SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: - **Indication**: HCV infection	**Drug Substance**: TMC435 **Trial no**.: TMC435350-TiDP16-C202 **Clinical Phase**: IIa
Title: An open-label trial in genotype 2, 3, 4, 5 and 6 hepatitis C-infected subjects to evaluate the antiviral activity, safety, tolerability and pharmacokinetics of TMC435350 following 7 days once daily dosing as monotherapy.	
Investigator: C. Moreno, M.D., Ph.D., Department of Gastroenterology and Hepatopancreatology, Free University of Brussels, Erasmus Hospital, [redacted], Belgium	**Countries**: Belgium, Germany, and Thailand
Trial Period: Start: 03-Mar-2009 End: 18-Nov-2009	**No. of Investigators**: 12 **No. of Subjects**: 37 subjects

Objectives:

The primary objective of this trial was:

- to determine the antiviral activity of TMC435 200 mg q.d. during 7 days as monotherapy in treatment-naïve, genotype 2 to 6 HCV-infected subjects.

Secondary objectives were:

- to determine the safety and tolerability of TMC435 200 mg q.d. during 7 days as monotherapy;
- to determine the pharmacokinetic profile of TMC435 200 mg q.d. after administration for 7 days as monotherapy.

Design: This was a Phase IIa, open-label trial to assess the antiviral activity, safety, tolerability, and pharmacokinetics of TMC435350 (further referred to as TMC435), administered at 200 mg once daily (q.d.) for 7 days as monotherapy in treatment-naïve, genotype 2 to 6 hepatitis C-infected subjects. TMC435 is a NS3/4A viral protease inhibitor under development for the treatment of chronic hepatitis C (HCV) infection.

Forty treatment-naïve subjects with chronic genotype 2, 3, 4, 5, or 6 HCV infection were to be included, divided over 5 cohorts of 8 subjects for each genotype.

After screening and confirmation of eligibility, plasma HCV RNA levels and liver enzymes were measured one week prior to treatment start. All subjects were treated with TMC435 200 mg q.d. for 7 consecutive days as monotherapy. After the TMC435 treatment period, subjects could start with standard of care (SoC) treatment for hepatitis C infection from Day 8 onwards, as decided upon by the subject in agreement with his/her treating physician.

Antiviral activity was assessed by measuring plasma HCV RNA levels. Full pharmacokinetic profiles of TMC435 were determined up to 96 hours after TMC435 intake on Day 7. Safety and tolerability were evaluated continuously.

There was a follow-up period of 30-35 days after the last TMC435 administration (on Day 7), during which plasma HCV RNA levels, safety and tolerability were evaluated.

Subject Selection

Inclusion Criteria

1. Male and female subjects aged between 18 and 70 years, extremes included.
2. Subjects with documented chronic (diagnosis of hepatitis C > 6 months before the screening period) genotype 2, 3, 4, 5 or 6 HCV infection (as assessed by sequence based subtyping, performed at screening).
   Note: HCV-infected subjects with hemophilia could be enrolled.
3. HCV treatment-naïve subjects (not receiving or having received any treatment including investigational treatment for HCV with the exception of non-hepatoxic herbal remedies).
4. Patients with either no cirrhosis or up to Child Pugh A (compensated cirrhosis) liver disease.
5. Plasma HCV RNA level of ≥ 100,000 IU/mL at screening (as assessed by the Taqman assay).
6. Informed Consent Form (ICF) signed voluntarily before the first trial related activity.
7. Able to comply with the protocol requirements and having good accessible veins.
8. Normal weight as defined by a Body Mass Index (BMI: weight in kg divided by the square of height in meters) of 18 to 32 kg/m^2, extremes included.

