Comparison of 48-week efficacy and safety of darunavir/ritonavir (DRV/r) with lopinavir/ritonavir (LPV/r) in LPV/r-naïve, treatment-experienced, patients: a randomised, controlled Phase III trial (TITAN)


TITAN = TMC114/r In Treatment-experienced pAtients Naïve to lopinavir
TITAN (TMC114-C214): Study Design

- Phase III randomised, controlled trial with primary analysis at Week 48

**Screening phase (4 weeks)**
- Treatment-experienced, LPV-naïve
- VL ≥1,000 copies/mL
- Stable HAART (≥12 wks) or STI (≥ 4 wks)

**Treatment phase (96 weeks)**
- DRV/r 600/100mg bid + OBR
- LPV/r* 400/100mg bid + OBR

785 screened, 595 patients randomised and treated

- All patients received optimised background therapy
  - at least two or three ARVs from approved NRTI and/or NNRTI classes; enfuvirtide disallowed

*LPV/r patients were allowed to switch to new formulation upon its approval by the regulatory authorities; VL = viral load; DRV/r = darunavir with low-dose ritonavir, LPV/r = lopinavir with low-dose ritonavir
TITAN: study objectives

• **Primary objective**
  – demonstrate non-inferiority in confirmed VL <400 copies/mL with DRV/r vs LPV/r at Week 48

• **Secondary objectives**
  – test for superiority of DRV/r over LPV/r in the event that the primary objective was achieved
  – evaluate other virological and immunological parameters
    • VL <50 copies/mL
    • change in CD4 cell count
  – evaluate efficacy, safety and tolerability over 96 weeks

TLOVR = time to loss of virological response; CI = confidence interval
# TITAN: baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>DRV/r* (n=298)</th>
<th>LPV/r (n=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>229 (77)</td>
<td>241 (81)</td>
</tr>
<tr>
<td>Mean (±SD) age (years)</td>
<td>41 ± 9.0</td>
<td>41 ± 8.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) baseline log_{10} VL</td>
<td>4.33 ± 0.79</td>
<td>4.28 ± 0.81</td>
</tr>
<tr>
<td>Median CD4 (cells/mm³ [range])</td>
<td>235 (3–831)</td>
<td>230 (2–1,096)</td>
</tr>
<tr>
<td>CDC class C, n (%)</td>
<td>101 (34)</td>
<td>94 (32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of ARV treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Structured treatment interruption, n (%)</td>
<td>64 (22)</td>
<td>71 (24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous ARV experience, n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs: ≥4</td>
<td>156 (52)</td>
<td>151 (51)</td>
</tr>
<tr>
<td>NNRTIs: ≥1</td>
<td>225 (76)</td>
<td>229 (77)</td>
</tr>
<tr>
<td>PIs: 0</td>
<td>94 (32)</td>
<td>93 (31)</td>
</tr>
<tr>
<td>PIs: 1</td>
<td>108 (36)</td>
<td>115 (39)</td>
</tr>
<tr>
<td>PIs: ≥2</td>
<td>96 (32)</td>
<td>89 (30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Optimised background therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sensitive† NRTIs used, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (10)</td>
<td>42 (15)</td>
</tr>
<tr>
<td>1</td>
<td>70 (24)</td>
<td>75 (26)</td>
</tr>
<tr>
<td>≥2</td>
<td>188 (65)</td>
<td>171 (59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Geometric median FC (range)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV</td>
<td>0.6 (0–37)</td>
<td>0.6 (0–44)</td>
</tr>
<tr>
<td>LPV</td>
<td>0.7 (0–74)</td>
<td>0.8 (0–74)</td>
</tr>
</tbody>
</table>

*DRV/r 600/100mg bid; †Phenotypes determined by Antivirogram®; FC = fold change in EC_{50}
TITAN: study completion/withdrawal

