Insertions at positions 33 and 35 of the HIV-1 protease: prevalence and role in virologic failure in darunavir-treated patients

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Introduction

• The protease inhibitor (PI) darunavir (DRV) (Boehringer Ingelheim) has shown significant broad-spectrum antiretroviral activity against both wild-type and multidrug-resistant HIV-1 isolates; DRV has a high genetic barrier, which limits the development of resistance and allows the prolongation of antiretroviral activity, despite the occurrence of mutations within the target viral protease.

• DRV with low-dose ritonavir (DRV/r) has shown significant efficacy and tolerability in a wide range of adults—frequent treatment-naive to highly treatment-experienced patients.

• Primary and secondary protease mutations, as well as protease cleavage-site mutations, are involved in HIV resistance to PI. More recently, amino acid insertions in the protease have been associated with increased levels of PI resistance. In vitro and structural analyses of amino acid insertions in the vicinity of the binding site also act as mutations at positions 33 (ins33) and 35 (ins35) adopting a novel mechanism of HIV resistance development to PI drugs.

• The role of amino acid ins33 and ins35 of the protease on virologic failure (VF) was investigated in highly PI-experienced patients (POWER and DUET trials) and treatment-naive ARTEMIS trial patients receiving DRV/r plus a background regimen.

• Virologic response was assessed in patient at baseline (HIV-1 RNA <50 copies/mL), at Week 24 (POWER 1–3 and DUET 1–3 and Week 96 ARTEMIS) (time points of virologic response [TLOVR; intent-to-treat analysis]).

• Development of ins33 and ins35 was investigated in samples from 195 from POWER 1–3 and DUET 1–2 and from ARTEMIS.

• ins35 were defined as patients at least reached Week 16 POWER and DUET or Week 1 ARTEMIS and who had at least one HIV-1 RNA ≤50 copies/mL.

• The TLOVR (time to virologic response) was based on the identification of ins35; meaning that data were not imputed as non-responders at timepoints after discontinuation for patients who discontinued for reasons other than (VF).

• A developing insertion was defined as one present at endpoint (i.e. last available virologic measurement within the treatment period), but not based on baseline.

• Virologic failure (VF) was defined as one present at endpoint (i.e. last available virologic measurement within the treatment period), but not based on baseline.

Methods

• These analyses were performed on 1) patients who initiated treatment with DRV/r 600/100 mg bid in POWER 1, 2 and 3, and with patients from the DRV/r 800/100 mg qd in POWER 1, 2 and 3, and with patients from ARTEMIS trial experienced VF, and of whom 31 had paired baseline and endpoint genotypes, and 2) patients from the ARTEMIS trial experienced VF, of whom 31 had paired baseline and endpoint genotypes, and of whom 31 had paired baseline and endpoint genotypes.

• Patients included at the time of the database lock for the Week 96 analysis of the POWER trials and for the primary Week 24 analysis of the DUET trials were included in the first analysis.4 All ARTEMIS patients from the DRV/r treatment arm of the Week 96 analysis were included in the second analysis.

• Genotypes and phenotypic profiles of plasma virus were determined using population-based sequencing and Antivirogram®, respectively (Viroche, Mechelen, Belgium).

• DRV resistance-associated mutations (RAMs) (V118I, V32I, L100I/F, V108M, I54V, I54M, L16V) were based on the IAS-USA guidelines (December 2008).5

• Phenotypic resistance to PI was defined as having a fold-change in 50% effective concentration (EC50) above the clinical cutoff (Antivirogram®). A clinical cut-off of 10 was used for both DRV and LPV/r; a clinical cut-off of 3 was used for atazanavir (ATV) (Antivirogram®); fold-change in IC50 for darunavir (DRV) (I54M), indinavir (IDV), nelfinavir (NFV), and ritonavir (RTV) were used.6

• The prevalence of ins33 and ins35 was investigated in baseline samples. Baseline genotypic data were available for 1645 patients from POWER 1–3 and DUET 1–2 trials, and for 342 patients from the ARTEMIS trial.