# Pharmacokinetic analysis for darunavir in HIV-1 infected patients on the cobicistat-boosted darunavir regimen in an Italian observational, multicenter, prospective study (The TMC114FD1HTX4003 – "ST.O.RE." Study)

P266

Focà Emanuele[1], Antinori Andrea[2], Ripamonti Diego[3], Maserati Renato[4], Rusconi Stefano[5], Rizzardini Giuliano[6], Palma Maria[7], Mancusi Daniela[7], Termini Roberta[7], Uglietti Alessia[7]

[1]University of Brescia and Spedali Civili General Hospital Department of Infectious and Tropical Diseases Brescia Italy; [2]National Institute for Infectious Diseases "Lazzaro Spallanzani" IRCCS HIV/AIDS Department Roma Italy; [3]ASST Papa Giovanni XXIII Division of Infectious Diseases Bergamo Italy; [4]Fondazione Policlinico San Matteo Clinica Malattie Infettive Pavia Italy; [5]DIBIC Luigi Sacco, Università degli Studi di Milano Divisione Malattie Infettive Milano Italy; Policlinico Infectious Diseases Milano Italy; [6]ASST Fatebenefratelli-Sacco 1st Division of Infectious Diseases Milano Italy; [7]Janssen-Cilag SpA Medical Affairs Cologno Monzese Italy

## INTRODUCTION

The "ST.O.RE." study is an Italian observational, single arm, multicenter, prospective study aimed at collecting real life data regarding the effectiveness and safety of an antiretroviral (ARV) regimen based on cobicistat-boosted darunavir (DRV/c) in HIV1-positive patients. A secondary objective of the study was to describe steady-state DRV $C_{trough}$ during observational period.

## STUDY DESIGN

"ST.O.RE." was a prospective, multicenter non-interventional, cohort study carried on HIV-1-infected, adult out-patients, being on stable ritonavir-boosted ARV-treatment with PIs (either darunavir 800mg q.d.-based or other boosted PIs) for at least 12 months and virologically suppressed (HIV-RNA< 50 copies/ml) for at least 6 months. Patients were offered to enter this study once their treating physician had considered they were eligible to be administered DRV/c-based treatment as per DRV/c Summary of Product Characteristics. Twenty-five Infectious Diseases centers throughout Italy enrolled 348 patients. Patients were observed prospectively for 48±6 weeks after starting DRV/c-based regimen.

## OBJECTIVE

The primary objective of this study was to describe the effectiveness of this regimen, defined as virological suppression at 48 weeks, measured as maintenance of HIV-RNA<50 cp/ml as per FDA snapshot algorithm; virological failure (VF) was defined as HIV-RNA≥50 cp/ml. Among secondary objectives, a description of the steady-state DRV $C_{trough}$ once during the observational period was included and it was evaluated only in centers which collected such data as part of routine clinical care.

## MATERIALS AND METHOS

Darunavir $C_{trough}$ values were recorded in the electronic Case Report Form (eCRF) by clinical centers that collect blood samples to perform $C_{trough}$ analysis in their routine practice. All patients included in this analysis were virologically suppressed when switched from a ritonavir boosted-protease inhibitor to the DRV/c based regimen and at the time of sampling. Comparisons between groups were performed using Mann Whitney test.

## RESULTS

Out of 348 patients enrolled, 336 were included as evaluable for primary analysis; 31% of them are females. We collected the DRV $C_{trough}$ values from blood samples of 56 patients and 14 of them have two repeated DRV- $C_{trough}$ sampling. Patients characteristics are shown in Table 1.

**Table 1.** Patients' baseline characteristics

| | Overall (N=56) | Male (N=39) | Female (N=17) |
|---|---|---|---|
| Age-Years-Mean (SD) | 47.6 (9.5) | 47.5 (9.5) | 47.1 (9.4) |
| BMI-Kg/mq-Mean (SD) | 24.2 (6.6) | 24.2 (6.6) | 24.1 (6.3) |
| Race - White-N (%) | 53 (94.6) | 37 (94.9) | 16 (94.1) |
| Ongoing and treated conditions N(%) | 25 (44.6) | 19 (48.7) | 6 (35.9) |
| % of TDF/FTC as backbone therapy | 58.9 | 59 | 58.8 |
| % of ABC/3TC as backbone therapy | 12.5 | 15.4 | 5.9 |
| % dual therapies | 28.6 | 25.6 | 35.3 |

Median (IQR) DRV $C_{trough}$ values were 2863 (2970) overall, 2634 (2322) ng/ml in males and 4221 (2881) ng/ml in females as represented in Figure 1. Female DRV $C_{trough}$ values were statistically higher (p=0.046).
Fourteen patients had two repeated DRV-$C_{trough}$ sampling; their characteristics are reported in Table 2.
Data of repeated $C_{trough}$ are shown in Figure 2. In first sampling all patients were virologically suppressed while in the second sampling, one patient had HIV-RNA value of 81 cp/mL concomitantly with $C_{trough}$ 1148 ng/ml. Among the fourteen patients, six males and three females were taking concomitant medications (vitamin-D, phosphate and antihypertensives). None of the recorded concomitant drugs is known to alter the pharmacokinetics of DRV/c.

