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Pharmacokinetics of once-daily regimens of the novel HCV NS3/4A-protease inhibitor TMC435350, with and without peg-IFN and ribavirin, in HCV-infected individuals

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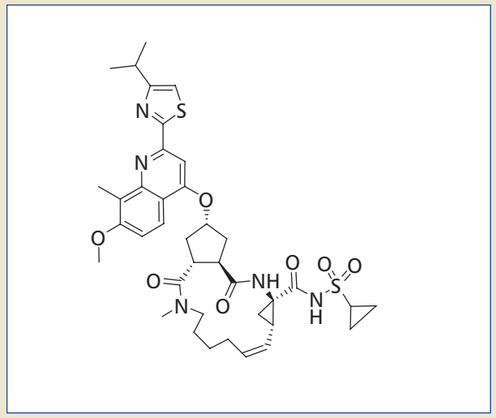
Background

TMC435 (Figure 1), formerly known as TMC435350, is a potent and selective HCV NS3/4A-protease inhibitor.

TMC435, preclinical profile:

- EC_{50} = 6 ng/mL (8 nM; genotype 1b replicon).
- ~2-fold shift of EC_{50} value in the presence of plasma proteins.
- Good oral bioavailability: 45-80%.
- High liver to plasma ratio: >30.

Figure 1: Molecular structure of TMC435



TMC435 clinical pharmacokinetics (PK):

- Supports once-daily (QD) dose regimens for efficacy evaluation at doses as low as 25 mg.[(1)]
- Lack of food effect with oral solution.[(2)]
- Mean plasma concentrations increase in a dose-proportional fashion for doses up to 100 mg, and more than dose-proportional for higher doses, both for single and repeated dosing.[(2)]
- Subject to prolonged absorption with a t_{max} of 6 hours.
- Time to steady state is determined by characteristics of absorption rather than elimination.[(1)]

We currently present steady-state PK data of TMC435, both in healthy volunteers (200 mg QD), and in HCV-infected individuals (25 and 75 mg QD), from a completed phase I trial (TMC435-C101) and an interim analysis in an ongoing dose ranging trial (OPERA-1, TMC435-C201).

This poster will be available on-line at www.tibotec.com

Methods

Healthy volunteers:

Healthy volunteers received TMC435 at a dose of 200 mg QD for 7 days, as a capsule (trial TMC435-C104). Data were compared to those from a prior clinical trial[(1)], in which TMC435 was given as an oral solution at 200 mg QD for 5 days in healthy volunteers.

HCV-infected patients:

A dose escalating, Phase IIa or proof-of-concept trial is ongoing in Europe to assess antiviral activity, safety and pharmacokinetics (PK) of once-daily (QD) regimens of TMC435 in HCV genotype-1 treatment-naive and treatment-experienced (prior non-responders/relapsers to IFN based therapy) patients (OPERA-1; Figure 3).

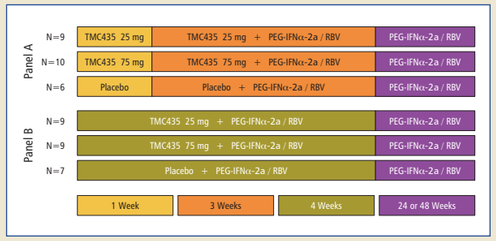
In the first cohort, treatment-naive patients were randomized to receive either:

- 7 days of mono therapy of TMC435, 25 or 75 mg QD, or placebo as capsules followed by 21 days of triple therapy with TMC435 QD or placebo, pegylated interferon-α-2a (PEG-IFNα-2a; 180 μg subcutaneous once-weekly) and ribavirin (RBV; 1000-1200 mg daily) (Figure 2; Panel A).
- or 28 days of triple therapy with TMC435 QD or placebo, PEG-IFNα-2a and RBV (Figure 2; Panel B).

After day 28, patients continued on PEG-IFNα-2a/RBV for a total of 24 or 48 weeks, at the discretion of the Investigator.

Plasma concentrations of TMC435 and of RBV were evaluated during the first 4 weeks.

Figure 2: Overview of study design of cohort 1 of the OPERA-1 trial in HCV-genotype 1 infected treatment-naive patients



Analytical methods:

TMC435 and RBV were quantified in (EDTA) plasma using a validated LC-MS/MS method, with a lower limit of quantification of 2.00 ng/mL.

PK analyses were performed using WinNonLin (Pharsight).

Results

Healthy volunteers:

- In healthy volunteers receiving 200 mg TMC435 QD for 7 days as a capsule formulation, steady state PK was attained within 7 days (Figure 3; Table 1).
- The overall PK profile in healthy volunteers for the capsule was similar to that for the oral solution, which was used in earlier 5-day trials with TMC435 in HCV-infected- and healthy volunteers[(1,2)], with a slightly lower overall bioavailability for TMC435 given as the capsule.

