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Population Pharmacokinetic and Pharmacodynamic Analysis to Evaluate a Switch to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate in People Living with HIV-1

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Target journal: Antimicrob Agents Chemother

Short/running title: Population PK/PD analysis for DOR/3TC/TDF switch (48/54 characters [inc. spaces])

Word count: 1195

Number of figures/tables: 2 figures, 1 table; 2 supplementary figures, 1 supplementary table

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ABSTRACT (72/75 words)

Doravirine is a non-nucleoside reverse transcriptase inhibitor for treatment of human immunodeficiency virus (HIV)-1 infection. A population pharmacokinetic (PK) model for treatment-naïve participants in doravirine clinical studies was updated with data from switch participants in the DRIVE-SHIFT trial, and used to estimate individual post-hoc PK parameter values and evaluate the efficacy exposure–response relationship. The results support the 100 mg dose for people living with HIV switching to a doravirine-based regimen (NCT02397096).
People living with HIV require lifelong antiretroviral (ARV) treatment, and may switch between several ARV regimens due to poor adherence or adverse events (1, 2). Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) available as single entity (3), and as a fixed-dose combination with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). DOR/3TC/TDF is approved for the treatment of HIV-1 infection in adults who have not received prior ARV treatment, or who are virologically suppressed on a stable ARV regimen that can be appropriately replaced by DOR/3TC/TDF (4). DOR is generally well tolerated in humans with no relevant drug-related adverse events (5-8).

DRIVE-SHIFT (7) (Protocol MK-1439A-024; NCT02397096), a Phase 3, open-label, randomized, active-controlled, noninferiority trial in virologically suppressed participants with HIV-1, evaluated switch from a stable regimen of two NRTIs plus a ritonavir- or cobicistat-boosted protease inhibitor, cobicistat-boosted elvitegravir or NNRTI to DOR/3TC/TDF. Participants were randomized (2:1) to switch to DOR/3TC/TDF on Day 1 (immediate switch group [ISG]), or to continue their baseline regimen until Week 24 and then switch to DOR/3TC/TDF (delayed switch group [DSG]).

The primary endpoint in DRIVE-SHIFT was the proportion of participants with HIV-1 RNA <50 copies/mL (US Food and Drug Administration [FDA] snapshot approach), with the primary comparison between ISG at Week 48 and DSG at Week 24. The main objective of the current analysis was to evaluate the consistency of DOR pharmacokinetics (PK) in the ISG population with that of the treatment-naive population described previously (9), and evaluate the
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exposure–response relationship between different quantiles of DOR exposure and the primary endpoint in ISG participants to further inform on the efficacy and appropriateness of switch to a DOR-based regimen.

670 participants on stable ARV regimens were recruited to the DRIVE-SHIFT (7) trial (ISG, N = 447; DSG, N = 223). DOR PK samples were collected from all participants on Day 1 (predose) and Week 48 (predose and within 0.5 to 2 hours postdose). Additional ISG PK samples were collected at Weeks 4 (predose), 12 (irrespective of dosing), and 24 (predose and 0.5 to 2 hours postdose). Only PK data from the ISG were included in the population PK analysis, given sparse sampling in the DSG (Week 48 only).

To evaluate consistency of DOR PK in the Phase 3 switch population with that of the Phase 3 treatment-naïve population, several approaches (described in the Supplemental Material) were evaluated. The exploratory analyses (approach 1) and the estimation of the combined model (approach 3b) are presented here. Observed data from DRIVE-SHIFT were initially compared with observed data from treatment-naïve participants within Phase 3 trials (MK-1439-018 [P018], DRIVE-FORWARD, NCT02275780; MK-1439A-021 [P021], DRIVE-AHEAD, NCT02403674). A previously described population PK model for the treatment-naïve population (9) was updated in the current analysis using DOR concentration data from the ISG of DRIVE-SHIFT. Population PK parameters, including covariates, were re-estimated, and the final model was used to estimate individual post-hoc PK parameter values for the switch and treatment-naïve populations.
The population PK analysis dataset comprised the original 341 healthy participants and 959 treatment-naive participants with HIV-1, with the addition of 443 virologically suppressed participants with HIV-1 from the DRIVE-SHIFT ISG (a total of 1402 participants with HIV-1) (9). Four of 447 ISG individuals were excluded due to data reconciliation issues. Comparison of PK data from treatment-naive participants in prior Phase 3 studies with those from DRIVE-SHIFT suggested a comparable range of DOR concentrations at different steady-state time points (Supplemental Figure 1) and indicated the suitability of the previously developed population PK model for the DRIVE-SHIFT ISG population PK analysis (7).

