL. At Day 6 (i.e., first assessment after last dose of TMC435350 was administered), viral load values were further decreased to 2.89 $\log_{10}$ IU/mL and values remained low at Day 7 (2.98 $\log_{10}$ IU/mL) and Day 8 (3.04 $\log_{10}$ IU/mL). During follow-up, median $\log_{10}$ viral load values returned to values before treatment, i.e., 5.95 and 6.42 $\log_{10}$ IU/mL at the first and the second follow-up visit, respectively. A similar profile in viral load values was seen for all subjects participating in Part III of the trial.

Conclusions

In the Single Ascending Dose (SAD) part, the most common reported AEs were headache, fatigue, nasopharyngitis and catheter (insertion) site related reaction. Apart from catheter (insertion) site related reaction, none of these AEs were reported following intake of placebo.
In Session VIIa, no subjects developed an AE following intake of TMC435350 200 mg under fasted conditions.
No consistent or clinically relevant changes over time in laboratory parameters were observed in healthy subjects during the SAD part of the trial.
In the SAD part, median changes in vital signs and ECG parameters were generally minor and none of the changes were considered clinically relevant.
Single doses of TMC435350 at 50 to 600 mg resulted in more than dose proportional increases in systemic exposure for doses exceeding 100 mg with a t_{max} of approximately 6 hours in each dose group. As mean $t_{1/2term}$ values were comparable between the dose groups, the more than dose proportional increase in exposure is probably the result of a dose dependent extent of absorption of TMC435350. Food did not affect TMC435350 exposure after a single dose at 200 mg. However the median t_{max} was prolonged by 2 hours in the presence of food.

In the Multiple Ascending Dose (MAD) part, the most commonly reported AEs were headache, photosensitivity reaction, diarrhea, abdominal pain upper, and abdominal distension. Apart from headache, none of these AEs were reported during intake of placebo.
In the MAD part, no consistent or clinically relevant changes over time in laboratory parameters were observed in healthy subjects.
Median changes in vital signs and ECG parameters were generally minor and none of the changes were considered clinically relevant. Changes of all the chest echocardiography parameters were generally minor. Except for abnormalities in BNP, abnormalities related to cardiac biomarkers were not observed during the MAD part of the trial.
After 5 days of once daily treatment with TMC435350 at 100 mg, 200 mg and 400 mg in healthy subjects, systemic exposure to TMC4354350 increased in a substantially more than dose proportional fashion, especially for the dose increase from 100 to 200 mg. On Day 5, a lag time in absorption was observed for all subjects in the 200 mg b.i.d. and 400 mg q.d. dose groups. Substantial accumulation was observed in the 200 mg q.d., 400 mg q.d. and 200 mg b.i.d. dose groups. Steady-state conditions had been reached at Day 5 in the 100 mg q.d. dose group. In the other q.d. dose groups, steady-state had generally not been fully attained by Day 5. For the 200 mg b.i.d. dose group, the Day 5 0 hours and Day 5 12 hours predose concentrations were comparable; however, as in this trial no information was obtained on circadian variation, it could not be concluded that steady-state had been reached at Day 5.

Both after single and multiple dosing either a second absorption peak or a small plateau was observed in the plasma concentration-time profile of a few subjects during the absorption phase, suggesting the presence of multiple absorption processes. The resulting prolonged absorption may have influenced the apparent mean $t_{1/2term}$ which, after multiple intake of TMC435350, increased with dose. In contrast, for single doses of TMC435350, mean $t_{1/2term}$ values were independent of the dose. Treatment with TMC435350 at 200 mg b.i.d. resulted in a slightly higher systemic exposure than once daily treatment at 400 mg, suggesting schedule-dependent pharmacokinetics.

In HCV-infected subjects, the most common AEs were headache and fatigue.
During TMC435350 administration, no treatment-emergent grade 4 laboratory abnormalities were observed. One HCV-infected subject was observed with a grade 3 increase in lipase levels after TMC435350 200 mg q.d. administration. No laboratory abnormalities were reported as AE.
In HCV-infected subjects, median changes in vital signs, ECG, and chest echocardiography parameters were generally minor and not considered clinically relevant. Except for N-terminal BNP above normal values observed in 1 subject, no abnormalities related to cardiac markers were observed.
Treatment of HCV-infected subjects with TMC435350 200 mg q.d. induced a reversible 3 up to 4 $\log_{10}$ IU/mL decrease in plasma HCV viral load.
In HCV-infected subjects, 5-day treatment with TMC435350 at 200 mg q.d. resulted in higher systemic exposure compared to healthy subjects. No differences were observed in median t_{max}, but median $t_{1/2term}$ was longer in HCV-infected subjects than in healthy subjects. On Day 5, a lag time in absorption was observed in 5 out of the 6 HCV-infected subjects. The mean percentage of the dose that was excreted in urine as unchanged TMC435350 was negligible for all treatments in healthy subjects and HCV-infected subjects ($\leq 0.021\%$).

In conclusion, single (range: 50 – 600 mg) or multiple intakes (100 mg q.d., 200 mg q.d., 200 mg b.i.d., and 400 mg q.d. for 5 days) of TMC435350 were generally safe and well tolerated at all doses tested in healthy subjects. Both for single and repeated dosing, the exposure to TMC435350 increased more than proportional with the dose. The pharmacokinetic profile supports q.d. dosing.
In addition, TMC435350 200 mg q.d. administered for 5 days to genotype 1 HCV-infected subjects was found to be generally safe and well tolerated and induced a reversible 3 up to 4 $\log_{10}$ IU/mL decrease in plasma HCV viral load.

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