

A Phase IIa, open-label study to assess the antiviral activity of TMC435 monotherapy in patients infected with HCV genotypes 2–6

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1. Premise

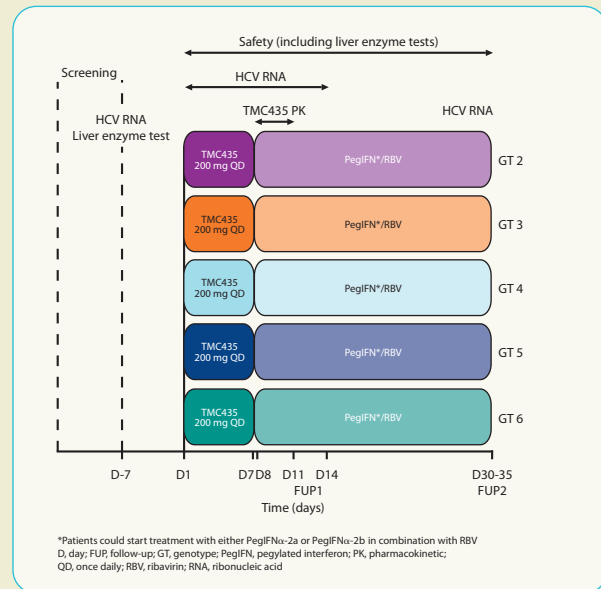
- TMC435 is a once-daily oral NS3/4A protease inhibitor currently in Phase IIb clinical development for the treatment of hepatitis C virus (HCV) infection.
- Findings from Phase I and IIa studies in both treatment-naïve and -experienced patients infected with HCV genotype-1 (GT 1) have shown that TMC435 is generally well tolerated, has a pharmacokinetic (PK) profile that supports a once-daily (QD) dosing regimen, and demonstrates potent antiviral activity.^{1,5}
- Findings from preclinical biochemical protease assays have shown that TMC435 is a potent NS3/4A protease inhibitor in GT 2, 4, 5, and 6, with a median inhibitory concentration (IC₅₀) of <13 nM for all HCV NS3/4A enzymes tested (IC₅₀ for GT 3 was 37 nM).⁶
- TMC435-C202 (NCT00812331) was a Phase IIa, open-label, proof-of-concept study to assess the antiviral activity, safety, tolerability, and PK of TMC435 200 mg QD for seven days in treatment-naïve patients infected with HCV GT 2–6.
- Here we present the antiviral activity, safety, and tolerability findings from this Phase IIa study.

2. Methods

2.1 Study design

- Treatment-naïve patients infected with HCV GT 2–6 were included in five cohorts by genotype and received seven consecutive days of monotherapy with oral TMC435 200 mg QD (Figure 1).

Figure 1. Study design.



- Patients could start treatment with pegylated interferon and ribavirin from Day 8 onwards, as decided by the patient and treating physician.
- The study included a follow-up period of 30–35 days after the last TMC435 administration.

2.2 Patient population

- Treatment-naïve patients were enrolled in this study.
- Eligible patients were male or female aged 18–70 years with documented chronic GT 2–6 HCV infection, with or without cirrhosis (up to Child Pugh A liver disease), and an HCV RNA level of $\geq 100,000$ IU/mL at screening.
 - Staging of fibrosis/cirrhosis was performed according to nationally accepted procedures.
- Key exclusion criteria were: prior treatment, including investigational 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; or co-infection with hepatitis A or B, HIV-1 or HIV-2, or active tuberculosis at screening.

