Treatment outcome and resistance analysis in HCV genotype 1 patients previously exposed to TMC435 monotherapy and retreated with TMC435 in combination with PegIFNα-2a/ribavirin

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ABSTRACT

INTRODUCTION

• TMC435 is a once daily (QD) oral NS3/4A protease inhibitor currently in development for the treatment of HCV genotype 1 infection.

• TMC435 is an investigational patient and selection inhibitor of the NS3A protease with activity against HCV genotypes 1, 2 and 3 (EC50 = 0.01 to 0.001 nM) in a genotype 1b replicon cell line.

• Phase I/II Phase 1/II Phase 2b trials have demonstrated that TMC435 is well tolerated, with promising efficacy reported in combination with pegylated interferon (PegIFN) and ribavirin (RBV).

• In vitro studies showed identified changes at amino acids positions 80, 155, 156 and 168 in the NS3 protease region derived from patient samples.

• Median through TMC435 concentrations obtained following dosing of 150 and 300 mg/kg for 3 consecutive days (D1-3) in HCV genotype 1b (6 ng/mL) were >100 IU/mL in a genotype 1b replicon cell line.

• In a Phase 1 study TMC435-C101, genotype 1 patients previously exposed to PegIFN/RBV for ≥24 weeks (D1; n=50) were treated with TMC435 (150 mg/kg) for 14 days. TMC435-C201 (300 mg/kg) for 8 days, followed by TMC435 for up to 24 weeks (D1; n=50).

• We report the full 24-week follow-up data from the TMC435-C101 and TMC435-C201 studies based on deep sequencing studies.

METHODS

• Patients enrolled during the TMC435-C101 and TMC435-C201 studies and HCV CORE/amplified genome (AG) were assessed with a Next Generation single genome sequencing (NGS) technology for the analysis of the NS3 protease region, including 100000 reads per patient. A reference wild-type (wt) AG was derived from the literature.

• Single ART containing the TMC435-C101 and TMC435-C201 studies and HCV CORE/amplified genome (AG) were assessed with a Next Generation single genome sequencing (NGS) technology for the analysis of the NS3 protease region, including 100000 reads per patient. A reference wild-type (wt) AG was derived from the literature.

• In addition to single mutations, variants encoding 2 or 3 amino acid changes in the NS3 protease region derived from patient samples.

• In patient 141, ultra-deep sequencing detected a Q80R and a D168E mutation encoding 2 amino acid changes in the NS3 protease region derived from patient samples.

RESULTS

Antiviral Activity and Efficacy

All 10 patients in study TMC435-C101 and 8 patients in study TMC435-C201 achieved a viral load of <50 IU/mL following 28 days and ultimately achieved SVR12 (12 weeks) in 9 out of 10 patients (90%) in study TMC435-C101 and 8 out of 8 patients (100%) in study TMC435-C201.

Evolution of Virus Load Over Time Based on Deep Sequencing

In patient 141, after ultra-deep sequencing detected a Q80R and a D168E mutation encoding 2 amino acid changes in the NS3 protease region derived from patient samples.

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REFERENCES