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>DRV/r*</th>
<th>LPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised – not treated</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Randomised – treated</td>
<td>298</td>
<td>297</td>
</tr>
<tr>
<td>Discontinued – treated</td>
<td>62 (20.8%)</td>
<td>86 (29.0%)</td>
</tr>
<tr>
<td>AE/HIV-related event</td>
<td>20 (6.7%)</td>
<td>21 (7.1%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>10 (3.4%)</td>
<td>10 (3.4%)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>9 (3.0%)</td>
<td>10 (3.4%)</td>
</tr>
<tr>
<td>Virological failure</td>
<td>4 (1.3%)</td>
<td>34 (11.4%)</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>11 (3.7%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.7%)</td>
<td>7 (2.4%)</td>
</tr>
</tbody>
</table>

Time to discontinuation for any reason (Kaplan-Meier curve)
TITAN: viral load <400 copies/mL to Week 48 (TLOVR)

Primary endpoint

Estimated‡ LSM difference in response vs LPV/r for:
ITT: 77–67 = 10% (95% CI 2;17)
PP: 77–68 = 9% (95% CI 2;16)

ITT

LSM= least square mean; *DRV/r 600/100mg bid, n=286 for PP; †n=293 for PP; ‡Estimated from a logistic regression model including treatment and stratification factors: baseline log_{10} VL and use of NNRTIs in the optimised background regimen

P=0.008
TITAN: difference (DRV/r–LPV/r) in viral load <400 copies/mL to Week 48 (TLOVR)

Estimated† LSM difference in response vs LPV/r for superiority (ITT) = 10% (95% CI 2;17); p=0.008

Estimated† LSM difference in response vs LPV/r for non-inferiority (PP) = 9% (95% CI 2;16); p<0.001

†Estimated from a logistic regression model including treatment and stratification factors: baseline log_{10} VL and use of NNRTIs in the optimised background regimen
TITAN: viral load <50 copies/mL to Week 48 (TLOVR) – all patients

Estimated† LSM difference in response vs LPV/r = 11% (95% CI 3;19); p = 0.005

*DRV/r 600/100mg bid; †Estimated from a logistic regression model including treatment and stratification factors: baseline log₁₀ VL and use of NNRTIs in the optimised background regimen
TITAN: viral load <50 copies/mL at Week 48 by baseline LPV FC (TLOVR)

<table>
<thead>
<tr>
<th>Patient population</th>
<th>DRV/r*</th>
<th>LPV/r</th>
<th>DRV/r–LPV/r</th>
<th>95% CI</th>
<th>Non-inferiority p value †</th>
<th>Superiority p value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=595)</td>
<td>71</td>
<td>60</td>
<td>11</td>
<td>3 – 19</td>
<td>&lt;0.0001</td>
<td>0.005</td>
</tr>
<tr>
<td>LPV FC ≤40 (n=569)</td>
<td>70</td>
<td>60</td>
<td>10</td>
<td>2 – 18</td>
<td>&lt;0.0001</td>
<td>0.013</td>
</tr>
<tr>
<td>LPV FC ≤10 (n=524)</td>
<td>70</td>
<td>63</td>
<td>7</td>
<td>-1 – 16</td>
<td>&lt;0.0001</td>
<td>0.068</td>
</tr>
</tbody>
</table>

*DRV/r 600/100mg bid †Estimated from a logistic regression model including treatment and stratification factors: baseline log_{10} HIV-RNA and use of NNRTIs in the optimised background regimen
TITAN: median change in absolute CD4 cell count to Week 48 (NC=F)

- TITAN: median change in absolute CD4 cell count from baseline (cells/mm$^3$)
- ITT

**LPV/r (n=297)**
- 81 cells/mm$^3$

**DRV/r* (n=298)**
- 88 cells/mm$^3$

*DRV/r 600/100mg bid

*P value for difference = 0.33*
TITAN: virological failure rates (ITT-TLOVR)

- Patients with virological failure (VF; >400 copies/mL) consisted of non-responders (■) and rebounders (■)