2.3 Assessments

- GT subtype was determined using Trugene, Versant LIPAv2 and/or NS5B sequence-based assays.
- Serum samples were obtained at baseline, Days 1–11, Day 14 (follow-up [FUP] 1), and Days 30–35 (FUP2); and HCV RNA levels were quantified using a COBAS Taqman HCV v2 assay (linear range from 25 to 391,000,000 IU/mL with a limit of quantification of 25 IU/mL).
- The primary efficacy endpoint was change from baseline in HCV RNA at Day 8.
- Other efficacy endpoints included the proportion of patients with HCV RNA of <25 IU/mL detectable and <25 IU/mL undetectable at Day 8, and the proportion of patients experiencing viral breakthrough (defined as a >1 log₁₀ IU/mL increase in HCV RNA level from nadir, or >100 IU/mL in those with a prior HCV RNA level of <25 IU/mL undetectable).
- Safety and tolerability were assessed throughout the study. Vital signs, electrocardiogram (ECG) recordings, and clinical laboratory tests were performed on Days 1, 7, 8, and FUP2. In case of drop-out during the 7-day TMC435 monotherapy period, additional safety assessments were performed at time of drop-out, FUP1, and FUP2.
- Data were analyzed using descriptive statistics.

3. Results

3.1 Patient demographics and baseline disease characteristics

- A total of 37 patients were enrolled across Germany, Belgium, and Thailand (GT 2 [n=6]; GT 3 [n=8]; GT 4 [n=8]; GT 5 [n=7]; GT 6 [n=8]).
- Patient demographics and baseline disease characteristics per genotype cohort are shown in Table 1. There were no major differences except that all patients with GT 6 were Asian and the median age of patients with GT 5 was higher compared with other genotype cohorts.

Table 1. Patient demographics and baseline disease characteristics for each GT cohort.

	GT 2 N=6	GT 3 N=8	GT 4 N=8	GT 5 N=7	GT 6 N=8
Gender, n (%)					
Female	4 (66.7)	3 (37.5)	5 (62.5)	4 (57.1)	2 (25.0)
Male	2 (33.3)	5 (62.5)	3 (37.5)	3 (42.9)	6 (75.0)
Age, years					
Median	43.0	42.0	47.0	65.0	49.0
Range	27–61	18–56	26–55	48–69	30–53
Race, n (%)					
Asian	0	1 (12.5)	0	0	8 (100)
Black or African American	1 (16.7)	0	2 (25.0)	0	0
White	5 (83.3)	7 (87.5)	6 (75.0)	7 (100)	0
BMI, (kg/m²)					
Median	23.4	21.4	24.5	26.7	23.7
Range	18.0–31.7	19.9–26.9	19.3–30.4	20.9–29.8	19.9–25.8
HCV RNA (log₁₀ IU/mL)					
Median	6.42	6.70	5.76	6.51	6.74
Range	5.6–6.8	4.5–7.2	5.2–6.7	5.9–7.1	5.7–7.3
HCV subtype (NS5B), n (%)					
2	6 (100)	8 (100)	7 (100)	7 (100)	5 (100)
2a	1 (16.7)	0	0	0	0
2b	2 (33.3)	0	0	0	0
2c	1 (16.7)	0	0	0	0
2i	1 (16.7)	0	0	0	0
2k	1 (16.7)	0	0	0	0
3a	0	8 (100)	0	0	0
4a	0	0	4 (57.1)	0	0
4c	0	0	1 (14.3)	0	0
4d	0	0	2 (28.6)	0	0
5a	0	0	0	7 (100)	0
6a	0	0	0	0	1 (20.0)
6b	0	0	0	0	1 (20.0)
6j	0	0	0	0	1 (20.0)
6n	0	0	0	0	2 (40.0)

BMI, body mass index; GT, genotype; HCV, hepatitis C virus; RNA, ribonucleic acid

