Poster 1873

Pharmacokinetic-pharmacodynamic analyses of TMC435 in patients infected with hepatitis C virus genotypes 2–6

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1. Premise

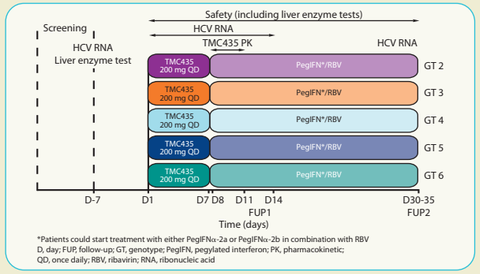
- TMC435 is a potent, once-daily oral NS3/4A protease inhibitor with demonstrated antiviral activity in patients infected with hepatitis C virus (HCV) genotype (GT) 1.
- TMC435 is a selective inhibitor of NS3/4A GT 2, 4, 5, and 6 *in vitro*, with a median inhibitory concentration (IC_{50}) of <13 nM for these HCV NS3/4A enzymes (IC_{50} for GT 3 was 37 nM).[1]
- Findings from Phase I and IIa studies in both treatment-naïve and -experienced patients infected with HCV GT 1 have shown that TMC435 possesses potent antiviral activity, is well tolerated and has a pharmacokinetic (PK) profile that supports a once-daily (QD) dosing regimen.[2-5]
- TMC435-C202 (NCT00812331) was a Phase IIa, open-label trial to assess the antiviral activity, safety, tolerability, and PK of TMC435, administered at 200 mg QD for seven days as monotherapy in treatment-naïve patients infected with HCV GT 2–6.
- Here we describe the pharmacokinetic-pharmacodynamic (PK-PD) relationships for TMC435 antiviral activity and safety markers in the TMC435-C202 trial.

2. Methods

2.1 Study design

- Treatment-naïve patients were enrolled. Eligible patients were male or female aged 18–70 years with documented chronic HCV GT 2–6 infection, with or without cirrhosis (up to Child Pugh A liver disease) and an HCV ribonucleic acid (RNA) level of ≥100,000 IU/mL at screening. Key exclusion criteria were: prior treatment for HCV infection; evidence of decompensated liver disease defined as a prior or current history of ascites, hepatic encephalopathy, esophageal, or gastric varices; drug- or alcohol-related cirrhosis; co-infection with hepatitis A or B, HIV-1 or HIV-2, or active tuberculosis at screening. Patients were divided between five GT cohorts (one cohort of ≥6 subjects per GT).
- Following the TMC435 200 mg (QD) treatment period of seven days, on Day 8, patients could start standard-of-care treatment (pegylated interferon and ribavirin) outside of the study, as decided by the patient in agreement with the treating physician (Figure 1).
- A follow-up period of 30–35 days after the last TMC435 administration was included.

Figure 1. TMC435-C202 study design.



*Patients could start treatment with either PegIFNα-2a or PegIFNα-2b in combination with RBV
D, day; FUP, follow-up; GT, genotype; PegIFN, pegylated interferon; PK, pharmacokinetic; QD, once daily; RBV, ribavirin; RNA, ribonucleic acid

2.2 Pharmacokinetic assessments and analysis methods

- Blood samples were drawn up to 96 hours post-dose following seven days of TMC435 dosing to determine steady-state plasma PK:
  - PK analysis was performed using non-compartmental methods using the WinNonlin Professional™ (Version 4.1; Pharsight Corporation, Mountain View, California, USA).
- Calculated PK parameters included:
  - Time to reach the maximum plasma concentration (t_{max})
  - Maximum plasma concentration (C_{max})
  - Minimum plasma concentration (C_{min})
  - Pre-dose plasma concentration (C_{0h})
  - Area under the plasma concentration-time curve (AUC) from time of administration up to 24 hours post-dosing (AUC_{24h}).
- Relationships between TMC435 PK and change from baseline in plasma HCV RNA (log_{10} IU/mL) at Day 7 were explored.
- PK-PD safety assessments at Day 7 included change from baseline in alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum bilirubin.

