LB8

Safety and antiviral activity of TMC435350 in treatment-naive genotype 1 HCV-infected patients

Corresponding author:
René Verloes
Tibotec BVBA
Gen De Wittelaan L11 B3
2800 Mechelen, Belgium
+32 15 461633
rverloes@its.jnj.com

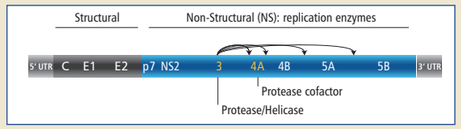
M. Manns[1], H. Reesink[2], C. Moreno[3], T. Berg[4], Y. Benhamou[5], Y. Horsmans[6], G. Dusheiko[7], R. Flisiak[8], P. Meyvisch[9], O. Lenz[9], K. Simmen[9], R. Verloes[9].

[1]Medizinische Hochschule Hannover, Germany; [2]Principal Investigator; Academic Medical Center, Amsterdam, The Netherlands; [3]Erasme Hospital, Université Libre de Bruxelles, Belgium; [4]Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Germany; [5]Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France; [6]Saint-Luc Université Catholique de Louvain, Belgium; [7]Royal Free Hospital, London, UK; [8]Medical University of Bialystok, Poland; [9]Tibotec BVBA, Mechelen, Belgium.

Introduction

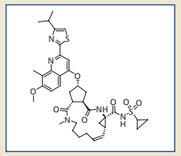
Activity of the HCV serine protease NS3/4A is essential for viral replication (Figure 1).

Figure 1: HCV genome (~10 kb).



TMC435 (formerly known as TMC435350; Figure 2):

Figure 2: TMC435



- Macrocyclic HCV NS3/4A protease inhibitor
- Potent *in vitro* activity against genotype 1a and 1b derived NS3/4A enzymes and replicon cell lines
- EC_{50} = 8 nM (genotype 1b replicon)
- ~2-fold shift of EC_{50} value in the presence of plasma proteins
- High liver to plasma ratio (>30 fold in pre-clinical studies)

OPERA-1 (TMC435-C201):

- A double blind, placebo-controlled, Phase IIa proof-of-concept trial, to assess antiviral activity, safety and pharmacokinetics (PK) of once-daily (QD) regimens of TMC435 in HCV genotype-1 infected treatment-naive and treatment-experienced (prior non-responders, relapsers or breakthroughs to IFN based therapy) patients.
- Interim results of the first 28 days of treatment from the first cohort of treatment naive patients (25 or 75 mg TMC435 versus placebo) are reported here.
- This study follows the Phase I trial in healthy volunteers showing safety and good tolerability at single doses up to 600 mg and repeated doses of 400 mg for 5 days. This Phase I trial also included a genotype 1 patient arm of previous non-responders/relapsers to IFN-based therapy dosed at 200 mg QD for 5 days.[1, 2]

Methods

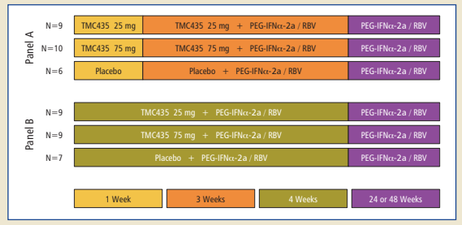
OPERA-1 trial design (Figure 3)

In cohort 1, patients were randomized to receive either:

- 7 days of monotherapy of TMC435, 25 or 75 mg QD, or placebo followed by 21 days of triple therapy with TMC435 or placebo, PegIFNα-2a (180 μg subcutaneous once-weekly) and ribavirin (RBV; 1000-1200 mg daily) (Panel A);
- or 28 days of triple therapy with TMC435 (25 or 75 mg QD) or placebo, PegIFNα-2a and RBV (Panel B).

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

Figure 3: Overview of Study Design of cohort 1 of OPERA-1 trial in treatment-naive patients.



Study objectives of OPERA-1 cohort 1

- To study the dose dependency of the antiviral effect of 2 doses of TMC435 QD during 1 week of monotherapy in HCV treatment-naive patients.
- To study the dose dependency of the antiviral effect of 2 doses of TMC435 QD during combined triple therapy with PegIFNα-2a and RBV in HCV treatment-naive patients.
- To determine safety, tolerability and PK profile of TMC435 QD during 7 days of monotherapy and combined with PegIFNα-2a and RBV for 21 or 28 days.

Results

Patients

- Demographics are shown in Table 1.
- 50 patients were randomized and started treatment.
- All patients completed the 4-week treatment period.
- All patients were continued on PegIFNα-2a/RBV after day 28.

Table 1: Demographics of Cohort 1, OPERA-1 trial, panel A and B combined.

