CTD 第 2 部

2.7　臨床概要

2.7.1　生物薬剤学試験及び関連する分析法

MSD 株式会社

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1 BACKGROUND AND OVERVIEW

Doravirine (DOR, MK-1439) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) dosed once daily for the treatment of human immunodeficiency virus type-1 (HIV-1) infection. DOR, in combination with other antiretroviral agents, has demonstrated potent antiretroviral activity and efficacy and a favorable safety profile in the treatment of HIV-1 infection.

Thirty-six (36) Phase 1 clinical trials were conducted to assess the safety, tolerability, pharmacokinetics (PK), biopharmaceutics, and pharmacodynamics (PD) of DOR [Appendix 2.7.1: 1], [Appendix 2.7.2: 1]. DOR is a BCS Class II compound and is formulated as [redacted] based tablet. Two key formulations of DOR, a fit-for-purpose (FFP) oral compressed tablet (OCT) and a pre-market formulation (PMF) OCT, both containing [redacted]% DOR in hypromellose acetate succinate (HPMCAS) as [redacted], were used in the clinical development program. Differences between the FFP and PMF OCTs were minimal and did not affect the bioavailability of DOR. The final market image (FMI) is a film coated tablet (FCT) that is identical to the PMF OCT Phase 3 formulation, with the exception of film coating. The film coating does not impact dissolution or bioavailability; a clinical trial (P039) [Sec. 2.7.1.2.1.1.1] established the bioequivalence (BE) of the PMF OCT to the FMI FCT intended for commercialization.

DOR has an absolute bioavailability of ~64% based on data from an IV microdose trial (P044) [Sec. 2.7.1.2.1.1.2] and the clinical bioequivalence trial evaluating the FMI FCT (P039) [Sec. 2.7.1.2.1.1.1], [Sec. 2.7.1.3.1], [Sec. 2.7.1.3.2.1].

Relative to fasting conditions, oral administration of DOR with a standard high fat and high calorie meal did not have a clinically meaningful effect on the PK of DOR (P037) [Sec. 2.7.1.2.2.1.1], [Sec. 2.7.1.3.3.1]. Therefore, the DOR FCT may be administered without regard to food; DOR was administered without regard to food in the Phase 2 and 3 trials.

Consistent with in vitro data indicating that the solubility of DOR is pH independent [Sec. 2.7.1.1.2.1], a drug-drug interaction (DDI) trial with DOR and an antacid, as well as a proton pump inhibitor, demonstrated that gastric acid modifying agents do not have a clinically meaningful effect on the PK of DOR (P042) [Sec. 2.7.2.2.3.1.7], [Sec. 2.7.2.3.1.1.6].

DOR was also developed as a fixed dose combination (FDC) tablet as a complete regimen for the treatment of HIV-1 infection. The FDC contains 100 mg DOR, 300 mg lamivudine (3TC), and 300 mg tenofovir disoproxil fumarate (TDF, 245 mg as tenofovir disoproxil), hereafter referred to as DOR/3TC/TDF (MK-1439A; [Appendix 2.7.1: 1]). The DOR/3TC/TDF tablet is a bilayer tablet consisting of DOR in one layer and 3TC and TDF in the other. Lamivudine (registered Trademark 3TC® in Canada and registered Trademark EPIVIR® in the United States [US] and European Union [EU]) and tenofovir disoproxil fumarate (TDF, Trademark VIREAD®) are nucleos(t)ide reverse transcriptase inhibitors (NRTIs) approved for use in the US, EU, Canada and other countries, and are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection [Sec. 2.5.1.1.1], [Sec. 2.5.1.1.2].

As described in [Sec. 2.7.1.2.1.2.1], a relative bioavailability trial (P026) showed that the DOR, 3TC, and TDF components of DOR/3TC/TDF demonstrated similar PK to those observed following co-administration of the individual components.

Based on the results of P026 [Sec. 2.7.1.2.1.2.1], [Sec. 2.7.1.3.2.2], as well as results from a drug-drug interaction trial (P038) [Sec. 2.7.2.2.3.1.8], which demonstrated no drug interaction between the DOR/3TC/TDF components (DOR, 3TC, and TDF), the clinical pharmacology, safety and efficacy profile of DOR established following treatment with DOR/3TC/TDF can be applied to the DOR single entity tablet and the converse is also true; the clinical pharmacology, safety and efficacy profile of the single entity DOR tablet is applicable to DOR/3TC/TDF.

The safety and efficacy of the DOR tablet, in combination with background antiretroviral therapy, were evaluated in a Phase 2 trial [Ref. 5.3.5.1: P007V01MK1439] and a Phase 3 trial [Ref. 5.3.5.1: P018V01MK1439] in treatment naïve HIV-1 infected subjects and DOR was found to be generally well tolerated [Sec. 2.7.4.2.3.5] and efficacious [Sec. 2.7.3.2.2.2-trtmtnve48wk]. DOR/3TC/TDF was evaluated in a pivotal Phase 3 trial (P021) in treatment-naïve, HIV-1 infected adults and was shown to be generally well tolerated [Sec. 2.7.4.2.4.6] and efficacious [Sec. 2.7.3.2.3.2-trtmtnve48wk].

This document focuses on the formulation details of DOR as a single entity. Certain details regarding the development of DOR/3TC/TDF are, however, included in this document in order to facilitate cross-referencing from other modules of the submission package.

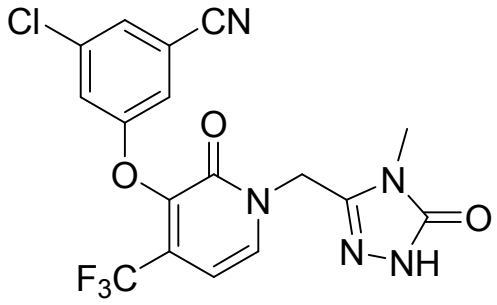
The key findings of the DOR biopharmaceutics program are as follows:

- DOR is a BCS class II compound, formulated as [redacted] based tablet. The OCT used throughout clinical development was shown to be bioequivalent to the FMI FCT in a clinical trial.
- Absolute bioavailability of the FMI DOR 100 mg FCT is ~64%.
- DOR tablets may be administered without regard to food.
- DOR tablets may be administered with gastric acid reducing agents without adjustments.

1.1 Overview of Formulation Development for Doravirine Tablet

DOR free acid drug substance is crystalline, with a molecular weight of 425.75 and molecular formula of $C_{17}H_{11}ClF_3N_5O_3$. The chemical structure is shown in [Figure 2.7.1: 1]. DOR Form [redacted] that is used for the manufacturing of the DOR tablets is a non-hygroscopic, off-white powder. Form [redacted] is the most stable crystalline form below approximately 75ºC and was selected for development and formulated as [redacted]. Only for the absorption/metabolism/excretion (AME) study, [C]MK-1439 sodium pentahydrate was used and formulated in dry filled capsules (DFC). The compound has one pKa of 9.47 that does not affect solubility in the physiological pH range. LogD was measured to be 2.26 at pH 7 [Sec. 3.2.S.1.3-doravirine]. [redacted] DOR exhibits low solubility, [redacted] - [redacted] µg/mL, across the physiological pH range.

Figure 2.7.1: 1 Chemical Structure of Doravirine



Data Source: [Sec. 3.2.S.1.2-doravirine]

The compositions of the FFP and PMF used for DOR clinical trials are shown in [Table 2.7.1: 1]. The bridging strategy is presented in [Figure 2.7.1: 2]. The formulations used in each clinical trial are provided in [Table 2.7.1: 2].

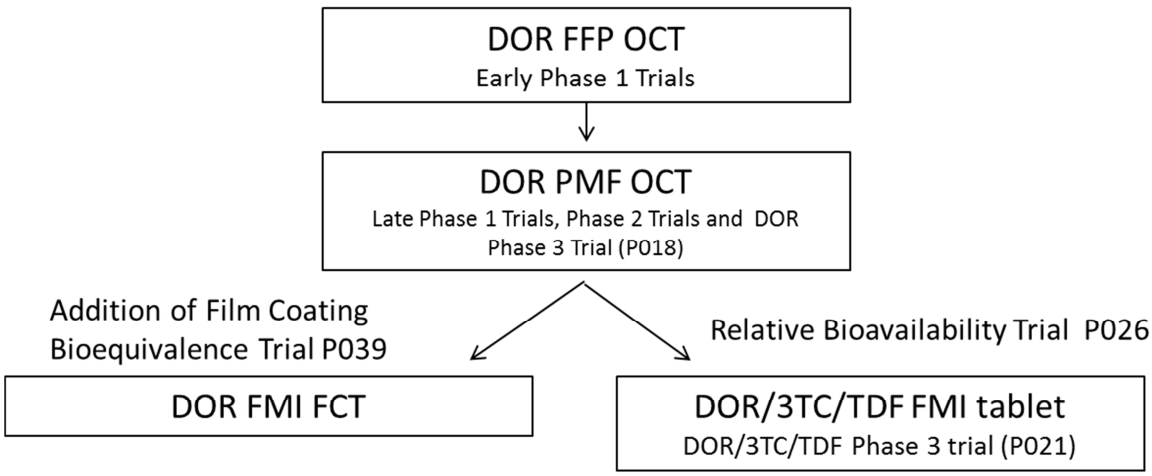
Table 2.7.1: 1 Composition of Key Doravirine Single Entity Formulations Used in Clinical Trials

Components	Composition (% w/w)*		
	FFP**	PMF***	FMI
Doravirine (free acid)	10.0	10.0	10.0
Hypromellose acetate succinate (HPMCAS)	[redacted]	[redacted]	[redacted]
Lactose monohydrate	[redacted]	[redacted]	[redacted]
Microcrystalline cellulose	[redacted]	[redacted]	[redacted]
Colloidal Silicon Dioxide ([redacted])	[redacted]	[redacted]	[redacted]
Croscarmellose Sodium ([redacted])	[redacted]	[redacted]	[redacted]
Magnesium Stearate ([redacted])	[redacted]	[redacted]	[redacted]
Colloidal Silicon Dioxide ([redacted])	[redacted]	-	-
Croscarmellose Sodium ([redacted])	-	[redacted]	[redacted]
Magnesium Stearate ([redacted])	[redacted]	[redacted]	[redacted]
Total	100	100	100
Film Coat	-	-	Film Coating System****

* % w/w is reported based on core tablet weight
** For FFP, 1, 10 and 100 mg potency tablets (weight multiples) were used
*** For PMF, 25 and 100 mg potency tablets (weight multiples) were used
**** Film coating system details are discussed in [Sec. 3.2.P.1-1439-tablet]

Data Source: [Sec. 3.2.P.2.2-1439-tablet]

Figure 2.7.1: 2 Formulation Bridging Strategy



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Table 2.7.1: 2 Doravirine and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate Tablets used in the Clinical Development Program. Exploratory formulations and pediatric formulations are not listed.

Formulation Type*	Dosage Strength	Protocols
FFP DFC	1, 10, 100 mg	P001
FFP OCT	1, 10, 100 mg	P001, P002, P003, P005, P006, P009
PMF OCT	25, 100 mg	P007, P010, P011, P012, P016, P017, P018, P019, P020, P031, P034, P035, P036, P037, P038, P042, P043, P048, P049, P050, P052, P053
FMI FCT	100 mg	P039, P045, P046, P051
AME DFC	58.33 mg	P008
FMI DOR/3TC/TDF	100 mg/300 mg/300 mg	P026, P029, P021

* A comprehensive list of the compositions of each formulation and information on individual batches used in clinical studies for DOR can be found in [Ref. 3.3: 04L0N2].

1.1.1 Doravirine Formulation

1.1.1.1 Doravirine Formulation in Early Development

[redacted] DOR has low solubility. To improve the solubility/dissolution rate of the compound and improve oral bioavailability, [redacted], with HPMCAS as [redacted], was generated and was formulated into a FFP OCT. [redacted] was prepared by [redacted] process [Sec. 3.2.P.2.2-1439-tablet]. This [redacted] formulation demonstrated the desired PK performance in early clinical trials (P001, P002) including significantly improved bioavailability relative to a formulation based on jet milled [redacted] API (P001) [Appendix 2.7.1: 1] [Ref. 5.3.3.1: P001V01: 2]. Thus, the [redacted] formulation was selected for further development. Since the [redacted] API based formulation was not selected for further development, it is not discussed further in this document.

1.1.1.2 Doravirine Formulation in Late Development and Final Market Image

The DOR PMF OCT used in late development was based on similar composition to the FFP formulation. While [redacted] and tablet manufacturing processes were further optimized towards preparing a FMI [Sec. 3.2.P.2.2-1439-tablet], as shown in [Table 2.7.1: 1], the composition of the formulation remained practically unchanged between the FFP and PMF OCT. The minor differences in [redacted] between FFP and PMF OCTs, as shown in [Table 2.7.1: 1], were intended to optimize processing while maintaining [redacted] for the PMF [Sec. 3.2.P.2.2-1439-tablet]. Given [redacted] and the use of the same [redacted], performance of the FFP and PMF is considered comparable. The DOR PMF OCT was used in the majority of clinical trials, including the Phase 3 trial (P018) as shown in [Table 2.7.1: 2]. The FMI formulation is identical to the PMF OCT with the exception of addition of film coating. The FMI formulation was shown to be bioequivalent to the PMF OCT in trial P039 [Sec. 2.7.1.2.1.1.1].

1.2 Overview of Solubility and Dissolution

1.2.1 Doravirine Solubility and Permeability

DOR is classified as a BCS class II compound (low solubility, high permeability). According to the BCS definition, a drug substance is considered highly soluble when the highest dose strength is soluble in ≤250 mL of aqueous media over the pH range of 1 to 6.8. Solubility for crystalline DOR API (Form [redacted]) was determined in buffer systems across the physiological pH range. Solubility (at 25 °C) in buffers between pH [redacted] and in water is low, approximately [redacted] µg/mL [Table 2.7.1: 3]. Based on these solubility data, DOR is classified as a low solubility compound. As shown in [Table 2.7.1: 3], DOR solubility does not show pH dependency. DOR is formulated as [redacted] to increase the solubility; [redacted] DOR solubility is estimated to be approximately [redacted] µg/mL.

Permeability of DOR was estimated at 25 × 10^{-6} cm/sec in LLC-PK1 cells [Sec. 2.6.4.7.2], [Sec. 2.6.5.7.4]. Based on the high passive permeability estimated preclinically (in the same system, permeability of reference compound minoxidil was ~ 11 × 10^{-6} cm/sec), DOR is classified as a highly permeable compound according to BCS.

Table 2.7.1: 3 Equilibrium Solubility of Crystalline Doravirine (Form [redacted])

Medium	Solubility (µg/mL)
Water	[redacted]
pH [redacted] Phosphate Buffer	[redacted]
pH [redacted] Phosphate Buffer	[redacted]
pH [redacted] Acetate Buffer	[redacted]
pH [redacted] Acetate Buffer	[redacted]
pH [redacted] Phosphate Buffer	[redacted]
pH [redacted] Phosphate Buffer	[redacted]
pH [redacted] Phosphate Buffer	[redacted]

Data Source: [Sec. 3.2.P.2.1-1439-tablet]

1.2.2 Doravirine Tablet Dissolution

A summary of the proposed dissolution method for DOR tablets is provided in [Table 2.7.1: 4]. Further details of the dissolution method and proposed specifications are provided in [Sec. 3.2.P.5.2.2-1439-tablet] and [Sec. 3.2.P.5.6-1439-tablet].

The dissolution performance of the DOR tablets was monitored using USP Dissolution Apparatus II at a rotational speed of [redacted] RPM in [redacted] mM [redacted] buffer at pH [redacted] with [redacted]% (w/v) [redacted]. [redacted] was selected as the surfactant as it can adequately solubilize DOR to provide complete dissolution. Dissolution data are depicted in [Figure 2.7.1: 3]. The -10% line (lower f2 dissolution similarity bound relative to bioequivalence batch [redacted]) is also depicted. Additional dissolution method details can be found in [Sec. 3.2.P.5.2.2-1439-tablet].

Determination of appropriate dissolution acceptance criteria was based on analysis of representative clinical batch data, formal stability study (FSS) data through 30 months, and commercial scale development batch data. The proposed specification for DOR tablets is amount of drug dissolved (Q) = [redacted]% at [redacted] min. Details are provided in [Sec. 3.2.P.5.6-1439-tablet].

Table 2.7.1: 4 Dissolution Method and Specifications for Doravirine Tablets

Dissolution Apparatus	USP Apparatus II (paddles) at [redacted] rpm
Dissolution Medium	[redacted] mM [redacted] Buffer pH [redacted] with [redacted] % (w/v) [redacted]
Medium Volume	900 mL
Medium Temperature	37 ± 0.5°C
Acceptance Criteria Doravirine Tablet	DOR Q= [redacted] % at [redacted] min

Source Data: [Sec. 3.2.P.5.2.2-1439-tablet], [Sec. 3.2.P.5.6-1439-tablet]

Figure 2.7.1: 3 Dissolution Profiles of Doravirine Clinical, Bioequivalence, and/or Stability Batches in the Proposed Dissolution Method. The Lower Dissolution Similarity Bound (BE – 10%) is Also Depicted.



Source Data: [Sec. 3.2.P.5.4-1439-tablet],[Sec. 3.2.P.5.6-1439-tablet]

1.3 Overview of Dosage Form In Vivo Performance

1.3.1 Doravirine Tablet Dosage Form In Vivo Performance

The in vivo performance of the key formulations in the clinical development program of DOR was evaluated in clinical trials. As discussed in [Sec. 2.7.1.1.1.1], a FFP OCT was used in early trials, followed by a PMF OCT with very similar composition, to investigate PK, safety, tolerability, and efficacy. The bioequivalence of the FMI FCT to the PMF OCT was established in P039. This trial is summarized in [Sec. 2.7.1.2.1.1.1]. Based on the outcome of this trial, the FCT was selected as the intended formulation for commercialization.

The effects of food and acid-reducing agents on the relative bioavailability of DOR are summarized in [Sec. 2.7.1.2], [Sec. 2.7.2.2.3.1.7] and discussed in [Sec. 2.7.1.3.3.1], [Sec. 2.7.1.3.3.2]. There was no clinically meaningful food effect or gastric pH effect on the PK of DOR.

1.3.2 Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate Dosage Form In Vivo Performance

The data in P026 established comparable relative bioavailability of the FMI DOR/3TC/TDF bilayer tablet used in Phase 3 and the separate tablets of DOR (PMF OCT), EPIVIR®, and VIREAD® [Sec. 2.7.1.2.1.2.1], [Sec. 2.7.1.3.2.2]. AUC0-inf and Cmax for DOR and 3TC and AUC0-inf for tenofovir (the active moiety that is measured in vivo following oral administration of TDF) fell within BE bounds when administered as the FMI DOR/3TC/TDF, compared to co-administration of each individual component. Tenofovir Cmax was slightly decreased (13%) when administered as DOR/3TC/TDF compared to administration of the marketed formulation of VIREAD®. The decrease in tenofovir Cmax is, however, not expected to impact efficacy or safety [Sec. 2.7.1.3.2.2]. DOR C24 90% CIs for GMR also fell within BE bounds when comparing DOR/3TC/TDF to the single entity DOR PMF OCT.

Further, a component interaction trial (P038) [Sec. 2.7.2.2.3.1.8] established that co-administration of 3TC and TDF with DOR did not have a clinically meaningful effect on the exposure or Cmax of any component compared to administration of DOR alone or 3TC and TDF alone. DOR and 3TC AUC0-inf and Cmax 90% CIs for GMR and DOR C24 90% CIs for GMR fell within BE bounds. AUC0-inf and Cmax 90% CIs for GMR for TDF were only slightly outside BE bounds (0.97 – 1.28 for AUC0-inf 90% CI for GMR and 0.96 – 1.42 for Cmax 90% CI for GMR); however, the changes were considered not clinically meaningful. Thus, the clinical pharmacology profile for each individual component is applicable to DOR/3TC/TDF. The effect of food on the relative bioavailability of DOR, 3TC, and tenofovir when administered as DOR/3TC/TDF was investigated in P029 and no clinically meaningful effects were seen. These results are summarized in [Sec. 2.7.1.2.2.1.2] and discussed in [Sec. 2.7.1.3].

1.4 Overview of Bioanalytical Methods

1.4.1 Bioanalytical Methods for Doravirine

Specific and sensitive bioanalytical assays using liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection for the determination of DOR in human plasma (DM-995 [Ref. 5.3.1.4: 03DTGR], DM-995A [Ref. 5.3.1.4: 046JM9], 15600MWP1439HPL_S [Ref. 5.3.1.4: 04MWLF], ANI 11059.01 [Ref. 5.3.1.4: 04MJH6], and BP-0155 [Ref. 5.3.1.4: 04C6B0]) were developed and validated in accordance with current regulatory guidance in order to support the clinical development program. DM-995, DM-995A, DM-995B, 15600MWP1439HPL_S, and ANI 11059.01 are the same method with name changes that reflect the utilization of the assay at different bioanalytical contract research organizations (CROs). A summary of each assay method is provided in [Table 2.7.1: 5].

The methods used to support each clinical trial, along with the inter-run accuracy and precision data for each study are listed in [Table 2.7.1: 6]. An incurred sample reproducibility (ISR) assessment was conducted for each analytical method. All clinical samples were analyzed within the established stability period of the analyte.

The parameters and validation metrics for the DM-995A bioanalytical method, which was used to support plasma sample analysis for the majority of the DOR trials, are presented in [Table 2.7.1: 7]. Similar information for the other assays used during the clinical development program can be found in the bioanalytical reports that are appended to the clinical study reports (CSRs), as well as in the method validation reports that are included in (Section 5.3.1.4) of this submission, Reports of Biopharmaceutic Studies – Reports of Bioanalytical and Analytical Methods for Human Studies.

Table 2.7.1: 5 Summary of Doravirine Validated Analytical Methods

Method Validation Report	Laboratory	LLOQ (ng/mL)	Linear Range (ng/mL)	Matrix
VR DM-995	West Point[a]	1.00	1.00 to 1000	Plasma
MR DM-995A	[redacted][b]	1.00	1.00 to 1000	Plasma
150820PVEA_MWP	[redacted][b]	1.00	1.00 to 1000	Plasma
157103ANVL	[redacted][c]	1.00	1.00 to 1000	Plasma
VR BP-0155	West Point[a]	0.020	0.020 to 10.0	Plasma

Abbreviations: LLOQ-lower limit of quantification
[a] Merck Research Labs, 770 Sumneytown Pike, West Point, PA 19486, USA
[b] [redacted] The Netherlands
[c] [redacted] Canada [redacted]

Source: [Ref. 5.3.1.4: 03DTGR], [Ref. 5.3.1.4: 046JM9], [Ref. 5.3.1.4: 04MWLF] [Ref. 5.3.1.4: 04MJH6], [Ref. 5.3.1.4: 04C6B0]

Table 2.7.1: 6 Bioanalytical Methods Used to Support Each Clinical Trial Together With Study Assay Performance

Clinical Trial	Method	Matrix	Inter-run Accuracy %RE[a]	Inter-run Precision %CV[a]
P001	DM-995	Plasma	-1.00% to 2.55%	≤ 7.97%
P002	DM-995	Plasma	5.33% to 9.87%	≤4.11%
P003	DM-995	Plasma	3.33% to 9.49%	≤6.45%
P005	DM-995	Plasma	1.42% to 9.77%	≤5.45%
P006	DM-995	Plasma	3.00% to 7.66%	≤4.53%
P008	DM-995A	Plasma	0.6% to 5.3%	≤2.8%
P009	DM-995A	Plasma	-7.06% to 2.33%	≤4.23%
P010	DM-995A	Plasma	-10.79% to -8.67%	≤6.49%
P011	DM-995A	Plasma	5.1% to 6.8%	≤6.1%
P014	DM-995A	Plasma	-7.6% to 1.6%	≤5.4%
P015	DM-995A	Plasma	-2.0% to 1.1	≤9.3%
P016	DM-995A	Plasma	-2.3% to 1.0%	≤3.0%
P017	DM-995A	Plasma	0.3% to 8.1%	≤5.2%
P019	DM-995A	Plasma	1.7% to 8.0%	≤5.6%
P020	DM-995A	Plasma	-0.5% to 6.4%	≤7.3%
P026	DM-995A	Plasma	-5.0% to -2.4	≤7.9%
P029	DM-995A	Plasma	-8.3% to -5.8%	≤9.2%
P031	150600MWP1439HPL_S[b]	Plasma	-3.1% to -0.7%	≤4.0%
P034	DM-995Av3	Plasma	-5.3% to 1.1%	≤3.8%
P035	DM-995A	Plasma	-5.0% to -0.6%	≤3.4%
P037	DM-995Av3	Plasma	-4.7% to -1.1%	≤8.8%
P038	DM-995Av3	Plasma	-3.0% to -0.5%	≤5.3%
P039	DM-995Av3	Plasma	-2.8% to -1.3%	≤4.1%
P042	150600MWP1439HPL_S[b]	Plasma	-2.3% to 1.3%	≤5.7%
P043	DM-995A	Plasma	-3.9% to 2.3%	≤6.4%
P044	BP-0155	Plasma	1.0% to 1.3%	≤3.1%
P045	150600MWP1439HPL_S[b]	Plasma	-8.9% to -1.7%	≤5.9%
P046	150600MWP1439HPL_S[b]	Plasma	-3.4% to -0.7%	≤3.1%
P049	150600MWP1439HPL_S[b]	Plasma	-2.5% to 1.0%	≤3.2%
P050	ANI 11059.01	Plasma	0.42% to 8.62%	≤8.49%
P051	ANI 11059.01	Plasma	-9.72% to 3.47%	≤3.37%

Clinical Trial	Method	Matrix	Inter-run Accuracy %RE[a]	Inter-run Precision %CV[a]
P052	ANI 11059.01	Plasma	-4.38% to 0.33%	≤13.49%
P053	ANI 11059.01	Plasma	-2.89% to 1.70%	≤6.28%

Abbreviations: %CV=percent coefficient of variation; %RE=percent relative error; ISR-incurred sample reproducibility; QC=quality control; SOP-standard operating procedure

[a] Statistics (%RE and %CV) based on mean assay performance of low, mid, high and dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.

[b] Following the acquisition of [redacted], the method known as DM-995A was re-issued as method 150600MWP1439HPL_S

Source: [Ref. 5.3.3.1: P001V01], [Ref. 5.3.3.4: P002MK1439], [Ref. 5.3.3.4: P003]; [Ref. 5.3.4.1: P005V01], [Ref. 5.3.3.1: P006MK1439], [Ref. 5.3.3.1: P008], [Ref. 5.3.3.3: P009], [Ref. 5.3.3.4: P010], [Ref. 5.3.3.4: P011V01], [Ref. 5.3.1.2: P014], [Ref. 5.3.1.2: P015], [Ref. 5.3.3.4: P016], [Ref. 5.3.4.1: P017], [Ref. 5.3.3.3: P019], [Ref. 5.3.3.4: P020], [Ref. 5.3.1.2: P026], [Ref. 5.3.1.1: P029], [Ref. 5.3.3.1: P031MK1439] ,[Ref. 5.3.1.2: P034], [Ref. 5.3.3.4: P035], [Ref. 5.3.1.1: P037], [Ref. 5.3.3.4: P038V01], [Ref. 5.3.1.2: P039], [Ref. 5.3.3.4: P042], [Ref. 5.3.1.2: P043]; [Ref. 5.3.1.1: P044], [Ref. 5.3.3.4: P045], [Ref. 5.3.1.2: P046MK1439], [Ref. 5.3.1.2: P049MK1439], [Ref. 5.3.3.4: P050MK1439], [Ref. 5.3.3.3: P051MK1439], [Ref. 5.3.1.2: P052MK1439], [Ref. 5.3.3.4: P053]

Table 2.7.1: 7 Parameters and Validation Metrics for Assay DM-955A

Assay Conditions	
Sample Storage Temperature	-20°C
Extraction Method	Liquid-liquid Extraction with MTBE
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	100 µL
Regression Weighting	Linear, $1/conc^2$
Quantification	Peak Area Ratios
Calibration Range	1.00 to 1000 ng/mL
ULOQ	1000 ng/mL
LLOQ	1.00 ng/mL
Validation (VQC) Sample Concentrations	1.00, 3.00, 80.0, 800, and 16,000 (VS-DIL) ng/mL
Assay Performance	
Intra-assay Validation (VQC) Sample Statistics	
Precision (%CV)	<12.26%
Accuracy (%)	97.79 – 109%
Recovery	
Mean Analyte Recovery	≥91%
Selectivity	
Matrix	6 out of 6 Human K_2EDTA plasma lots passed including 1 lot of hemolyzed plasma and 1 lot of hyperlipidemic plasma
Mean IS Normalized Matrix Factor	>0.94 determined in 6 lots of Human K_2EDTA plasma
Analyte Carryover	≤ 20% of mean analyte LLOQ response
Internal Standard Carryover	≤ 5% of internal standard response

Assay Performance	
Stability	
Primary Stock Solution	134 days at 4°C
High Working Solution	128 days at 4°C
	127 days at 4°C followed by 18 hours at room temperature
Low Working Solution	128 days at 4°C
	127 days at 4°C followed by 18 hours at room temperature
Ambient Matrix Stability	5 days at room temperature in Human K_2EDTA plasma
Frozen Storage Matrix Stability Established at Validation	409 days at -20°C and -70°C
Freeze/Thaw Matrix Stability	6 cycles at -20°C in Human K_2EDTA plasma
Extract Stability	177 hours at -20°C for dried extracts
	176 hours at 4°C for extracts reconstituted in 50:50 ACN:water containing 0.1% formic acid.
	105 hours at 10°C in 50:50 ACN:water containing 0.1% formic acid.
Re-injection Reproducibility Stability	117.5 hours at 10 °C
Abbreviations: %CV=percent coefficient of variation; QC=quality control; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification; VS-DIL=validation sample-dilution QC.	

Source: [Ref. 5.3.1.4: 046JM9]

1.4.2 Bioanalytical Methods for Lamivudine

Concentrations of 3TC were determined using LC/MS-MS detection methods that were validated in accordance with current regulatory guidance. The development and validation of these bioanalytical methods were performed at CROs and were used to support plasma sample analysis for the DOR and DOR/3TC/TDF clinical development programs. A summary of each assay method is provided in [Table 2.7.1: 8].

The bioanalytical method used to support the 3TC assay in the clinical trials listed in this submission, along with the inter-run accuracy and precision data for each study, are listed in [Table 2.7.1: 9]. ISR assessment was conducted and met the acceptance criteria for all 3TC analyses associated with trials listed in [Table 2.7.1: 9]. All clinical samples were analyzed within the established stability period of the analyte.

The parameters and validation metrics for the 3TC bioanalytical method used to support plasma sample analysis for the majority of the trials in this submission are presented in [

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Table 2.7.1: 10]. Similar information for the second assay used during this clinical development program can be found in the bioanalytical reports that are appended to the CSRs as well as in the method validation reports that are included in [Sec. 5.3.1.4] of this submission, Reports of Biopharmaceutic Studies – Reports of Bioanalytical and Analytical Methods for Human Studies.

Table 2.7.1: 8 Summary of Lamivudine Validated Analytical Methods

Method Validation Report	Laboratory	Analyte	LLOQ (ng/mL)	Linear Range (ng/mL)	Matrix
95077VGD	[redacted][a]	3TC	10.01	10.03 to 5012.6	Plasma
[redacted]-1453-13	[redacted][b]	3TC	5.00	5.00 to 3000	Plasma

Abbreviations: LLOQ-lower limit of quantification.
[a] [redacted] Canada [redacted]
[b] [redacted] Canada, [redacted]

Source: [Ref. 5.3.1.4: 04MH89], [Ref. 5.3.1.4: 04MJKD], [Ref. 5.3.1.4: 04PFY0]

Table 2.7.1: 9 Bioanalytical Methods Used to Support Lamivudine Determination in Each Clinical Trial Together With Study Assay Performance

Clinical Trial	Method	Analyte	Inter-run Accuracy %RE[a]	Inter-run Precision %CV[a]
P014	ANI 9866.02	3TC	-0.68% to 4.34%	≤5.15%
P015	[redacted]-1453-13 v.00	3TC	-3.7% to -1.4%	≤2.9%
P026	[redacted]-1453-13 v.00	3TC	-11.5% to -0.20%	≤12.5%
P029	[redacted]-1453-13 v.00	3TC	-8.5% to 1.3%	≤11.2%

Abbreviations: %CV=percent coefficient of variation; %RE=percent relative error; ISR-incurred sample reproducibility; QC=quality control; SOP-standard operating procedure

[a] Statistics (%RE and %CV) based on mean assay performance of low, mid, high and dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.

Source: [Ref. 5.3.1.2: P014], [Ref. 5.3.1.2: P015], [Ref. 5.3.1.2: P026], [Ref. 5.3.1.1: P029]

Table 2.7.1: 10 Parameters and Validation Metrics for Assay [redacted]-1453-13 v.00

Assay Conditions	
Sample Storage Temperature	-25°C
Extraction Method	Protein Precipitation
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	100 µL
Regression Weighting	Quadratic, 1/conc.
Quantification	Peak Area Ratios
Calibration Range	5.00 to 3000 ng/mL
ULOQ	3000 ng/mL
LLOQ	5.00 ng/mL
Validation (VQC) Sample Concentrations	15.0, 1500, 2300, and 4600 ng/mL
Assay Performance	
Intra-assay Validation (VQC) Sample Statistics	
Precision (%CV)	≤4.3%
Accuracy (%)	95.3% to 108.5%
Recovery	
Mean Analyte Recovery	≥92.1%
Mean Internal Standard Recovery	95.6%
Selectivity	
Matrix	6 out of 6 Human K_2EDTA plasma lots passed
Mean IS Normalized Matrix Factor	≥0.981 determined in 8 lots of Human K_2EDTA plasma
Analyte Carryover	≤ 20% of mean analyte LLOQ response
Internal Standard Carryover	≤ 5% of internal standard response
Stability	
Primary Stock Solution	6 hours at room temperature
	425 days at 5°C
Working Solution	6.0 hours at room temperature
Short Term Matrix Stability	19.0 hours at room temperature in Human K_2EDTA plasma
	19.0 hours at 5°C in Human K_2EDTA plasma
Frozen Storage Matrix Stability Established at Validation	1148 days at -25°C in Human K_2EDTA plasma
Freeze/Thaw Matrix Stability	5 cycles at -25°C in Human K_2EDTA plasma
Extract Stability	140.5 hours at 5°C
Abbreviations: %CV=percent coefficient of variation; QC=quality control; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification.	

Source: [Ref. 5.3.1.4: 04MJKD], [Ref. 5.3.1.4: 04PFY0]

1.4.3 Bioanalytical Methods for Tenofovir

Concentrations of tenofovir in human plasma were determined using LC/MS-MS detection methods that were validated in accordance with current regulatory guidance. The development and validation of these bioanalytical methods were performed at CROs and were used to support plasma sample analysis for the DOR and DOR/3TC/TDF clinical development programs. A summary of each assay method is provided in [Table 2.7.1: 11].

The bioanalytical methods used to support the tenofovir assay in the clinical trials listed in this submission, along with the inter-run accuracy and precision data for each trial, are listed in [Table 2.7.1: 12]. ISR assessment was conducted and met the acceptance criteria for tenofovir analyses associated with trials listed in [Table 2.7.1: 12]. All clinical samples were analyzed within the established stability period of the analyte.

The parameters and validation metrics for the primary tenofovir bioanalytical plasma method used for this submission are presented in [Table 2.7.1: 13]. Similar information for the other assays used during this clinical development program can be found in the bioanalytical reports that are appended to the CSRs as well as in the method validation reports that are included in (Section. 5.3.1.4) of this submission, Reports of Biopharmaceutic Studies – Reports of Bioanalytical and Analytical Methods for Human Studies.

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Table 2.7.1: 11 Summary of Tenofovir Validated Analytical Methods

Method Validation Report	Laboratory	Analyte	LLOQ (ng/mL)	Linear Range (ng/mL)	Matrix
135013AHUE	[redacted][a]	Tenofovir	0.50	0.05 to 500.00	Plasma
[redacted]-1271-11	[redacted][b]	Tenofovir	2.00	2.00 to 500	Plasma

Abbreviations: LLOQ-lower limit of quantification.

[a] [redacted] Canada [redacted]

[b] [redacted] Canada, [redacted]

Source: [Ref. 5.3.1.4: 04MJLQ], [Ref. 5.3.1.4: 04MJKD], [Ref. 5.3.1.4: 04PFWK], [Ref. 5.3.1.4: 04PFV0]

Table 2.7.1: 12 Bioanalytical Methods Used to Support Tenofovir Bioanalysis in Each Clinical Trial Together With Study Assay Performance

Clinical Trial	Method	Analyte	Inter-run Accuracy %RE[a]	Inter-run Precision %CV[a]
P014	ANI 10554.03	Tenofovir	-1.2% to 0.69%	≤7.30%
P015	[redacted]-1271-11 v.00	Tenofovir	-0.5% to 1.0%	≤2.2%
P026	[redacted]-1271-11 v.00	Tenofovir	-1.7% to 0.1%	≤2.8%
P029	[redacted]-1271-11 v.00	Tenofovir	-2.2% to -0.3%	≤2.7%

Abbreviations: %CV=percent coefficient of variation; %RE=percent relative error; ISR-incurred sample reproducibility; QC=quality control; SOP-standard operating procedure

[a] Statistics (%RE and %CV) based on mean assay performance of low, mid, high and dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.

Source: [Ref. 5.3.1.2: P014], [Ref. 5.3.1.2: P015], [Ref. 5.3.1.2: P026], [Ref. 5.3.1.1: P029]

Table 2.7.1: 13 Parameters and Validation Metrics for Assay [redacted]-1271-11 v.00

Assay Conditions	
Sample Storage Temperature	-25°C
Extraction Method	Derivatization followed by solid phase extraction
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	100 µL
Regression Weighting	Linear, 1/conc.
Quantification	Peak Area Ratios
Calibration Range	2.00 to 500 ng/mL
ULOQ	500 ng/mL
LLOQ	2.00 ng/mL
Validation (VQC) Sample Concentrations	2.00, 6.00, 200, 400 and 800 ng/mL
Assay Performance	
Intra-assay Validation (VQC) Sample Statistics	
Precision (%CV)	≤6.1%
Accuracy (%)	98.0% to 106.5%
Recovery	
Mean Analyte Recovery	≥55.5%
Mean Internal Standard Recovery	63.6%
Selectivity	
Matrix	15 out of 15 Human K_2EDTA plasma lots passed
Mean IS Normalized Matrix Factor	≥0.990 determined in 8 lots of Human K_2EDTA plasma
Analyte Carryover	≤ 20% of mean analyte LLOQ response
Internal Standard Carryover	≤ 5% of internal standard response
Stability	
Primary Stock Solution	6.0 hours at room temperature 327 days at 5°C
Working Solution	24.0 hours at room temperature
Short Term Matrix Stability	18.75 hours at room temperature in Human K_2EDTA plasma 19.0 hours at 5°C in Human K_2EDTA plasma
Frozen Storage Matrix Stability Established at Validation	1166 days at -25°C in Human K_2EDTA plasma
Freeze/Thaw Matrix Stability	5 cycles at -25°C in Human K_2EDTA plasma
Extract Stability	80.50 hours at 5°C

Abbreviations: %CV=percent coefficient of variation; QC=quality control; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification.

Source: [Ref. 5.3.1.4: 04MJHK], [Ref. 5.3.1.4: 04PFWK], [Ref. 5.3.1.4: 04PFV0]

1.4.4 Other Bioanalytical Methods Used During the Clinical Program

Methods for the determination of midazolam [Ref. 5.3.1.4: 04MJQV], [Ref. 5.3.1.4: 04MJRQ], [Ref. 5.3.1.4: 04MJRX], [Ref. 5.3.1.4: 04MJS5], [Ref. 5.3.1.4: 04MJS9], ethinyl estradiol [Ref. 5.3.1.4: 04MH85], efavirenz [Ref. 5.3.1.4: 04NQZH], levonorgestrel [Ref. 5.3.1.4: 04MHBK], atorvastatin [Ref. 5.3.1.4: 04MJKW], methadone [Ref. 5.3.1.4: 04MJHG], metformin [Ref. 5.3.1.4: 04MJKN], elbasvir and grazoprevir [Ref. 5.3.1.4: 04MJH8], ledipasvir [Ref. 5.3.1.4: 04MH8R], and sofosbuvir and GS-331007 [Ref. 5.3.1.4: 04MJLF] were utilized during the clinical development program to support trials in which these compounds were co-administered with DOR. Assay performance details may be found in the bioanalytical reports, which are appended to the CSR of the trial in which the assay was used. Validation reports for these methods are included in (Section 5.3.1.4) of this submission, Reports of Biopharmaceutic Studies – Reports of Bioanalytical and Analytical Methods for Human Studies.

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1 Biocomparison and Bioavailability Trials

2.1.1 Doravirine Relative and Absolute Bioavailability Trials

2.1.1.1 Comparative Bioavailability Study to Determine the Bioequivalence of Doravirine Coated and Uncoated Tablets in Healthy Subjects (P039)

This was an open-label, single-dose, randomized, 2-period, 2-treatment, 2-sequence, crossover trial in twenty-four (24) healthy male and female subjects, under fasted conditions. In one period, subjects received a 100 mg DOR uncoated tablet (PMF OCT). In the other period, subjects received a 100 mg DOR coated tablet (FMI FCT). There was a 7-day washout between periods.

Results

The GMR (90% CI) for DOR PK results are presented in in [Table 2.7.1: 14]. For discussion and interpretation of results, refer to [Sec. 2.7.1.3.1], [Sec. 2.7.1.3.2.1].

Table 2.7.1: 14 Comparative Bioavailability of Doravirine Coated and Uncoated Tablets

Comparison	N	AUC0-inf	Cmax	C24
		GMR (90% CI)	GMR(90% CI)	GMR (90% CI)
Coated tablet / Uncoated tablet	24	1.03 (0.99, 1.08)	1.10 (1.01, 1.20)	1.05 (1.00, 1.11)

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2.1.1.2 Pharmacokinetics of the Intravenous Microdose Formulation of Doravirine in Healthy Subjects (P044)

This was a single-dose, single-period, open-label trial in twelve (12) healthy male and female subjects under fasted conditions. Eleven (11) of the twelve subjects were included in the PK analysis. Each subject received a single intravenous (IV) dose of 100 µg DOR administered via infusion syringe over a period of 15 minutes.

Results

The geometric mean (% CV) for DOR PK results following a single IV dose of 100 µg DOR are presented in [Table 2.7.1: 15]. For discussion and interpretation of results, refer to [Sec. 2.7.1.3.1].

Table 2.7.1: 15 Pharmacokinetic Results of Doravirine Intravenous Microdose Formulation Study

Regimen	N	Geometric Mean (% CV)				
		AUC0-inf (nM•hr)	Cmax [Ceoi]* (nM)	CL (L/h)	Vdss (L)	Terminal t1/2 (hr)
DOR 100 µg IV infusion	11	63.1 (28.3)	8.47 (30.1)	3.73 (28.3)	60.5 (18.5)	12.16 (25.3)
*Ceoi = concentration at the end of infusion						

2.1.2 Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate Relative Bioavailability Trials

2.1.2.1 Comparative Bioavailability of Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate in Healthy Subjects under Fasted Conditions (P026)

This was an open-label, single-dose, randomized, 2-period, crossover trial in twenty-four (24) healthy male and female subjects. In one period, subjects received a tablet of FMI DOR/3TC/TDF. In the other period, subjects received 100 mg DOR (PMF OCT), 245 mg VIREAD® (tenofovir disoproxil as fumarate), and 300 mg EPIVIR® as individual tablets. There was a 7-day washout between periods.

Results

The GMR (90% CI) for DOR, 3TC and tenofovir PK results are presented in [Table 2.7.1: 16]. For discussion and interpretation of results, refer to [Sec. 2.7.1.3.2.2].

Table 2.7.1: 16 Relative Bioavailability Comparison of Final Market Image Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate to Co-administration of Individual Components

Comparison	Compound (Dose [mg])	N	AUC0-inf	Cmax	C24
			GMR (90% CI)	GMR(90% CI)	GMR (90% CI)
FMI DOR/3TC/TDF / DOR+3TC+TDF	DOR (100 mg)	24	1.01 (0.94, 1.08)	0.99 (0.91, 1.09)	1.02 (0.94, 1.12)
	3TC (300 mg)	24	1.04 (1.00, 1.09)	1.00 (0.91, 1.09)	NC†
	TDF* (245 mg)	24	0.98 (0.93, 1.03)	0.87 (0.78, 0.97)	NC†
†NC = not calculated; * tenofovir disoproxil as fumarate; PK parameters represent plasma tenofovir concentrations					

2.2 Effect of Food

2.2.1 Comparative Fed and Fasted Bioavailability Trials

2.2.1.1 Comparative Fed and Fasted Bioavailability of Doravirine in Healthy Subjects (P037)

This was an open-label, single-dose, randomized, 2-period, 2-treatment, 2-sequence crossover trial in fourteen (14) healthy male and female subjects. In one period, subjects received a 100 mg tablet of DOR (PMF OCT) under fasted conditions. In the other period, subjects received a 100 mg tablet of DOR (PMF OCT) under high-fat fed conditions. There was a 7-day washout between periods.

Results

The GMR (90% CI) for DOR PK results are presented in [Table 2.7.1: 17]. For discussion and interpretation of results, refer to [Sec. 2.7.1.3.3.1].

Table 2.7.1: 17 Relative Bioavailability Comparison of Doravirine under Fed and Fasted Conditions

Comparison	N	AUC0-inf	Cmax	C24
		GMR (90% CI)	GMR(90% CI)	GMR (90% CI)
Fed / Fasted	14	1.16 (1.06, 1.26)	1.03 (0.89, 1.19)	1.36 (1.19, 1.55)

2.2.1.2 Comparative Fed and Fasted Bioavailability of Doravirine/Lamivudine /Tenofovir Disoproxil Fumarate in Healthy Subjects (P029)

This was an open-label, single-dose, randomized, 2-period, 2-treatment crossover trial in fourteen (14) healthy male and female subjects. In one period, subjects received FMI DOR/3TC/TDF under fasted conditions. In the other period, subjects received FMI DOR/3TC/TDF under high fat fed conditions. There was a 7-day washout between periods.

Results

The GMR (90% CI) for DOR, 3TC and tenofovir PK results are presented in [Table 2.7.1: 18]. For discussion and interpretation of results, refer to [Sec. 2.7.1.3.3.1].

Table 2.7.1: 18 Relative Bioavailability Comparison of the Final Market Image Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate under Fed and Fasted Conditions

Comparison	Compound (Dose [mg])	N	AUC0-inf	Cmax	C24
			GMR (90% CI)	GMR(90% CI)	GMR (90% CI)
Fed/Fasted	DOR (100 mg)	14	1.10 (1.01, 1.20)	0.95 (0.80, 1.12)	1.26 (1.13, 1.41)
	3TC (300 mg)	14	0.93 (0.84, 1.03)	0.81 (0.65, 1.01)	NC†
	TDF* (300 mg)	14	1.27 (1.17, 1.37)	0.88 (0.74, 1.04)	NC†
†NC = not calculated; * PK parameters represent plasma tenofovir concentrations					

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1 Doravirine Bioavailability

Absolute oral bioavailability of the FMI 100 mg DOR tablet was estimated using a population PK model-based approach with PK data following administration of a 100 µg IV microdose (P044) and following oral administration of the FMI in the trial establishing bioequivalence between the OCT and FMI (P039). The absolute oral bioavailability of the FMI 100 mg DOR tablet is ~64% [Ref. 5.3.5.3: 04R3RP]. Following single oral ascending doses between 6 and 450 mg, DOR exposure was less than dose proportional (P001) [Sec. 2.7.2.3.1.1.3]. Of note, the less than dose proportional PK of DOR is consistent with absorption limitations due to low solubility [Sec. 2.7.1.1.2.1] and is observed following oral administration. Consequently, the less than dose proportional PK does not impact the estimation of absolute bioavailability at the 100 mg dose using the IV microdose data.

3.2 Biocomparison/Bioequivalence

3.2.1 Doravirine Relative Bioavailability/Bioequivalence

The key formulations used in the clinical development of DOR are the FFP and PMF uncoated OCTs. The FFP OCT was used for the first in human and early trials. The PMF OCT was used in the majority of Phase 1, Phase 2 and Phase 3 trials to understand the biopharmaceutic and PK characteristics of the compound, and to evaluate the efficacy and safety of DOR. The differences between the FFP and PMF formulations were minor and not considered likely to impact in vivo performance. The only difference between the PMF OCT and the FMI FCT is the addition of the film coating to the latter.

The in vivo performance of the DOR PMF OCT and the FCT was bridged in a bioequivalence trial (P039), where the bioequivalence of the FCT and the PMF OCT was established. Intersubject variability in the PK parameter values was generally low for both formulations [Ref. 5.3.1.2: P039: 2]. As shown in [Table 2.7.1: 19], the geometric mean ratios (GMRs) of AUC0-inf and Cmax for DOR and 90% CIs are contained within [0.80, 1.25]. This result supports the use of the FCT as the intended formulation for commercialization.

Table 2.7.1: 19 Bioequivalence of the Pre-Market Formulation Oral Compressed Tablet (OCT) and the Final Market Image Film Coated Tablet (FCT) (P039)

Comparison	Compound (Dose [mg])	N	AUC0-inf	Cmax	C24
			GMR (90% CI)	GMR(90% CI)	GMR (90% CI)
DOR(FCT) / DOR (OCT)	DOR (100 mg)	24	1.03 (0.99, 1.08)	1.10 (1.01, 1.20)	1.05 (1.00, 1.11)

3.2.2 Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate Relative Bioavailability

The relative bioavailability of the FMI DOR/3TC/TDF tablet used in a pivotal Phase 3 trial (P021) and intended for commercialization was measured against co-administration of single tablets of DOR (PMF OCT), EPIVIR® and VIREAD® (P026). Exposures (AUC0-inf) of the three components in DOR/3TC/TDF fell within BE bounds when compared to those following co-administration of the individual component tablets. The GMR and 90% CIs for Cmax and C24 for DOR and Cmax for 3TC were also within BE bounds, but fell slightly outside BE bounds for tenofovir Cmax. Tenofovir Cmax was slightly decreased (13%) when administered as DOR/3TC/TDF compared to administration of the marketed formulation of VIREAD®. These data are summarized in [Table 2.7.1: 20]. The efficacy of TDF is associated with tenofovir Cmin and AUC [Ref. 5.4: 045VD4]. Reductions of up to 38% in tenofovir Cmax have not warranted dose adjustment [Ref. 5.4: 03QB08]. Therefore, the decrease in Cmax is not expected to be clinically meaningful. This statement is supported by

the Phase 3 safety and efficacy results of DOR/3TC/TDF (P021) [Sec. 2.7.4.2.4.6], [Sec. 2.7.3.2.3.2-trtmtnve48wk]. The relative bioavailability trial (P026) bridged the Phase 1, 2, and 3 trial results using the DOR single entity tablet to DOR/3TC/TDF, as well as bridging the marketed doses of EPIVIR® (300 mg) and VIREAD® (300 mg TDF/245 mg tenofovir disoproxil as fumarate) to DOR/3TC/TDF. Therefore, the safety and efficacy profile of DOR demonstrated following administration of DOR/3TC/TDF can be applied to the DOR single tablet entity and the single entity profiles can be applied to DOR/3TC/TDF.

Table 2.7.1: 20 Comparable Performance of Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate vs. Individual Tablets (P026)

Comparison	Compound (Dose [mg])	N	AUC0-inf	Cmax	C24
			GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
FMI DOR/3TC/TDF / DOR+ 3TC + TDF	DOR (100mg)	24	1.01 (0.94, 1.08)	0.99 (0.91, 1.09)	1.02 (0.94, 1.12)
	3TC (300 mg)	24	1.04 (1.00, 1.09)	1.00 (0.91, 1.09)	NC†
	TDF* (245 mg)	24	0.98 (0.93, 1.03)	0.87 (0.78, 0.97)	NC†

†NC = not calculated; *tenofovir disoproxil as fumarate; PK parameters represent plasma tenofovir concentrations

3.3 Food and Acid Reducing Agent Effect

3.3.1 Food Effect

A probe food effect assessment of DOR was conducted in P001 with the single entity FFP OCT at 50 mg. Administration with a high fat meal increased DOR AUC0-inf and C24 by 33% and 56%, respectively, but didn't remarkably change Cmax (decreased by 5%). To further support dosing recommendations for the pivotal Phase 3 trials and product registration, the effect of a standard high-fat meal on the PK of the DOR OCT and DOR/3TC/TDF was formally assessed in definitive food effect trials in healthy subjects (P037 for the DOR OCT and P029 for FMI DOR/3TC/TDF). Food increased DOR AUC0-inf and C24 by 16% and 36%, respectively, and again did not remarkably change Cmax (increased by 3%). These results are expected to apply to the FMI DOR FCT, given the bioequivalence of the FMI DOR FCT to the DOR OCT. Similarly, administration of DOR/3TC/TDF with food increased DOR AUC0-inf and C24 by 10% and 26%, respectively, but had no significant effect on Cmax (decreased by 5%) [Table 2.7.1: 21]. Increases to C24 with food are likely due to slightly delayed Tmax [Appendix 2.7.1: 1]. 3TC AUC0-inf and Cmax decreased by 7% and 19% respectively, while tenofovir AUC0-inf increased by 27% and Cmax decreased by 12%.

