In vitro studies investigating the mechanism of interaction between TMC435 and hepatic transporters

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1. Premise

- TMC435 is a potent, once-daily NS3/4A protease inhibitor in Phase Ib clinical development for the treatment of hepatitis C virus (HCV) infection in combination with pegylated interferon and ribavirin (Figure 1).

2. Methods

- Bilirubin clearance from the blood is a three-step process (Figure 2): First, bilirubin and bilirubin conjugates are taken up by the liver cells, mainly by the organic anion transporter, OATP1B1. Next, unconjugated bilirubin is conjugated, primarily by glucuronyl transferase enzyme, UGT1A1, and then transported into the bile, mostly by the efflux transporter, MRP2.

3. Results

- TMC435 inhibited OATP1B1 with a 50% inhibitory concentration (IC50) of 0.2±0.1 μM (Figure 3). This compared with IC50 values of 2.5±0.05 μM for cyclosporine A and rifampicin, respectively.

4. Conclusions

- TMC435 is an inhibitor of the transporters OATP1B1 (influx) and MRP2 (efflux), which may explain the mild and transient increases in bilirubin that were observed in Phase II trials, predominately with higher doses of TMC435.

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6. References