SYNOPSIS

Trial Identification and Protocol Summary

Company: Janssen Research & Development* **Trade Name**: - **Indication**: Hepatitis C	**Drug Substance**: TMC435 **Trial no**.: TMC435-TiDP16-C113 **Clinical Phase**: I
Title: A Phase I, open-label, sequential trial to investigate the pharmacokinetics, safety, and tolerability of TMC435 in subjects with moderately or severely impaired hepatic function.	
Investigators: E. Lawitz, M.D., Alamo Medical Research, 621 Camden St, San Antonio, TX 78215 T. Marbury, M.D., Orlando Clinical Research, 5055 South Orange Avenue, Orlando, FL 32809 P. Winkle, M.D., ACRI-Phase I LLC, 1085 North Harbor Boulevard, Anaheim, CA 92801	**Country**: USA
Trial Period: Start: 05-Feb-2010 (consent date first subject) End: 11-Jul-2011 (last contact last subject)	**No. of Investigators**: 3 **No. of Subjects**: 24

Objectives:

The primary objectives of this study were:

- to assess the steady-state pharmacokinetics of TMC435 in subjects with moderate hepatic impairment;
- to assess the steady-state pharmacokinetics of TMC435 in subjects with severe hepatic impairment.

Secondary objectives were:

- to assess the short-term safety and tolerability of TMC435 in subjects with moderate hepatic impairment;
- to assess the short-term safety and tolerability of TMC435 in subjects with severe hepatic impairment.

Design:

This was a Phase I, open-label, sequential trial to investigate the steady-state pharmacokinetics and short-term safety and tolerability of TMC435 in subjects with moderate or severe hepatic impairment.

The trial population consisted of a total of 24 subjects between 18 and 65 years old. Panel A consisted of 8 subjects with moderate hepatic impairment (Child-Pugh B) and 8 matched controls with normal hepatic function. Panel B consisted of 8 subjects with severe hepatic impairment (Child-Pugh C).

Control subjects were matched to subjects with hepatic impairment based on:

- same sex;
- same race;
- comparable age (± 5 years and within the age limits as specified in inclusion criterion 1);
- comparable body mass index (BMI) (± 15% and within the BMI limits as specified in inclusion criterion 3);
- smoking status.

Dosing in Panel A and Panel B occurred sequentially. Subjects in Panel A received TMC435 150 mg q.d. for 7 days. Full pharmacokinetic profiles of TMC435 were determined on Day 7 up to 48 hours postdose.

The short-term safety and tolerability was assessed on an ongoing basis. Recruitment of subjects for Panel B started after no major pharmacokinetic or safety concerns had been observed in subjects from Panel A.

After review of the safety, tolerability and pharmacokinetic data from Panel A, the dose to be administered for subjects in Panel B (severe hepatic impairment) was determined to be 150 mg q.d. for 7 days and a decision was made that no matched controls were to be included in Panel B. TMC435 pharmacokinetic data from Panels A and B were compared to data obtained from genotype 1 hepatitis C virus (HCV)-infected subjects from study C201 (150 mg q.d. dose cohort), since these subjects reflect the intended patient population better than young healthy volunteers. In addition, TMC435 pharmacokinetic data and safety results from Panels A and B were compared to each other.

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities.

Subject Selection

Inclusion Criteria

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

1. Male or female subjects, aged between 18 and 65 years, extremes included.
2. Nonsmoking, or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 3 months prior to screening.
3. BMI (weight in kg divided by the square of height in meters) of 18.0 to 35.0 kg/m², extremes included.
   Note: Subjects with hepatic impairment and ascites who had a paracentesis during screening, had to have their BMI recalculated afterwards. The recalculated BMI determined the subject's eligibility.
4. Informed consent form (ICF) signed voluntarily before the first trial-related activity.
5. Able to comply with protocol requirements.

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

6. Documented medical history of cirrhosis, diagnosed by liver biopsy (preferred option) or ultrasound scan, Computed Tomography (CT) scan, or Magnetic Resonance Imaging (MRI) (in case of contraindication for biopsy).
7. Stable hepatic function as indicated by stable clinical and/or laboratory signs of hepatic impairment (i.e., stable albumin, bilirubin, international normalized ratio [INR], and platelet counts) for at least 3 months prior to the start of the study. See also exclusion criterion 20.
8. Moderate or severe hepatic impairment as defined by the Child-Pugh classification: moderate (Panel A): Child-Pugh score of 7 to 9; severe (Panel B): Child-Pugh score of 10 to 15.
9. General medical condition, in the investigator's opinion, that did not interfere with the assessments and the completion of the trial.

