Pharmacokinetics of TMC435 in subjects with moderate hepatic impairment

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INTRODUCTION

- TMC435 is a once daily (QD) oral NS3/4A protease inhibitor currently in Phase III clinical development for the treatment of hepatitis C virus (HCV) infection.
- TMC435 is an investigational potent and selective inhibitor of NS3/4A *in vitro*, with median effective concentrations (EC_{50}) ranging from 8 to 28 nM across different genotype 1a and 1b replicon cell lines.[1,2]
- Findings from Phase I and II studies have shown that TMC435 is well tolerated at doses ranging from 25-200 mg QD, with a pharmacokinetic (PK) profile that supports a QD dosing regimen.[2-7]
- As many HCV-infected patients requiring antiviral therapy will have impaired hepatic function, it is necessary to evaluate the impact of hepatic impairment on the PK and safety of TMC435.
- Here, we describe findings from a Phase I, open-label study (TMC435-C113; NCT01046058) which investigated the steady-state PK and short-term safety/tolerability profile of TMC435 in HCV-negative volunteers with moderate hepatic impairment (Child-Pugh B).

METHODS

Study Design and Treatment

- This was a Phase I, open-label, study. Panel A included 16 subjects: 8 with moderate hepatic impairment and 8 healthy controls (subjects in Panel B are not yet fully recruited, so are not reported here).
- Eligible subjects were males or females, aged 18-65 years old, with a body mass index (BMI) of 18-35 kg/m^2, and were non-smokers or smoking ⩽10 cigarettes, 2 cigars, or 2 pipes for ⩾3 months prior to screening.
- Subjects with hepatic impairment were also required to have a documented history of cirrhosis diagnosed by liver biopsy, ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI); Child-Pugh score of 7-9 indicative of moderate hepatic impairment (i.e. Child-Pugh B); and stable hepatic function for ⩾3 months, as determined by clinical and/or laboratory parameters (i.e. stable albumin, bilirubin, international normalised ratio [INR], and platelet counts).[8]
- Control subjects with normal hepatic function were matched to those with hepatic impairment according to sex, race, age (±5 years), BMI (±15%) and smoking status.
- Subjects with HIV type 1 or 2, or hepatitis A, B or C infection at screening were excluded.
- All subjects received TMC435 150 mg QD from Day 1 to Day 7, taken between 07:30 am and 10:00 am with approximately 240 mL of water after breakfast; all drug intakes were supervised.

Assessments

- Full PK profiles for TMC435 were determined on Day 7 up to 48 hours post-dose. Plasma concentrations of TMC435 were determined using validated liquid chromatographic – mass spectrometry/mass spectrometry (LC-MS/MS) methods with a lower limit of quantification of 2.0 ng/mL for TMC435.
- PK analysis was performed using non-compartmental methods using the WinNonlin Professional™ (Version 4.1; Pharsight Corporation, Mountain View, California, USA), Microsoft Excel® (Microsoft Redmond, Washington, USA) and/or SAS 9.1 (SAS Institute Inc., Cary, NC, USA).
- Calculated TMC435 PK parameters included pre-dose plasma concentration (C_{0h}), maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time to reach the maximum plasma concentration (t_{max}), area under the concentration-time curve (AUC) from time of administration up to 24 hours post-dosing (AUC_{24h}).
- TMC435 PK parameters were summarised using descriptive statistics. PK parameters on Day 7 for subjects with moderate hepatic impairment were compared with those obtained on Day 7 for the healthy matched controls in this study.
- Steady-state PK for TMC435 is achieved by Day 7. PK parameters on Day 7 for subjects with moderate hepatic impairment were also compared with those obtained on Day 28 for the subgroup of HCV-infected patients with mild hepatic impairment (Child-Pugh A) included in study TMC435-C201 (OPERA-1; NCT00561353) who received four weeks of treatment with the same dose of TMC435 as in this study (i.e. 150 mg QD) in combination with pegylated (Peg) interferon (IFN)α-2a and ribavirin (RBV) (n=8 patients for whom we had PK data).[9]
- Safety was assessed at screening, throughout the TMC435 treatment period, and at 10-14 days and 30-35 days after last intake of TMC435 or study withdrawal. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, and graded according to the World Health Organization (WHO) toxicity grading scale. The severity of all reported AEs and their relationship to study drug was tabulated.
- Vital signs, electrocardiogram (ECG) recordings and clinical laboratory tests were also performed at screening, on Day 7, and at 10-14 days and 30-35 days after last intake of TMC435 or study withdrawal.

