The emergence of resistance to highly active antiretroviral therapy (HAART) presents a significant challenge to managing HIV-1 infection. Darunavir (DRV; TMC114) is a protease inhibitor (PI) that exhibits significant in-vitro activity against both wild-type and drug-resistant HIV isolates, including multi-drug resistant strains. DRV possesses a high genetic barrier to resistance development, defined as the drug’s ability to delay resistance development and to retain antiretroviral activity despite the occurrence of mutations within the viral target protein.

In the POWER 2 trial and 2 studies (TMC14-213 and C202), significant virological and immunological improvements were seen in treatment-experienced patients using DRV with low-dose ritonavir (RTV; DRV/RTV), compared with currently available PIs. Similar efficacy was confirmed in a larger patient population in the non-comparative POWER 3 (TMC14-215/C203/208) analysis. DRV at a dose of 600/100 mg bid has been approved in the USA and other countries including those in Europe for the treatment of HIV-1 infection in treatment-experienced adults.

TITAN (TMC14-214; TMC144) is a Treatment-experienced patients (Naïve to lopinavir) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV in a broad range of treatment experience commonly encountered in the clinical setting. Primary 48-week data are presented at this congress. This analysis examined the influence of baseline and on-treatment resistance-associated mutations (RAMs) on the antiviral activity of DRV and lopinavir with low RTV (LPV/RTV) in the TITAN trial.

### Results

#### Baseline data

- 95% patients randomised and treated; 31% were PI naïve. Eighty-two percent of per cent of baseline isolates were susceptible to ≥4 PIs.
- Overall baseline characteristics were balanced between both arms.

#### Virological characteristics

- The frequency of DRV RAMs was low
  - 81% of patients’ baseline isolates had no DRV RAMs
  - 4% of patients’ baseline isolates had ≥3 DRV RAMs

#### Efficacy analysis results

- Overall efficacy results in the TITAN trial at 48 weeks showed that DRV was non-inferior to LPV as determined by the primary endpoint (VL < 400 copies/mL). Results of a secondary analysis showed that DRV was superior to LPV at this timepoint.
- Higher response rates were observed at 48 weeks in the DRV arm compared with the LPV arm regardless of the number of DRV RAMs at baseline (Figure 2) – a diminished response to DRV was observed in patients with ≥3 DRV RAMs at baseline; this subgroup had a median number of 13 IAS-USA PI RAMs.
- The virological response to LPV was already reduced (response <75% of the overall response) in patients with two DRV RAMs at baseline.

#### Development of resistance in VF

- VF was observed in 31% (102 patients) in the DRV arm and 65% (229 patients) in the LPV arm (the numbers of VF in the appropriate representative at Week 48) – after excluding patients with LPV FC ≥10, the VF rate in the LPV arm (19%) was still twice that of the DRV arm (10%).

#### Conclusion

- Properly fewer patients with VF on DRV than on LPV developed primary PI mutations or NRTI RAMs. In addition, fewer patients with VF developed DRV or LPV RAMs on the DRV arm compared with those in the LPV arm – after excluding patients with LPV FC >10, the proportion of patients with VF developing primary PI mutations or NRTI RAMs was still higher in the LPV arm compared with the DRV arm (35% vs 4%, and 22% vs 13%, respectively).

### References


### Figure 1. Study flow of the TITAN trial.

### Figure 2. Virological response by baseline DRV RAMs (TLOVR non-VF censored).

- (A) VL <400 copies/mL, (B) VL <50 copies/mL.

### Figure 3. Virological response by baseline LPV RAMs (TLOVR non-VF censored).

- (A) VL <400 copies/mL, (B) VL <50 copies/mL.

### Figure 4. Development of primary PI mutations and NRTI RAMs in patients with VF at endpoint.

- The V32I mutation developed in >10% of patients with VF (226, 116%) on DRV treatment.
- Fewer patients with VF on DRV than on LPV lost susceptibility compared with baseline to the PI or an NRTI used in the treatment regimen (Figure 5).

### Figure 5. Loss of susceptibility in patients with VF at endpoint.

- In the treatment-experienced, LPV-naïve TITAN patient population, higher response rates were observed at 48 weeks in the DRV arm compared with the LPV arm, regardless of the number of DRV or LPV RAMs at baseline.
- The number of baseline DRV RAMs was low in this population.

- Virological response to DRV was correlated with the number of DRV RAMs at baseline, confirming the results of the POWER trial analysis.
- The highest virological response (VL <40 or <400 copies/mL) were seen in patients with <1 DRV RAMs.
- DRV-treated patients experienced less VF and developed less resistance upon VF than LPV-treated patients.
- Compared with LPV, fewer primary PI mutations and NRTI RAMs; and lower rates of loss of susceptibility to the PI or NRTIs in the treatment regimen occurred following VF with DRV’s PI-based therapy as compared with the former PI-based treatment options and protected the antiretroviral treatment “backbone” in TITAN more effectively than LPV.
- Findings from this analysis confirmed the high genetic barrier to resistance of DRV, and suggested its ability to preserve future therapeutic options against HIV-1.