Exclusion Criteria

1. Evidence of Child Pugh B or C liver disease at screening; evidence of decompensated liver disease defined as prior or current history of ascites, hepatic encephalopathy, esophageal or gastric varices.
2. Any other cause of significant liver disease in addition to hepatitis C; this may include but is not limited to hepatitis B, drug- or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, non-alcoholic steatohepatitis, or primary biliary cirrhosis.
3. Subjects with diagnosed or suspected hepatocellular carcinoma.
4. Subjects (male or women of childbearing potential) not agreeing to use highly effective birth control methods, i.e., two separate forms of contraception, from screening through 90 days after the last dose of TMC435 and to continue if applicable (i.e., when continuing on SoC treatment) as dictated by the approved product information of the medication administered.
5. Use of herbal medications, dietary supplements and products containing *Hypericum perforatum* (e.g., St. John's wort) in a period of 14 days before the first trial medication intake until end of pharmacokinetic assessments (96 h post last dose of study medication).
6. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the Investigator's opinion would compromise the subject's safety and/or compliance with the trial procedures (period of non-drug/alcoholic misuse must at least be 1 month before the first administration of trial medication).
7. A positive urine drug test at screening. Urine was tested to check the current use of amphetamines, cocaine, and opioids (with the exclusion of methadone or equivalents).
8. Subjects with at least one of the following laboratory abnormalities as defined by the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table at screening:
   - Bilirubin > 1.25x upper limit of laboratory normal range (ULN) (when accompanied by any increase in other liver function test) or > 1.5 x ULN (when other liver functions are in the normal range);
   - Platelet count < $90,000/mm^3$;
   - White blood cell (WBC) count < $2,000$ cells/mm^3;
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) grade 4;
   - Any other lab toxicity found to be clinically significant by the Investigator.

   Note: Retesting of abnormal screening values that led to exclusion was allowed once using an unscheduled visit during the screening period.
9. Subjects coinfected with human immunodeficiency virus type 1 or 2 (HIV-1 or HIV-2), or hepatitis A or B virus infection (confirmed by hepatitis A antibody immunoglobulin [IgM], or hepatitis B surface antigen [HBsAg]) or active tuberculosis at screening.
10. Subjects with any active clinically significant disease (e.g., cardiac dysfunction, cardio(myo)pathy, cardiac insufficiency, pancreatitis, renal insuffiency), or medical history or physical examination or electrocardiogram (ECG) findings during screening that, in the Investigator's opinion, would compromise the outcome of the trial.
11. Subjects having uncontrolled/unstable diabetes, active epilepsy or history of epilepsy, history of moderate, severe or uncontrolled psychiatric disease, especially depression, including a history of hospitalization or prior suicidal attempt.
12. Subjects enrolled in another clinical trial within 90 days prior to screening.

Treatment	**TMC435**
Concentration Dosage Form (F No.) Usage	100 mg capsules (F007) oral
Batch Number	08G25/F007
Dose Regimen	TMC435 200 mg q.d. as monotherapy
Duration of Treatment	7 days
Duration of Trial	Maximum 7 days (excluding screening and follow-up)
Disallowed Medication	The following medications were not allowed during the 7-day TMC435 treatment period and up to end of pharmacokinetic (PK) assessments. - any investigational drugs other than TMC435; - any vaccine or immunomodulator (e.g. interleukins, systemic corticosteroids) other than TMC435; - any herbal extracts claimed to have activity against viral hepatitis (e.g. milk thistle, silymarin); - any anti-HCV therapy, including interferon (IFN) and ribavirin (RBV). The following drugs should not have been used during the trial. - anti-HIV therapies; - cytochrome P450 (CYP)3A4 inducers: • rifabutin, rifampicin • carbamazepine, phenytoin, phenobarbital • products containing *Hypericum perforatum* (St. John's Wort) • systemic dexamethasone - CYP3A4 inhibitors • systemic ketoconazole and itraconazole • macrolide antibiotics: erythromycin, clarithromycin, troleandomycin and telithromycin - CYP3A4 substrates with a small therapeutic index: terfenadine, astemizole, cisapride, amiodarone, quinidine, triazolam, midazolam, ergot derivatives, simvastatin, lovastatin, sildenafil, vardenafil, warfarin, tadalafil, bepridil, flecainide, propafenone, systemic lidocaine, mexiletine, disopyramide, calcium channel blockers. - CYP2D6 substrates with a small therapeutic index: tricyclic antidepressants, tetracyclic antidepressants.

