SYNOPSIS

Study Identification and Protocol Summary

Sponsor: Janssen Research & Development[*] **Trade Name**: - **Indication**: Chronic hepatitis C virus (HCV) infection	**Drug Substance**: TMC435 **Study no**.: TMC435-TiDP16-C126 **Clinical Phase**: I
Title: A Phase I, open-label trial to investigate the effect of severe renal impairment on the pharmacokinetics and safety of TMC435.	
Investigator: Petr Šrámek, M.D., Ph.D., PRA International, Jankovcova 1569/2c n, 170 00 Prague 7, Czech Republic	**Country**: Czech Republic
Study Period: Start: 02-Aug-2011 End: 09-Jan-2012	**No. of Investigators**: 1 **No. of Subjects**: 16 (8 healthy subjects and 8 subjects with severe renal impairment)

Objectives:

The primary objective of this study was to assess the steady-state pharmacokinetics of TMC435 in subjects with severe renal impairment and to compare these with the pharmacokinetics in matched subjects with normal renal function.

The secondary objective was to assess the short-term safety and tolerability of TMC435 in subjects with severe renal impairment and in subjects with normal renal function.

Design:

This was a Phase I, open-label study to investigate the steady-state plasma pharmacokinetics and short-term safety and tolerability of TMC435 in subjects with severe renal impairment compared to matched healthy subjects with normal renal function. Severe renal impairment was defined by an estimated glomerular filtration rate (eGFR) $\leq$ 29 mL/min/1.73m^2 as determined by the Modification of Diet in Renal Disease (MDRD) equation, as per regulatory guidelines for the evaluation of the pharmacokinetics of drugs in subjects with impaired renal function. Subjects with severe renal impairment were only allowed in this study if they were not on dialysis. Normal renal function was considered as an eGFR $\geq$ 80 mL/min/1.73m^2 (MDRD).

The study population consisted of a total of 16 male or female subjects between 18 and 70 years of age. Eight healthy subjects with a normal renal function as defined above and 8 subjects with severe renal impairment were included. A healthy subject was matched to a subject with severe renal impairment with regards to sex, race, age (± 10 years), and body mass index (BMI) (± 20%). Dosing of the matched healthy subjects could only start once the corresponding subject with severe renal impairment had completed the Day 10 assessments (including physical examination). All subjects received TMC435 150 mg once daily (q.d.) for 7 days.

Full pharmacokinetic profiles of TMC435 up to 72 hours postdose were determined on Day 7. In addition, unbound TMC435 plasma concentrations were determined at specified time points. Safety and tolerability were monitored throughout the study.

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Subject Selection

Inclusion Criteria

All subjects had to meet all of the following inclusion criteria:

1. Male or female, aged between 18 and 70 years, extremes included.
2. Women had to:
   - be postmenopausal for at least 2 years, OR
   - be surgically sterile (had to have a total hysterectomy or bilateral oophorectomy, tubal ligation/bilateral tubal clips without reversal operation, or otherwise be incapable of becoming pregnant), OR
   - be not heterosexually active, OR
   - if of childbearing potential and heterosexually active, be practicing a highly effective method of birth control before entry.
3. Women had to have a negative serum pregnancy test at screening.
4. Women could not breastfeed from screening onwards.
5. Nonsmoking or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 3 months before study screening.
6. Informed consent form (ICF) signed voluntarily before the first study-related activity.
7. A BMI (weight in kg divided by the square of height in meters) of 18 to 35 kg/m^2, extremes included.
8. Able and agreeing to adhere to the prohibitions and restrictions specified in the protocol.

