ONCE-DAILY REGIMENS OF THE HCV NS3/4A-PROTEASE INHIBITOR TMC435350 ARE PREDICTED TO PROVIDE THERAPEUTIC EXPOSURE IN PLASMA AND LIVER

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Introduction

TMC435350 is a potent inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease. TMC435350 was evaluated in enzymatic HCV protease 1,1 (PR) cell-free assays (Simmern et al. 2007): - IC50 > 40 nM for HCV genotype 1 in a panel of six (IC50 > 24 nM) - Human serum protein only increased IC50 by 2-4 fold (whereas the TMC435350 protein binding is >90%); - IC50 > 10 fold against a panel of DNA and RNA viruses and human protease inhibitors tested. - Minimal cytotoxicity in tested human cell lines (GI > 2000).

TMC435350 was extensively distributed to the liver and gastro-intestinal tract, with a liver to plasma ratio of >10:1 after a single oral dose of 40 mg/kg in Sprague-Dawley rats (Simmern et al. 2007) and after 1/4 days of repeat dose dosing at 10 mg/kg/day in dogs (data on file). In HCV-infected non-responders/relapsers, 200 mg TMC435350 once-daily was associated with a median decrease in HCV RNA of 3.9 log10 (Reesink et al. 2008).

Here, the pharmacokinetics (PK) of TMC435350 in healthy and HCV-infected volunteers are presented. PK modeling of TMC435350 was conducted to predict therapeutic dose regimens prior to entering Phase II clinical trials.

Methods

Study design

- Study TMC435350-Top16-C101 (C101) was a randomized, 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 100-400 mg, as oral solution in PEG400; 4 panels (panels 3-6)

Multiple ascending dose (MAD)

- TMC435350 50-600 mg, as oral solution in PEG400; 2 panels of 9 healthy volunteers (Figure 1), 6 of whom received TMC435350 and 3 received placebo; 2:1 randomisation to TMC435350 and placebo; 14 days of repeated oral dosing at 10 mg/kg/day in dogs (data on file).

- For dogs, TMC435350 was evaluated in enzymatic (HCV genotype 1 NS3 proteases) and/or cellular replicon models (Simmen et al., 2007):
  - Minimal cytotoxicity in tested human cell lines (SI > 2590)
  - EC50 Human serum protein only increases EC50 by 2.4 fold (whereas the proteases tested in vitro)
  - EC50/H11022 similar in humans) and the 80% bioavailability of a new capsule formulation in Sprague Dawley rats (Simmen et al., 2007)

- As once-daily doses in HCV-infected individuals. Also considered were the observed clinical data in HCV-infected individuals (Figure 5).

- At 25 mg QD, trough plasma and liver levels of TMC435350 are estimated at 10 μM against a panel of DNA and RNA viruses and human protease inhibitors tested.

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PK fitting and modelling to support predictions of exposure in HCV-infected individuals

- A simulation model of TMC435350-exposure, based on data from healthy volunteers, was developed to evaluate key determinants of the PK properties of TMC435350 and to predict the dose at which steady state levels could be achieved.

- Considerations for the model were:
  - dose-dependent bioavailability after single dose, with dose-dependent clearance (Figure 2)
  - degree of plasma accumulation is dose-dependent.

- Exploratory analyses of PK modelling were conducted, assuming:
  - both concentration-dependent and independent drug clearance
  - a dose-dependent, sigmoidal model of bioavailability

- Based on clustering observed in the single accumulating dose study, dose groups were separated into low (10-100 mg), medium (200-325 mg) and high (455-600 mg), which allowed acceptable PK fits.

- A connection depression equation was used to describe the delayed absorption profile (Preij et al. 2007).

- Simulations showed a high degree of accuracy when compared with observed clinical data in HCV-infected individuals (Figure 5).

- The model was used to calculate target trough levels of TMC435350 given as once-daily doses in HCV-infected individuals. Also considered were the high liver to plasma tissue distribution ratio in animals (assumed to be similar in humans) and the 80% bioavailability of a new capsule formulation relative to the oral solution (data on file).

- A once-daily dose regimen of TMC435350 in HCV-infected volunteers is estimated at steady state to exceed the protein binding corrected EC50 by 15 times (300 μg/mL) (Figure 6).

Results

PK data from panel 5 (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).

Safety

- TMC435350 was well tolerated and no drug-related serious adverse events were reported. No significant safety or tolerability concerns were identified.

Pharmacokinetics

- PK and safety analyses were conducted using WinNonLin Professional™ (Pharsight Corporation, CA, USA) and/or SAS (SAS Institute Inc, NC, USA).

AD

- TMC435350 concentrations of TMC435350 were determined by LC-MS/MS (lower limit of quantification = 2.00 ng/ml).

- Single- and multiple-dose PK support the use of once-daily dosing for 5 days reduced HCV RNA by 3.9 log10 in genotype 1 HCV-infected non-responders/relapsers (Reesink et al. 2008).

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

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

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 log10 in genotype 1 HCV-infected non-responders/relapsers (Reesink et al. 2008).

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

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

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

Acknowledgements

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References

Verloes et al. Presented at the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL), Milan, Italy, 23-27 April 2008. (oral presentation)

Freijer et al. Presented at the 9th Annual Meeting of the American Association for the Study of the Liver (AASLH), Baltimore, Maryland, 20-23 April 1996. (abstract presentation)

Preij et al. Presented at the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL), Milan, Italy, 23-27 April 2008. (oral presentation)