The decrease in Cmax seen for 3TC has been described previously. The US and EU prescribing information [Ref. 5.4: 04P95N] [Ref. 5.4: 03TFTP] describe a 40 - 47% decrease in Cmax when EPIVIR® is administered with food. However, due to lack of change in AUC0-inf with food, EPIVIR® may be taken without regard to food.

According to the US and EU prescribing information, administration of VIREAD® 300 mg tablets following a high-fat meal increases the oral bioavailability, with an increase in tenofovir AUC0-inf of approximately 40% and an increase in Cmax of approximately 14%. Administration of TDF with a light meal did not have a significant effect on the PK of tenofovir when compared to fasted administration of the drug [Ref. 5.4: 04P95P] [Ref. 5.4: 04N7D7]. These data are, however, interpreted differently in the two VIREAD® prescribing information documents. The US prescribing information [Ref. 5.4: 04P95P] states that TDF may be taken without respect to food, whereas the EU prescribing information [Ref. 5.4: 04N7D7] states that TDF should be administered with food in order to maximize exposure. The ATRIPLA® (FDC of efavirenz/emtricitabine/TDF) EU prescribing information, however, states that it should not be taken with food (to reduce the likelihood of adverse events associated with efavirenz) and that the resulting reduction in tenofovir exposure is not expected to be clinically relevant in virologically suppressed patients [Ref. 5.4: 0455SJ]. In the Phase 3 program, which achieved positive safety [Sec. 2.7.4.2.4.6] and efficacy [Sec. 2.7.3.2.3.2-trtmtnve48wk] results, DOR/3TC/TDF was dosed without regard to food. Therefore, DOR and DOR/3TC/TDF may be dosed without regard to food.

Table 2.7.1: 21 The Effect of Food on Component Pharmacokinetics Following Administration of the DOR Tablet or Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

Protocol	Comparison	Compound (Dose [mg])	N	AUC0-inf GMR (90% CI)	Cmax GMR (90% CI)	C24 GMR (90% CI)
P001	Fed/Fasted	DOR OCT (50 mg)	6	1.33 (1.07, 1.65)	0.95 (0.74, 1.23)	1.56 (1.22, 2.01)
P037	Fed/Fasted	DOR OCT (100 mg)	14	1.16 (1.06, 1.26)	1.03 (0.89, 1.19)	1.36 (1.19, 1.55)
P029[I]	Fed/Fasted	DOR (100 mg)	14	1.10 (1.01, 1.20)	0.95 (0.80, 1.12)	1.26 (1.13, 1.41)
		3TC (300 mg)		0.93 (0.84, 1.03)	0.81 (0.65, 1.01)	NC[†]
		TDF* (300 mg)		1.27 (1.17, 1.37)	0.88 (0.74, 1.04)	NC[†]

[I]Dosed as FMI DOR/3TC/TDF; [†]NC = not calculated; * PK parameters represent plasma tenofovir concentrations

3.3.2 Effect of Acid Reducing Agents

The solubility of DOR is not pH dependent [Sec. 2.7.1.1.2.1]. The PK performance of the DOR tablet was evaluated in the presence of gastric acid modifying agents, namely antacids (oral suspension containing aluminum hydroxide, magnesium hydroxide and simethicone) and pantoprazole, a proton pump inhibitor (P042) [Sec. 2.7.2.2.3.1.7], [Sec. 2.7.2.3.1.1.6]. In this trial, only minor changes in trough concentration (16% reduction) and exposure (AUC0-inf) (17% reduction) were observed for the DOR tablet when co-administered with antacids or pantoprazole relative to administration without these agents, consistent with the lack of pH dependent solubility of DOR. These changes are well within the DOR PK comparability bounds of (0.6, 3.0) [Sec. 2.7.2.1.5.4] and are not clinically meaningful. Given that administration of DOR has been assessed across a wide range of gastric pH conditions including administration without pH altering agents (pH <2), with antacids (pH ~3), and with pantoprazole (pH ~3-5 [Ref. 5.4: 043X96]), the lack of a meaningful impact on DOR exposure supports that any alteration of gastric pH with an acid-reducing agent will not affect absorption. Thus, DOR may be co-administered without any restriction with agents that modulate gastric pH.

4 CONCLUSIONS

The in vitro and in vivo studies summarized in this section support the following conclusions regarding the biopharmaceutic properties of DOR:

- DOR is a BCS class II compound. DOR is formulated as [redacted] based tablet and key formulations were shown to be bioequivalent in a clinical trial.

- DOR, 3TC and TDF, dosed as a FDC tablet, were shown to have exposures within bioequivalence bounds to DOR, EPIVIR®, and VIREAD®, dosed in combination as single entity tablets. Thus, the PK, safety, and efficacy of DOR when administered as DOR/3TC/TDF can be applied to DOR.

- Absolute bioavailability of the DOR 100 mg FMI tablet is ~64%.

- Food does not have a clinically meaningful effect on the PK of DOR. DOR may be administered without regard to food.

- Co-administration of DOR with acid-reducing agents has no clinically meaningful effect on DOR PK, consistent with the lack of pH dependent solubility. Thus, DOR may be co-administered without any restrictions for agents that modulate gastric pH.

5 APPENDIX

Appendix 2.7.1: 1 Table of Pharmacokinetic Data From Biopharmaceutics Trials for Doravirine (DOR, MK-1439) and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF, MK-1439A)

Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% CI)					GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439A-014††	A Fasted Bioavailability Study of Two Probe MK-1439A Formulations	2 x (50 mg MK-1439 / 150 mg 3TC / 150 mg TDF) (MK-1439A Monolithic FFP1 Formulation)	Healthy Male and Female Subjects, Aged 18-55 yrs	1	24	MK-1439	1.51 (1.32, 1.71)	0.687 (0.608, 0.776)	3.00 (1.00, 12.00)	42.7 (38.5, 47.4)	17.35 (25.5)	0.98 (0.89, 1.07)	1.02 (0.93, 1.12)	1.00 (0.93, 1.08)	MK-1439A FFP1 / (MK-1439 + 3TC + TDF)
				1	24	3TC	2170 (1900, 2480)	--	2.00 (1.00, 3.00)	11100 (10000, 12300)	12.59 (62.3)	0.93 (0.86, 1.00)	--	1.02 (0.98, 1.07)	
				1	24	TFV	202 (174, 235)	--	1.00 (1.00, 2.08)	1980 (1710, 2300)	18.03(12.2)	0.91 (0.81, 1.03)	--	0.99 (0.95, 1.04)	
		100 mg MK-1439 / 300 mg 3TC / 300 mg TDF (MK-1439A Probe Bilayer Formulation)		1	24	MK-1439	1.10 (0.986, 1.23)	0.588 (0.530, 0.652)	4.00 (2.00, 6.03)	36.5 (33.2, 40.3)	18.57(26.0)	0.71 (0.65, 0.78)	0.87 (0.82, 0.93)	0.86 (0.80, 0.92)	MK-1439A Probe Bilayer Formulation / (MK-1439 + 3TC + TDF)
				1	24	3TC	2540 (2260, 2850)	--	1.00 (1.00, 2.00)	11900 (10600, 13200)	12.51 (77.3)	1.08 (1.02, 1.15)	--	1.09 (1.05, 1.12)	
				1	24	TFV	192 (167, 222)	--	1.01 (0.50, 3.00)	1950 (1680, 2260)	17.82 (13.3)	0.87 (0.79, 0.96)	--	0.98 (0.92, 1.03)	
		100 mg MK-1439 + 300 mg 3TC + 300 mg TDF		1	23	MK-1439	1.54 (1.37, 1.73)	0.675 (0.609, 0.747)	3.00 (0.50, 6.00)	42.6 (38.5, 47.2)	17.77 (26.6)	--	--	--	--
				1	23	3TC	2340 (2050, 2680)	--	1.00 (0.50, 3.00)	10900 (9760, 12200)	11.56 (66.2)	--	--	--	
				1	23	TFV	221 (183, 268)	--	1.00 (0.50, 3.00)	2000 (1720, 2310)	18.14 (14.1)	--	--	--	

Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% CI)					GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439A-015††	A Fasted Bioavailability Study of a Probe MK-1439A Formulation	100 mg MK-1439/ 300 mg 3TC/ 300 mg TDF (MK-1439A FFP2 Probe Bilayer Formulation)	Healthy Male and Female Subjects, Aged 18-55 yrs	1	24	MK-1439	1.84 (1.59, 2.14)	0.628 (0.538, 0.733)	3.00 (0.50, 6.03)	43.3 (38.5, 48.7)	15.5 (30.9)	1.13 (1.01, 1.26)	1.05 (0.99, 1.13)	1.10 (1.02, 1.18)	MK-1439A FFP2 / (MK-1439 + 3TC + TDF)
				1	24	3TC	2620 (2330, 2940)	--	1.01 (1.00, 4.00)	12900 (12000, 13900)	18.8 (56.7)	0.92 (0.83, 1.02)	--	0.98 (0.94, 1.04)	
				1	24	TFV	242 (205, 286)	--	1.00 (1.00, 3.02)	2440 (2170, 2750)	19.2 (17.7)	0.84 (0.75, 0.93)	--	0.99 (0.92, 1.05)	
		100 mg MK-1439 + 300 mg 3TC + 300 mg TDF		1	24	MK-1439	1.63 (1.48, 1.80)	0.596 (0.517, 0.687)	3.00 (1.00, 4.00)	39.5 (35.8, 43.6)	15.7 (25.1)	--	--	--	--
				1	24	3TC	2840 (2490, 3240)	--	1.00 (0.50, 3.00)	13100 (12100, 14200)	18.5 (58.7)	--	--	--	
				1	24	TFV	289 (259, 323)	--	0.76 (0.50, 2.08)	2480 (2200, 2790)	18.7 (12.3)	--	--	--	

Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% CI)					GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439A-026§	A Comparative Bioavailability Study of MK-1439A under Fasted Conditions	100 mg MK-1439/300 mg 3TC/300 mg TDF (MK-1439A FMI Tablet)	Healthy Male and Female Subjects, Aged 18-65 yrs	1	24	MK-1439	1780 (1540 , 2050)	546 (461, 646)	3.00 (0.50, 12.00)	38.1 (33.1, 43.7)	15.26 (35.1)	0.99 (0.91, 1.09)	1.02 (0.94, 1.12)	1.01 (0.94, 1.08)	MK-1439A FMI Tablet / (MK-1439 + 3TC + TDF)
				1	24	3TC	2730 (2420, 3090)	--	2.00 (1.00, 3.00)	13600 (12400, 14800)	17.29(53.3)	1.00 (0.91, 1.09)	--	1.04 (1.00 ,1.09)	
				1	24	TFV	244 (214 , 279)	--	1.00 (0.50, 3.00)	2400 (2180, 2640)	20.81(15.8)	0.87 (0.78 , 0.97)	--	0.98 (0.93, 1.03)	
		100 mg MK-1439 + 300 mg 3TC +300 mg TDF		1	24	MK-1439	1790 (1580, 2030)	533 (447, 634)	3.51 (1.00, 6.00)	37.7 (32.4, 43.7)	15.89(37.1)	--	--	--	--
				1	24	3TC	2750 (2410, 3130)	--	1.00 (1.00, 4.00)	13000 (11800,14300)	17.36 (45.9)	--	--	--	
				1	24	TFV	282 (239, 331)	--	1.00 (0.50, 2.00)	2450 (2180, 2750)	20.31 (17.4)	--	--	----	
1439A-029§	A Study of the Comparative Fed and Fasted Bioavailability of MK-1439A	Fed: 100 mg MK-1439 / 300 mg 3TC/ 300 mg TDF (MK-1439A FMI Tablet)	Healthy Male and Female Subjects, Aged 18-65 yrs	1	14	MK-1439	1850 (1610, 2120)	680 (548, 843)	6.00 (0.50, 6.00)	41.4 (34.8, 49.4)	13.15 (23.2)	0.95 (0.80, 1.12)	1.26 (1.13, 1.41)	1.10 (1.01, 1.20)	Fed / Fasted
				1	14	3TC	2000 (1680, 2390)	--	3.00 (1.00, 4.02)	12400 (11400, 13400)	17.75 (45.1)	0.81 (0.65, 1.01)	--	0.93 (0.84, 1.03)	
				1	14	TFV	240 (191, 302)	--	3.00 (1.00, 6.00)	3100 (2730, 3530)	19.08 (15.5)	0.88 (0.74, 1.04)	--	1.27 (1.17, 1.37)	
		Fasted: 100 mg MK-1439 / 300 mg 3TC/ 300 mg TDF (MK-1439A FMI Tablet)		1	13	MK-1439	1950 (1600, 2380)	539 (424, 684)	3.00 (0.50, 6.00)	37.7 (31.2, 45.5)	14.18 (29.3)	--	--	--	--
				1	13	3TC	2480 (2120, 2900)	--	1.00 (1.00, 4.00)	13300 (12000, 14600)	17.76 (48.9)	--	--	--	
				1	13	TFV	272 (231, 320)	--	1.00 (0.50, 2.02)	2450 (2190, 2740)	19.33 (13.6)	--	--	--	

Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% Cl)					GMR (90% Cl)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439-034	An Open-Label, Single-Dose, Fixed-Sequence Study to Evaluate the Comparative Bioavailability of Two Nanoparticle Formulations of MK-1439 to the Current Market Image Tablet	100 mg MK-1439 Large Nanoparticles (LN)	Healthy Male and Female Subjects, Aged 19-55 yrs	1	18	MK-1439	1000 (865, 1170)	398 (338, 468)	3.00 (1.00, 6.04)	27.9 (24.2, 32.1)	19.64 (44.6)	0.57 (0.49, 0.65)	0.66 (0.61, 0.72)	0.69 (0.64, 0.75)	MK-1439 LN / MK-1439 Tablet
		100 mg MK-1439 Small Nanoparticles (SN)		1	18	MK-1439	1190 (1070, 1330)	463 (394, 543)	3.50 (1.00, 6.01)	32.0 (28.1, 36.4)	18.86 (35.8)	0.67 (0.60, 0.75)	0.77 (0.73, 0.82)	0.80 (0.75, 0.85)	MK-1439 SN / MK-1439 Tablet
		100 mg MK-1439 Tablet		1	17	MK-1439	1780 (1540, 2050)	599 (508, 706)	3.00 (1.00, 6.00)	40.2 (35.1, 46.0)	15.90 (17.5)	--	--	--	--
1439-037	A Study of the Comparative Fed and Fasted Bioavailability of MK-1439	Fed: 100 mg MK-1439 Oral Compressed Tablet	Healthy Male and Female Subjects, Aged 18-65 yrs	1	14	MK-1439	2010 (1740, 2310)	661 (520, 839)	4.00 (2.00, 12.00)	40.9 (33.7, 49.7)	11.75 (18.6)	1.03 (0.89, 1.19)	1.36 (1.19, 1.55)	1.16 (1.06, 1.26)	Fed/ Fasted
		Fasted: 100 mg MK-1439 Oral Compressed Tablet		1	14	MK-1439	1940 (1670, 2260)	487 (381, 622)	2.50 (1.00, 6.00)	35.4 (30.0, 41.7)	14.35 (31.0)	--	--	--	--
1439-039	A Study to Determine the Bioequivalence of MK-1439 Coated and Uncoated Tablets	100 mg MK-1439 Coated Tablet (FMI Tablet)	Healthy Male and Female Subjects, Aged 18-64 yrs	1	24	MK-1439	2080 (1840, 2350)	569 (462, 700)	2.00 (0.50, 6.00)	41.0 (35.2, 47.7)	15.03 (31.4)	1.10 (1.01, 1.20)	1.05 (1.00, 1.11)	1.03 (0.99, 1.08)	Coated / Uncoated
		100 mg MK-1439 Uncoated Tablet (PMF OCT)		1	24	MK-1439	1890 (1710, 2080)	540 (436, 668)	2.00 (1.00, 6.00)	39.7 (34.1, 46.1)	16.38 (35.9)	--	--	--	--

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Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% Cl)					GMR (90% Cl)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439-043	A Study to Evaluate the Comparative Bioavailability of the Investigational Oral Pediatric Minitablet Formulation of MK-1439 Compared to the Adult Formulation of MK-1439	100 mg MK-1439 Pediatric Minitablets	Healthy Male and Female Subjects, Aged 18-55 yrs	1	24	MK-1439	1150 (992, 1320)	434 (349, 539)	3.02 (0.50, 6.00)	28.1 (23.4, 33.9)	19.06 (34.1)	0.53 (0.47, 0.59)	0.73 (0.64, 0.85)	0.73 (0.68, 0.80)	Pediatric Minitablets /Adult tablet
		100 mg MK-1439 Tablet		1	24	MK-1439	2170 (1820, 2580)	591 (491, 712)	2.00 (0.50, 4.00)	38.3 (32.3, 45.3)	14.21 (27.1)	--	--	--	--
1439-044##	A Study of the Pharmacokinetics of the Intravenous Microdose Formulation of MK-1439	100 μg MK-1439	Healthy Male and Female Subjects, Aged 18-55 yrs	1	11	MK-1439	8.47 (6.95 10.3)	--	0.25 (0.17, 0.25)	63.1 (52.3, 76.0)	12.16 (25.3)	--	--	--	--

Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% CI)					GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439-046‡‡‡	A Rapid Pharmacokinetic Trial of the Bioavailability of Four MK-1439 Nano Formulations in Healthy Adults	150 mg MK-1439 Nanoparticle Formulation ([redacted]% drug loaded [redacted])	Healthy Male and Female Subjects, Aged 18-55 yrs	1	16	MK-1439	1070 (26.5)	395 (31.9)	1.50 (2.51, 6.02)	28.6 (34.6)	20.23 (34.5)	0.70 (0.61, 0.82)	0.82 (0.72, 0.93)	0.96 (0.85, 1.09)	150 mg MK-1439 Nanoparticle Formulation ([redacted]% drug loaded [redacted]) /100 mg MK-1439 Film Coated Tablet
		150 mg MK-1439 Nanoparticle Formulation ([redacted]% drug loaded [redacted])		1	16	MK-1439	1320 (27.8)	508 (23.2)	1.50 (3.01, 6.00)	35.5 (29.6)	19.65 (30.7)	0.87 (0.75, 1.01)	1.05 (0.94, 1.18)	1.13 (1.02, 1.26)	150 mg Nanoparticle Formulation ([redacted]% drug loaded [redacted]) / Coated Tablet
		150 mg MK-1439 Nanoparticle Formulation ([redacted]% drug loaded [redacted])		1	16	MK-1439	1060 (27.0)	412 (28.0)	1.48 (3.00, 6.00)	29.1 (30.3)	20.35 (30.0)	0.70 (0.60, 0.81)	0.85 (0.76, 0.96)	0.99 (0.88, 1.11)	150 mg Nanoparticle Formulation ([redacted]% drug loaded [redacted]) / Coated Tablet
		100 mg MK-1439 Nanoparticle Formulation ([redacted]% drug loaded [redacted])		1	16	MK-1439	1160 (24.2)	402 (32.0)	1.02 (2.00, 4.02)	28.0 (27.5)	18.85 (32.8)	0.76 (0.66, 0.88)	0.83 (0.74, 0.94)	0.89 (0.80, 0.99)	100 mg Nanoparticle Formulation ([redacted]% drug loaded [redacted]) / Coated Tablet
		100 mg MK-1439 Coated Tablet		1	16	MK-1439	1520 (32.5)	483 (33.3)	0.50 (2.00, 4.00)	31.9 (33.9)	16.82 (28.6)	--	--	--	--

Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% CI)					GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439-049	A Comparative Bioavailability Study of Adult MK-1439 and Pediatric Oral Granules Formulations	100 mg MK-1439 Pediatric Oral Granules	Healthy Male and Female Subjects, Aged 18-55 yrs	1	24	MK-1439	926 (787, 1090)	497 (441, 561)	3.00 (1.50, 24.00)	31.7 (27.5, 36.5)	20.19 (39.5)	0.47 (0.40, 0.54)	0.77 (0.71, 0.83)	0.77 (0.71, 0.84)	Pediatric Oral Granules / Tablet
		125 mg MK-1439 Pediatric Oral Granules, with vanilla yogurt		1	12	MK-1439	1720 (1460, 2010)	726 (635, 829)	3.00 (1.00, 4.00)	44.4 (38.3, 51.6)	17.07 (24.9)	0.86 (0.76, 0.99)	1.12 (1.07 , 1.18)	1.08 (1.00, 1.18)	125 mg Pediatric Oral Granules in Vanilla Yogurt / Tablet
		100 mg MK-1439 Pediatric Oral Granules, with vanilla pudding		1	12	MK-1439	743 (640, 863)	512 (452, 580)	6.00 (2.50, 24.00)	29.0 (25.3, 33.3)	19.76 (32.2)	0.37 (0.32, 0.44)	0.79 (0.72, 0.87)	0.71 (0.64, 0.79)	100 mg Pediatric Oral Granules in Vanilla Pudding / Tablet
		100 mg MK-1439 Tablet		1	24	MK-1439	1990 (1740, 2270)	648 (571, 734)	1.81 (0.50, 6.00)	41.0 (36.7, 45.8)	15.82 (24.7)	--	--	--	--

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Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% Cl)					GMR (90% Cl)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
1439-052	A Study of the Comparative Bioavailability of Two Second-Generation Investigational Pediatric Oral Granule Formulations of MK-1439 Compared to the Adult Formulation	100 mg MK-1439 Tablet	Healthy Male and Female Subjects, Aged 18-55 yrs	1	23	MK-1439	2100 (1880, 2340)	650 (556, 759)	2.00 (0.50, 5.00)	43.1 (37.7, 49.3)	15.22 (35.3)	--	--	--	--
		100 mg MK-1439 Uncoated Pediatric Granules		1	24	MK-1439	1950 (1780, 2140)	622 (527, 735)	2.50 (1.00, 4.00)	39.6 (34.3, 45.7)	14.64 (22.8)	0.93 (0.86, 1.01)	0.96 (0.90, 1.02)	0.92 (0.87, 0.97)	Uncoated Pediatric Granules / Tablet
		100 mg MK-1439 Coated Pediatric Granules		1	24	MK-1439	1610 (1440, 1790)	615 (541, 700)	2.50 (1.00, 5.00)	38.5 (33.9, 43.7)	16.16 (31.9)	0.77 (0.70, 0.84)	0.95 (0.89, 1.01)	0.89 (0.85, 0.94)	Coated Pediatric Granules / Tablet
		100 mg MK-1439 Uncoated Pediatric Granules, with vanilla pudding		1	12	MK-1439	2030 (1750, 2360)	645 (539, 773)	1.00 (1.00, 4.00)	43.7 (37.1, 51.5)	14.86 (31.6)	1.04 (0.93, 1.17)	1.04 (0.95, 1.13)	1.10 (1.02, 1.19)	Uncoated Pediatric Granules with vanilla pudding / Uncoated Pediatric Granules
		100 mg MK-1439 Uncoated Pediatric Granules, with apple sauce		1	12	MK-1439	3040 (2750, 3370)	743 (615, 899)	2.00 (0.50, 4.00)	51.2 (43.9, 59.7)	12.06 (26.7)	1.56 (1.43, 1.70)	1.20 (1.09, 1.31)	1.29 (1.20, 1.39)	Uncoated Pediatric Granules with apple sauce / Uncoated Pediatric Granules
		100 mg MK-1439 Coated Pediatric Granules, with vanilla pudding		1	10	MK-1439	1460 (1230, 1730)	588 (502, 689)	2.50 (1.50, 4.00)	38.1 (32.3, 44.9)	17.35 (34.1)	0.90 (0.79, 1.03)	0.96 (0.88, 1.04)	0.99 (0.91, 1.07)	Coated Pediatric Granules with vanilla pudding / Coated Pediatric Granules
		100 mg MK-1439 Coated Pediatric Granules, with		1	11	MK-1439	2560 (2390, 2760)	745 (641, 866)	2.50 (1.00, 4.00)	48.4 (42.5, 55.1)	13.86 (23.3)	1.59 (1.47, 1.73)	1.21 (1.12, 1.30)	1.26 (1.18, 1.34)	Coated Pediatric Granules with apple sauce

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Protocol	Objective	Treatment (Single Dose)	Population	Day	N	Analyte	GM (95% Cl)					GMR (90% Cl)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-inf (μM.hr)	t1/2 ‡ (hr)	Cmax	C24	AUC0-inf	
		apple sauce													/ Coated Pediatric Granules

GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval, 3TC=Lamivudine, TFV= tenofovir (analyte of dosed TDF).
†Tmax: median (range).
‡Geometric mean and percent geometric CV reported for apparent t1/2.
††3TC and TFV AUCs and Cmax were reported in (ng.hr/mL) and (ng/mL) respectively. For MK-1439, Cmax and C24hr were reported in μM units.
§ 3TC and TFV AUCs and Cmax were reported in (ng.hr/mL) and (ng/mL) respectively.
MK-1439 AUCs were reported in nM.hr units.
‡‡‡Geometric mean and percent geometric CV reported for all Pharmacokinetic parameters except Tmax, reported as median (minimum, maximum)

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2.7　臨床概要

2.7.2　臨床薬理試験

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1. BACKGROUND AND OVERVIEW OF DORAVIRINE AND DORAVIRINE/LAMIVUDINE/TENOFOVIR DISOPROXIL FUMARATE

1.1 General Background

Human immunodeficiency virus type 1 (HIV-1) infection remains a significant medical problem despite available therapies and there remains a need for new antiretroviral therapies to improve convenience and tolerability, and to reduce long-term toxicity, while maintaining a high level of efficacy.

Several classes of drugs inhibit various stages of the HIV-1 lifecycle: nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand-transfer inhibitors (InSTIs), and various classes of viral entry. These therapies have been shown to be effective in both reducing plasma HIV-1 RNA below the level of detection and restoring immune system functioning.

Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by the Applicant as a once-daily (QD) oral treatment for HIV-1 infection in adults. It is being developed as both the single agent, DOR, and as a fixed-dose combination (FDC) of DOR 100 mg /lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (equivalent to 245 mg of tenofovir disoproxil) (DOR/3TC/TDF).

Lamivudine (3TC, EPIVIR) is a dideoxy analog of the nucleoside cytidine and, after phosphorylation, inhibits HIV reverse transcriptase and causes premature DNA chain termination. Lamivudine is approved by the FDA, EMA, and other health authorities for use in combination with other antiretroviral therapies for the treatment of HIV-1 infected adults and pediatric patients 3 months of age and older [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD].

Tenofovir disoproxil fumarate (TDF, VIREAD) is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir disoproxil fumarate is approved by the FDA, EMA, and other health authorities for use in combination with other antiretroviral therapies for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older [Ref. 5.4: 04P95P], [Ref. 5.4: 04QHYF].

Proposed Indications and Dose Regimens:

DOR, in combination with other antiretroviral medicinal products, and DOR/3TC/TDF have been developed for the treatment of HIV-1 infection in adults. The recommended dosage of DOR in adults is one 100 mg tablet taken orally QD with or without food. The recommended dose of DOR/3TC/TDF is 1 tablet (containing 100 mg of DOR, 300 mg of 3TC, and 300 mg TDF) taken orally QD with or without food.

Overview of 2.7.2

The Summary of Clinical Pharmacology provides an overview of the clinical pharmacology program that characterized initial safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of DOR (also referred to as MK-1439) administered as a single entity and as part of DOR/3TC/TDF (also referred to as MK-1439A). Clinical pharmacology trials, which enrolled ~ 700 subjects, were primarily conducted in healthy subjects. Clinical pharmacology trials included single- and multiple-rising dose trials which evaluated the safety, tolerability and PK of DOR as well as intrinsic factor trials evaluating the effects of age, gender, moderate hepatic impairment, severe renal impairment, and HIV-1 infection on DOR PK. In addition, several drug-drug interaction (DDI) trials, as well as a supratherapeutic QT/QTc trial were conducted. An overview of the Phase 1 trials conducted is presented in [Table 2.7.2: 1]. Biopharmaceutics trials conducted with DOR and DOR/3TC/TDF are summarized in [Sec. 2.7.1]. Safety and tolerability data from these trials are summarized in [Sec. 2.7.4.2] and [Sec. 5.3.5.3.1-trtmtnve48wk].

Table 2.7.2: 1 Phase 1 Trials

Trial Type	Protocol Number
PK and Initial Tolerability Trials	
Single Rising Dose, Multiple Rising Dose and Drug Interaction with Midazolam	P001
Supratherapeutic Single and Multiple Rising Dose	P006
Human Absorption, Metabolism, and Excretion	P008
PK of Long Acting Parenteral Intramuscular Injections[1]	P031
Intrinsic Factor PK Trials	
PK in Male vs. Female and Young vs. Elderly Subjects	P009
PK in Patients with Hepatic Impairment	P019
PK in Patients with Severe Renal Impairment	P051
Extrinsic Factor PK Trials	
Drug Interaction with Tenofovir Disoproxyl Fumarate	P003
Drug Interaction with Ritonavir	P002
Drug Interaction with Ketoconazole	P010
Drug Interaction with Rifampin	P011
Drug Interaction with Rifabutin	P035
Pharmacokinetic Effect of Switching From Efavirenz to MK-1439	P020
Drug Interaction with Aluminum and Magnesium Containing Antacid and a Proton-pump Inhibitor	P042
MK-1439A Component Interaction	P038
Drug Interaction with Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel)	P012
Drug Interaction with Dolutegravir	P016
Drug Interaction with Atorvastatin	P036
Drug Interaction with Metformin	P048
Drug Interaction with Methadone	P045

Trial Type	Protocol Number
Drug Interaction with Elbasvir / Grazoprevir	P050
Drug Interaction with Ledipasvir / Sofosbuvir	P053
PD and PK/PD Trials	
Multiple Dose in HIV-1 Infected Patients	P005
QT/QTc Trial	P017
Biocomparison and Bioequivalence Trials	
Bioavailability of Two Probe MK-1439A Formulations	P014
Bioavailability of a Probe MK-1439A Formulation	P015
MK-1439A Comparative Bioavailability	P026
Comparative Bioavailability of Nanoparticle Formulations[1]	P034
Bioequivalence of Coated and Uncoated Tablets	P039
Comparative Bioavailability of Oral Pediatric Minitablets[1]	P043
Bioavailability of Nanoparticle Formulations[1]	P046
Comparative Bioavailability of Pediatric Oral-Granules[1]	P049
Comparative Bioavailability of 2nd Generation Pediatric Oral-granules[1]	P052
Bioavailability Trials	
Food Effect	P037
IV Microdose	P044
MK-1439A Food Effect	P029

1. These exploratory formulation trials are not relevant to the present submission; therefore, trial summaries are not included in 2.7.1. However, PK parameter values from these trials, with the exception of P031 Part 2, are summarized in [Appendix 2.7.1: 1] and safety data from these trials are included in the Clinical Pharmacology Summary of Safety [Sec. 5.3.5.3.1-trtmtnve48wk]. Part 2 of P031 was an exploratory trial with a long acting parenteral formulation and data from this evaluation are not included in the present submission.
Data Source: [Appendix 2.7.2: 1]

In addition, this summary presents an analysis of the population PK modeling performed with data from 1 Phase 2b (P007) trial evaluating the safety and efficacy of DOR in combination with antiretroviral therapy (emtricitabine [FTC]/TDF, as TRUVADA™) and 2 Phase 3 trials evaluating the safety and efficacy of DOR in combination with FTC/TDF or abacavir (ABC)/3TC (as EPZICOM/KIVEXA™) and when administered as part of DOR/3TC/TDF (P018 and P021, respectively), along with a subset of the Phase 1 trials. In total, this analysis included 341 healthy subjects and 959 HIV-1-infected subjects receiving DOR as a single entity or as DOR/3TC/TDF. Exposure-response analyses were conducted to characterize the relationship between DOR PK and efficacy and safety. The modeling supports the selection of the 100 mg dose of DOR, bounds defining a clinically relevant change in DOR exposure, and the effect of intrinsic and extrinsic factors on the exposure and response of DOR.

This module also summarizes key clinical pharmacology data for the marketed components of DOR/3TC/TDF, 3TC and TDF. As described in [Sec. 2.7.1.2.1.2], the PK of all components are similar when administered individually or when administered as part of DOR/3TC/TDF. Furthermore, there is no clinically meaningful DDI between the components of DOR/3TC/TDF. Therefore, the clinical pharmacology profile for each individual component, including the effect of intrinsic and extrinsic factors on PK, is applicable to the components when administered as part of DOR/3TC/TDF.

1.2 Overview of Clinical Pharmacology Program

Thirty-six (36) Phase 1 clinical trials were conducted to assess safety, tolerability, PK, and PD of DOR and DOR/3TC/TDF [Table 2.7.2: 1], [Appendix 2.7.2: 1]. These trials included 2 rising single- and rising multiple- dose trials (P001 and P006), a monotherapy PD and PK trial in treatment-naïve HIV-1 infected male subjects (P005), a single-dose thorough QT/QTc trial (P017) (conducted with a supratherapeutic dose [1200 mg] of DOR, which achieved exposures 3.1-fold and Cmax 4.1-fold those associated with the clinical dose at steady state), and a definitive food-effect trial (P037). Key intrinsic factors of renal (P051) and hepatic impairment (P019) and age and gender (P009) were evaluated in dedicated clinical pharmacology trials. In addition, 16 Phase 1 trials were conducted to evaluate DOR as a perpetrator and/or victim of DDIs.

A complete listing of the 36 trials conducted as part of the clinical pharmacology program are presented in [Table 2.7.2: 1]. Of the 36 trials, 7 trials (P014, P015, P026, P039, P037, P044, P029) were conducted as part of the DOR and DOR/3TC/TDF biopharmaceutics program and are presented in [Table 2.7.2: 1]

The clinical pharmacology trials were conducted primarily with DOR, administered as the single-entity tablet. Two key formulations of DOR, a fit-for-purpose (FFP) oral compressed tablet (OCT) and a pre-market formulation (PMF) OCT, were used in the clinical development program. Differences between the FFP and PMF were minimal and were not anticipated to affect the bioavailability of DOR [Sec. 2.7.1.3.2.1]. A bioequivalence trial (P039) [Sec. 2.7.1.2.1.1.1] established the bioequivalence of the PMF OCT used in a pivotal Phase 3 trial to the film-coated tablet (FCT) intended for commercialization.

Two biopharmaceutics trials (P026 and P029) conducted with the DOR/3TC/TDF final market image (FMI) [Sec. 2.7.1.2.1.2], [Sec. 2.7.1.2.2.1.2] and a component interaction trial (P038) [Sec. 2.7.2.2.3.1.8] were conducted to support development of DOR/3TC/TDF. The effect of food on DOR (P037) and DOR/3TC/TDF (P029) is described in [Sec. 2.7.1.3.3.1]. The FMI DOR/3TC/TDF was also used in a pivotal Phase 3 trial (P021) [Sec. 2.7.3.2.3-trtmtnve48wk]. No additional clinical pharmacology trials were conducted with DOR/3TC/TDF. As described in [Sec. 2.7.1.2.1.2], the DOR, 3TC and TDF components of the FMI of DOR/3TC/TDF demonstrated similar PK compared to co-administration of each individual component in a relative bioavailability trial. Thus, the clinical pharmacology profile for each individual component administered as a single entity is applicable to DOR/3TC/TDF.

In Phase 1 trials, 700 subjects were enrolled and received at least 1 dose of trial treatment, including 435 male and 265 female subjects. The majority of subjects (666) were healthy adults; of these healthy subjects, 12 were elderly (> 65 years of age) males and 12 were elderly females. Other subject populations enrolled included: 8 subjects with moderate hepatic impairment, 8 subjects with severe renal impairment, and 18 male HIV-1 infected subjects.

Across Phase 1 trials, 678 subjects received at least 1 dose of DOR. DOR has been administered as a single dose up to 1200 mg and as multiple doses up to 750 mg QD for 10 days. Of the 678 subjects, 592 received DOR as a single entity and without co-administration of 3TC + TDF; 407 received single-doses of DOR with 385 receiving a dose ≥100 mg, and 197 subjects received consecutive multiple doses, of which 179 received a dose ≥100 mg [Appendix 5.3.5.3.1-trtmtnve48wk: 9]. In addition, across the Phase 1 program, 101 subjects received either DOR+3TC+TDF or DOR/3TC/TDF; of those 101 subjects 86 received DOR/3TC/TDF [Appendix 5.3.5.3.1-trtmtnve48wk: 9] (Note: due to the nature of Phase 1 trials, subjects may have received more than 1 treatment in a given trial and therefore be counted in more than 1 category).

Also supporting this clinical pharmacology summary is a population PK analysis for DOR based on densely sampled PK data from Phase 1 (353 subjects) and sparsely sampled PK data from Phase 2b (~217 subjects with HIV-1 infection) and Phase 3 (~730 subjects with HIV-1 infection) in subjects receiving either the DOR tablet (with concomitant background antiretroviral therapy) or DOR/3TC/TDF. The population PK analysis includes covariate analyses to inform intrinsic and extrinsic factor effects on DOR.

The key findings of the DOR and DOR/3TC/TDF clinical pharmacology program are as follows:

<u>DOR</u>

- Following oral administration, DOR is rapidly absorbed with a median time to maximum plasma concentration (Tmax) of 2 hours. Plasma concentrations of DOR decline in a monophasic manner with a geometric mean terminal t1/2 of approximately 15 hours.
- The steady state AUC0-24, C24, and Cmax of DOR at the 100 mg QD dose in HIV-1 infected subjects are 37.8 µM•hr (%CV: 29.2%), 930 nM (%CV: 63.1%), and 2.26 µM (%CV: 18.5%), respectively.
- Steady state is generally achieved by day 2 of QD dosing, with accumulation ratios of 1.2 to 1.4 for AUC0-24, Cmax, and C24. The PK of DOR is not time dependent, i.e., single dose PK of DOR is predictive of steady state PK following multiple dosing.
- DOR exposure, Cmax, and C24 in healthy subjects increase less than dose proportionally.
- The absolute bioavailability of DOR is approximately 64%.

- DOR is metabolized by CYP3A primarily to the oxidative metabolite M9. DOR and the oxidative metabolite M9 are the major circulating components, accounting for 75% and 12.9%, respectively, of total radioactivity in plasma after a single dose of [^{14}C]DOR. M9, which does not inhibit the HIV reverse transcriptase nor has off-target activity, was observed in preclinical safety species with appropriate exposure coverage relative to human exposure and has been characterized in vitro.
- DOR is primarily eliminated by oxidative metabolism, with M9 as the major metabolite in excreta. Excretion of unchanged drug via urinary or biliary excretion is minor.
- DOR is moderately (~76%) bound to plasma proteins.
- Food and gastric acid modifying agents do not have a clinically meaningful effect on DOR PK.
- A supratherapeutic dose of DOR, providing 4.1-fold and 3.1-fold multiples over the anticipated steady state Cmax and AUC values, respectively, at the clinical dose of 100 mg QD, does not have a clinically meaningful effect on the QTc interval.

Phase 3 Dose Selection, Exposure –Response Relationships, and Comparability Bounds:

- Based on the Phase 2b dose-ranging trial, the exposures achieved over the 25 mg to 200 mg doses are on the plateau of the exposure-response curve for efficacy and no safety concerns were identified over this dose range. Consequently, a dose of 100 mg QD DOR was selected for evaluation in Phase 3 as it was projected to provide adequate C24 values in the setting of common NNRTI resistance mutations against which DOR is active in vitro and provides margins for potential DDIs.
- In the Phase 3 trials, the exposure-response relationships between DOR C24 and the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 using the snapshot or observed failure (OF) approaches are generally flat over the range of exposures achieved at the 100 mg dose, with a slight decrease in efficacy in subjects in the lowest 10th percentile of steady state DOR C24 values.
- Given the incidence of neuropsychiatric AEs or unfavorable changes from baseline in fasting lipids for other HIV-1 antiretroviral treatments, the DOR exposure-response relationship for these endpoints was investigated. There was no association between the incidence of neuropsychiatric AEs or fasting LDL-C levels and DOR exposure over the 25 mg to 200 mg QD dose range evaluated in the Phase 2b and Phase 3 trials. While a significant relationship was identified for DOR exposure and non-HDL-C, non-HDL-C levels over the range of exposures associated with the 100 mg QD dose were below baseline levels of non-HLD-C, consistent with an overall decrease in non-HDL-C levels relative to baseline. Therefore, the exposure-response relationship is not clinically meaningful.
- The comparability bounds for DOR are (0.6, 3.0) and are based on the clinical experience from Phase 1, Phase 2b and Phase 3.

Intrinsic factors:

- Age, gender, race, ethnicity, and body weight/BMI do not have a clinically meaningful effect on DOR PK, with changes in DOR AUC, Cmax, or C24 of no more than 63%.
- Moderate hepatic impairment does not have a clinically meaningful effect on DOR PK. Based on the small effect of moderate hepatic impairment on DOR PK and the low clearance of DOR, clinically meaningful increases in DOR exposures are not anticipated in patients with severe hepatic impairment. However, the PK of DOR has not been evaluated in this population in the DOR development program.
- Severe renal impairment does not have a clinically meaningful effect on DOR PK. Subjects with end-stage renal disease and subjects on dialysis have not been evaluated in the DOR development program.

Extrinsic factors/Drug-Drug Interactions:

- While preclinical data demonstrate DOR is a substrate for P-gp, based on clinical data, P-gp does not play an important role in the absorption or disposition of DOR.
- DOR is not a significant inhibitor or inducer of any major transporter, cytochrome P450 (CYP) enzymes or uridine diphosphate glucuronosyltransferase (UGT) 1A.
- Clinical DDI trials confirm that DOR is not a perpetrator of any clinically meaningful DDIs.
- Only CYP3A inducers or inhibitors are expected to modulate the PK of DOR and only CYP3A inducers affect DOR PK to a clinically meaningful extent.
  - When DOR is co-administered with multiple doses of moderate and strong CYP3A inducers, there is a clinically meaningful decrease in DOR AUC and C24.
    - Co-administration of strong CYP3A inducers with DOR results in a decrease in DOR AUC and C24 by approximately 88% and 97%, respectively.
    - Co-administration with the more moderate CYP3A inducer, rifabutin, resulted in a decrease of DOR AUC and C24 by approximately 50% and 68%, respectively.
  - Co-administration with strong CYP3A inhibitors results in ~3-fold increase in AUC and only a 25-30% increase in Cmax.

DOR/3TC/TDF

- As the PK of the individual components are similar when administered as single entities or as DOR/3TC/TDF, the DOR clinical pharmacology profile is applicable to DOR/3TC/TDF. Likewise, the clinical pharmacology profiles described in the US and EU prescribing information for EPIVIR [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD] and VIREAD [Ref. 5.4: 04P95P], [Ref. 5.4: 04QHYF] are also applicable when these agents are administered as part of DOR/3TC/TDF.

Intrinsic Factors:

- As per the US and/or EU prescribing information for EPIVIR and VIREAD and the clinical pharmacology program for DOR and DOR/3TC/TDF, age, gender, race, weight, BMI, or mild/moderate hepatic impairment are not expected to have a clinically meaningful effect on the PK of DOR/3TC/TDF
  - There are no data for DOR or DOR/3TC/TDF in patients with severe hepatic impairment.
  - As per the US and EU prescribing information for EPIVIR and VIREAD, impaired renal function (creatinine clearance of <50 mL/min) is associated with a clinically meaningful increase in exposure of these agents. Similar changes would be expected when these agents are administered as part of the DOR/3TC/TDF.

Extrinsic Factors:

- Co-administration of moderate or strong CYP3A inducers with DOR/3TC/TDF is expected to reduce exposures of DOR but not have a clinically meaningful effect on 3TC or tenofovir PK.
- As per the VIREAD US and EU prescribing information:
  - As a result of ledipasvir and velpatasvir transporter inhibition, co-administration of DOR/3TC/TDF and ledipasvir/sofosbuvir or sofosbuvir/velpatasvir may increase tenofovir exposure.
  - Due to the TDF component of DOR/3TC/TDF, DOR/3TC/TDF should not be co-administered with adefovir dipivoxil.
  - Due to the TDF component, co-administration of DOR/3TC/TDF with drugs that reduce renal function or compete for active tubular secretion may result in increased serum concentrations of tenofovir and/or tenofovir may increase the concentrations of other renally eliminated drugs.
- As per the EPIVIR US and EU prescribing information, due to the 3TC component which is predominantly eliminated in the urine by active organic cationic secretion, the possibility of interactions with DOR/3TC/TDF and other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system.
- Food does not have a clinically meaningful effect on the PK of the individual components of DOR/3TC/TDF.

1.3 Doravirine Clinical Pharmacology Profile

1.3.1 Doravirine Pharmacokinetics

The PK of DOR has been extensively evaluated, both as a single entity and as DOR/3TC/TDF, in healthy subjects and in subjects with HIV-1 infection. The PK of DOR is similar in healthy subjects and in subjects with HIV-1 infection such that PK assessed in healthy subjects is representative of PK in subjects with HIV-1 infection.

Based on a population PK analysis, the steady state AUC0-24, C24, and Cmax of DOR following administration of 100 mg QD to HIV-1 infected subjects are 37.8 µM•hr (%CV: 29.2%), 930 nM (%CV: 63.1%), and 2.26 µM (%CV: 18.5%), respectively. DOR PK variability is moderate. Steady state was generally achieved by Day 2 of QD dosing, with accumulation ratios of 1.2 to 1.4 for AUC0-24, Cmax, and C24. Accumulation and time to steady state were consistent with the single-dose PK of DOR, indicating the PK of DOR is not time dependent. After single-dose administration, DOR exposure and Cmax in healthy subjects increased less than dose proportionally.

1.3.1.1 Doravirine Absorption, Distribution, Metabolism, Excretion (ADME)

Absorption

DOR is a biopharmaceutics classification system (BCS) Class II compound with high permeability and low solubility [Sec. 2.7.1.1.2.1]. Following single oral dosing, absorption is rapid with median peak plasma concentrations occurring approximately 2 hours after dosing. DOR has an estimated absolute bioavailability (F) of approximately 64% for the 100 mg FMI tablet [Sec. 2.7.1.3.1]. The bioavailability of DOR is thought to be limited predominantly by its solubility, with a minimal role of metabolism enzymes and transporters. The solubility of DOR is not pH dependent and co-administration with antacids or PPIs in a clinical DDI trial did not have a clinically meaningful effect on the PK of DOR. DOR may be administered with gastric acid modifiers.

The rate and extent of absorption following administration with a high-fat meal is similar to that following administration in the fasted state based on a food effect trial [Sec. 2.7.1.3.3] conducted with the FMI tablet of DOR. DOR may be administered without regard to food.

Distribution

Based on administration of an IV microdose (P044), the volume of distribution of DOR is 60.5 L. This is slightly larger than the total volume of body water (45 L) and indicates that DOR may be distributed into tissue. DOR is moderately (~76%) bound to plasma proteins.

Metabolism

DOR is primarily metabolized by CYP3A. Based on the human Absorption, Metabolism, Excretion (hAME) trial (P008) [Sec. 2.7.2.2.1.3], oxidation to form the metabolite M9 is the major metabolic pathway in humans. M9 was the major metabolite circulating in plasma, with levels corresponding to 12.9% of the total radioactivity. [^{14}C]DOR was the primary component circulating in plasma accounting for 75% of total radioactivity [Sec. 2.7.2.1.4]. M9 was seen in preclinical safety species with appropriate exposure coverage relative to human exposure and has been characterized in vitro [Sec. 2.6.4.5.6].

Excretion

DOR is primarily eliminated as the oxidative metabolite M9. Excretion of unchanged drug via urinary or biliary excretion is minor. In a hAME trial (P008) [Sec. 2.7.2.2.1.3], approximately 55% of the absorbed dose was eliminated as M9, predominantly in urine,

while 13% of the absorbed dose was eliminated renally as unchanged DOR. When DOR was administered as a tablet, 6% of the dose was excreted as DOR in urine (P001) [Sec. 2.7.2.2.1.1].

DOR has low hepatic clearance in humans, with a plasma clearance of 3.72 L/hr following an IV microdose of 100 µg. DOR plasma concentrations decline from peak in a monoexponential manner, with a terminal half-life ($t_{1/2}$) of approximately 15 hours; this supports QD dosing.

1.3.1.2 Intrinsic factors

As determined from Phase 1 trials and/or population PK analyses, the effects of age, gender, body weight/BMI, race, ethnicity, mild, moderate and severe renal impairment (eGFR values <30 mL/min/1.73 m² and not on dialysis), and mild or moderate hepatic impairment on DOR PK are not clinically meaningful and no dose adjustments are needed.

Based on the lack of effect of moderate hepatic impairment (based on the Child-Pugh classification) on DOR exposure in a single-dose Phase 1 trial, clinically significant increases in exposure in patients with severe hepatic impairment (based on the Child-Pugh classification) are not anticipated. However, a Phase 1 trial has not been conducted with DOR in subjects with severe hepatic impairment.

The effect of ESRD or dialysis on DOR PK is unknown. While in a Phase 1 trial, the single-dose PK of DOR was evaluated in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m2 based on Modification of Diet in Renal Disease [MDRD] equation) only 2 subjects had eGFR values consistent with end-stage renal disease (ESRD); these subjects with ESRD had PK values that were similar to those without ESRD (i.e., eGFR ≥ 15 mL/min/1.73 m2). No subjects were on dialysis in this trial.

1.3.1.3 Extrinsic factors

Consistent with preclinical data [Sec. 2.6.4.7], clinical trial DDI data demonstrate that DOR is not expected to have a clinically meaningful effect on the PK of co-administered medications, including substrates of all major CYPs and drug transporters [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4]. In vitro data demonstrate that DOR is not a substrate for major CYPs other than CYP3A [Sec. 2.6.4.7.1], [Sec. 2.7.2.1.4.2], [Sec. 2.7.2.1.4.3].

Phase 1 DDI trial data [Sec. 2.7.2.2.3.1.3], [Sec. 2.7.2.2.3.1.2] demonstrate that strong CYP3A inhibition (ketoconazole and ritonavir) results in a ~3-fold increase in DOR AUC, while the increase in Cmax is only ~25%, and therefore, these changes are not clinically relevant based on the bounds of clinical relevance (0.6, 3.0) [Sec. 2.7.2.1.5.4].

As the magnitude of increase in DOR PK was anticipated to be less with moderate CYP3A inhibitors as compared to strong CYP3A inhibitors, clinical DDI trials with moderate inhibitors (e.g., verapamil and diltiazem) were not conducted. As expected, physiologically-based PK model simulations with Simcyp® [Sec. 2.7.2.2.5.3] indicate that moderate CYP3A inhibitors are expected to have a more modest effect on DOR PK (~2-fold increase in AUC).

CYP3A inducers have a clinically meaningful effect on the PK of DOR, and based on the bounds of clinical relevance (0.6, 3.0) [Sec. 2.7.2.1.5.4], as discussed below, special instructions are needed for co-administration of moderate and strong CYP3A inducers.

Based on the lower bound of clinical relevance for efficacy, 0.6, concomitant use of strong and moderate CYP3A inducers is likely to reduce DOR plasma concentrations leading to decreased efficacy. Therefore, the use of strong CYP3A inducers, such as the antimcyobacterials rifampin and rifapentine, the anticonvulsants carbamazepine, oxcarbazepine, phenytoin, and phenobarbital, and the herbal supplement St John's wort (Hypericum perforatum) are contraindicated with DOR. However, as determined by non-parametric superposition (NPS)-based projections of steady state DOR PK using DOR plasma concentrations from a Phase 1 DDI trial following co-administration of DOR and the more moderate CYP3A inducer, rifabutin, rifabutin may be co-administered with DOR if the dose regimen of DOR is adjusted to a 100 mg dose of DOR administered twice-daily (BID). Patients taking DOR/3TC/TDF with rifabutin should take the DOR single-entity tablet 12 hours apart from the DOR/3TC/TDF dose to maintain DOR plasma concentrations above the lower clinical bound. As the magnitude of induction associated with CYP3A moderate inducers varies across compounds (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, nevirapine), and is also dependent on the substrate, the effect of other CYP3A inducers on the PK of DOR cannot easily be predicted. Therefore the dose adjustment proposed for co-administration of rifabutin and DOR or DOR/3TC/TDF may not be sufficient for other moderate inducers which may be co-administered with DOR.

In summary, DOR is not expected to have a clinically meaningful effect on the PK of co-administered drugs and moderate and strong CYP3A inhibitors do not have a clinically meaningful effect on the PK of DOR. Strong CYP3A inducers are contraindicated with DOR treatment, but rifabutin may be co-administered with dose regimen adjustment from 100 mg of DOR administered QD to 100 mg of DOR administered BID. The magnitude of effect of other moderate CYP3A inducers, which may be co-administered with DOR or DOR/3TC/TDF, on DOR PK is unknown.

1.3.2 Pharmacodynamics and Special Safety

1.3.2.1 Antiviral Activity

As suppression of HIV-1 RNA viral load is a primary efficacy endpoint, viral load suppression data are discussed in detail in [Sec. 2.7.3.1.4-trtmtnve48wk] and only the Phase 1b proof-of-concept (POC) trial (P005) [Sec. 2.7.2.2.4.1] is briefly summarized here. In the POC trial [Ref. 5.3.4.1: P005V01], which enrolled treatment-naïve HIV-1 infected male subjects, DOR doses of 25 mg and 200 mg, administered QD as monotherapy for 7 days, resulted in a robust reduction in HIV-1 RNA. On Day 8, 24 hours after the Day 7 dose, the mean placebo-corrected HIV-1 RNA change from baseline was ~1.3 log10 copies/ mL for both the 25 and 200 mg dose in treatment-naïve subjects with HIV-1 infection. There was no meaningful difference in HIV-1 RNA viral load decline between the 25 and 200 mg dose groups [Sec. 2.7.2.2.4.1].