3. Results

3.1 Patients

- Thirty-seven patients were enrolled and treated with TMC435 (GT 2 [n=6]; GT 3 [n=8]; GT 4 [n=8]; GT 5 [n=7]; GT 6 [n=8]).
- No major differences in demographic parameters or baseline characteristics between the GT cohorts were observed, except that all patients in the GT 6 cohort were Asian whereas the patients in the other cohorts were mostly White (Table 1). In addition, median patient age was higher in the GT 5 cohort than in the other cohorts.

Table 1. Patient demographics and baseline characteristics for all cohorts by HCV genotype.

Parameter (%)	GT 2 (N=6)	GT 3 (N=8)	GT 4 (N=8)	GT 5 (N=7)	GT 6 (N=8)	Total (N=37)
Gender						
Female	4 (66.7)	3 (37.5)	5 (62.5)	4 (57.1)	2 (25.0)	18 (48.6)
Male	2 (33.3)	5 (62.5)	3 (37.5)	3 (42.9)	6 (75.0)	19 (51.4)
Age (years)						
Median	43	42	47	65	49	48
Range	27–61	18–56	26–55	48–69	30–53	18–69
Age (years) (categorical)						
40 < age ≥64	3 (50.0)	5 (62.5)	5 (62.5)	3 (42.9)	6 (75.0)	22 (59.5)
Age ≤40	3 (50.0)	3 (37.5)	3 (37.5)	0	2 (25.0)	11 (29.7)
Age ≥65	0	0	0	4 (57.1)	0	4 (10.8)
Race						
Asian	0	1 (12.5)	0	0	8 (100)	9 (24.3)
Black or African American	1 (6.7)	0	2 (5.0)	0	0	3 (8.1)
White	5 (83.3)	7 (87.5)	6 (75.0)	7 (100)	0	25 (67.6)
Ethnicity						
Non-Hispanic, non-Latino	6 (100)	8 (100)	8 (100)	7 (100)	8 (100)	37 (100)
Weight (kg)						
Median	69.60	65.00	77.00	75.30	65.95	68.80
Range	49.5–95.4	50.0–91.0	51.3–105.0	53.5–87.0	46.6–71.1	46.6–105.0
Height (cm)						
Median	167.0	176.0	168.0	165.0	167.0	168.0
Range	160–178	153–196	162–190	150–180	151–180	150–196
Body mass index (kg/m²)						
Median	23.4	21.4	24.5	26.7	23.7	23.7
Range	18.0–31.7	19.9–26.9	19.3–30.4	20.9–29.8	19.9–25.8	18.0–31.7

GT, genotype; HCV, hepatitis C virus

3.2 Pharmacokinetic profile of TMC435

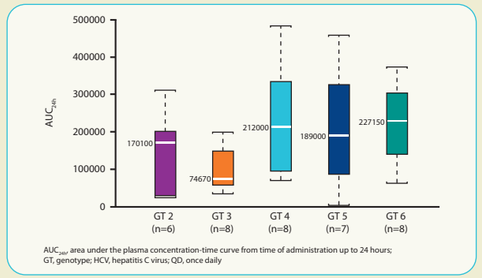
- PK data for TMC435 on Day 7 for all patients are shown in Table 2 and Figure 2.
- Steady-state TMC435 C_{0h}, C_{min}, C_{max}, and AUC_{24h} were similar for the GT 4, 5, and 6 cohorts, while lower values were observed for the GT 2 and 3 cohorts with the lowest values in the GT 3 cohort; t_{max} values were generally similar for all GT cohorts.

Table 2. Pharmacokinetic profile of TMC435 in patients infected with HCV GT 2–6 following administration of TMC435 200 mg (QD) monotherapy for 7 days.