Healthy subjects also had to meet the following inclusion criteria:

10. Demographically comparable to a subject in the hepatic impairment group with respect to sex, race, age, BMI and smoking habits.
11. Healthy on the basis of a physical examination, medical history, electrocardiogram (ECG), vital signs and the results of blood biochemistry and hematology tests, and a urinalysis carried out at screening.

Exclusion Criteria

All subjects were not to have any of the following characteristics:

1. Human immunodeficiency virus - type 1 (HIV-1) or HIV-2 infection at screening.
2. Active hepatitis A, B, or C infection at screening.
3. Female subject of childbearing potential without use of effective birth control methods, or not willing to continue practicing these birth control methods during the trial and for at least 30 days after the end of the treatment period. Women of childbearing potential had to either:
   - use a double barrier method (i.e., using a condom with either diaphragm or cervical cap) or;
   - use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom) or;
   - use a intrauterine device in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom) or;
   - be only non-heterosexually active, practice heterosexual abstinence, or have a vasectomized partner (confirmed sterile).

   A male and female condom were not to be used together due to risk of breakage or damage caused by latex friction.

   Women who were postmenopausal since more than 2 years (amenorrheal for at least 3 years), or posthysterectomy (total) or post-oophorectomy (bilateral), or postsurgical sterilization (without reversal operation) were considered of nonchildbearing potential.
4. Positive pregnancy test or breastfeeding at screening.
5. Evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the investigator's opinion would have compromised subject's safety and/or compliance with the trial procedures.

6. A positive urine drug test at screening. Urine was tested to check the current use of amphetamines, benzodiazepines, cocaine, cannabinoids, and opioids.
   Subjects 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 Trial Physician/Medical Leader and Clinical Pharmacology Leader.
7. Use of disallowed concomitant medication.
8. Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrinologic, genitourinary, renal, respiratory, inflammatory, or infectious disease that in the opinion of the investigator would have compromised the subject's safety or outcome of the trial.
9. Any surgical or medical condition that could interfere with the conduct of the study, could jeopardize the subject in case of participation in the study, or could significantly alter the absorption, distribution, metabolism, or excretion of drugs that in the opinion of the investigator would have compromised the subject's safety or outcome of the trial.
10. Currently significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could have influenced drug absorption or bioavailability.
11. Any history of significant skin disease such as, but not limited to, rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, folliculitis, or urticaria.
12. History of clinically significant drug allergy such as, but not limited to, sulfonamides and penicillin, or drug allergy witnessed in previous trials with experimental drugs.
13. Previously demonstrated clinically significant photosensitivity, allergy, or hypersensitivity to any of the excipients of the investigational medication administered in this trial.
14. Participation in an investigational drug trial within 30 days prior to the first intake of study medication.
15. Subject is the investigator, or any subinvestigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof, directly involved in the conduct of the study.
16. Donation of blood or plasma within 60 days preceding the first intake of study medication.
17. Having previously participated in a multiple-dose study with TMC435.
18. Having previously participated in more than 3 single-dose studies with TMC435.

Subjects with hepatic impairment also were not to have any of the following characteristics:

19. Acute hepatitis, due to any cause.
20. Fluctuating or rapidly deteriorating hepatic function as indicated by widely varying or worsening of clinical and/or laboratory signs of hepatic impairment 3 months prior to screening or within the screening period. Subjects with fluctuations and/or abnormalities could be included only if the investigator judged the fluctuations and/or abnormalities not to be clinically relevant and consistent with the deviations seen in the study population. This determination had to be recorded in the subject's source documents.
21. Cirrhosis secondary to chronic HCV or hepatitis B virus (HBV) infection.
22. Evidence of primary biliary cirrhosis or primary sclerosing cholangitis.
23. Grade 3 or 4 bilirubin elevation, i.e., bilirubin > 2.5 x upper limit of laboratory normal range (ULN) (only for Panel A).
24. Grade 3 or 4 alanine aminotransferase/aspartate amino transferase (ALT/AST) elevation, i.e., ALT/AST > 5.0 x ULN (only for Panel A).
25. Imminent liver transplantation (i.e., during the trial period).
26. Evidence of hepatocellular carcinoma (HCC) as indicated by medical history or alpha-fetoprotein (AFP) > 50 ng/mL at screening. Subjects with a history of successful HCC resection or ablation and AFP < 50 ng/mL at screening could be included.
27. Hepatorenal syndrome.
28. Subjects with one or more of the following laboratory abnormalities at screening as defined by the World Health Organization (WHO) Adult Toxicity Table and in accordance with the normal ranges of the clinical laboratory:
    - Serum creatinine > 1.5 x ULN.
    - Lipase > 1.5 x ULN.
    - Hemoglobin < 9.5 g/dL. Subjects with hemoglobin levels between 9.5-10.5 g/dL could be included only if the investigator judged the abnormalities to be consistent with the deviations seen in the study population and were not to compromise the trial or the subject's well being in the trial.

