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CHARACTERIZATION OF TREATMENT-EMERGENT RESISTANCE MUTATIONS IN TWO PHASE II STUDIES OF TIPRANAVIR

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D Hall, S McCallister, D Neubacher, M Kraft and DL Mayers
Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn., USA

BACKGROUND: Tipranavir (TPV) is the first nonpeptidic protease inhibitor (NPPI). Phase II clinical trials have demonstrated a sustained viral load response for up to 80 weeks of treatment in single and multiple protease inhibitor (PI)-experienced patients. Furthermore, these studies have demonstrated that as many as 16 to 20 protease gene mutations may be required for reduced susceptibility to TPV. This analysis investigates treatment-emergent mutations seen in two Phase II trials in treatment-experienced HIV-1-positive adults.

METHODS: In two Phase II, open-label, randomized trials (BI 1182.4 and BI 1182.2), 91 HIV-1-positive adults with single- or multiple-PI failure received various doses of TPV/ritonavir (TPV/r). Fifty single PI-experienced patients received two new nucleoside reverse transcriptase inhibitors (NRTIs) plus either low-dose or high-dose TPV/r twice daily; and 41 multiple PI-experienced, non-NRTI (NNRTI)-naïve patients received low-dose or high-dose TPV/r plus efavirenz (EFV) and one new NRTI. Genotypic testing was performed at baseline and at follow-up.

RESULTS: On-treatment genotypes were available for 24 patients from BI 1182.4 and 39 from BI 1182.2. The mean number of protease gene mutations at study entry was 10 in BI 1182.4 and 12 in BI 1182.2. The most frequent treatment-emergent protease mutations were L33I/F/V, V82L/T and I84V, occurring in 11, 9 and 9 isolates, respectively. Recent studies have shown that >2 universal PI-associated mutations (UPAMs; defined as any mutation at codons 33, 82, 84 or 90) may be required for reduced susceptibility to TPV at clinically relevant doses and reduced antiviral activity; 1 or 2 UPAMs may be sufficient for reduced susceptibility to available PIs. Three of five patients in BI 1182.2 who developed reduced susceptibility to TPV during treatment had 2 UPAMs at baseline, and went on to accumulate a third; one had 3 UPAMs at baseline. Other treatment-emergent mutations at codons associated with protease resistance that occurred in three or more

patients across the two studies include L10I/V (5), K20M/L/T (3), M46I (3), I54V (4) and L63A/D/T (3). Mutations occurring in three or more patients out of a total 63, at codons not generally associated with resistance, were I13V (3), K55R/Q (3), H69Y (3) and T74A (3).

CONCLUSIONS: Analysis of HIV-1 viral isolates from patients enrolled in studies of treatment-experienced patients has identified several mutations that emerged during TPV/r treatment of patients with a mean of approximately 10 baseline protease gene mutations. The most frequent mutations seen in this study at codons 33, 82 and 84 are UPAMs located in the protease active site. The presence of ≥ 2 of these mutations, therefore, appears to require the accumulation of 16–20 other protease mutations, and may have important implications for the fitness of TPV-resistant HIV-1. Few patients in these studies accumulated >2 UPAMs.

PRESENTING AUTHOR: D Hall

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