Assessments	
Antiviral Activity	Samples for the determination of plasma HCV RNA levels were taken at screening, 1 week before start of TMC435 treatment, Day 1 (predose, 3h, 4h, 5h, 6h, 8h, 10h postdose), Day 2 (predose, 10h), Days 3 to 7 (all predose), Days 8 to 11 (i.e., Day 7 24h, 48h, 72h, 96h postdose), and follow-up visits 14 days and 30-35 days after last TMC435 intake; and at time of dropout or the following morning (if applicable).
Resistance Determinations	Samples for sequencing of the protease domain of NS3 (viral genome sequencing) were taken at: screening, Days 1, 4, and 7 (all predose), and follow-up visits 14 days and 30-35 days after last TMC435 intake; and at time of dropout or the following morning (if applicable). Viral genome sequencing on additional time points could be triggered by the Sponsor's virologist based on individual changes in plasma HCV RNA levels and HCV RNA levels (> 1000 IU/mL) required for entering sequencing protocol.
Exploratory Biomarker Analyses	Samples for cytokine expression and host mRNA analysis were taken at: Day 1 (predose, 4h, 10h), Day 3 (predose), Day 7 (predose, 4h), and follow-up visits 14 days and 30-35 days after last TMC435 intake; and at time of dropout or the following morning (if applicable). PBMC samples for immune cell function were taken on Day 1 (predose), Day 3 (predose), Day 7 (predose), and follow-up visits 14 days and 30-35 days after last TMC435 intake; and at time of dropout or the following morning (if applicable). In addition, for subjects who consented, a sample was taken on Day 1 (predose) for genomic DNA typing. The samples are stored and could be analyzed as part of exploratory analyses in the future.
Pharmacokinetics	Samples to determine TMC435 plasma concentrations were taken at: Days 1, 5 and 6 (all predose), Day 7 (predose, 0.5h, 1h, 2h, 4h, 6h, 8h, 10h), and Days 8 to 11 (i.e., Day 7 24h, 48h, 72h, 96h postdose); and at time of dropout or the following morning (if applicable).
Adverse Events	Adverse events were continuously monitored from signing of the Informed Consent Form (ICF) onwards until the last trial-related visit.
Clinical Laboratory	Samples for hematology, biochemistry (fasted for at least 10 hours), and coagulation were taken at: screening, 1 week before start of TMC435 treatment (only for liver enzyme panel), Days 1 and 7 (both predose), Day 8 (i.e., Day 7 24h postdose), and at follow-up visit 30-35 days after last TMC435 intake; and, if applicable, in case of dropout during TMC435 treatment: at time of dropout or the following morning. At screening: Samples for HIV-1 and -2 tests, hepatitis A, B, C tests (hepatitis A antibody IgM, hepatitis B surface antigen, and hepatitis C virus antibody, respectively). Urinalysis at: screening, Days 1 and 7 (both predose), and Day 8 (i.e., Day 7 24h postdose); and, if applicable, in case of dropout during TMC435 treatment: at time of dropout or the following morning and at follow-up visits 14 days and 30-35 days after last TMC435 intake.
Cardiovascular Safety	Vital signs and ECGs were recorded at: screening, Days 1 and 7 (both predose), Day 8 (i.e., Day 7 24h postdose), and at the follow-up visit 30-35 days after last TMC435 intake; and, if applicable, in case of dropout during TMC435 treatment: at time of dropout or the following morning and at the follow-up visit 14 days (at this visit: vital signs only).
Physical Examination	Physical examinations were performed at screening, Days 1 and 4 (both predose), Day 8 (i.e., Day 7 24h postdose), and follow-up visits 14 days and 30-35 days after last TMC435 intake; and at time of dropout or the following morning (if applicable).
Statistical Methods	Intent-to-Treat analysis, descriptive statistics, frequency tabulations, Wilcoxon's matched pairs signed ranks test.

