Doravirine exposure and HIV-1 suppression after switching from an efavirenz-based regimen to doravirine/lamivudine/tenofovir disoproxil fumarate

Wayne Greaves*#, Hong Wanb, Ka Lai Yee*, Bhargava Kandala*, Pavan Vaddady*, Carey Hwang*

*Global Clinical Development Infectious Diseases, Merck & Co., Inc., Kenilworth NJ, USA
bBiostatistics and Research Decision Sciences, Merck & Co., Inc., Kenilworth NJ, USA
cPharmacokinetics, Pharmacodynamics and Drug Metabolism, Merck & Co., Inc., Kenilworth NJ, USA

Running title: Doravirine PK and efficacy after switch from efavirenz

#Corresponding Author: Wayne Greaves, MD; 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA; wayne.greaves@merck.com; 1-732-594-3736.

Word count: 1029.

Keywords: doravirine; efavirenz; pharmacokinetics; efficacy; HIV-1
Doravirine is a non-nucleoside reverse transcriptase inhibitor approved for the treatment of HIV-1. In a phase 1 trial, doravirine exposure was transiently decreased when treatment was started immediately after stopping efavirenz. In a post-hoc subgroup analysis of participants who switched from an efavirenz-based regimen to doravirine/lamivudine/tenofovir disoproxil fumarate in the phase 3 DRIVE-SHIFT trial, doravirine plasma levels at week 4 were similar to non-induced levels, and HIV-1 suppression was maintained at weeks 24 and 48.
Doravirine is a novel, non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1 at a dosage of 100 mg once daily. Doravirine 100 mg is available as a single-entity tablet(1) and a fixed-dose combination tablet with lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF)(2). The efficacy and safety of doravirine in treatment-naïve adults with HIV-1 were demonstrated in two phase 3 clinical trials, DRIVE-FORWARD(3) and DRIVE-AHEAD(4). More recently, maintenance of HIV-1 suppression was demonstrated in adults who switched from a stable antiretroviral regimen to DOR/3TC/TDF in another phase 3 clinical trial, DRIVE-SHIFT(5).

Doravirine may be an effective alternative for patients who do not tolerate efavirenz, a commonly used NNRTI included in many HIV-1 treatment regimens. The predominant route of elimination for doravirine is oxidative metabolism mediated primarily by cytochrome P450 3A4 (CYP3A4)(6). Because efavirenz is a moderate inducer of CYP3A, a drug-drug interaction study was previously conducted in healthy adults to assess the pharmacokinetics of both drugs following a switch from efavirenz to doravirine (7). In that study, plasma concentrations of doravirine on day 1 and day 14 after switching from efavirenz were lower than those determined in the absence of prior efavirenz treatment.

The doravirine trough concentration reached the in vitro-based target for inhibition of wild-type HIV-1 (78 nM) on day 2 after efavirenz cessation, while efavirenz was present at therapeutic concentrations (>1,000 ng/mL) until day 4. To understand the clinical relevance of this interaction, we conducted post hoc analyses of doravirine plasma levels and the maintenance of viral suppression in participants who switched from an efavirenz-based regimen to DOR/3TC/TDF in the DRIVE-SHIFT clinical trial.

**Study Design and Participants.** DRIVE-SHIFT was an open-label, active-controlled, non-inferiority trial in adults with HIV-1 who were virologically suppressed for at least 6 months on two nucleoside reverse transcriptase inhibitors (NRTIs) plus a boosted protease inhibitor (PI), boosted elvitegravir, or an NNRTI(5). The protocol was approved by the independent ethics committee for each study site, and all participants provided written informed consent before any study procedures were performed. Participants were randomly assigned in a 2:1 ratio to switch to once-daily DOR/3TC/TDF on day 1 (Immediate
Switch Group, ISG) or to continue their current therapy and switch to DOR/3TC/TDF at week 24 (Delayed Switch Group, DSG). Of the 670 participants who entered the trial, 114 (17%) were receiving an efavirenz-based regimen, and 556 (83%) were receiving two NRTIs with a boosted PI, boosted elvitegravir, nevirapine, or rilpivirine. Baseline characteristics of these two groups were generally similar (Table 1).