Parameter	TMC435 25mg	TMC435 75mg	Placebo
	N=18	N=19	N=13
Gender, n			
Female	5	8	3
Male	13	11	10
Race, n			
Black	1	0	0
Caucasian/white	17	19	12
Other	0	0	1
Body Mass Index, kg/m²			
Median	27.35	25.00	25.70
Age Category, years			
≤ 40	3	7	5
41- 54	9	7	5
> 55	6	5	3
Median	52	47	45
HCV-RNA (Baseline) IU/mL, n			
Median, Log10	6.69	6.39	6.55
< 800,000	1	5	2
>= 800,000	17	14	11
HCV Genotype, n			
1a	5	7	7
1b	11	11	6
1, other or subtype not determined	2	1	0
Liver transaminase levels at baseline, U/L			
ALT, Median	66.0	60.0	71.0
AST, Median	37.5	42.5	52.0

There were no major differences between the dose groups and the placebo group.

Pharmacokinetics

- The mean steady-state plasma C_{min} values (± standard deviation) of TMC435 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} for genotype 1 HCV.
- Full PK results for Panel A and B are presented in a separate poster by Van 't Klooster et al.[3]

Safety

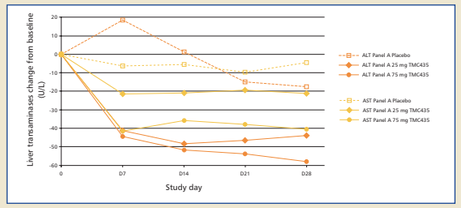
- Adverse events are shown in Table 2.
- No dose-related safety findings.
- No treatment-discontinuations due to TMC435-related safety or lab abnormalities.
- All TMC435 possibly related adverse events (AEs) were mild or moderate in severity (grade 1 or 2); no grade 3 or 4 AEs at least possibly related to TMC435.
- The most common AEs considered related to TMC435 treatment were headache, nausea and diarrhea.
- No clinically significant findings on laboratory parameters, including liver function (Figure 4), vital signs, ECG or physical examination.
- The safety analysis showed that doses of 25 and 75 mg were generally safe and well tolerated and allowed dosing of the next cohort (200 mg QD).

Table 2: Adverse events reported in week 1-4 by preferred term (regardless severity and causality) in cohort 1, panel A and B combined. Number of patients and incidence (%; between brackets) are given.

Any adverse event occurring in ≥2 patients	TMC435 25 mg N=18	TMC435 75 mg N=19	Placebo N=13
Anemia	0	1 (5.3)	2 (15.4)
Arthralgia	2 (11.1)	2 (10.5)	1 (7.7)
Asthenia	4 (22.2)	4 (21.1)	1 (7.7)
Bone pain	1 (5.6)	2 (10.5)	0
Chills	2 (11.1)	1 (5.3)	3 (23.1)
Cough	1 (5.6)	3 (15.8)	1 (7.7)
Decreased appetite	4 (22.2)	2 (10.5)	1 (7.7)
Diarrhea	3 (16.7)	3 (15.8)	0
Dizziness	2 (11.1)	1 (5.3)	2 (15.4)
Fatigue	8 (44.4)	4 (21.1)	4 (30.8)
Feeling cold	1 (5.6)	2 (10.5)	0
Headache	9 (50.0)	9 (47.4)	5 (38.5)
Influenza like illness	5 (27.8)	6 (31.6)	2 (15.4)
Insomnia	1 (5.6)	1 (5.3)	2 (15.4)
Myalgia	3 (16.7)	2 (10.5)	2 (15.4)
Nausea	5 (27.8)	5 (26.3)	1 (7.7)
Neutropenia	1 (5.6)	3 (15.8)	1 (7.7)
Paresthesia	0	2 (10.5)	0
Pyrexia	3 (16.7)	3 (15.8)	1 (7.7)
Rash	0	1 (5.3)	3 (23.1)
Vertigo	2 (11.1)	0	0

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

Figure 4: Variation of liver transaminases (alanine transaminase, ALT; aspartate transaminase, AST) over time.



Antiviral Activity

- Change in HCV RNA levels in the first 4 weeks of therapy is shown in Figure 5.
- 25 mg and 75 mg QD of TMC435 plus PegIFNα-2a/RBV resulted in greater mean HCV RNA reduction than PegIFNα-2a/RBV alone.
- Mean Reduction of HCV RNA from baseline at day 7 in the 75 mg dose groups (3.43 and 4.55 Log_{10} IU/mL for panel A and B, respectively) was greater than in the corresponding 25 mg dose groups (2.63 and 3.47 Log_{10} IU/mL for panel A and B, respectively).
- Addition of PegIFNα-2a/RBV to TMC435 increased the mean HCV RNA reduction at day 7 by 0.84 and 1.12 Log_{10} IU/mL for 25 mg and 75 mg dose groups, respectively.
- During the first 28 days of treatment, 2 viral breakthroughs (defined as >1 Log_{10} IU/mL increase of HCV RNA from nadir) in the 25 mg and 75 mg dose groups of panel A were observed, respectively. No viral breakthrough was noted in panel B. Sequence analysis is in progress.
- In the 25 mg 4-week triple therapy arm, 6/9 patients achieved HCV RNA below lower limit of quantification (LLQ) (<25 IU/mL) and 3/9 patients were below lower limit of detection (LLD) (<10 IU/mL) at day 28 (rapid viral response, RVR = 33%).
- In the 75 mg 4-week triple therapy arm, 9/9 patients were below LLQ and 8/9 patients achieved undetectable HCV RNA (<LLD) at day 28 (RVR=89%).

