Poster 1563

Antiviral activity and safety of TMC435 combined with pegylated interferon and ribavirin in hepatitis C patients with genotype 1 who had previous exposure to TMC435

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Premise

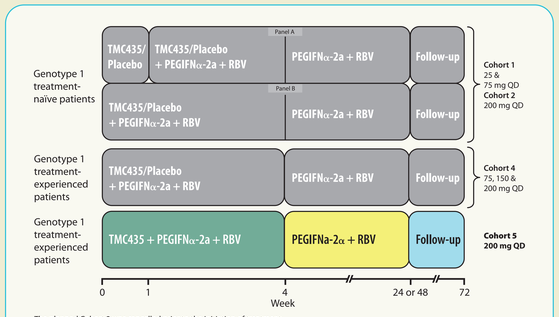
- **TMC435 is a macrocyclic inhibitor of the hepatitis C virus (HCV) NS3/4A protease, and is currently in Phase IIb development as an oral, once-daily therapy, given in combination with pegylated interferon α-2a (PEGIFN) and ribavirin (RBV), for patients infected with HCV.**
- **OPERA-1 (TMC435-C201) is a Phase IIa, double-blind, randomized, placebo-controlled trial of TMC435 in both treatment-naïve and treatment-experienced patients infected with HCV genotype 1.**
- **Cohort 5 of the OPERA-1 study is an investigational open-label cohort of patients who had previous exposure to TMC435 (200 mg QD for 5 days) during Study TMC435-C101, a Phase I study in genotype 1-infected patients who had previously failed interferon-based therapy. During OPERA-1 they were treated with TMC435 200 mg QD in combination with PEGIFN and RBV for 4 weeks, followed by standard of care (SoC) for up to 48 weeks.**
- **Five-day monotherapy of 200 mg QD TMC435 during TMC435-C101 resulted in a maximal median decrease in HCV RNA of 3.9 $\log_{10}$ at Day 6, before returning to baseline values during 4-week follow-up.[1]**

Methods

Study design

- The overall study design is shown in Figure 1.

Figure 1. Study design.



The planned Cohort 3 was cancelled prior to the initiation of treatment
PEGIFNα-2a, pegylated interferon α-2a; RBV, ribavirin; SVR, sustained virologic response

- Patients in Cohort 5 received 28 days of open-label triple therapy with TMC435 200 mg QD in combination with PEGIFN (180 mcg per week; [PEGASYS®]) and RBV (1000–1200 mg per day; [COPEGUS®]) followed by dual therapy with PEGIFN and RBV up to Week 48.
- Patients were aged 18–70 years with documented chronic genotype-1a or -1b HCV infection and had failed previous IFN-based therapy (non-response or relapse) before participation in Study TMC435-C101. All patients had plasma HCV RNA levels ⩾10,000 IU/mL at screening, with no signs of decompensated liver disease.

Objective

- The objective of Cohort 5 was to assess the antiviral activity, safety, and tolerability of TMC435 in patients with previous exposure to TMC435.

Study assessments

- During the 4-week TMC435 treatment period, HCV RNA testing was performed at baseline and on Days 1 (4 h and 10 h), 2, 3, 4, 5, 6, 7, 8, 11, 14, 21, and 28. HCV RNA levels were quantified using the Roche COBAS® TaqMan HCV/HPS assay v2.0.
- Categorical HCV RNA response was defined as: HCV RNA below the lower limit of quantification and detectable (<25 IU/mL) or undetectable HCV RNA, lower limit of detection, <10 IU/mL. Viral breakthrough was defined as: >1 $\log_{10}$ increase in HCV RNA from nadir during therapy, or HCV RNA levels >100 IU/mL in patients with previous HCV RNA levels <10 IU/mL.
- Population sequencing was performed to identify mutations in the HCV NS3/4A region.

Statistical analysis

- A pre-planned interim analysis was performed when all patients had completed Week 4 of treatment or discontinued earlier. All available data were included in the descriptive analysis.

Results

Patient demographics and baseline disease characteristics

- OPERA-1 Cohort 5 was initiated approximately 1.5 years after completion of Study TMC435-C101.
- Five out of six patients who participated in Study TMC435-C101 were enrolled in Cohort 5 of OPERA-1 (one patient died one year after the end of Study TMC435-C101). The cause of death was unrelated to HCV treatment.
- Patient demographics and baseline disease characteristics are shown in Table 1.

Table 1. Patient demographics and baseline disease characteristics.