![Graph showing virological failure rates for All patients and Patients with LPV FC ≤10]
TITAN: development of primary PI mutations and NRTI RAMs upon treatment failure

All VFs

VF with developing mutations (%)

- Primary PI mutations
  - DRV/r (n=28) 21%
  - LPV/r (n=56) 36%
- NRTI RAMs
  - DRV/r (n=28) 14%
  - LPV/r (n=56) 27%

VF with developing mutations (%) for VFs with LPV FC ≤10

- Primary PI mutations
  - DRV/r (n=23) 4%
  - LPV/r (n=43) 33%
- NRTI RAMs
  - DRV/r (n=23) 13%
  - LPV/r (n=43) 23%

For more details – please see poster WEPEB038
de Bethune et al.

*Johnson et al. Top HIV Med 2006; 14:125–130
TITAN: most common AEs

Diarrhoea
- DRV/r (n=298): 31.9% (23, 7.7%)
- LPV/r (n=297): 41.8% (43, 14.5%)

Nausea
- DRV/r (n=298): 18.5% (12, 4.0%)
- LPV/r (n=297): 20.9% (13, 4.4%)

Rash (all types)
- DRV/r (n=298): 16.1% (9, 3.0%)
- LPV/r (n=297): 6.7% (3, 1.0%)

Nasopharyngitis
- DRV/r (n=298): 12.4% (11.1%)
- LPV/r (n=297): 11.1% (7.4%)

Headache
- DRV/r (n=298): 11.1% (7.4%)
- LPV/r (n=297): 10.1% (7.4%)

Upper respiratory tract infection
- DRV/r (n=298): 10.1% (7.4%)
- LPV/r (n=297): 7.4%

Grade 2–4 possibly related AEs* with ≥2% incidence, n (%)

<table>
<thead>
<tr>
<th></th>
<th>DRV/r (n=298)</th>
<th>LPV/r (n=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>23 (7.7)</td>
<td>43 (14.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (4.0)</td>
<td>13 (4.4)</td>
</tr>
<tr>
<td>Rash (all types)</td>
<td>9 (3.0)</td>
<td>3 (1.0)</td>
</tr>
</tbody>
</table>

*excluding laboratory abnormalities reported as AEs
# TITAN: grade 2–4 laboratory abnormalities (≥2% incidence)

<table>
<thead>
<tr>
<th>Grade 2–4 laboratory abnormalities†</th>
<th>DRV/r* (n=298)</th>
<th>LPV/r (n=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>94 (31.5)</td>
<td>86 (29.0)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>57 (19.1)</td>
<td>75 (25.3)</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>56 (18.8)</td>
<td>50 (16.8)</td>
</tr>
<tr>
<td>Pancreatic amylase</td>
<td>33 (11.1)</td>
<td>26 (8.8)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>26 (8.7)</td>
<td>28 (9.4)</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>26 (8.7)</td>
<td>26 (8.8)</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>20 (6.7)</td>
<td>26 (8.8)</td>
</tr>
<tr>
<td>Pancreatic lipase</td>
<td>14 (4.7)</td>
<td>11 (3.7)</td>
</tr>
</tbody>
</table>

*DRV/r 600/100mg bid; †By decreasing darunavir/r frequency
TITAN: conclusions

In this treatment-experienced, LPV-naïve population:

• DRV/r was not only non-inferior, but virologically superior to LPV/r

• DRV/r was safe and well tolerated

• DRV/r provided better protection of the NRTI and the PI classes upon failure versus LPV/r
TITAN: acknowledgments