Figure 5: Mean HCV-RNA change per treatment arm from baseline to Day 28

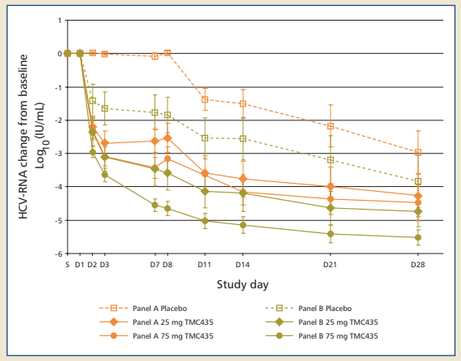


Table 3: Mean HCV RNA changes from baseline and number of patients with HCV RNA levels below lower limit of quantification (LLQ) and detection (LLD) per treatment arm.

Dose/Treatment	Time point (Day)	Mean HCV-RNA change (Log_{10} IU/mL)	< LLQ n/N <25 IU/mL	< LLD n/N <10 IU/mL
Panel A Placebo	7	-0.08	0/6	0/6
Panel A TMC435 25 mg	7	-2.63	1/9	0/9
Panel A TMC435 75 mg	7	-3.43	0/9	0/9
Panel B Placebo	7	-1.77	0/6	0/6
	14	-2.56	0/6	0/6
	28	-3.83	3/6	2/6
Panel B TMC435 25 mg	7	-3.47	1/9	0/9
	14	-4.19	3/9	1/9
	28	-4.74	6/9	3/9
Panel B TMC435 75 mg	7	-4.55	1/9	0/9
	14	-5.15	7/9	3/9
	28	-5.52	9/9	8/9

HCV RNA levels were assessed with Roche COBAS Taq Man HCV/HPS assay v2 with an LLQ of 25 IU/mL and an LLD of ~10 IU/mL. To calculate mean HCV RNA values, results below LLQ are imputed with 24 IU/mL and values below LLD with 9 IU/mL.

Summary

- TMC435, at doses of 25 and 75 mg QD was well tolerated in combination with PegIFNα-2a/RBV in treatment-naive HCV genotype 1 patients for up to 28 days.
- All AEs possibly related to TMC435 were mild to moderate in severity (grade 1-2).
- Mean reductions of HCV-RNA from baseline at day 7 with TMC435 alone (panel A) and combined with PegIFNα-2a/RBV (panel B) were 2.63 and 3.47 Log_{10} IU/mL, respectively, in the 25 mg dose group, and 3.43 and 4.55 Log_{10} IU/mL, respectively, in the 75 mg dose group.
- In the 75 mg 4-week triple therapy arm (panel B), no viral breakthrough was observed and 9/9 patients achieved HCV-RNA levels below LLQ (<25 IU/mL) and 8/9 patients achieved undetectable HCV-RNA (<10 IU/mL) at day 28 (RVR=89%).

Conclusions

- In cohort 1 of the OPERA-1 study, 25 mg and 75 mg TMC435 administered once-daily in combination with standard of care (PegIFNα-2a/RBV), demonstrated dose-dependent potent antiviral activity and a favorable safety and tolerability profile up to 28 days of dosing in treatment-naive, chronic hepatitis C patients with genotype 1.
- A 200 mg dose group of TMC 435 is now being evaluated in patients of cohort 2 of the OPERA-1 study.

REFERENCES
1. Verloes R et al., 58th AASLD, Boston, MA, November 2-6, 2007, Poster 1318.
2. Reesink H et al., 43rd EASL, Milan, Italy, April 23-27, 2008, Oral Presentation.
3. Van 't Klooster et al., 59th AASLD, San Francisco, CA, October 31 – November 4, 2008, Poster 1895.

ACKNOWLEDGEMENTS:
The patients who are participating in the OPERA-1 study. The investigators and the study center staff who contributed to this study cohort. Medivir AB, Sweden (Bertil Samuelsson, Åsa Rosenquist, Magnus Nilsson, Lotta Vrang, Michael Edlund, Borje Darpo). Tibotec BVBA, Belgium. The service companies supporting this trial.