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TMC114, A POTENT NEXT-GENERATION PROTEASE INHIBITOR: CHARACTERIZATION OF ANTIVIRAL ACTIVITY IN MULTIPLE PROTEASE INHIBITOR-EXPERIENCED PATIENTS PARTICIPATING IN A PHASE IIA STUDY

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BACKGROUND: TMC114 is a potent next-generation protease inhibitor (PI), active against wild-type as well as PI-resistant HIV. The study TMC114-C207 was a placebo-controlled Phase Iia trial to evaluate the antiviral activity, safety and tolerability of TMC114 over 14 days treatment. Fifty multiple PI-experienced subjects (range 2–4 PIs) on a failing nucleoside reverse transcriptase inhibitor (NRTI)- and PI-containing regimen (HIV-1 RNA >2000 copies/ml) were enrolled. They received TMC114 with low-dose ritonavir (TMC114/RTV) at one of three doses (300/100 mg twice daily, 600/100 mg twice daily or 900/100 mg q.d.) as a substitution for their current PI or remained on their current regimen (control group) for 14 days. Afterwards, all patients switched to an investigatorselected highly active antiretroviral therapy (HAART) regimen. Overall, the median change in plasma HIV-1 RNA for the three TMC114/RTV groups at day 14 was $-1.35 \log_{10}$ compared to $+0.02 \log_{10}$ for the control group. No significant difference was observed between the three TMC114/RTV treatment arms. In this study, phenotypic and genotypic resistance data from screening, baseline and end of therapy were analysed.

METHODS: Phenotypic analysis was conducted using the Antivirogram® assay and genotypic analysis using the *VirtualPhenotype*TM. Both determinations were performed on plasma samples taken at screening (within 28 days prior to treatment start), baseline (day 1) and end of therapy (day 15) time-points.

RESULTS: Subjects in this study had a broad range of protease mutations at baseline. The median number of total protease gene mutations was 15 (range 8–26) and the median number of PI resistance-associated mutations was 6 (range 1–11), with a median number of primary PI mutations of 3 (range 0–5) (including D30N, M46I/L, G48V, I50V/L,

V82A/F/T/S, I84V or L90M). More than 80% of subjects had more than one primary PI mutation. All primary PI mutations, except I50L and V82S, were present at baseline in at least one sample. Phenotyping of the baseline samples showed that 46% of the subjects were resistant to all currently approved PIs and only 27% of the subjects were sensitive to two or more PIs (cut-offs as defined by the Antivirogram®). In the treatment arms, the median fold change in EC₅₀ as compared to wild-type for TMC114 was 1.8 (range 0.3 to >21) at baseline and 1.5 (range 0.3–13.1) at end of treatment. There was no correlation between TMC114 susceptibility at baseline and virological outcome at day 14. Many genotypic changes were observed between screening, baseline and end of treatment. No mutation pattern could be associated with virological response to TMC114.

CONCLUSIONS: This study demonstrates the potent antiviral activity of TMC114, a next-generation PI, in multiple PI-experienced patients over 14 days. No mutation patterns influencing the response to treatment with TMC114 could be detected in this study.

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15

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