Subjects with severe renal impairment also had to meet the following inclusion criteria:

1. Consistent with the disease process causing the chronic renal failure and associated symptoms, otherwise judged to be in good health in the opinion of the investigator on the basis of a medical evaluation (including a physical examination, medical history, electrocardiogram [ECG], vital signs, and the results of blood biochemistry, blood coagulation, and hematology tests and a urinalysis carried out at screening).
2. Patients with severe renal impairment with an eGFR $\leq$ 29 $mL/min/1.73m^2$, as determined by the MDRD equation*, who were not on dialysis and were not expected to start dialysis in the next 3 months.
3. Severity of renal disease had to be stable: no significant change in renal function as evidenced by the serum creatinine value within ± 25% from the last determination, obtained within at least 6 months before study entry.
4. Patients with diabetes mellitus could be included provided that the disease was controlled (i.e., hemoglobin A1c < 7%).
5. Stable treatment regimen for renal impairment from 2 months prior to treatment start. Diuretics were allowed when needed.
6. Concomitant medications to treat underlying disease states or medical conditions related to renal insufficiency could be used, except when specifically excluded by name or pharmacological class, and provided that dosages were stable for at least 2 months prior to treatment start.

Matched healthy subjects also had to meet the following inclusion criteria:

1. Judged to be in good health in the opinion of the investigator on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, ECG, vital signs, and the results of blood biochemistry, blood coagulation, and hematology tests and a urinalysis carried out at screening.
2. Normal renal function, i.e., eGFR $\geq$ 80 $mL/min/1.73m^2$ as determined by the MDRD equation*.
3. Matched to a subject with severe renal impairment with regards to sex, race, age (± 10 years) and BMI (± 20%).

* MDRD equation:

eGFR ($mL/min/1.73\ m^2$) = 175 x $(\text{serum creatinine})^{-1.154}$ x $(\text{age})^{-0.203}$ x (0.742 if female) x (1.212 if African American).

Exclusion Criteria

All subjects could not have any of the following characteristics:

1. A positive human immunodeficiency virus type – 1 or 2 (HIV-1 or HIV-2) test at study screening.
2. Hepatitis A, B, or C infection (confirmed by hepatitis A antibody immunoglobulin M [IgM], hepatitis B surface antigen, or HCV antibody, respectively) at screening.
3. History of any illness (unrelated to renal impairment, as appropriate) that, in the opinion of the investigator, could confound the results of the study or pose an additional risk in administering study medication to the subject. This could include but was not limited to: history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; chronic skin disease; or history of mental disease.
4. Known allergies, hypersensitivity, or intolerance to TMC435 or its excipients.
5. Use of disallowed concomitant medication.
6. Received an investigational drug (including investigational vaccines) or used an investigational medical device within 90 days before the planned start of treatment.
7. Any condition that, in the opinion of the investigator, would have compromised the study or the well-being of the subject or prevent the subject from meeting or performing study requirements.
8. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use that in the investigator's opinion would have compromised the subject's safety and/or compliance with the study procedures.
   Note: Subjects with a positive urine drug test at screening were excluded. Urine was tested to check the current use of amphetamines, benzodiazepines, cocaine, cannabinoids, methadone, barbiturates, and opioids. Subjects with severe renal impairment with a positive urine test for drugs prescribed by their physician (e.g., sleeping pill, pain medication) could be included following prior discussion with the Study Physican/Medical Leader and Clinical Pharmacology Leader.
9. Any history of significant skin disease such as, but not limited to, rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, systemic lupus erythematosus, or urticaria.
10. Donation of blood or plasma within 90 days preceding the first intake of study drug.
11. Having previously been dosed with TMC435 in a multiple-dose study with TMC435.
12. Having previously been dosed with TMC435 in more than 3 single-dose studies with TMC435.

Subjects with severe renal impairment could also not have any of the following characteristics:

1. History of renal transplant or renal carcinoma. Subjects with a history of renal carcinoma who had been cancer free for at least 5 years could be included.
2. Uncontrolled hypertension.
3. Hepatorenal syndrome.
4. Imminent renal replacement therapy (i.e., during the study period).

Matched healthy subjects could also not have the following characteristics:

1. History of congenital or hereditary kidney disease (including polycystic kidney disease), nephrectomy, renal transplant, or nephrolitiasis.

