Combination of TMC114/ritonavir and TMC125 in patients with multidrug resistant HIV

Julio Montaner1, Marianne Harris1, Thomas Kakuda2, Gerene Larsen1, Brian Woodfall3, Diego Miralles2, P. Richard Harrigan1

1BC Centre for Excellence in HIV/AIDS, St. Paul’s Hospital, Vancouver Canada; 2Tibotec Inc., Yardley, Pennsylvania, USA; 3Tibotec, Mechelen, Belgium

Background

TMC114 and TMC125 are investigational antiretroviral drugs with activity against HIV that is resistant to available PIs and NNRTIs, respectively. Patients with multidrug-resistant HIV may benefit from the use of these agents in combination.

Methods

Patients

• HIV+ adults
• extensive treatment experience with NRTIs/NNRTIs, NNRIs, and PIs
• evidence of drug resistance on genotypic testing

Medication regimens

TMC114 400 mg with ritonavir 100 mg twice daily
TMC125 200 mg twice daily
+/- NRTIs/NNRTIs
+/- efavirenz (T20)

Clinical and Laboratory Assessments

Plasma viral load (VL), CD4 cell count, and safety parameters (hematology, chemistry)
• at baseline
• weekly until week 4
• every 2 weeks until week 12
• every 4 weeks until week 24

Genotypic resistance

• virtual phenotype-1 Virtual Phenotype was assessed at baseline from archived samples and on the most recent sample with VL>200 copies/mL.
• Virtual Phenotype was repeated on samples where VL >200 copies/mL. on therapy

Pharmacokinetic (PK) methods

• 12-hour PK assessments were conducted between weeks 4 and 8
• Plasma concentrations of TMC114, TMC125, and ritonavir were determined using a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) method
• PK analyses were performed using WinNonlin professional TM (version 5.1;Pharsight Corporation, Mountain View, California, USA)
• A non-compartmental model with extravascular input was used
• The primary PK parameters were maximum and minimum plasma concentration (Cmax and Cmin, respectively), time to Cmax (Tmax), and area under the plasma concentration-time curve from 0 to 12 hours (AUC12) as calculated using the linear-up/log-down trapezoidal rule

Results

PATIENT 1
Previous Treatment History

Regimen: TMC125/TMC114/RTV/TDF/ABC/3TC

Weeks

Log10 VL (copies/mL)

0 1 2 3 4 5

0 1 2 3

TMC114 Plasma Concentration Time Curves

TMC125 Plasma Concentration Time Curves

RTV Plasma Concentration Time Curves

Conclusions

• Combination therapy including TMC114/ritonavir and TMC125 resulted in substantial viral load declines and CD4 cell count increases over 20-24 weeks in these 5 treatment-experienced patients with drug-resistant HIV.
• 4/5 achieved undetectable viral load (<50 copies/mL).
• No major safety concerns were identified.
• TMC114 and TMC125 plasma levels were generally comparable with data previously presented for HIV+ patients (given the substantial variability of levels for both drugs), and not obviously related to virologic response (NB patient 5).
• This combination may present a viable treatment option for patients with multidrug-resistant HIV.

For additional information, please contact:

Julio Montaner, MD
BC Centre for Excellence in HIV/AIDS
St. Paul’s Hospital
1081 Burrard Street, Vancouver, British Columbia, Canada. V6Z 1Y6
Tel. 604-697-6133 / Fax 604-697-6124 / Email julio.montaner@ubc.ca