1.3.2.2 Safety-Effect on QTc Interval

In a thorough QT/QTc trial (P017) [Sec. 2.7.2.2.4.2], a supratherapeutic dose of 1200 mg of DOR, which provides 3.1-fold and 4.1-fold increases in exposure and Cmax, respectively, relative to the 100 mg dose, did not have a clinically meaningful effect on the QT interval corrected for heart rate by the population method (QTcP). Specifically, in a comparison of the mean QTcP change from baseline following oral administration of DOR 1200 mg versus placebo, the upper limit of the 90% CI did not exceed 10 msec at any time point postdose [Figure 2.7.2: 7] and [Table 2.7.2: 11]. The largest mean difference (90% CI) was 3.12 (0.824, 5.42), at 5 hours postdose.

1.4 Overview of In Vitro Human Biomaterial Studies

In vitro studies using human liver preparations and recombinant enzymes and transporters were conducted to assess DOR metabolic pathways, the enzymes involved in its metabolism, and the enzyme and transporter drug-interaction potential. In vitro and in vivo characterization of human biotransformation is described in more detail and compared with data from animal studies in [Sec. 2.6.4] and the tabulated data of the studies are in [Sec. 2.6.5] of the nonclinical summary document with links to the original reports.

DOR was metabolized in vitro by CYP3A [Sec. 2.6.4.7.1] and is expected to be a victim of drug interactions with inhibitors/inducers of CYP3A. DOR is not anticipated to perpetrate clinically meaningful drug interactions via inhibition or induction of major drug-metabolizing enzymes. Furthermore, DOR displayed no or weak inhibition of major drug transporters such that clinically meaningful interactions are not anticipated.

DOR displayed moderate binding to plasma proteins and equal distribution between blood cells and plasma [Sec. 2.6.4.4.3].

The metabolite M9, an inactive hydroxylated metabolite identified as the major human circulating metabolite, was characterized in vitro and detailed studies are included in [Sec. 2.6.4.5.8].

1.4.1 Plasma Protein Binding and Partitioning into Blood

Binding of DOR to proteins in human plasma was determined using an equilibrium dialysis method. At concentrations up to 5 µM, binding of DOR is moderate, so that approximately 24% circulates free in plasma, independent of concentration [Sec. 2.6.4.4.3]. DOR distributes equally between blood cells and plasma. Blood-plasma partitioning is ~1 and independent of total concentration [Sec. 2.6.4.4.4]. Both binding to plasma proteins and partitioning into blood are comparable between human and safety species.

The binding of the major circulating metabolite M9 to proteins in human plasma was higher than that of DOR, so that only 9% of M9 is unbound. Binding was independent of concentration (0.1 to 1 µM) [Sec. 2.6.4.4.3].

1.4.2 In Vitro Metabolism

The intrinsic clearance of DOR in liver preparations from humans (both liver microsomes and hepatocytes) was low.

The only metabolic pathway observed in vitro was oxidation, primarily to metabolite M9; qualitatively similar metabolic profiles were observed in liver microsomal preparations from safety species [Sec. 2.6.4.5.7].

Extensive studies with recombinant human CYP enzymes indicated that CYP3A4 and CYP3A5 are the only enzymes that metabolize DOR, with M9 as the predominant metabolite. In agreement with this, studies conducted in human liver microsomes using inhibitory monoclonal anti-CYP antibodies confirmed that CYP3A enzymes are the major enzymes involved in the metabolism of DOR [Sec. 2.6.4.7.1]. Conjugation pathways, such as glucuronidation, were not observed in vitro [Sec. 2.6.4.5.7]. Results from kinetic studies using recombinant CYP3A4 and CYP3A5 indicated greater capacity of CYP3A4 to metabolize DOR [Sec. 2.6.4.7.1]. These results, added to the relatively lower abundance of CYP3A5 in liver indicated that CYP3A4 and, to a lesser extent, CYP3A5 metabolism represent the primary metabolic pathways of DOR.

The metabolite M9 did not undergo further biotransformation in human hepatocytes, in agreement with clinical data indicating renal excretion as the primary route of elimination of M9 with minimal metabolism via further oxidation or conjugation [Sec. 2.6.4.5.8].

1.4.3 In Vitro Inhibition and Induction of Human Cytochromes P450 and Other Relevant Enzymes

Studies conducted in vitro using CYP-selective probe substrates demonstrated that at concentrations up to 100 µM, DOR did not inhibit major drug metabolizing enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 [Sec. 2.6.4.7.3.1], and UGT1A1 [Sec. 2.6.4.7.3.2].

Studies in human hepatocytes indicated that DOR (0.1 to 20 µM) induced CYP3A4 mRNA only at concentrations 10 µM or higher. This effect was small (3.1 to 20.3% across 3 subjects, relative to the positive control rifampicin at 10 µM) and had no corresponding effect on CYP3A4 enzyme activity. Neither CYP1A2 mRNA nor CYP1A2 enzyme activity was altered significantly by DOR at concentrations of up to 20 µM. Similarly, DOR did not induce CYP2B6 mRNA or activity [Sec. 2.6.4.7.4].

A 100 mg QD dose of DOR is associated with a steady state Cmax of 2.26 µM (0.54 µM unbound). Therefore at the clinical dose of 100 mg, DOR is unlikely to perpetrate drug interactions via inhibition or induction of major metabolism enzymes.

1.4.4 In Vitro Transporter Studies

DOR (0.1, 0.5, and 1 µM) was evaluated in LLC-PK1 cells transfected with human P-glycoprotein (P-gp) (i.e., multidrug resistance protein 1 [MDR1]). A ratio of 4.2 for basolateral-to-apical/apical-to-basolateral (B-A/A-B) uptake in P-gp transfected cells compared to approximately 1 in non-transfected cells indicates that DOR is a substrate of P-gp. The mean apparent permeability coefficient (P_{app}) in control cells was 25 x 10^{-6} cm/sec, suggestive of good passive permeability [Sec. 2.6.4.7.2]. Thus, P-gp inhibitors are not expected to affect the PK of DOR.

Additional studies conducted in cells expressing Breast Cancer Resistance Protein (BCRP), Organic Anion Transport Polypeptide 1B1 (OATP1B1), and OATP1B3 indicated that DOR is not a substrate for these transporters and, therefore, not likely to be a victim of drug interactions via inhibition of these transporters [Sec. 2.6.4.7.2].

Based on its elimination mechanism (predominantly oxidation), DOR was not evaluated as a substrate of other hepatic or renal transporters. In studies conducted in cell lines expressing major hepatic and renal transporters, DOR inhibited BCRP, OATP1B1, OATP1B3, Organic Anion Transporter 1 (OAT1), OAT3, Organic Cation Transporter 2 (OCT2), Multidrug and Toxin Extrusion Protein (MATE)1, and MATE2K, with IC_{50} values of 51, 39, 31, >75, 16, 67, >50 and >50 µM, respectively, so that no clinically relevant interactions with substrates of these transporters are anticipated based on a clinical dose of 100 mg, an unbound C_{max} under 1 µM and an unbound liver inlet concentration of approximately 4 µM. In addition, DOR did not inhibit the Bile Salt Export Pump (BSEP) or P-gp at the maximal concentrations tested in the respective assays (50 and 100 µM, respectively) [Sec. 2.6.4.7.3].

1.5 Dose Selection and Comparability Bounds

The recommended dose of DOR is 100 mg QD administered orally. As described in [Sec. 2.7.3.4.1-trtmtnve48wk], this dose is supported by an assessment of benefit-risk balance based on virologic response data from the Phase 2b and Phase 3 trials, safety/tolerability data examined across the development program, and the in vitro resistance profile of DOR.

The bounds defining a clinically important change in DOR PK are (0.6, 3.0); the bounds define the range of change relative to the steady state C24 (lower bound) and AUC0-24 (upper bound) values associated with the 100 mg QD dose in subjects with HIV-1 infection where safety and efficacy are expected to be comparable to that of the recommended clinical dose of 100 mg QD DOR. The definition of a clinically important change in DOR exposure is based on the demonstrated efficacy and safety in the Phase 1, Phase 2b and Phase 3 trials.

In this section, summaries of the rationale for selection of the 100 mg QD dose of DOR and the exposure-response analyses for DOR with respect to efficacy and safety are provided, followed by the justification for the clinical bounds based on an integrated understanding of exposure-response. Lastly, a justification for the applicability of the current prescribing information for TDF and 3TC to these components when administered as part of DOR/3TC/TDF is provided.

1.5.1 Doravirine Dose Selection

Doses of 25 mg and 200 mg QD DOR were evaluated in a Phase 1b trial (P005) [Sec. 2.7.2.2.4.1] in HIV-1-infected subjects. The 25 mg dose was projected to achieve trough plasma concentrations exceeding the inhibition target of more than 6-fold the in vitro EC_{50} for inhibition of WT virus (12 nM, [Sec. 2.6.2.2.1.2.1]). The 200 mg dose was selected to explore safety, tolerability, PK, and the potential for PD differentiation at higher exposure. In the Phase 1b trial, both the 25 mg and 200 mg QD doses demonstrated similar viral response (HIV-1 RNA placebo-corrected change from baseline) and were generally well tolerated. Consequently, DOR doses of 25, 50, 100, and 200 mg QD were selected for evaluation in a Phase 2b dose ranging trial.

In the Phase 2b trial (P007) [Sec. 2.7.3.2.1-trtmtnve48wk], treatment-naïve subjects without NNRTI resistance mutations were randomized to receive DOR doses of 25 mg to 200 mg or efavirenz in addition to FTC/TDF. DOR doses of 25 mg to 200 mg resulted in similar decreases in viral load over 24 and 48 weeks relative to efavirenz. These results indicate that the exposure achieved over the 25 mg to 200 mg doses are on the plateau of the dose-response curve in this population. Furthermore, no safety concerns were identified over the 25 mg to 200 mg dose range. Based on these data, a dose of 100 mg QD DOR was selected for evaluation in Phase 3 as it was projected to provide adequate C24 values in the setting of common NNRTI resistance mutations against which DOR is considered to be active in vitro, including the K103N, Y181C, and Y190A mutations, as well as the dual K103N/Y181C mutation [Sec. 2.6.2.2.1.2.1]. As similar decreases in viral load were observed over the 25 mg to 200 mg dose range, 100 mg provides a maximal response with no further efficacy advantage to dosing higher than 100 mg. Furthermore, the 100 mg dose had the potential to provide adequate safety margins in the setting of factors that could result in increased DOR exposure, such as concomitant administration of CYP3A inhibitors. Similarly, as the 100 mg dose is on the plateau of the dose-response relationship, the 100 mg dose also had potential to provide margins for decreases in DOR PK without impacting efficacy, such as in the setting of moderate CYP3A inducers. The appropriateness of the 100 mg QD dose with respect to benefit-risk balance is further demonstrated by data from the pivotal Phase 3 trials [Sec. 2.7.3.3-trtmtnve48wk], [Sec. 2.7.4.2].

1.5.2 Exposure Response for Efficacy

Efficacy exposure-response analyses were conducted to investigate the relationship between DOR PK and the proportion of subjects achieving HIV-1 RNA <50 copies/mL and <40 copies/mL at Week 48 in the Phase 2b and Phase 3 trials; these analyses are described in detail in [Ref. 5.3.5.3: 04PPZ7]. As the definition of protocol-defined virologic failure and inclusion of these subjects in evaluation of the final endpoint are different between the Phase 2b and Phase 3 trials, the exposure-response analysis for the Phase 2b trial over the 25 mg to 200 mg dose range was conducted separately from the analysis for the Phase 3 trials. Data from the two Phase 3 trials were pooled as the PK of DOR were similar when administered as a single entity tablet (P018) or as DOR/3TC/TDF (P021). The proportion of subjects achieving HIV-1 RNA <50 copies/mL or <40 copies/mL was determined using both the FDA snapshot approach, which is the primary approach specified in the Phase 3 trial protocols, and the OF approach [Sec. 2.7.3.1.4.2.2-trtmtnve48wk].

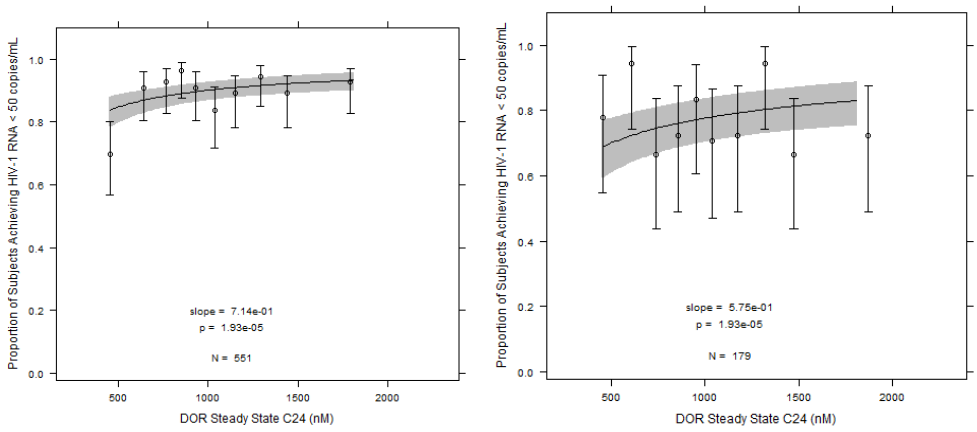
No statistically significant exposure-response relationships were identified between any of the DOR PK parameters (AUC, C24, or Cmax) and efficacy endpoints over the range of exposures achieved at the 25 mg to 200 mg QD doses in the Phase 2b (P007) analysis. While statistically significant exposure-response relationships were identified between DOR PK and all efficacy endpoints evaluated in the Phase 3 analysis for exposures achieved at the 100 mg QD dose, the relationships were generally flat with a minimal decrease in efficacy in subjects with the lowest 10% of DOR PK values. The strongest exposure-response associations were observed for DOR steady state C24 compared to steady state AUC0-24 or Cmax. Consequently, the focus of this efficacy exposure-response summary will be on DOR steady state C24. The exposure-response relationships between DOR C24 and the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 using the snapshot or OF approaches are characterized by a shallowly increasing log-linear relationship over the range of exposures achieved at the 100 mg dose in the Phase 3 trials. HIV-1 viral load at screening (low: ≤ 100,000 copies/mL or high: > 100,000 copies/mL) was also identified as a significant covariate impacting the slope of the exposure-response relationship, with a flatter exposure-response relationship observed for subjects with high viral load at screening. To visualize the relationship between DOR C24 and the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 using the snapshot approach, model-predicted and observed virologic response are illustrated graphically for the range of exposures achieved at the 100 mg dose in the Phase 3 trials by exposure decile in [Figure 2.7.2: 1] for subjects with high or low screening viral load. Similar trends were observed for the proportion of subjects achieving HIV-1 RNA <50 copies/mL or <40 copies/mL using the OF approach as well. The relationship between DOR C24 and virologic response in subjects with low screening viral load appeared to be driven mainly by slightly lower virologic response in subjects with the lowest 10% of DOR C24 values, with a flat exposure-response relationship across the range of exposure above the 10^{th} percentile. In contrast, the relationship between DOR C24 and virologic response is flat in subjects with high screening viral load.

Of note, there was a disproportionate number of subjects in the first decile of DOR C24 values who had at least 1 PK sample below the limit of quantitation (BLQ) during the 48 week treatment period (8 in the first decile compared to 4 or less in each of the other deciles). Based on typical concentration-time profiles observed across the clinical program at the 100 mg dose, BLQ values would not be expected within 24 hours of a 100 mg dose. Therefore, presence of a BLQ value may be indicative of missed doses or sub-optimal compliance. Moreover, subjects with at least one BLQ PK sample also achieved the endpoint of <50 copies/mL or <40 copies/mL at a lower rate than other subjects. Consequently, the disproportionate presence of these subjects in the lowest 10% of C24 values contributes to the lower virologic response observed in this group. To assess the impact of subjects with potential missed doses on the virologic response exposure-response relationship, a sensitivity analysis was conducted where subjects with at least 1 BLQ PK sample were excluded from the exposure-response analysis. After exclusion of subjects with at least 1 BLQ PK sample, exposure-response relationships for the proportion of subjects achieving <50 copies/mL or <40 copies/mL based on the snapshot and OF approaches were weakened with visibly flatter slopes [Figure 2.7.2: 2]. These results suggest that the apparent trend in exposure-response observed for the proportion of subjects achieving <50 copies/mL or <40 copies/mL in Phase 3 is a reflection of lower compliance and therefore reduced efficacy in a subset of subjects in

the lowest 10% of exposures, rather than a true reduction in efficacy at lower exposures. Consistent with this finding, the exposure-response relationship was also flat for the proportion of subjects achieving HIV-1 RNA <50 copies/mL or <40 copies/mL at Week 48 over the exposures achieved in the 25 mg to 200 mg dose range in the Phase 2b trial [Figure 2.7.2: 3].

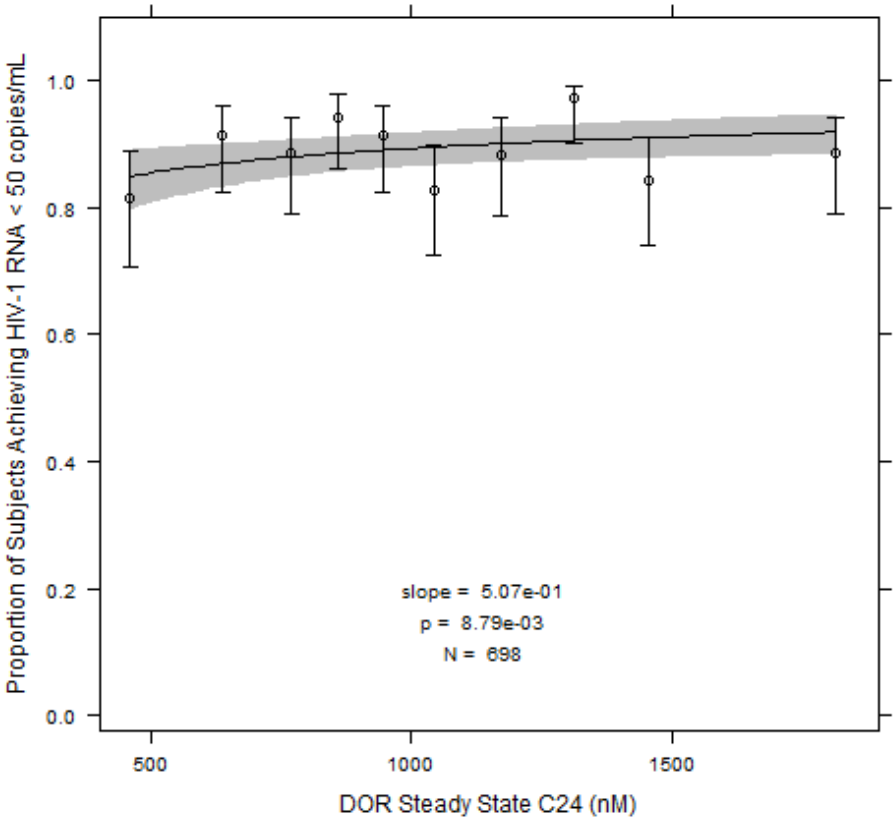
Figure 2.7.2: 1 Predicted and Observed Proportion of HIV-1 Infected Subjects Achieving < 50 copies/mL as a Function of DOR Steady State C24 Deciles Stratified by Screening Viral Load Following Administration of 100 mg QD DOR with FTC/TDF or ABC/3TC or QD Administration of DOR/3TC/TDF (N = 730)

Screening Viral Load ≤ 100,000 copies/mL Screening Viral Load > 100,000 copies/mL



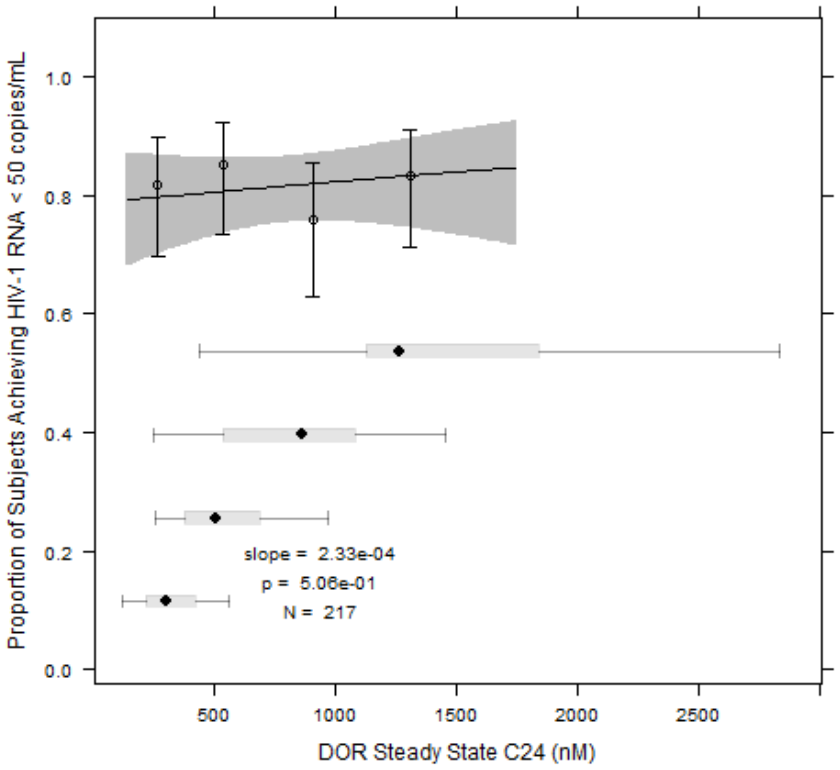
Points correspond to observed data with 95% CI; solid line and gray area to model-predicted fit 95% CI

Figure 2.7.2: 2 Predicted and Observed Proportion of HIV-1 Infected Subjects Achieving < 50 copies/mL as a Function of DOR Steady State C24 Deciles Excluding Subjects with at Least One BLQ Sample Following Administration of 100 mg QD DOR with FTC/TDF or ABC/3TC or QD Administration of DOR/3TC/TDF (N = 698)



Points correspond to observed data with 95% CI; solid line and gray area to model-predicted fit 95% CI

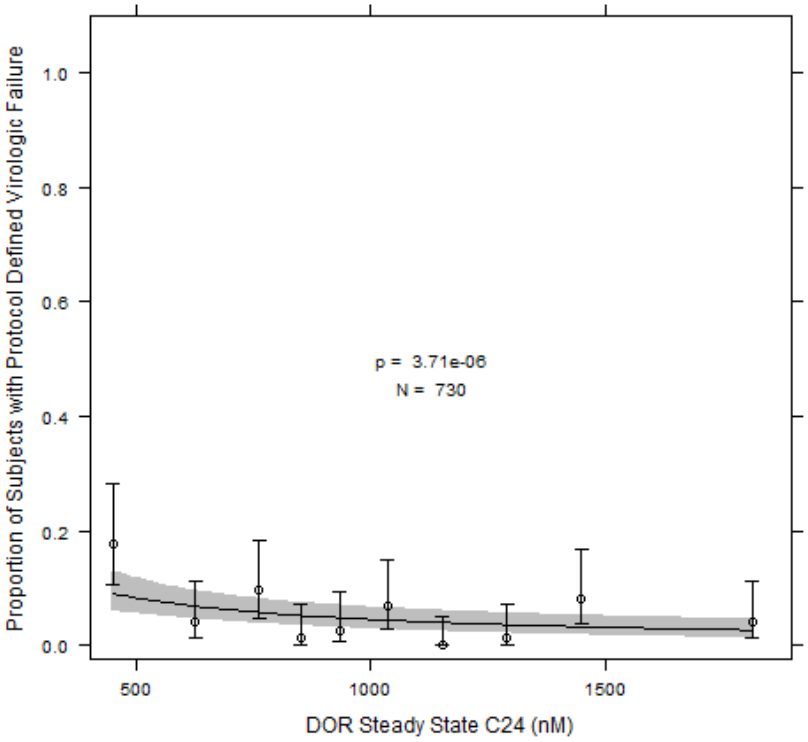
Figure 2.7.2: 3 Predicted and Observed Proportion of Subjects Achieving HIV-1 RNA <50 copies/mL (Snapshot Approach) as a Function of Doravirine Steady State C24 Quartiles Following Administration of 25 mg to 200 mg QD Doravirine with FTC/TDF (P007, N=217)



Points correspond to observed data with 95% CI; solid line and gray area to model-predicted fit 95% CI over the 5th to 95th percentile of exposures; horizontal boxplots denote the distribution of individual AUC0-24 values at the 25, 50, 100 and 200 mg QD doses in P007, where the point is the median, the box corresponds to the 25th and 75th percentiles, and the whiskers correspond to the 5th and 95th percentiles.

Additional exposure-response analyses were conducted to assess the relationship between DOR PK and protocol-defined virologic failure (PDVF) through Week 48 in HIV-1-infected subjects in the Phase 2b and Phase 3 trials. As with the virologic response endpoint, separate analyses were conducted for Phase 2b and for Phase 3 due to the different definition of PDVF [Sec. 2.7.3.3.3.5-trtmtnve48wk] used between Phase 2b and Phase 3. Similar to the virologic response analysis, the relationship between PDVF through Week 48 and DOR plasma PK was generally flat over the range of exposures achieved at the 100 mg dose in the Phase 3 trials [Figure 2.7.2: 4], with a slightly higher virologic failure rate in subjects with the lowest 10% of DOR C24 values. The relationship between DOR C24 and likelihood of PDVF is illustrated in [Figure 2.7.2: 4] with the model-predicted relationship overlaid with observed data by exposure decile. These plots illustrate that there is a weak trend for a negative exposure-response relationship between DOR C24 and PDVF due to a slightly higher virologic failure rate in the first decile with a flat exposure-response relationship at higher exposures beyond the 10th percentile. No trends in exposure-response were identified for PDVF in the Phase 2b analysis.

Figure 2.7.2: 4 Predicted and Observed Proportion of HIV-1-Infected Subjects with Protocol Defined Virologic Failure as a Function of DOR Steady State C24 Deciles Following Administration of 100 mg QD DOR with FTC/TDF or ABC/3TC or QD Administration of DOR/3TC/TDF (N = 730)



Points correspond to observed data with 95% CI; solid line and gray area to model-predicted fit 95% CI

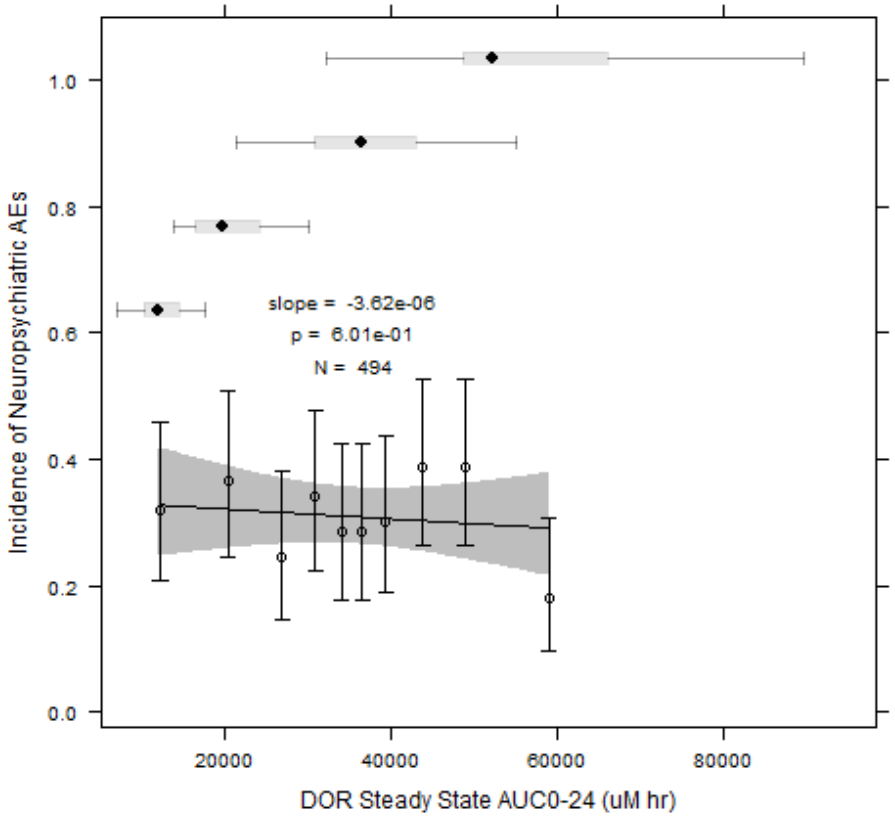
Taken together, the exposure-response analyses for efficacy indicate that the exposure-response relationship is generally flat and that steady state DOR C24 values achieved following a 100 mg QD dose are associated with high levels of antiretroviral activity and low rate of virologic failure. In addition, the exposure-response relationship for virologic response and virologic failure were flat over the range of exposures achieved at the 25 mg to 200 mg dose range evaluated in the Phase 2b trial. Hence, higher DOR exposures than those achieved with the 100 mg QD dose do not appear to lead to additional clinical benefit.

1.5.3 Exposure Response for Safety

Results of safety analyses for the Phase 2b and Phase 3 trials indicate that 100 mg QD DOR is generally well tolerated [Sec. 2.7.4]. In addition, the proportion of subjects in the DOR or DOR/3TC/TDF treatment group reporting 1 or more AEs was similar compared to the active control group. No safety findings of concern have been identified in the clinical program. Nevertheless, given the incidence of neuropsychiatric AEs or unfavorable changes from baseline in fasting lipids for other HIV-1 antiretroviral treatments, the DOR exposure-response relationship for these endpoints was investigated.

An exposure-response analysis was conducted for neuropsychiatric AEs through Week 48 with the special safety pool from the Phase 2b trial (P007) and the Phase 3 trial (P021) that was used in the integrated statistical analysis [Sec. 2.7.4.2.5.2]. Of note, the special safety pool used in the integrated statistical analysis included only the 100 mg dose from P007, while all dose levels are included in the exposure-response analysis. Neuropsychiatric AEs were defined based on a pre-selected list of terms from the SOC Nervous System and Psychiatric Disorders including the following categories: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders. In this analysis, there was no association between the incidence of neuropsychiatric AEs and DOR steady state AUC0-24 or Cmax ($p > 0.05$). [Figure 2.7.2: 5] displays simulated and observed incidence of neuropsychiatric AE occurrence by DOR steady state exposure decile. There was a similarly low incidence of neuropsychiatric AEs across all quantiles of DOR exposure over the range of exposures achieved at the 25 mg to 200 mg doses in Phase 2b and the 100 mg dose in P021. Thus, the incidence of neuropsychiatric AE occurrence is not dependent on exposure over the range of exposures achieved across the 25 mg to 200 mg QD doses in Phase 2b and Phase 3.

Figure 2.7.2: 5 Predicted and Observed Incidence of Neuropsychiatric Adverse Events by Week 48 as a Function of DOR Steady State AUC0-24 Deciles Following Administration of 25 mg to 200 mg QD DOR with FTC/TDF (P007) or QD Administration of DOR/3TC/TDF (P021) in HIV-1 Infected Subjects (N = 574)

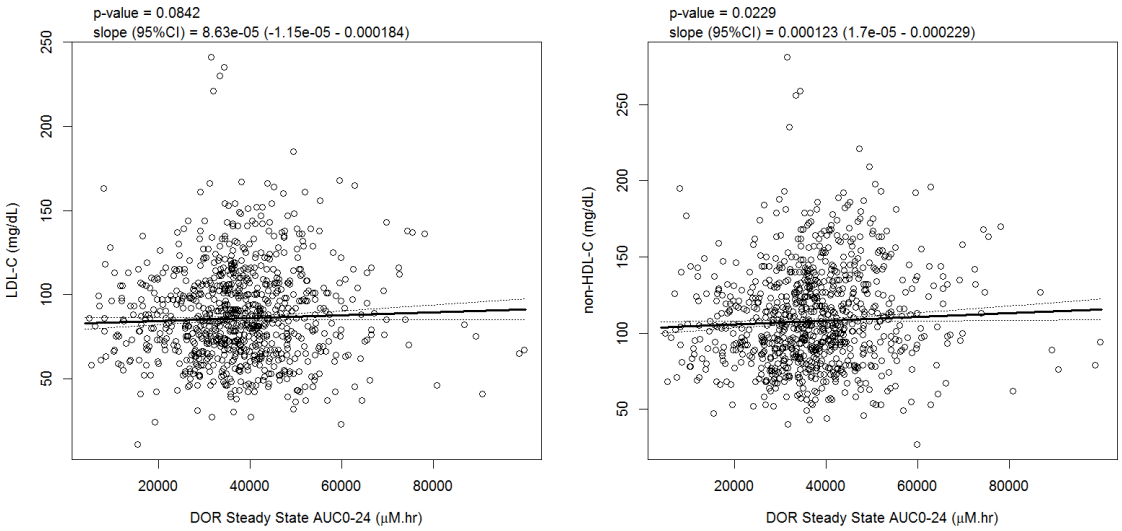


Points correspond to observed data with 95% CI; solid line and gray area to model-predicted fit 95% CI over the 5th to 95th percentile of exposures; horizontal boxplots denote the distribution of individual AUC0-24 values at the 25, 50, 100 and 200 mg QD doses in P007, where the point is the median, the box corresponds to the 25th and 75th percentiles, and the whiskers correspond to the 5th and 95th percentiles.

A pooled exposure-response analysis was also conducted for fasting LDL-C and non-HDL-C, based on the main safety pool used in the integrated safety analysis [Sec. 2.7.4.3.5.1.2]. While the main safety pool only included subjects at the 100 mg dose from the Phase 2b and Phase 3 trials, the exposure-response analysis also included data from the administration of 25 mg, 50 mg, and 200 mg in the Phase 2b trial. The relationship between LDL-C levels and DOR exposure was flat over the range of exposures achieved at the 25 mg to 200 mg doses in the Phase 2b and 3 trials [Figure 2.7.2: 6]. There was a weak positive relationship between non-HDL-C and DOR steady state AUC0-24 (p = 0.023), corresponding to a 2.8 point increase in non-HDL-C between the 10th and 90th percentiles of DOR exposure at the 100 mg QD dose. Importantly, model-predicted non-HDL-C levels over the range of exposures associated with the 100 mg QD dose (106 – 110 mg/dL over the 10th – 90th percentiles of exposure) were below baseline levels of non-HDL-C (~115 mg/dL), consistent with the

findings of the primary statistical analysis [Sec. 2.7.4.3.5.1.2]. Thus, the exposure-response relationship for non-HLD-C is not clinically meaningful.

Figure 2.7.2: 6 Predicted and Observed DOR Steady State AUC0-24 and Fasting LDL-C (N = 754) or non-HDL-C (N=762) at Week 48 Following Administration of 25 mg to 200 mg QD DOR with FTC/TDF (P007), 100 mg QD DOR with FTC/TDF or ABC/3TC (P018), or QD Administration of DOR/3TC/TDF (P021) in HIV-1 Infected Subjects



Line indicates model-predicted relationship

These analyses indicate that there is no clinically meaningful association between DOR steady state exposure and incidence of neuropsychiatric AEs or fasting lipids over the range of exposures achieved at the 25 mg to 200 mg QD doses.

1.5.4 Rationale for Comparability Bounds

The term "comparability bounds" in this section refers to a range of DOR PK exposures relative to those achieved at steady state after administration of a clinical dose of 100 mg QD DOR in HIV-1 infected subjects, that has been demonstrated to have clinical comparability with respect to the safety and efficacy of DOR. When observed or predicted changes in the PK exposure of DOR fall within these pre-specified comparability bounds, safety and efficacy are expected to be comparable to that of the recommended clinical dose of 100 mg QD DOR.

The comparability bounds of (0.6, 3.0) for DOR are based on preclinical safety data and the clinical experience from Phase 1, Phase 2b and Phase 3, and are defined relative to the geometric mean steady state C24 (for the lower bound with respect to efficacy) and geometric mean steady state AUC0-24 (for the upper bound with respect to safety) achieved at the 100 mg QD dose in HIV-1 infected subjects in the Phase 3 trials. These clinical

bounds are supported by the exposure-efficacy relationships observed over the range of exposures achieved in Phase 2b and Phase 3, the lack of apparent association between AEs and increased dose or exposure, and efficacy and safety analyses for subpopulations.

The lower bound of 0.6 for DOR steady state C24 is defined based on the totality of the efficacy and DOR exposure data from Phase 2b and 3 trials. Steady state C24 (Ctrough) was selected as the exposure measure from which to judge clinical relevance from an efficacy perspective (lower bound) as maintenance of C24 is typically associated with efficacy for antiretroviral therapies. In addition, exposure-response evaluations indicate that steady state Cmax and AUC0-24 are not more predictive than C24 for virologic response [Ref. 5.3.5.3: 04PPZ7]. The lower bound corresponds to the 10th percentile of C24 values achieved at the 100 mg QD dose in the Phase 3 trials, where robust antiretroviral activity was demonstrated at this dose in the Phase 3 trials. In particular, the lower bound is supported by the exposure-response relationships between DOR steady state C24 and the proportion of subjects achieving <50 copies/mL and <40 copies/mL at Week 48 and virologic failure. In these exposure-response relationships, a slightly lower proportion of subjects achieving virologic response and a slightly higher virologic failure rate was observed at the lowest 10% of DOR steady state C24 values. Above the 10th percentile of DOR steady state C24 values, the exposure-response relationships for virologic response and virologic failure was flat over the entire range of DOR steady state C24 values. Moreover, the observed exposure-response trends in the first decile of DOR steady state C24 values are largely driven by subjects with potentially lower adherence, who have lower efficacy rates rather than reflecting a true decrease in response at lower exposures. Consequently, the 10th percentile of DOR steady state C24 values represents a conservative lower bound. The lower bound is further supported by the flat exposure- and dose-response relationships observed over the 25 mg to 200 mg QD dose range in the Phase 2b trial. The lower bound also corresponds approximately to the geometric mean C24 value from the 50 mg QD dose (~0.5-fold of the C24 associated with the 100 mg QD dose), which was studied in the Phase 2b trial and had efficacy similar to 100 mg QD. Similar efficacy was also observed at the 25 mg QD dose in the Phase 2b trial, which corresponds to a geometric mean C24 value ~0.3-fold of the values associated with the 100 mg QD dose. However, the lower bound is set somewhat higher than steady state C24 associated with the 25 mg QD dose in order to provide DOR steady state C24 values that will cover common NNRTI-associated resistance mutations. The geometric mean C24 associated with the 50 mg QD dose exceeds the PK targets used to support dose selection for the Phase 2b trial of a C24 value that is more than 6-fold the in vitro EC_{50} for inhibition of WT virus, of common single resistance mutations (K103N, Y181C, G190A), and of the K103N/Y181C double mutant [Sec. 2.6.2.2.1.2.1].

The upper bound of 3.0 for DOR steady state AUC0-24 is based on clinical experience across Phase 1, Phase 2b, and Phase 3. AUC0-24 was selected as the exposure measure from which to judge clinical relevance from a safety perspective (upper bound), as this parameter is an integration of concentrations over the 24 hour dosing interval in which subjects are exposed to DOR at steady state after QD administration. In the Phase 1 program, there was no evidence that the incidence of overall AEs or specific AEs, with the exception of somnolence (which was not dose-dependent), was temporally associated with the time of maximum DOR concentration (Tmax), suggesting that Cmax does not play a major role in safety or tolerability [Sec. 5.3.5.3.1-trtmtnve48wk]. In the Phase 2b trial, there was no evidence of

exposure or dose-related toxicities across the range of 25 mg to 200 mg doses evaluated. Similarly, the 100 mg QD dose was generally well tolerated in the Phase 3 trials where no treatment related adverse events of concern were identified. There was also no meaningful association between DOR steady state exposure and the incidence of neuropsychiatric AEs or fasting lipid levels in the Phase 2b and Phase 3 trials over the range of exposures achieved at the 25 mg to 200 mg QD doses that would further limit the exposure of DOR from a safety perspective. While the geometric mean steady state AUC0-24 achieved at the 200 mg QD dose, the highest dose examined in the Phase 2b trial administered for at least 48 weeks, corresponded to approximately 50% higher exposures compared to the steady state AUC0-24 associated with the 100 mg QD dose, further evidence from the Phase 1 trials supports the low risk associated with higher exposures. At steady state exposures at least 3-fold those observed with the 100 mg QD dose in the Phase 3 trials, there have been no safety signals in short term clinical pharmacology trials. Specifically, multiple doses of up to 750 mg QD for 10 days and single doses of up to 1200 mg of DOR (P001, P006) were generally well tolerated and provide exposure multiples of approximately 3.7-fold and 6.5-fold, respectively, relative to the steady state AUC values observed following administration of 100 mg QD DOR [Sec. 2.7.4.1.2], [Sec. 5.3.5.3.1-trtmtnve48wk]. In addition, a single dose of 1200 mg of DOR had no clinically meaningful effect on QTc values (P017) [Sec. 2.7.2.2.4.2] at approximately 4.1-fold and 3.1-fold exposure multiples to Cmax and AUC0-24, respectively. In preclinical chronic toxicology studies, there were no meaningful safety findings at the highest exposures achieved in rat and dog, which were approximately 7.4-fold and 18-fold, respectively, the steady exposure observed at the clinical dose [Sec. 2.6.6.9]. These data supported the use of strong and moderate CYP3A inhibitors in Phase 3 trials, which are expected to be associated with 2 to 3-fold higher exposures relative to typical levels associated with the 100 mg QD dose [Sec. 2.7.2.3.1.1.6]. In the Phase 3 trials, 67 subjects were co-administered moderate or strong CYP3A inhibitors for at least 7 days (with 13 subjects using strong CYP3A inhibitors and 16 subjects using moderate CYP3A inhibitors for 30 days or longer) with no meaningful differences in this population's safety profile when compared to those without concomitant strong or moderate CYP3A inhibitor use [Sec. 2.7.4.5.3]. Thus, based on the totality of the preclinical and clinical experience for DOR, an upper bound of 3.0 is proposed. It is important to note that the upper bound reflects the limit of current clinical experience with DOR but does not reflect any known safety issues with a 3.0-fold higher exposure. Higher exposures may also be safe but have not been studied extensively.

1.6 Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate Fixed Dose Combination

The marketed doses of 300 mg TDF and 300 mg 3TC are used in DOR/3TC/TDF. Efficacy for DOR/3TC/TDF was demonstrated in a pivotal Phase 3 trial (P021) [Sec. 2.7.3.2.3-trtmtnve48wk]. Additionally, no meaningful differences in tenofovir or 3TC PK were observed in a relative bioavailability trial when TDF and 3TC were administered as part of DOR/3TC/TDF or co-administered as the individual components [Sec. 2.7.1.2.1.2]. Similarly, the PK of DOR is similar when administered as a single-entity or when administered as part of DOR/3TC/TDF [Sec. 2.7.1.1.3.2]. Moreover, in a component interaction trial evaluating the PK of tenofovir and 3TC when co-administered in the presence or absence of 100 mg DOR, co-administration of DOR with TDF and 3TC had no

meaningful impact on the PK of tenofovir, 3TC, or DOR (P038) [Sec. 2.7.2.2.3.1.8]. Thus, the clinical pharmacology profiles, dose, and dose recommendations with respect to intrinsic and extrinsic factors described in the VIREAD and EPIVIR US [Ref. 5.4: 04P95P], [Ref. 5.4: 04P95N] and EU [Ref. 5.4: 04QHYF],[Ref. 5.4: 04QHYD] prescribing information and summarized in [Sec. 2.7.2.3.1.2], [Sec. 2.7.2.3.1.3], are applicable to TDF and 3TC, respectively, when administered as part of DOR/3TC/TDF. Likewise, the clinical pharmacology profile, proposed dose and dose recommendations for DOR with respect to intrinsic and extrinsic factors as summarized in [Sec. 2.7.2.3.1.1.5] and [Sec. 2.7.2.3.1.1.6] are applicable to DOR when administered as part of DOR/3TC/TDF.

Intrinsic Factors:

No dose adjustment is required for the DOR/3TC/TDF tablet based on age, gender, race, weight, BMI, or mild/moderate hepatic impairment. Dose adjustment is required for both 3TC and TDF in patients with an estimated creatinine clearance below 50 mL/min [Sec. 2.7.2.3.1.2], [Sec. 2.7.2.3.1.3]; therefore, DOR/3TC/TDF should not be used in this population.

Extrinsic Factors:

DOR/3TC/TDF is a complete regimen for the treatment of HIV-1 infection; therefore, DOR/3TC/TDF is not intended to be administered with other antiretroviral medications in treatment-naïve patients. Therefore, information regarding potential DDIs with other antiretroviral medications is not summarized here.

Due to the DOR component, DOR/3TC/TDF is contraindicated for use with CYP3A strong inducers, and when co-administered with the more moderate inducer, rifabutin, an additional dose of the 100 mg DOR tablet should be taken approximately 12 hours apart from DOR/3TC/TDF. The magnitude of effect of other moderate CYP3A inducers, which may be co-administered with DOR, on DOR PK is unknown.

Due to the TDF component of the DOR/3TC/TDF, DOR/3TC/TDF should not be administered with adefovir dipivoxil. Furthermore, co-administration of TDF and ledipasvir/sofosbuvir or sofosbuvir/velpatasvir has been shown to increase tenofovir exposure and patients should be monitored for tenofovir associated AEs. Co-administration of TDF with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs and AEs associated with these agents should be monitored [Sec. 2.7.2.3.1.2.3]. In addition DOR/3TC/TDF should be avoided with concurrent or recent use of nephrotoxic agents.

Due to the 3TC component which is predominantly eliminated in the urine by active organic cationic secretion, the possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system.

Effect of Food on DOR/3TC/TDF

When DOR/3TC/TDF was administered with a high-calorie, high fat meal in a food effect trial, there was no clinically meaningful effect of food on the PK of any of the components of DOR/3TC/TDF [Sec. 2.7.1.3.3.1]. Furthermore, DOR/3TC/TDF was administered without regard to meals in Phase 3 (P021) [Sec. 2.7.3.2.3-trtmtnve48wk]. Therefore, DOR/3TC/TDF may be administered without regard to meals.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Thirty-six (36) Phase 1 clinical trials were conducted to assess safety, tolerability, PK, PD, biopharmaceutics and key intrinsic and extrinsic factors of DOR and/or the DOR/3TC/TDF [Appendix 2.7.2: 1].

In Phase 1 trials, 700 subjects were enrolled and received at least 1 dose of trial treatment, including 435 male and 265 female subjects. The majority of subjects (666) were healthy adults; of these subjects, 12 were elderly (>65 years of age) male and 12 were elderly female. Other subject populations enrolled included the following: 8 subjects with moderate hepatic impairment, 8 subjects with severe renal impairment, and 18 male HIV-1 infected subjects.

Two key formulations of DOR, a FFP OCT and a PMF OCT, were used in the clinical development program. Differences between the FFP and PMF were minimal and were not anticipated to affect the bioperformance of DOR. A bioequivalence trial (P039) [Sec. 2.7.1.3.2.1] established the bioequivalence of the PMF OCT to the FCT intended for commercialization [Sec. 2.7.1.3.2.2].

Two biopharmaceutics trials (P026 and P029) [Sec. 2.7.1.2.1.2], [Sec. 2.7.1.2.2.1.2] with the FMI and a component interaction trial (P038) [Sec. 2.7.2.2.3.1.8] were conducted to support development of DOR/3TC/TDF [Sec. 2.7.1.1.3.2]. As described in [Sec. 2.7.1.2.1.2], following administration of the FMI of DOR/3TC/TDF, the DOR, 3TC, and TDF components demonstrated similar PK to co-administration each individual component in a relative bioavailability trial. Thus, the results of the clinical pharmacology trials for DOR presented below are applicable to DOR when administered as part of DOR/3TC/TDF.

This section briefly summarizes the trial designs and key results of the clinical pharmacology trials. The Phase 1 program evaluated the PK of DOR in healthy adult male subjects [Sec. 2.7.2.2.1], healthy adult female and healthy elderly male and female subjects [Sec. 2.7.2.2.2.1]. The PK and PD of DOR were also evaluated in subjects with HIV-1 infection [Sec. 2.7.2.2.4.1], subjects with renal impairment [Sec. 2.7.2.2.2.3], and subjects with hepatic impairment [Sec. 2.7.2.2.2.2]. Sixteen DDI trials were conducted with DOR [Sec. 2.7.2.2.3], including a component interaction trial described in [Sec. 2.7.2.2.3.1.8]. In addition, a thorough QT/QTc trial was conducted and is summarized in [Sec. 2.7.2.2.4.2].

Biopharmaceutics trials and food-effect trials were conducted with both DOR and DOR/3TC/TDF which are described in [Sec. 2.7.1.2.1.2], [Sec. 2.7.1.2.2]. Relative bioavailability/exploratory formulation trials conducted with DOR which are not considered relevant for this submission are not summarized in 2.7.1 (P031, P034, P043, P046, P049, and

P052); however, PK and safety data from these trials are included in [Appendix 2.7.1: 1] and the Clinical Pharmacology Summary of Safety (CPSOS) [Sec. 5.3.5.3.1-trtmtnve48wk], respectively.

A tabular summary of biopharmaceutics and clinical pharmacology trials in the development of DOR and DOR /3TC/TDF is provided in [Appendix 2.7.2: 1]. A tabular summary of PK parameter values from the biopharmaceutics trials and clinical pharmacology trials is presented in [Appendix 2.7.1: 1] and [Appendix 2.7.2: 2], respectively.

The conclusions and interpretations of the individual trial data are provided collectively in the cross trial comparison in [Sec. 2.7.2.3] rather than in the summaries of each individual trial to reflect conclusions based on integrated data from relevant studies.

2.1 Healthy Subject Pharmacokinetics and Initial Tolerability Trials

2.1.1 Single-and Multiple-Ascending Dose Trial (P001)

This was a 3-part, double-blind, randomized, placebo-controlled trial in 58 healthy male subjects, 18 to 50 years of age [Ref. 5.3.3.1: P001V01: 2].

Part I explored the safety, tolerability and PK of rising single-doses up to 450 mg of DOR in 16 healthy male subjects. Two alternating panels, Panels A and B, of 8 subjects each were randomized to receive DOR (n=6) or matching placebo (n=2) in up to 5 (Panel A) and 4 (Panel B) treatment periods. The doses for Panel A were 6, 25, 100, 300, and 450 mg administered in a fasted state. The doses for Panel B were 12, 50, and 150 mg dosed in the fasted state and 50 mg dosed with food. There was at least a 7-day washout between intrasubject dosing.

Part II explored the safety, tolerability, and PK of rising multiple-doses of DOR or matching placebo in 4 serial rising-dose panels. In addition, the effect of DOR on the PK of oral midazolam was assessed. Panels C (30 mg), D (60 mg), and F (240 mg) each consisted of 8 subjects who were randomized to receive DOR (n=6) or matching placebo (n=2) QD for 10 days. For Panels C, D, and F, PK was evaluated through 24 hours following the Day 1 dose, predose on Days 3 through 9, and for 120 hours following the last dose. Subjects in Panel E received 120 mg DOR QD for 14 days, and in addition, the effect of DOR on midazolam PK was assessed. In Panel E, 10 subjects received a single-oral dose of 2 mg midazolam hydrochloride (HCL) syrup (2 mg/mL) on Days -1 and 13, and 120 mg DOR (n=8) or matching placebo (n=2) QD for 14 days. DOR PK was evaluated through 24 hours following the Day 1 dose, predose on Days 3 through 13, and for 120 hours following the last dose. Midazolam PK was evaluated on Days -1 and 13. At least 3 days elapsed between panels.

Part III was designed to compare the tablet (enabled) formulation of DOR used in Parts I and II of this trial with a capsule (probe conventional) formulation. As the conventional formulation was exploratory and not further developed, the PK results are not discussed in depth, but are summarized in [Appendix 2.7.2: 2].

Results

Part I: Following single dose administration, DOR (enabled formulation; tablet) was rapidly absorbed with median Tmax ranging from 1 to 5 hours and apparent terminal half-life ranging from 11.67 to 15.67 hours over the 6-mg to 450-mg dose range ([Table 2.7.2: 2]). DOR AUC0-inf, AUC0-24, Cmax, and C24 increased in a less than dose proportional fashion over the dose range studied. For a single dose of 50 mg, the GMRs (fed/fasted) and 90% CIs were 1.33 (1.07, 1.65) and 0.95 (0.74, 1.23) for DOR AUC0-inf and Cmax, respectively. Based on a single 50 mg oral fasted dose of DOR, ~6% of the DOR dose was recovered unchanged in urine. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1].