Treatment	TMC435
Concentration Dosage Form (G No.) Usage	150 mg capsule (G007) oral
Batch Number	11B03
Dose Regimen	150 mg TMC435 q.d.
Duration of Treatment	7 days
Duration of Study	Screening: maximum 21 days Treatment: 7 days Follow-up: 30 to 35 days

Disallowed Medication	**For subjects with severe renal impairment:** Subjects with severe renal impairment could continue to use their regular medications for the management of their renal insufficiency or related conditions. All concomitant medication, indication, and dose/duration were to be documented and discussed with the Study Physician/Medical Leader and Clinical Pharmacology Leader prior to inclusion, except for paracetamol (acetaminophen) or ibuprofen. As TMC435 is an inhibitor of organic anion transporting polypeptide 1B1, the plasma exposure to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) could increase when coadministered with TMC435. Renally impaired subjects who were eligible for study participation were not to receive statin therapy and those receiving statin therapy at the time of screening could only be included in the study if in the opinion of the investigator, a temporary interruption of the statin regimen (i.e., stopping statin therapy 7 days prior to the first TMC435 intake and resuming statin therapy after the last pharmacokinetic sample was obtained) was judged not to impact the subject's safety. Other concomitant therapy that was allowed, was not to be changed (started, stopped, or changed in regimen) between screening and until the last pharmacokinetic sample had been obtained, except for ibuprofen or paracetamol. However, if there was a need to change (start, stop, or change in regimen) concomitant therapies during the study, dosage and regimen had to be discussed in advance with the above-mentioned sponsor representatives. **For healthy subjects:** All medication had to be discontinued at least 14 days before the first intake of study drug, except for paracetamol or ibuprofen. Subjects were not to use any medication other than the study drug until the first follow-up visit scheduled between 5 and 7 days after the last intake of study medication or after dropout, except for paracetamol or ibuprofen. **For all subjects:** Subjects were not to use any systemic herbal medications or dietary supplements including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the first intake of study drug until the first follow-up visit scheduled between 5 and 7 days after the last intake of study medication or after dropout. Paracetamol or ibuprofen could be used up to 3 days before the first intake of study drug. The clinical investigator could permit the use of paracetamol or ibuprofen from 3 days before the first intake of study drug until the last pharmacokinetic sample had been taken at no more than 3 x 500 mg per day and no more than 3 grams per week for paracetamol or at no more than 1 x 400 mg per day for ibuprofen. Females of childbearing potential had to use effective birth control methods during the entire study and for at least 30 days after last intake of study drug. Applicable procedures and treatment guidance based on package inserts were to be respected. Hormone replacement therapy was allowed in postmenopausal women. Applicable procedures and treatment guidance based on package inserts were to be respected. Other comedication was allowed in the following cases: • In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents in the recommended dosing scheme was permitted. • In case of nausea, the use of antiemetics was permitted. • In case of diarrhea, the use of loperamide was permitted.