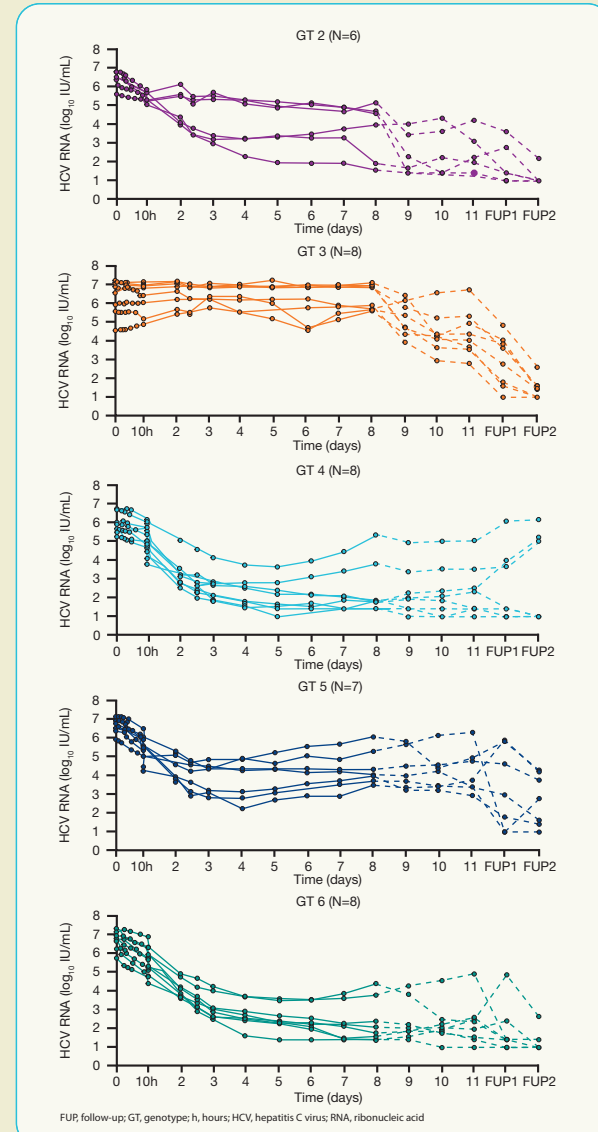
- After the 7-day TMC435 treatment period, all patients received PegIFN/RBV.
 - Thirty-one patients started PegIFN/RBV on Day 8 or 9, whereas one patient with GT 3 and five with GT 6 started PegIFN/RBV after Day 9 in the follow-up period.

3.2 Antiviral activity

3.2.1 Changes in plasma HCV RNA from baseline

- Individual patient HCV RNA profiles per GT cohort are shown in Figure 2.
- An initial rapid decline in HCV RNA was evident by Day 3 of TMC435 monotherapy for all patients infected with HCV GT 4–6.
 - A rapid decline in HCV RNA was evident for three out of six patients with GT 2.
 - No clear antiviral activity was evident for patients with GT 3.

Figure 2. Individual changes in plasma HCV RNA (log₁₀ IU/mL) over time for each GT cohort.



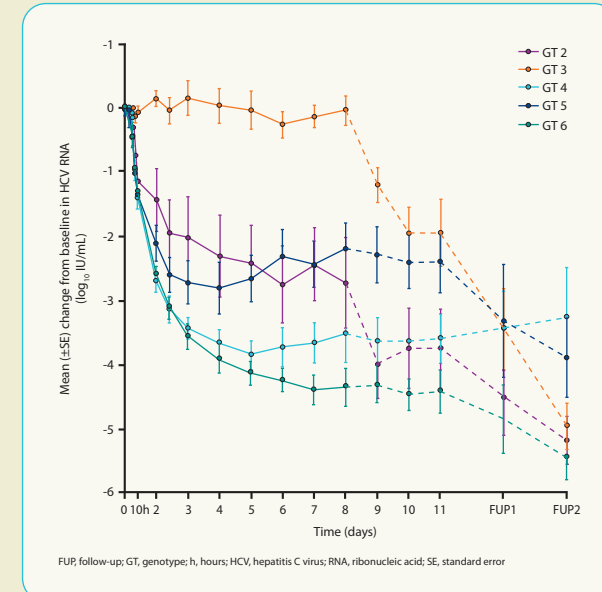
- Mean changes from baseline in HCV RNA over time for each GT cohort are shown in Table 2 and Figure 3.

Table 2. Mean (±SE) change from baseline in plasma HCV RNA (log₁₀ IU/mL) for each GT cohort during the TMC435 monotherapy period.