- For Panel A: Platelet count < 50,000/mm³. Subjects with a platelet count between 50,000 and 75,000/mm³ could be included only if the investigator judged the abnormalities to be consistent with the deviations seen in the study population and were not to compromise the trial or the subject's well being in the trial.
- For Panel B: Platelet count < 20,000/mm³. Subjects with a platelet count between 20,000 and 50,000/mm³ could be included only if the investigator judged the abnormalities to be consistent with the decreases in platelet count seen in this population and were not likely to compromise the study or the subject's safety in the study.
- Absolute neutrophil count < 1500/mm³.
- Any other toxicity grade 2 or above.

Healthy subjects also were not to have any of the following characteristics:

29. Any significant history or presence of hepatic disease.
30. Subjects with the following laboratory abnormalities at screening as defined by the WHO Adult Toxicity Table and in accordance with the normal ranges of the clinical laboratory:
    - serum creatinine grade 1 or greater (≥ 1.1 x 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 (≤ 99.000 x 10^9/L);
    - absolute neutrophil count grade 1 or greater (≤ 1500/mm³);
    - AST or ALT grade 1 or greater (> 1.25 x ULN);
    - total bilirubin grade 1 or greater (> 1.1 x ULN);
    - any other laboratory abnormality of grade 2 or above.
      For proteinuria (spot urine ≥ 2+) and microscopic hematuria (> 10 red blood cell / high power field [HPF]), a urine retest could be performed in women after the menstrual period.

Treatment	**TMC435**
Concentration Dosage Form (TF No.) Usage	75 mg capsule (F021) oral
Batch Number	09C09/F021 and 10A26/F021
Dose Regimen	Panels A and B received TMC435 150 mg q.d. from Day 1 to Day 7
Duration of Treatment	7 days
Duration of Trial	9 days for subjects in each panel, excluding screening and follow-up
Disallowed Medication	Healthy subjects were not allowed to use any concomitant medication, except for ibuprofen or paracetamol which could be used up to 3 days before the first intake of study medication. After that, the clinical investigator could permit the use of ibuprofen (at no more than 1 x 400 mg per day) and paracetamol (at no more than 3 x 500 mg per day) from 3 days before the first intake of study medication until the last pharmacokinetic sample had been taken. Subjects were not to use any herbal medications or dietary supplements including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the first intake of trial medication until the first follow-up visit scheduled between 10 and 14 days after the last intake of trial medication or after dropout. Subjects with hepatic impairment could continue to use their regular medications for the management of their hepatic insufficiency or related conditions, e.g., albumin, diuretics, lactulose, beta-blockers and vitamins. All concomitant medication, indication, dose/duration had to be documented and discussed with the Trial Physician/Medical Leader and Clinical Pharmacology Leader prior to inclusion. Other 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 was permitted. • In case of diarrhea, the use of loperamide was permitted.