**Pharmacokinetics.** Doravirine plasma concentrations were measured in the 447 participants who switched to DOR/3TC/TDF on day 1; the previous antiretroviral regimen included efavirenz in 78 of these participants. Plasma samples for determination of doravirine concentrations were collected before dosing at weeks 4, 24, and 48. Doravirine plasma concentrations were determined by Q2Solutions (Morrisville, NC) using reverse-phase ultraperformance liquid chromatography with tandem mass spectrometric detection (lower limit of quantification 1.00 ng/mL).(8)

Plasma concentrations at week 4 were stratified by the pre-trial regimen (efavirenz-based versus other) and summarized by nominal sample time (Figure 1). At week 4, pre-dose plasma concentrations of doravirine in participants who switched from an efavirenz-based regimen were consistent with those in participants who switched from another baseline regimen. Since the actual sampling times varied depending on when the participant arrived at the study site, doravirine concentrations at week 4 were also plotted against the actual times since the last dose (Figure 2). The concentration profiles were similar between the two groups, supporting the comparison based on nominal time.

**Clinical Efficacy.** The primary efficacy endpoint in DRIVE-SHIFT was the proportion of participants with HIV-1 RNA <50 copies/mL at the primary timepoints of week 48 for the ISG versus week 24 for the DSG, and at the secondary timepoint of week 24 for both groups. The proportion of participants with HIV-1 RNA ≥50 copies/mL was a secondary endpoint and was also assessed at the primary and secondary timepoints. The efficacy analyses used the FDA Snapshot approach, which counts all missing
data as failures regardless of the reason. The difference between treatment groups and the associated 95% confidence interval (CI) were calculated using the stratum-adjusted Mantel-Haenszel method.

The antiretroviral efficacy of DOR/3TC/TDF was similar for ISG participants who switched from an efavirenz-based regimen and those who switched from another baseline regimen (Table 2). At weeks 24 and 48, respectively, HIV-1 RNA <50 copies/mL was achieved in 97.4% and 93.6% of the ISG participants who switched from an efavirenz-based regimen, compared with 93.0% and 90.2% of those who switched from another baseline regimen. On the secondary endpoint, the proportion of participants with HIV-1 RNA ≥50 copies/mL at weeks 24 and 48, respectively, was 1.3% and 0.0% of the ISG participants who switched from efavirenz, compared with 1.9% and 1.9% of those who switched from another baseline regimen. Only one ISG participant who switched from efavirenz had HIV-1 RNA ≥50 copies/mL at week 24, with a reported value of 51 copies/mL; this participant had HIV-1 RNA <50 copies/mL at all other timepoints in the study, including week 48. Only one participant with HIV-1 RNA ≥50 copies/mL had sufficient virus for resistance testing. This participant had switched from a non-efavirenz-based regimen and was discontinued from the study at week 36 due to lack of efficacy. No DOR resistance mutations were identified in this participant.

These post hoc analyses of data from the phase 3 DRIVE-SHIFT trial show that plasma levels of doravirine after 4 weeks of treatment with DOR/3TC/TDF were not different between participants who switched from an efavirenz-based regimen and those who switched from a protease inhibitor, elvitegravir, or another NNRTI-based regimen. Because doravirine plasma concentrations were not measured until 4 weeks after initiation of therapy, our analyses do not address whether doravirine exposure was reduced in the immediate period after switching from efavirenz, as was observed in the phase 1 drug interaction study (6). Our analyses also show that the antiretroviral efficacy of doravirine at week 24 and week 48 was similar between participants who switched from an efavirenz-based regimen and those who switched from another baseline regimen. Thus, the antiretroviral efficacy of doravirine was not adversely affected by prior treatment with efavirenz.
ACKNOWLEDGEMENTS

We thank all the patients who participated in the DRIVE-SHIFT trial, along with the investigators and their staff. Medical writing and editorial assistance were provided by Kim M. Strohmaier and Carol Zecca, employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Funding statement: This work was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, which provided financial support and investigational drug supplies for the trial.