PK parameter	GT 2 (N=6)	GT 3 (N=8)	GT 4 (N=8)	GT 5 (N=7)	GT 6 (N=8)
AUC_{24h} (ng.h/mL)	170100 (26350–311000)	74670 (34500–199500)	212000 (70400–483000)	189000 (3084–457600)	227150 (63430–373500)
C_{max} (ng/mL)	11250 (2360–18500)	6575 (2760–13200)	13500 (4530–26200)	13600 (215–24700)	14800 (3460–23000)
C_{min} (ng/mL)	3315 (156–8420)	1110 (463–3440)	5450 (1030–13100)	4230 (48.2–14300)	4960 (2080–10600)
C_{0h} (ng/mL)	3715 (164–8420)	1305 (492–4220)	6265 (1030–13100)	4650 (80.1–14500)	5435 (2280–11700)
t_{max} (h)	4.00 (4.00–7.80)	6.05 (4.00–10.10)	6.05 (4.00–8.10)	6.00 (4.00–8.00)	6.00 (4.00–6.20)

AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours; C_{0h}, pre-dose plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; GT, genotype; HCV, hepatitis C virus; PK, pharmacokinetic; QD, once daily; t_{max}, time to reach the maximum plasma concentration

Figure 2. TMC435 AUC_{24h} on Day 7 following administration of TMC435 200 mg (QD) monotherapy for patients infected with HCV GT 2–6. Values indicated by the white bars and numbers are median values, the bars are the 25th and 75th percentiles, and the whiskers are the minimum and maximum values.

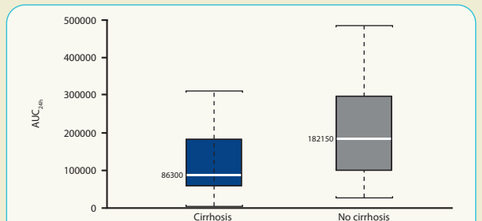


AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours; GT, genotype; HCV, hepatitis C virus; QD, once daily

3.3 TMC435 pharmacokinetics in subgroups

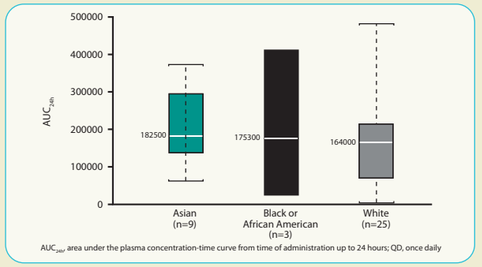
- Subgroup analyses showed that TMC435 exposure appeared to be approximately two-fold higher in patients without cirrhosis (n=26) versus those with cirrhosis (n=11) (Figure 3), and was comparable between the different races (Asian [n=9], Black or African American [n=3], White [n=25]) (Figure 4).
- Age, weight, and gender did not appear to influence TMC435 exposure.

Figure 3. TMC435 AUC_{24h} on Day 7 following administration of TMC435 200 mg (QD) monotherapy, for patients with cirrhosis (Child Pugh A liver disease) or without cirrhosis. Values indicated by the white bars and numbers are median values, the bars are the 25th and 75th percentiles, and the whiskers are the minimum and maximum values.



AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours; QD, once daily

Figure 4. TMC435 AUC_{24h} on Day 7 following administration of TMC435 200 mg (QD) monotherapy, for patients of different race. Values indicated by the white bars and numbers are median values, the bars are the 25th and 75th percentiles, and the whiskers are the minimum and maximum values. For the Black or African American group (n=3), the bars represent the minimum and maximum values.

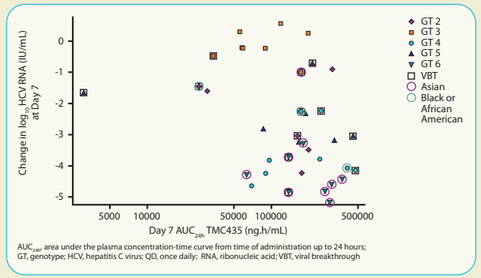


AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours; QD, once daily

3.4 Pharmacokinetics-pharmacodynamics: antiviral activity

- No apparent relationship was observed between TMC435 exposure and antiviral activity on Day 7 for the different GTs (Figure 5).