Disallowed Medication, continued	Hormone replacement therapy was allowed in postmenopausal women. Applicable procedures and treatment guidance based on package inserts had to be respected. Concomitant therapy that was allowed was not to be changed (started, stopped, or change 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 trial, dosage and regimen had to be discussed in advance with the sponsor.
Assessments	
Pharmacokinetics	Blood samples for TMC435 determination were taken for both panels: - At Days 2, 5, 6, and 7 immediately before intake of TMC435; - At Day 7 at 0.5, 1, 1.5, 2, 3, 4 [a], 6 [a], 9, 12 and 16 h postdose; - At Day 8 [a] (24 h postdose); - At Day 9 (48 h postdose); - At time of dropout or the following morning. [a] Additional pharmacokinetic sample for the measurement of unbound TMC435
Adverse Events	Adverse events (AEs) and concomitant medication were monitored throughout the trial from signing of the ICF onwards until last trial-related activity.
Clinical Laboratory	Blood [a] and urine samples were taken for both panels: - At screening; - At Day −1 (only blood sample); - At Days 3 and 5 predose (only blood sample); - At Day7 [b] predose and 6 h postdose; - At Day 8 (24 h postdose) (only blood sample); - During follow-up at 10-14 and 30-35 days after the last drug intake; - At time of dropout or the following morning and 10-14 and 30-35 days after dropout. [a] Hematology and biochemistry, including coagulation testing. Biochemistry sample had to be taken fasted for at least 10 hours, except for the sample taken 6 hours after intake of TMC435 on Day 7 and the biochemistry sample taken at time of dropout that preferably had to be taken fasted for at least 10 hours. [b] Within 2 hours before intake of TMC435
Cardiovascular safety	Vital signs[a] and ECG were taken for both panels: - At screening; - At Day 7 predose [b,c] and 6 h postdose [d]; - During follow-up at 10-14 and 30-35 days after the last drug intake; - At time of dropout or the following morning and 10-14 and 30-35 days after dropout. [a] Blood pressure and pulse rate: supine after 5 minutes rest and after 1 minute standing. [b] Within 2 hours before intake of TMC435. [c] ECG had to be recorded within 2 hours before breakfast. [d] ECG had to be recorded within 10 minutes before the pharmacokinetic sample was taken.
Physical Examination	Subjects in both panels underwent physical examination: - At screening; - At Day -1; - At Day 9; - During follow-up at 10-14 and 30-35 days after the last drug intake; - At time of dropout or the following morning and 10-14 and 30-35 days after dropout.
Statistical Methods Performed	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	Matched Healthy Controls	Moderately Hepatic Impaired	Severely Hepatic Impaired	All Subjects
Number of subjects entered	8	8	8	24
(male/female)	(6/2)	(6/2)	(6/2)	(18/6)
Age: median (range), years	56.0 (43, 60)	56.0 (42, 62)	52.0 (42, 65)	55.5 (42, 65)
Discontinuations	0	0	0	0

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	TMC435-C113			TMC435-C201[a]
	150 mg TMC435 q.d. for 7 days in subjects with normal hepatic function	150 mg TMC435 q.d. for 7 days in subjects with moderate hepatic impairment	150 mg TMC435 q.d. for 7 days in subjects with severe hepatic impairment	150 mg TMC435 q.d. + bodyweight-based RBV b.i.d. for 28 days + 180 µg PegIFNα-2a s.c. on Days 1, 8, 15, and 22
n	8	8[b]	8	8[c]
Day 2				
C_{0h}, ng/mL	210.0 ± 82.60	403.3 ± 180.0	1223 ± 625.5	-
Day 5				
C_{0h}, ng/mL	429.1 ± 244.4	1407 ± 954.9	4361 ± 3042	-
Day 6				
C_{0h}, ng/mL	439.3 ± 302.6	1488 ± 1018	4923 ± 3110	-
Day 7 / Day 28[d]				
C_{0h}, ng/mL	454.8 ± 337.1	1637 ± 1191	5568 ± 3519	1431 ± 1501
C_{min}, ng/mL	378.1 ± 266.1	1517 ± 1092	4414 ± 2923	1408 ± 1588
C_{max}, ng/mL	2096 ± 958.5	3780 ± 1980	7184 ± 4272	4383 ± 2374
t_{max}, h	6.0 (4.0 - 9.0)	6.0 (6.0 - 9.0)	6.0 (3.0 - 12.0)	6.02 (2.03 - 9.87)
AUC_{24h}, ng.h/mL	23740 ± 10920	65140 ± 38130	138000 ± 89890	57440 ± 44730
$C_{ss,av}$, ng/mL	989.0 ± 455.2	2714 ± 1589	5751 ± 3745	2435 ± 1909
FI, %	180.3 ± 63.33	94.42 ± 63.45	51.83 ± 10.87	160.2 ± 86.03
LSmean ratio (90% CI)				
		moderate vs normal	**severe vs normal[e]**	
n		6 vs 8	8 vs 8	
C_{max}	-	1.71 (1.02 - 2.88)	3.13 (1.87 - 5.26)	-
AUC_{24h}	-	2.44 (1.36 - 4.38)	5.22 (3.10 - 8.79)	-
			severe vs moderate	
n			8 vs 6	
C_{max}	-		1.83 (0.97 - 3.46)	-
AUC_{24h}	-		2.14 (1.06 - 4.32)	-
		moderate vs HCV-infected (C201)[a,f]	**severe vs HCV-infected (C201)[a,f]**	
n		6 vs 8[c]	8 vs 8[c]	
C_{max}	-	0.93 (0.46 - 1.87)	1.69 (0.88 - 3.26)	-
AUC_{24h}	-	1.30 (0.53 - 3.20)	2.78 (1.28 - 6.06)	-