The original DOR population PK model was a one-compartment model with first order absorption and linear apparent clearance (CL/F). Body weight and healthy versus HIV-1 infection status were covariates on apparent volume of distribution and age on apparent clearance. This model characterized the ISG data well, as supported by the diagnostic plots (Supplemental Material; Supplemental Figure 2; Supplemental Table 1).

The final PK parameters of the model (Supplemental Table 1) were well estimated with small standard errors. These estimates were very similar to the previously developed population PK model based only on data from healthy subjects and treatment-naive participants with HIV-1 (9).

PK parameters including area under the concentration–time curve from 0 to 24 hours (AUC\(_{0-24}\)), maximum serum concentration (C\(_{\text{max}}\)), and plasma concentration 24 hours after dose administration (C\(_{24}\)) at steady state were simulated from post-hoc compartmental parameter
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estimates for each participant in the Phase 3 studies. Table 1 and Figure 1 show the
distributions of individual steady-state AUC\(_{0-24}\), \(C_{\text{max}}\), and \(C_{24}\) from the DRIVE-SHIFT ISG are
comparable to treatment-naïve Phase 3 studies (P018 and P021).

The AUC\(_{0-24}\), \(C_{\text{max}}\), and \(C_{24}\) estimates for the DRIVE-SHIFT ISG were used in efficacy
exposure–response exploratory analyses for this population. The efficacy endpoints used were
the proportion of ISG participants maintaining HIV-1 RNA <50 copies/mL and <40 copies/mL at
Week 48 (yes/no). Analyses were conducted for (1) the primary snapshot approach specified in
the Phase 3 trial protocols that classified any participant with missing data as a failure, and (2)
the observed failure approach, where monotone (non-intermittent) missing data for
participants who discontinued treatment prematurely due to lack of efficacy were assigned as
failures after discontinuation, whereas those with missing data for other reasons were
excluded.

The exposure–response analysis dataset included virological response data from 443
individuals. A linear exposure–effect model performed very similarly to the log exposure–effect
model based on the Akaike Information Criterion values, hence the linear model was chosen for
the analyses. The slope and 95% confidence interval (CI) of the exposure–response relationship
was estimated. A \(P\)-value was calculated for the slope to evaluate whether it was significant
(non-zero) or insignificant (not different from zero).

Slope estimates from the exposure–response analyses were not significantly different
from zero (\(P\)-values > 0.05) suggesting a flat exposure–response relationship with no trends
between virologic response and DOR exposure over the range of exposures achieved with once-
daily 100 mg doses in the DRIVE-SHIFT ISG. Consequently, structural models of increased
complexity were not explored and no covariate analysis was performed. Figure 2 shows the
exposure–response relationships with DOR steady-state $C_{24}$ (snapshot approach).

As DOR steady-state PK and exposure–response are the same between treatment-naïve
and switch populations, the DOR clinical pharmacology profile characterized in the treatment-
naïve population, including the effects of intrinsic factors and drug–drug interactions, is also
applicable to the switch population. In patients switching from efavirenz, a moderate
cytochrome P450 (CYP) 3A inducer, plasma concentrations of DOR may be transiently
decreased as the induction effects of efavirenz are washed out (10, 11). However, the efficacy
and PK profile of DOR in participants switching from efavirenz was found to be similar to that of
participants switching from other ARV therapies (10). From a physiological perspective,
sustained virologic suppression is not anticipated to impact the PK of DOR, consistent with the
findings of this analysis. The similarity of DOR PK between treatment-naïve and switch
populations indicates that dose recommendations for DOR determined in the treatment-naïve
population are directly applicable to the switch population without adjustments, and support
the appropriateness of the 100 mg dose of DOR within the switch population.

**Data Availability**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA’s data
sharing policy, including restrictions, is available at
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http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Acknowledgments

The authors would like to thank Larissa Wenning for her scientific mentorship on this project, Robert J. Valesky for data reconciliation, and Patricia Guldin for dataset programming. Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. P.V., B.K., and K.L.Y. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

Medical writing assistance, under the direction of the authors, was provided by Chris Whittle, PhD, of CMC AFFINITY, McCann Health Medical Communications, in accordance with Good Publication Practice (GPP3) guidelines. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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FIGURE LEGENDS

**FIG 1** Comparison of steady-state DOR (A) $C_{24}$, (B) AUC$_{0-24}$, and (C) $C_{\text{max}}$, following administration of 100 mg once-daily DOR between treatment-naïve trials (P018 and P021) and participants from the ISG of DRIVE-SHIFT (P024).