Table 2.7.2: 2 Summary Statistics of Plasma MK-1439 Pharmacokinetics Following Single Oral Fasted Doses of 6- to 450-mg MK-1439 in Healthy Male Subjects (Part I)

Pharmacokinetic Parameters	Panel A 6 mg			Panel B 12 mg			Panel A 25 mg			Panel B 50 mg		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
$AUC_{0-\infty}$ (µM*hr)†	6	2.88	(2.35, 3.52)	6	4.88	(3.98, 5.98)	6	11.2	(9.17, 13.7)	6	17.6	(14.4, 21.6)
AUC_{0-24} (µM*hr)†	6	2.02	(1.70, 2.41)	6	3.66	(3.07, 4.35)	6	7.03	(5.91, 8.36)	6	12.7	(10.6, 15.1)
C_{max} (nM) †	6	156	(126, 193)	6	297	(240, 367)	6	460	(372, 569)	6	1070	(860, 1320)
C_{24hr} (nM) †	6	43.9	(35.1, 54.8)	6	73.0	(58.2, 91.4)	6	194	(155, 243)	6	269	(215, 338)
T_{max} (hr) ‡	6	1.00	(1.00, 4.00)	6	1.00	(1.00, 3.00)	6	5.00	(1.00, 6.00)	6	1.00	(1.00, 4.00)
Apparent $t_{1/2}$ (hr) §	6	11.68	9.95	6	11.67	15.70	6	15.67	20.42	6	13.29	10.59
Pharmacokinetic Parameters	**Panel A 100 mg**			**Panel B 150 mg**			**Panel A 300 mg**			**Panel A 450 mg**		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
$AUC_{0-\infty}$ (µM*hr) †	6	38.3	(31.3, 46.8)	6	49.9	(40.7, 61.2)	6	92.6	(75.7, 113)	6	127	(104, 155)
AUC_{0-24} (µM*hr) †	6	22.8	(19.2, 27.1)	6	34.0	(28.6, 40.5)	6	58.9	(49.5, 70.1)	6	82.4	(69.3, 98.0)
C_{max} (nM) †	6	1720	(1390, 2120)	6	2680	(2170, 3320)	6	3810	(3090, 4710)	6	6010	(4870, 7430)
C_{24hr} (nM) †	6	593	(475, 741)	6	750	(599, 940)	6	1490	(1190, 1870)	6	2070	(1660, 2580)
T_{max} (hr) ‡	6	1.50	(1.00, 5.00)	6	1.50	(1.00, 4.00)	6	3.50	(2.00, 5.00)	6	2.00	(1.00, 5.00)
Apparent $t_{1/2}$ (hr) §	6	15.26	43.9	6	13.84	27.6	6	15.62	27.1	6	14.80	34.5

† Back-transformed least squares mean and confidence interval from linear mixed effects model performed on natural log-transformed fasted values.
‡ Median (min, max) reported for T_{max}.
§ Geometric mean and percent geometric CV reported for apparent $t_{1/2}$.
Square root of conditional mean squared error (residual error) from the linear mixed effects model = 0.178 for $AUC_{0-\infty}$, 0.181 for AUC_{0-24}, 0.195 for C_{max}, and 0.207 for C_{24hr}. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
GM = Geometric least-squares mean; CI = Confidence interval.

Part II: Following multiple-dose administration for 10 days of 30, 60, and 240 mg and for 14 days of 120 mg, DOR (enabled tablet formulation) had a median Tmax ranging from 2 to 4 hours and apparent terminal half-life ranging from 12.59 to 14.99 hours over the 30- to 240-mg dose range [Table 2.7.2: 3]. DOR AUC0-24, Cmax, and C24 increased in a slightly less than proportional fashion over the 30 to 240 mg range on Day 10 (Day 14 for 120 mg). Median time to 90% of steady state was after 2 days for all dose levels. Consistent with the half-life of DOR, the accumulation ratios for doses of 30 to 240 mg ranged from 1.23 to 1.38 for AUC0-24. Similarly, the accumulation ratios for doses 30 to 240 mg ranged from 1.15 to 1.39 for C24, and 1.18 to 1.38 for Cmax, respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1].

Table 2.7.2: 3 Summary of MK-1439 Pharmacokinetics Following QD Multiple Dose Administration for 10 or 14 Days of 30- to 240-mg in Healthy Male Subjects (Part II)

Pharmacokinetic Parameters	30 mg N = 6	60 mg N = 6	120 mg N = 8 ††	240 mg N = 6
Day 1 (First Dose)				
AUC_{0-24} (µM*hr) †	8.42 (6.49, 10.9)	14.1 (10.9, 18.3)	27.3 (21.8, 34.2)	43.8 (33.7, 56.7)
C_{24hr} (nM) †	177 (125, 250)	336 (237, 475)	671 (497, 906)	1060 (751, 1500)
C_{max} (nM) †	672 (515, 875)	1020 (785, 1330)	1920 (1530, 2420)	3240 (2490, 4230)
T_{max} (hr) ‡	1.00 (1.00,5.00)	3.00 (1.00,4.02)	2.00 (1.00,4.00)	1.50 (1.00,5.00)
Day 10 (Last Dose)#				
AUC_{0-24} (µM*hr) †	11.5 (8.84, 14.9)	17.3 (13.4, 22.5)	36.8 (29.2, 46.3)	60.6 (46.7, 78.6)
C_{24hr} (nM) †	246 (174, 348)	385 (272, 544)	875 (644, 1190)	1340 (948, 1900)
C_{max} (nM) †	796 (611, 1040)	1300 (1000, 1700)	2520 (1990, 3190)	4470 (3430, 5830)
Apparent $t_{1/2}$ (hr) §	13.63 (11.27)	12.59 (18.28)	14.99 (22.90)	13.35 (15.94)
T_{max} (hr) ‡	3.50 (1.00,5.00)	2.00 (1.00,4.00)	4.00 (1.00,5.00)	3.00 (1.00,5.00)
Accumulation Ratio: Day 10# / Day 1				
AUC_{0-24} (µM*hr) ¶	1.36 (1.19, 1.56)	1.23 (1.07, 1.41)	1.35 (1.19, 1.53)	1.38 (1.21, 1.59)
C_{24hr} (nM) ¶	1.39 (1.17, 1.64)	1.15 (0.97, 1.36)	1.30 (1.12, 1.52)	1.26 (1.07, 1.49)
C_{max} (nM) ¶	1.18 (0.99, 1.42)	1.27 (1.07, 1.52)	1.31 (1.11, 1.54)	1.38 (1.16, 1.65)

† Back-transformed least squares mean and 95% confidence interval from linear mixed effects model performed on natural log-transformed values.

‡ Median (min, max) reported for T_{max}.

§ Geometric mean and percent geometric CV reported for apparent $t_{1/2}$.

Day 14 for 120 mg.

¶ Back-transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log-transformed values.

Square root of conditional mean squared error (residual error) from the linear mixed effect model = 0.140 for AUC_{0-24}, 0.179 for C_{max} and 0.168 for C_{24hr}. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.

†† Panel E 120 mg, N = 7 for day 14.

Midazolam drug interaction results are presented in [Sec. 2.7.2.2.3.2.1].

2.1.2 Supratherapeutic Single and Multiple Ascending Dose Trial (P006)

This was a double-blind, randomized, placebo-controlled, multiple-period, supratherapeutic single-rising and multiple-rising dose study in healthy male subjects [Ref. 5.3.3.1: P006MK1439: 2]. Two panels (Panels A and B) of 8 subjects each were randomized to receive DOR or matching placebo in a 3:1 ratio, respectively, in 3 treatment periods (Periods 1 to 3). In Panel A, subjects received a single-oral dose of 600 mg of DOR or matching placebo (Period 1) and 800 mg of DOR or matching placebo (Period 2). In Panel B, subjects received a single-oral dose of 1000 mg or matching placebo (Period 1) and 1200 mg of DOR or matching placebo (Period 2). In Period 3, subjects received 450 mg of DOR or matching placebo (Panel A) or 750 mg of DOR or matching placebo (Panel B) QD for 10 days, respectively.

Results

The PK results from Period 1 and Period 2 suggest that following a single dose of DOR, over a dose range of 600 to 1200 mg, DOR was rapidly absorbed with median Tmax ranging from 2 to 4 hours and geometric mean apparent half-life ranging from 13.58 to 18.88 hours [Table 2.7.2: 4]. Plasma concentrations declined in a monophasic manner and the apparent half-life was independent of dose. DOR AUC0-inf, Cmax, and C24hr increased less than dose-proportionally over the 600 to 1200 mg dose range. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1].

Table 2.7.2: 4 Summary Statistics of Plasma MK-1439 Pharmacokinetics Following Single Doses of 600- to 1200-mg MK-1439 in Healthy Adult Males (Period 1 and 2)

Pharmacokinetic Parameters	Panel A 600 mg			Panel A 800 mg		
	N	GM	90% CI	N	GM	90% CI
AUC0-inf (µM*hr) †	6	146	(126, 169)	6	179	(154, 208)
AUC0-24hr (µM*hr) †	6	101	(88.8, 115)	6	118	(104, 134)
Cmax (nM) †	6	7420	(6380, 8630)	6	8180	(7030, 9520)
C24hr (nM) †	6	2240	(1900, 2650)	6	2570	(2180, 3040)
Tmax (hr) ‡	6	2.50	(0.50, 4.00)	6	4.00	(2.00, 5.00)
Apparent t1/2 (hr) §	6	13.58	(14.10)	6	16.45	(26.97)
Pharmacokinetic Parameters	**Panel B 1000 mg**			**Panel B 1200 mg**		
	N	GM	90% CI	N	GM	90% CI
AUC0-inf (µM*hr) †	6	216	(186, 250)	6	246	(212, 286)
AUC0-24hr (µM*hr) †	6	138	(121, 156)	6	152	(134, 173)
Cmax (nM) †	6	10100	(8670, 11700)	6	10800	(9270, 12600)
C24hr (nM) †	6	3200	(2710, 3780)	6	3640	(3080, 4300)
Tmax (hr) ‡	6	2.00	(0.50, 5.00)	6	3.00	(1.00, 5.00)
Apparent t1/2 (hr) §	6	15.42	(10.97)	6	18.88	(34.23)

† Back-transformed least-squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
‡ Median (min, max) reported for Tmax.
§ Geometric mean and percent geometric CV reported for apparent t1/2.
Square root of conditional mean squared error (residual error) from the linear mixed effects model = 0.135 for AUC0-inf, 0.112 for AUC0-24hr, 0.130 for Cmax and 0.138 for C24hr. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
GM = Geometric least-squares mean; CI = Confidence interval.

During Period 3, following multiple-dose administration for 10 days of 450 and 750 mg, DOR had a median Tmax ranging from 1 to 3 hours and apparent half-life ranging from 14.67 to 20.95 hours over the 450 to 750 mg dose range [Table 2.7.2: 5]. Exploratory analysis of dose proportionality on Day 10 suggests that the point estimates of AUC0-24hr, Cmax, and C24hr increase in a slightly less than dose-proportional manner. Geometric mean and 90% CI of C24hr on Day 10 was 2090 (1710, 2560) nM for 450 mg and 2850 (2320, 3510) nM for 750 mg, respectively. Median time to 90% of steady state was 2 days for both dose levels. The accumulation ratios for doses of 450 mg to 750 mg ranged from 1.22 to 1.39 for AUC0-24hr. Similarly, the accumulation ratios for doses 450- to 750-mg ranged from 1.08 to 1.21 for C24hr, and 1.36 to 1.50 for Cmax, respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1].

Table 2.7.2: 5 Summary Statistics of Plasma MK-1439 Pharmacokinetics Following QD Multiple-dose Administration for 10 Days of 450- and 750-mg MK-1439 in Healthy Adult Male Subjects (Period 3)

Pharmacokinetic Parameter	Panel A 450 mg (N=6)	Panel B 750 mg (N=6 ¶)
Day1 (First Dose)		
AUC0-24hr (µM*hr) †	82.0 (70.2, 95.7)	99.1 (84.9, 116)
Cmax (nM) †	5580 (4810, 6460)	6980 (6020, 8080)
C24hr (nM) †	1940 (1520, 2470)	2370 (1850, 3020)
Tmax (hr) ‡	3.00 (1.00, 4.00)	3.00 (1.00, 5.00)
Day 10 (Last Dose)		
AUC0-24hr (µM*hr) †	100 (85.7, 117)	138 (118, 161)
Cmax (nM) †	7590 (6550, 8790)	10500 (8910, 12400)
C24hr (nM) †	2090 (1640, 2670)	2850 (2220, 3670)
Tmax (hr) ‡	1.50 (1.00, 4.00)	1.00 (0.52, 5.00)
Apparent t1/2 (hr) §	14.67 (30.50)	20.95 (55.14)
Accumulation Ratio (Day 10/ Day 1)		
AUC0-24hr #	1.22 (1.13, 1.32)	1.39 (1.28, 1.51)
Cmax #	1.36 (1.15, 1.61)	1.50 (1.26, 1.79)
C24hr #	1.08 (0.95, 1.23)	1.21 (1.04, 1.39)

† Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.

‡ Median (min, max) for Tmax.

§ Geometric mean and percent geometric CV reported for apparent t1/2.

Back-transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log-transformed values.

¶ N=5 for 750 mg (Panel B) on day 10.

Square root of conditional mean squared error (residual error) from the linear mixed effect model = 0.072 for AUC0-24hr, 0.154 for Cmax and 0.126 for C24hr. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.

2.1.3 Single Dose Absorption, Metabolism, and Excretion Trial (P008)

This was a single-dose, open-label trial to investigate the absorption, metabolism, excretion, and mass balance of DOR in healthy male subjects (N=6) [Ref. 5.3.3.1: P008: 2]. Each subject received a single average oral dose of 351 mg (~211 µCi) [^{14}C] DOR (actual doses ranged from 349 mg – 353 mg), which achieved similar plasma exposures to those obtained with the 100 mg tablet. Blood, urine, and fecal samples were collected up to a maximum of 28 days to measure total radioactivity, DOR concentrations, and metabolic profiling.

Results

The mean recovery of the radioactive dose was 101.2%, with 90.4% in feces and 10.8% in urine. In feces, unchanged DOR accounted for approximately 84.1% of total radioactivity, most likely from unabsorbed drug due to the low bioavailability of the formulation used in this trial. An oxidative metabolite, M9, accounted for 2.7%, with other minor metabolites detected including 2 N-dealkylated products (M8 and M11), oxidative or hydrolysis products (M5, M10, M18, and M19), and conjugates of oxidative products (M14, M15). The primary components in urine were M9 and unchanged DOR, accounting for approximately 6.7% and 2.2% of the administered dose, respectively.

DOR was the major component of total radioactivity detected in plasma, accounting for approximately 76% of the plasma total radioactivity (AUC0-48). The major metabolite in plasma was the oxidative product (M9, 12.9%). An N-acetylcysteine conjugate (M15) and a glucuronide conjugate of an oxidative metabolite (M7) accounted for a further 2.8% of the total radioactivity. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.4].

2.2 Intrinsic Factor Trials

2.2.1 Pharmacokinetics in Male and Female Subjects and Healthy Elderly and Young Adult Subjects (P009)

This was an open-label, single-period, parallel-group trial to assess the relative bioavailability of DOR in healthy elderly (65 to 80 years of age) male (n=12) and elderly female (n=12) subjects and healthy young (18 to 50 years of age) female subjects (n=12). Subjects received a single of 100 mg of DOR following an overnight fast [Ref. 5.3.3.3: P009: 2].

Results

The GMR and 90% CIs for AUC0-inf, Cmax and C24 (elderly male/young male) for DOR were 0.85 (0.67, 1.10), 0.92 (0.73, 1.16) and 0.81 (0.59, 1.11), respectively. The GMR and 90% CIs for AUC0-inf, Cmax, and C24hrs GMR (elderly female/young female) for DOR were 0.97 (0.79, 1.19), 1.18 (0.98, 1.42), and 0.94 (0.72, 1.21), respectively. The comparison of DOR PK between genders was conducted based on PK data pooled across elderly and young subjects (i.e., elderly + young female versus elderly + young male). The GMR and 90% CIs for DOR AUC0-inf, Cmax, and C24 (female/male) were 1.20 (1.03, 1.40), 1.42

(1.23, 1.64), and 1.02 (0.84, 1.24), respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.5].

2.2.2 Pharmacokinetics in Subjects with Hepatic Impairment (P019)

This was an open-label, single-dose trial to compare the PK of DOR in subjects with moderate hepatic impairment (based on the Child-Pugh classification) to healthy matched subjects. Eight subjects with a moderate hepatic impairment score (Child-Pugh classification of 7-9) and 8 healthy matched control subjects were enrolled and received a single-oral dose of 100 mg of DOR [Ref. 5.3.3.3: P019: 2].

Results

The DOR AUC0-inf, Cmax, and C24 GMRs (moderate hepatic subjects/healthy subjects) (90% CIs) were 0.99 (0.72, 1.35), 0.90 (0.66, 1.24), and 0.99 (0.74, 1.33), respectively. The median Tmax and the observed apparent terminal t1/2 GM were similar in healthy subjects and subjects with moderate hepatic impairment. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.5].

2.2.3 Pharmacokinetics in Subjects with Renal Impairment (P051)

This was an open-label, single dose trial to compare the PK of DOR in subjects with severe renal impairment to healthy matched subjects. Eight subjects with severe renal impairment ([eGFR] < 30 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease [MDRD] equation) not requiring hemodialysis and 8 healthy matched control subjects were enrolled and received a single oral dose of 100 mg of DOR [Ref. 5.3.3.3: P051MK1439: 2].

Results

The DOR AUC0-inf, Cmax, and C24 GMRs (severe renal subjects /healthy subjects) (90% CIs) were 1.43 (1.00, 2.04), 0.83 (0.61, 1.15), and 1.38 (0.99, 1.92) respectively. The median Tmax of DOR was comparable in both treatment populations. The observed apparent terminal t1/2 GM was longer in subjects with severe renal impairment (25.02 hours) compared to that in healthy matched control subjects (16.69 hours). For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.5].

2.3 Extrinsic Factor Trials

2.3.1 Effect of Concomitant Medication on Doravirine Pharmacokinetics

2.3.1.1 Doravirine Drug Interaction Trial with Tenofovir Disoproxil Fumarate (P003)

This was an open-label, 2-period, fixed-sequence trial in 8 healthy male subjects to evaluate the effect of TDF on DOR PK. In Period 1, all subjects received a single-oral dose of 100 mg DOR. There was a washout period of at least 7 days from the first dose of DOR in Period 1 to the start of Period 2. In Period 2, the same subjects received 300 mg of TDF QD

for 18 days with co-administration of a single dose of 100 mg DOR on Day 14 [Ref. 5.3.3.4: P003: 2].

Results

The DOR AUC0-inf, C24, and Cmax GMRs (DOR + TDF /DOR alone) (90%CI) were 0.95 (0.80, 1.12), 0.94 (0.78, 1.12), and 0.80 (0.64, 1.01) respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.1.2 Doravirine Drug Interaction Trial with Ritonavir (P002)

This was an open-label, fixed-sequence, 2-period trial in 8 healthy male subjects to evaluate the PK profile of a single-oral dose of DOR co-administered with ritonavir. In Period 1, all subjects received a single oral dose of 50 mg of DOR. There was a washout period of at least 7 days between study drug administration in Period 1 and the first dose of study drug in Period 2. In Period 2, the same subjects received 100 mg of ritonavir twice daily (BID) for 20 days. On Day 14, all subjects received the morning dose of ritonavir in combination with a single-oral dose of 50 mg DOR [Ref. 5.3.3.4: P002MK1439: 2].

Results

The DOR AUC0-inf, C24, and Cmax GMRs (DOR + ritonavir /DOR alone) (90% CI) were 3.54 (3.04, 4.11), 2.91 (2.33, 3.62), and 1.31 (1.17, 1.46) respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.1.3 Doravirine Drug Interaction Trial with Ketoconazole (P010)

This was an open-label, 2-period, fixed-sequence trial to assess the effect of multiple doses of ketoconazole on the single-dose plasma PK of DOR. Ten (10) healthy adult male and female subjects were enrolled in the trial. In Period 1, subjects received a single-oral dose of 100 mg DOR, followed by a 7 day washout. In Period 2, subjects received oral doses of 400-mg ketoconazole QD for 10 days, with co-administration of a single-oral dose of 100 mg DOR on Day 2 [Ref. 5.3.3.4: P010: 2].

Results

The DOR AUC0-inf GMR (DOR + ketoconazole /DOR alone) (90% CI) was 3.06 (2.85, 3.29). The Cmax and C24 GMRs (DOR + ketoconazole /DOR alone) (90% CI) were 1.25 (1.05, 1.49) and 2.75 (2.54, 2.98), respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.1.4 Doravirine Drug Interaction Trial with Rifampin (P011)

This was an open-label, 2-period, fixed-sequence trial to assess the effects of single- and multiple-doses of rifampin on the single-dose PK of DOR. Eleven (11) healthy male adult subjects were enrolled in this trial. In Period 1, subjects received a single oral dose of 100 mg DOR on Day 1 followed by a 7-day washout. In Period 2, subjects received a single-oral dose of 600 mg rifampin co-administered with a single-oral dose of 100 mg DOR on Day 1.

In Period 2, subjects also received multiple-oral doses of 600 mg rifampin QD for 15 days (Days 4 to 18) co-administered with a single-oral dose of 100 mg DOR on Day 17 [Ref. 5.3.3.4: P011V01: 2].

Results

Single Dose (SD):

The AUC0-inf and C24 GMRs (DOR + SD rifampin /DOR alone) (90% CIs) were 0.91 (0.78, 1.06) and 0.90 (0.80, 1.01), respectively. The Cmax GMR (DOR + SD rifampin /DOR alone) (90% CI) was 1.40 (1.21, 1.63).

Multiple Dose (MD):

The AUC0-inf, C24, and Cmax GMRs (DOR + MD rifampin /DOR alone) (90% CIs) were 0.12 (0.10, 0.15), 0.03 (0.02, 0.04), and 0.43 (0.35, 0.52), respectively.

For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.1.5 Doravirine Drug Interaction Trial with Rifabutin (P035)

This was an open-label, 2-period, fixed-sequence trial to evaluate the effect of multiple doses of rifabutin on the single-dose PK of DOR. Eighteen healthy subjects were enrolled. In Period 1, subjects received a single 100 mg dose of DOR followed by a 7-day washout. In Period 2 subjects received 300 mg QD of rifabutin on Day 1 through Day 16. On Day 14 a single dose of DOR was co-administered with rifabutin [Ref. 5.3.3.4: P035: 2].

Results

The AUC0-inf, C24hr, and Cmax GMRs (DOR + rifabutin/ DOR alone) (90% CIs) were 0.50 (0.45, 0.55), 0.32 (0.28, 0.35), and 0.99 (0.85, 1.15), respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.1.6 Doravirine Drug Interaction Trial With Efavirenz (P020)

This was an open-label, 3-period, fixed-sequence, multiple-dose trial to investigate the effect of switching from efavirenz therapy to DOR on the PK of DOR. Twenty (20) healthy male and female subjects were enrolled. In Period 1, subjects received multiple-oral doses of 100 mg DOR QD from Days 1 to 5. In Period 2, subjects received multiple-oral doses of 600 mg efavirenz QD from Days 1 to 14. In Period 3, subjects received multiple-oral doses of 100 mg DOR QD from Days 1 to 14. There was a 7-day washout between the last dose of DOR in Period 1 and the first dose of efavirenz in Period 2. There was no washout between Periods 2 and 3 [Ref. 5.3.3.4: P020: 2].

Results

The DOR single dose AUC0-24, Cmax, and C24 GMRs (DOR + EFV pretreatment/DOR alone) (90% CI) were 0.38 (0.33, 0.45), 0.65 (0.58, 0.73), and 0.15 (0.10, 0.23), respectively.

In Period 3, after 14 days of dosing with DOR QD, the multiple-dose DOR AUC0-24, Cmax, and C24 GMRs (DOR + EFV pretreatment/DOR alone) (90% CI) were 0.68 (0.58, 0.80), 0.86 (0.77, 0.97), 0.50 (0.39, 0.64), respectively. The Period 3 DOR C24 values and efavirenz concentrations following cessation of efavirenz and initiation of DOR are summarized in [Table 2.7.2: 6]. The target trough concentration associated with efavirenz efficacy is considered to be 1000 ng/mL and based on the bounds of clinical relevance for DOR, the target C24 value is 560 nM. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

Table 2.7.2: 6 Summary Statistics of MK-1439 Plasma C24 and Efavirenz Plasma Cefv During Multiple-dose Administration of 100-mg MK-1439 QD for 14 Days With Pretreatment of 600-mg Efavirenz QD for 14 Days in Healthy Adult Subjects

MK-1439 C24[†] (nM)				Cefv[†] (ng/mL)			
Day[‡]	N	GM	90% CI	Day[‡]	N	GM	90% CI
.				Day 1	16	3180	(1960, 5150)
Predose day 2	17	93.5	(67.4, 130)	Day 2	16	1690	(1050, 2740)
Predose day 3	17	112	(80.4, 155)	Day 3	16	1210	(744, 1950)
Predose day 4	17	119	(85.9, 165)	Day 4	16	919	(568, 1490)
Predose day 5	17	146	(105, 202)	Day 5	16	689	(425, 1120)
Predose day 6	17	170	(122, 236)	Day 6	16	542	(334, 877)
Predose day 7	17	197	(142, 274)	Day 7	16	423	(261, 685)
Predose day 8	17	243	(175, 337)	Day 8	16	352	(218, 571)
Predose day 9	17	267	(192, 370)	Day 9	16	280	(173, 453)
Predose day 10	17	328	(236, 456)	Day 10	16	223	(138, 362)
Predose day 11	17	367	(264, 509)	Day 11	16	189	(117, 307)
Predose day 12	17	424	(306, 589)	Day 12	16	161	(99.4, 261)
Predose day 13	17	485	(350, 674)	Day 13	16	144	(88.7, 233)
Predose day 14	17	475	(343, 660)	Day 14	16	113	(69.9, 183)
Predose day 15	17	449	(323, 623)	Day 15§	14	95.7	(58.8, 156)

MD MK-1439 + Efavirenz: Multiple doses of 100 mg MK-1439 QD for 14 days with efavirenz pretreatment (multiple doses of 600 mg efavirenz QD for 14 days in Period 2).
[†]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[‡]Samples were taken prior to MK-1439 dosing on the day scheduled for the sample.
[§]Concentrations for Subjects AN 0015 (Day 15) and AN 0017 (Day 15) were not included in the Cefv analysis since the concentrations are questionable.
Efavirenz concentrations for Subject AN 0008 were not included in the Cefv analysis since this subject is a slow metabolizer (CYP2B6*6/*6).
Cefv BLQ values were set to ½ LLOQ (LLOQ = 20 ng/mL) for Subjects AN 0002 (Days 10 to 15), AN 0011 (Day 15), AN 0013 (Days 14 to 15), and AN 0020 (Days 12 to 15).
Note: Subject AN 0004 dropped on Day 11 of Period 2, Subject AN 0006 dropped on Day 4 of Period 1 and Subject AN 0014 dropped on Day 6 of Period 2.
GM = Geometric least-squares mean; CI = Confidence interval.

2.3.1.7 Doravirine Drug Interaction Trial with Aluminum Hydroxide and Magnesium hydroxide Containing Antacids and Pantoprazole (P042)

This was an open-label, 3-period, fixed-sequence trial to evaluate the effect of concomitant administration of an antacid and a proton pump inhibitor (PPI) on the PK of DOR. Fourteen healthy subjects were enrolled [Ref. 5.3.3.4: P042: 2]. Subjects received a single-oral dose of 100 mg DOR in Period 1, and subjects received a single-oral dose of 100 mg DOR co-administered with a single 20 mL dose of an antacid oral suspension containing 1600 mg aluminum hydroxide, 1600 mg magnesium hydroxide, and 160 mg simethicone in Period 2. In Period 3, subjects received a 40 mg daily oral dose of pantoprazole sodium (1 delayed-release tablet per day) for 5 days and a single 100 mg oral dose of DOR (1 tablet) on Day 5. There was a 10-day washout interval between each treatment period.

Results

Antacid

The DOR AUC0-inf, Cmax, and C24 GMRs (90% CI) (DOR + antacid /DOR) were 1.01 (0.92, 1.11), 0.86 (0.74, 1.01), and 1.03 (0.94, 1.12), respectively.

Pantoprazole

The DOR AUC0-inf, Cmax, and C24 GMRs (90% CI) (DOR + pantoprazole /DOR) were 0.83 (0.76, 0.91), 0.88 (0.76, 1.01), and 0.84 (0.77, 0.92), respectively.

For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.1.8 A Component Interaction Study of MK-1439A in Healthy Subjects under Fasting Conditions (P038)

This was an open-label, single-dose, randomized, 3-period, crossover, component interaction study of DOR, 3TC, and tenofovir. A total of 15 healthy subjects were administered the following in 3 treatment periods in the fasted state: 100 mg DOR, 300 mg 3TC + 245 mg tenofovir disoproxil as fumarate (300 mg TDF), and 100 mg DOR + 300 mg 3TC + 245 mg tenofovir disoproxil as fumarate (300 mg TDF). The washout period between drug administration for each subject was at least 7 days [Ref. 5.3.3.4: P038V01: 2].

Results

The GMR (90% CI) for DOR, 3TC and tenofovir PK results are presented in [Table 2.7.2: 7]. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

Table 2.7.2: 7 Statistical Comparison of DOR, 3TC, and Tenofovir Pharmacokinetics Following Administration of 3TC+TDF(Co-administered) and DOR Alone and When all 3 Drugs Are Co-administered in Healthy Subjects (N=15)

Analyte	DOR	3TC	Tenofovir*
Parameter	GMR (90%CI) DOR / DOR + 3TC + TDF	GMR (90%CI) 3TC + TDF / DOR + 3TC +TDF	GMR (90%CI) 3TC + TDF / DOR + 3TC +TDF
AUC0-inf	0.96 (0.87, 1.06)	0.94 (0.88, 1.00)	1.11 (0.97, 1.28)
Cmax	0.97 (0.88, 1.07)	0.92 (0.81, 1.05)	1.17 (0.96, 1.42)
GMR= geometric mean ratio, CI=confidence interval *dosed as tenofovir disoproxil as fumarate			

2.3.2 Effect of Doravirine on Concomitant Medication

2.3.2.1 Doravirine Drug Interaction Trial with Midazolam (P001)

The midazolam DDI was conducted as part of trial P001 [Ref. 5.3.3.1: P001V01: 2]; see [Sec. 2.7.2.2.1.1] for the description of the trial design.

Results

The midazolam AUC0-inf and Cmax GMRs (90%CI) (midazolam + DOR /midazolam alone) were 0.82 (0.70, 0.97) and 1.02 and (0.81, 1.28), respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.2.2 Doravirine Drug Interaction Trial with Oral Contraceptives (P012)

This was an open-label, 2-period, fixed-sequence trial investigating the effect of multiple doses of DOR on the single-dose PK of a monophasic combination of ethinyl estradiol/levonorgestrel (EE/LNG) in healthy female subjects. Twenty (20) healthy, postmenopausal or oophorectomized, adult female subjects were enrolled in the trial. In Period 1, subjects received a single-oral dose of 0.03 mg EE/0.15 mg LNG on Day 1. In Period 2, subjects received multiple-oral doses of 100 mg DOR QD for 17 consecutive days, with a single-oral dose of 0.03 mg EE/0.15 mg LNG co-administered with DOR on Day 14. There was a washout of at least 7 days between dosing in Period 1 and the first dose in Period 2 [Ref. 5.3.3.4: P012: 2].

Results

The EE AUC0-inf, AUC0-last, and Cmax GMRs (90% CI) (EE + LNG + DOR / EE + LNG alone) were 0.98 (0.94, 1.03), 0.98 (0.94, 1.03), and 0.83 (0.80, 0.87), respectively.

The LNG AUC0-inf, AUC0-last, and Cmax GMRs (90% CI) (EE + LNG + DOR /EE + LNG alone) were 1.21 (1.14, 1.28), 1.15 (1.10, 1.21), and 0.96 (0.88, 1.05), respectively.

For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.2.3 Doravirine Drug Interaction Trial with Dolutegravir (P016)

This was an open-label, 3-period, fixed-sequence trial to evaluate the PK of DOR and dolutegravir when co-administered in healthy male and female subjects. In Period 1, subjects received 50-mg dolutegravir QD for 7 days. In Period 2, subjects were administered 200-mg DOR QD for 7 days. In Period 3, subjects were administered 50-mg dolutegravir + 200-mg DOR QD for 7 days. There was at least a 7-day washout between Period 1 and Period 2. There was no washout between Period 2 and Period 3. Twelve subjects were enrolled [Ref. 5.3.3.4: P016: 2].

Results

The dolutegravir steady state AUC0-24, C24, and Cmax GMRs (dolutegravir + DOR/dolutegravir alone) (90% CI) values were 1.36 (1.15, 1.62), 1.27 (1.06, 1.53), and 1.43 (1.20, 1.71), respectively.

The steady state DOR AUC0-24, C24, and Cmax GMRs (DOR + dolutegravir /DOR alone) (90% CI) values were 1.00 (0.89, 1.12), 0.98 (0.88, 1.09), and 1.06 (0.88, 1.28), respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.2.4 Doravirine Drug Interaction Trial with Atorvastatin (P036)

This was an open-label, 2-period, fixed-sequence, PK drug interaction trial to evaluate the effect of DOR on the PK of atorvastatin in healthy male and female subjects. In Period 1, subjects received a single dose of 20 mg atorvastatin. In Period 2 subjects were administered 100 mg DOR QD from Days 1 to 8 and a single dose of 20 mg atorvastatin on Day 5. There was a 72 hour washout between Periods 1 and 2. Sixteen subjects were enrolled in this trial [Ref. 5.3.3.4: P036: 2].

Results

Atorvastatin AUC0-inf and Cmax GMRs (atorvastatin + DOR /atorvastatin) (90% CI) values were 0.98 (0.90, 1.06) and 0.67 (0.52, 0.85) respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.2.5 Doravirine Drug Interaction Trial with Metformin (P048)

This was an open-label, 2-period, fixed-sequence PK drug interaction trial to evaluate the effect of multiple doses of DOR on the single-dose PK of metformin in 14 healthy male and female subjects. In Period 1, subjects were administered a single-oral dose of a 1000 mg tablet of metformin (immediate release). In Period 2, subjects were administered QD oral dose of a 100 mg tablet of DOR on Day 1 to Day 7 and single-oral dose of a 1000 mg metformin on Day 5. There was a washout period of at least 3 days between metformin drug administration in Period 1 and the first DOR drug administration in Period 2 [Ref. 5.3.3.4: P048: 2].

Results

The metformin AUC0-inf, AUC0-last, and Cmax GMRs (90% CI) (metformin + DOR/metformin alone) were 0.94 (0.88, 1.00), 0.93 (0.87, 1.00), and 0.94 (0.86, 1.03), respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

2.3.2.6 Doravirine Drug Interaction Trial with Methadone (P045)

This was an open-label, single-period, multiple-dose, fixed-sequence, drug-interaction trial in 14 male and female subjects receiving methadone treatment (20 to 200 mg). Subjects received their usual methadone dose on Days 1 through 7. On Days 2 through 6, subjects received DOR 100 mg QD. Blood samples were collected predose through 24 hours postdose on Day 1 and Day 6 to assay R-, S-, and total methadone concentrations. DOR PK was assessed on Day 6 only. Methadone PK (dose normalized) on Day 6 and Day 1 were compared based on a linear mixed-effect model, with R-methadone as the primary endpoint. DOR PK, when co-administrated with methadone on Day 6, was compared with DOR administrated alone (historical data) based on an ANCOVA model with age and BMI as potential covariates [Ref. 5.3.3.4: P045: 2].

Results

The GMR (90% CI) for R-methadone (dose normalized) and DOR PK results are presented in [Table 2.7.2: 8]. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

Table 2.7.2: 8 Statistical Comparison of R-methadone and Doravirine Pharmacokinetics Following Administration of Methadone and Doravirine Alone and When They are Co-administered in Subjects Receiving Methadone Treatment (N=14)

Analyte	R-Methadone*	DOR
Parameter	GMR methadone + DOR/methadone alone (90% CI)	GMR methadone +DOR/DOR alone (90% CI)
AUC0-24	0.95 (0.90, 1.01)	0.74 (0.61, 0.90)
C24	0.95 (0.88, 1.03)	0.80 (0.63, 1.03)
Cmax	0.98 (0.93, 1.03)	0.76 (0.63, 0.91)
GMR = geometric mean ratio, CI = confidence interval *similar results observed for S- and total methadone		

2.3.2.7 Doravirine Drug Interaction Trial with Elbasvir and Grazoprevir (P050)

This was a fixed-sequence, open-label trial of DOR, elbasvir (also referred to as MK-8742), and grazoprevir (also referred to as MK-5172) in 12 healthy male and female adult subjects. A dose of 100-mg DOR was administered QD on Days 1 to 5 of Period 1. In Period 2, subject were co-administered a 50-mg dose of elbasvir and a 200-mg dose of grazoprevir on Days 1 through 10. In Period 3, subjects were co-administered 100 mg of DOR, 50 mg of elbasvir, and 200 mg of grazoprevir. There was a 5-day washout between Period 1 and

Period 2. There was no washout between Period 2 and Period 3 [Ref. 5.3.3.4: P050MK1439: 2].

Results

The GMR (90% CI) for elbasvir, grazoprevir, and DOR PK results are presented in [Table 2.7.2: 9]. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

Table 2.7.2: 9 Statistical Comparison of Elbasvir, Grazoprevir and Doravirine PK Following Administration of Elbasvir + Grazoprevir (Co-administered) and Doravirine Alone and When All Three drugs are Co-administered in Healthy Subjects (N=12)

Analyte	Elbasvir	Grazoprevir	DOR
Parameter	GMR (90%CI) elbasvir + grazoprevir + DOR/elbasvir+grazoprevir alone (90% CI)	GMR (90%CI) elbasvir + grazoprevir + DOR/elbasvir+grazoprevir alone (90% CI)	GMR (90%CI) elbasvir + grazoprevir + DOR/DOR alone (90% CI)
AUC0-24	0.96 (0.90. 1.02)	1.07 (0.94, 1.23)	1.56 (1.45, 1,68)
C24	0.96 (0.89, 1.04)	0.90 (0.83, 0.96)	1.61 (1.45, 1.79)
Cmax	0.96 (0,91, 1.01)	1.22 (1.01, 1.47)	1.41 (1.25, 1.58)
GMR = geometric mean ratio, CI = confidence interval			

2.3.2.8 Doravirine Drug Interaction Trial with Sofosbuvir/Ledipasvir (P053)

This was an open-label, randomized, 3-period, crossover trial to evaluate the PK interaction of DOR and ledipasvir/sofosbuvir in 14 healthy adult subjects. On Day 1 of each period, subjects received a single-oral dose of either DOR alone, ledipasvir/sofosbuvir alone, or DOR co-administered with ledipasvir/sofosbuvir in a randomized manner. There was a washout interval of 14 days between each dose [Ref. 5.3.3.4: P053: 2].

Results

The GMR (90% CI) for the ledipasvir, sofosbuvir, GS-331007 (sofosbuvir nucleoside metabolite), and DOR PK results are presented in [Table 2.7.2: 10]. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.1.1.6].

Table 2.7.2: 10 Statistical Comparison of Ledipasvir, Sofosbuvir, GS-33107, and DOR Pharmacokinetics Following Administration of Ledipasvir/Sofosbuvir and DOR Alone and When They are Co-administered in Healthy Subjects (N=14)

Analyte	Ledipasvir	Sofosbuvir	GS-331007	Doravirine
Parameter	GMR (90%CI) ledipasvir/sofosbuvir + DOR/ledipasvir/sofosbuvir alone (90% CI)	GMR (90%CI) ledipasvir/sofosbuvir + DOR/ledipasvir/sofosbuvir alone (90% CI)	GMR (90%CI) ledipasvir/sofosbuvir + DOR/ledipasvir/sofosbuvir alone (90% CI)	GMR (90%CI) DOR +ledipasvir/sofosbuvir /DOR alone (90% CI)
AUC0-Inf	0.92 (0.80, 1.06)	1.04 (0.91, 1.18)	1.03 (0.98. 109)	1.15 (1.07, 1.24)
C24	-*	-*	-*	1.24 (1.13, 1.36)
Cmax	0.91 (0.80, 1.02)	0,89 (0.79, 1.00)	1.03 (0.97, 1.09)	1.11 (0.97, 1.27)
GMR = geometric mean ratio, CI = confidence interval *PK parameter was not a primary variable and; therefore, not shown.				

2.4 Pharmacodynamic and Special Safety Trials

2.4.1 Antiviral Effect in Treatment Naïve HIV-1 Infected Subjects (P005)

This was a double-blind, randomized, placebo-controlled, multiple-panel study to evaluate the safety, tolerability, PK, and antiretroviral activity of DOR as short term monotherapy in antiretroviral therapy naïve, HIV-1 infected subjects. Two panels (Panels A and B) of 9 subjects each were randomized to receive DOR or matching placebo (in a 6:3 ratio, respectively). Subjects in Panel A received DOR 25 mg or matching placebo and subjects in Panel B received DOR 200 mg or matching placebo QD for 7 days [Ref. 5.3.4.1: P005V01: 2].

Results

At the 200 mg dose, the least-squares (LS) mean difference between DOR and placebo in log10 plasma HIV RNA change from baseline and corresponding 90% CI was -1.26 (-1.51, -1.02). At the 25 mg dose, the LS mean difference between DOR and placebo in log10 plasma HIV RNA change from baseline and corresponding 90% CI was -1.37 (-1.60, -1.14). There was no difference in the VL reduction following 25 mg compared with 200 mg.

The DOR C24 GM (90% CI) was 1540 (1150, 2060) and 251 (188, 355) nM on Day 7 following the administration of 200 and 25 mg QD for 7 days, respectively. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.3.1].

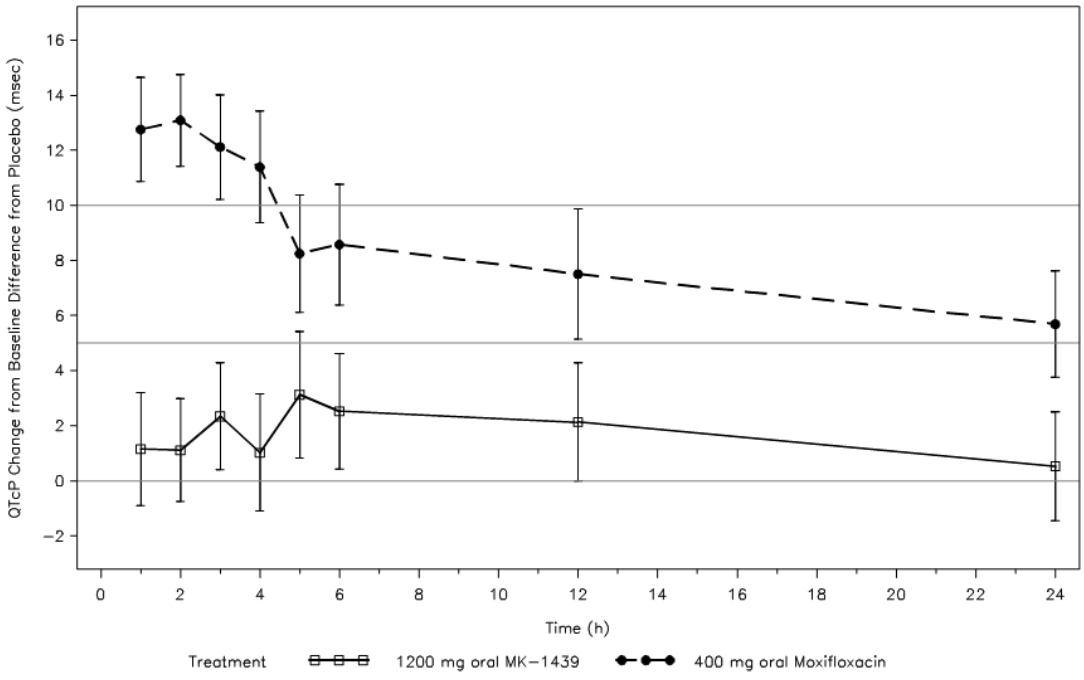
2.4.2 Thorough QT/QTc Trial (P017)

This was a placebo-controlled, double blind with respect to DOR, randomized, 3-period, crossover trial to evaluate the effect of a single oral supratherapeutic dose of DOR on the QT interval corrected for heart rate (HR) (QTc) in healthy subjects. Moxifloxacin was administered as a positive control in an open-label manner. Forty-five healthy male and female subjects were enrolled. Subjects participated in 3 treatment periods, and each received the following treatments in a randomized sequence: 1200 mg oral dose of DOR (supra-therapeutic dose), 400 mg oral dose of moxifloxacin, and matching oral placebo for DOR. There was a washout of at least 7 days between periods [Ref. 5.3.4.1: P017: 2].

Results

The population method for HR correction of the QT interval (QTcP) was found to be the most appropriate. In a comparison of the mean change from baseline of QTcP of 1200 mg DOR (supra-therapeutic dose), DOR versus placebo, the upper limit of the 90% CI did not exceed 10 msec at any time point postdose [Figure 2.7.2: 7] and [Table 2.7.2: 11]. The largest mean difference (90% CI) was 3.12 (0.824, 5.42), at 5 hours postdose.

Figure 2.7.2: 7 Mean Holter ECG Change from Baseline Difference from Placebo and 90% Confidence Interval - by Time Point and Treatment - QTcP (msec) Following a Single Dose of 1200-mg MK-1439 and 400-mg Moxifloxacin to Healthy Fasted Adult Subjects (N=45)



Data Source: [Ref. 5.3.4.1: P017]

Table 2.7.2: 11 Placebo-Adjusted Mean Change from Baseline in QTcP (ΔΔQTcP) Following a Single Dose of Placebo or 1200-mg MK-1439 or 400-mg Moxifloxacin to Healthy Fasted Adult Subjects

		QTcP Value (msec)			Change From Baseline (msec)		Difference in Change From Baseline From Placebo (msec)	
Treatment	Time (h)	N	Mean	95% CI	Mean	95% CI	LSMean Difference	90% CI
Placebo	0	40	402	(397, 408)				
	1	39	400	(395, 405)	-3.11	(-4.93, -1.30)		
	2	40	400	(395, 404)	-2.79	(-4.93, -0.653)		
	3	40	400	(395, 405)	-2.01	(-4.20, 0.178)		
	4	40	402	(397, 406)	-0.769	(-2.70, 1.16)		
	5	40	400	(396, 405)	-2.20	(-5.39, 0.995)		
	6	40	396	(391, 401)	-6.23	(-9.02, -3.44)		
	12	39	400	(396, 404)	-3.29	(-5.78, -0.814)		
	24	39	400	(395, 405)	-2.92	(-5.14, -0.712)		
1200 mg oral MK-1439	0	41	400	(396, 405)				
	1	41	399	(394, 404)	-1.49	(-3.22, 0.240)	1.15	(-0.902, 3.21)
	2	41	399	(394, 404)	-1.38	(-3.06, 0.305)	1.11	(-0.748, 2.97)
	3	41	402	(397, 407)	1.23	(-0.698, 3.16)	2.34	(0.406, 4.28)
	4	41	402	(396, 407)	1.28	(-0.791, 3.35)	1.02	(-1.10, 3.15)
	5	41	402	(398, 407)	1.79	(-1.15, 4.74)	3.12	(0.824, 5.42)
	6	41	398	(393, 402)	-2.75	(-5.10, -0.400)	2.53	(0.434, 4.62)
	12	41	400	(396, 405)	-0.226	(-3.13, 2.68)	2.13	(-0.021, 4.29)
	24	41	398	(394, 403)	-1.94	(-4.36, 0.491)	0.530	(-1.45, 2.51)
400 mg oral Moxifloxacin	0	41	403	(398, 407)				
	1	40	411	(406, 416)	8.01	(5.86, 10.2)	12.8	(10.9, 14.6)
	2	40	412	(407, 417)	9.10	(7.39, 10.8)	13.1	(11.4, 14.8)
	3	41	412	(407, 417)	9.01	(7.19, 10.8)	12.1	(10.2, 14.0)
	4	40	413	(408, 418)	9.85	(7.42, 12.3)	11.4	(9.36, 13.4)
	5	41	408	(403, 412)	4.81	(1.98, 7.65)	8.25	(6.12, 10.4)
	6	41	404	(400, 409)	1.49	(-0.830, 3.81)	8.58	(6.38, 10.8)
	12	39	406	(401, 411)	3.28	(0.504, 6.06)	7.50	(5.15, 9.86)
	24	39	404	(399, 409)	1.86	(-0.154, 3.87)	5.69	(3.76, 7.62)

CI = confidence interval; LS mean = least squares mean; N = number of subjects; QTcP = population specific rate correction method
The 2-sided 90% CIs is equivalent to 1-sided upper 95% CIs.
An analysis of covariance (ANCOVA) linear model was used to analyze the difference of change from baseline in QTcP by time point for MK-1439 at each treatment versus placebo.
Means and 95% CI for the QTcP and QTcP change-from-baseline are descriptively summarized for each treatment by time point. Time 0 represents the baseline time point derived as the average of the 3 pre-dose assessments within each period.
Data Source: [Ref. 5.3.4.1: P017]

The mean difference between moxifloxacin change from baseline and placebo was significantly greater than 5 msec at all time points from 1 through 4 hours postdose,

demonstrating assay sensitivity for this trial. The largest effect (moxifloxacin – placebo) occurred at 2 hours postdose, with a mean (90% CI) of 13.1 (11.4, 14.8) msec.

None of the subjects had average QTcF or QTcP readings of >450 msec. All subjects had a QTcF and QTcP change from baseline of ≤ 30 msec at all treatments at all time points.

Following a single-oral DOR dose at 1200 mg, concentrations increased rapidly with peak concentrations occurring at approximately 3.1 hours. Concentrations declined in a single exponential phase over the 24-hour sampling period. After a single 1200 mg dose, DOR AUC0-24hr and Cmax were 119 µM•hr and 9240 nM, respectively, and were generally comparable to the AUC0-24hr of 157 µM•hr and Cmax of 11,200 nM, observed in a previous trial (P006) [Ref. 5.3.3.1: P006MK1439: 2] in healthy adult male subjects at 1200 mg. The Cmax and AUC0-24hr values in this trial were approximately 4-fold and 3-fold, respectively, those observed with the clinical dose of 100 mg. For discussion and interpretation of results refer to section [Sec. 2.7.2.3.3.2].

2.5 Summaries of Data Analyses from More than One Trial

2.5.1 Population Pharmacokinetic Analysis

A population PK model was used to characterize the PK of DOR across Phase 1, 2b, and 3 trials, to investigate effects of intrinsic and extrinsic factors on DOR PK, and to generate individual DOR PK parameter estimates for Phase 2b and Phase 3 HIV-1 infected subjects to support exposure-response analyses for efficacy and safety. Results and conclusions from the population PK analysis are discussed in [Sec. 2.7.2.3.1].

The population PK model included 20 Phase 1 trials, 1 Phase 2b trial, and 2 Phase 3 trials, comprising 341 healthy subjects and 959 HIV-1-infected subjects receiving DOR as a single entity or as DOR/3TC/TDF. PK samples from the Phase 1 trials were densely sampled, while a sparse sampling scheme was used in the Phase 2b and Phase 3 trials. Due to less than dose proportional increases in exposure over the range of doses evaluated in clinical development, only doses 200 mg or less were included in the analysis.

The analysis population was comprised predominantly of male (81%), white (65%), non-Hispanic (77%) subjects, with black and Asian subjects comprising 22% and 7% of the population, respectively. The overall median (range) age and weight of the population were 34 (18 to 78) years and 75 (37 to 196) kg, respectively.

The PK of DOR was characterized with a one-compartment model described by first-order absorption (ka), central volume of distribution (Vc), and linear clearance (CL) from the central compartment. The less than dose-proportional increases in DOR exposure were described by estimation of relative bioavailabilities (F1) for doses above and below a reference dose range of 30 to 120 mg (F1 = 1) that included the clinical dose of 100 mg. Inter-individual variability (IIV) random effects on CL and Vc were included. An additive residual error model was employed for log-transformed data, with separate residual error terms for the Phase 1 data versus the Phase 2b/3 data, and within the Phase 1 data for the first 0.5 h post-dose versus the remaining time points.

Identification of significant covariates was based on step-wise forward addition ($p < 0.01$) and backward elimination ($p < 0.001$) using the step-wise covariate modeling (SCM) process. The final population PK model included statistically significant but not clinically important effects of body weight and healthy versus HIV-1-infected subject status on volume of distribution and age on clearance. Other evaluated covariates included gender, renal function (MDRD eGFR), race, ethnicity, and administration as the single entity or DOR/3TC/TDF. The identification of healthy versus HIV-1-infected subject status as a significant covariate on volume of distribution likely reflects the dense versus sparse sampling used in the Phase 1 and Phase 2b/3 trials, where better characterization of Cmax with the dense sampling scheme in Phase 1 is accounted for by a difference in estimated volume of distribution. [Appendix 2.7.2: 5] provides the population PK parameter values, along with the corresponding percent change relative to reference levels for significant covariates.

Model evaluation using simulation-based visual predictive checks showed that the model accurately characterized the central tendency of the observed data and that an appropriate distribution of the observed data fell with the 5th and 95th percentiles of model-simulated data, indicating that the model adequately describes DOR plasma concentrations.