Day	GT 2 N=6	GT 3 N=8	GT 4 N=8	GT 5 N=7	GT 6 N=8
2	-1.43 (0.48)	0.15 (0.12)	-2.70 (0.18)	-2.10 (0.27)	-2.60 (0.13)
3	-2.02 (0.63)	0.16 (0.26)	-3.43 (0.17)	-2.71 (0.34)	-3.57 (0.20)
5	-2.42 (0.59)	-0.03* (0.28)	-3.85 (0.22)	-2.66 (0.36)	-4.14 (0.18)
6	-2.75 [†] (0.60)	-0.26 (0.20)	-3.73 [†] (0.30)	-2.30 (0.40)	-4.24 (0.18)
7	-2.46 (0.54)	-0.13 (0.18)	-3.66 (0.32)	-2.43 (0.36)	-4.40 (0.22)
8	-2.73 (0.71)	-0.04 (0.23)	-3.52 (0.43)	-2.19 (0.39)	-4.35 (0.29)

*Samples available for 7 patients; [†]samples available for 5 patients; [‡]samples available for 7 patients
GT, genotype; HCV, hepatitis C virus; RNA, ribonucleic acid; SE, standard error

Figure 3. Mean (±SE) change from baseline in plasma HCV RNA (log₁₀ IU/mL) for each GT cohort.



- At Day 3 of TMC435 monotherapy, the mean (range) change from baseline in plasma HCV RNA (log₁₀ IU/mL) was greatest for GT 6 (-3.57 [-4.2; -2.7]) and GT 4 (-3.43 [-3.9; -2.6]) cohorts, followed by GT 5 (-2.71 [-4.0; -1.5]) and GT 2 (-2.02 [-3.6; -0.3]) cohorts (Table 2).
- For the primary endpoint at Day 8, the mean (range) change from baseline in plasma HCV RNA (log₁₀ IU/mL) was greatest for GT 6 (-4.35 [-5.2; -2.8]) and GT 4 (-3.52 [-4.8; -1.4]) cohorts, followed by GT 2 (-2.73 [-4.9; -0.4]) and GT 5 (-2.19 [-3.1; -0.3]) cohorts (Table 2).

3.2.2 Virologic response

- At Day 8, four patients (two patients with GT 4 and two with GT 6) achieved HCV RNA levels of <25 IU/mL undetectable.

3.2.3 Viral breakthrough

- One patient in GT 3, two in GT 4, and three in GT 5 cohorts experienced viral breakthrough (increase of >1 log₁₀ IU/mL in HCV RNA from nadir) during the TMC435 monotherapy period.

3.3 Safety and tolerability

- A summary of adverse events (AEs) occurring in at least 5% of patients during the TMC435 treatment period is shown in Table 3.
 - The type and incidence of AEs (all Grade 1–2) were similar across cohorts; the most common AEs were influenza-like illness and headache.
- There were no discontinuations and no serious AEs (SAEs) during the 7-day TMC435 monotherapy period.

Table 3. Adverse events occurring in at least 5% of patients during the TMC435 treatment period, split by GT cohort.

N (%)	GT 2 N=6	GT 3 N=8	GT 4 N=8	GT 5 N=7	GT 6 N=8
Any AE	5 (83.3)	6 (75.0)	8 (100)	4 (57.1)	5 (62.5)
Influenza-like illness	2 (33.3)	1 (12.5)	4 (50.0)	1 (14.3)	1 (12.5)
Headache	2 (33.3)	1 (12.5)	2 (25.0)	0	0
Diarrhea	2 (33.3)	1 (12.5)	1 (12.5)	0	0
Fatigue	2 (33.3)	1 (12.5)	0	0	1 (12.5)
Pruritus	1 (16.7)	1 (12.5)	1 (12.5)	1 (14.3)	0
Anorexia	1 (16.7)	2 (25.0)	0	0	0
Back pain	0	1 (12.5)	1 (12.5)	0	1 (12.5)
Myalgia	0	2 (25.0)	1 (12.5)	0	0
Palpitations	0	0	2 (25.0)	0	0
Constipation	0	1 (12.5)	0	0	1 (12.5)
Lip swelling	0	0	1 (12.5)	1 (14.3)	0
Pyrexia	0	1 (12.5)	0	0	1 (12.5)

