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ANTIVIRAL AGENTS

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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ABSTRACT Doravirine is a non-nucleoside reverse transcriptase inhibitor for treatment of human immunodeficiency virus type 1 (HIV-1) infection. A population pharmacokinetic (PK) model for treatment-naive 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 (This study has been registered at ClinicalTrials.gov under ClinicalTrials registration no. NCT02397096.)

KEYWORDS doravirine, fixed-dose combination, non-nucleoside reverse transcriptase inhibitor, population pharmacokinetic model, switch treatment

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; ClinicalTrials registration no. NCT02397096), a phase 3, open-label, randomized, active-controlled, noninferiority trial in virologically suppressed participants with HIV-1, evaluated a 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 an HIV-1 RNA level of <50 copies/ml (U.S. Food and Drug Administration [FDA] snapshot approach), with the primary comparison between ISG at week 48 and DSG at week 24. The main objectives of the current analysis were to evaluate the consistency of DOR pharmacokinetics (PK) in the ISG population with that of the treatment-naive population described previously (9) and to evaluate the 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 a switch to a DOR-based regimen.

A total of 670 participants on stable ARV regimens were recruited to the DRIVE-SHIFT trial (ISG, $N = 447$; DSG, $N = 223$) (7). DOR PK samples were collected from all participants on day 1 (predose) and week 48 (predose and within 0.5 to 2 h postdose).

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TABLE 1 Summary statistics of DOR steady-state AUC_{0-24}, C_{max}, and C_{24} following administration of once-daily 100 mg DOR in treatment-naive study participants and participants randomized to the ISG in the DRIVE-SHIFT trial (P024)[a]

Phase 3 study population	Dose (mg)	Parameter	*N*	Geometric mean	Geometric % CV
Treatment naive (P018 and P021)	100	AUC_{0-24} (μM · h)	730	38.1	28.8
		C_{24} (nM)	730	932	62.7
		C_{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_{max} (nM)	443	2,390	16.5

[a]AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{24}, plasma concentration 24 h after dose administration; C_{max}, maximum serum drug concentration; CV, coefficient of variation; DOR, doravirine; ISG, immediate switch group; *N*, number of participants.

Additional ISG PK samples were collected at weeks 4 (predose), 12 (irrespective of dosing), and 24 (predose and 0.5 to 2 h 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-naive population, several approaches (described in Text S1 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-naive participants within phase 3 trials (MK-1439-018 [P018], DRIVE-FORWARD, ClinicalTrials registration no. NCT02275780; MK-1439A-021 [P021], DRIVE-AHEAD, ClinicalTrials registration no. NCT02403674). A previously described population PK model for the treatment-naive population (9) was updated in the current analysis using DOR concentration data from the ISG of DRIVE-SHIFT. Population PK parameters, including covariates, were reestimated, and the final model was used to estimate individual *post hoc* PK parameter values for the switch and treatment-naive populations.

The population PK analysis data set 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 1,402 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 (see Fig. S1 in the supplemental material) 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 (see Text S1, Fig. S2, and Table S1 in the supplemental material).

The final PK parameters of the model (Table S1) were well estimated, with small standard errors. These estimates were very similar to those of 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 h (AUC_{0-24}), maximum serum concentration (C_{max}), and plasma drug concentration 24 h after dose administration (C_{24}) at steady state, were simulated from *post hoc* compartmental parameter estimates for each participant in the phase 3 studies. Table 1 and Fig. 1 show the distributions of individual steady-state AUC_{0-24}, C_{max}, and C_{24} from the DRIVE-SHIFT ISG are comparable to those in treatment-naive phase 3 studies (P018 and P021).

The AUC_{0-24}, C_{max}, and C_{24} estimates for the DRIVE-SHIFT ISG were used in efficacy