The clinical relevance of intrinsic factors was evaluated through simulation of steady-state DOR AUC0-24 and C24 values and comparison against the clinical significance bounds described in [Sec. 2.7.2.1.5.4]; results of these assessments are discussed in [Sec. 2.7.2.3.1.1.5]. Post hoc estimates of individual PK parameters for the HIV-1-infected subjects enrolled in the Phase 2b and 3 trials were also obtained from the final population PK model and used for exposure-response analyses for efficacy and safety. A full description of the population PK analysis can be found in the related report [Ref. 5.3.5.3: 04PPZ5].

2.5.2 Exposure-Response Analysis

2.5.2.1 Exposure-Efficacy Analyses

Exposure-response relationships for Week 48 viral response were evaluated for the proportion of subjects achieving HIV-1 RNA <50 copies/mL or <40 copies/mL as determined using both the "snapshot" approach, which is the primary approach specified in the Phase 3 trial protocols, and the OF approach. Under the OF approach, monotone (non-intermittent) missing data for subjects who prematurely discontinued assigned treatment due to lack of efficacy were assigned to be failures after treatment discontinuation; subjects with data missing for reasons other than lack of efficacy were excluded. The exposure-response relationship for protocol defined virologic failure (PDVF) through Week 48 was also assessed. For each of the viral response and virologic failure endpoints, separate analyses were conducted for the Phase 2b trial and for pooled data from the Phase 3 trials (P018, P021) due to different handling of subjects with PDVF between the Phase 2b and Phase 3 trials [Sec. 2.7.3.3.1-trtmtnve48wk]. The PK endpoints examined were DOR steady state C24, AUC0-24, and Cmax, estimated from the population PK model described in [Sec. 2.7.2.2.5.1]. For the Phase 2b trial, the analysis population described in [Sec. 2.7.3.2.1-trtmtnve48wk] was used and contained data from 217 subjects administered 25 mg, 50 mg, 100 mg, or 200 mg QD DOR in combination with FTC/TDF. The Phase 3 analysis population included 730 subjects administered 100 mg QD DOR in combination with

FTC/TDF or ABC/3TC [Ref. 5.3.5.1: P018V01MK1439] or DOR/3TC/TDF [Ref. 5.3.5.1: P021V01MK1439A].

Administration of DOR as the FDC does not impact DOR PK based on Phase 1 relative bioavailability trials with the FDC [Sec. 2.7.1.3.2.2] and the population PK analysis. Consequently, investigation of the DOR exposure-response relationship based on pooled data from patients receiving the DOR tablet (in combination with FTC/TDF or ABC/3TC) and DOR/3TC/TDF is applicable to both DOR and DOR/3TC/TDF. In addition, all Phase 3 trials also contained TDF, 3TC, ABC, or FTC at their marketed doses, and exposures of these other antiretrovirals were assumed to be on the exposure-response plateau such that their contribution to efficacy was constant; therefore, only potential relationships between DOR exposure and efficacy were examined.

Logistic regression models were used to investigate the relationship between the virologic response endpoints and virologic failure and PK parameter values. For the Phase 3 trials, statistically significant log-linear exposure-response relationships were identified between DOR PK and each of the virologic response endpoints and virologic failure. The virologic response endpoints were characterized by a shallow positive relationship with DOR PK, largely driven by slightly lower response in the lowest 10% of exposures. A similar relationship was observed for virologic failure, though the direction of the trend was reversed. The effect of covariates (age, gender, weight, race, ethnicity, screening viral load) were also evaluated on the significant exposure-response relationships to address potential confounding between the effects of DOR exposure and these covariates. Identification of significant covariates was based on step-wise forward addition (p <0.01) and backward elimination (p < 0.001); the only significant covariate identified was screening viral load on the slope of the exposure-response relationship for the virologic response endpoints. The exposure-response relationships for virologic response and virologic failure at Week 48 were flat over the range of DOR exposures achieved in the Phase 2b trials over the 25 mg to 200 mg doses. Model predicted exposure-response relationships with 95% CIs were plotted with observed data to illustrate the relationship for each endpoint. A full description of the analysis can be found in the related report [Ref. 5.3.5.3: 04PPZ7]; results from these analyses are discussed in [Sec. 2.7.2.1.5.2].

2.5.2.2 Exposure-Safety Analyses

Safety exposure-response analyses were conducted with neuropsychiatric AEs through Week 48 and fasting lipids (LDL-C and non-HDL-C) at Week 48. The exposure-response relationship for neuropsychiatric AEs were evaluated with pooled data from the Phase 2b trial (P007) and the Phase 3 trial (P021), using the same analysis population (special safety pool) described in the integrated statistical analysis for this endpoint [Sec. 2.7.4.2.5.2], with the addition of patients receiving 25 mg, 50 mg, and 200 mg from P007 (n = 494). Neuropsychiatric AEs were defined based on a pre-selected list of terms from the SOC Nervous System and Psychiatric Disorders including the following categories: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders. A logistic regression model was used to explore the relationship between DOR PK parameters (steady state C24, AUC0-24, and Cmax) and

incidence of neuropsychiatric AEs, and demonstrated no evidence of exposure-related increase in incidence in the Phase 2b and 3 trials.

The exposure-response relationships between the fasting lipids, LDL-C (n = 854) and non-HDL-C (n = 854), and DOR PK parameters were evaluated with data pooled across all 3 Phase 2b and Phase 3 trials using the same lipid analysis population described in [Sec. 2.7.4.3.5], with the addition of patients receiving 25 mg, 50 mg, and 200 mg from P007. Fasting lipid levels were modeled as continuous data using linear regression with baseline lipid level as a structural covariate. The exposure-response relationship between LDL-C and DOR PK was flat over the range of exposures achieved at the 25 mg to 200 mg doses across the Phase 2b and Phase 3 trials. While a weak positive relationship was identified for non-HDL-C and DOR PK, the relationship is not clinically meaningful as non-HDL-C levels over the range of exposures associated with the 100 mg QD dose were lower than baseline non-HDL-C levels. A full description of the analysis can be found in the related report [Ref. 5.3.5.3: 04PPZ7]; results from these analyses are discussed in [Sec. 2.7.2.1.5.3].

2.5.3 Physiologically Based Pharmacokinetic Model Analyses

A physiologically-based pharmacokinetic (PBPK) model was developed to explore the effect of co-administration of moderate CYP3A inhibitors on the PK of DOR. Simcyp® version 16 was used to construct and qualify the PBPK model. The DOR PBPK model was built with physicochemical and in vitro data, clinical IV data, single-oral dose PK data, and hAME data. Clearance was parameterized using clinical IV data, with the majority of the elimination attributed to CYP3A4-mediated metabolism, after accounting for the minor amount of renal clearance observed in clinical PK trials. Absorption was modeled using single oral dose PK data and in vitro permeability data. Distribution was modeled as one-compartment, with the steady state volume of distribution (V_{ss}) obtained from clinical IV data. Simulated concentration-time profiles with the DOR model closely followed observed concentration-time data for a single 100 mg DOR oral dose (P039) [Sec. 2.7.1.2.1.1.1] and a 100 µg DOR IV dose (P044) [Sec. 2.7.1.2.1.1.2]. Additionally, simulated AUC0-inf and oral Cmax values were within 10% of those observed.

The DOR PBPK model was qualified by comparison of simulated and observed AUC, C_{max}, and C_{24} ratios for DDIs with ketoconazole (strong CYP3A inhibitor) (P010) [Sec. 2.7.2.2.3.1.3], rifampin (strong CYP3A inducer) (P011) [Sec. 2.7.2.2.3.1.4], and efavirenz (moderate CYP3A inducer; DOR plasma concentrations following cessation of efavirenz therapy were simulated) (P020) [Sec. 2.7.2.2.3.1.6]. Based on these comparisons, the DOR PBPK model was considered qualified to adequately capture the CYP3A4-mediated clearance of DOR.

DDI simulations were conducted with the DOR PBPK model for the moderate CYP3A inhibitors diltiazem and verapamil at clinically relevant dose regimens. A published model for extended release (XR) diltiazem (240 mg XR QD) [Ref. 5.4: 03RKZ0] and the built-in Simcyp® V16 library compound file for conventional release (CR) diltiazem (120 mg TID) and verapamil (80 mg 3 times a day [TID]) were used. Regimens of 240 mg XR QD diltiazem or 120 mg CR TID diltiazem with co-administration of DOR on Day 2 were simulated. For verapamil, a dose regimen of 80 mg TID with co-administration of DOR on

Day 2 was simulated. A full description of the analysis can be found in the related report [Ref. 5.3.5.3: 04NRY9]. The results of this model are discussed in [Sec. 2.7.2.3.1.1.6].

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This section contains a detailed, integrated discussion of the PK profile of DOR, including the impact of intrinsic and extrinsic factors on DOR PK based on Phase 1 trials and the population PK analysis described in [Sec. 2.7.2.2.5.1]. A summary of the PK characteristics of DOR as assessed in the Phase 1 trials in healthy and HIV-1-infected subjects is provided in [Appendix 2.7.2: 2]. The PK of DOR is summarized here with an emphasis on the proposed clinical dose of 100 mg in HIV-1 infected subjects.

The DOR development program characterized the PK of DOR in healthy subjects and HIV-1 infected subjects administered DOR as a single-entity tablet or as part of DOR/3TC/TDF. A DOR single entity OCT was used throughout clinical development. As bioequivalence of the OCT and the FCT intended for commercialization has been demonstrated in a dedicated clinical trial (P039) [Sec. 2.7.1.2.1.1.1], the PK characterization presented herein is representative of that expected in the target patient population with the intended commercial product.

As described in [Sec. 2.7.1.3.2.2], the components of DOR/3TC/TDF demonstrated bioequivalence to co-administration of the individual components for all PK parameters except for tenofovir Cmax where a 13% decrease in Cmax was observed for DOR/3TC/TDF but was deemed not clinically relevant. Moreover, there is no clinically meaningful drug interaction between DOR and the other components of the DOR/3TC/TDF (P038) [Sec. 2.7.2.2.3.1.8]. Consistent with these results, administration of DOR as part of DOR/3TC/TDF did not have a significant impact on DOR PK based on the population PK analysis. Consequently, DOR PK after administration of DOR/3TC/TDF is representative of DOR PK when administered as the single entity and the clinical pharmacology profile of DOR is applicable to DOR when administered as part of DOR/3TC/TDF. Similarly, the clinical pharmacology profiles of TDF and 3TC are applicable to these components of DOR/3TC/TDF. The clinical pharmacology profiles of tenofovir and 3TC are described in US and EU prescribing information for the respective monotherapy tablets [Ref. 5.4: 04P95P], [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYF], and [Ref. 5.4: 04QHYD], are excerpted briefly herein. The 300 mg QD doses of TDF and 3TC in DOR/3TC/TDF are consistent with the current dosing recommendations for TDF and 3TC.

3.1 Pharmacokinetic Profile

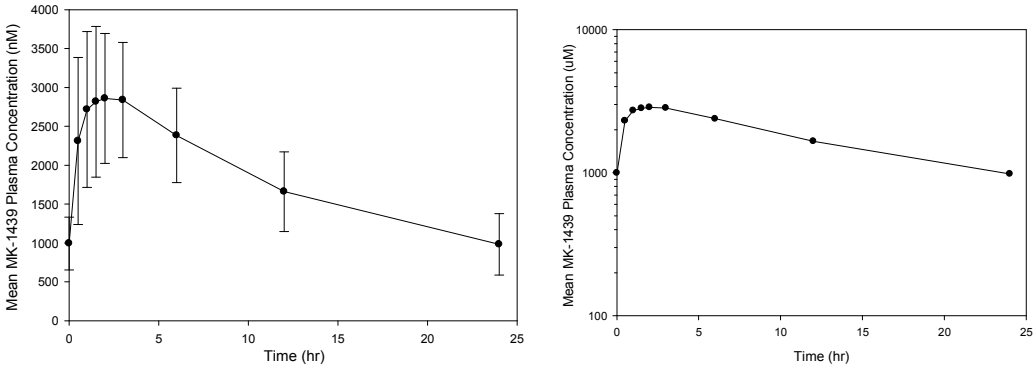
3.1.1 Doravirine Pharmacokinetics in Humans

The PK of DOR administered as a single entity or as DOR/3TC/TDF has been extensively studied in healthy subjects and HIV-1 infected subjects in Phase 1 trials and a pooled population PK analysis of Phase 1, 2b, and 3 trials. The PK parameter estimates for healthy subjects obtained from the population PK analysis are consistent with those obtained by conventional non-compartmental analysis (NCA) [Appendix 2.7.2: 2], further supporting the appropriateness of the population PK analysis for characterization of DOR PK.

Based on the population PK analysis, DOR PK were generally similar in subjects infected with HIV-1 and healthy subjects, such that the PK data obtained in healthy subjects in the Phase 1 program are informative of DOR PK and covariate effects in the patient population. The steady state AUC0-24, C24, and Cmax of DOR at the 100 mg QD dose in HIV-1 infected subjects are 37.8 µM•hr (%CV: 29.2%), 930 nM (%CV: 63.1%), and 2.26 µM (%CV: 18.5%), respectively. DOR steady state PK estimated from intensive sampling in healthy subjects in Phase 1 (P020, n=19) were generally consistent, with steady state geometric mean AUC0-24, C24, and Cmax values of 41.1 µM hr (%CV: 32.3%), 902 nM (%CV: 46.4%), and 2.88 µM (%CV: 32.8%), respectively. DOR PK exhibited moderate variability.

The steady state mean concentration-time profile of DOR following administration of 100 mg QD for 5 days in healthy subjects is illustrated in [Figure 2.7.2: 8]. Following oral administration, DOR was rapidly absorbed with a median Tmax of 2 hours. Plasma concentrations of DOR declined in a monophasic manner.

Figure 2.7.2: 8 Mean (SD) Steady State Concentration-Time Profiles for DOR Following Administration of 100 mg QD DOR for 5 Days in Healthy Subjects (n=19) (Left Panel: Linear Scale; Right Panel: Semilog Scale)



[Ref. 5.3.3.4: P020]

3.1.1.1 Steady State

Based on QD dosing in Phase 1 trials over the 30- to 240-mg dose range, the median time to 90% of steady state is 2 days (P001) [Sec. 2.7.2.2.1.1]. Mean accumulation ratios for DOR AUC0-24, Cmax, and C24 after QD dosing ranged from 1.2 to 1.4 at the 120-mg dose (P001). Both time to steady state and accumulation ratios for AUC0-24, Cmax, and C24 were consistent with the single dose geometric mean apparent terminal t1/2 of 15 hours observed for the 100 mg FMI tablet (P039) [Sec. 2.7.1.2.1.1.1].

3.1.1.2 Linearity (Time Dependence)

Based on the Phase 1 data in healthy subjects, DOR PK is linear and time-independent. A linearity index (MD AUC0-24ss/SD AUC0-inf) was estimated based on mean steady state data (P020) [Sec. 2.7.2.2.3.1.6] and single-dose data (P039) [Sec. 2.7.1.2.1.1.1] for the 100

mg dose in healthy subjects. This index was used to assess time-dependent PK: a ratio of 1 indicates linear kinetics. The DOR linearity index is ~1, reflecting time-independent PK. Similarly, in the population PK analysis, both single- and multiple-dose DOR PK were characterized without concentration or time-dependent clearance.

3.1.1.3 Dose proportionality

Dose proportionality of DOR has been assessed in single- and multiple-ascending dose Phase 1 trials and in the population PK analysis. Based on the single-ascending dose Phase 1 trial (P001) [Sec. 2.7.2.2.1.1], estimates (95% CIs) for the slope from the power model used to assess dose proportionality of DOR AUC0-inf, Cmax, and C24 were 0.88 (0.85, 0.92), 0.85 (0.81, 0.89), and 0.89 (0.85, 0.93), respectively, where a slope of 1 corresponds to perfect dose proportionality. Thus, the exposure, Cmax and C24 of DOR in healthy subjects increase slightly less than dose proportionally over the 6 to 450 mg dose range (P001). The expected fold-change with perfect dose proportionality is 75, while the predicted fold change was approximately 45.5, 38.8, and 46.6 for DOR AUC0-inf, Cmax, and C24, respectively. Similarly, DOR steady state AUC0-24 and Cmax after QD dosing increased slightly less than dose proportionally over the 30 to 240 dose range (P001) with the estimates (95% CI) for the slope of 0.83 (0.65, 1.02) and 0.84 (0.65, 1.03) for DOR AUC0-24 and Cmax, respectively. The expected fold-change with perfect dose proportionality was 8, while the predicted fold change was around 5.65 and 5.78 for DOR AUC0-24 and Cmax, respectively [Sec. 2.7.2.2.1.1]. In the population PK analysis, the estimated relative bioavailability of DOR was approximately similar over the 30 mg to 120 mg dose range and approximately 11% lower at the 150 mg and 200 mg doses and approximately 20% higher at doses below 30 mg. The less than dose proportional behavior is likely associated with the low solubility of DOR [Sec. 2.7.1.1.2.1].

3.1.1.4 Human ADME

3.1.1.4.1 Absorption

DOR is a low solubility drug substance that is highly permeable across biological membranes. Therefore, this drug substance is Class II according to the Biopharmaceutics Classification System (low solubility, high permeability).

Following a single dose of the 100 mg FMI tablet of DOR under fasted conditions, absorption is rapid with median peak plasma concentrations occurring at approximately 2 hours after dosing. DOR has an estimated absolute bioavailability (F) of 64% for the 100 mg FMI tablet [Sec. 2.7.1.3.1]. The rate and extent of DOR absorption following administration with a high-fat meal is similar to that following administration in the fasted state for both the DOR tablet (P037) and DOR/3TC/TDF (P029) [Sec. 2.7.1.3.3.1]. The DOR tablet and DOR/3TC/TDF were administered without regard to food in the Phase 3 trials. The DOR tablet may be administered without regard to food.

The solubility of DOR is not pH dependent [Sec. 2.7.1.1.2.1]. Co-administration of DOR with antacids or PPIs did not have a clinically meaningful effect on the PK of DOR (P042)

[Sec. 2.7.2.2.3.1.7]; therefore, DOR may be administered with gastric acid modifiers without restriction.

3.1.1.4.2 Distribution

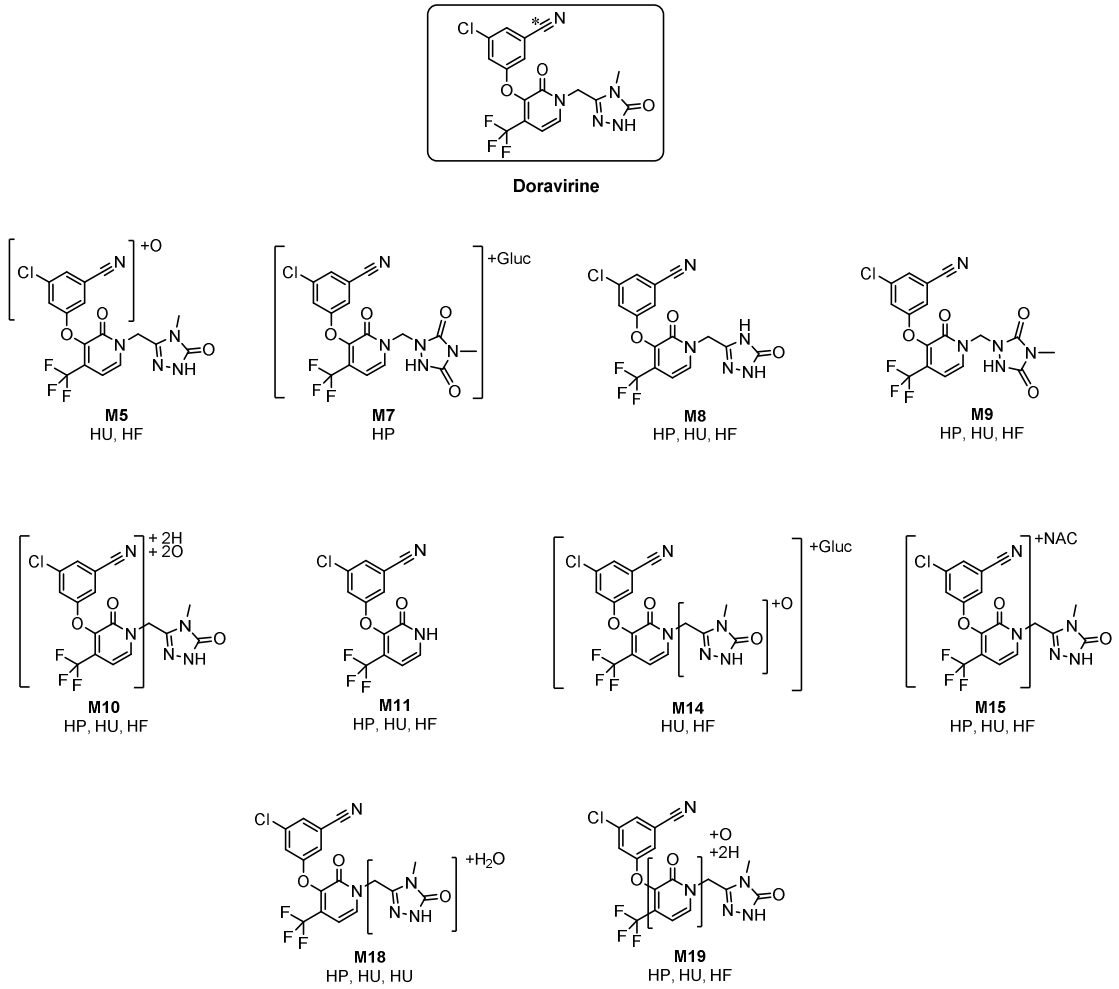
DOR is moderately bound to plasma proteins (~76% bound) based on in vitro studies. Plasma protein binding was not concentration dependent over the 1 to 5 µM concentration range.

Based on administration of an IV microdose (100 µg), the volume of distribution of DOR is 60.5 L. This is slightly larger than the total volume of body water (45 L) and indicates that DOR distributes into tissues. Based on the population PK analysis, the apparent volume of distribution is 126 L for healthy subject, which is consistent with the IV data after adjusting for oral bioavailability and with Vz/F reported for the FMI tablet (P039) [Sec. 2.7.1.2.1.1.1]. The population PK estimated apparent volume of distribution for an HIV-1 infected subject was 162 L.

3.1.1.4.3 Metabolism

DOR undergoes oxidative metabolism in humans, with a very small contribution of conjugation pathways. The oxidative metabolite M9 was the major metabolite observed in excreta, predominantly urine, in the hAME trial (P008) [Sec. 2.7.2.2.1.3] (~55% of the absorbed dose). Other metabolites, including oxidative metabolites and conjugates (N-acetyl cysteine and glucose) were observed in excreta in minor amounts (each ≤2% of the absorbed dose). DOR is the primary component circulating in plasma (76% of the total drug-related material), along with the oxidative metabolite M9 (12.9% of total radioactivity in plasma) following a single dose of [^{14}C]DOR. In a semiquantitative metabolite profiling analysis in plasma from healthy subjects dosed with 240 mg QD for 10 days, M9 represented 6.7% of the total DOR-related components [Sec. 2.6.4.5.5]. Based on its levels in plasma, M9 is considered a major metabolite, and therefore, additional characterization was conducted. M9 is not active against the HIV-1 reverse transcriptase and has no activity against pharmacologically-relevant endogenous targets. Furthermore, levels of M9 in plasma from safety species, including mouse, rat, and dog, were at least within 2-fold of levels in humans so that the safety of M9 was adequately characterized in preclinical studies [Sec. 2.6.4.5.6]. The proposed pathways of DOR metabolism in humans are provided in [Figure 2.7.2: 9].

Figure 2.7.2: 9 Proposed Structures of the Doravirine Metabolites Observed in the Human Absorption, Metabolism, and Excretion Trial



Gluc = Glucuronide, NAC = *N*-acetylcysteine, HF = Human feces, HU = Human urine, HP = Human plasma
* Denotes position of ^{14}C label

3.1.1.4.4 Excretion

The major routes of elimination of DOR were studied in the hAME trial (P008) [Sec. 2.7.2.2.1.3] conducted using a sodium-salt capsule of DOR that had lower bioavailability than the FMI (17% compared to 64% for the FMI). However, the dose was adjusted to achieve similar plasma exposures to those obtained with the 100 mg tablet. Recovery of the radioactive dose was complete within 8 days. The majority of the radioactive dose (90.4%) was recovered in feces. In agreement with the low bioavailability of the sodium-salt capsule used in this trial, 84.1% of the radioactivity in feces corresponded to unchanged DOR and the rest to metabolites, predominantly M9. An additional 10.8% of the radioactive dose was recovered in urine, predominantly as M9.

The absorbed fraction of the dose in the hAME trial (P008) [Sec. 2.7.2.2.1.3] was used to estimate the relative contribution of metabolism and DOR excretion to the elimination of DOR. The disposition of the absorbed fraction in the hAME data indicated that metabolism is the major route of elimination. The primary product of elimination was M9, corresponding to 55% of the absorbed dose (~39% recovered in urine and ~16% in feces) [Sec. 2.6.4]. Other products of oxidation (some secondary to M9) and conjugation (i.e., N-acetyl cysteine and glucose conjugates) each contributed less than 2% to the total elimination. Only 13% of the absorbed dose was eliminated in urine as unchanged DOR and biliary excretion is anticipated to play a minor role in the elimination of DOR. These results, in conjunction with in vitro data, indicate that CYP3A-mediated formation of M9 is the major route of elimination of DOR in humans. In addition, M9 is eliminated primarily via renal excretion.

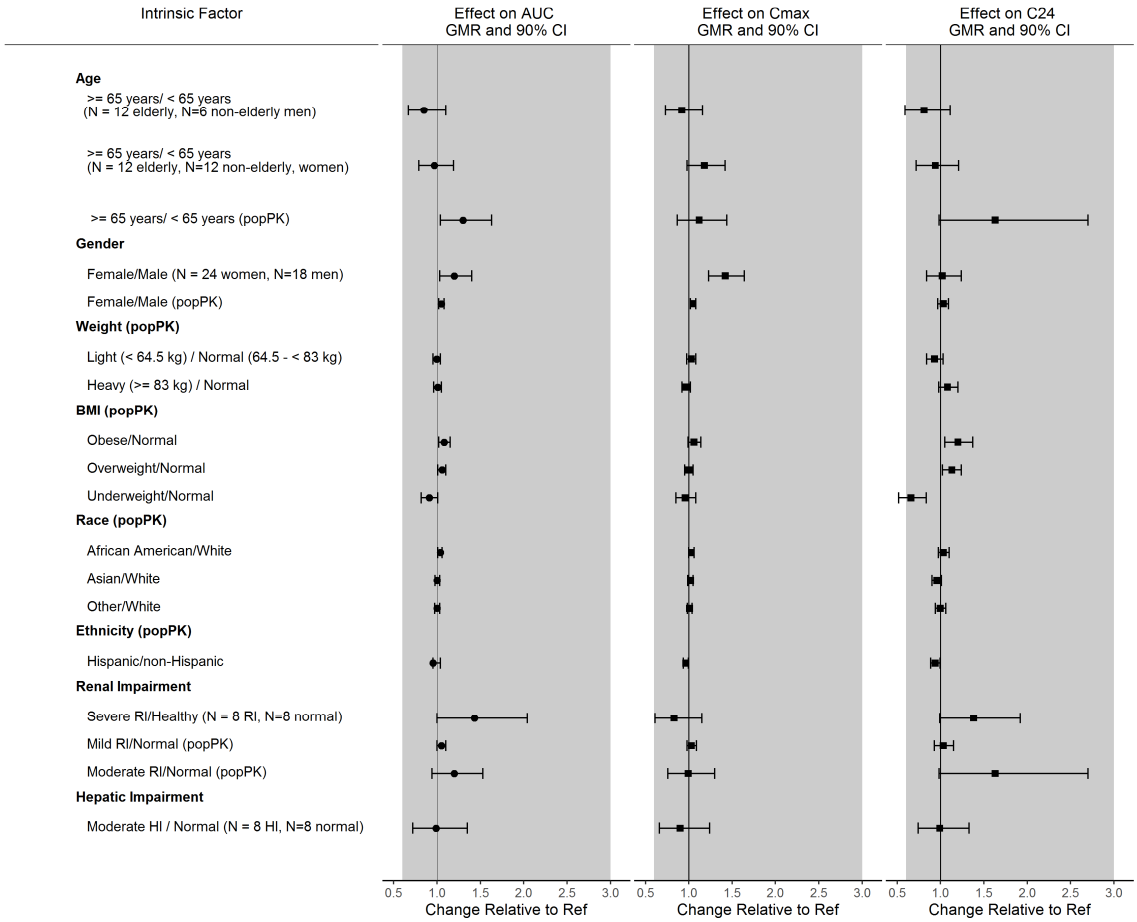
The plasma clearance of DOR in healthy subjects is 3.73 L/hr following an IV microdose of 100 µg (P044) [Sec. 2.7.1.2.1.1.2]. After accounting for the blood to plasma ratio of DOR, the blood clearance is approximately 10% of hepatic blood flow, indicating that DOR is a low hepatic clearance drug. Based on the population PK analysis, the apparent clearance is 6.34 L/h, which is consistent with the IV data after adjusting for oral bioavailability and with CL/F reported for the FMI tablet (P039) [Sec. 2.7.1.2.1.1.1]. DOR plasma concentrations decline from peak in a monoexponential manner with no evidence of concentration-dependence. The geometric mean (GM %CV) terminal half-life (t1/2) following a 100 mg dose in healthy subjects (P039) [Sec. 2.7.1.2.1.1.1] was approximately 15 hours (%CV: 31.4%).

3.1.1.5 Intrinsic Factor Evaluation

This section provides an integrated discussion of the results from Phase 1 clinical pharmacology trials and covariate analyses from the DOR population PK model using pooled PK data from Phase 1, 2b, and 3 trials as they pertain to the influence of intrinsic factors on DOR PK. In addition to clinical pharmacology trials that were conducted to directly evaluate the effect of intrinsic factors on DOR PK (age, gender, hepatic impairment, and renal impairment), population PK analysis provided a comprehensive insight into the influence of these factors on DOR PK in HIV-1 infected subjects. In general, the results from the population PK analyses corroborated the PK results observed in clinical pharmacology trials. The effects of the intrinsic factors are summarized in the forest plot in [Figure 2.7.2: 10]; the shaded areas on the plot represent the clinical bounds discussed in [Sec. 2.7.2.1.5.4]

The PK evaluation is complemented by the statistical analysis of efficacy [Sec. 2.7.3.3.4-trtmtnve48wk] and safety [Sec. 2.7.4.5] across subpopulations in the Phase 3 trials, which also inform dosing recommendations in subgroups and special populations. Subgroup analyses for efficacy were conducted for key patient subpopulations (e.g., by age, gender, race, ethnicity). Overall, subgroup analyses showed consistency of the effect of treatment versus the active comparator. Results of safety analyses for the Phase 3 trials indicate that 100 mg QD DOR is generally well tolerated. The overall incidence of AEs in subjects treated with DOR was comparable to, or lower than the active comparator groups, and this was true also for a variety of intrinsic factors and extrinsic factors.

Figure 2.7.2: 10 Effect of Intrinsic Factors on DOR Steady State C24 and AUC0-24



popPK GMR and 90% CI based on simulation of N = 1000 HIV-1 infected subjects per covariate subgroup for categorical covariates or total for continuous covariates

[Ref. 5.3.5.3: 04PPZ5], [Ref. 5.3.3.3: P009: 11], [Ref. 5.3.3.3: P019: 11], [Ref. 5.3.3.3: P051MK1439: 11]

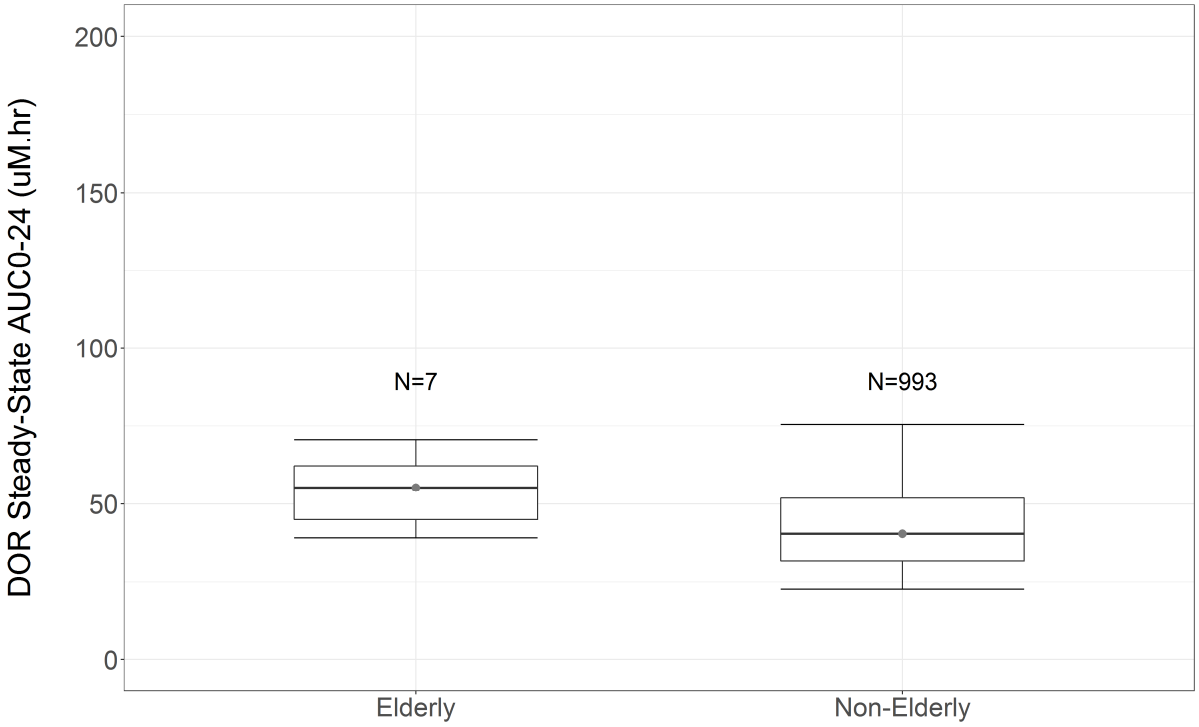
3.1.1.5.1 Age

In a cross-trial comparison of DOR PK from a single-dose Phase 1 trial (P009) [Sec. 2.7.2.2.2.1] conducted in elderly (≥65 years) and non-elderly (<65 years) men and women and a single dose trial in non-elderly men (P001), age did not have a clinically meaningful effect on DOR PK. Comparisons between elderly and non-elderly subjects were conducted separately for men and for women. DOR AUC0-inf, C24, and Cmax were decreased by 15%, 19%, and 8%, respectively, in elderly men compared with non-elderly men [Appendix 2.7.2: 2]). DOR AUC0-inf and C24 were generally similar in elderly and non-elderly women, while DOR Cmax was 18% higher in elderly women compared with non-elderly women [Appendix 2.7.2: 2]). The slight differences in PK in elderly subjects fall within the comparability bounds of (0.6, 3.0) as described in [Sec. 2.7.2.1.5.4].

In the population PK analysis, which included both healthy and HIV-1 infected subjects aged 18 to 78, of which 3% were elderly (≥65 years), an effect of age was identified on the CL of

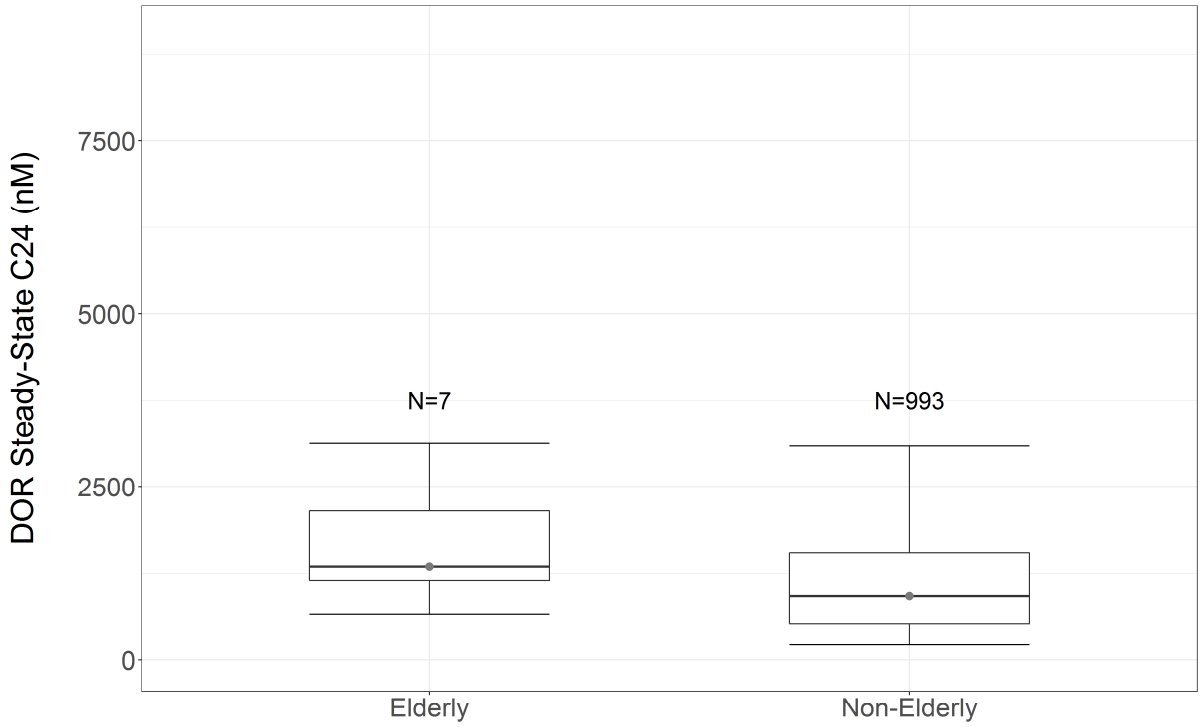
DOR as a continuous covariate. This effect corresponds to DOR AUC estimates that are ~15% higher for a 59 year-old (95th percentile of age in the dataset) and ~6% lower for a 21 year-old (5th percentile of age in the dataset) compared to a 34 year-old (median age in the dataset) when all other covariates are held constant [Ref. 5.3.5.3: 04PPZ5]. To characterize the effect of age in the intended target population, DOR steady state AUC0-24 and C24 for elderly and non-elderly HIV-1 infected subjects were simulated based on the covariate distributions as observed in the Phase 2b and 3 trials. DOR steady state AUC0-24 is 30% higher and steady state C24 is 63% higher in HIV-1 infected subjects ≥65 compared with subjects <65 years [Figure 2.7.2: 11] [Figure 2.7.2: 12]. Consistent with the comparisons conducted with Phase 1 trials, the modest differences in PK in elderly subjects fall within the comparability bounds of (0.6, 3.0) as described in [Sec. 2.7.2.1.5.4]. Virologic response rates were similar regardless of age in HIV-1-infected subjects treated with 100 mg QD DOR administered as DOR or as DOR/3TC/TDF [Sec. 2.7.3.3.4-trtmtnve48wk] and the safety profile was consistent between elderly and non-elderly subjects [Sec. 2.7.4.5.1]. Thus, the effect of age on DOR PK is not clinically meaningful and no dose adjustment is warranted for DOR.

Figure 2.7.2: 11 Simulated Distribution of DOR Steady State AUC0-24 in HIV-1-Infected Elderly and non-Elderly Subjects (<65 Years or ≥65 Years) Following Administration of QD Doses of 100 mg DOR



Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

Figure 2.7.2: 12 Simulated Distribution of Steady State DOR C24 in HIV-1 Infected Elderly and non-Elderly Subjects (<65 Years or ≥65 Years) Following Administration of QD Doses of 100 mg DOR



Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

3.1.1.5.2 Gender

Based on a cross-trial comparison of DOR PK from a single-dose Phase 1 trial conducted in elderly men and women and non-elderly women (P009) [Sec. 2.7.2.2.2.1], and a single-dose trial in non-elderly men (P001) [Sec. 2.7.2.2.1.1], gender did not have a clinically meaningful effect on DOR PK. Comparisons of DOR AUC0-inf, C24, and Cmax between men and women were conducted with pooled elderly and non-elderly data. DOR AUC0-inf and Cmax were 20% and 42% higher, respectively, in women compared with men, while DOR C24 was generally similar in men and women [Appendix 2.7.2: 2]. The differences in DOR PK between men and women are small and fell within the comparability bounds of (0.6, 3.0) as described in [Sec. 2.7.2.1.5.4].

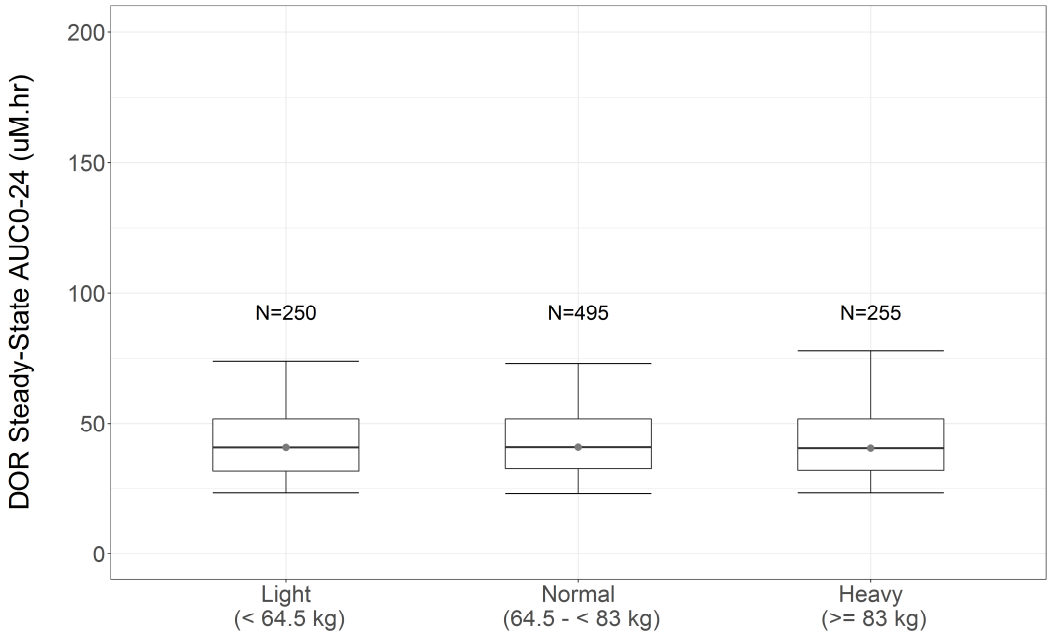
Women comprised 19% of the analysis population in the Phase 1, 2b, and 3 trials included in the population PK analysis. No influence of gender on the PK of DOR was identified from the population PK analysis. In order to better understand potential differences in DOR PK between men and women in the intended target population, DOR steady state AUC0-24 and C24 were simulated for a representative HIV-1-infected population based on the covariate distributions observed in the Phase 2b and 3 trials. DOR steady state AUC0-24 and C24

were 5% higher in women compared to men. The slight increase in exposure in female subjects falls within the comparability bounds of (0.6, 3.0) as described in [Sec. 2.7.2.1.5.4]. Virologic response rates were similar in men and women treated with 100 mg QD DOR administered as DOR or as DOR/3TC/TDF [Sec. 2.7.3.3.4-trtmtnve48wk] and the safety profile was consistent between men and women [Sec. 2.7.4.5.1]. Thus, the effect of gender on DOR PK is not clinically meaningful and no dose adjustment is warranted.

3.1.1.5.3 Weight and BMI

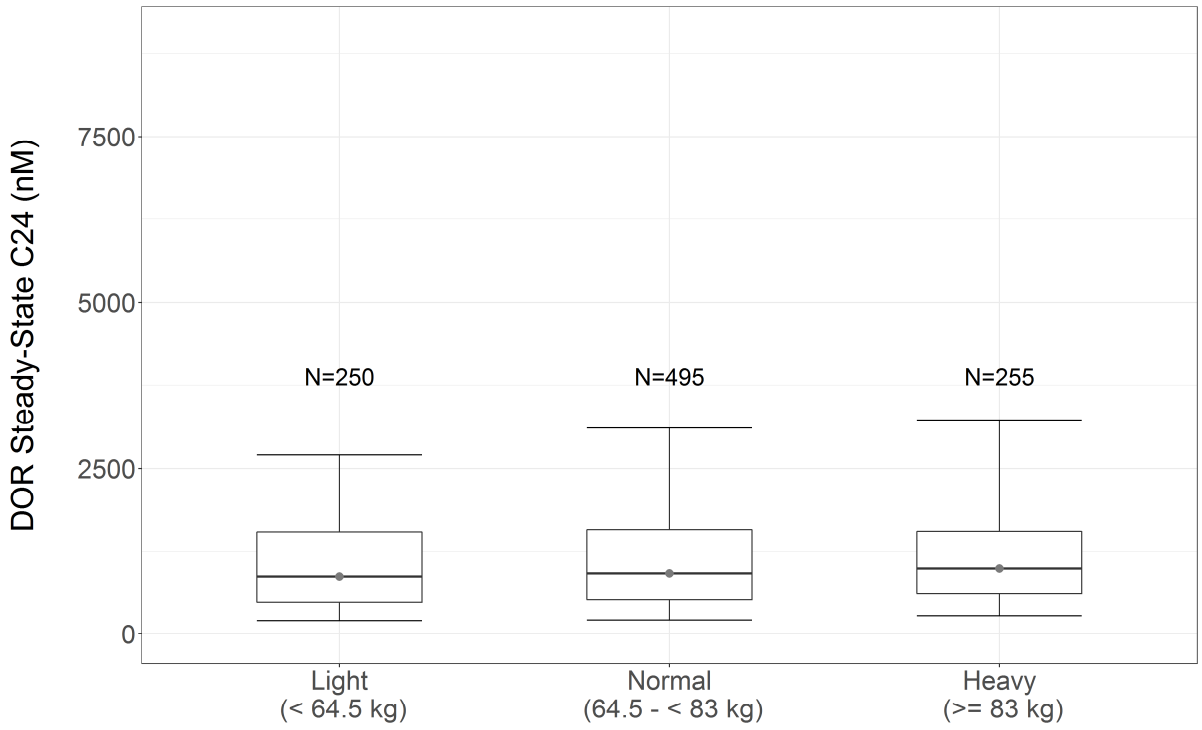
Covariate analyses from the population PK analysis using Phase 1, 2b, and 3 pooled data identified an effect of weight on DOR volume of distribution. This effect corresponds to a ~6% change in DOR steady state C24 and Cmax at the 5th (54 kg) and 95th (103 kg) percentiles of weight in the dataset relative to a subject at the median weight (75 kg) when all other covariates are held constant [Ref. 5.3.5.3: 04PPZ5]. The population PK model was used to simulate DOR PK in HIV-1-infected subjects using the covariate distributions as observed in the Phase 2b and 3 trials. Steady state DOR AUC0-24 and C24 segmented by weight quartile are shown in [Figure 2.7.2: 13] and [Figure 2.7.2: 14], where light (weight <64.5 kg) and heavy (weight ≥ 83 kg) refer to the first and forth quartiles and normal weight refers to the middle 2 quartiles (≥64.5 kg to <83 kg). Steady state DOR AUC0-24 GMRs for light and heavy weight HIV-1 infected subjects differed by less than 1% relative to those with normal weight. Similarly, steady state DOR C24 GMRs for light subjects was 7% lower and for heavy subjects was 8% higher relative to normal weight subjects. These effects are well within the clinical significance bounds of (0.6, 3.0). Therefore, any minor exposure difference across weight groups is not considered to be clinically meaningful, and no dose adjustment for weight is warranted.

Figure 2.7.2: 13 Simulated Distribution of Steady State DOR AUC0-24 in HIV-1-Infected Subjects Following Administration of QD 100 mg DOR Across Body Weight Quartiles



Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

Figure 2.7.2: 14 Simulated Distribution of Steady State DOR C24 in HIV-1-Infected Subjects Following Administration of 100 mg DOR QD Across Body Weight Quartiles

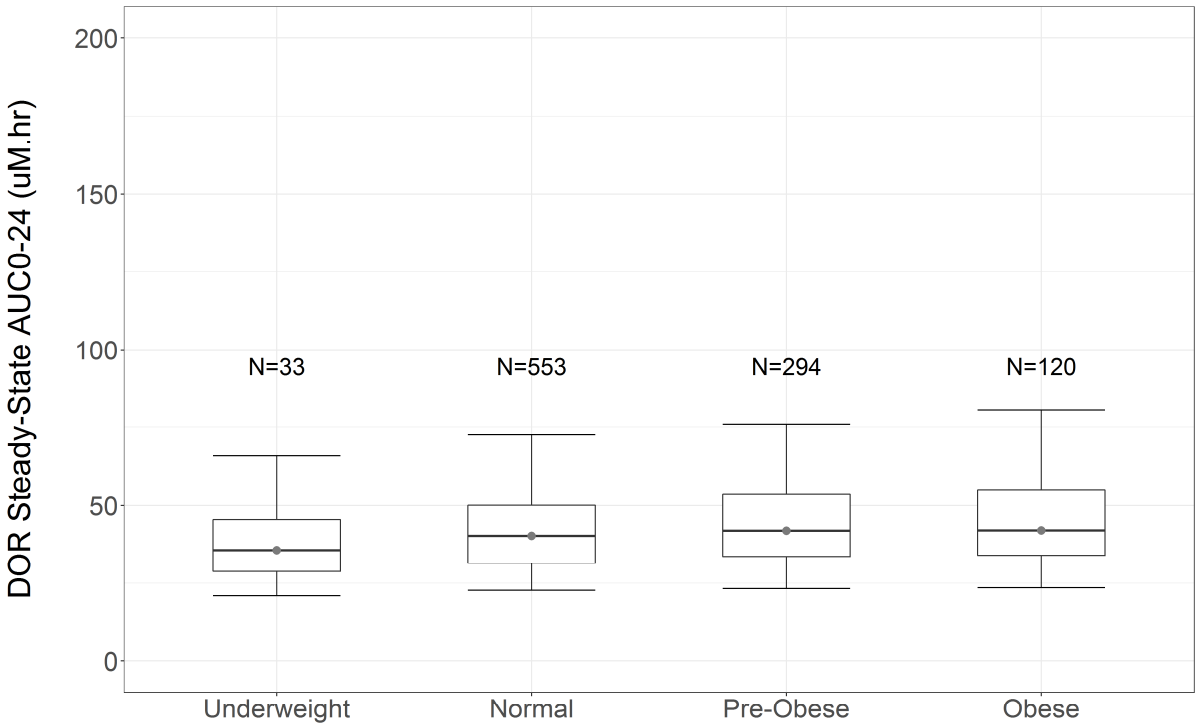


Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

Given the correlation between weight and BMI, BMI was not evaluated as a covariate in the population PK model. However, the effect of BMI on model-predicted DOR PK in HIV-1 infected subjects, based on covariate distributions as observed in the Phase 2b and 3 trials, were explored to better understand any differences in steady state DOR PK exposures in the intended target population. Steady state DOR AUC0-24 and C24 for a representative HIV-1 infected population were stratified as Underweight (<18.5 kg/m^2), Normal (18.5 – 24.99 kg/m^2), Pre-Obese or Overweight (25.0 – 29.99 kg/m^2), or Obese (≥ 30 kg/m^2) based on the World Health Organization (WHO) BMI Classification [Ref. 5.4: 03QGVH].

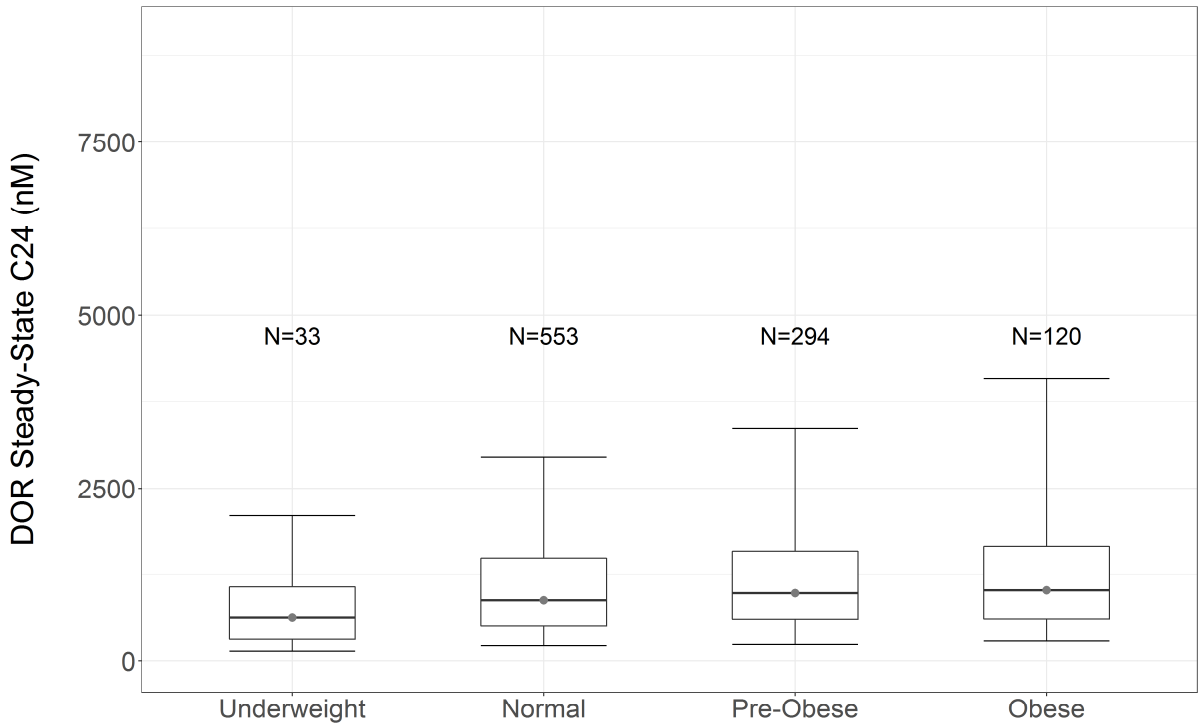
DOR steady state AUC0-24 for underweight, pre-obese, and obese subjects were within 9% of those associated with subjects with normal BMI [Figure 2.7.2: 15]. DOR steady state C24 was 34% lower in underweight HIV-1 infected subjects and 13% and 20% higher in pre-obese and obese subjects, respectively, compared with normal BMI subjects [Figure 2.7.2: 16]. These differences in exposure related to BMI are minimal and fall within the comparability bounds of (0.6, 3.0). Thus, no dose adjustment for BMI is warranted.