Main Features of the Subject Sample and Summary of the Results

	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6	All Subjects
Subject Disposition						
Number of Subjects Entered	***6***	***8***	***8***	***7***	***8***	***37***
Discontinuations - reason, n (%)	***1 (16.7)***	***0***	***0***	***0***	***0***	***0***
Adverse Event (AE)	1 (16.7)[a]	0	0	0	0	0
Demographic and Baseline Characteristics						
Demographics						
Gender, n (%)						
Male	2 (33.3)	5 (62.5)	3 (37.5)	3 (42.9)	6 (75.0)	19 (51.4)
Female	4 (66.7)	3 (37.5)	5 (62.5)	4 (57.1)	2 (25.0)	18 (48.6)
Age: median (range), years	43 (27; 61)	42 (18; 56)	47 (26; 55)	65 (48; 69)	49 (30; 53)	48 (18; 69)
Weight: median (range), kg	70 (50; 95)	65 (50; 91)	77 (51; 105)	75 (54; 87)	66 (47; 71)	69 (47; 105)
Race, n (%)						
Caucasian/White	5 (83.3)	7 (87.5)	6 (75.0)	7 (100)	0	25 (67.6)
Asian	0	1 (12.5)	0	0	8 (100)	9 (24.3)
Black	1 (16.7)	0	2 (25.0)	0	0	3 (8.1)
Baseline Characteristics						
HCV RNA (log_{10} IU/mL)						
median	6.4	6.7	5.8	6.5	6.7	6.5
(range)	(5.6;6.8)	(4.5;7.2)	(5.2;6.7)	(5.9;7.1)	(5.7;7.3)	(4.5;7.3)
HCV RNA (Category), n (%)						
< 800,000 IU/mL	1 (16.7)	2 (25.0)	5 (62.5)	0	1 (12.5)	9 (24.3)
≥ 800,000 IU/mL	5 (83.3)	6 (75.0)	3 (37.5)	7 (100)	7 (87.5)	28 (75.7)
Duration of HCV infection, years						
Median	0.9	3.6	6.5	11.3	1.5	3.5
(range)	(0.6; 10.4)	(0.2[b]; 19.4)	(0.9; 13.0)	(3.4; 20.2)	(0.5; 16.9)	(0.2[b]; 20.2)
HCV Subtype (NS5B), n (%[c])						
2	1 (16.7)	-	-	-	-	1 (3.0)
2b	2 (33.3)	-	-	-	-	2 (6.1)
2c	1 (16.7)	-	-	-	-	1 (3.0)
2i	1 (16.7)	-	-	-	-	1 (3.0)
2k	1 (16.7)	-	-	-	-	1 (3.0)
3a	-	8 (100)	-	-	-	8 (24.2)
4a	-	-	4 (57.1)	-	-	4 (12.1)
4c	-	-	1 (14.3)	-	-	1 (3.0)
4d	-	-	2 (28.6)	-	-	2 (6.1)
NS5B subtype not available	-	-	1[c,d]	-	-	1[c]
5a	-	-	-	7 (100)	-	7 (21.2)
6a	-	-	-	-	1 (20.0)	1 (3.0)
6b	-	-	-	-	1 (20.0)	1 (3.0)
6j	-	-	-	-	1 (20.0)	1 (3.0)
6n	-	-	-	-	2 (40.0)	2 (6.1)
NS5B subtype not available	-	-	-	-	3[c,e]	3[c]
Metavir Score, n (%)						
F0	0	0	1 (12.5)	0	1 (12.5)	2 (5.4)
F1	2 (33.3)	5 (62.5)	5 (62.5)	3 (42.9)	5 (62.5)	20 (54.1)
F2	2 (33.3)	2 (25.0)	0	2 (28.6)	1 (12.5)	7 (18.9)
F3	1 (16.7)	0	2 (25.0)	0	1 (12.5)	4 (10.8)
F4	1 (16.7)	1 (12.5)	0	2 (28.6)	0	4 (10.8)
ALT Toxicity Grade at baseline, n (%)						
Grade 0[f]	1 (16.7)	2 (25.0)	1 (12.5)	1 (14.3)	1 (12.5)	6 (16.2)
Grade 1	4 (66.7)	1 (12.5)	5 (62.5)	6 (85.7)	6 (75.0)	22 (59.5)
Grade 2	0	4 (50.0)	1 (12.5)	0	0	5 (13.5)
Grade 3	1 (16.7)	1 (12.5)	1 (12.5)	0	1 (12.5)	4 (10.8)

[a] Subject [redacted] discontinued due to a serious adverse event (SAE, ileitis) during the follow-up period on Day 8.
[b] One subject did not meet the protocol definition of chronicity i.e. presence of HCV RNA for > 6 months, however, HCV infection was sufficiently documented (biopsy confirmation of cirrhosis and no other etiology).
[c] Percentages are based on subjects with data.
[d] Results with Siemens Trugene HCV assay: 1 subject has HCV subtype 4, 3 subjects have HCV subtype 4a, 2 subjects have HCV subtype 4c, 1 subject has HCV subtype 4e, and 1 subect has HCV subtype 4i.
[e] Results with Siemens Versant HCV LIPA II assay: 2 subjects have HCV subtype 6a/6b and 6 subject have HCV subtype 6c-l.
[f] Grade 0 represents normal values.