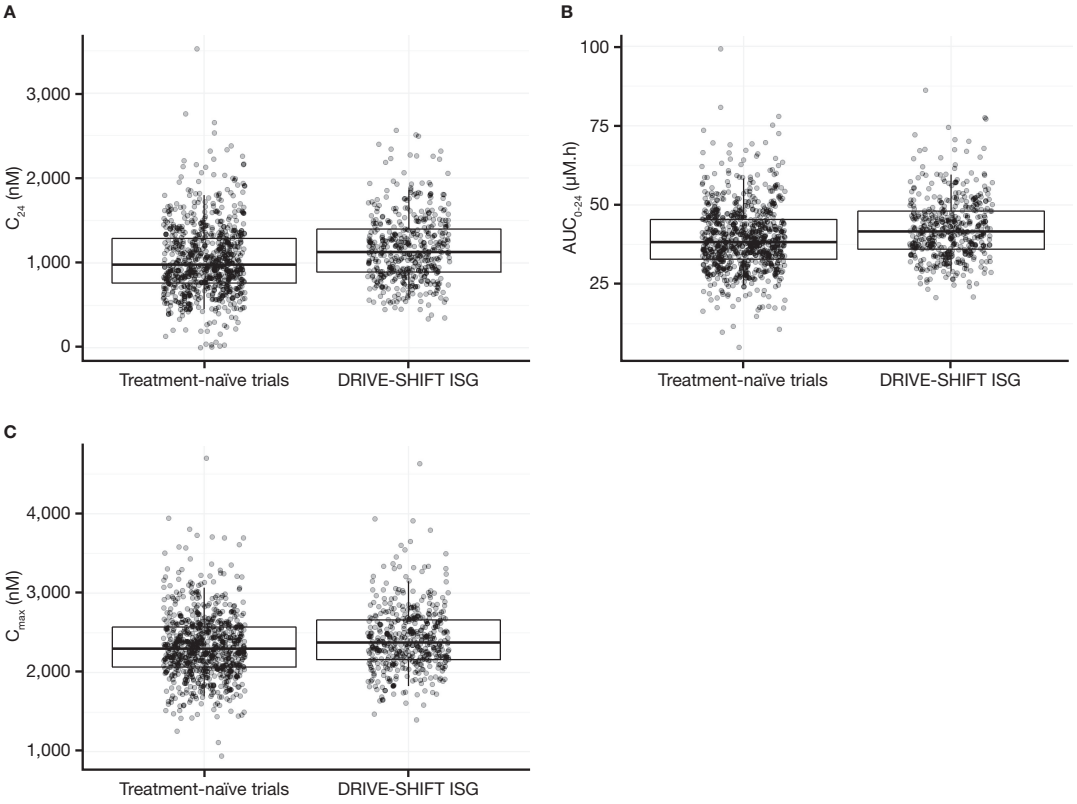

FIG 1 Comparison of steady-state DOR (A) C_{24}, (B) AUC_{0-24}, and (C) C_{max} following administration of 100 mg once-daily DOR between treatment-naive trials (P018 and P021) and participants from the ISG of DRIVE-SHIFT (P024). Boxes represent 25th, 50th, and 75th percentiles. Whiskers represent the 5th and 95th percentiles of the respective distributions for C_{24}, AUC_{0-24}, or C_{max}. AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{24}, plasma concentration 24 h after dose administration; C_{max}, maximum serum drug concentration; DOR, doravirine; ISG, immediate switch group.

exposure-response exploratory analyses for this population. The efficacy endpoints used were the proportion of ISG participants maintaining HIV-1 RNA levels of $<$50 copies/ml and $<$40 copies/ml at week 48 (yes/no). Analyses were conducted for (i) the primary snapshot approach specified in the phase 3 trial protocols that classified any participant with missing data as a failure and (ii) the observed failure approach, where monotone (nonintermittent) 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 data set 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 were estimated. A *P* value was calculated for the slope to evaluate whether it was significant (nonzero) or insignificant (not different from zero).

Slope estimates from the exposure-response analyses were not significantly different from zero (*P* values of $>$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 relationship are the same between treatment-naive and switch populations, the DOR clinical pharmacology profile char-

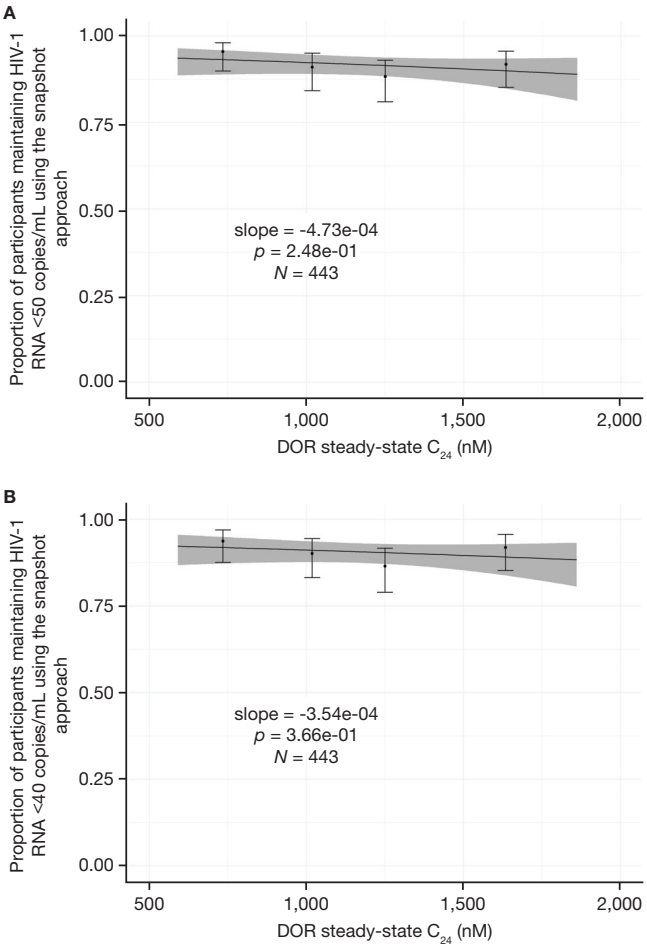

FIG 2 Predicted and observed proportion of ISG participants maintaining HIV-1 RNA at (A) <50 copies/ml or (B) <40 copies/ml using the snapshot approach as a function of DOR steady-state C_{24} quartiles following administration of 100 mg once-daily DOR ($N = 443$). Solid lines signify the mean predicted exposure-response relationship. Shaded areas represent the 95% CI of the prediction over the 5th to 95th percentiles 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 h after dose administration; C_{max}, maximum serum drug concentration; DOR, doravirine; ISG, immediate switch group.

acterized in the treatment-naive 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 were found to be similar to those 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-naive and switch populations indicates that dose recommendations for DOR determined in the treatment-naive population are directly applicable to the switch population without adjustments and supports the appropriateness of the 100-mg dose of DOR within the switch population.

Data availability. The data sharing policy of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, including restrictions, is available at 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.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.5 MB.

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