Figure 2.7.2: 15 Simulated Distribution of DOR Steady State AUC0-24 for HIV-1-Infected Patients Following Administration of 100 mg DOR QD Across Body Mass Index Categories



Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

Figure 2.7.2: 16 Simulated Distribution of DOR Steady State C24 for HIV-1-Infected Patients Following Administration of 100 mg DOR QD Across Body Mass Index Categories



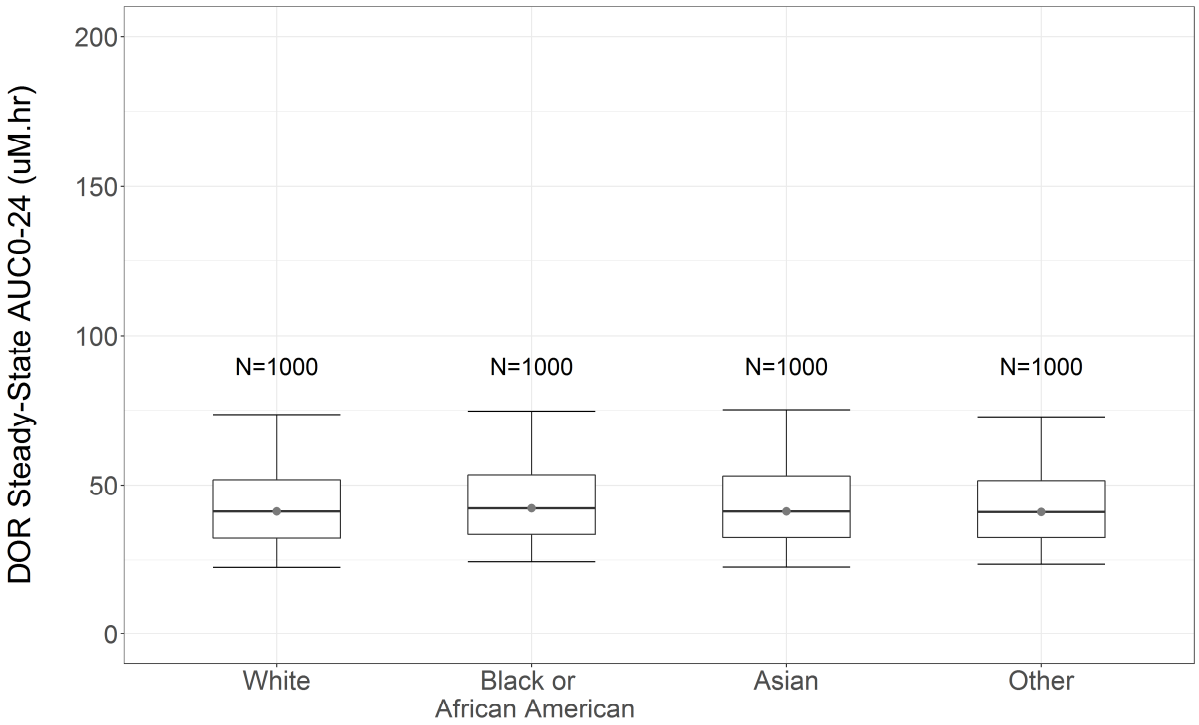
Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

3.1.1.5.4 Race and Ethnicity

Race

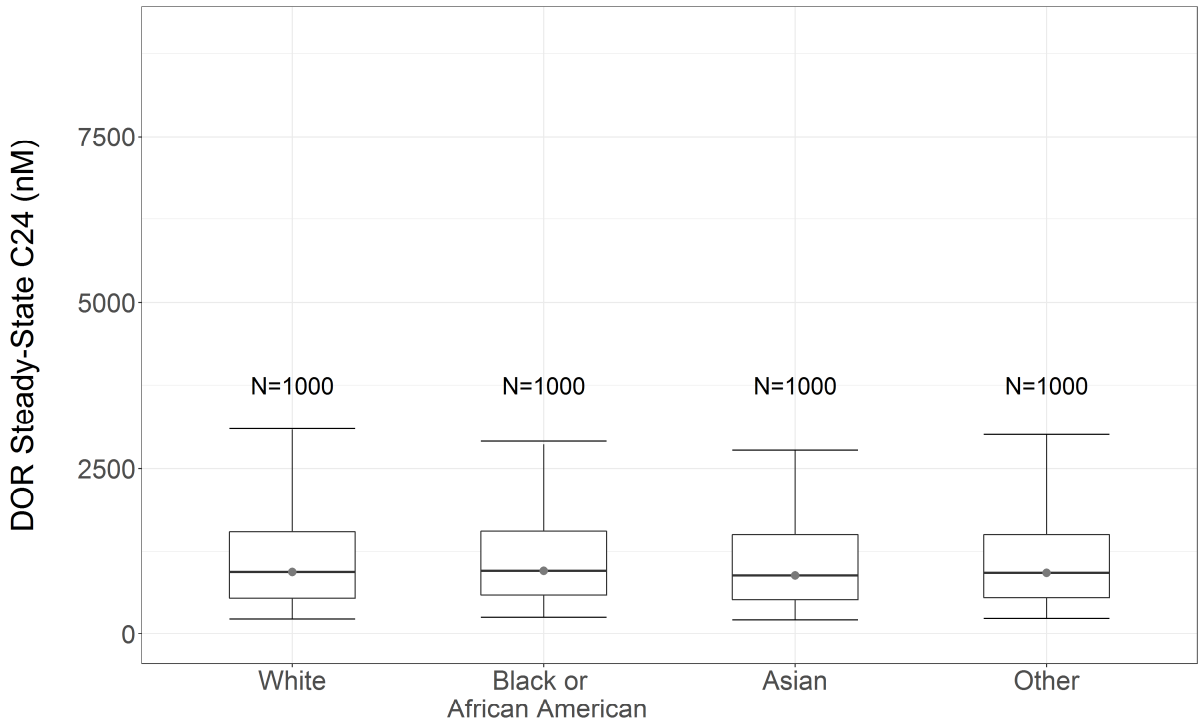
The majority of individuals in the population PK analysis were white (65%), with black and Asian individuals representing 22% and 7% of the analysis population, respectively, and other (including multiracial and Native American) individuals representing ~6% of the analysis population. Formal testing of the effect of this covariate indicated that race did not have a statistically significant effect on the PK of DOR. In order to visualize DOR PK in the intended target population, DOR steady state AUC0-24 and C24 were simulated for a representative HIV-1-infected subject population based on the covariate distributions as observed in the Phase 2b and 3 trials and summarized by race. DOR steady state AUC0-24 and C24 for black, Asian, and all other races differed by no more than 5% from those for white subjects [Figure 2.7.2: 17] [Figure 2.7.2: 18] [Appendix 2.7.2: 6]. The differences in DOR AUC0-24 and C24 in subjects across race categories fall within the comparability bounds of (0.6, 3.0) as described in [Sec. 2.7.2.1.5.4]. Virologic response rates were similar across races for subjects treated with 100 mg QD DOR. The safety profile following treatment with 100 mg QD DOR was broadly similar in white patients and all other races. Thus, the effect of race on DOR PK is not clinically meaningful and no dose adjustment is warranted.

Figure 2.7.2: 17 Simulated Distribution of DOR Steady State AUC0-24 for HIV-1 Infected Subjects Following Administration of 100 mg DOR QD by Race



Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

Figure 2.7.2: 18 Simulated Distribution of DOR Steady State C24 for HIV-1 Infected Subjects Following Administration of 100 mg DOR QD by Race



Note: The boxes represent 25th and 75th percentiles; the line reflects the median; the whiskers are 5th and 95th percentiles.

Ethnicity

The majority of subjects in the population PK analysis were non-Hispanic (77%), with subjects of Hispanic ethnicity representing 22% of the analysis population and ethnicity information missing for the remaining 1%. No influence of ethnicity on DOR PK was identified from the population PK analysis. To understand the effect of ethnicity on DOR PK in the intended patient population, DOR PK were simulated for a representative HIV-1-infected subject population based on the covariate distributions as observed in the Phase 2b and 3 trials and steady state AUC0-24 and C24 were summarized by ethnicity. DOR steady-state AUC0-24 and C24 were approximately 5% and 6% lower, respectively, in Hispanic subjects compared to non-Hispanic subjects. The decrease in steady-state AUC0-24 and C24 in Hispanic patients is minimal and falls within the comparability bounds of (0.6, 3.0) as described in [Sec. 2.7.2.1.5.4]. In addition, virologic response rates and the safety profile were similar regardless of ethnicity for subjects treated with 100 mg QD DOR [Sec. 2.7.3.3.4-trtmtnve48wk] [Sec. 2.7.4.5.1]. Consequently, the effect of ethnicity on DOR PK is not clinically meaningful and no dose adjustment is warranted.

3.1.1.5.5 Hepatic Impairment

While subjects with moderate hepatic impairment were not included in Phase 3 trials, in a dedicated Phase 1 trial, the PK of DOR was evaluated in subjects with moderate hepatic impairment (CP-B score of 7-9) and compared with healthy subjects (P019) [Sec. 2.7.2.2.2.2]. In this trial, the DOR AUC0-inf, Cmax, and C24 GMRs (moderate hepatic subjects /healthy subjects) (90% CIs) were 0.99 (0.72, 1.35), 0.90 (0.66, 1.24), and 0.99 (0.74, 1.33), respectively [Appendix 2.7.2: 2]. The changes in DOR PK observed in subjects with moderate hepatic impairment fell within the clinical bounds of (0.6, 3.0) and thus, dose adjustments of DOR for HIV-1-infected subjects with mild and moderate hepatic impairment are not needed.

Based on the lack of effect of moderate hepatic impairment on DOR PK, clinically significant increases in exposure in patients with severe hepatic impairment are not anticipated; however, DOR has not been studied in this population in either a Phase 1 PK trial or in Phase 3 trials.

3.1.1.5.6 Renal Impairment

Only a small portion of DOR (~6%) is eliminated via renal excretion. Therefore, the PK of DOR were evaluated in a dedicated Phase 1 trial in subjects with severe renal impairment (eGFR values <30 mL/min/1.73 m² and not on dialysis) compared to healthy subjects (P051) [Sec. 2.7.2.2.2.3]. Two of the subjects enrolled had an eGFR of <15 mL/min/1.73 m^2. The DOR AUC0-inf, Cmax, and C24 GMRs (severe renal impairment subjects/healthy subjects) (90% CIs) were 1.43 (1.00, 2.04), 0.83 (0.61, 1.15), and 1.38 (0.99, 1.92), respectively (Appendix 2.7.2: 2). The change in DOR PK in subjects with severe renal impairment fell within the clinical bounds of (0.6, 3.0).

In the DOR population PK analyses, eGFR as calculated based on the MDRD equation was not identified as a significant covariate. DOR PK were simulated for a representative HIV-1-infected subject population based on the covariate distributions as observed in the Phase 2b and 3 trials and steady state AUC0-24 and C24 were plotted against individual eGFR values in [Figure 2.7.2: 19] and [Figure 2.7.2: 20]. There were no trends between individual steady state AUC0-24 and C24, and eGFR. As subjects with severe renal impairment were not enrolled in the Phase 2b and 3 trials, simulations were also conducted based on covariate distributions including subjects from Phase 1 to characterize DOR PK in subjects with low eGFR values. Consistent with the findings above, DOR AUC0-24, C24, and Cmax values in subjects with severe renal impairment were similar to DOR PK in subjects with normal renal function, or mild or moderate renal impairment [Ref. 5.3.5.3: 04PPZ5]. Thus, dose adjustments for DOR in HIV-1 infected subjects with mild, moderate, or severe renal impairment are not needed. Subjects on dialysis were not included in Phase 1 or Phase 3 trials; therefore, the effect of dialysis on DOR PK is unknown.

Figure 2.7.2: 19 DOR Steady State AUC0-24 for HIV-1-Infected Patients Versus Renal Function Following Administration of 100 mg DOR QD

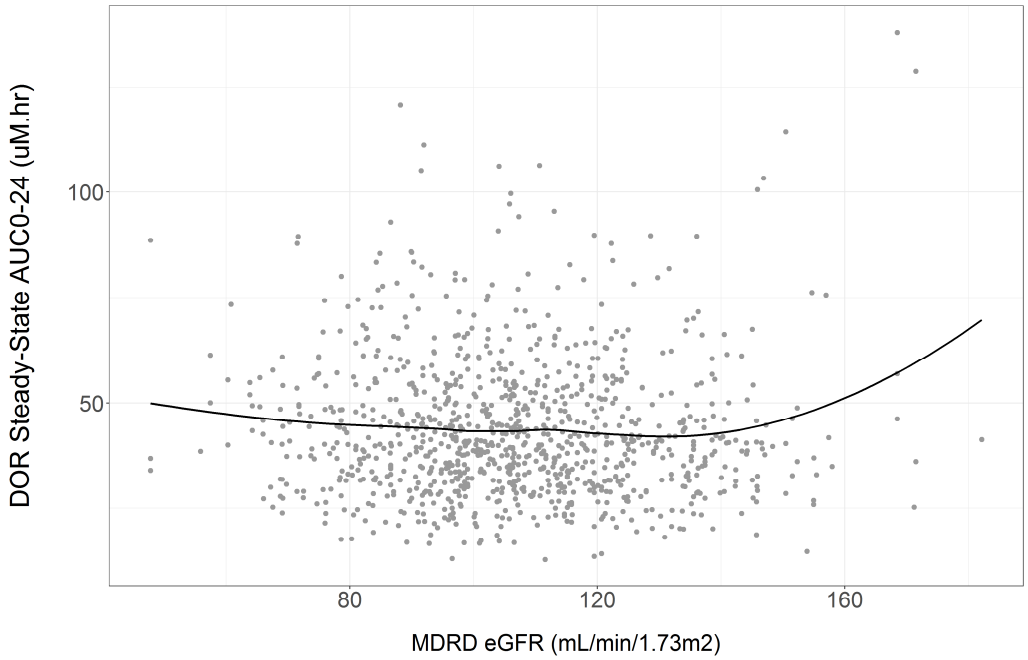
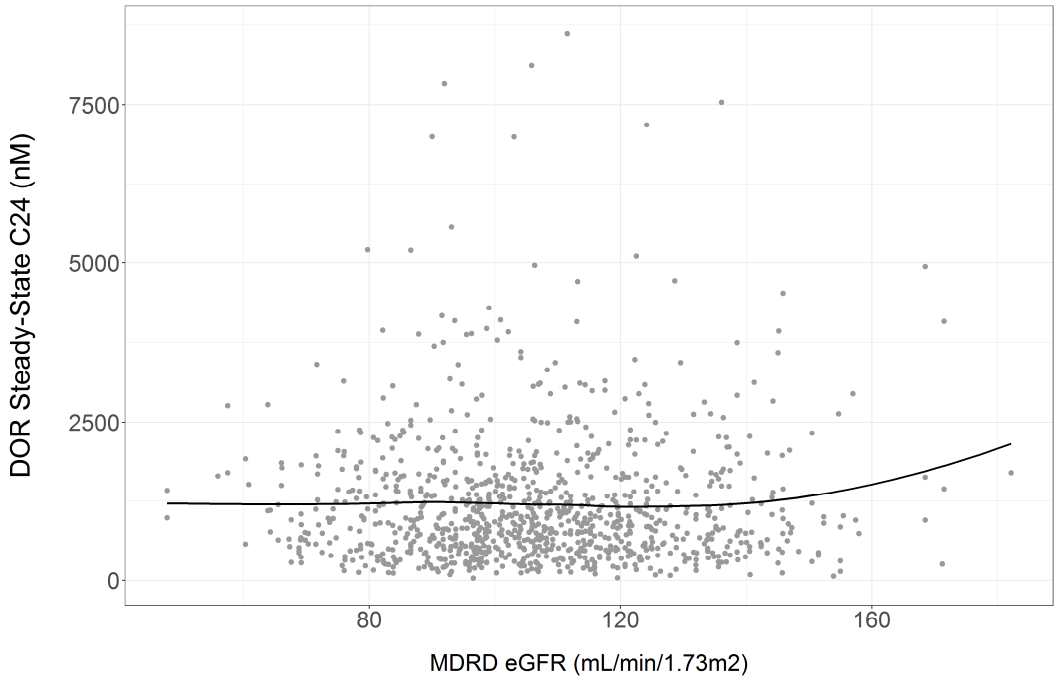


Figure 2.7.2: 20 DOR Steady State C24 for HIV-1-Infected Patients Versus Renal Function Following Administration of 100-mg DOR QD



3.1.1.6 Evaluation of the Drug-Drug Interaction Potential of Doravirine

Several clinical pharmacology trials were conducted to evaluate the potential for DOR to be a victim and/or perpetrator of DDIs. Based on preclinical data indicating DOR is a substrate for CYP3A [Sec. 2.7.2.1.4.2], DDI trials were conducted with CYP3A inhibitors (ketoconazole, ritonavir) (P010) [Sec. 2.7.2.2.3.1.3], (P002) [Sec. 2.7.2.2.3.1.2] and inducers (rifampin, rifabutin, efavirenz) (P011) [Sec. 2.7.2.2.3.1.4], (P035) [Sec. 2.7.2.2.3.1.5], (P020) [Sec. 2.7.2.2.3.1.6]. As these agents also modulate P-gp, and DOR is a P-gp substrate in vitro, the effect of P-gp inhibition (multiple-dose ketoconazole and ritonavir) and induction (multiple-dose rifampin and rifabutin) was also evaluated in these trials. Preclinical data suggest that DOR is not expected to be a victim of other CYP [Sec. 2.7.2.1.4.2] or transporter-based interactions [Sec. 2.7.2.1.4.4]; however, the effect of OATP1B1 inhibition (single-dose rifampin) on DOR PK was also evaluated in a Phase 1 PK trial. In addition, the effects of dolutegravir (P016) [Sec. 2.7.2.2.3.2.3] and tenofovir (P003) [Sec. 2.7.2.2.3.1.1] (two agents which may be used in combination with DOR to treat HIV-1 infection) on DOR PK were also evaluated.

As antacids and proton-pump inhibitors are common concomitant medications in the HIV-1 infected population, the effect of these agents on DOR PK was evaluated (P042) [Sec. 2.7.2.2.3.1.7]. Hepatitis C virus (HCV) infection is a common comorbidity; therefore, DDI trials were conducted with DOR and commonly used HCV treatment regimens, namely sofosbuvir/ledipasvir (P053) [Sec. 2.7.2.2.3.2.8] and elbasvir/grazoprevir (P050) [Sec. 2.7.2.2.3.2.7].

In summary, data from these clinical pharmacology trials support that the PK of DOR is altered by modulators of CYP3A. However, modulators of other CYPs or transporters are not expected to have a meaningful effect on the PK of DOR.

While preclinical data do not suggest that DOR is likely to be a perpetrator of clinically meaningful DDIs [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4]), several DDI trials were conducted to evaluate the effect of DOR on the PK of drugs that are commonly used by the HIV-1 infected population or may be used as part of their HIV-1 treatment regimen including atorvastatin (P036) [Sec. 2.7.2.2.3.2.4], an oral contraceptive (EE/LNG) (P012) [Sec. 2.7.2.2.3.2.2], sofosbuvir/ledipasvir (P053) [Sec. 2.7.2.2.3.2.8], grazoprevir/elbasvir (P050) [Sec. 2.7.2.2.3.2.7], dolutegravir (P016) [Sec. 2.7.2.2.3.2.3], TDF (P038) [Sec. 2.7.2.2.3.1.1], 3TC (P038) [Sec. 2.7.2.2.3.1.8], metformin (P048) [Sec. 2.7.2.2.3.2.5], methadone (P045) [Sec. 2.7.2.2.3.2.6] and midazolam (P001) [Sec. 2.7.2.2.3.2.1] (a prototype for CYP3A metabolized drugs). Consistent with the preclinical data, DOR did not have a clinically meaningful effect on the PK of these drugs and DOR is unlikely to perpetrate any clinically meaningful DDIs.

This section discusses the DDI potential of DOR, first as a victim then as a perpetrator and lastly with concomitant medications. [Table 2.7.2: 12] summarizes established and potentially significant DDIs with DOR.

Table 2.7.2: 12 Summary of Established and Other Potentially Significant Drug Interactions with DOR

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV-Antiviral Agents		
efavirenz* etravirine nevirapine	↓ DOR	Concomitant use of DOR with efavirenz, etravirine and nevirapine may decrease plasma concentrations of DOR (CYP3A induction).
ritonavir†- boosted PIs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, tipranavir) ritonavir-boosted elvitegravir	↑ DOR ↔ boosted PIs ↔ elvitegravir	Concomitant use of DOR with ritonavir-boosted PIs or ritonavir-boosted elvitegravir may cause an increase in the plasma concentrations of DOR (inhibition of CYP3A enzymes). No dose adjustment is required when DOR is co-administered with ritonavir-boosted PIs or ritonavir-boosted elvitegravir.
cobicistat-boosted PIs (darunavir, atazanavir) cobicistat-boosted elvitegravir	↑ DOR ↔ boosted PIs ↔ elvitegravir	Concomitant use of DOR with cobicistat-boosted PIs or cobicistat-boosted elvitegravir may cause an increase in the plasma concentrations of DOR (inhibition of CYP3A enzymes). No dose adjustment is required when DOR is co-administered with cobicistat-boosted PIs or cobicistat-boosted elvitegravir.
unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir)	↑ DOR ↔ unboosted PIs	Concomitant use of DOR with unboosted PIs may cause an increase in the plasma concentrations of DOR (inhibition of CYP3A enzymes). No dose adjustment is required when DOR is co-administered with unboosted PIs.
Antimycobacterials		
rifabutin*	↓ DOR ↔ rifabutin	Concomitant use of DOR with rifabutin may cause a decrease in the plasma concentrations of DOR (induction of CYP3A enzymes). If DOR is co-administered with rifabutin, one tablet of DOR should be taken twice daily (approximately 12 hours apart) *[see Dosage and Administration (2.2)]*.
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole* posaconazole voriconazole	↑ DOR ↔ azole antifungal agents	Concomitant use of DOR with azole antifungal agents may cause an increase in the plasma concentrations of DOR (inhibition of CYP3A enzymes). No DOR dose adjustment is required when DOR is co-administered with azole antifungal agents.

↑ = increase, ↓ = decrease, ↔ = no change
*The interaction between DOR and the drug was evaluated in a clinical study.
†The interaction was evaluated with ritonavir only.
All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.
PIs- Protease Inhibitors

3.1.1.6.1 Doravirine as a Victim of Drug Interactions

Preclinical data demonstrate that DOR is a substrate for CYP3A metabolism and P-gp transport [Sec. 2.7.2.1.4.2], [Sec. 2.7.2.1.4.4], and dedicated clinical trials were conducted with drugs that inhibit or induce these pathways. A summary of changes in AUC, C24, and Cmax for drug interactions with DOR as the victim is provided in [Figure 2.7.2: 21].

In clinical trials, where DOR was co-administered with the strong CYP3A inhibitors ketoconazole (P010) [Sec. 2.7.2.2.3.1.3] and ritonavir (P002) [Sec. 2.7.2.2.3.1.2], DOR AUC increased approximately 3-fold, with a smaller effect (25-40% increase) on Cmax. These increases are not considered clinically meaningful based on the bounds of clinical relevance

[Sec. 2.7.2.1.5.4]. Therefore, strong CYP3A inhibitors such as the azole antifungal agents fluconazole, ketoconazole, itraconazole, posaconazole, and voriconazole, the PK enhancers cobicistat and ritonavir, and the unboosted and boosted protease inhibitors (PIs) atazanavir, atazanavir/cobicistat, darunavir, darunavir/cobicistat, fosamprenavir (with or without a PK booster), indinavir (with or without a PK booster), lopinavir/ritonavir, nelfinavir (with or without PK booster), ritonavir, saquinavir (with or without PK booster), and tipranavir (with a PK booster) can be co-administered with DOR.

A clinical DDI trial with moderate CYP3A inhibitors has not been conducted. However, PBPK simulations of the interaction between DOR and the moderate inhibitors, diltiazem and verapamil, with Simcyp® predict that moderate CYP3A inhibitors will have a more modest effect on DOR PK compared to strong inhibitors of approximately 2-fold increase in AUC [Ref. 5.3.5.3: 04NRY9]. These data suggest that moderate inhibitors are not likely to lead to a clinically meaningful increase in DOR exposure.

While the effect of grapefruit juice was not evaluated, grapefruit juice is anticipated to have a limited effect on DOR exposure, as it primarily affects CYP enzymes in the gut. Compounds with low intrinsic clearance and good bioavailability are not expected to undergo significant first-pass effect or be sensitive to gut CYP3A inhibition [Ref. 5.4: 04QXF9]. DOR has low intrinsic clearance and it is unlikely to undergo significant first-pass metabolism. As a consequence, DOR is not very sensitive to the effects of CYP3A inhibitors acting primarily in the gut, such as the potent CYP3A time-dependent inhibitors present in grapefruit juice. Therefore, an effect on gut metabolism will likely correspond to small changes in DOR exposure, reflected as a small increase in Cmax but not total exposure. Therefore, a clinically meaningful interaction is not anticipated when grapefruit juice is co-administered with DOR.

When DOR is co-administered with multiple doses of strong CYP3A inducers, there is a clinically meaningful decrease in DOR AUC and C24. Following co-administration of DOR with multiple doses of the strong CYP3A inducer, rifampin (P011), DOR AUC and C24 were decreased by approximately 88% and 97%, respectively [Sec. 2.7.2.2.3.1.4]. Specifically, the AUC0-inf and C24 GMRs (DOR + MD rifampin /DOR alone) (90% CIs) were 0.12 (0.10, 0.15) and 0.03 (0.02, 0.04), respectively. Therefore, the use of strong CYP3A inducers, such as the antimcyobacterials rifampin and rifapentine, the anticonvulsants carbamazepine, oxcarbazepine, phenytoin, and phenobarbital, and the herbal supplement St John's wort (Hypericum perforatum) are contraindicated with DOR.

When a 100 mg single dose of DOR was co-administered with the more moderate CYP3A inducer, rifabutin (P035) [Sec. 2.7.2.2.3.1.5], DOR AUC and C24 decreased by approximately 50% and 68%, respectively. Specifically, the AUC0-inf, and C24 GMRs (DOR + rifabutin/ DOR alone) (90% CIs) were 0.50 (0.45, 0.55) and 0.32 (0.28, 0.35), respectively [Sec. 2.7.2.2.3.1.5]. The reduction in DOR C24 with rifabutin co-administration falls below the lower bound of 0.6 associated with efficacy. However, based on NPS projections of DOR plasma concentrations when co-administered with rifabutin, the administration of 100 mg BID DOR with rifabutin is projected to maintain therapeutic exposures at steady state (i.e., similar to those achieved with 100 mg QD DOR in the absence of inducers) [Ref. 5.3.5.3: 04R3RC]. As the magnitude of induction associated with CYP3A

moderate inducers varies across compounds (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, nevirapine), and is also dependent on the substrate, the effect of other CYP3A inducers on the PK of DOR cannot easily be predicted. Therefore the dose adjustment proposed for co-administration of rifabutin and DOR may not be sufficient for other moderate inducers which may be co-administered with DOR.

While CYP3A inhibitors (ketoconazole and ritonavir) and inducers (rifampin, rifabutin) are also inhibitors and inducers of P-gp, respectively, DOR Cmax was not affected to a meaningful extent after co-administration, which is consistent with the high permeability of DOR. For example, ketoconazole (P010) and ritonavir (P002) co-administration resulted in 25% and 31% increases in DOR Cmax, respectively [Sec. 2.7.2.2.3.1.3], [Sec. 2.7.2.2.3.1.2]. The decrease in DOR Cmax when DOR is co-administered with multiple-doses of rifampin (P011) is ~57% [Sec. 2.7.2.2.3.1.4]; however, following multiple doses of rifabutin (P035), a moderate inducer, Cmax was not affected, as evidenced by a Cmax GMR (rifabutin + DOR/DOR alone) (90% CI) of 0.99 (0.85, 1.15) [Sec. 2.7.2.2.3.1.5]. The significant reduction in Cmax observed with multiple dose rifampin co-administration is in agreement with its strong inductive effect on both gut and hepatic CYP3A enzymes. Induction of gut P-gp may also contribute to the reduction in Cmax but it is not expected to be significant as the magnitude of P-gp induction is lower relative to CYP3A [Ref. 5.4: 044NF4].

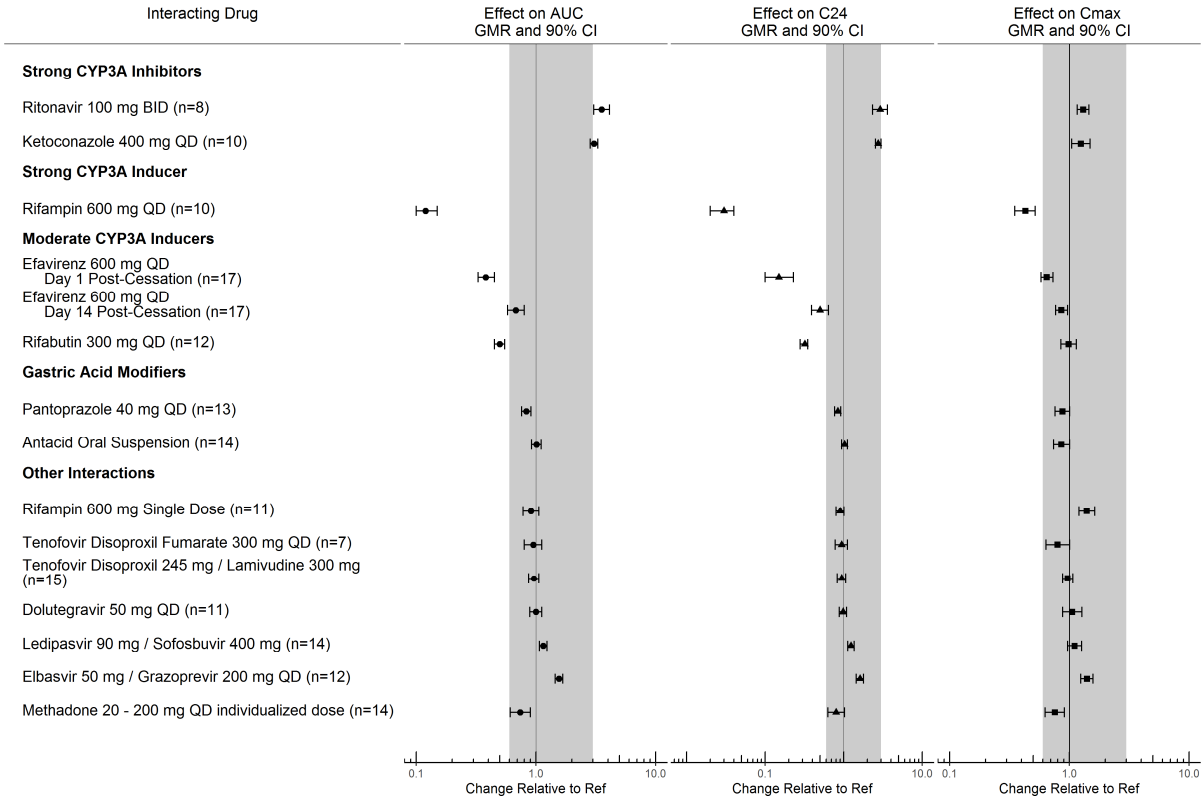
In addition, rifampin, when administered as a single dose, has the potential to inhibit OAT1B1 and P-gp. In the clinical trial evaluating the DDI between DOR and rifampin, the single-dose effect of rifampin on DOR was also evaluated (P011) [Sec. 2.7.2.2.3.1.4]. There was a modest and not clinically meaningful increase in DOR Cmax (~40% increase). In addition there was no clinically meaningful effect of single-dose rifampin on DOR AUC (~10% decrease) [Sec. 2.7.2.2.3.1.4]. These results indicate that despite being a P-gp substrate, P-gp has minimal involvement in intestinal efflux of DOR. Furthermore, consistent with the high permeability of DOR and the in vitro OATP1B1 evaluation, these results also indicate that OATP1B1 inhibition has no meaningful effect on DOR PK.

In conclusion, use of DOR is contraindicated with strong CYP3A inducers (e.g., rifampin, carbamezipine, oxcarbazepine, phenobarbital, phenytoin, St. John's wort) and DOR may be co-administered with the more moderate CYP3A inducer, rifabutin, if the DOR dose frequency is increased to 100 mg BID. The magnitude of effect of other moderate CYP3A inducers, which may be co-administered with DOR, on DOR PK is unknown. DOR may be co-administered with moderate and strong CYP3A inhibitors without dose adjustment. Agents which inhibit OATP1B1 or modulate P-gp are not expected to have a clinically meaningful effect on the PK of DOR.

TDF (P003, P038), 3TC (P038), and dolutegravir (P016), 3 agents which have the potential to be co-administered with DOR did not have a clinically meaningful effect on the PK of DOR [Sec. 2.7.2.2.3.1.1], [Sec. 2.7.2.2.3.1.8], [Sec. 2.7.2.2.3.2.3]. Furthermore, co-administration of a magnesium, aluminum, and simethicone containing antacid/anti-gas treatment (P042) [Sec. 2.7.2.2.3.1.7] did not have a clinically meaningful effect on the PK of DOR. Similarly, co-administration of sofosbuvir/ledipasvir (P053) or elbasvir/grazoprevir (P050) had no clinically meaningful effect on the PK of DOR [Sec. 2.7.2.2.3.2.8],

[Sec. 2.7.2.2.3.2.7]. [Figure 2.7.2: 21] summarizes the effects of co-administered drugs on the PK of DOR.

Figure 2.7.2: 21 Effect of Co-administered Compounds on the AUC, C24, and Cmax of DOR



Note: Different x-axis scale used for C24 panel.

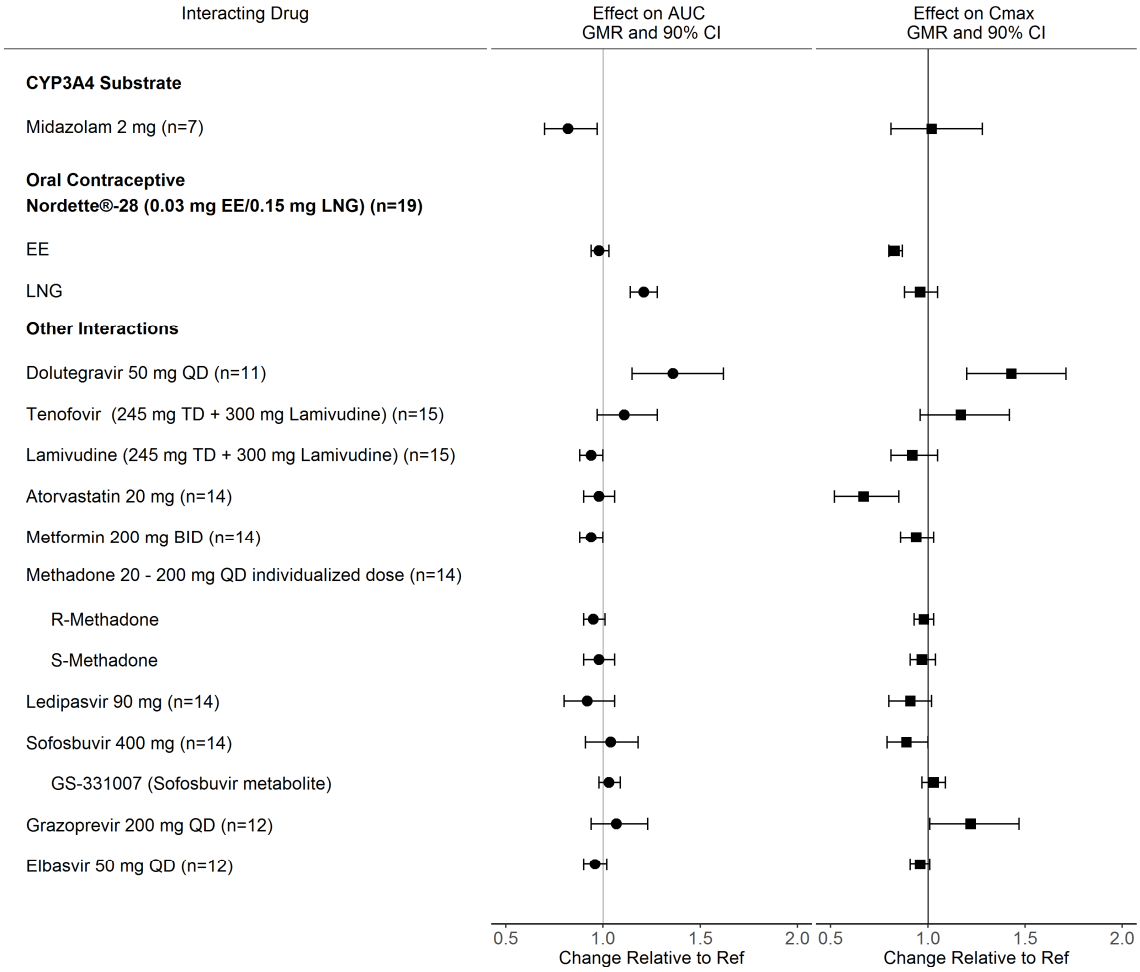
3.1.1.6.2 Doravirine as Perpetrator of Drug Interactions

Based on in vitro data, DOR is not likely to be a perpetrator of CYP- or transporter-mediated DDIs [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4]. Multiple-dose clinical DDI trials at or above the clinical dose of DOR further support this conclusion. No clinically meaningful effect of DOR has been observed on the PK of oral midazolam (an 18% decrease in midazolam AUC0-inf was observed) (P001) [Sec. 2.7.2.2.3.2.1], a sensitive CYP3A substrate, an oral contraceptive containing EE and LNG (P012) [Sec. 2.7.2.2.3.2.2], atorvastatin (P036) [Sec. 2.7.2.2.3.2.4], and methadone (P045) [Sec. 2.7.2.2.3.2.6], which all have a CYP3A component of metabolism. DOR had no clinically meaningful effect on the PK of the OCT2 substrates metformin (P048) [Sec. 2.7.2.2.3.2.5] and 3TC [Sec. 2.7.2.2.3.1.8]. DOR had no clinically meaningful effect on the PK of tenofovir (P038), which is an OAT1/3 and P-gp substrate [Sec. 2.7.2.2.3.1.8]. Similarly, co-administration of DOR with sofosbuvir/ledipasvir (P053) or elbasvir/grazoprevir (P050) had no clinically meaningful effect on the PK of ledipasvir (P-gp, BCRP substrate), elbasvir (CYP3A substrate), grazoprevir (CYP3A substrate), sofosbuvir (P-gp, BCRP substrate), or its major metabolite GS-331007 [Sec. 2.7.2.2.3.2.8], [Sec. 2.7.2.2.3.2.7]. In addition, there was no clinically

meaningful effect of DOR co-administration on the PK of the BCRP substrates dolutegravir (P016) [Sec. 2.7.2.2.3.2.3] and atorvastatin (P036) [Sec. 2.7.2.2.3.2.4]. While there was a modest (~40%) increase in dolutegravir AUC and Cmax, likely due to inhibition of BCRP, inhibition of BCRP is concentration dependent and the dolutegravir interaction trial was conducted with a dose of 200 mg QD DOR. Consequently, the magnitude of effect observed in the dolutegravir trial (P016) is greater than what is anticipated to be observed with administration of the DOR clinical dose of 100 mg. Furthermore in the atorvastatin trial (P036), which was conducted with a 100 mg dose of DOR, there were no increases in atorvastatin AUC or Cmax. The effect of DOR co-administration on the exposure and Cmax of concomitant therapies studied in dedicated DDI trials is summarized in [Figure 2.7.2: 22].

In conclusion, these data suggest that co-administration with DOR will not result in clinically meaningful changes in the PK of concomitant therapy.

Figure 2.7.2: 22 Effect of DOR on the AUC and Cmax of Co-administered Drugs



3.1.1.6.3 Drug Interactions Assessing Potential Concomitant Medications

3.1.1.6.3.1 HIV-1 Antiviral Agents

DOR is indicated for treatment of HIV-1 in combination with other antiretroviral agents; therefore, the potential for a DDI between DOR and other likely co-administered HIV-1 antiretrovirals is assessed below.

Nucleoside Reverse Transcriptase Inhibitors: DOR is not anticipated to perpetrate any clinically meaningful DDIs with HIV-1 antiretrovirals. Clinical data support the co-administration of DOR with NRTIs. In a dedicated single-dose DDI trial, there was no clinically significant DDI between DOR and the other components of DOR/3TC/TDF (co-administered 3TC and TDF) (P038) [Sec. 2.7.2.2.3.1.8]. Furthermore a DDI trial demonstrated no meaningful effect of multiple-dose TDF administration on the PK of DOR (P003) [Sec. 2.7.2.2.3.1.1]. In the population PK analysis of the Phase 2b and Phase 3 trial data, where DOR was co-administered with NRTI background therapy including TDF/FTC and ABC/3TC (P018) or as DOR/3TC/TDF, there was no significant impact on the PK of DOR [Sec. 2.7.2.2.5.1]. Additionally, in the Phase 2b and Phase 3 clinical trials, DOR was efficacious and generally well tolerated when co-administered TDF/FTC and ABC/3TC and when administered as DOR/3TC/TDF [Sec. 2.7.3-trtmtnve48wk], [Sec. 2.7.4]. While DOR has not been evaluated in a DDI trial with the NRTI tenofovir alafenamide (TAF), DOR is not expected to perpetrate DDIs via P-gp, BCRP, OATP1B1, and OATP1B3, for which TAF is a substrate [Ref. 5.4: 04R6X5]. Furthermore, TAF is not expected to have a clinically relevant effect on the PK of DOR as TAF is not an inhibitor or inducer of CYP3A in vivo [Ref. 5.4: 04R6X5]. Therefore, these two agents may be co-administered.

Integrase Strand Transfer Inhibitors: DOR may also be co-administered with integrase strand transfer inhibitors (InSTIs) that are administered with a PK enhancer (elvitegravir) or without a PK enhancer (raltegravir, dolutegravir). In a 2-way clinical DDI trial, there was no clinically meaningful interaction between DOR and dolutegravir (P016) [Sec. 2.7.2.2.3.2.3] and co-administration of these two agents was generally well tolerated. While a DDI trial was not conducted with raltegravir, raltegravir is not a perpetrator of CY3A drug interactions [Ref. 5.4: 04R37G]. Raltegravir is primarily metabolized by UGT1A1 mediated glucuronidation and DOR is not anticipated to perturb this pathway [Sec. 2.7.2.1.4.3]. A DDI trial was not conducted with elvitegravir, however, elvitegravir is not a modulator of CYP3A [Ref. 5.4: 04MK7F]; therefore, a clinically meaningful DDI is not anticipated between elvitegravir and DOR. However, elvitegravir as a single-entity tablet, if used, is recommended to be co-administered with a boosted PI. The potential for an interaction between DOR and PIs or DOR and PK enhancers (boosters) is discussed below.

Protease Inhibitors and Boosting Agents: Strong CYP3A inhibitors are expected to increase DOR exposures by approximately 3-fold [Sec. 2.7.2.2.3.1.2], [Sec. 2.7.2.2.3.1.3] which is within the bounds of clinical relevance (0.6, 3.0) [Sec. 2.7.2.1.5.4]. Therefore, DOR may be co-administered with strong CYP3A inhibitors, including PK enhancers (boosters) (i.e., cobicistat or ritonavir) and boosted or unboosted PIs; atazanavir, atazanavir/cobicistat, darunavir, darunavir/cobicistat, fosamprenavir (with or without a PK booster), indinavir (with or without a PK booster), lopinavir/ritonavir, nelfinavir (with or without PK booster),

ritonavir, saquinavir (with or without PK booster), and tipranavir (with a PK booster). See earlier text in this section [Sec. 2.7.2.3.1.1.6] for a more detailed assessment of the co-adminstration of DOR and CYP3A inhibitors. With regards to the administration of unboosted tipranavir, as it is a CYP3A inhibitor and P-gp inducer, suggesting it also induces CYP3A, the net effects on DOR PK cannot be easily predicted. However, as ritonavir has been documented to increase DOR AUC ~3.5-fold (P002) [Sec. 2.7.2.2.3.1.2], the net effect of co-administration of ritonavir boosted tipranavir on DOR PK is expected to be an increase in DOR PK.

Though a DDI trial with cobicistat and DOR was not conducted, and it is known that cobicistat inhibits CYP2D6, P-gp, BCRP, OATP1B1, and OATP1B3, in addition to CYP3A [Ref. 5.4: 04PDJV], only inhibition of CYP3A is expected to increase DOR AUC based on in vitro [Sec. 2.7.2.1.3.1.3], [Sec. 2.6.4.7.1], [Sec. 2.6.4.7.2], [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4], and clinical DDI data [Sec. 2.7.2.2.3.1]. Therefore the effects of cobicistat on DOR PK are not expected to be greater than those observed with ketoconazole or ritonavir (i.e., ~3-fold increase in DOR exposure) [Sec. 2.7.2.2.3.1.2], [Sec. 2.7.2.2.3.1.3]. However, this increase is not considered to be clinically relevant based on the bounds of clinical relevance (0.6, 3.0).

Non-Nucleoside Reverse Transcriptase Inhibitors: As DOR exposure is significantly decreased by moderate and strong CYP3A inducers, and induction effects may take some time to dissipate following cessation of the inducer, the effect of switching from efavirenz, a moderate CYP3A inducer, to DOR on the PK of DOR was evaluated in a DDI trial (P020) [Sec. 2.7.2.2.3.1.6]. Following treatment with the NNRTI, efavirenz, C24 and AUC values of DOR, on the first day following cessation of efavirenz, were reduced on average by 85% and 62%, respectively, when compared with DOR exposure without prior treatment of efavirenz. Following continued dosing of DOR for 14 days (without efavirenz), DOR C24 and AUC were reduced on average by 50% and 32%, respectively, by Day 14. During the transition period when efavirenz is stopped and DOR is initiated, concentrations for both efavirenz and DOR are below their optimal therapeutic levels. In particular, DOR C24 values are below the lower clinical comparability bound of 0.6 until the inductive effect of efavirenz washes out and efavirenz concentrations fall below its target therapeutic concentration of 1000 ng/mL 4 days following cessation of dosing [Sec. 2.7.2.2.3.1.6]; it should be noted, that while DOR C24 values were below the lower bound for efficacy, concentrations were above the in vitro target for efficacy (6-fold EC50). Moreover, in the clinical setting of switch from efavirenz, where patients are virologically suppressed and receiving 2 other antiretroviral agents, this temporary decrease in DOR exposure is not anticipated to be clinically meaningful. Therefore, patients with HIV-1 infection may be switched from an efavirenz based regimen to a DOR based regimen without dose adjustment.

Etravirine and nevirapine [Ref. 5.4: 04QHXX], [Ref. 5.4: 04QHY6], are also NNRTIs which have the potential to induce CYP3A. Clinical DDI trials with DOR and these agents have not been conducted. As discussed previously, the magnitude of the effect of other CYP3A inducers on DOR PK cannot easily be predicted and the duration of decreased DOR concentration is unknown. However, based on the shorter half-lives of these agents, it is unlikely that the duration of effect would exceed that of efavirenz, and switch from these agents to DOR is supported. DOR is not expected to perpetrate clinically relevant DDIs with

etravirine which is a substrate for CYP2C9, CYP2C19, and CYP3A4 [Ref. 5.4: 04QHXX] or with nevirapine which is a substrate for CYP3A and CYP2B6 [Ref. 5.4: 04QHY6] [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4]. [Sec. 2.7.2.2.3.2.1].

Entry and Fusion Inhibitors: Maraviroc, a CCR5 co-receptor antagonist, is a substrate for CYP3A and P-gp [Ref. 5.4: 04R796]; therefore, DOR is not anticipated to have a clinically meaningful effect on the PK of this agent [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4]. [Sec. 2.7.2.2.3.2.1]. Maraviroc is not a perpetrator of CYP3A DDIs [Ref. 5.4: 04R796] and; therefore, these two agents may be co-administered without dose adjustment.

Enfuviritide, a fusion inhibitor, is a peptide that is injected and expected to undergo catabolism to amino acids. Enfuviritide is not susceptible to DDI via CYP450 inhibiton or induction. In addition, enfuviritide does not alter metabolism of major CYPs, including CYP3A [Ref. 5.4: 04R7PM]. Therefore, no DDI is anticipated between DOR and enfuviritide and these two agents may be co-administered without dose adjustment.

3.1.1.6.3.2 Hepatitis C Antiviral Agents

As a significant portion of the HIV-1 patient population is anticipated to be co-infected with HCV, and; therefore, treated with HCV therapy, DDI trials were conducted to assess the potential for PK interactions between DOR and commonly used HCV therapy.

In a two-way DDI trial with sofosbuvir/ledipasvir, there were no clinical meaningful changes in the PK of DOR, sofosbuvir (and its metabolite), or ledipasvir (P053) [Sec. 2.7.2.2.3.2.8]. Similarly, in a 2-way DDI trial between DOR and elbasvir/grazoprevir, there were no clinically meaningful changes in the PK of DOR, elbasvir, or grazoprevir (P050) [Sec. 2.7.2.2.3.2.7].

Consistent with preclinical [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4] and clinical data (earlier text in this section [Sec. 2.7.2.3.1.1.6]), DOR is not anticipated to perpetrate clinically meaningful DDIs with HCV therapies. Data from the DDI trials with elbasvir/grazoprevir and sofosbuvir/ledipasvir further support that DOR does not perpetrate clinically meaningful DDIs via CYP3A, P-gp, BCRP, and OATP1B1, which are involved in the disposition of the HCV antivirals evaluated in the aforementioned DDI trials [Ref. 5.4: 04GQWZ], [Ref. 5.4: 04D8JW].

Daclatasvir and simeprevir are substrates for CYP3A4; therefore, DOR, which is not a perpetrator of CYP3A interactions (see earlier text in this section [Sec. 2.7.2.3.1.1.6]), [Sec. 2.7.2.1.4.3], is not expected to affect the PK of these agents. Simeprevir is not a perpetrator of drug interactions [Ref. 5.4: 04QB7F] and daclatasvir is a very weak inhibitor of CYP3A4 and inhibitor of OATP1B1, BCRP, and OCT1 [Ref. 5.4: 04QB8N]; therefore, these agents are not anticipated to have a clinically meaningful effect on DOR PK, [Sec. 2.7.2.1.4.2], [Sec. 2.7.2.1.4.4].

As ribavirin (RBV) is a nucleoside analog that undergoes typical nucleoside metabolism with little or no CYP-mediated metabolism in vitro [Ref. 5.4: 04RBG6], it is unlikely that there

would be a drug interaction between DOR and RBV and no dose adjustment would be required for these agents when co-administered.

Peg-interferon (IFN) α2b, did not inhibit metabolism of midazolam, a sensitive CYP3A substrate but resulted in a small (16%) increase in exposure of methadone, also a CYP3A substrate. Co-administration of Peg-IFN α2b [Ref. 5.4: 04R37H] is not anticipated to have a clinically meaningful effect on the PK of DOR.

Thus, DOR may be co-administered with elbasvir/grazoprevir, sofosbuvir/ledipasvir, daclatasvir, simeprevir, RBV or Peg-INF α2b without dose adjustment of DOR or any of these HCV therapies.

Telaprevir [Ref. 5.4: 03ZYK3], boceprevir [Ref. 5.4: 04R37J], and the ritonavir containing FDC paritaprevir/ombitasvir/ritonavir are CYP3A inhibitors and are expected to increase DOR exposures approximately 3-fold, within the bounds of clinical relevance [Sec. 2.7.2.1.5.4]; therefore, DOR may be co-administered with these agents.