Figure 3: TMC435 PK profile in healthy volunteers

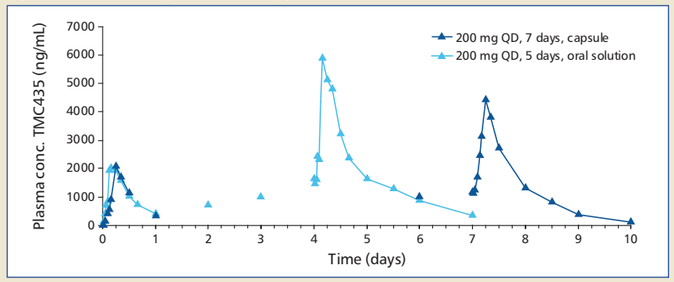


Table 1: TMC435 PK parameters in healthy volunteers following 200 mg QD TMC435

	Capsule, 7 days				Solution, 5 days			
Parameter	Day	N	Mean	SD	Day	N	Mean	SD
C_{max}, ng/mL	1	12	2194	801.5	1	5	2304	917.8
t_{max}, h	1	12	-	-	1	5	-	-
AUC_{24h}, ng.h/mL	1	12	22540	8197	1	5	24630	7331
C_{0h}, ng/mL	6	12	1019	981.1	4	5	1005	560.0
C_{0h}, ng/mL	7	12	1140	970.4	5	5	1482	791.3
C_{min}, ng/mL	7	12	1030	971.6	5	5	1445	767.3
C_{max}, ng/mL	7	12	4617	2788	5	5	6172	2859
t_{max}, h	7	12	-	-	5	5	-	-
AUC_{24h}, ng.h/mL	7	12	60340	41370	5	5	79710	37230
$t_{1/2term}$, h	7	12	11.4	2.0	5	5	16.0	5.1

HCV-infected patients:

Results of 48 patients receiving QD regimens of 25 mg or 75 mg TMC435 (or placebo) as capsules (Figure 4; Table 2 and 3):

- Details on antiviral activity and safety are presented in a separate poster by Manns et al.[(3)]
- For both regimens, steady state conditions were attained within 3 days (Fig 4A), with plasma concentrations essentially proportional to the dose.
- The mean steady-state C_{min} (± standard deviation) values were 71 ± 51 ng/mL for the 25 mg QD regimen, and 266 ± 159 ng/mL for the 75 mg QD regimen, 12 to 44-fold in excess of the EC_{50} based on plasma concentrations, and over 300-fold when taking into account the anticipated liver distribution extrapolated from animal studies.
- No relevant differences were observed in TMC435 plasma levels with or without PEG-IFNα-2a and RBV (Fig 4B, Table 3), and no major differences were observed in RBV plasma concentrations with or without TMC435 (Table 3).

Figure 4: PK profile in HCV-infected patients, 7 days TMC435 QD mono therapy + 21 days combination with PEG-IFNα-2a/RBV (Panel A) vs. 28 days combination with PEG-IFNα-2a/RBV (Panel B). (A) 28-days; (B) 7 days.

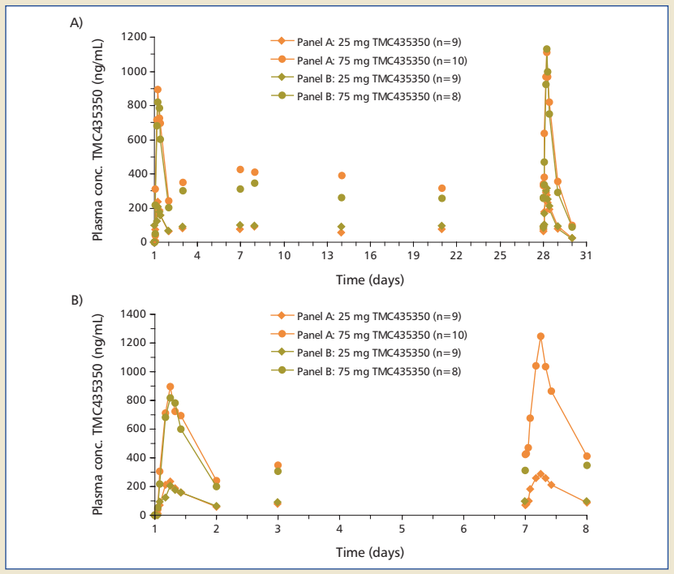


Table 2: PK parameters for TMC435 QD

		25 mg TMC435 QD			75 mg TMC435 QD		
Day	Parameter	N	Mean	SD	N*	Mean	SD
14	C_{0h}, ng/mL	18	73	47	18	332	187
21	C_{0h}, ng/mL	18	83	67	18	289	244
28	C_{min}, ng/mL	18	71	51	18	266	159
28	C_{max}, ng/mL	18	318	142	18	1166	580
28	t_{max}, h	18	5	-	18	-	-
28	AUC_{24h}, ng.h/mL	18	4280	2177	18	15997	7423

*: 1 patient was excluded from the PK analysis (outlier values)

Table 3: Steady-state PK parameters of RBV, with and without TMC435 QD, in HCV-infected patients

		Placebo			25 mg TMC435 QD			75 mg TMC435 QD		
Day	Parameter	N	Mean	SD	N	Mean	SD	N	Mean	SD
28	C_{0h}, ng/mL	13	1663	387	18	1828	596	18	2213	765
28	C_{min}, ng/mL	13	1515	499	18	1675	523	18	2048	746
28	C_{max}, ng/mL	13	2343	605	18	2484	774	18	3353	1072
28	t_{max}, h	13	3	2	18	3	2	18	3	1
28	AUC_{10h}, ng.h/mL	13	19208	5162	18	20486	6080	18	26422	7341

Conclusion

Once-daily regimens of 25 mg, 75 mg, and 200 mg TMC435 yield plasma concentrations well in excess of its EC_{50}, and pharmacokinetic steady-state is attained by day 7 following these doses.

REFERENCES
[(1)] G. Van 't Klooster et al., 43rd EASL, Milan, Italy, April 23-27, 2008, Poster 2590.
[(2)] R. Verloes et al., 58th AASLD, Boston, MA, November 2-6, 2007, Poster 1318.
[(3)] M. Manns et al., 59th AASLD, San Francisco, CA, October 31 – November 4, 2008, Poster LB08.

59th Annual Meeting of the American Association for the Study of Liver Diseases, October 31-November 4, 2008, San Francisco, CA, United States