Introduction

TMC435350 is a potent inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease.

TMC435350 was evaluated in entecavir-naive HCV genotype 1 NS3 protease- and -NS5B replicate-containing human cell (HepG2) models.

EC_{50} = 5 nM for HCV genotype 1 replication assays (EC_{50} = 24 nM).

Human serum protein only reduces EC_{50} by 2.4-fold (whereas the TMC435350 protein binding is 96.9%).

EC_{50} = 0.02 nM for HCV NS3 and RNA viruses and human proteases tested in vitro.

Multiple ascending dose (MAD) fed conditions for all doses tested followed by an investigation of effects of fasting on PK profile and exposure of a single 200 mg dose of TMC435350.

Steady state was not achieved for TMC435350 doses >100 mg.

PK data from panel 5 (200 mg BID) will be reported elsewhere.

Study TMC435350-TiDP16-C101 (C101) was a randomised, double-blind, placebo-controlled trial to determine the safety, tolerability and PK of TMC435350 after single and multiple oral dosing.

Single ascending dose (SAD)

TMC435350 50-600 mg, as oral solution in PKG600, 2 panels of 9 healthy volunteers (Figure 1). 6 of whom received TMC435350 and 3 received placebo per session.

Final conditions for all doses tested followed by an investigation of effects of fasting on PK profile and exposure of a single 200 mg dose of TMC435350.

Subsequent doses were separated by a washout period of minimally 30 days.

Full PK profile was studied with samples taken up to 72 post-dose.

Multiple ascending dose (MAD)

TMC435350 200-300 mg, as oral solution in PKG400: 4 panels (panels 3-6) of 9 healthy volunteers (Figure 1) with a 2:1 randomisation to TMC435350 or placebo. In addition, 2 volunteers with HCV genotype 1 (panel 1, 2a, 2b) who were non-responders or relapsers to previous interferon-based therapy.

Full PK profiles were studied on Days 1 and 5, with pre-dose samples on Days 2, 3, 6 and 7.

Methods

Study design

- Study TMC435350-TiDP16-C101 (C101) was a randomised, double-blind, placebo-controlled trial to determine the safety, tolerability and PK of TMC435350 after single and multiple oral dosing.

- Single ascending dose (SAD)
  - TMC435350 50-600 mg, as oral solution in a panel of 9 healthy volunteers (Figure 1). 6 of whom received TMC435350 and 3 received placebo per session.
  - Fed conditions for all doses tested followed by an investigation of effects of fasting on PK profile and exposure of a single 200 mg dose of TMC435350.
  - Subsequent doses were separated by a washout period of minimally 30 days.
  - Full PK profile was studied with samples taken up to 72 post-dose.

- Multiple ascending dose (MAD)
  - TMC435350 200-300 mg, as oral solution in a panel of 4 panels of 9 healthy volunteers (Figure 1) with a 2:1 randomisation to TMC435350 or placebo. In addition, 2 volunteers with HCV genotype 1 (panel 1, 2a, 2b) who were non-responders or relapsers to previous interferon-based therapy.
  - Full PK profiles were studied on Days 1 and 5, with pre-dose samples on Days 2, 3, 6 and 7.

- PK data from panel 1 (200 mg BID) will be reported elsewhere.

- Safety and tolerability data from these studies have been described previously (Verloes et al, 2007; Reesink et al, 2008).

Bioavailability

- Plasma concentrations of TMC435350 were determined by LC-MS/MS (lower limit of quantification 0.2 ng/mL).

Statistical analysis

- PK and statistical analyses were conducted using WinNonlin Professional™ (Pharsight Corporation, CA, USA) and for SAS (SAS Institute Inc, NC, USA).

Results

SAD

- Delayed time to maximum concentration (t_{max}) indicated slow or prolonged absorption of TMC435350.

- Plasma exposure increase in TMC435350 was more than dose-proportional.

- Dose proportionality was not associated with dose-dependent clearance (Figure 2).

- There was no relevant effect of food on the PK of TMC435350.

MAD

- Slowly state was attained for TMC435350 100 mg QD dosing, with C_{min} being below in excess of 200 mg (PGC600) X 300.

- Steady state was not achieved for TMC435350 doses >100 mg QD.

- Mean exposures of TMC435350 in HCV-infected individuals were 1.5-fold higher than in healthy volunteers and were associated with a longer elimination half-life in HCV-infected individuals (41 ± 33 h vs 16 ± 5 h).

Conclusions

- Data from trial C101 presented elsewhere demonstrate that TMC435350 was well tolerated in healthy volunteers at all dose levels studied (Verloes et al, 2007), and that 200 mg TMC435350 once-daily for 5 days reduced HCV RNA by 3.9 log_{10}, in genotype 1 HCV-infected non-responders/relapsers (Reesink et al, 2008).

- Single- and multiple-DK PK support the use of once-daily dosing of TMC435350.

- The dose-disproportionality of TMC435350 PK can be accurately simulated using the model described.

- PK modeling estimates indicate that efficacious dosages may be as low as 25 mg QD in future Phase II clinical trials.