		N=5
Gender, n	Male	5
Race, n	Caucasian/White	5
Age, years	Median (range)	56.0 (33–66)
Body weight, kg	Median (range)	86.0 (62–92)
HCV subtype (NS5B), n	1a 1b	3 2
HCV RNA ($\log_{10}$ IU/mL)	Median (range)	6.9 (6.6–7.3)
Duration of HCV infection (years)	Median (range)	24.3 (22–27)
Response to prior IFN-based therapy for HCV	Non-responder Relapser	3 2

HCV, hepatitis C virus; IFN, interferon

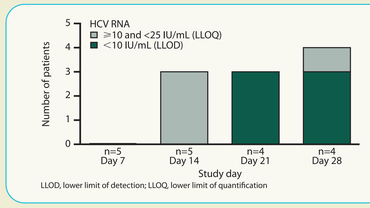
Baseline mutations

- Mutations in NS3, known to decrease susceptibility to TMC435 in vitro, which emerged during TMC435 exposure in Study TMC435-C101, were no longer detected at baseline of OPERA-1, using population sequencing (Table 2).

Antiviral activity

- Change from baseline in HCV RNA ($\log_{10}$ IU/mL) is shown in Figure 2. A rapid and consistent drop in HCV RNA was observed in this cohort of patients in both Study TMC435-C101 and OPERA-1, indicating similar potency of TMC435 on first and second exposure.
- Four out of five patients completed treatment with TMC435 (see 'Safety and tolerability'); each achieved HCV RNA levels below the lower limit of quantification (25 IU/mL) at Day 28 (Figure 3).
- No viral breakthroughs were observed to Day 28.
- The R155K mutation observed in one patient (201-0142) at Day 7 of OPERA-1 (also present in Study TMC435-C101) did not affect response during 28 days of TMC435 triple therapy.
- The presence of the D168D/E mutation at baseline in patient 201-0140 did not affect response to TMC435 in Study TMC435-C101 or OPERA-1.

Figure 3. Number of patients with HCV RNA i) below the lower limit of quantification and detectable (LLOQ) or ii) undetectable (LLOD) during 28 days of treatment with TMC435 in combination with pegylated interferon and ribavirin.



LLOD, lower limit of detection; LLOQ, lower limit of quantification

Table 2. Mutations in NS3 protease domain (defined as changes from reference sequence) detected in patients participating in TMC435-C101 and Cohort 5 of OPERA-1

		G015	I018	V029	T054	V055	P067	K068	D079	Q080	S122	I132	S133	R155	D168	N174
Genotype 1a																
Patient 201-0140	Study TMC435-101 Baseline		V		S	I/V	S				N/S		F/S		D/E	
	Study TMC435-101 Day 5		V		S	I	S		D/G	Q/R				K/R	E	
	OPERA-1 Baseline		V		S	I/V	S				N/S				D/E	
Patient 201-0142	Study TMC435-101 Baseline			A												
	Study TMC435-101 Day 5			A										K/R	A/D	
	OPERA-1 Baseline			A												
	OPERA-1 Day 7			A										K		
	OPERA-1 Day 14	G/W		A								L		K		
Patient 201-0144	Study TMC435-101 Baseline						S	K/N			N/S					G
	Study TMC435-101 Day 6						S	N			N				D/V	G
	OPERA-1 Baseline						S									G

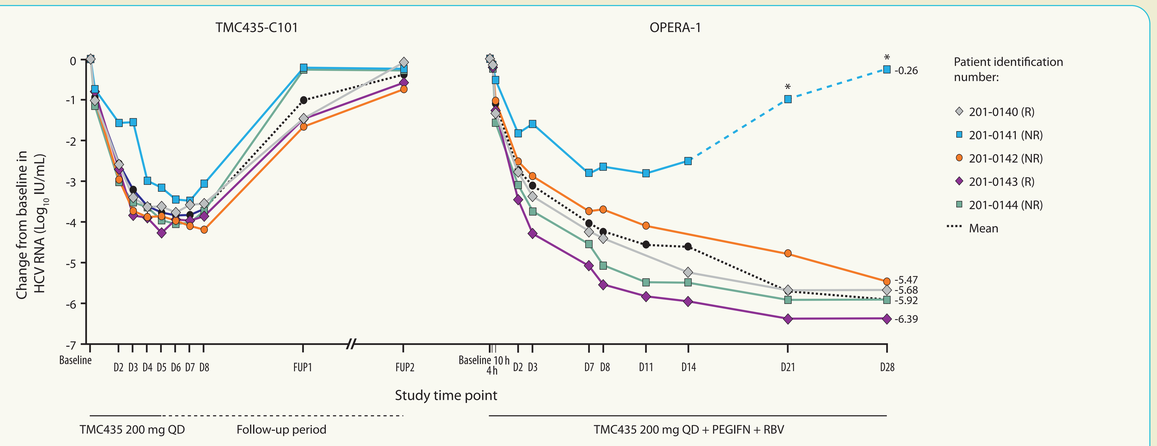
In addition mutations T040, S091 and L153 were found in all 1a patients at all time points analysed

		S007	V048	Y056	Q080	P089	A150	D168	F169
Genotype 1b									
Patient 201-0141	Study TMC435-101 Baseline	A	I	F		S	V		
	Study TMC435-101 Day 6	A	I	F		S	V	V*	
	OPERA-1 Baseline	A	I	F		S	V		
	OPERA-1 Day 7	A	I	F	R	S	V	E	
	OPERA-1 Day 14	A	I	F	R	S	V	E	L
Patient 201-0143	Study TMC435-101 Baseline								
	Study TMC435-101 Day 5							V	
	OPERA-1 Baseline								

