Poster 2675

Antiviral activity and safety of TMC435 combined with peginterferon α-2a and ribavirin in patients with genotype-1 hepatitis C infection who failed previous IFN-based therapy

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Introduction

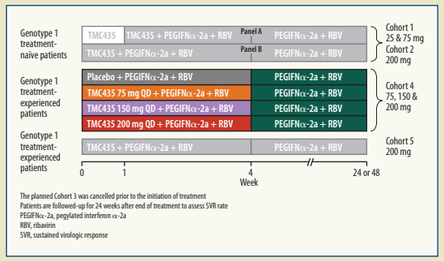
- A substantial proportion of patients infected with hepatitis C virus (HCV) genotype 1 do not achieve a sustained virologic response (SVR) after combination therapy with pegylated interferon (PEGIFN) and ribavirin (RBV).[1]
- Better treatment options are required for treatment-experienced patients: in a recent international, multicentre study, SVR response rates to PEGIFN and RBV were only 10% in genotype-1 prior non-responders and 27% in genotype-1 prior relapsers.[2]
- TMC435 is a macrocyclic and selective HCV NS3/4A protease inhibitor with an *in vitro* EC_{50} value of 8 nM in a genotype-1b replicon cell line.[3]
- In Phase I studies, TMC435 was generally safe and well tolerated, and the pharmacokinetic profile supported a once-daily (QD) dosing regimen. A median decrease of 3.9 log_{10} IU/mL in HCV RNA was observed after five days of monotherapy with TMC435 200 mg QD in genotype-1-infected individuals who failed previous IFN-based therapies.[3-5]
- OPERA-1 (TMC435350-TiDP16-C201) is a double-blind, placebo-controlled, Phase IIa, proof-of-concept trial to assess the antiviral activity, safety and pharmacokinetics of once-daily regimens of TMC435 in HCV genotype-1 treatment-naïve and treatment-experienced patients.
- Here we report the four-week results of OPERA-1 Cohort 4, for treatment-experienced patients receiving TMC435 in combination with PEGIFN and RBV.

Methods

Study design

- The study design for OPERA-1 is summarised in Figure 1.

Figure 1. OPERA-1 study design.



- At the start of the double-blind treatment period of Cohort 4, patients were randomised to receive either TMC435 75 mg QD, 150 mg QD, 200 mg QD or placebo as part of a triple therapy regimen, in combination with pegylated interferon α-2a (PEGIFNα-2a) (180 µg subcutaneously, once weekly) and RBV (1000–1200 mg BID, body-weight dependent) for 28 days, followed by PEGIFNα-2a and RBV alone for a total treatment duration of 48 weeks.

Patient population

- The treatment-experienced patients enrolled in this part of the study were:
  - prior non responders: <2 log_{10} IU/mL decrease from baseline in HCV RNA after 12 weeks of prior IFN-based therapy, or
  - prior relapsers: confirmed detectable HCV RNA after achieving undetectable HCV RNA at the end of treatment.
- Eligible patients were: aged 18–70 years with documented chronic HCV (genotype 1; diagnosis >6 months prior to screening); required to have HCV plasma RNA of ≥10,000 IU/mL at screening; required to have compensated liver disease.
- Key exclusion criteria included: receipt of a polymerase inhibitor, protease inhibitor or dual therapy with PEGIFN and RBV during the six months prior to screening; co-infection with HIV-1 or HIV-2, hepatitis A or B, or active tuberculosis at screening.

Study assessments

Antiviral activity

- The primary efficacy objective was to determine the change from baseline in HCV RNA levels at Day 28. Serum samples were obtained at baseline and on Days 1 (4 h and 10 h), 2, 3, 7, 8, 11, 14, 21 and 28, and HCV RNA levels were quantified using the Roche COBAS® TaqMan HCV/HPS assay v2.0.
- Other efficacy endpoints were to evaluate the response to treatment (HCV RNA below the lower limit of detection, <10 IU/mL and the lower limit of quantification, <25 IU/mL) and to assess the number of viral breakthroughs (>1 log_{10} IU/mL increase from nadir or HCV RNA levels >100 IU/mL in patients with previous HCV RNA levels <10 IU/mL).

Safety and tolerability

- Safety and tolerability were monitored continuously throughout the trial. Vital signs, electrocardiogram (ECG) recordings and clinical laboratory tests were taken on Days 1, 7, 14, 21 and 28.

Statistical analysis

- A pre-planned intent-to-treat analysis was performed when all patients had either completed 28 days of treatment or had discontinued earlier. All data are presented descriptively.

