

# Virologic analysis of genotype-1-infected patients treated with once-daily TMC435 during the Optimal Protease inhibitor Enhancement of Response to TherApy (OPERA)-1 study

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## 1. Premise

- TMC435 is a potent, once-daily hepatitis C virus (HCV) NS3/4A protease inhibitor with an *in vitro* 50% effective concentration ( $EC_{50}$ ) value of 8 nM in a genotype-1b replicon cell line.<sup>1</sup>
- In *vitro* resistance studies identified changes at amino acid positions 43, 80, 155, 156, and 168 within the NS3 protease region that confer variable degrees of reduced susceptibility to TMC435.<sup>2</sup>
- In a Phase IIa proof-of-concept study (OPERA-1; TMC435-C201; NCT00561353), HCV genotype-1-infected treatment-naïve and -experienced patients were treated for four weeks with TMC435 at doses between 25 mg and 200 mg once daily (QD) in combination with pegylated (Peg) interferon (IFN) $\alpha$ -2a and ribavirin (RBV), followed by PegIFN $\alpha$ -2a/RBV up to Week 48. At the four-week interim analysis:<sup>3,5</sup>
  - All doses of TMC435 were generally safe and well tolerated.
  - TMC435 demonstrated potent, dose-dependent antiviral activity in both treatment-naïve and -experienced patients.
  - All treatment-naïve patients receiving TMC435 at doses of 75 mg or 200 mg QD in combination with PegIFN $\alpha$ -2a/RBV, and 4/9, 7/9, and 7/10 treatment-experienced patients receiving TMC435 at doses of 75 mg, 150 mg, or 200 mg QD in combination with PegIFN $\alpha$ -2a/RBV, respectively, achieved HCV ribonucleic acid (RNA) levels of <25 IU/mL at Week 4.
  - Mean trough TMC435 concentrations at Day 28 following TMC435 doses of 25 mg, 75 mg, and 200 mg QD were approximately 10-fold, 50-fold, and 800-fold higher than the  $EC_{50}$  value of 8 nM (6 ng/mL).
- TMC435 is currently in Phase IIb development.
- For patients included in the OPERA-1 study, we investigated the relationship between specific NS3 variants at baseline and:
  - In vitro* susceptibility to TMC435
  - Response during four weeks of treatment with TMC435.
- Emerging viral variants in patients with viral breakthrough were characterized using population sequencing and genotype-1b transient chimeric replicon assays.

## 2. Methods

### 2.1 Study design

- The OPERA-1 study design is summarized in Figure 1.
  - Patients from Cohorts 1, 2, and 4 were included in this analysis.
- OPERA-1 was a double-blind, placebo-controlled Phase IIa study to assess the antiviral activity, safety, and pharmacokinetics (PK) of TMC435 in HCV genotype-1-infected patients. Treatment-naïve patients (Cohorts 1 and 2) were randomized to receive either 7 days of monotherapy with TMC435 at doses of 25 mg, 75 mg, or 200 mg QD, or placebo, followed by 21 days of triple therapy with TMC435 or placebo in combination with PegIFN $\alpha$ -2a/RBV (Panel A), or 28 days of triple therapy with TMC435 (at the same doses as in Panel A) or placebo (Panel B). In Cohort 4, patients who had failed previous (Peg)IFN/RBV therapy received 28 days of triple therapy with TMC435 at doses of 75 mg, 150 mg, or 200 mg QD, or placebo.