RESULTS

Subject Disposition

- Subject demographics were well balanced between treatment groups in terms of sex, race, age, BMI (Table 1) and smoking status.
- Subject demographics were similar to those of patients infected with HCV who participated in the OPERA-1 trial.

TABLE 1: Baseline subject demographics (N=16).

	Healthy	Moderately impaired	All subjects
Gender, n (%)	8	8	16
Female	2 (25.0)	2 (25.0)	4 (25.0)
Male	6 (75.0)	6 (75.0)	12 (75.0)
Race, n (%)	8	8	16
White	8 (100)	8 (100)	16 (100)
Age			
Median	56.0	56.0	56.0
(Range)	(43, 60)	(42, 62)	(42, 62)
Weight			
Median	82.7	79.2	80.7
(Range)	(56, 106)	(51, 100)	(51, 106)
BMI			
Median	26.4	26.5	26.4
(Range)	(21, 34)	(20, 33)	(20, 34)

Pharmacokinetics of TMC435

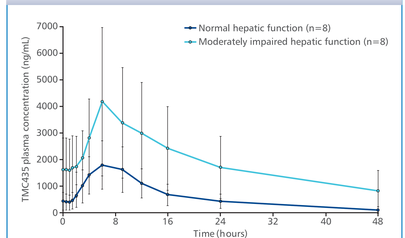
- Steady-state conditions were reached by Day 7 for TMC435 both in subjects with moderate hepatic impairment and in healthy matched controls.
- TMC435 PK parameters on Day 7 for subjects with moderate hepatic impairment were higher than those for healthy matched controls (Table 2, Figure 1).
  - The median (range) ratios for TMC435 exposure (AUC_{24h}) and C_{max} at Day 7 for subjects with moderate hepatic impairment relative to healthy matched controls were 2.62 (1.04–7.48) and 1.76 (0.63–9.36), respectively.

TABLE 2: Pharmacokinetic profile of TMC435 after 7 days of dosing in subjects with moderate hepatic impairment and healthy matched controls, and after 28 days of dosing in HCV-infected patients with mild hepatic impairment.

Pharmacokinetic parameter	Subjects with normal hepatic function Median (range) (n=8)	Subjects with moderate hepatic impairment Median (range) (n=8)	Treatment-experienced HCV-infected subjects (TMC435-C201)[9] Median (range) (n=8)
C_{0h}, ng/mL	387 (123 – 1220)	1710 (240 – 3500)	1020 (176 – 4680)
C_{min}, ng/mL	304 (116 – 949)	1510 (216 – 3090)	801 (96 – 4050)
C_{max}, ng/mL	2040 (1020 – 3690)	4600 (1320 – 9550)	4970 (902 – 7310)
t_{max}, h	6.0 (4.0 – 9.0)	6.0 (6.0 – 9.0)	6.0 (2.0 – 10.0)
AUC_{24h}, ng.h/mL	21500 (12410 – 43840)	69460 (16950 – 108700)	56080 (8390 – 142600)
Ratio C_{max}, hepatic/control	1.76 (0.63 – 9.36)		-
Ratio AUC_{24h}, hepatic/control	2.62 (1.04 – 7.48)		-

AUC_{24h}, area under the concentration-time curve from time of administration up to 24 hours post-dosing; C_{0h}, pre-dose plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; t_{max}, time to reach the maximum plasma concentration

FIGURE 1: Mean (±SD) plasma concentration vs time profile for TMC435 on Day 7 up to 48 hours post-dose for subjects with moderate hepatic impairment compared with healthy matched controls.



SD, standard deviation

- TMC435 PK parameters on Day 7 for subjects with moderate hepatic impairment were comparable to those reported on Day 28 for HCV-infected patients with mild hepatic impairment in study TMC435-C201 (Table 2).[9]
- In this study, there were no relevant differences in unbound TMC435 between treatment groups (data not shown).

TABLE 3: Adverse events reported during the 7-day TMC435 treatment period in subjects with moderate hepatic impairment and healthy matched controls (regardless of severity or causality).