Assessments	
Pharmacokinetics	Blood samples for determination of TMC435 concentrations were taken: • On Days 5 and 6 (immediately before intake of TMC435); • On Day 7, predose (immediately before intake of TMC435) and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 16 hours postdose; • On Day 8 (24 hours postdose), Day 9 (48 hours postdose), and Day 10 (72 hours postdose); • At the time of dropout or as soon as possible after discontinuation. Additional samples were taken for the measurement of unbound TMC435 concentrations on Day 7, predose (immediately before intake of TMC435) and 4 hours postdose.
Safety	
Adverse Events	Adverse events (AEs) were reported throughout the study (i.e., from the time a signed and dated ICF was obtained until completion of the subject's last study-related procedure).
Clinical Laboratory	Blood samples for assessment of hematology, biochemistry, and coagulation parameters were collected: • At screening; • On Day 1 predose (within 2 hours before intake of TMC435); • On Days 3 and 5 predose (within 2 hours before intake of TMC435; assessments limited to renal function); • On Day 7, predose (within 2 hours before intake of TMC435) and 6 hours postdose (assessments limited to renal function); • On Day 8 (24 hours postdose); • At the time of dropout or as soon as possible after discontinuation; • At follow-up 5 to 7 days and 30 to 35 days after last intake of study medication or after dropout. Urine samples for urinalysis were collected: • At screening; • On Day 1 predose (within 2 hours before intake of TMC435); • On Day 7, predose (within 2 hours before intake of TMC435) and 6 hours postdose; • At the time of dropout or as soon as possible after discontinuation; • At follow-up 5 to 7 days and 30 to 35 days after last intake of study medication or after dropout.
Cardiovascular Safety	Triplicate ECGs were recorded and vital signs were assessed: • At screening; • On Day 1 predose (within 2 hours before intake of TMC435); • On Day 7, predose (within 2 hours before intake of TMC435) and 6 hours postdose; • At the time of dropout or as soon as possible after discontinuation; • At follow-up 5 to 7 days and 30 to 35 days after last intake of study medication or after dropout.
Physical Examination	Physical examinations were performed: • At screening; • On Day -1; • On Day 10 (72 hours postdose); • At the time of dropout or as soon as possible after discontinuation; • At follow-up 5 to 7 days and 30 to 35 days after last intake of study medication or after dropout.
Statistical Methods Performed	Descriptive statistics, frequency tabulations, intent-to-treat analysis, linear mixed effects modeling, nonparametric test (Wilcoxon rank sum test) for t_{max}

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	Renally Impaired Subjects	Matched Healthy Controls
Number of subjects entered (male/female)	7/1	7/1
Age: median (range), years	55.0 (36-67)	57.0 (37-61)
Discontinuations	0	0
At baseline, the median (range) eGFR of renally impaired subjects was 19.9 (12-28) mL/min/1.73m^2 and the median (range) eGFR of the healthy matched controls was 94.4 (84-110) mL/min/1.73m^2. Of the renally impaired subjects, 3 (37.5%) subjects had an eGFR level of < 15 mL/min/1.73m^2 and 5 (62.5%) subjects had an eGFR level between 15 and 29 mL/min/1.73m^2.		

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	**Matched Healthy Controls (Reference)**	**Renally Impaired Subjects (Test)**
N	8	8
Day 5		
C_{0h}, ng/mL	825.1 ± 1004	1688 ± 1882
Day 6		
C_{0h}, ng/mL	939.0 ± 1142	1944 ± 2254
Day 7		
C_{0h}, ng/mL	1112 ± 1480	2220 ± 2696
C_{min}, ng/mL	961.3 ± 1191	1707 ± 1741
C_{max}, ng/mL	3378 ± 2636	4671 ± 3823
t_{max}, h	6.0 (4.0 - 9.0)	6.0 (4.0 - 9.0)
AUC_{24h}, ng.h/mL	44380 ± 39920	76690 ± 71740
$t_{1/2term}$, h	16.66 ± 10.21	24.00 ± 18.79
$C_{ss,av}$, ng/mL	1849 ± 1663	3195 ± 2989
FI, %	151.6 ± 47.83	115.0 ± 33.59
LSmean ratio (90% confidence interval)		
		Test versus reference
N		8 versus 8
Day 7		
C_{min}	-	1.71 (0.65 - 4.50)
C_{max}	-	1.34 (0.66 - 2.72)
AUC_{24h}	-	1.62 (0.73 - 3.59)

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	**Matched Healthy Controls**	**Renally Impaired Subjects**
N	8	8
Day 7		
$C_{total, 0h}$, ng/mL	1112 ± 1480	2220 ± 2696
$C_{total, 4h}$, ng/mL	2786 ± 2545	4072 ± 3070
$C_{u, 0h}$, ng/mL	0.1142 ± 0.1567	0.2892 ± 0.4411
$C_{u, 4h}$, ng/mL	0.2714 ± 0.2574	0.4216 ± 0.3319
$F_{u, 0h}$	0.00009863 ± 0.000009997	0.0001078 ± 0.00002445
$F_{u, 4h}$	0.00009711 ± 0.000008662	0.00009986 ± 0.00001684