- The patients and their families for their participation and support during the study
- TMC114-C214 study team and the investigators and co-investigators
  - **Argentina**: Pedro Cahn, Arnaldo Casiró, Isabel Cassetti, Daniel David, Marcelo Losso and Sergio Lupo
  - **Australia**: David Cooper, Robert Finlayson, Jenny Hoy, Patricia Martinez, Marilyn McMurchie and Cassy Workman;
  - **Austria**: Armin Rieger and Norbert Vetter
  - **Belgium**: Nathan Clumeck, Jean-Christophe Goffard and Lutgarde Lynen
  - **Brazil**: Clovis Da Cunha, Beatriz Grinsztejn, Claudio Gonzale, Jose Valdez-Madruge, Rogerio de Jesus Pedro, Jose Henrique Pilotto,
    Mauro Schechter and Artur Timerman
  - **Canada**: John Gill, Norbert Gilmore, Don Kilby, Patrice Junod, Anita Rachlis, Benoit Trottier, Chris Tsoukas and Sharon Walmsley
  - **Chile**: Juan Ballesteros, Rebeca Northland and Carlos Pérez
  - **Denmark**: Henrik Nielsen
  - **France**: Jacques Durant, Pierre-Marie Girard, Christine Katlama, Christian Michelet, Jean-Michel Molina, Gilles Pialoux, Christophe Piketty, Dominique
    Salmon, Daniel Vittecoq and Patrick Yeni
  - **Germany**: Keikawus Arasteh, Gerd Fäktkenheuer, Heribert Knechten, Antonius Mutz, Carl Knud Schew, Dieter Schuster, Albrecht Stoehr
    and Andreas Trein
  - **Greece**: George Panos
  - **Guatemala**: Eduardo Arathoon and Carlos Mejia-Villatoro
  - **Hungary**: Denes Banhegyi
  - **Italy**: Andrea Antinori, Giampiero Carosi, Roberto Esposito, Adriano Lazzarin, Francesco Mazzotta, Anna Maria Orani, Stefano Rusconi,
    Laura Sighinolfi and Fredy Suter
  - **Malaysia**: Adeeba Kamarulzaman and Christopher Lee
  - **Mexico**: Jaime Andrade
  - **Netherlands**: Kees Brinkman, Bart Rijnders and Herman Sprenger
  - **Panama**: Nestor Sosa
  - **Portugal**: Teresa Branco, António Diniz and Rui Sramento e Castro
  - **Puerto Rico**: Javier Morales Ramirez
  - **Russia**: Oleg Kozyrev, Grigory Moshkovich, Alexander Pronin, Oleg Romanenko, Elena Vinogradova and Alexey Yakovlev
  - **South Africa**: Ezio Baraldi, Francesca Conradie, Gulam Hoosen Latif, Lerato Mhapi, Catherine Orell, Osman Ebrahim and David Spencer
  - **Spain**: Jose Ramon Arribas, Angel Daniel Podzamczer and Maria Perez-Elias
  - **Switzerland**: Milos Opravil
  - **Thailand**: Ploenchon Chetchotisakd, Kiat Ruxrungtham, Wichai Techasathit and Chaiwat Ungsedhapand (key coordinator)
  - **United Kingdom**: Philippa Easterbrook and Anton Pozniak
  - **United States**: Ben Barnett, John Baxter, Paul Benson, Daniel S Berger, Jack Bissett, Cynthia Brinson, Alfred Burnside, Thomas Campbell, Amy Colson,
    Frederick Cruickshank, Edwin DeJesus, Robin Detter, Robert Eng, Charles Farthing, Jeffrey Fessel, Michael Frank, David Hardy, Dushyantha Jayaweera,
    Thomas Jefferson, Harold Katner, Clifford Kinder, Harry Lampiris, Marc LaRiviere, Jason Leider, Steven Marlowe, Cynthia Mayer, David McDonough, Jose
    Montero, Karam Mounzer, Robert Myers, Dorece Norris, Frank Palella, Gerald Pierone, Bruce Rashbaum, Afsone Roberts, Barry Rodwick, Peter Ruane,
    Kunthavi Sathasivam, Stefan Schneider, Shannon Schrader, Anita Scribner, Michael Sension, Peter Shalit, William Short, Stephen Smith, Alan Taege,
    Melanie Thompson, Timothy Wilkin and Bienvenido Yangco.

Supported by Tibotec