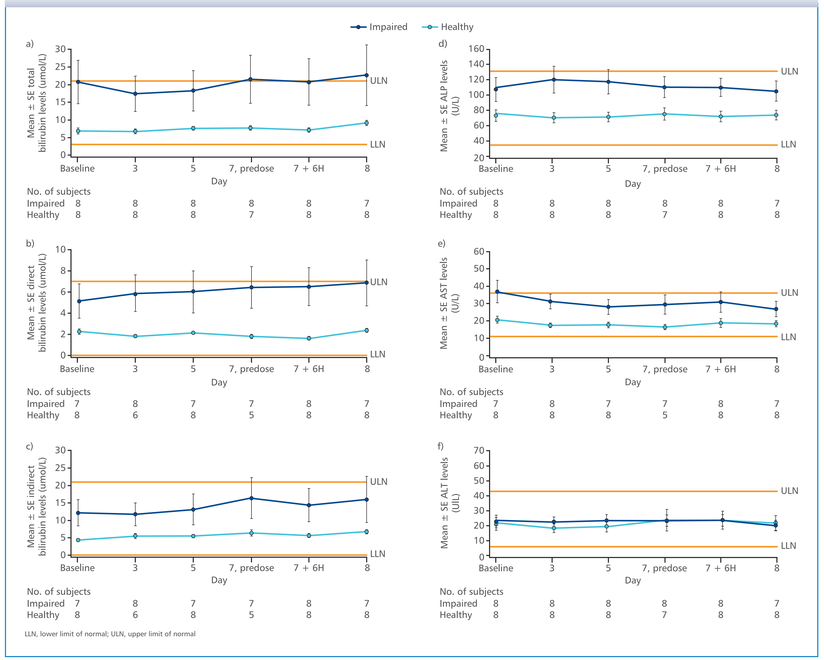
AEs by body system class and preferred term n (%)	Impaired N = 8	Healthy N = 8	All N = 16
Eye disorders	1 (12.5)	1 (12.5)	2 (12.5)
Lacrimation increased	1 (12.5)	0	1 (6.3)
Visual impairment	0	1 (12.5)	1 (6.3)
Infections and infestations	1 (12.5)	0	1 (6.3)
Rhinitis	1 (12.5)	0	1 (6.3)
Metabolism and nutrition disorders	1 (12.5)	0	1 (6.3)
Hypoglycaemia	1 (12.5)	0	1 (6.3)
Musculoskeletal and connective tissue disorders	0	1 (12.5)	1 (6.3)
Myalgia	0	1 (12.5)	1 (6.3)
Nervous system disorders	2 (25.0)	1 (12.5)	3 (18.8)
Headache	2 (25.0)	1 (12.5)	3 (18.8)
Restless legs syndrome	0	1 (12.5)	1 (6.3)

AE, adverse event

Safety

- A summary of all AEs reported during the TMC435 treatment period is shown in Table 3. The most common AE, reported by three subjects, was headache.
- Most AEs were Grade 1-2. One serious AE (Grade 4 pneumonia), which was not considered treatment-related, was reported.
- There were no discontinuations due to AEs.
- Mean baseline to Day 8 levels of total, direct, and indirect bilirubin; alkaline phosphatase (ALP); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are shown in Figure 2.
- Subjects with moderate hepatic impairment (Child-Pugh B) had transiently higher levels of serum bilirubin (total, direct and indirect), ALP and AST from baseline to Day 8, compared with healthy matched controls.
- In both groups, no clinically relevant changes in hepatic parameters were observed during the TMC435 treatment period.
  - One subject with hepatic impairment experienced a transient total bilirubin increase from Grade 2 at baseline to Grade 3 at Day 7 and Day 8 (increase from 51 to 53 and 63 umol/L, respectively). This hyperbilirubinemia was not associated with an increase in other hepatic parameters.
- There were no clinically relevant changes in any other laboratory parameters, and no clinically significant findings in terms of vital signs or ECG recordings during the study.

FIGURE 2: Mean (±SE) baseline to Day 8 levels of (a) total, (b) direct and (c) indirect bilirubin; (d) alkaline phosphotase (ALP); (e) aspartate aminotransferase (AST) and (f) alanine aminotransferase (ALT) for subjects with moderate hepatic impairment compared with healthy matched controls.



LLN, lower limit of normal; ULN, upper limit of normal

CONCLUSIONS

- **TMC435 exposure in HCV-infected patients with moderate hepatic impairment (Child-Pugh B) is comparable to that observed in HCV-infected patients with mild hepatic impairment (Child-Pugh A), who participated in OPERA-1.**
- **Treatment with TMC435 150 mg QD for 7 days was generally well tolerated in all subjects, and there were no clinically relevant changes in any hepatic parameters during the TMC435 treatment period.**
- **These findings suggest that no TMC435 dose adjustment is necessary for HCV-infected patients with moderate liver impairment, and routine clinical monitoring may be considered adequate.**
- **This study is ongoing in panel B.**

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