3.1.1.6.3.3 Opioid Substitution Therapies

Injection drug use (IDU) is a common risk factor for HIV-1 infection, and patients with a history of IDU often undergo treatment with opiate substitution therapy, such as methadone. Therefore, a DDI trial was conducted to evaluate the effect of DOR on the PK of R-methadone, the methadone enantiomer linked to efficacy. DOR co-administration had no statistically significant effect on the PK of R-methadone (P045) [Sec. 2.7.2.2.3.2.6], which is primarily metabolized by CYP3A4, CYP2D6, and CYP2B6. Furthermore there was no statistically significant effect of DOR on the PK of S- or total methadone. Another common treatment of opioid dependence is buprenorphine/naloxone. CYP3A is important in the metabolism of buprenorphine, which would not be affected by co-administration of DOR [Sec. 2.7.2.1.4.3], (P001) [Sec. 2.7.2.2.3.2.1]. Naloxone does not undergo CYP metabolism. While buprenorphine is a CYP3A and CYP2D6 inhibitor in vitro, according to the prescribing information for buprenorphine/naloxone, DDIs are not a concern as therapeutic concentrations are expected to be too low to perpetrate clinically meaningful DDIs [Ref. 5.4: 04QBZ3]. Therefore, DOR and opioid substitution therapies may be co-administered without dose adjustment.

3.1.1.6.3.4 HMG CoA Reductase Inhibitors (Statins)

As 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors are common concomitant medications in the HIV-1 infected patient population, a dedicated DDI trial was conducted with DOR and atorvastatin (P036) [Sec. 2.7.2.2.3.2.4], one of the most commonly used statins. Atorvastatin undergoes hepatic metabolism and is a substrate of the hepatic uptake transporters OATP1B1, P-gp, and BCRP [Ref. 5.4: 04N925], [Ref. 5.4: 04N94C]. Similar to DOR, atorvastatin is metabolized by CYP3A4 [Ref. 5.4: 04N925], and CYP3A modulators have demonstrated a marked effect on its PK [Ref. 5.4: 04N93N].

Following multiple-dose administration of 100 mg DOR, the single-dose atorvastatin AUC GMR (atorvastatin + DOR/atorvastatin alone) fell within BE bounds while Cmax was

decreased by approximately 30% [Sec. 2.7.2.2.3.2.4]. While the reason for the reduction in Cmax is unknown, a similar magnitude reduction in Cmax is observed when atorvastatin is given with food or administered at night and, according to the prescribing information, atorvastatin may be given with food or at any time of the day [Ref. 5.4: 04QB7L]. Furthermore, literature suggests that peak concentrations of statin are not likely a driver of efficacy [Ref. 5.4: 04JMMV]. Therefore, the observed modest decrease in atorvastatin Cmax with co-administration of DOR is not considered to be clinically relevant. These data are consistent with in vitro study results that indicate DOR is unlikely to have a clinically meaningful effect on the metabolism or elimination of substrates for CYP3A, P-gp, OATP1B1, or BCRP, [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4]. As the relevant transporters involved in the disposition of atorvastatin and simvastatin are similar, DOR is not anticipated to have a clinically meaningful effect on the PK of simvastatin [Ref. 5.4: 04QCB2].

Pravastatin is a CYP3A, OATP1B, and to a much lesser extent, BCRP substrate [Ref. 5.4: 03ZNFN]. Rosuvastatin is both an OATP1B and BCRP substrate; fluvastatin is an OATP1B1, CYP2C9, and BCRP substrate and lovastatin is a CYP3A substrate ([Ref. 5.4: 04QB73], [Ref. 5.4: 04QC88], [Ref. 5.4: 04QC7D]). Pitavastatin is a substrate for OATP1B1/3 and primarily metabolized by UGT1A3 and UGT2B7, with CYP metabolism only a minor pathway of metabolism [Ref. 5.4: 04QB74] [Ref. 5.4: 0446MW]). Therefore, based on data from the atorvastatin (P036) [Sec. 2.7.2.2.3.2.4] and midazolam (a sensitive CYP3A substrate) (P001) [Sec. 2.7.2.2.3.2.1], DDI trials, as well as DOR preclinical data [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4], DOR is not expected to have a clinically meaningful effect on the PK of these statins.

Furthermore, none of these statins is known to be clinically meaningful perpetrators of DDIs via CYP3A-mediated metabolism [Ref. 5.4: 04QCB2], [Ref. 5.4: 04QC88], [Ref. 5.4: 04QC7D], [Ref. 5.4: 04QB74], [Ref. 5.4: 04QB7L], [Ref. 5.4: 04N90S], [Ref. 5.4: 04NB2S], [Ref. 5.4: 04N8XF], and are; therefore, not expected to have a clinically meaningful effect on the PK of DOR.

Therefore, DOR may be co-administered with atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin or simvastatin, without dose adjustment of DOR or any of these statins.

3.1.1.6.3.5 Angiotensin Converting Enzyme Inhibitors

The angiotensin converting enzyme (ACE) inhibitor lisinopril has not been reported to be an inducer or inhibitor of CYPs. Therefore, lisinopril is not anticipated to affect the PK of DOR. Lisinopril does not undergo metabolism and is excreted unchanged entirely in urine. In a study in rats, the renal clearance of lisinopril was essentially the same as the glomerular filtration rate (GFR) indicating no active tubular secretion or reabsorption [Ref. 5.4: 04QGV8]. Renal elimination does not play a major role in the elimination of DOR [Sec. 2.7.2.3.1.1.4] and there has been no evidence to suggest that DOR would affect GFR [Sec. 2.7.4.3]; therefore, a drug interaction between lisinopril and DOR is unlikely.

3.1.1.6.3.6 Oral Contraceptives

As oral contraceptives are commonly used medications in HIV-1-infected women, a DDI trial evaluated the effect of DOR on the PK of an oral contraceptive containing EE and LNG (P012) [Sec. 2.7.2.2.3.2.2].

The metabolism of EE has been evaluated in humans and involves sulfation catalyzed by sulfotransferases (SULTs), glucuronidation via UGTs, and hydroxylation catalyzed by CYPs In vitro metabolism studies have demonstrated that SULT1E1, UGT1A1, and CYP3A are the main enzymes involved [Ref. 5.4: 04N94Q]. Phase II conjugations contribute to a large fraction (~60%) of the first pass metabolism and likely govern the absolute oral bioavailability of EE [Ref. 5.4: 04N94Q]. Clearance of EE in human is largely due to metabolism, with minimal unchanged drug detected in urine or feces following oral doses of EE [Ref. 5.4: 04N94Q].

Levonorgestrel is extensively metabolized. More than 20 metabolites (multiple stereoisomers) have been detected in humans. It appears that the primary metabolic pathways of LNG include oxidation, reduction, and direct sulfation [Ref. 5.4: 03ZNFR]. However, no in vitro enzyme reaction phenotyping information has been published.

DOR did not have a clinically meaningful effect on the PK of either of these commonly used components of oral contraceptives (P012) [Sec. 2.7.2.2.3.2.2]. Though there was a 21% increase in AUC0-inf, the values observed were similar to those following use of other approved oral contraceptive formulations [Ref. 5.4: 03ZR80]. In addition, similar increases reported in other DDI trials with LNG are not considered clinically meaningful [Ref. 5.4: 04D8JW]. Therefore, DOR may be co-administered with these agents without dose adjustments.

3.1.1.6.3.7 Acid Reducing Agents

As acid reducing agents are a common concomitant therapy in the HIV-1-infected population, a dedicated DDI trial evaluated the effect of an aluminum and magnesium hydroxide containing antacid, which also contained simethicone (anti-gas agent), as well as the effect of the PPI pantoprazole, on the PK of DOR (P042) [Sec. 2.7.2.2.3.1.7]. Neither acid reducing agent had a clinically meaningful effect on the PK of DOR as exposures were maintained within the clinical bounds. Therefore, DOR is not affected by increased gastric pH nor is it affected by antacids containing cations (e.g., magnesium, aluminum, or calcium) which also have the potential for chelation as an additional potential mechanism to reduce drug absorption. These clinical data are consistent with the observed pH independent solubility of DOR [Sec. 2.7.1.1.2.1]. Therefore, DOR may be co-administered with acid modifying agents such as pantoprazole and antacids without dose adjustment.

Pantoprazole as well as the PPIs omeprazole and lansoprazole are metabolized by CYP3A4 and CYP2C19 to varying extents [Ref. 5.4: 04QC8W], [Ref. 5.4: 04QC8B], [Ref. 5.4: 04QC83], [Ref. 5.4: 04PL3B]. Based on in vitro data [Sec. 2.7.2.1.4.3] and clinical DDI trials (earlier text in this section [Sec. 2.7.2.3.1.1.6]), DOR is not an inducer or

inhibitor of any of the major CYP enzymes. Therefore, DOR is unlikely to affect the PK of these agents.

The PK of DOR is potentially affected by modulators of CYP3A. While omeprazole and lansoprazole induce CYP3A4 in vitro, no meaningful CYP3A drug-interactions have been reported [Ref. 5.4: 04QC8B], [Ref. 5.4: 04QC83], [Ref. 5.4: 04PL3B]. Therefore, DOR may be co-administered with lansoprazole, omeprazole and pantoprazole without dose adjustment for DOR or these PPIs.

3.1.1.6.3.8 Anti-Diabetics

As diabetes is a common comorbidity in patients with HIV-1 infection, a clinical pharmacology trial evaluated the effect of DOR on the PK of metformin (P048) [Sec. 2.7.2.2.3.2.5], a common first line treatment for Type 2 diabetes. Metformin is excreted unchanged in the urine and does not undergo metabolism or biliary excretion. The uptake of metformin in liver, which is the primary target of metformin action, appears to be mediated primarily by OCT1. Metformin is eliminated into the urine through a combination of glomerular filtration and active tubular secretion. Secretion across the tubular epithelium is thought to be mediated by uptake transporter OCT2 and efflux transporters MATE1 and MATE2K [Ref. 5.4: 04MVB0], [Ref. 5.4: 04M4T2], [Ref. 5.4: 042H8R]. DOR did not have a statistically significant effect on the PK of metformin [Sec. 2.7.2.2.3.2.5]. It has not been documented in the literature that metformin inhibits or induces CYP3A, the enzyme responsible for metabolism of DOR. Therefore, metformin is not expected to have a clinically meaningful effect on the PK of DOR. DOR and metformin may be co-administered without dose adjustment.

An assessment of the potential for DOR to have clinically meaningful DDIs with other commonly used anti-diabetic agents is presented below:

Sulfonylureas: Based on in vitro data [Sec. 2.7.2.1.4.3] and clinical trial DDI data (earlier text in this section [Sec. 2.7.2.3.1.1.6]), DOR is not an inducer or inhibitor of CYP enzymes. Therefore, clinically meaningful interactions would not be anticipated with sulfonylureas, including glyburide, glipizide, tolbutamide, and glimepiride, which are primarily metabolized by CYP2C9 [Ref. 5.4: 04QBY6], [Ref. 5.4: 04QBZ0], [Ref. 5.4: 04QC04], [Ref. 5.4: 04QBYZ]. In addition, these agents are not perpetrators of CYP3A-mediated DDIs and; therefore, would not have a clinically meaningful effect on DOR PK. It should be noted that glyburide is a weak inhibitor of CYP3A (Ref DMD 31:1090–1092, 2003); however, a clinically meaningful interaction with DOR would not be anticipated. Therefore DOR may be co-administered with these agents without dose adjustment for DOR or these sulfonylureas.

Dipeptidyl peptidase-4 (DPP-4) inhibitors: DOR is not be expected to affect the PK of saxagliptin, which is primarily metabolized by CYP3A or sitagliptin which is primarily excreted unchanged in urine, with a small fraction of parent undergoing metabolism via CYP3A and CYP2C9 [Ref. 5.4: 04QBYQ], [Ref. 5.4: 04R3ZH], [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.3.1.1.4], (see earlier text in this section [Sec. 2.7.2.3.1.1.6]). As per the prescribing information for sitagliptin and saxagliptin, these agents are not CYP3A inhibitors or inducers

and; therefore, would not be expected to affect the PK of DOR [Ref. 5.4: 04R3ZH], [Ref. 5.4: 04QBYQ]. Therefore, DOR may be co-administered with saxagliptin or sitagliptin without dose adjustment of DOR or these DPP-4 inhibitors.

Thiazolidinediones: Based on the prescribing information of rosiglitazone [Ref. 5.4: 04QBZM], it is not an inhibitor of CYPs at clinically relevant concentrations and literature suggests it is not an enzyme inducer [Ref. 5.4: 04QGV9]. Therefore, rosiglitazone is not anticipated to affect the PK of DOR. Rosiglitazone is predominately metabolized by CYP2C8, and to a lesser extent CYP2C9. Therefore, DOR is not anticipated to affect the metabolism of rosiglitazone to a clinically meaningful extent [Sec. 2.7.2.1.4.3]. Therefore DOR may be co-administered with rosiglitazone without dose adjustment of either agent.

While DOR is not expected to affect the metabolism of pioglitazone, a CYP2C8 substrate [Sec. 2.7.2.1.4.3], pioglitazone is a weak CYP3A inducer [Ref. 5.4: 04QBYY] and; therefore, DOR concentrations may be reduced.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors: canagliflozin is primarily glucuronidated via UGT1A9 and UGT2B4. As DOR is not a substrate for UGT enzymes and it is not an inducer [Sec. 2.7.2.1.4.3], DOR is unlikely to affect the PK of canagliflozin [Ref. 5.4: 04QB8M]. In vitro, canagliflozin does not induce major CYPs and only weakly inhibits CYP2B6, CYP2C8, CYP2C9, and CYP3A4 based on in vitro studies with human hepatic microsomes. However, canagliflozin did not have a clinically meaningful effect on the PK of the CYP3A substrate cyclosporine [Ref. 5.4: 04QB8M]. Therefore, a clinically meaningful DDI is not anticipated between DOR and canagliflozin.

DOR is not expected to affect the PK of dapagliflozin, which is primarily metabolized by UTG1A9 and is a weak substrate of P-gp and OAT3 [Ref. 5.4: 04QB8R], [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.1.4.4], (see earlier text in this section [Sec. 2.7.2.3.1.1.6]), [Sec. 2.7.2.2.3]. Neither dapagliflozin, nor its metabolite dapagliflozin 3-O-glucuronide, are inhibitors or inducers of major CYPs [Ref. 5.4: 04QB8R]. Therefore, a clinically meaningful DDI is not anticipated between DOR and dapagliflozin.

DOR is not expected to affect the PK of empagliflozin which is primarily metabolized by glucuronidation by UGT2B7, UGT1A3, UGT1A8, and UGT1A9 [Ref. 5.4: 04QBYX], [Sec. 2.7.2.1.4.3]. Empagliflozin is not an inhibitor or inducer of major CYPs [Ref. 5.4: 04QBYX]. Therefore, a clinically meaningful DDI is not anticipated between DOR and empagliflozin.

Based on the information presented above, DOR may be co-administered with canagliflozin, dapagliflozin and empagliflozin without a dose adjustment of DOR or these SGLT2 inhibitors.

Glucagon-like peptide-1 receptor agonists: DOR is not anticipated to affect the PK of liraglutide, a subcutaneously administered GLP1 receptor agonist, since liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Liraglutide has been shown to alter absorption of concomitantly administered oral agents through delayed gastric emptying; however, liraglutide did not

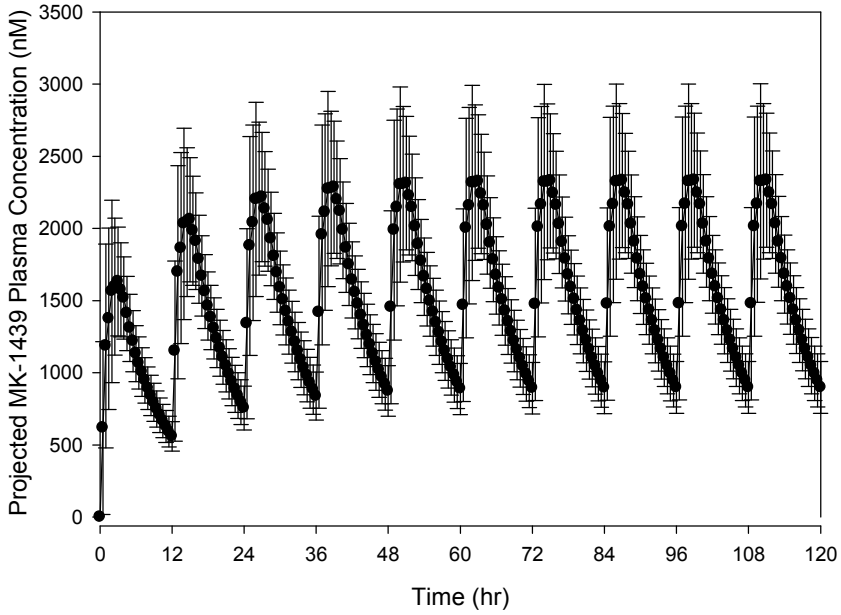
affect the absorption of the tested products to a clinically relevant degree; AUC changes for digoxin, lisinopril, atorvastatin, acetaminophen, and EE/LNG ranged from a decrease of 16% to an increase of 18% [Ref. 5.4: 04QBYP]. The effect of liraglutide on DOR, a BCS Class II compound, is not expected to be clinically meaningful based on the bounds of clinical relevance, 0.6 to 3.0 [Sec. 2.7.2.1.5.4].

3.1.1.6.3.9 Anti-Mycobacterials

DOR is contraindicated for use with the anti-mycobacterial agents, rifampin and rifapentine, since these agents are strong CYP3A inducers. Based on a DDI trial (P011), co-administration of DOR and rifampin results in a significant reduction in DOR PK which may reduce efficacy [Sec. 2.7.2.2.3.1.4], [Sec. 2.7.2.3.1.1.6].

Rifabutin may be an alternate therapy for tuberculosis in HIV-1 infected patients. A clinical pharmacology trial was conducted with rifabutin to evaluate the effect of the moderate CYP3A inducer on DOR PK (P035). Multiple-dose treatment with rifabutin resulted in a significant 68% decrease in DOR Ctrough, which fell below the prespecified lower clinical bound for efficacy of 0.60 [Sec. 2.7.2.2.3.1.5]. However, based on NPS projections [Figure 2.7.2: 23], administration of 100 mg BID DOR with rifabutin is projected to achieve similar steady state AUC, Cmax, and Ctrough values to those associated with the 100 mg QD dose without co-administration of rifabutin, restoring Ctrough values to within clinical bounds [Table 2.7.2: 13]. Therefore, DOR should be administered as 100 mg BID when co-administered with rifabutin.

Figure 2.7.2: 23 Arithmetic Mean Projected Plasma Concentration-Time Profiles of DOR Following Administration of 100 mg BID DOR Co-administered with 300 mg QD Rifabutin in Healthy Subjects



[Ref. 5.3.5.3: 04R3RC]

Table 2.7.2: 13 Non-parametric Superposition Derived Geometric Mean DOR Steady State PK Parameters for 100 mg BID DOR Co-administered with 300 mg QD Rifabutin

Dose Regimen	Day	Ctrough (nM)	Cmax (µM)	AUC0-24 (µM*hr)
100 mg BID MK-1439 + 300 mg QD Rifabutin	5	881	2.46	38.4
100 mg QD MK-1439	Steady State	930	2.26	37.8
Fold change Relative to MK-1439 100 mg QD at Steady State	5	0.95	1.1	1.0

[Ref. 5.3.5.3: 04R3RC]

3.1.1.6.3.10 Azole Antifungal Agents

Strong CYP3A inhibitors are expected to increase DOR exposures by approximately 3-fold [Sec. 2.7.2.2.3.1.2], [Sec. 2.7.2.2.3.1.3] which is within the bounds of clinical relevance (0.6, 3.0) [Sec. 2.7.2.1.5.4]. Therefore, DOR may be co-administered with strong CYP3A inhibitors, including the azole antifungal agents fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole.

Fluconazole primarily undergoes renal excretion, with ~80% of the administered dose eliminated unchanged in the urine. DOR is not anticipated to affect renal excretion [Sec. 2.7.4.3], [Sec. 2.7.2.3.1.1.4.4], [Sec. 2.7.2.1.4.4], and therefore no clinically meaningful interaction is anticipated between the fluconazole and DOR.

Itraconazole is primarily metabolized by CYP3A4 and as DOR does not have a clinically meaningful effect on CYP3A metabolism [Sec. 2.7.2.1.4.3], a clinically meaningful interaction is not anticipated between itraconazole and DOR.

Posaconazole is primarily metabolized by UDP glucuronosyltransferase and is a substrate for P-gp. DOR is not an inhibitor of UGT1A1 [Sec. 2.7.2.1.4.3], is not metabolized by glucuronidation [Sec. 2.7.2.1.4.2] and is not an inhibitor of P-gp [Sec. 2.7.2.1.4.4], so it is not anticipated to have a clinically meaningful effect on either UDP glucuronosyltransferase or P-gp; therefore a clinically meaningful interaction is not anticipated between posaconozole and DOR.

Ketoconazole is primarily metabolized through oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. As DOR is not anticipated to affect these metabolism pathways [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.2.3.2.1], a clinically meaningful interaction is not anticipated between ketoconazole and DOR.

Voriconazole is metabolized by CYP2C19, CYP2C9, and CYP3A4 and CYP2C19. As DOR is not expected to affect CYP metabolism [Sec. 2.7.2.1.4.3], [Sec. 2.7.2.2.3.2.1], a clinically meaningful interaction is not anticipated between voriconazole and DOR. Therefore, DOR may be co-administered with fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole without dose adjustment.

3.1.2 Tenofovir Disoproxil Fumarate

PK and PD profiles of the marketed drug TDF are well-characterized and have been reported in the public domain. As described in [Sec. 2.7.1.2.1.2], co-administration of TDF with 3TC and DOR as part of DOR/3TC/TDF does not have a clinically meaningful impact on the PK of tenofovir. Thus, the PK and PD profiles of TDF described in the US and EU prescribing information for VIREAD [Ref. 5.4: 04P95P], [Ref. 5.4: 04QHYF] are applicable to DOR/3TC/TDF and are described briefly in this section.

3.1.2.1 Pharmacokinetics/ADME

The PK of tenofovir after administration of TDF has been evaluated in healthy subjects and HIV-1 infected individuals. Tenofovir PK is similar between these populations.

Absorption

TDF is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir in fasted subjects following administration of TDF is approximately 25%. Following oral administration of a single dose of TDF 300 mg to HIV-1-infected subjects in the fasted state, maximum serum concentrations (Cmax) are achieved

in 1.0 ± 0.4 hours. Cmax and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 µg•hr/mL, respectively.

The PK of tenofovir is dose proportional over a TDF dose range of 75 to 600 mg and is not affected by repeated dosing.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following IV administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Excretion

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated. The half-life is approximately 17 hours [Ref. 5.4: 04P95P].

Effects of Food on Oral Absorption

Administration of TDF 300 mg tablets following a high-fat meal increases the oral bioavailability, with an increase in tenofovir AUC0-inf of approximately 40% and an increase in Cmax of approximately 14%. However, administration of TDF with a light meal did not have a significant effect on the PK of tenofovir when compared to fasted administration of the drug. These data result in differing interpretations in the US versus EU prescribing information. The US prescribing information states that TDF may be taken without respect to food whereas the EU SmPC states that it should be administered with food in order to maximize exposure. However, as per the European AIDS Clinical Society, some HIV-1 antiretroviral TDF containing regimens may be administered without regard to meals [Ref. 5.4: 04QVMX]. In the food effect trial with DOR/3TC/TDF (P029), tenofovir AUC0-inf was only increased by 26%, and DOR/3TC/TDF was dosed without regard to food in Phase 3. Therefore, DOR/3TC/TDF may be dosed without regard to food.

3.1.2.2 Intrinsic factors

Race: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential PK differences among these populations.

Gender: Tenofovir PK is similar in male and female subjects.

Geriatric Patients: Clinical trials of TDF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, TDF should be used in the elderly patient with caution, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Impaired Renal Function: The PK of tenofovir is altered in subjects with renal impairment. TDF is recommended to be taken every 24 hours in individuals with creatinine clearance >50 mL/min. Longer TDF dosing intervals are recommended in individuals with creatinine clearance <50 mL/min.

Patients with Hepatic Impairment: There were no substantial alterations in tenofovir PK in subjects with hepatic impairment compared with unimpaired subjects. No change in TDF dosing is required in patients with hepatic impairment.

3.1.2.3 Drug Interactions

As TDF is being administered as part of DOR/3TC/TDF and DOR/3TC/TDF is a complete regimen for the treatment of HIV-1 infection, no other antiretroviral agents are intended to be administered with DOR/3TC/TDF for treatment-naïve infection. Therefore, information regarding potential DDIs with other antiretroviral medications and TDF is not provided.

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP-mediated interactions involving tenofovir with other medicinal products is low.

No clinically significant drug interactions have been observed between tenofovir DF and the following medications: entecavir, methadone, oral contraceptives, or tacrolimus.

3.1.2.3.1 Hepatitis C Antiviral Agents

No clinically significant drug interaction has been observed between TDF and sofosbuvir. Co-administration of TDF and ledipasvir/sofosbuvir has been shown to increase tenofovir exposure. Patients receiving TDF concomitantly with ledipasvir/sofosbuvir should be monitored for adverse reactions associated with TDF. Sofosbuvir/velpatasvir may increase tenofovir concentrations. Therefore, patients receiving HIV-1 antiretroviral regimens containing TDF need to be monitored for TDF associated adverse reactions if they are also concomitantly receiving sofosbuvir/velpatasvir, or other velpatasvir or ledipasvir containing regimens.

3.1.2.3.2 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs. It is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of TDF, and periodically during TDF therapy.

3.1.3 Lamivudine

PK and PD profiles of the marketed drug 3TC are well-characterized and have been reported in the public domain. As described in [Sec. 2.7.1.2.1.2], co-administration of 3TC with TDF and DOR as part of DOR/3TC/TDF does not have a clinically meaningful impact on the PK of 3TC. Thus, the PK and PD profiles of 3TC described in the US and EU prescribing information for EPIVIR ([Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD]) are applicable to DOR/3TC/TDF and are described briefly in this section.

3.1.3.1 Pharmacokinetics/ADME

Absorption and Bioavailability: Following oral administration, 3TC is rapidly absorbed and extensively distributed. Absolute bioavailability is 86% ± 16% for the 150 mg tablet. Following administration of 150 mg 3TC twice daily, in combination with other antiretroviral agents, the geometric mean (95% CI) for AUC(0-12) was 5.53 (4.58, 6.67) µg•hr/mL and for Cmax was 1.40 (1.17, 1.69) mcg/mL. At steady state, once daily administration of 300 mg resulted in 3TC AUC24, Cmax, and trough values that were similar, 66% higher, and 53% lower, respectively, compared with the 150-mg twice-daily regimen [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD].

Effects of Food on Oral Absorption: There was no significant difference in systemic exposure (AUC) in the fed and fasted states.

Distribution: The apparent volume of distribution after IV administration of 3TC to HIV-1 infected subjects was 1.3 ± 0.4 L/kg, suggesting that 3TC distributes into extravascular spaces.

Metabolism: Metabolism of 3TC is a minor route of elimination. In humans, the only known metabolite of 3TC is the trans-sulfoxide metabolite.

Excretion: The majority of 3TC is eliminated unchanged in urine by a combination of glomerular filtration and active tubular secretion. The half-life of 3TC is approximately 5 to 7 hours.

3.1.3.2 Intrinsic factors

Because animal reproduction studies are not always predictive of human response, 3TC should be used during pregnancy only if the potential benefits outweigh the potential risks to the fetus.

Geriatric Use

Clinical trials of 3TC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of 3TC in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

Patients With Impaired Renal Function

Reduction of the dosage of 3TC is recommended for patients with impaired renal function.

Patients With Impaired Liver Function

No dose adjustment for 3TC is required for patients with impaired hepatic function.

3.1.3.3 Drug Interactions

As 3TC is being administered as part of DOR/3TC/TDF and DOR/3TC/TDF is a complete regimen for the treatment of HIV-1 infection, no other antiretroviral agents are intended to be administered with DOR/3TC/TDF to treatment-naïve patients. Therefore, information regarding potential DDIs with other HIV-1 antiretroviral medications and 3TC is not provided.

Elimination of 3TC occurs predominantly in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) [Ref. 5.4: 04P95N] [Ref. 5.4: 04QHYD].

3.1.3.3.1 Trimethoprim

Co-administration of sulfamethoxazole/trimethoprim with 3TC resulted in a ~40% mean increase in 3TC AUC, a mean decrease of 29% in 3TC CL/F and a mean decrease of 30% in 3TC CLR. However, 3TC dose adjustment is not warranted as it appears to be safe and well tolerated. The PK properties of trimethoprim and sulfamethoxazole were not altered by 3TC co-administration [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD].

Other medicinal products (e.g., ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine [Ref. 5.4: 04QHYD].

3.1.3.3.2 Interferon-α-2b

In a DDI trial conducted in 19 healthy subjects, the PK of 3TC and interferon-α-2b after co-administration and after administration as single agents were not significantly different.

3.2 Intrinsic and Extrinsic Factors of DOR/3TC/TDF

Intrinsic and extrinsic factor trials were not conducted with DOR/3TC/TDF. However, DOR PK data from administration of DOR/3TC/TDF in Phase 3 was included in the population PK analysis that assessed the impact of age, gender, weight, race, ethnicity, and renal function. As described in [Sec. 2.7.1.2.1.2], the PK of all components are similar when administered as single entities or when administered as part of DOR/3TC/TDF. Furthermore, there is no clinically meaningful drug interaction between DOR and the other components of DOR/3TC/TDF (P038) [Sec. 2.7.2.2.3.1.8]. This is further supported by the DOR population PK analysis, where there was no difference in DOR PK when administered as the tablet or

DOR/3TC/TDF. Therefore, the clinical pharmacology profile for each individual component, including the effect of intrinsic and extrinsic factors on PK, is applicable to the components when administered as part of DOR/3TC/TDF. Instances where labeling considerations are different across the individual components (DOR, 3TC, TDF) are explored in this section.

3.2.1 Intrinsic Factors of DOR/3TC/TDF

There are no clinically meaningful effects of age, gender, weight, BMI, race, ethnicity, renal impairment, or mild/moderate hepatic impairment on DOR PK, and no dose adjustment for DOR is required based on these factors [Sec. 2.7.2.3.1.1.5]. There are no significant effects of impaired hepatic function, race, or gender on 3TC PK, and no dose adjustment for 3TC is required based on these factors [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD]. In addition no dose adjustment is proposed for elderly patients. Similarly, there are no significant effects of impaired hepatic function or gender on tenofovir PK, and no dose adjustment for TDF is required based on these factors [Ref. 5.4: 04P95P], [Ref. 5.4: 04QHYF]. In addition no dose adjustment is proposed for elderly patients or different races. While there is no dose adjustment to 3TC and TDF recommended for the elderly, the elderly population was not evaluated in clinical trials with 3TC or TDF and the US and EU prescribing information indicates both these agents should be used cautiously in elderly patients [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD], [Ref. 5.4: 04P95P], [Ref. 5.4: 04QHYF]. Therefore, no dose adjustment is required for DOR/3TC/TDF based on age, gender, race, weight, BMI, or mild/moderate hepatic impairment.

Severe Hepatic Impairment: The PK of 3TC and tenofovir are not substantially altered by hepatic impairment [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD], [Ref. 5.4: 04P95P], [Ref. 5.4: 04QHYF]. Similarly, moderate hepatic impairment had no effect on DOR PK. However, DOR PK has not been evaluated in patients with severe hepatic impairment. Therefore administration of DOR/3TC/TDF to patients with mild and moderate hepatic impairment is supported; however there is a lack of clinical data in patients with severe hepatic impairment.

Renal Impairment: No dose adjustment is needed for DOR in patients with mild, moderate or severe renal impairment patients. Dose adjustment is required for both 3TC and TDF in patients with estimated creatinine clearance below 50 mL/min [Ref. 5.4: 04P95N], [Ref. 5.4: 04QHYD], [Ref. 5.4: 04P95P], [Ref. 5.4: 04QHYF]. As dose adjustments from the 300 mg doses of 3TC and TDF are not possible with DOR/3TC/TDF, it should not be used in this population.

3.2.2 Extrinsic Factors of DOR/3TC/TDF

The DDI profiles and recommendations for the individual components also apply to DOR/3TC/TDF [Sec. 2.7.2.3.1.1.6], [Sec. 2.7.2.3.1.3.3], [Sec. 2.7.2.3.1.2.3]. Therefore, DOR/3TC/TDF use is contraindicated with strong CYP3A inducers. DOR/3TC/TDF may be co-administered with the more moderate inducer, rifabutin, with an additional dose of 100 mg DOR separated by approximately 12 hours [Sec. 2.7.2.3.1.1.6]. As the magnitude of induction associated with CYP3A moderate inducers varies across compounds (e.g.,

efavirenz, etravirine, nevirapine, bosentan, nafcillin, modafinil), and is also dependent on the substrate, the effect of other moderate inducers on the PK of DOR cannot easily be predicted. Therefore, the dose adjustment proposed for co-administration of rifabutin and DOR may not be sufficient for other moderate inducers which may be co-administered with DOR/3TC/TDF.

Due to the TDF component of DOR/3TC/TDF, in the treatment of chronic hepatitis B, DOR/3TC/TDF should not be administered with adefovir dipivoxil. Furthermore, co-administration of TDF and ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or other ledipasvir or velpatasvir containing regimens may increase tenofovir exposure and patients receiving DOR/3TC/TDF concomitantly with any of these agents should be monitored for tenofovir associated AEs. Co-administration of TDF with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs and AEs associated with these agents should be monitored [Sec. 2.7.2.3.1.2.3]. In addition, DOR/3TC/TDF should be avoided with concurrent or recent use of nephrotoxic agents.

Due to the 3TC component, which is predominantly eliminated in the urine by active organic cationic secretion, the possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

[Table 2.7.2: 14] summarizes established and potentially significant DDIs with the components of DOR/3TC/TDF. As DOR/3TC/TDF is a complete regimen for the treatment of HIV-1 infection, information regarding potential DDIs with other HIV-1 antiretroviral medications is not provided. Refer to [Sec. 2.7.2.3.1.2] and [Sec. 2.7.2.3.1.3] for additional information on the DDI potential of TDF and 3TC, respectively.

Table 2.7.2: 14 Summary of Established and Other Potentially Significant Drug Interactions with the Components of DOR/3TC/TDF

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antimycobacterials		
rifabutin*	↓ DOR ↔ rifabutin	Concomitant use of DOR/3TC/TDF with rifabutin may cause a decrease in the plasma concentrations of DOR (induction of CYP3A enzymes). If DOR/3TC/TDF is co-administered with rifabutin, one tablet of DOR-DOR/3TC/TDF should be taken approximately 12 hours after the dose of DOR/3TC/TDF *[see Dosage and Administration (2.3)]*.
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole* posaconazole voriconazole	↑ DOR ↔ azole antifungal agents	Concomitant use of DOR/3TC/TDF with azole antifungal agents may cause an increase in the plasma concentrations of DOR/3TC/TDF (inhibition of CYP3A enzymes). No DOR dose adjustment is required when DOR/3TC/TDF is co-administered with azole antifungal agents.
Hepatitis C Antiviral Agents		
ledipasvir/sofosbuvir sofosbuvir/velpatasvir	↑ tenofovir	Patients receiving DOR/3TC/TDF concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir should be monitored for adverse reactions associated with TDF.

↑ = increase, ↓ = decrease, ↔ = no change
*The interaction between DOR and the drug was evaluated in a clinical study.
All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.

3.2.3 Effect of Food on DOR/3TC/TDF

Food did not have a clinically meaningful effect on DOR PK (P037) [Sec. 2.7.1.2.2.1.1]. Similarly, food did not have a clinically meaningful effect on the PK of the components of DOR/3TC/TDF (P029) [Sec. 2.7.1.2.2.1.2], [Ref. 5.4: 04P95N], [Ref. 5.4: 04P95P]. In addition, in the pivotal Phase 3 trial using DOR/3TC/TDF (P021), DOR/3TC/TDF was administered without regard to food. Consequently, DOR/3TC/TDF may be administered without regard to food.

3.3 Pharmacodynamics and Special Safety Trials

No PD trials were conducted with TDF, 3TC, or DOR/3TC/TDF. However, the effect of DOR on HIV-1 RNA in treatment-naïve HIV-1-infected male subjects (P005) [Sec. 2.7.2.3.3.1] and the effect of DOR on the QTc interval in healthy subjects (P017) [Sec. 2.7.2.3.3.2] were evaluated in clinical pharmacology trials and are summarized below.

3.3.1 Antiviral Activity in Treatment-Naïve HIV-1 Infected Subjects

A Phase 1 trial (P005) [Sec. 2.7.2.1.3.2.1] was conducted in treatment-naïve subjects infected with HIV-1. After 7 days of QD dosing with 25 mg or 200 mg of DOR, the placebo-corrected change from baseline in HIV-1 RNA was ~1.3 logs. These data demonstrated activity of DOR monotherapy and supported the continued clinical development of DOR in combination with other antiretroviral therapy. Effect on viral load suppression is a key primary endpoint in the Phase 2b and Phase 3 trials and is discussed in [Sec. 2.7.3-trtmtnve48wk].

3.3.2 Effect of Doravirine on QT/QTc

Throughout the DOR clinical development program there was no clinically meaningful effect of DOR on the QT/QTc interval [Sec. 2.7.4.4.1]. In a thorough QT/QTc trial, a supratherapeutic dose of 1200 mg of DOR did not have a clinically meaningful effect on the QTc interval as described in [Sec. 2.7.2.2.4.2].

4. SPECIAL STUDIES

A thorough QT/QTc trial was conducted which is summarized in [Sec. 2.7.2.3.3.2]. No other special studies were conducted.

5. CONCLUSIONS

The clinical pharmacology of DOR and DOR/3TC/TDF are thoroughly characterized. Key conclusions are summarized below.

5.1 Doravirine

Conclusions for pharmacokinetics and ADME of DOR as a single entity or as part of DOR/3TC/TDF:

- DOR PK is similar when administered as a single entity or when administered as part of DOR/3TC/TDF and there is no DDI between DOR and the other components of DOR/3TC/TDF. Therefore, the clinical pharmacology profile of each single entity is applicable to DOR/3TC/TDF.
- DOR is absorbed with a median Tmax of 2 hours and an estimated absolute bioavailability of 64% for the 100 mg FMI tablet. DOR exhibits less than dose proportional increases in PK. Plasma concentrations of DOR decline in a monophasic manner with a geometric mean terminal t1/2 of approximately 15 hours. Steady-state is attained in ~2 days and DOR PK is not time-dependent.
- DOR is primarily metabolized by CYP3A. Oxidation to form the metabolite M9 is the major metabolic pathway in humans. DOR is primarily eliminated as M9 in the urine, while urinary excretion of unchanged DOR is minor.
- DOR is not a substrate for any other CYPs. In vitro, DOR is a substrate for P-gp; however, good passive permeability of DOR and clinical DDI data indicate modulation of P-gp will not have a clinically meaningful effect on DOR PK.

Conclusion for effect of DOR on QTc

- A supratherapeutic dose of DOR, providing 4.1-fold and 3.1-fold multiples over the anticipated steady state Cmax and AUC values, respectively, at the clinical dose of 100 mg, does not have a clinically meaningful effect on the QTc interval.

Conclusions for Dose and Bounds

- The results of the Phase 1b and Phase 2b trial and the exposure-response analyses for safety and efficacy with Phase 2b and Phase 3 data support the selection of 100 mg of DOR as the clinical dose; maximal efficacy is achieved with an acceptable safety profile. This analysis is in agreement with the observed efficacy and safety data in the Phase 2b and Phase 3 program.
- Clinical comparability bounds of (0.6, 3.0) for DOR are established as reflecting the range of relative change in C24 (lower bound) and AUC (upper bound) that would be expected to be clinically comparable to 100 mg of DOR in HIV-1-infected patients with respect to efficacy and safety. Intrinsic and extrinsic factor effects that fall within this range are considered not clinically relevant and no alteration in the dosing guidance would be needed for those factors.

Intrinsic Factors

- The effects of age, gender, body weight/BMI, race, ethnicity, mild, moderate or severe renal impairment, mild or moderate hepatic impairment on DOR PK are not clinically meaningful and no dose adjustments are needed.

Extrinsic Factors

- DOR is not a perpetrator of clinically meaningful DDIs; therefore, dose adjustment of co-administered agents is not required.
  - In vitro, DOR does not inhibit or induce major drug-metabolizing CYPs.
  - DOR is a weak inhibitor of major drug transporters in vitro so that clinically meaningful interactions via those transporters are unlikely and have not been observed in clinical trials.
- Food and gastric acid modifying agents do not have a clinically meaningful effect on DOR PK and therefore DOR may be administered without regards to food or use of gastric modifying agents.

- DOR may be co-administered with CYP3A inhibitors without dose adjustment.
- Moderate and strong CYP3A inducers have a clinically meaningful effect on the PK of DOR:
  - DOR is contraindicated with use of strong CYP3A inducers as C24 values fall below the lower bound for efficacy when DOR is co-administered with these agents.
  - DOR 100 mg should be administered BID when co-administered with the more moderate CYP3A inducer, rifabutin, to ensure C24 values are above the lower bound for efficacy. The magnitude of effect on DOR PK of other moderate CYP3A inducers, which may be co-administered with DOR, is unknown.

5.2 Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

Dose Selection and Bounds

- Efficacy for DOR/3TC/TDF which included 100 mg DOR and the marketed doses of TDF (300 mg) and 3TC (300 mg) has been demonstrated in a pivotal Phase 3 trial. There are no meaningful differences in DOR, tenofovir, or 3TC PK when DOR, TDF, and 3TC were administered as part of DOR/3TC/TDF or as the individual components. Thus, the dose recommendations with respect to clinical dose, intrinsic, and extrinsic factors described in this document for DOR and in the VIREAD and EPIVIR prescribing information are applicable to each component when administered as DOR/3TC/TDF.

Conclusions for Pharmacokinetics and ADME

Doravirine

- The PK of DOR administered as DOR/3TC/TDF is similar to the PK following administration of the 100 mg FMI tablet and there is no statistically significant DDI between DOR and the components of DOR/3TC/TDF. Therefore, the PK profile of DOR following administration of the single entity tablet is applicable to DOR/3TC/TDF as described above.

Lamivudine

- The PK of 3TC administered as part of DOR/3TC/TDF is similar to the PK of 3TC following administration of EPIVIR (concomitant with VIREAD) and there is no statistically significant DDI between 3TC and the other components of DOR/3TC/TDF. Therefore, the PK profile of 3TC, as described in the prescribing information for EPIVIR, is applicable to DOR/3TC/TDF.

Tenofovir Disoproxil Fumarate

- The PK of tenofovir administered as part of DOR/3TC/TDF is similar to the PK of tenofovir following administration of VIREAD (concomitant with EPIVIR) and there is no clinically meaningful DDI between tenofovir and the other components of the DOR/3TC/TDF. Therefore, the PK profile of tenofovir, as described in the prescribing information for VIREAD, is applicable to DOR/3TC/TDF.

Intrinsic Factors

- No dose adjustment is required for the DOR/3TC/TDF tablet based on age, gender, race, weight, BMI, or mild/moderate hepatic impairment. However, DOR has not been evaluated in patients with severe hepatic impairment. DOR/3TC/TDF should not be administered to patients with a creatinine clearance below 50 mL/min as dose adjustment is required for 3TC and TDF in this population. As the effects of age have not been evaluated for 3TC and TDF, DOR/3TC/TDF should be used with caution in the elderly population.

Extrinsic Factors

- Due to the DOR component, DOR/3TC/TDF is contraindicated for use with CYP3A strong inducers. DOR/3TC/TDF may be co-administered with the more moderate inducer, rifabutin, with an additional dose of 100 mg DOR separated by approximately 12 hours. The magnitude of effect of other moderate CYP3A inducers, which may be co-administered with DOR, on DOR PK is unknown.
- Due to the TDF component of DOR/3TC/TDF, DOR/3TC/TDF should not be co-administered with adefovir dipivoxil.
- Due to the TDF component of DOR/3TC/TDF, when DOR/3TC/TDF is co-administered with ledipasvir/sofosbuvir or velpatasvir/sofosbuvir, patients should be monitored for adverse reaction to TDF.
- Due to the TDF component of DOR/3TC/TDF, when DOR/3TC/TDF is co-administered with drugs that reduce renal function or compete for active tubular secretion, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of TDF and periodically during TDF therapy.
- Due to the 3TC component of DOR/3TC/TDF, which is predominantly eliminated in the urine by active organic cationic secretion, the possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).
- Food does not have a clinically meaningful effect on the PK of the individual components of DOR/3TC/TDF. DOR/3TC/TDF may be administered without regard to food.

6. APPENDIX

Appendix 2.7.2: 1 Overview of Biopharmaceutics and Clinical Pharmacology Program

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
Biopharmaceutics Studies				
5.3.1.1 Bioavailability (BA) Study Reports				
MK-1439				
1439-037	A Study of the Comparative Fed and Fasted Bioavailability of MK-1439 in Healthy Subjects	Open label, randomized, two period crossover	100 mg MK-1439 SD Fed and Fasted	14/14 (7/7)
1439-044	A Study of the Pharmacokinetics of the Intravenous Microdose Formulation of MK-1439 in Healthy Subjects	Open label, single period	100 µg MK-1439 SD	12/11 (4/8)
MK-1439A				
1439A-029	A Study of the Comparative Fed and Fasted Bioavailability of MK-1439A in Healthy Subjects	Open label, randomized, two period, crossover	MK-1439A-FDC (100mg MK-1439 / 300 mg Lamivudine / 300 mg TDF) SD Fed and Fasted	14/13 (9/5)
Module 5.3.1.2 Biocomparison/Bioequivalence Studies				
MK-1439				
1439-034	An Open-Label, Single-Dose, Fixed-Sequence Study to Evaluate the Comparative Bioavailability of Two Nanoparticle Formulations of MK-1439 to the Current Market Image Tablet	Open label, three period, fixed sequence	Period 1: 100 mg MK-1439 Large Nanoparticles Formulation SD, Period 2: 100 mg MK-1439 Small Nanoparticles Formulation SD, Period 3: 100 mg SD MK-1439 Market Image Tablet SD	18/17 (11/7)
1439-039	A Study to Determine the Bioequivalence of MK-1439 Coated and Uncoated Tablets in Healthy Subjects	Open label, randomized, two period, crossover	100 mg MK-1439 Uncoated Oral Compressed Tablet (OCT) SD, 100 mg MK-1439 Film Coated Tablet (FCT) SD	24/ 24 (12/12)
1439-043	A Study to Evaluate the Comparative Bioavailability of the Investigational Oral Pediatric Minitablet Formulation of MK-1439	Open label, randomized, two period, crossover	100 mg MK-1439 (Adult Tablet with Yogurt) SD, 100 mg MK-1439 (Pediatric Mini Tablet with Yogurt) SD	24/24 (17/7)

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
	Compared to the Adult Formulation of MK-1439 in Healthy Subjects			
1439-046	A Rapid Pharmacokinetic Trial of the Bioavailability of Four MK-1439 Nano Formulations in Healthy Subjects	Open label, fixed sequence, five period,	Period 1: 150 mg MK-1439 Type 1 nanoparticle ([redacted]% drug loaded [redacted]) SD Period 2: 100 mg MK-1439 tablet SD Period 3: 150 mg MK-1439 Type 2 nanoparticle ([redacted]% drug loaded [redacted]) SD Period 4: 150 mg MK-1439 Type 3 nanoparticle ([redacted]% drug loaded [redacted]) SD Period 5: 150 mg MK-1439 Type 4 nanoparticle ([redacted]% drug loaded [redacted]) SD	16/16 (10/6)
1439-049	A Comparative Bioavailability Study of Adult MK-1439 and Pediatric Oral Granules Formulations	Open label, partially randomized, three period, crossover	Period 1 and Period 2: 100 mg MK-1439 Adult Tablet SD, 100 mg MK-1439 (Oral Pediatric Granule Formulation) SD Period 3: 125 mg MK-1439 (Oral Pediatric Granule Formulation) SD, 100 mg MK-1439 (Oral Pediatric Granule Formulation) SD	24/24 (6/18)
1439-052	A Comparative Bioavailability Study of Adult MK-1439 and 2nd Gen Pediatric Oral Granule Formulations	Open label, partially randomized, five period, crossover	100 mg MK-1439 (OCT) SD, 100 mg MK-1439 (Oral Granule, Coated Formulation) SD and 100 mg MK-1439 (Oral granule, Uncoated Formulation) SD	24/22 (13/11)
MK-1439A				
1439A-014	A Fasted Bioavailability Study of Two Probe MK-1439A Formulations in Healthy Subjects	Open label, randomized, three period, crossover	MK-1439A FDC BC1 Bilayer Tablet (50 mg MK-1439 /150 mg Lamivudine / 150 mg TDF) SD, MK-1439A FDC (100 mg MK-1439 /300 mg Lamivudine / 300 mg	24/23 (11/13)

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
			TDF) Monolithic Tablet SD, and MK-1439 100 mg OCT / Epivir® 300 mg (Lamivudine) / Viread® 300 mg (TDF) SD	
1439A-015	A Fasted Bioavailability Study of a Probe MK-1439A Formulation in Healthy Subjects	Open label, randomized, two period, crossover	MK-1439A FDC BC2 Bilayer Tablet (100 mg MK-1439/300 mg Lamivudine/300 mg TDF) SD, MK-1439 100 mg OCT/ Epivir® 300 mg (Lamivudine)/ Viread® 300 mg (TDF) SD	24/24 (11/13)
1439A-026	A Comparative Bioavailability Study of MK-1439A in Healthy Subjects under Fasted Conditions	Open label, randomized, two period, crossover	MK-1439A FDC FMI Tablet (100 mg MK-1439/300 mg Lamivudine/300 mg TDF) SD, MK-1439 100 mg / Epivir® 300 mg (Lamivudine) / Viread® 245 mg (Tenofovir disoproxil as fumarate) SD	24/24 (9/15)
Module 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports				
1439-001	A Study to Evaluate the Safety and Pharmacokinetics of MK-1439 and to Evaluate the Effect of Multiple Doses of MK-1439 on Midazolam	Part 1: Double blind, randomized, placebo controlled, multiple period, alternating panel, single rising dose	Part 1 Panel A: 6 mg, 25 mg,100 mg, 300 mg, 450 mg MK-1439 SD, and placebo matched to MK-1439	8/8 (8/-)
			Part 1 Panel B: 12 mg, 50 mg, 50 mg Fed, 150 mg MK-1439 SD, and placebo matched to MK-1439	8/8 (8/-)
		Part 2: Double blind, randomized, placebo controlled, serial panel, rising	Part 2 Panel C: 30 mg MK-1439 QD x 10 Days and placebo matched to MK-1439	8/7 (8/-)
			Part 2 Panel D: 60 mg MK-1439 QD x 10 Days and placebo matched to MK-1439	8/8 (8/-)

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
		multiple dose	Part 2 Panel E: Midazolam 2 mg SD alone and 120 mg MK-1439 QD x 14 Days + 2mg Midazolam on Day 13 and placebo matched to MK-1439	10/9 (10/-)
			Part 2 Panel F: 240 mg MK-1439 QD x 10 Days and placebo matched to MK-1439	8/8 (8/-)
		Part 3: Double blind, randomized, placebo controlled, four period	Part 3 Panel G: 50 mg, 50 mg Capsule Fasted , 50 mg Capsule Fed, 300 mg Capsule MK-1439 SD and placebo matched to MK-1439	8/8 (8/-)
1439-006	A Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1439	Double-blind, randomized, placebo-controlled, two panel (alternating), multiple period, single rising and multiple dose	Panel A: Period 1: 600 mg MK-1439 SD/ placebo matched to MK-1439 Period 2: 800 mg MK-1439 SD/ placebo matched to MK-1439 Period 3: 450 mg MK-1439 QD x 10 Days/ placebo matched to MK-1439 Panel B: Period 1: 1000 mg MK-1439 SD/ placebo matched to MK-1439 Period 2: 1200 mg MK-1439 SD/ placebo matched to MK-1439 Period 3: 750 mg MK-1439 QD x 10 Days / placebo matched to MK-1439	16/15 (16/-)
1439-008	A Study to Investigate the Absorption, Metabolism, Excretion, and Mass Balance of MK-1439	Open label, one period	350 mg (200 µCi) [^{14}C]MK-1439 SD	6/6 (6/-)
1439-031[†]	A Single-Dose, Parallel, Pharmacokinetic, Safety and Tolerability Study of MK-1439 Long Acting Parenteral (LAP) Intramuscular Injections	Open label, two part, parallel group	Part 1: 100 mg MK-1439 QD x 14 Days Part 2: 200 mg MK-1439 (one 1 mL [20% suspension] IM injection), 200 mg MK-1439 (one 0.66 mL [30%	42/41 (26/16)