Safety	**Renally Impaired Subjects (N = 8)**		**Matched Healthy Controls (N = 8)**	
	Treatment Phase (TMC435 150 mg)	**Whole Study[a]**	**Treatment Phase (TMC435 150 mg)**	**Whole Study[a]**
Adverse Events				
All AEs, n (%)				
Hyperbilirubinemia	1 (12.5)	1 (12.5)	1 (12.5)	2 (25.0)
Pneumonia	0	1 (12.5)	0	0
Activated partial thromboplastin time prolonged	0	1 (12.5)	0	0
Blood alkaline phosphatase (ALP) increased	1 (12.5)	1 (12.5)	0	0
Hepatic enzyme increased	0	0	0	1 (12.5)
Myalgia	1 (12.5)	1 (12.5)	0	0
Rhabdomyolysis	1 (12.5)	1 (12.5)	0	0
Hypertension	1 (12.5)	1 (12.5)	0	0
n (%) with at least 1 AE	4 (50.0)	4 (50.0)	1 (12.5)	3 (37.5)
n (%) with at least 1 grade 3-4 AE	1 (12.5)	1 (12.5)	0	0
n (%) with at least 1 serious AE (SAE)	1 (12.5)	1 (12.5)	0	0
n (%) with at least 1 AE leading to discontinuation of TMC435	0	0	0	0
n (%) of deaths	0	0	0	0
None of the subjects died during this study and none of the subjects permanently discontinued TMC435 treatment prematurely due to an AE. One (12.5%) renally impaired subject had an SAE (rhabdomyolysis). All AEs were grade 1 or 2 in severity, except for the SAE rhabdomyolysis, which was grade 3 in severity. Rhabdomyolysis started 1 day after the last dose of TMC435 (Day 8) and was considered probably related to TMC435 treatment by the investigator. Four days prior to the onset of rhabdomyolysis, the subject had grade 2 myalgia. In this subject, creatine kinase, myoglobin, and aspartate aminotransferase (AST) levels were significantly increased.				
Clinical Laboratory Tests	No clinically relevant trends or changes in laboratory values were observed. In healthy subjects, treatment-emergent graded laboratory abnormalities were only observed during the follow-up phase and not during the treatment phase. In renally impaired subjects, treatment-emergent graded abnormalities were observed during both phases. During the treatment phase, abnormalities occurred in at most 1 (12.5%) renally impaired subject, except for increased blood urea nitrogen levels and hyperglycemia, which were each observed in 2 (25.0%) subjects. In renally impaired subjects, 1 (12.5%) subject had a grade 4 increased AST level during the treatment phase. For this subject, the SAE rhabdomyolysis was reported. No grade 3 abnormalities were observed in renally impaired subjects during the treatment phase. Two (25.0%) renally impaired subjects had laboratory abnormalities that were reported during the treatment phase as an AE (hyperbilirubinemia and blood ALP increased). One (12.5%) healthy subject had a laboratory-related AE (hyperbilirubinemia) during the treatment phase.			

N: number of subjects; n: number of subjects with 1 or more events
[a] Including screening and follow-up phase

Cardiovascular Safety	Median changes in ECG and vital signs parameters were generally small and none of the changes were considered clinically relevant. No ECG abnormal values were observed during the treatment phase. One (12.5%) renally impaired subject had an abnormal QTcB value (between 480 and 500 ms) during follow-up. None of the subjects had an increase in QTcB or QTcF from baseline of more than 60 ms. No ECG-related AEs were reported. Treatment-emergent vital signs abnormalities were observed in at most 1 (12.5%) healthy or renally impaired subject, except for abnormalities in standing systolic blood pressure (SBP). Grade 1 or 2 increased standing SBP was observed in 2 (25.0%) renally impaired subjects during the treatment phase. None of the subjects had a grade 3 increase in SBP or diastolic blood pressure (DBP). Grade 2 increased standing SBP was reported as an AE (hypertension) in 1 (12.5%) renally impaired subject. No other vital signs abnormalities were reported as an AE.
Physical Examination	None of the subjects had new abnormal findings.

Conclusions - Removed from document

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