Conflict of interest disclosure: The authors are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock in Merck & Co., Inc., Kenilworth, NJ, USA.
FIGURE LEGENDS

Figure 1. Doravirine Plasma Concentrations Collected at Study Week 4 (Pre-Dose Sample) by Baseline Regimen (Efavirenz vs Other) in the Immediate Switch Group. Boxplot overlaid with observed data as points. Boxes denote 25th, 50th, and 75th percentiles and the whiskers denote 1.5* inter-quartile range of distribution of pre-dose samples.

Figure 2. Individual Plasma Concentrations of Doravirine vs. Actual Time Since Last Dose at Study Week 4 in the Immediate Switch Group.
REFERENCES

1. Merck Sharp & Dohme Corp. 2018. PIFELTRO Prescribing Information, Whitehouse Station, NJ, USA.

2. Merck Sharp & Dohme Corp. 2018. DELSTRIGO Prescribing Information, Whitehouse Station, NJ, USA.

3. Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, Lai MT, Xu X, Rodgers A, Lupinacci L, Kumar S, Sklar P, Nguyen BY, Hanna GJ, Hwang C, Group D-FS. 2018. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 5:e211-e220.

4. Orkin C, Squires KE, Molina JM, Sax PE, Wong WW, Sussmann O, Kaplan R, Lupinacci L, Rodgers A, Xu X, Lin G, Kumar S, Sklar P, Nguyen BY, Hanna GJ, Hwang C, Martin EA, Group D-AS. 2018. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis doi:10.1093/cid/ciy540.

5. Johnson M, Kumar P, Molina JM, Rizzardini G, Cahn P, Bickel M, Mallolas J, Zhou Y, Morais C, Kumar S, Sklar P, Hanna GJ, Hwang C, Greaves W, Group D-SS. 2019. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr doi:10.1097/QAI.0000000000002056.

6. Sanchez RI, Fillgrove KL, Yee KL, Li Q, Lu B, Tatavarti A, Liu R, Anderson MS, Behm MO, Fan L, Li Y, Butterton JR, Iwamoto M, Khalilieh SG. 2019. Characterisation of the absorption, distribution, metabolism, excretion and mass balance of doravirine, a non-nucleoside reverse transcriptase inhibitor in humans. Xenobiotica 49:422-432.

7. Yee KL, Sanchez RI, Auger P, Liu R, Fan L, Triantafyllou I, Lai MT, Di Spirito M, Iwamoto M, Khalilieh SG. 2017. Evaluation of Doravirine Pharmacokinetics When Switching from Efavirenz to Doravirine in Healthy Subjects. Antimicrob Agents Chemother 61.

8. Khalilieh S, Yee KL, Sanchez RI, Vaynshteyn K, Fan L, Searle S, Boughjib M, Iwamoto M. 2019. Evaluation of the Pharmacokinetic Interaction Between Doravirine and Methadone. Clin Pharmacol Drug Dev doi:10.1002/cpdd.699.
Table 1. Baseline Demographics and Clinical Characteristics