## RESULTS - Continued

**Figure 1.** DRV $C_{trough}$ values

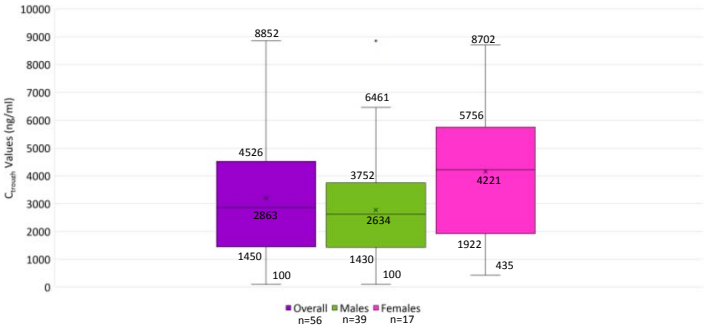
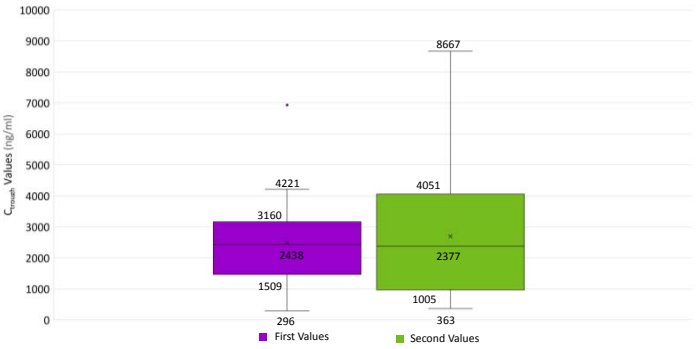



**Table 2.** Patients' characteristics with 2 $C_{trough}$ values

| | Overall (N=14) | Male (N=11) | Female (N=3) |
|---|---|---|---|
| Age-Years-Mean (SD) | 47.3 (8.3) | 46 (9) | 52.0 (2.6) |
| BMI-Kg/mq-Mean (SD) | 23.4 (7.32) | 23.6 (3.5) | 22.7 (6.2) |
| Race - White-N(%) | 14 (100) | 11(100) | 3 (100) |
| CD4 nadir - cell/mm3 - Mean (SD) | 269.2 (231.4) | 254.3 (262.8) | 319 (75.9) |
| CDC category C- N(%) | 4 (28.6) | 4 (36.4) | 0 |
| HCV Positive -N(%) | 4 (27.3%) | 3 (27.3%) | 1 (33.3) |
| Ongoing and treated conditions N(%) | 10 (71.4) | 7 (63.6) | 3 (100) |
| % of TDF/FTC as backbone therapy | 57.2 | 54.5 | 66.6 |
| % of ABC/3TC as backbone therapy | 21.4 | 100 | 0 |
| % dual therapies | 21.4 | 18.2 | 33.3 |

Considering 70 samples (56 single and 14 repeated) no patients had values below the 55 ng/ml, the protein-binding adjusted EC50 for wild-type HIV; six reported values below the threshold of 550 ng/ml, the protein-binding adjusted EC50 for PI-resistant HIV: five males (100, 159, 296, 363 and 494 ng/ml) and one female (435 ng/ml). Of those patients with double samplings only one of the two values was below the threshold of 550 ng/ml. None showed adverse events at the time of samplings.

**Figure 2.** DRV $C_{trough}$ values: repeated sampling




## CONCLUSIONS

In clinical practice we observed a DRV concentration sufficient to be effective in all patients. Cobicistat allowed to obtain $C_{trough}$ values far above the protein-binding adjusted EC50 for wild type HIV virus. The observed intra-and interpatient variability can be due to the observational nature of this study where samplings might not have been collected at the real $C_{trough}$.

THE ST.O.RE. STUDY GROUP
We acknowledge all the patients participating in the study and all the investigators.

Massimo Andreoni-Policlinico Tor Vergata, Roma; Andrea Antinori-INMI L. Spallanzani, Roma; Francesco Castelli-ASST degli Spedali Civili, Brescia; Annamaria Cattelan-AOU Padova, Padova; Roberto Cauda-Fondazione Policlinico A.Gemelli, Roma; Maurizio Celesia-ARNAS Garibaldi, Catania; Lucio Cosco-A.O. Pugliese Ciaccio, Catanzaro; Antonella d'Arminio Monforte-ASST Santi Paolo e Carlo, Milano; Andrea De Luca-A.O.U. Senese, Siena; Giovanni Di Perri-Ospedale Amedeo di Savoia, Torino; Elio Manzillo-P.O. Cotugno, Napoli; Andrea Gori- University of Milan; Adriano Lazzarin-Ospedale San Raffaele, Milano; Giordano Madeddu-A.O.U. Sassari, Sassari; Renato Maserati-Fondazione IRCCS Policlinico San Matteo, Pavia; Maurizio Mineo-A.O.U. Policlinico Giaccone, Palermo; Giancarlo Orofino-Ospedale Amedeo di Savoia, Torino; Giovanni Penco-EO Ospedali Galliera, Genova; Barbara Menzaghi-Ospedale di Circolo, Busto Arsizio; Diego Ripamonti-ASST Papa Giovanni XXIII, Bergamo; Giuliano Rizzardini-Ospedale Luigi Sacco, Milano; Stefano Rusconi-Ospedale Luigi Sacco, Milano; Teresa Antonia Santantonio-A.O.U. Ospedali Riuniti, Foggia; Gaetana Sterrantino-A.O.U. Careggi, Firenze; Vincenzo Vullo-Policlinico Umberto I, Roma.

«STORE» study was funded by Janssen-Cilag SpA, Italy