[a] Subjects from trial TMC435-C201 who received TMC435 150 mg q.d. for 28 days in combination with Peg-IFN/RBV; all had chronic genotype 1 HCV infection and compensated liver disease.
[b] n = 6 for C_{max}, t_{max}, AUC_{24h}, $C_{ss,av}$, and FI
[c] n = 7 for AUC_{24h}, $C_{ss,av}$, and FI
[d] Pharmacokinetic parameters from trial TMC435-C201 were determined on Day 28.
[e] Note that control subjects were matched to moderately hepatic impaired subjects and not to severely hepatic impaired subjects.
[f] Note that TMC435 exposure in HCV-infected subjects is generally about 2-fold greater than in healthy volunteers.

Safety	**Matched Healthy Controls N = 8**	**Moderately Hepatic Impaired N = 8**	**Severely Hepatic Impaired N = 8**
Adverse Events			
Most frequent AEs (reported in > 1 subject), n (%)			
Headache	1 (12.5)	2 (25.0)	0
n (%) with at least 1 AE	2 (25.0)	5 (62.5)	1 (12.5)
n (%) with at least 1 grade 3-4 AE	0	1 (12.5)	0
n (%) with at least 1 serious AE (SAE)	0	1 (12.5)	0
n (%) with at least 1 AE leading to discontinuation	0	0	0
n (%) of deaths	0	0	0
No deaths were reported during this trial; one moderately hepatic impaired subject experienced a grade 4 SAE (pneumonia) 8 days after last intake of TMC435 that was considered not related to study medication by the investigator. Except for this grade 4 SAE, all AEs were grade 1 or 2 in severity. None of the subjects in this trial permanently discontinued study medication because of an AE. No skin events of interest were reported.			
Clinical Laboratory Tests	No relevant median changes in laboratory liver parameters were observed. A small increase during treatment was noted in moderately hepatic impaired subjects for pancreatic amylase and for pancreatic lipase, which was not observed in matched healthy controls. In severely hepatic impaired subjects, high median baseline values were observed for these parameters but median increases from baseline were smaller compared to those in moderately hepatic impaired subjects. For other laboratory parameters, there were no consistent or clinically relevant changes over time in median laboratory values. Most graded laboratory abnormalities during treatment were grade 1 or grade 2 in severity. Treatment-emergent grade 3 toxicities were observed for pancreatic amylase (in 1 moderately hepatic impaired subject), for platelets (in 1 severely hepatic impaired subject), and for total bilirubin (in 1 moderately and 2 severely hepatic impaired subjects; these subjects were observed with abnormally high values for both direct and indirect bilirubin at nearly all assessment time points). No relevant differences in laboratory abnormalities were observed between matched healthy controls, moderately hepatic impaired, and severely hepatic impaired subjects, except for hyperbilirubinemia, decreased platelets, and MCV above normal that were only observed in moderately and severely hepatic impaired subjects but not in matched healthy control subjects. Note that control subjects were matched to moderately hepatic impaired subjects and not to severely hepatic impaired subjects. No clinically relevant urinalysis abnormalities were observed. None of the observed laboratory abnormalities were reported as an AE.		
Cardiovascular Safety	Median changes in vital signs and ECG parameters were generally minor and none of them were considered clinically relevant. No QTcB or QTcF values of more than 500 ms or changes from reference of more than 60 ms were observed. All ECG or vital signs abnormalities were observed in at most 1 (12.5%) subject in any group of subjects. None of them were reported as an AE.		
Physical Examination	No treatment-emergent abnormal findings were observed upon physical examination.		

N = number of subjects; n = number of subjects with one or more events

Conclusions - Removed from document

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.