Safety and antiviral activity of TMC453530 in treatment-naive genotype 1 HCV-infected patients

Introduction

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

Figure 1: HCV genome (<10 kb).

Table 1: 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 study center staff who contributed to this study cohort. Medivir AB, Sweden). 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.

Table 2: Antiviral Activity.

Figure 2: Pharmacokinetics of once-daily (QD) regimens of TMC435. Medizinische Hochschule Hannover, Germany; Principal Investigator: Academic Medical Center, Amsterdam, The Netherlands; Erasmus Hospital, Université Libre de Bruxelles, Belgium; Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Germany; Centre Hospitalier Universitaire Pitéï-Salpêtrière, Paris, France; Saint-Luc Université Catholique de Louvain, Belgium; Royal Free Hospital, London, UK; Medical University of Bialystok, Poland; RBV, ribavirin.

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, PegIFN-2a/2b (180 μg subcutaneously 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, PegIFN-2a/2b and RBV (Panel B).

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

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 PegIFN-2a/2b and RBV in HCV treatment-naive patients.
- To determine safety, tolerability and PK profile of TMC435 QD during 7 days of monotherapy combined with PegIFN-2a/2b and RBV for 21 or 28 days.

Results

Patients

Demographics are shown in Table 1.

All patients completed the 4-week treatment period.

All patients were continued on PegIFN-2a/2b/RBV after day 28.

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

Pharmacokinetics

The mean steady-state plasma C50 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 EC50 for genotype 1 HCV.

Full PK results for Panel A and B are presented in a separate poster by Van’t Klooster et al.

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 patients in the 25 mg 4-week triple therapy arm, 9/9 patients achieved HCV RNA below lower limit of quantification (<25 IU/mL) (rapid viral response, RVR = 33%).

In the 25 mg 4-week triple therapy arm, 6/9 patients achieved HCV-RNA levels below LLQ (<25 IU/mL) in the 25 mg and 75 mg dose groups, respectively.

In the 25 mg 4-week triple therapy arm, 9/9 patients achieved HCV RNA below lower limit of quantification (LLQ) (<25 IU/mL) and 9/9 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 (<10 IU/mL) at day 28 (RVR=89%).

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) (IU/mL).

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Conclusion

- 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.

- TMC435, at doses of 25 and 75 mg QD was well tolerated in combination with PegIFN-2a/2b/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); no grade ≥3 AEs were observed.

- Mean reduction of HCV RNA from baseline at day 7 in the 25 mg dose groups (3.43 and 4.55 Log10 IU/mL for panel A and B, respectively) was greater than in the corresponding 25 mg dose groups (2.63 and 3.47 Log10 IU/mL for panel A and B, respectively).

- Addition of PegIFN-2a/2b/RBV to TMC435 increased the mean HCV RNA reduction at day 7 by 0.84 and 1.12 Log10 IU/mL for 25 mg and 75 mg dose groups, respectively.

- During the first 28 days of treatment, 2 viral breakthroughs (defined as ≥1 Log10 IU/mL increase of HCV RNA from nadir) in the 25 mg and 75 mg dose groups of panel A were observed, respectively.

- In the 75 mg 4-week triple therapy arm, 9/9 patients achieved HCV RNA below lower limit of quantification (>25 IU/mL) and 9/9 patients achieved undetectable HCV RNA (<10 IU/mL) at day 28 (rapid viral response, RVR = 89%).

- 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%).

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References


4. Verloes R et al., 58th AASLD, Boston, MA, November 2-6, 2007, Poster 1318.