Antiviral Activity	Genotype 2 N = 6	Genotype 3 N = 8	Genotype 4 N = 8	Genotype 5 N = 7	Genotype 6 N = 8
Primary Variable: Change From Baseline in HCV RNA (Log_{10} IU/mL)					
Day 3					
Mean ±SE	-2.02 ±0.625	0.16 ±0.263	-3.43 ±0.167	-2.71 ±0.335	-3.57 ±0.197
Median (range)	-2.09 (-3.6; -0.3)	0.07 (-0.7; 1.8)	-3.55 (-3.9; -2.6)	-2.74 (-4.0; -1.5)	-3.69 (-4.2; -2.7)
Day 8					
Mean ±SE	-2.73 ±0.710	-0.04 ±0.228	-3.52 ±0.431	-2.19 ±0.388	-4.35 ±0.293
Median (range)	-2.39 (-4.9; -0.4)	-0.16 (-1.2; 1.0)	-3.95 (-4.8; -1.4)	-2.50 (-3.1; -0.3)	-4.53 (-5.2; -2.8)
Secondary Variables					
Virologic Response, n (%)					
Day 3					
≥ 2 log_{10} IU/mL reduction from baseline	3 (50.0)	0	8 (100)	6 (85.7)	8 (100)
< 25 IU/mL	0	0	0	0	0
< 25 IU/mL undetectable	0	0	0	0	0
Day 8					
≥ 2 log_{10} IU/mL reduction from baseline	3 (50.0)	0	6 (75.0)	5 (71.4)	8 (100)
< 25 IU/mL	0	0	2 (25.0)	0	2 (25.0)
< 25 IU/mL undetectable	0	0	0	0	0
Viral Breakthrough[a], n (%)					
Days 1 to 8	0	1 (12.5)	2 (25.0)	3 (42.9)	0
Follow-up period	2 (33.3)	1	1	0	2

N = number of subjects, n = number of observations.

[a] Viral breakthrough was defined as an increase > 1 log10 IU/mL in HCV RNA from the lowest level reached, or a HCV RNA level > 100 IU/mL in subjects who previously had reached undetectable (< 25 IU/mL undetectable) or not quantifiable (< 25 IU/mL detectable) HCV RNA levels.

Resistance Determinations

Baseline mutations (defined as differences from genotype 1a H77 reference sequence) in the NS3 protease domain were observed in all 34 subjects with sequence data of the NS3 protease domain at baseline (or screening).

In genotype 2 and 3 subjects with viral breakthrough, no emerging mutations were detected in the samples analyzed. Viral sequence analysis from most genotype 4, genotype 5, and genotype 6 infected subjects with viral breakthrough showed emerging mutations. The most frequently observed emerging mutations in the NS3 protease domain (found in at least 3 subjects with viral breakthrough) were D168E and D168V.

Safety (n = number of subjects with data)	**Genotype 2 N = 6**	**Genotype 3 N = 8**	**Genotype 4 N = 8**	**Genotype 5 N = 7**	**Genotype 6 N = 8**	**All Subjects N = 37**
Treatment-Emergent AEs (TMC435 Treatment Period), n (%)						
Most frequently reported AEs (in ≥ 10% of all subjects)						
Influenza Like Illness	2 (33.3)	1 (12.5)	4 (50.0)	1 (14.3)	1 (12.5)	9 (24.3)
Headache	2 (33.3)	1 (12.5)	2 (25.0)	0	0	5 (13.5)
Diarrhea	2 (33.3)	1 (12.5)	1 (12.5)	0	0	4 (10.8)
Fatigue	2 (33.3)	1 (12.5)	0	0	1 (12.5)	4 (10.8)
Pruritus	1 (16.7)	1 (12.5)	1 (12.5)	1 (14.3)	0	4 (10.8)
n (%) with 1 or more AEs	5 (83.3)	6 (75.0)	8 (100)	4 (57.1)	5 (62.5)	28 (75.7)
n (%) of deaths	0	0	0	0	0	0
n (%) with 1 or more SAEs	1 (16.7) [a]	0	0	0	0	1 (2.7)
n (%) of treatment discontinued due to AEs	0 [a]	0	0	0	0	0
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0	0	0
Laboratory Safety (TMC435 Treatment Period)						
Mean ALT and AST levels decreased in all cohorts. Mild elevations in mean bilirubin (total, direct and indirect) levels were observed in all genotype cohorts; mean values remained within the normal lab range. There were no relevant changes in mean alkaline phosphatase (ALP) levels. Mean total cholesterol and high-density lipoprotein (HDL) cholesterol as well as hemoglobin, hematocrit, and RBC counts tended to decrease. There were no consistent trends or clinically relevant changes over time in any of the other laboratory parameters. The incidence of treatment-emergent grade 3 and 4 laboratory abnormalities was low (1 subject with a grade 3 bilirubin increase and 1 subject with a grade 4 plasma prothrombin time [PTT] increase). Treatment-emergent bilirubin abnormalities were observed in 5 subjects (1 subject with a grade 3, 2 subjects with a grade 2 and 1 subject with a grade 1 bilirubine elevation). No treatment-emergent abnormalities in ALT, AST, or ALP were observed.						