Results

Baseline demographics and characteristics

- In total in Cohort 4, 37 treatment-experienced patients were randomised to the four treatment groups: 25 prior non-responders and 12 prior relapsers to previous IFN-based therapy for HCV. All patients completed treatment to Day 28.
- Patient demographics and baseline characteristics are shown in Table 1.

Table 1. Patient demographics and baseline characteristics.

	Placebo	TMC435		
		75 mg QD	150 mg QD	200 mg QD
	N=9	N=9	N=9	N=10
Gender, n (%)				
Female	0	3 (33.3)	1 (11.1)	2 (20.0)
Male	9 (100)	6 (66.7)	8 (88.9)	8 (80.0)
Race, n (%)				
Caucasian	9 (100)	9 (100)	9 (100)	10 (100)
Age, years				
Median (Range)	47.0 (21–57)	53.0 (38–62)	56.0 (32–67)	55.5 (28–69)
Body weight, kg				
Median (Range)	78.0 (67–94)	74.0 (55–92)	75.0 (50–99)	92.5 (54–101)
HCV subtype (NS5B), n (%)				
1a	2 (22.2)	2 (22.2)	4 (44.4)	3 (30.0)
1b	7 (77.8)	7 (77.8)	5 (55.6)	7 (70.0)
HCV RNA (log_{10} IU/mL)				
Median (Range)	6.4 (6–7)	6.9 (6–7)	6.9 (7–8)	6.9 (6–7)
Cirrhosis, n (%)				
	5 (55.6)	5 (55.6)	5 (55.6)	6 (60.0)
Response to prior IFN-based therapy* for HCV, n (%)				
Non-responder	6 (66.7)	7 (77.8)	6 (66.7)	6 (60.0)
Relapser	3 (33.3)	2 (22.2)	3 (33.3)	4 (40.0)

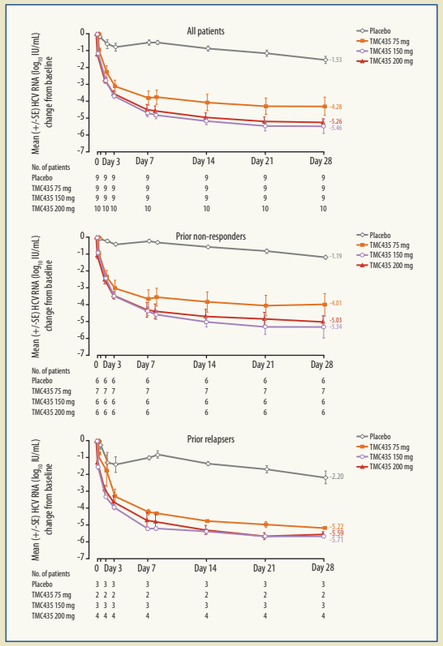
*88% of patients received PEGIFN-based therapy

Antiviral activity

Change in plasma HCV RNA from baseline

- Mean decreases in plasma HCV RNA from baseline were 4.3, 5.5 and 5.3 log_{10} IU/mL for the TMC435 75, 150 and 200 mg QD groups, respectively, at Day 28, compared with 1.5 log_{10} IU/mL in the placebo group.
- Mean decreases in plasma HCV RNA over time for each treatment group are shown in Figure 2.

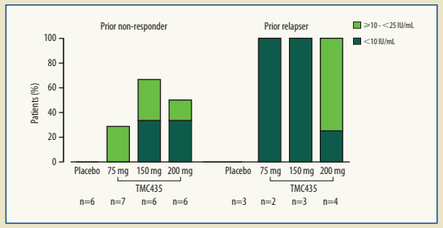
Figure 2. Mean (SE) change in plasma HCV RNA from baseline for treatment-experienced patients receiving once-daily TMC435 75, 150 and 200 mg or placebo over time to Day 28.



Week-4 virologic response

- At Day 28, 4/9 (44%), 7/9 (78%) and 7/10 (70%) patients achieved plasma HCV RNA levels <25 IU/mL in the 75, 150 and 200 mg QD treatment groups, respectively, compared with no patients (0/9) in the placebo group.
- The proportion of patients achieving plasma HCV RNA <10 IU/mL and <25 IU/mL for both prior non-responders and relapsers is shown in Figure 3.

Figure 3. Response to treatment with once-daily TMC435 75, 150 and 200 mg or placebo in treatment-experienced patients at Day 28.



Viral breakthrough

- Three viral breakthroughs were observed, exclusively in patients infected with HCV genotype 1b who were prior non-responders to treatment; two in the 75 mg QD group and one in the 150 mg QD group.
- At the time of the confirmed viral breakthrough, a D168V mutation in the NS3 protease domain was detected in all three patients using standard population sequencing.