Boxes represent 25th, 50th, and 75th percentiles. Whiskers represent the 5th and 95th percentiles of the respective distributions for $C_{24}$, AUC$_{0-24}$, or $C_{\text{max}}$.

AUC$_{0-24}$, area under the concentration-time curve from 0 to 24 h; $C_{24}$, plasma concentration 24 hours after dose administration; $C_{\text{max}}$, maximum serum concentration; DOR, doravirine; ISG, immediate switch group.

**FIG 2** Predicted and observed proportion of ISG participants maintaining HIV-1 RNA at (A) <50 copies/mL or (B) <40 copies/mL using the snapshot approach as a function of DOR steady-state $C_{24}$ quartiles following administration of 100 mg once-daily DOR ($N = 443$).

Solid lines signify the mean predicted exposure–response relationship. Shaded areas represent the 95% CI of the prediction over the 5th to 95th percentile of exposures. Markers and whiskers summarize the observed endpoint and 95% CI by $C_{24}$ quantile.

AUC$_{0-24}$, area under the concentration-time curve from 0 to 24 h; $C_{24}$, plasma concentration 24 hours after dose administration; $C_{\text{max}}$, maximum serum concentration; DOR, doravirine; ISG, immediate switch group.
### TABLE 1 Summary statistics of DOR steady-state AUC\(_{0-24}\), C\(_{\text{max}}\), and C\(_{24}\) following administration of once-daily 100 mg DOR in treatment-naïve study participants and participants randomized to the ISG in the DRIVE-SHIFT trial (P024)

| Phase 3 study population | Dose (mg) | Parameter | N   | Geometric mean | Geometric %CV |
|--------------------------|-----------|-----------|-----|----------------|---------------|
| Treatment naïve (P018 and P021) | 100 | AUC\(_{0-24}\) (µM*h) | 730 | 38.1 | 28.8 |
|                         |          | C\(_{24}\) (nM) | 730 | 932 | 62.7 |
|                         |          | C\(_{\text{max}}\) (nM) | 730 | 2,290 | 18.2 |
| DRIVE-SHIFT ISG (P024)  | 100 | AUC\(_{0-24}\) (µM*h) | 443 | 41.5 | 22.8 |
|                         |          | C\(_{24}\) (nM) | 443 | 1,110 | 36.1 |
|                         |          | C\(_{\text{max}}\) (nM) | 443 | 2,390 | 16.5 |

AUC\(_{0-24}\), concentration–time curve from 0 to 24 h; C\(_{24}\), plasma concentration 24 hours after dose administration; C\(_{\text{max}}\), maximum serum concentration; CV, coefficient of variation; DOR, doravirine; ISG, immediate switch group; N, number of participants.
Figure 1

A

Comparison of steady-state DOR (A) $C_{24}$, (B) AUC$_{0-24}$, and (C) $C_{\text{max}}$ following administration of 100 mg once-daily DOR between treatment-naïve trials (P018 and P021) and participants from the ISG of DRIVE-SHIFT (P024).

Boxes represent 25th, 50th, and 75th percentiles. Whiskers represent the 5th and 95th percentiles of the respective distributions for $C_{24}$, AUC$_{0-24}$, or $C_{\text{max}}$.

AUC$_{0-24}$, area under the concentration-time curve from 0 to 24 h; $C_{24}$, plasma concentration 24 hours after dose administration; $C_{\text{max}}$, maximum serum concentration; DOR, doravirine; ISG, immediate switch group.
Figure 2

Predicted and observed proportion of ISG participants maintaining HIV-1 RNA at (A) <50 copies/mL or (B) <40 copies/mL using the snapshot approach as a function of DOR steady-state $C_{24}$ quartiles following administration of 100 mg once-daily DOR ($N = 443$).

Solid lines signify the mean predicted exposure–response relationship. Shaded areas represent the 95% CI of the prediction over the 5th to 95th percentile of exposures. Markers and whiskers summarize the observed endpoint and 95% CI by $C_{24}$ quartile.

$C_{24}$, plasma concentration 24 hours after dose administration; DOR, doravirine; ISG, immediate switch group.