Figure 5. Change in log_{10} plasma HCV RNA from baseline to Day 7 as a function of TMC435 exposure (AUC_{24h}) for patients of different race infected with HCV GT 2–6, and incidence of VBT.

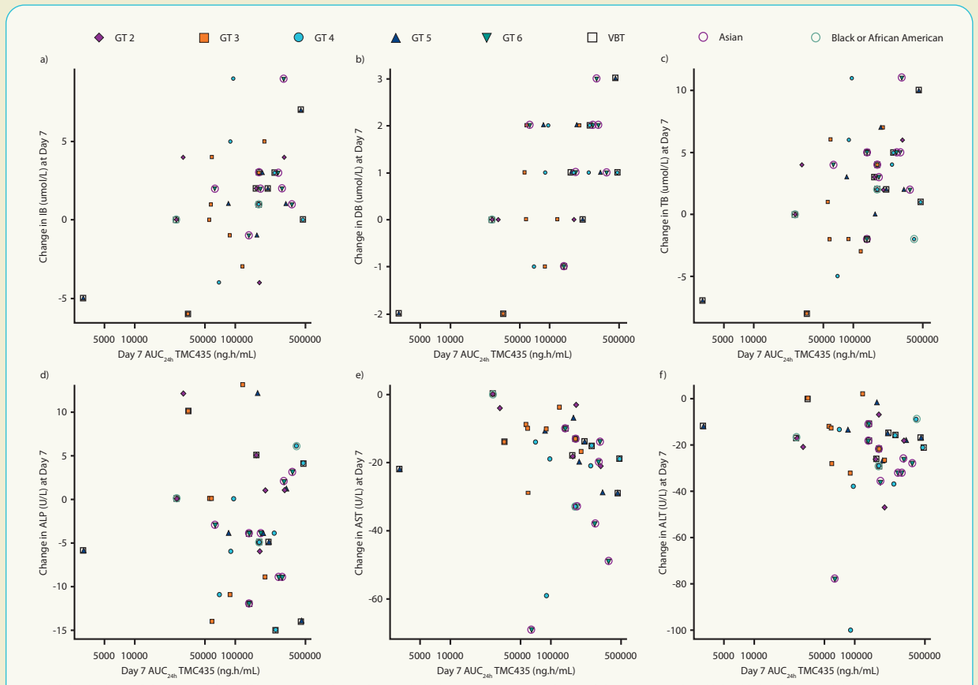


AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours; GT, genotype; HCV, hepatitis C virus; QD, once daily; RNA, ribonucleic acid; VBT, viral breakthrough

3.5 Pharmacokinetics-pharmacodynamics: safety

- Change from baseline to Day 7 in bilirubin (total, direct, and indirect), ALT, ALP, and AST levels as a function of TMC435 exposure (defined as AUC_{24h}) are shown in Figure 6.
- A trend towards mild increases in serum bilirubin was observed with increasing TMC435 exposure, with no PK-PD relationship observed for other liver parameters.

Figure 6. Change from baseline to Day 7 in (a) indirect bilirubin, (b) direct bilirubin, (c) total bilirubin, (d) ALP, (e) AST, and (f) ALT levels as a function of TMC435 exposure (AUC_{24h}) for patients of different race infected with HCV GT 2–6, and incidence of VBT.



ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours; DB, direct bilirubin; GT, genotype; HCV, hepatitis C virus; IB, indirect bilirubin; QD, once daily; TB, total bilirubin; VBT, viral breakthrough

4. Conclusions

- **Monotherapy with once-daily TMC435 (200 mg QD) demonstrated potent antiviral activity in patients infected with HCV GT 2 and GT 4, 5, and 6.**
- **No relationship between TMC435 PK and antiviral activity was observed for the different GTs.**
- **Mild, reversible increases in serum bilirubin were exposure-related, but there was no relationship between TMC435 PK and other hepatic laboratory parameters.**
- **TMC435 exposure was comparable by race.**

5. References

1. Lin TI et al. Poster presented at the 59th American Association for the Study of Liver Diseases (AASLD) Meeting, San Francisco, CA, USA, October 31-November 4, 2008.
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