Safety and tolerability

- A summary of adverse events (AEs) is shown in Table 2.

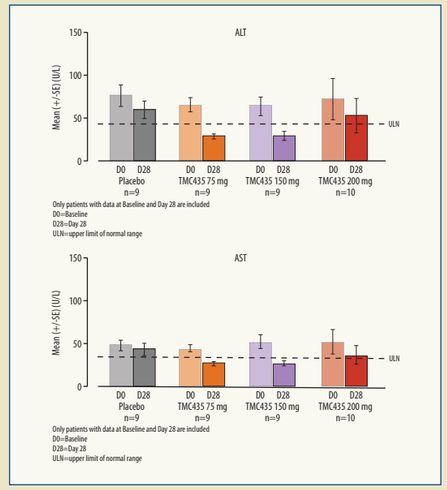
Table 2. Summary of adverse events (AEs).

n (%)	Placebo N=9	TMC435 75 mg QD N=9	TMC435 150 mg QD N=9	TMC435 200 mg QD N=10
Patients with:				
Any AE	8 (88.9)	8 (88.9)	9 (100)	10 (100)
Grade 1 AEs	8 (88.9)	7 (77.8)	8 (88.9)	8 (80.0)
Grade 2 AEs	5 (55.6)	3 (33.3)	5 (55.6)	7 (70.0)
Grade 3/4 AEs	0	0	0	2 (20.0)*
Most common AEs§				
Headache	6 (66.7)	5 (55.6)	5 (55.6)	3 (30.0)
Influenza-like illness	1 (11.1)	3 (33.3)	1 (11.1)	5 (50.0)
Dyspnoea	0	2 (22.2)	2 (22.2)	4 (40.0)
Nausea	1 (11.1)	3 (33.3)	2 (22.2)	2(20.0)
Pyrexia	1 (11.1)	2 (22.2)	2 (22.2)	2 (20.0)
Arthralgia	2 (22.2)	1 (11.1)	4 (44.4)	0
Asthenia	2 (22.2)	1 (11.1)	2 (22.2)	2 (20.0)
Fatigue	2 (22.2)	1 (11.1)	2 (22.2)	2 (20.0)
Pruritis	3 (33.3)	1 (11.1)	1 (11.1)	3 (30.0)

*Fatigue and influenza-like illness (1 patient) and hyperbilirubinaemia (1 patient)
§Reported in ≥5 patients (TMC435 treatment groups combined)

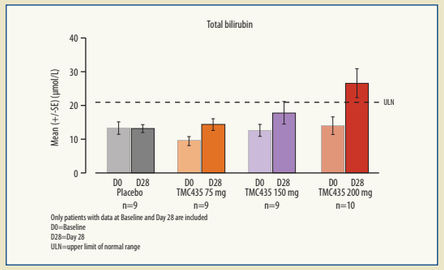
- There were no discontinuations due to AEs, serious AEs or deaths during the study.
- Alanine aminotransferase and aspartate aminotransferase levels decreased over time in all TMC435 treatment groups (Figure 4.).

Figure 4. Serum aminotransferase levels for treatment-experienced patients at baseline and after 28 days of treatment with once-daily TMC435 75, 150 and 200 mg or placebo. a) Alanine aminotransferase, ALT; b) Aspartate aminotransferase, AST.



- Bilirubin elevations were observed in some patients receiving TMC435 (total, direct and indirect), mostly with the 200 mg dose. These elevations were generally mild and reversible in nature.

Figure 5. Total serum bilirubin levels for treatment-experienced patients at baseline and after 28 days of treatment with once-daily TMC435 75, 150 and 200 mg or placebo.



- No dose trends or clinically relevant changes were noted in any other laboratory parameters, ECG parameters or vital signs.

Conclusions

- In treatment experienced patients infected with HCV genotype 1, 28 days of once-daily treatment with TMC435 (75, 150 and 200 mg) as part of a triple-therapy regimen with PEGIFNα-2a and RBV:
  - demonstrated potent, dose-dependent antiviral activity
  - was generally safe and well tolerated
  - was not associated with AE-related treatment discontinuations.
- Bilirubin elevations were observed in some patients receiving TMC435, mostly with the 200 mg dose, and were generally mild and reversible in nature.
- TMC435 was superior to placebo (both in combination with PEGIFNα-2a + RBV) at all time points in the reduction of plasma HCV RNA from baseline, for both prior non-responders and relapsers.
- These results support the development of TMC435 for patients who failed previous IFN-based HCV therapies.

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