AE, adverse event; GT, genotype

- One patient experienced an SAE on Day 8 (Grade 1 ileitis) which was not considered related to TMC435 therapy. The patient discontinued from the study and recovered after four days.
- There were no other discontinuations due to AEs or SAEs during the follow-up period.
- Changes from baseline to Day 7 in hepatic parameters (total, indirect, and direct bilirubin; alanine aminotransferase [ALT]; aspartate aminotransferase [AST]; and alkaline phosphatase [ALP]) are shown in Table 4.
 - Slight elevations in bilirubin (total, direct, and indirect) levels were observed in all cohorts. These were reversible and were not associated with clinical symptoms or AST/ALT elevations.
 - ALT and AST decreased over time in all genotype cohorts.
 - There were no relevant changes in ALP levels.

Table 4. Mean (±SE) baseline and Day 7 hepatic parameters for each GT cohort.

	GT 2 N=6	GT 3 N=8	GT 4 N=8	GT 5 N=7	GT 6 N=8
ALT (U/L)					
Baseline	59.0 (15.6)	85.6 (20.8)	68.6 (17.3)	46.0 (5.9)	69.9 (14.0)
Day 7	36.3 (10.5)	69.1 (17.7)	35.8 (7.7)	31.0 (4.4)	37.3 (7.3)
AST (U/L)					
Baseline	47.5 (15.2)	62.9 (12.5)	46.4 (8.4)	49.9 (7.4)	57.8 (10.8)
Day 7	23.4* (2.9)	49.6 (10.4)	24.7* (3.4)	31.0 (5.6)	28.3* (4.7)
ALP (U/L)					
Baseline	62.3 (5.7)	71.0 (6.5)	58.8 (4.4)	80.0 (10.7)	72.8 (6.4)
Day 7	64.5 (6.2)	69.0 (5.5)	54.9 (2.5)	77.1 (10.7)	68.3 (5.3)
Total bilirubin (μmol/L)					
Baseline	9.2 (1.3)	9.0 (0.8)	10.6 (2.3)	10.9 (1.6)	12.6 (2.6)
Day 7	12.3 (1.2)	9.4 (1.8)	13.4 (2.6)	13.3 (2.1)	16.8 (2.6)
Direct bilirubin (μmol/L)					
Baseline	2.8 (0.4)	2.8 (0.2)	3.1 (0.5)	3.4 (0.5)	3.3 (0.8)
Day 7	3.4* (0.5)	3.1 (0.5)	4.3* (0.5)	4.4 (0.5)	5.0* (0.9)
Indirect bilirubin (μmol/L)					
Baseline	7.7 (0.8)	5.9 (0.7)	6.6 (1.9)	7.7 (1.1)	9.2 (1.9)
Day 7	9.0* (1.1)	6.3 (1.3)	9.6* (2.5)	8.9 (1.6)	12.3* (2.3)

*Samples available for 5 patients; [†]samples available for 7 patients

Conversion factor from μmol/L to mg/dL: 1 x 0.0585

Normal ranges: ALT, 6–43 U/L; ALP, 31–129 U/L; AST, 11–36 U/L; total bilirubin, 3–21 μmol/L; direct bilirubin, 0–7 μmol/L; indirect bilirubin, 0–21 μmol/L

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GT, genotype; SE, standard error

- There were no consistent trends or clinically relevant changes in any laboratory parameters, and there were no clinically significant findings in terms of vital signs, physical examinations, or ECG recordings during the study.

4. Conclusions

- Monotherapy with oral TMC435 200 mg QD for seven days was associated with potent antiviral activity in patients infected with HCV GT 2, 4, 5, and 6.
 - The greatest antiviral activity was observed among patients infected with HCV GT 4 and 6, followed by GT 5.
 - Potent antiviral activity was observed in three patients with GT 2, with limited activity observed in the other three patients in this cohort.
 - No antiviral activity was seen against GT 3.
- TMC435 was generally well tolerated. All AEs were mild to moderate, with no discontinuations occurring during TMC435 monotherapy treatment.
- Seven days of monotherapy with TMC435 was not associated with any untoward changes in hepatic parameters.

5. References

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