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
			suspension] IM injection), 200 mg MK-1439 (two 0.5 mL [20% suspension] IM injections)	
Module 5.3.3.2 Patient PK and Initial Tolerability Study Reports				
No studies under this section: MK-1439 -005, a PK and PD trial in subjects with HIV-1 infection is discussed under Module 5.3.4.1				
Module 5.3.3.3 Intrinsic Factor PK Study Reports				
1439-009	A Relative Bioavailability Study to Compare the Pharmacokinetics of MK-1439 in Male and Female Subjects and Healthy Elderly and Young Subjects	Open label, one period, parallel group	100 mg MK-1439 SD	36/36 (12/24) (Elderly Male-12, Elderly Female-12 and Young Female-12)
1439-019	A Study to Investigate the Influence of Hepatic Insufficiency on the Pharmacokinetics of MK-1439	Two part, open label	Part 1: 100 mg MK-1439 SD Part 2: Not conducted	16/16 (12/4) (8 Moderate Hepatic Insufficient, 8 Healthy Control)
1439-051	An Open Label, Single Dose Study to Evaluate the Pharmacokinetics of MK-1439 in Subjects With Severe Renal Impairment	Open label, parallel assignment	100 mg MK-1439 SD	16/16 (11/5) (8 Severe Renal Impairment, 8 Healthy Control)
Module 5.3.3.4 Extrinsic Factor PK Study Reports				
1439-002	A Study to Evaluate the Effect of Multiple Doses of Ritonavir on the Single Dose Pharmacokinetics of MK-1439	Open label, fixed sequence, two period	Period 1: 50 mg MK-1439 SD Alone, Period 2; 100 mg BID Ritonavir Days 1- 20 and 50 mg MK-1439 SD on Day 14	8/8 (8/-)
1439-003	A Study to Evaluate the Effect of Multiple Doses of Tenofovir on the Single Dose Pharmacokinetics of MK-1439	Open label, two period, fixed sequence	Period 1: 100 mg MK-1439 SD Alone, Period 2: 300 mg TDF QD x18 Days and 100 mg MK-1439 SD on Day 14	8/7 (8/-)
1439-010	A Study to Assess the Effects of Multiple Oral Doses of Ketoconazole on the Single Dose Pharmacokinetics of MK-1439 in Healthy Subjects	Open label, two period, fixed sequence	Period 1: 100 mg MK-1439 SD Alone, Period 2: 400 mg Ketoconazole QD Days 1-10 and 100 mg MK-1439 SD on Day 2	10/10 (8/2)

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
1439-011	A Study to Assess the Effects of Single and Multiple Doses of Rifampin on the Single Dose Pharmacokinetics of MK-1439 in Healthy Subjects	Open label, two period, fixed sequence	Period 1: 100 mg MK-1439 SD Alone, Period 2: Treatment B- 600 mg Rifampin and 100 mg MK-1439 SD on Day 1. Treatment C- 600 mg Rifampin QD Days 4-18 and 100 mg MK-1439 SD on Day 17.	11/10 (11/-)
1439-012	A Study to Assess the Effects of Multiple Oral Doses of MK-1439 on the Single Dose Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel) in Healthy Female Subjects	Open label, two period, fixed sequence	Period 1: 0.15 mg/0.03 mg Nordette®-28 (Levonorgestrel (LNG) & Ethinyl (EE) Estradiol) SD Alone Period 2: 100 mg MK-1439 QD Days 1- 17 and 0.15 mg/0.03 mg Nordette®-28 (Levonorgestrel (LNG) & Ethinyl (EE) Estradiol) SD on Day 14	20/19 (-/20)
1439-016	A 2-way Steady State Interaction Study of MK-1439 and Dolutegravir	Open label, three period, fixed sequence	Period 1: 50 mg Dolutegravir QD Days 1-7 Period 2: 200 mg MK-1439 QD Days 1-7, Period 3: 200 mg MK-1439 QD + 50 mg Dolutegravir QD Days 1-7	12/11 (6/6)
1439-020	An Open Label, Multiple Dose Study to Investigate the Effect of Switching From Efavirenz Therapy to MK-1439 on the Pharmacokinetics of MK-1439	Open label, three period, fixed sequence, multiple dose	Period 1:100 mg MK-1439 QD Days 1-5, Period 2: 600 mg Efavirenz QD Days 1-14, Period 3: 100 mg MK-1439 QD Days 1-14,	20/17 (17/3)
1439-035	A Study to Evaluate the Effect of Multiple Doses of Rifabutin on the Single-Dose Pharmacokinetics of MK-1439 in Healthy Subjects	Open label, two period, fixed sequence, PK drug interaction	Period 1: 100 mg MK-1439 SD Alone, Period 2: 300 mg Rifabutin QD Days 1-16 and 100 mg MK-1439 SD on Day 14	18/12 (15/3)
1439-036	A Study to Evaluate the Effect of MK-1439 at Steady State on the Pharmacokinetics of Atorvastatin in Healthy Subjects	Open label, two period, fixed sequence, PK drug interaction	Period 1: 20 mg Atorvastatin SD Alone, Period 2: 100 mg MK-1439 QD Days 1-8 and 20 mg Atorvastatin SD on Day 5	16 /14 (8/8)

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
1439-038	A Component Interaction Study of MK-1439A in Healthy Subjects under Fasting Conditions	Open label, randomized, three period, crossover	MK-1439 100 mg / Epivir® 300 mg (Lamivudine) / Viread® 245 mg (Tenofovir disoproxil as fumarate) SD	15/15 (7/8)
1439-042	A Study to Evaluate the Effect of an Aluminum and Magnesium Containing Antacid and a Proton Pump Inhibitor on the Single-dose Pharmacokinetics of MK-1439 in Healthy Subjects	Open label, three period, fixed sequence, PK drug interaction	Period 1: 100 mg MK-1439 SD Alone, Period 2: 100 mg MK-1439 SD + 20 mL Antacid Oral Suspension (400 mg/5 mL aluminium hydroxide, 400mg/5 mL magnesium hydroxide, and 40 mg/5 mL simethicone) SD Period 3: 40 mg Pantoprazole QD Days 1-5 and 100 mg MK-1439 SD on Day 5	14/13 (8/6)
1439-045	A Multiple-Dose Clinical Trial to Study the Effect of MK-1439 on Methadone Pharmacokinetics	Open label, fixed sequence, multiple dose	20-200 mg Methadone QD Days 1-7 and 100 mg MK-1439 QD Days 2-6	14/14 (7/7)
1439-048	A Study to Evaluate the Effect of Multiple Doses of MK-1439 on Metformin Pharmacokinetics in Healthy Subjects	Open label, two period, fixed sequence, PK drug interaction	Period 1: 1000 mg Metformin SD Fed Alone, Period 2: 100 mg MK-1439 QD Days 1-7 Fed and 1000 mg Metformin SD on Day 5 Fed	14/14 (9/5)
1439-050	A Drug-Drug Interaction Study of MK-1439 with MK-8742 + MK-5172 (Elbasvir + Grazoprevir) in Healthy Subjects	Open label, three period, fixed sequence	Period 1: 100 mg MK-1439 QD Days 1-5, Period 2: 50 mg MK-8742 + 200 mg MK-5172 QD Days 1-10 Period 3: 100 mg MK-1439 QD and 50 mg MK-8742+ 200 mg MK-5172 QD Days 1-5	12/12 (5/7)
1439-053	A Drug-Drug Interaction Study of MK-1439 with Ledipasvir / Sofobusvir in Healthy Subjects	Open label, randomized, three period, crossover	100 mg MK-1439	14/14 (12/2)

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/Completed (Male/Female)
Module 5.3.4.1 Healthy Subject PD and PK/PD Study Reports				
1439-005	A Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiretroviral Activity of MK-1439 in HIV-1 Infected Patients	Randomized, double blind, placebo controlled, two panel, parallel group	Panel A: 25 mg MK-1439 QD Days 1-7 / Placebo matched to MK-1439, Panel B: 200 mg MK-1439 QD Days 1-7/ Placebo matched to MK-1439	18/18 (18/-)
1439-017	A Single Dose Trial to Assess the Effect of a supratherapeutic dose of MK-1439 on QTc Interval in Healthy Subjects	Randomized, double blinded placebo and active controlled, three period, crossover	1200 mg MK-1439 (Supra-therapeutic dose) SD, Placebo matched to MK-1439 and 400 mg Moxifloxacin	45/39 (27/17)

[†]Part 1 of P031 data are included as part of the summary of safety in the present application. Part 2 of P031 was an exploratory trial with a long acting parenteral formulation and therefore not applicable to the present marketing application

Appendix 2.7.2: 2 Tabular Summary of Pharmacokinetic Parameter Values

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (μM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
1439-001	A Study to Evaluate the Safety and Pharmacokinetics of MK-1439 and to Evaluate the Effect of Multiple Doses of MK-1439 on Midazolam	6 mg Fasted	Healthy Male Subjects, Aged 18 to 50 yrs	1	6	MK-1439	156 (126, 193)	43.9 (35.1, 54.8)	1.00 (1.00, 4.00)	2.88 (2.35, 3.52)	Inf	11.68 (9.9)	--	--	--	--
		12 mg Fasted		1	6	MK-1439	297 (240, 367)	73.0 (58.2, 91.4)	1.00 (1.00, 3.00)	4.88 (3.98, 5.98)	Inf	11.67 (15.7)	--	--	--	--
		25 mg Fasted		1	6	MK-1439	460 (372, 569)	194 (155, 243)	5.00 (1.00, 6.00)	11.2 (9.17, 13.7)	Inf	15.67 (20.4)	--	--	--	--
		50 mg Fed		1	6	MK-1439	1020 (825, 1270)	433 (349, 537)	5.00 (3.00, 6.00)	24.0 (20.4, 28.1)	Inf	13.07 (12.0)	0.95 (0.74, 1.23)	1.56 (1.22, 2.01)	1.33 (1.07, 1.65)	Fed/Fasted
		50 mg Fasted		1	6	MK-1439	1070 (865, 1330)	277 (223, 343)	1.00 (1.00, 4.00)	18.0 (15.3, 21.2)	Inf	13.29 (10.6)	--	--	--	--
		100 mg Fasted		1	6	MK-1439	1720 (1390, 2120)	593 (475, 741)	1.50 (1.00, 5.00)	38.3 (31.3, 46.8)	Inf	15.26 (43.9)	--	--	--	--
		150 mg Fasted		1	6	MK-1439	2680 (2170, 3320)	750 (599, 940)	1.50 (1.00, 4.00)	49.9 (40.7, 61.2)	Inf	13.84 (27.6)	--	--	--	--
		300 mg Fasted		1	6	MK-1439	3810 (3090, 4710)	1490 (1190, 1870)	3.50 (2.00, 5.00)	92.6 (75.7, 113)	Inf	15.62 (27.1)	--	--	--	--
		450 mg Fasted		1	6	MK-1439	6010 (4870, 7430)	2070 (1660, 2580)	2.00 (1.00, 5.00)	127 (104, 155)	Inf	14.80 (34.5)	--	--	--	--
		30 mg		1	6	MK-1439	672 (515, 875)	177 (125, 250)	1.00 (1.00, 5.00)	8.42 (6.49, 10.9)	24	--	--	--	--	--
				10	6	MK-1439	796 (611, 1040)	246 (174, 348)	3.50 (1.00, 5.00)	11.5 (8.84, 14.9)	24	13.63 (11.3)	1.18 (0.99, 1.42)	1.39 (1.17, 1.64)	1.36 (1.19, 1.56)	Day 10 / Day1
		60 mg		1	6	MK-1439	1020 (785, 1330)	336 (237, 475)	3.00 (1.00, 4.02)	14.1 (10.9, 18.3)	24	--	--	--	--	--
				10	6	MK-1439	1300 (1000, 1700)	385 (272, 544)	2.00 (1.00, 4.00)	17.3 (13.4, 22.5)	24	12.59 (18.3)	1.27 (1.07, 1.52)	1.15 (0.97, 1.36)	1.23 (1.07, 1.41)	Day 10 / Day1

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (µM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
		120 mg		1	8	MK-1439	1920 (1530, 2420)	671 (497, 906)	2.00 (1.00, 4.00)	27.3 (21.8, 34.2)	24	--	--	--	--	--
				14	7	MK-1439	2520 (1990, 3190)	875 (644, 1190)	4.00 (1.00, 5.00)	36.8 (29.2, 46.3)	24	14.99 (22.9)	1.31 (1.11, 1.54)	1.30 (1.12, 1.52)	1.35 (1.19, 1.53)	Day 14 / Day1
		240 mg		1	6	MK-1439	3240 (2490, 4230)	1060 (751, 1500)	1.50 (1.00, 5.00)	43.8 (33.7, 56.7)	24	--	--	--	--	--
				10	6	MK-1439	4470 (3430, 5830)	1340 (948, 1900)	3.00 (1.00, 5.00)	60.6 (46.7, 78.6)	24	13.35 (15.9)	1.38 (1.16, 1.65)	1.26 (1.07, 1.49)	1.38 (1.21, 1.59)	Day 10 / Day1
		2 mg Midazolam		1	8	Midazolam	9.97 (6.83, 14.6)	--	1.00 (0.50, 1.50)	32.9 (19.4, 55.7)	Inf	3.81 (62.2)	--	--	--	--
		120 mg MK-1439 + 2 mg Midazolam		14	7	Midazolam	10.1 (6.90, 14.9)	--	0.50 (0.33, 0.5)	27.0 (15.9, 45.8)	Inf	3.41 (65.5)	1.02 (0.81, 1.28)	--	0.82 (0.70, 0.97)	MK-1439 + Midazolam / Midazolam
		50 mg Enabled Fasted		1	6	MK-1439	1220 (1000, 1500)	356 (277, 458)	2.00 (1.00, 4,00)	23.2 (17.9, 29.9)	Inf	12.28 (12.1)	0.34 (0.27, 0.41)	0.57 (0.47, 0.69)	0.51 (0.43, 0.61)	50 mg Conventional Fasted / 50 mg Enabled Fasted
		50 mg Conventional Fasted		1	6	MK-1439	412 (337, 504)	203 (158, 262)	3.50 (2.00, 8.00)	11.9 (9.21, 15.4)	Inf	13.97 (9.7)	2.52 (2.05, 3.10)	2.19 (1.81, 2.65)	2.07 (1.75, 2.45)	50 mg Conventional Fed / 50 mg Conventional Fasted
		50 mg Conventional Fed		1	6	MK-1439	1040 (848, 1270)	446 (346, 573)	5.50 (2.00, 10.00)	24.7 (19.1, 31.8)	Inf	13.54 (15.5)	1.64 (1.33, 2.01)	1.39 (1.15, 1.68)	1.74 (1.47, 2.06)	300 mg Conventional Fasted / 50 mg Conventional Fasted
		300 mg Conventional Fasted		1	6	MK-1439	675 (552, 826)	282 (219, 363)	5.00 (2.00, 5.00)	20.7 (16.0, 26.7)	Inf	21.52 (41.2)	--	--	--	--
1439-002	A Study to Evaluate the Effect of Multiple Doses of Ritonavir on	50 mg MK-1439 Alone	Healthy Male Subjects, Aged 18 to 50 yrs	1	8	MK-1439	963 (825, 1120)	322 (266, 390)	3.50 (2.00, 5.00)	20.8 (17.5, 24.6)	Inf	13.97 (10.6)	-	-	-	--
		50 mg MK-		14	8	MK-1439	1260	935	5.00	73.5	Inf	35.16	1.31	2.91	3.54	MK-1439 +

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (μM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
	the Single Dose Pharmacokinetics of MK-1439	1439 SD + 100 mg Ritonavir BID					(1080, 1470)	(772, 1130)	(1.00, 16.00)	(62.0, 87.1)		(12.3)	(1.17, 1.46)	(2.33, 3.62)	(3.04, 4.11)	Ritonavir / MK-1439 Alone
1439-003	A Study to Evaluate the Effect of Multiple Doses of Tenofovir on the Single Dose Pharmacokinetics of MK-1439	100 mg MK-1439	Healthy Male Subjects, Aged 18 to 50 yrs	1	8	MK-1439	1630 (1210, 2190)	584 (463, 738)	2.50 (0.50, 4.98)	35.3 (27.5, 45.3)	Inf	14.42 (24.7)	--	--	--	--
		100 mg MK-1439 SD + 300 mg Tenofovir Disoproxil Fumarate		14	7	MK-1439	1310 (965, 1780)	547 (430, 697)	3.00 (0.98, 7.92)	33.4 (25.9, 43.2)	Inf	15.39 (25.0)	0.80 (0.64, 1.01)	0.94 (0.78, 1.12)	0.95 (0.80, 1.12)	MK-1439 + Tenofovir Disoproxil Fumarate / MK-1439
1439-005	A Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiretroviral Activity of MK-1439 in HIV-1 Infected Patients	25 mg MK-1439 QD	HIV-1 Infected Patients, Aged 18 to 55 yrs	1	6	MK-1439	682 (594, 783)	166 (119, 230)	1.50 (1.00, 2.00)	8.24 (6.85, 9.92)	24	--	--	--	--	--
				7	6	MK-1439	826 (727, 938)	251 (188, 335)	1.00 (1.00, 2.00)	11.2 (9.35, 13.4)	24	32.4 (33.9)	--	--	--	--
		200 mg MK-1439 QD		1	6	MK-1439	2760 (2400, 3170)	964 (694, 1340)	2.00 (1.00, 4.00)	40.1 (33.3, 48.3)	24	--	--	--	--	--
				7	6	MK-1439	4300 (3790, 4890)	1540 (1150, 2060)	2.00 (1.00, 4.00)	62.2 (52.0, 74.4)	24	41.3 (16.5)	--	--	--	--
1439-006	A Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1439	600 mg MK-1439 SD	Healthy Male Subjects, Aged 18 to 50 yrs	1	6	MK-1439	7420 (6380, 8630)	2240 (1900, 2650)	2.50 (0.50, 4.00)	146 (126, 169)	Inf	13.58 (14.1)	--	--	--	--
		800 mg MK-1439 SD		1	6	MK-1439	8180 (7030, 9520)	2570 (2180, 3040)	4.00 (2.00, 5.00)	179 (154, 208)	Inf	16.45 (27.0)	--	--	--	--
		1000 mg MK-1439 SD		1	6	MK-1439	10100 (8670, 11700)	3200 (2710, 3780)	2.00 (0.50, 5.00)	216 (186, 250)	Inf	15.42 (11.0)	--	--	--	--
		1200 mg MK-1439 SD		1	6	MK-1439	10800 (9270, 12600)	3640 (3080, 300)	3.00 (1.00, 5.00)	246 (212, 286)	Inf	18.88 (34.2)	--	--	--	--
		450 mg MK-1439		1	6	MK-1439	5580 (4810,	1940 (1520,	3.00 (1.00,	82.0 (70.2,	24	--	--	--	--	--

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (µM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
		QD					6460)	2470)	4.00)	95.7)						
				7	6	MK-1439	7590 (6550, 8790)	2090 (1640, 2670)	1.50 (1.00, 4.00)	100 (85.7, 117)	24	14.67 (30.5)	1.36 (1.15,1.61)	1.08 (0.95, 1.23)	1.22 (1.13, 1.32)	Day 7/ Day 1
		750 mg MK-1439 QD		1	6	MK-1439	6980 (6020, 8080)	2370 (1850, 3020)	3.00 (1.00, 5.00)	99.1 (84.9, 116)	24	--	--	--	--	--
				10	5	MK-1439	10500 (8910, 12400)	2850 (2220, 3670)	1.00 (0.52, 5.00)	138 (118, 161)	24	20.95 (55.1)	1.50 (1.26, 1.79)	1.21 (1.04, 1.39)	1.39 (1.28, 1.51)	Day 10 / Day 1
1439-008	A Study to Investigate the Absorption, Metabolism, Excretion and Mass Balance of MK-1439	350 mg MK-1439	Healthy Male Subjects, Aged 19 to 55 yrs	1	6	MK-1439	501 (348, 723	347(253, 478)	4.50 (3.00, 12.00)	27.6 (20.8, 36.6)	Inf	22.95 (50.7)	0.78 (0.67,0.90)	0.75 (0.64,0.88)	--	MK-1439/ Total Radioactivity
				1	6	MK-1439	--	--	--	17.0 (12.5, 23.2)	48	--	--	--	0.76 (0.67, 0.88)	MK-1439/ Total Radioactivity
				1	6	Total Radioactivity	646 (448, 931)	463 (337, 636)	3.02 (3.01, 48.01)	22.3 (16.3, 30.3)	48	--	--	--	--	--
1439-009	A Relative Bioavailability Study to Compare the Pharmacokinetics of MK-1439in Male and Female Subjects and Healthy Elderly and Young Adult Subjects	100 mg MK-1439	Healthy Elderly Male Subjects, Aged 65-80 yrs	1	12	MK-1439	1480 (1260, 1740)	482 (387, 600)	3.00 (1.00, 6.00)	32.5 (27.2, 38.9)	Inf	16.5 (39.0)	91.8 (73.0, 116)§	81.2 (59.2, 111.5)§	85.4 (66.5, 110)§	Elderly Male / Young Male¶
		100 mg MK-1439	Healthy Elderly Female Subjects, Aged 65-80 yrs	1	12	MK-1439	2350 (2000, 2750)	509 (409, 634)	3.00 (0.50, 5.00)	40.6 (34.2, 48.1)	Inf	13.9 (29.0)	118 (97.8, 142)§	93.79 (72.41, 121.47)§	96.98 (79.35, 118.52)§	Elderly Female / Young Female
		100 mg MK-1439		1	12	MK-1439	--	--	--	--	--	--	159 (131, 191)§	105 (81.5, 137)§	125 (102, 153)§	Elderly Female / Elderly Male
		100 mg MK-1439	Healthy Young Female Subjects, Aged 18-50 yrs	1	12	MK-1439	1990 (1690, 2330)	543 (436, 676)	2.00 (1.50, 10.00)	41.8 (35.3, 49.6)	Inf	16.5 (41.0)	123 (98.0, 155)§	91.4 (66.6, 125)§	110 (85.9, 140)§	Young Female / Young Male¶

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax[†] (hr)	AUC0-t (μM hr)	t	Apparent terminal t1/2 (hr)[‡]	Cmax	C24	AUC0-t	
		100 mg MK-1439	Healthy Female Subjects, Pooled Elderly and Young	1	24	MK-1439	2160 (1930, 2420)	526 (451, 613)	2.00 (0.50, 10.00)	41.2 (36.6, 46.4)	Inf	15.1 (37.0)	142 (123, 164)[§]	102 (83.6, 124)[§]	120 (103, 140)[§]	Female / Male[¶]
		100 mg MK-1439	Healthy Male Subjects, Pooled Elderly and Young	1	18	MK-1439	1520 (1340, 1740)	517(433 , 618)	2.50 (1.00, 6.00)	34.4 (29.8, 39.6)	Inf	16.0 (42.0)	--	--	--	--
1439-010	A Study to Assess the Effects of Multiple Oral Doses of Ketoconazole on the Single Dose Pharmacokinetics of MK-1439	100 mg MK-1439 SD	Healthy Male and Female Subjects, Aged 19-50 yrs	1	10	MK-1439	1400 (1160, 1690)	430 (383, 482)	2.00 (1.00, 6.00)	29.9 (26.6, 33.6)	Inf	15.23 (28.1)	--	--	--	--
		100 mg MK-1439 SD + 400 mg Ketoconazole QD		1	10	MK-1439	1760 (1460, 2120)	1180 (991, 1400)	3.00 (1.00, 24.00)	91.5 (76.4, 110)	Inf	32.37 (12.5)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)	3.06 (2.85, 3.29)	MK-1439 + Ketoconazole / MK-1439
1439-011	A Study to Assess the Effects of Single and Multiple Doses of Rifampin on the Single Dose Pharmacokinetics of MK-1439	100 mg MK-1439 SD	Healthy Male Subjects, Aged 19-55 yrs	1	11	MK-1439	1540 (1230, 1920)	511 (360, 725)	3.00 (1.00, 6.00)	36.5 (26.7, 49.8)	Inf	18.60 (44.5)	--	--	--	--
		100 mg MK-1439 SD + 600 mg Rifampin SD		1	11	MK-1439	2160 (1890, 2470)	459 (347, 608)	2.00 (1.00, 6.00)	33.1 (28.2, 38.9)	Inf	5.50 (18.9)	1.40 (1.21, 1.63)	0.90 (0.80, 1.01)	0.91 (0.78, 1.06)	MK-1439 + Rifampin / MK-1439
		100 mg MK-1439 SD + 600 mg QD Rifampin		1	10	MK-1439	661 (562, 778)	16.4 (11.6, 23.2)	2.00 (0.50, 3.04)	4.47 (3.87, 5.15)	Inf	6.30 (40.1)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)	0.12 (0.10, 0.15)	MK-1439 + Rifampin / MK-1439
1439-012[††]	A Study to Assess the Effects of Multiple Oral Doses of MK-	0.03 mg Ethinyl Estradiol + 0.15 mg Levonorgest	Healthy Female Subjects, Aged 18-65 yrs	1	20	Ethinyl Estradiol	66.0 (59.1, 73.8)	--	1.50 (1.00, 2.00)	846 (758, 943)	Inf	18.64 (17.5)	--	--	--	--
				1	20	Levonorgestrel	2.57 (2.13,	--	1.27 (1.01,	37.7 (30.8,	Inf	37.66 (31.2)	--	--	--	--

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (µM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
	1439 on the Single Dose Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel; Nordette®-28)	rel (Nordette®-28) SD Alone					3.09)		4.05)	46.2)						
		0.03 mg Ethinyl Estradiol + 0.15 mg Levonorgestrel (Nordette®-28) SD + 100 mg MK-1439 QD		14	19	Ethinyl Estradiol	55.1 (49.3, 61.6)	--	1.50 (1.00, 3.00)	832 (750, 923)	Inf	18.75 (16.6)	0.83 (0.80, 0.87)	--	0.98 (0.94, 1.03)	Nordette®-28 + MK-1439 / Nordette®-28
				14	19	Levonorgestrel	2.47 (2.02, 3.01)	--	1.51 (0.51, 6.00)	45.6 (36.4, 57.1)	Inf	42.96 (34.3)	0.96 (0.88, 1.05)	--	1.21 (1.14, 1.28)	Nordette®-28 + MK-1439/Nordette®-28
1439-016‡‡	A 2-way Steady State Interaction Study of MK-1439 and Dolutegravir	50 mg Dolutegravir QD	Healthy Male and Female Subjects, Aged 18-45 yrs	7	12	Dolutegravir	3070 (2590, 3640)	1010 (844, 1220)	1.50 (0.50, 3.02)	42900 (37000, 49600)	24	--	--	--	--	--
		200 mg MK-1439 QD		7	11	MK-1439	3540 (2900, 4330)	993 (797, 1240)	1.50 (0.52, 3.02)	47600 (40100, 56400)	24	--	--	--	--	--
		200 mg MK-1439 QD + 50 mg Dolutegravir QD		7	11	Dolutegravir	4400 (3810, 5070)	1290 (1010, 1650)	1.50 (1.00, 3.00)	58500 (48600, 70500)	24	--	1.43 (1.20, 1.71)	1.27 (1.06, 1.53)	1.36 (1.15, 1.62)	Dolutegravir + MK-1439 / MK-1439
				7	11	MK-1439	3760 (3080, 4590)	975 (753, 1260)	2.00 (0.50, 3.00)	47600 (39700, 57100)	24	--	1.06 (0.88, 1.28)	0.98 (0.88, 1.09)	1.00 (0.89, 1.12)	
1439-017§§	A Single Dose Trial to Assess the Effect of a supratherapeutic dose of MK-1439 on QTc Interval	1200 mg MK-1439 SD + 400 mg Moxifloxacin	Healthy Male and Female Subjects, Aged 18-55 yrs	1	41	MK-1439	9240 (30.7)	2590 (41.9)	2.40 (54.0)	119 (33.0)	24	--	--	--	--	--
1439-019	A 2-Part, Open-Label, Single-Dose Study to Investigate the Influence of Hepatic	100 mg MK-1439	Male and Female Healthy Matched Control Subjects, Aged 18-75	1	8	MK-1439	2050 (1570, 2680)	847 (662, 1080)	2.50 (1.00, 3.00)	54.6 (42.1, 71.0)	Inf	18.12 (30.5)	--	--	--	--

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (μM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
	Insufficiency on the Pharmacokinetics of MK-1439		yrs													
			Male and Female Subjects with Moderate Hepatic Insufficiency	1	8	MK-1439	1850 (1420, 2420)	842 (658, 1080)	2.00 (1.00, 6.00)	53.9 (41.5, 70.0)	Inf	17.97 (30.8)	0.90 (0.66,1.24)	0.99 (0.74,1.33)	0.99 (0.72,1.35)	Moderate Hepatic Impairment/ Healthy subjects
1439-020	An Open Label, Multiple Dose Study to Investigate the Effect of Switching From Efavirenz Therapy to MK-1439 on the Pharmacokinetics of MK-1439	100 mg MK-1439 QD Day 1	Healthy Male and Female Subjects, Aged 19-55 yrs	1	20	MK-1439	2080 (1810, 2380)	625 (528, 740)	2.00 (1.00, 6.00)	28.0 (24.9, 31.6)	24	--	--	--	--	--
		100 mg MK-1439 QD Day 1 following cessation of 600 mg Efavirenz QD		1	17	MK-1439	1350 (1160, 1570)	93.3 (56.5, 154)	1.50 (0.50, 3.04)	10.7 (9.00, 12.8)	24	--	0.65 (0.58, 0.73)	0.15 (0.10, 0.23)	0.38 (0.33, 0.45)	MK-1439 + Efavirenz/ MK-1439
		100 mg MK-1439 QD Day 5		5	19	MK-1439	2880 (2470, 3360)	902 (730, 1120)	2.00 (0.50, 3.00)	41.1 (35.3, 47.9)	24	--	--	--	--	--
		100 mg MK-1439 QD Day 14 following cessation of 600 mg Efavirenz QD		14	17	MK-1439	2490 (2230, 2780)	449 (331, 610)	1.50 (1.00, 6.00)	28.0 (23.9, 33.0)	24	--	0.86 (0.77, 0.97)	0.50 (0.39, 0.64)	0.68 (0.58, 0.80)	MK-1439 + Efavirenz/ MK-1439
1439-035	A Study to Evaluate the Effect of Multiple Doses of Rifabutin on the Single-Dose Pharmacokinet	100 mg MK-1439 SD	Healthy Male and Female Subjects, Aged 18-65 yrs	1	18	MK-1439	1740 (1560, 1950)	625 (530, 737)	3.00 (1.00, 6.00)	39.5 (34.3 , 45.5)	Inf	15.7 (18.0)	--	--	--	--
		100 mg MK-1439 SD + Rifabutin 300 mg QD		14	12	MK-1439	1730 (1470, 2030)	197 (169, 230)	2.50 (0.50, 4.00)	19.7 (17.7, 21.8)	Inf	9.39 (17.0)	0.99 (0.85, 1.15)	0.32 (0.28, 0.35)	0.50 (0.45, 0.55)	MK-1439 + Rifabutin / MK-1439

Study Number	Brief Description of Study ics of MK-1439	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (µM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
1439-036 ¶¶	A Study to Evaluate the Effect of MK-1439 at Steady State on the Pharmacokinetics of Atorvastatin	20 mg Atorvastatin SD	Healthy Male and Female Subjects, Aged 18-65 yrs	1	16	Atorvastatin	7.87 (5.93, 10.4)	--	0.50 (0.50, 1.00)	39.9 (32.0, 49.8)	Inf	11.06 (28.2)	--	--	--	--
		20 mg Atorvastatin SD + 100 mg MK-1439 QD		5	14	Atorvastatin	5.25 (3.54, 7.78)	--	1.00 (0.50, 6.00)	39.0 (31.2, 48.8)	Inf	10.80 (38.3)	0.67 (0.52, 0.85)	--	0.98 (0.90 , 1.06)	Atorvastatin+ MK-1439 / Atorvastatin
1439-042	A Study to Evaluate the Effect of an Aluminum and Magnesium Containing Antacid and a Proton Pump Inhibitor on the Single-dose Pharmacokinetics of MK-1439	100 mg MK-1439 SD	Healthy Male and Female Subjects, Aged 18-64 yrs	1	14	MK-1439	2130 (1860, 2440)	680 (548, 844)	3.00 (1.00, 4.00)	43.5 (37.4, 50.6)	Inf	14.08 (19.5)	--	--	--	--
		100 mg MK-1439 SD + 20 mL Antacid Oral Suspension SD		1	14	MK-1439	1840 (1480, 2290)	698 (573, 849)	2.50 (1.00, 4.00)	43.9 (36.6, 52.7)	Inf	14.87 (26.5)	0.86 (0.74, 1.01)	1.03 (0.94, 1.12)	1.01 (0.92, 1.11)	MK-1439 + Antacid Oral Suspension/ MK-1439
		100 mg MK-1439 SD + Pantoprazole 40 mg QD		5	13%%%%	MK-1439	1870 (1550, 2260)	572 (465, 703)	2.00 (1.00, 6.00)	36.1 (30.3, 43.1)	Inf	12.94 (17.1)	0.88 (0.76, 1.01)	0.84 (0.77, 0.92)	0.83 (0.76, 0.91)	MK-1439 + Pantoprazole / MK-1439
1439-045†††	A Multiple-Dose Clinical Trial to Study the Effect of MK-1439 on Methadone Pharmacokinetics	20-200 mg Methadone QD	Healthy Male and Female Subjects, Aged 18-65 yrs	1	14	R-Methadone	3.41 (2.89, 4.01)[l]	1.91 (1.56, 2.34)[l]	2.00 (1.00, 6.00)	55.8 (46.4, 67.1)[l]	24	--	--	--	--	--
				1	14	S-Methadone	3.77 (2.95,4.82)[l]	1.51 (1.03, 2.22)[l]	1.99 (1.00, 3.00)	52.0 (38.3, 70.4)[l]	24	--	--	--	--	--
				1	14	Total-Methadone	7.19 (5.86, 8.82)[l]	3.48 (2.65, 4.57)[l]	2.00 (1.00, 6.00)	109 (86.0, 137)[l]	24	--	--	--	--	--
		20-200 mg Methadone QD + 100		6	14	R-Methadone	3.33 (2.83, 3.91)	1.82 (1.45, 2.27)	2.01 (1.02, 4.00)	53.2 (44.6,63.5)	24	--	0.98 (0.93, 1.03)	0.95 (0.88, 1.03)	0.95 (0.90, 1.01)	Methadone + MK-1439 / Methadone

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (μM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
		mg MK-1439 QD		6	14	S-Methadone	3.67 (2.87, 4.68)	1.47 (0.974, 2.21)	2.00 (1.02, 4.00)	50.8 (37.5, 68.8)	24	--	0.97 (0.91, 1.04)	0.97 (0.86, 1.10)	0.98 (0.90, 1.06)	
				6	14	Total-Methadone	7.01 (5.72, 8.60)	3.34 (2.48, 4.51)	2.01 (1.02, 4.00)	105 (82.9, 132)	24	--	0.98 (0.92, 1.03)	0.96 (0.87, 1.05)	0.96 (0.90, 1.03)	
				5	14	MK-1439	2180 (1840, 2580)	710 (570, 886)	3.00 (0.50, 6.00)	30.4 (25.3, 36.2)	24	--	0.76 (0.63, 0.91)	0.80 (0.63, 1.03)	0.74 (0.61, 0.90)	Methadone + MK-1439 / MK-1439‡‡‡
1439-048§§§	A Study to Evaluate the Effect of Multiple Doses of MK-1439 on Metformin Pharmacokinetics	1000 mg Metformin SD Fed	Healthy Male and Female Subjects, Aged 18-55 yrs	1	14	Metformin	1350 (1150, 1570)	--	3.00 (1.00, 4.00)	10300 (8740, 12200)	Inf	13.82 (45.6)	--	--	--	--
		1000 mg Metformin SD Fed + MK-1439 100 mg QD		5	14	Metformin	1270 (1130, 1420)	--	2.50 (1.50, 4.02)	9660 (8290, 11300)	Inf	12.53 (48.8)	0.94 (0.86, 1.03)	--	0.94 (0.88, 1.00)	Metformin + MK-1439 / Metformin
1439-050	Drug-Drug Interaction Study of MK-1439 with MK-8742 + MK-5172 (Elbasvir + Grazoprevir)	100 mg MK-1439 QD	Healthy Male and Female Subjects, Aged 19-55 yrs	5	12	MK-1439	3400 (2950, 3910)	814 (657, 1010)	3.98 (3.00, 4.00)	41.3 (35.5, 48.1)	24	--	--	--	--	--
		50 mg Elbasvir QD + 200 mg Grazoprevir QD		10	12	Elbasvir	298 (238, 373)	110 (88.8, 136)	4.00 (2.98, 5.00)	3.89 (3.24, 4.67)	24	--	--	--	--	--
				10	12	Grazoprevir	1800 (1090, 2950)	19.5 (14.2, 26.8)	3.00 (2.00, 4.00)	5.64 (3.68, 8.66)	24	--	--	--	--	--
		100 mg MK-1439 QD + 50 mg Elbasvir QD + 200 mg Grazoprevir QD		5	12	MK-1439	4770 (4080, 5590)	1310 (1020, 1690)	3.99 (2.98, 6.00)	64.6 (54.1, 77.3)	24	--	1.41 (1.25, 1.58)	1.61 (1.45, 1.79)	1.56 (1.45, 1.68)	MK-1439 + Elbasvir + Grazoprevir / MK-1439
				5	12	Elbasvir	287 (222, 370)	106 (81.2, 138)	4.00 (3.00, 5.00)	3.73 (3.00, 4.63)	24	--	0.96 (0.91, 1.01)	0.96 (0.89, 1.04)	0.96 (0.90, 1.02)	MK-1439 + Elbasvir + Grazoprevir / Elbasvir + Grazoprevir
				5	12	Grazoprevir	2190 (1400, 3410)	17.5 (12.9, 23.8)	3.00 (1.98, 4.00)	6.05 (4.12, 8.87)	24	--	1.22 (1.01, 1.47)	0.90 (0.83, 0.96)	1.07 (0.94, 1.23)	MK-1439 + Elbasvir + Grazoprevir / Elbasvir +

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax† (hr)	AUC0-t (μM hr)	t	Apparent terminal t1/2 (hr)‡	Cmax	C24	AUC0-t	
																Grazoprevir
1439-051	An Open Label, Single Dose Study to Evaluate the Pharmacokinetics of MK-1439 in Subjects With Severe Renal Impairment	100 mg MK-1439	Healthy Matched Control Subjects, Aged 18 -75 yrs	1	8	MK-1439	1900 (1450, 2500)	684 (515, 908)	1.50 (0.50, 6.00)	45.1 (33.2, 61.4)	Inf	16.69 (26.1)	--	--	--	--
			Severe Renal Impairment Subjects, Aged 18-75 yrs	1	8	MK-1439	1580 (1210, 2080)	943 (710, 1250)	2.00 (0.50, 4.00)	64.5 (47.4, 87.8)	Inf	25.02 (36.4)	0.83 (0.61, 1.15)	1.38 (0.99, 1.92)	1.43 (1.00, 2.04)	Severe Renal Impairment / Healthy Matched Control
1439-053[III]	A Randomized, Open-Label, 3-Period Crossover Study to Evaluate the Pharmacokinetic Interaction of MK-1439 and Ledipasvir/Sofosbuvir in Healthy Adult Subjects	100 mg MK-1439 SD	Healthy Male and Female Subjects, Aged 19-64 yrs	1	14	MK-1439	1670 (1400, 1990)	550 (438, 690)	4.00 (1.00, 6.00)	36.3 (30.2, 43.7)	Inf	14.25 (25.6)	--	--	--	
		90 mg Ledipasvir SD + 400 mg Sofosbuvir SD		1	14	Ledipasvir	248 (182, 339)	--	5.00 (5.00, 8.00)	8080 (6060, 10800)	Inf	41.96 (31.9)	--	--	--	
				1	14	Sofosbuvir	1190 (949, 1500)	--	0.50 (0.50, 2.50)	1130 (886, 1440)	Inf	0.49 (51.1)	--	--	--	--
				1	14	GS-331007	981 (866, 1110)	--	2.76 (1.00, 4.03)	15800 (13900, 18000)	Inf	27.67 (18.8)	--	--	--	--
		90 mg Ledipasvir SD + 400 mg Sofosbuvir SD + 100 mg MK-1439 SD		1	14	MK-1439	1850 (1550, 2210)	682 (568, 818)	3.00 (0.50, 6.00)	41.8 (36.2, 48.3)	Inf	13.63 (26.8)	1.11 (0.97, 1.27)	1.24 (1.13, 1.36)	1.15 (1.07, 1.24)	Ledipasvir + Sofosbuvir + MK-1439/ MK-1439
				1	14	Ledipasvir	225 (165, 308)	--	5.00 (5.00, 6.01)	7450 (5470, 10100)	Inf	41.59 (24.9)	0.91 (0.80, 1.02)	--	0.92 (0.80, 1.06)	Ledipasvir + Sofosbuvir + MK-1439 / Ledipasvir + Sofosbuvir

Study Number	Brief Description of Study	Dose (mg)	Population	Day	N	Analyte	GM (95% CI)						GMR (90% CI)			Test/Ref
							Cmax (nM)	C24 (nM)	Tmax[†] (hr)	AUC0-t (μM hr)	t	Apparent terminal t1/2 (hr)[‡]	Cmax	C24	AUC0-t	
				1	14	Sofosbuvir	1060 (829, 1350)	--	0.67 (0.51, 2.50)	1170 (949, 1440)	Inf	0.49 (35.9)	0.89 (0.79, 1.00)	--	1.04 (0.91, 1.18)	Ledipasvir + Sofosbuvir + MK-1439 / Ledipasvir + Sofosbuvir
				1	14	GS-331007	1010 (877, 1160)	--	2.75 (1.01, 5.00)	16400 (14400, 18600)	Inf	27.4 (15.6)	1.03 (0.97, 1.09)	--	1.03 (0.98, 1.09)	Ledipasvir + Sofosbuvir + MK-1439 / Ledipasvir + Sofosbuvir

GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval; SD = Single Dose; QD = Once Daily
[†]Tmax: median (range).
[‡]Geometric mean and percent geometric CV reported for apparent t1/2.
[§] GMR is expressed as %
[¶]Young male data obtained from P001 (N=6)
[††]Ethinyl estradiol, AUCs and Cmax were reported in (pg•hr/mL) and (pg/mL) units respectively and for levonorgestrel, AUCs and Cmax were reported in (ng•hr/mL) and ng/mL units respectively.
[‡‡] Dolutegravir, AUCs and Cmax were reported in (ng•hr/mL) and (ng/mL) units respectively
[§§]Geometric mean and percent geometric CV reported for all Pharmacokinetic parameters except Tmax
[¶¶]Atorvastatin, AUCs and Cmax were reported as (ng.hr/mL) and ng/mL) units respectively.
[†††] Methadone AUC, Cmax, and C24 were dose normalized and reported as (ng*hr/mL/mg), (ng/mL/mg) and (ng/mL/mg) respectively.
[‡‡‡]MK-1439 Alone data obtained from 100 mg MK-1439 QD Day 5 from P020
[§§§]Metformin, AUCs and Cmax were reported as (ng.hr/mL) and ng/mL) units respectively.
[|||]Ledipasvir, sofosbuvir and GS-331007 (metabolite of sofosbuvir), AUCs and Cmax were reported as (ng*hr/mL) and (ng/mL) respectively.

Appendix 2.7.2: 3 Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)		
				AUC*	C_{max}	C_{24}
Azole Antifungal Agents						
ketoconazole	400 mg QD	100 mg SD	10	3.06 (2.85, 3.29)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)
Antimycobacterials						
rifampin	600 mg SD	100 mg SD	11	0.91 (0.78, 1.06)	1.40 (1.21, 1.63)	0.90 (0.80, 1.01)
	600 mg QD	100 mg SD	10	0.12 (0.10, 0.15)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)
rifabutin	300 mg QD	100 mg SD	12	0.50 (0.45, 0.55)	0.99 (0.85, 1.15)	0.32 (0.28, 0.35)
HIV Antiviral Agents						
ritonavir	100 mg BID	50 mg SD	8	3.54 (3.04, 4.11)	1.31 (1.17, 1.46)	2.91 (2.33, 3.62)
dolutegravir	50 mg QD	200 mg QD	11	1.00 (0.89, 1.12)	1.06 (0.88, 1.28)	0.98 (0.88, 1.09)
efavirenz†	600 mg QD	100 mg QD Day 1	17	0.38 (0.33, 0.45)	0.65 (0.58, 0.73)	0.15 (0.10, 0.23)
	600 mg QD	100 mg QD Steady State	17	0.68 (0.58, 0.80)	0.86 (0.77, 0.97)	0.50 (0.39, 0.64)
tenofovir DF	300 mg QD	100 mg SD	7	0.95 (0.80,1.12)	0.80 (0.64,1.01)	0.94 (0.78, 1.12)
lamivudine + tenofovir DF	300 mg lamivudine SD + 300 mg tenofovir DF SD	100 mg SD	15	0.96 (0.87, 1.06)	0.97 (0.88, 1.07)	0.94 (0.83, 1.06)
Hepatitis C Antiviral Agents						
elbasvir + grazoprevir	50 mg elbasvir QD + 200 mg grazoprevir QD	100 mg QD	12	1.56 (1.45, 1.68)	1.41 (1.25, 1.58)	1.61 (1.45, 1.79)
ledipasvir + sofosbuvir	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	1.15 (1.07, 1.24)	1.11 (0.97, 1.27)	1.24 (1.13, 1.36)
Acid-Reducing Agents						
antacid (aluminum and magnesium hydroxide oral suspension)	20 mL SD	100 mg SD	14	1.01 (0.92, 1.11)	0.86 (0.74, 1.01)	1.03 (0.94, 1.12)
pantoprazole	40 mg QD	100 mg SD	13	0.83 (0.76, 0.91)	0.88 (0.76, 1.01)	0.84 (0.77, 0.92)
Opioid Analgesics						
methadone	20-200 mg QD individualized dose	100 mg QD	14	0.74 (0.61, 0.90)	0.76 (0.63, 0.91)	0.80 (0.63, 1.03)

CI = Confidence interval; SD = Single Dose; QD = Once Daily; BID = Twice Daily

*AUC0-inf for single-dose, AUC0-24 for once daily.

†Interaction was assessed following the cessation of efavirenz therapy.

Appendix 2.7.2: 4 Changes in Pharmacokinetic Parameter Values for Co-administered Drugs in the Presence of Doravirine

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio [90% CI] Drug Pharmacokinetics with/without Co-administered Doravirine (No Effect=1.00)		
				AUC*	C_{max}	C_{24}
CYP3A Substrate						
midazolam	2 mg SD	120 mg QD	7	0.82 (0.70, 0.97)	1.02 (0.81, 1.28)	-
HIV Antiviral Agents						
dolutegravir	50 mg QD	200 mg QD	11	1.36 (1.15, 1.62)	1.43 (1.20, 1.71)	1.27 (1.06, 1.53)
lamivudine	300 mg lamivudine SD + 300 mg tenofovir DF SD	100 mg SD	15	0.94 (0.88, 1.00)	0.92 (0.81, 1.05)	-
tenofovir DF	300 mg lamivudine SD + 300 mg tenofovir DF SD	100 mg SD	15	1.11 (0.97, 1.28)	1.17 (0.96, 1.42)	-
Hepatitis C Antiviral Agents						
elbasvir	50 mg elbasvir QD + 200 mg grazoprevir QD	100 mg QD	12	0.96 (0.90, 1.02)	0.96 (0.91, 1.01)	0.96 (0.89, 1.04)
grazoprevir	50 mg elbasvir QD + 200 mg grazoprevir QD	100 mg QD	12	1.07 (0.94, 1.23)	1.22 (1.01, 1.47)	0.90 (0.83, 0.96)
ledipasvir	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	0.92 (0.80, 1.06)	0.91 (0.80, 1.02)	--
sofosbuvir	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	1.04 (0.91, 1.18)	0.89 (0.79, 1.00)	--
GS-331007	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	1.03 (0.98, 1.09)	1.03 (0.97, 1.09)	--
Oral Contraceptives						
ethinyl estradiol	0.03 mg ethinyl estradiol + 0.15 mg levonorgestrel (Nordette®-28) SD	100 mg QD	19	0.98 (0.94, 1.03)	0.83 (0.80, 0.87)	--
levonorgestrel	0.03 mg ethinyl estradiol + 0.15 mg levonorgestrel (Nordette®-28) SD	100 mg QD	19	1.21 (1.14, 1.28)	0.96 (0.88, 1.05)	--
Statins						
atorvastatin	20 mg SD	100 mg QD	14	0.98 (0.90, 1.06)	0.67 (0.52, 0.85)	-
Antidiabetics						
metformin	1000 mg SD	100 mg QD	14	0.94 (0.88 , 1.00)	0.94 (0.86 , 1.03)	-
Opioid Analgesics						
methadone (R-methadone)	20-200 mg QD individualized dose	100 mg QD	14	0.95 (0.90, 1.01)	0.98 (0.93, 1.03)	0.95 (0.88, 1.03)
methadone (S-methadone)	20-200 mg QD individualized dose	100 mg QD	14	0.98 (0.90, 1.06)	0.97 (0.91, 1.04)	0.97 (0.86, 1.10)

CI = Confidence interval; SD = Single Dose; QD = Once Daily.
*AUC0-inf for single-dose, AUC0-24 for once daily.

Appendix 2.7.2: 5 Doravirine Population Pharmacokinetic Parameter Values and Covariate Effects

PK Parameter		Covariate Value	Estimate	Change from Typical (%)	Interindividual Variability (%)
Typical ka (1/hr)			1.40	--	--
Typical CL/F (L/hr) (34 year old, 75 kg, HIV-1 Infected subject)			6.34	--	35.2
Age	5th Percentile	21 years	6.76	6.6	--
	95th Percentile	59 years	5.53	-13	--
Typical Vc/F (L) (34 year old, 75 kg, HIV-1 Infected subject)			162	--	32.6
Weight	5th Percentile	54 kg	135	-17	--
	95th Percentile	103 kg	198	22	--
Healthy vs HIV-1 Infected		Healthy	126	-22	--
Typical Relative Bioavailability F1 30 – 120 mg			1 (Fixed)	--	--
Typical Relative Bioavailability F1 < 30 mg			1.20	--	--
Typical Relative Bioavailability F1 > 120 mg			0.895	--	--
Residual Error (Log Additive), Standard Deviation					
Phase 1 ≤ 0.5 hr			0.224	--	--
Phase 1 > 0.5 hr			1.25	--	--
Phase 2b			0.521	--	--

Data Source: [Ref. 5.3.5.3: 04PPZ5]

Appendix 2.7.2: 6 Covariate Effects on Steady State DOR Pharmacokinetics in HIV-1 Infected Subjects Following Administration of 100 mg QD Based on Population PK Analysis

Covariate	Comparison	AUC0-24 GMR (90% CI)	C24 GMR (90% CI)	Cmax GMR (90% CI)
Body weight	< 64.5 kg / 64.5 – < 83 kg	1.00 (0.95, 1.04)	0.93 (0.84, 1.03)	1.03 (0.98, 1.08)
	≥ 83 kg / 64.5 – < 83 kg	1.01 (0.96, 1.05)	1.08 (0.98, 1.20)	0.97 (0.92, 1.02)
BMI	Underweight / Normal	0.91 (0.82, 1.01)	0.66 (0.52, 0.84)	0.96 (0.85, 1.08)
	Overweight / Normal	1.06 (1.01, 1.10)	1.13 (1.02, 1.24)	1.00 (0.95, 1.05)
	Obese / Normal	1.08 (1.02, 1.15)	1.20 (1.05, 1.37)	1.06 (0.99, 1.14)
Gender	Female / Male (popPK)	1.05 (1.02, 1.08)	1.03 (0.97, 1.09)	1.05 (1.02, 1.08)
	Female / Male (Phase 1 Single Dose, n = 24 female, n = 18 male)	1.20 (1.03, 1.40)[a]	1.02 (0.84, 1.24)	1.42 (1.23, 1.64)
Age	Elderly (≥ 65)/ Non-Elderly (< 65) (popPK)	1.30 (1.04, 1.63)	1.63 (0.98, 2.70)	1.12 (0.87, 1.44)
	Elderly men / Young men (Phase 1 Single Dose, n = 12 elderly, n = 6 non-elderly)	0.85 (0.67, 1.10)[a]	0.81 (0.59, 1.11)	0.92 (0.73, 1.16)
	Elderly women/ non-Elderly women (Phase 1 Single Dose, n = 12 elderly, n = 12 non-elderly)	0.97 (0.79, 1.19)[a]	0.94 (0.72, 1.21)	1.18 (0.98, 1.42)
Race	Black or African American / White	1.04 (1.01, 1.06)	1.03 (0.98, 1.10)	1.03 (1.00, 1.06)
	Asian / White	1.00 (0.98, 1.03)	0.96 (0.90, 1.01)	1.02 (0.99, 1.05)
	Other / White	1.00 (0.97, 1.03)	1.00 (0.94, 1.06)	1.01 (0.98, 1.04)
Ethnicity	Hispanic / non-Hispanic	0.95 (0.93, 0.98)	0.94 (0.89, 1.00)	0.97 (0.94, 0.99)
Renal Impairment	Mild RI / Normal (popPK)	1.05 (1.00, 1.10)	1.03 (0.93, 1.15)	1.03 (0.98, 1.09)
	Moderate RI / Normal (popPK)	1.20 (0.94, 1.53)	1.69 (0.97, 2.94)	0.99 (0.76, 1.30)
	Severe RI / Normal (Phase 1 Single Dose, n = 8 RI, n = 8 normal)	1.43 (1.00-2.04)[a]	1.38 (0.99, 1.92)	0.83 (0.61, 1.15)
Hepatic Impairment	Hepatic Impaired / No Hepatic Impairment (Phase 1 Single Dose, n = 8 HI, n = 8 no HI)	0.99 (0.72, 1.35)[a]	0.99 (0.74, 1.33)	0.90 (0.66, 1.24)
[a]AUC0-inf				

Data Source: [Ref. 5.3.5.3: 04PPZ5]