In addition mutation R026 was found in all 1b patients at all time points analysed
* Day 5, no mutation at position 168 was present

Mutations are defined as changes from reference sequence (Con1 [AJ238799] for genotype 1b and H77 [AF009606] for genotype 1a); sequencing was attempted for all patients with HCV RNA levels >100 IU/mL at Day 7 and Day 14 of OPERA-1

Figure 2. Change from baseline in HCV RNA over time in patients who received TMC435 5-day monotherapy in Study TMC435-C101 and TMC435 as part of a 28-day triple therapy regimen in OPERA-1 Cohort 5.

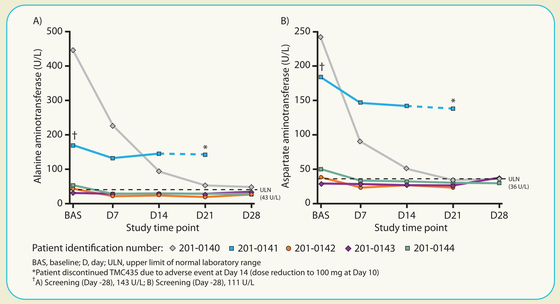


D, day; FUP, follow-up period; NR, non-responder; PEGIFN, pegylated interferon; R, relapser; RBV, ribavirin
*Patient discontinued TMC435 due to adverse event at Day 14 (dose reduction to 100 mg at Day 10)

Safety and tolerability

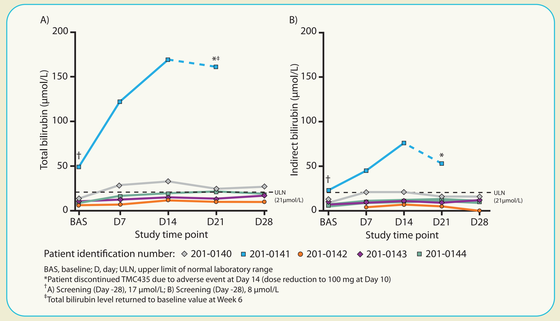
- There were no serious adverse events (AEs), and individual AEs were reported in one or two patients, with the exception of influenza-like illness which was reported in four patients. Most AEs were mild to moderate in severity and not, or doubtfully, related to TMC435.
- Four out of five patients completed triple therapy to Day 28. One patient (201-0141) discontinued treatment after 14 days due to an increase in serum bilirubin (grade 4). This patient had elevated bilirubin Grade 2 (direct and indirect) levels at study entry, although values at screening were within normal limits. Bilirubin levels decreased after treatment discontinuation. There were no other grade-3 or -4 AEs or laboratory toxicities reported.
- Alanine aminotransferase and aspartate aminotransferase levels are shown in Figure 4.
- Serum bilirubin levels are shown in Figure 5.
- No clinically relevant changes were observed in any other laboratory parameters, electrocardiogram parameters, or vital signs.

Figure 4. Changes in serum aminotransferase levels.



BAS, baseline; D, day; ULN, upper limit of normal laboratory range
*Patient discontinued TMC435 due to adverse event at Day 14 (dose reduction to 100 mg at Day 10)
†A) Screening (Day -28), 143 U/L; B) Screening (Day -28), 111 U/L

Figure 5. Changes in bilirubin levels.



BAS, baseline; D, day; ULN, upper limit of normal laboratory range
*Patient discontinued TMC435 due to adverse event at Day 14 (dose reduction to 100 mg at Day 10)
†A) Screening (Day -28), 17 µmol/L; B) Screening (Day -28), 8 µmol/L
‡Total bilirubin level returned to baseline value at Week 6

Conclusions

- **Treatment with TMC435 200 mg QD in combination with SoC showed potent antiviral activity in HCV genotype-1 patients who failed prior IFN-based therapy and had previously been exposed to TMC435.**
- **Mutations known to reduce susceptibility to TMC435 in vitro, which emerged during prior exposure to TMC435, were no longer detected at baseline in OPERA-1, suggesting a return to baseline viral variants.**
- **The overall safety profile of TMC435 was similar to that observed in the other OPERA-1 cohorts.[2,3] One patient in Cohort 5 discontinued due to an increase in serum bilirubin whilst receiving TMC435 200 mg QD, PEGIFN, and RBV. Bilirubin levels decreased after treatment discontinuation.**
- **Cohort 5 data confirm the antiviral activity of TMC435 observed in other OPERA-1 cohorts.**

References

1. Reesink H et al. J Hepatol 2008; 48 (Suppl 1): S28.
2. Manns M et al. J Hepatol 2009; 50 (Suppl 1): 11A.
3. Marcellin P et al. J Hepatol 2009; 1058A.

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