|                                | Previous EFV Regimen (N = 114) | Other Previous Regimen (N = 556) |
|--------------------------------|---------------------------------|----------------------------------|
| Age (years), Median (range)    | 46 (24, 71)                     | 42 (21, 71)                      |
| Male, n (%)                    | 98 (86.0)                       | 468 (84.2)                       |
| Race/ethnicity, n (%)          |                                 |                                  |
| White                          | 78 (68.4)                       | 434 (78.1)                       |
| Black or African American      | 18 (15.8)                       | 72 (12.9)                        |
| Asian                          | 7 (6.1)                         | 18 (3.2)                         |
| Multiracial                    | 6 (5.3)                         | 29 (5.2)                         |
| Other race²                    | 5 (4.4)                         | 3 (0.5)                          |
| Hispanic or Latino ethnicity   | 34 (29.8)                       | 110 (19.8)                       |
| Region, n (%)                  |                                 |                                  |
| Asia/Pacific                   | 13 (11.4)                       | 18 (3.2)                         |
| Europe                         | 52 (45.6)                       | 353 (63.5)                       |
| Latin America                  | 18 (15.8)                       | 55 (9.9)                         |
| North America                  | 31 (27.2)                       | 130 (23.4)                       |
| CD4+ T-Cell Count              |                                 |                                  |
| Median (range), cells/mm³      | 633 (184, 1711)                 | 626.5 (82, 1928)                 |
| < 200 cells/mm³, n (%)         | 1 (0.9)                         | 16 (2.9)                         |
| ≥ 200 cells/mm³, n (%)         | 112 (98.2)                      | 530 (95.3)                       |
| Duration of prior regimen      |                                 |                                  |
| Median (range), months         | 65.1 (7.0, 264.9)               | 46.9 (6.9, 217.6)                |
| ≥ 12 months, n (%)             | 107 (93.9)                      | 525 (94.4)                       |
| History of AIDS, n (%)         | 20 (17.5)                       | 95 (17.1)                        |
| Hepatitis B and/or C positive, n (%) | 3 (2.6) | 20 (3.6) |

¹ Other previous regimen includes two NRTIs with nevirapine, rilpivirine, boosted elvitegravir, or a boosted protease inhibitor (atazanavir, darunavir, or lopinavir).

² Other race includes American Indian and Alaska Native.
|                          | Immediate Switch Group | Delayed Switch Group | Difference |
|--------------------------|------------------------|----------------------|------------|
|                          | n/N                    | % (95% CI)           | n/N        | % (95% CI) | % (95% CI) |
| HIV-1 RNA <50 copies/mL  |                        |                      |            |            |            |
| Week 24                  |                        |                      |            |            |            |
| EFV                      | 76/78                  | 97.4 (91.0, 99.7)    | 36/36      | 100 (90.3, 100) | -2.6 (-8.0, 2.9) |
| Non-EFV                  | 343/369                | 93.0 (89.8, 95.3)    | 175/187    | 93.6 (89.1, 96.6) | -0.8 (-5.4, 3.8) |
| ISG Week 48 vs DSG Week 24 |                       |                      |            |            |            |
| EFV                      | 73/78                  | 93.6 (85.7, 97.9)    | 36/36      | 100 (90.3, 100) | -6.4 (-13.3, 0.4) |
| Non-EFV                  | 333/369                | 90.2 (86.7, 93.1)    | 175/187    | 93.6 (89.1, 96.6) | -3.3 (-8.1, 1.5) |
| HIV-1 RNA ≥50 copies/mL† |                        |                      |            |            |            |
| Week 24                  |                        |                      |            |            |            |
| EFV                      | 1/78                   | 1.3 (0.0, 6.9)       | 0/36       | 0.0 (0.0, 9.7) | 1.3 (-3.6, 6.2) |
| Non-EFV                  | 7/369                  | 1.9 (0.8, 3.9)       | 4/187      | 2.1 (0.6, 5.4) | -0.1 (-3.0, 2.7) |
| ISG Week 48 vs DSG Week 24 |                       |                      |            |            |            |
| EFV                      | 0/78                   | 0.0 (0.0, 4.6)       | 0/36       | 0.0 (0.0, 9.7) | 0.0 (-4.2, 4.2) |
| Non-EFV                  | 7/369                  | 1.9 (0.8, 3.9)       | 4/187      | 2.1 (0.6, 5.4) | -0.2 (-3.1, 2.6) |

† Includes participants who changed (a) any component of background therapy to a new drug class, or (b) background components that were not permitted per protocol, or (c) any background drug in the regimen because of lack of efficacy (perceived or documented) before Study Week 24; and participants who discontinued study drug or study before Study Week 48 for lack or loss of efficacy; and participants with HIV-1 RNA ≥50 copies/mL in the time window.