N = number of subjects.

[a] One subject (Subject [redacted]) discontinued due to a SAE (ileitis) during the follow-up period on Day 8.

Cardiovascular Safety
There were no consistent or clinically relevant changes over time in vital signs or ECG parameters including QTc, and no consistent or clinically relevant trends in treatment-emergent individual abnormalities.
Physical Examination
There were no clinically relevant changes over time in physical examination findings.

Pharmacokinetics of TMC435

Parameter, median (range)	**Genotype 2 N = 6[a]**	**Genotype 3 N = 8[c]**	**Genotype 4 N = 8[d]**	**Genotype 5 N = 7[e]**	**Genotype 6 N = 8**
Day 7					
C_{0h}, ng/mL	3720 (164; 8420)	1310 (492; 4220)	6270 (1030; 13100)	4650 (80.1; 14500)	5440 (2280; 11700)
C_{min}, ng/mL	3320 (156; 8420)	1110 (463; 3440)	5450 (1030; 13100)	4230 (48.2; 14300)	4960 (2080; 10600)
C_{max}, ng/mL	11250 (2360; 18500)	6580 (2760; 13200)	13500 (4530; 26200)	13600 (215; 24700)	14800 (3460; 23000)
t_{max}, h	4.01 (4.00; 7.83)	6.025 (4.02; 10.08)	6.04 (4.00; 8.08)	6.00 (4.00; 8.02)	6.00 (4.00; 6.20)
AUC_{24h}, ng.h/mL	170100 (26350; 311000)	74670 (34500; 199500)	212000 (70400; 483000)	189000 (3084; 457600)	227100 (63430; 373500)
$t_{1/2term}$, h	13.75 (7.998; 39.04[b])	11.51 (8.105; 17.09)	16.09 (9.966; 38.44[b])	18.12 (8.959; 20.91)	18.32 (11.70; 37.95[b])

In treatment-naïve HCV-infected subjects following a dose of TMC435 200 mg q.d., steady-state C_{0h}, C_{min}, C_{max} and AUC_{24h} values for TMC435 were comparable for the genotype 4, 5, and 6 cohorts, while lower values were observed for the genotype 2 and 3 cohorts with the lowest values in the latter cohort.

N = number of subjects.
[a] N=5 for AUC_{last}, λ_z and $t_{1/2term}$, [b] Accurate determination not possible, [c] N=7 for Day 5, [d] N=7 for Day 6, [e] N=6 for Day 6.

Pharmacokinetic/Pharmacodynamic Relationships

No consistent relationship was observed between TMC435 exposures and antiviral activity on Day 7 for the different genotypes.
Higher exposures to TMC435 were associated with increases in direct, indirect and total bilirubin from baseline. No consistent relationship was observed between TMC435 exposures and changes in ALP, AST, or ALT.

Conclusions

Monotherapy with oral TMC435 200 mg q.d. for 7 days showed potent antiviral activity, with highest antiviral activity against HCV genotypes 4 and 6, followed by genotype 5, and a mixed antiviral activity against genotype 2. No clear antiviral activity was seen against HCV genotype 3. Short-term treatment with TMC435 200 mg q.d. was generally safe and well tolerated.

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