CTD 第 2 部

2.6　非臨床試験の概要文及び概要表

2.6.1　緒言

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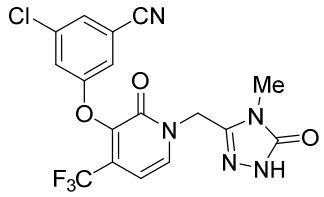
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1 INTRODUCTION

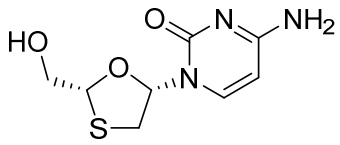
Doravirine (also referred to as DOR or MK-1439) is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) with chemical name 3-Chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl]oxy]benzonitrile. DOR/3TC/TDF (MK-1439A) is a fixed-dose combination (FDC) product containing doravirine (DOR) (100 mg), lamivudine (3TC) (300 mg) and tenofovir disoproxil fumarate (TDF) (300 mg). Lamivudine and TDF are both approved by FDA, EMA, and other health authorities for use in combination with other antiretroviral therapies for the treatment of HIV-1 infection. Lamivudine is an HIV-1 nucleoside analog reverse transcriptase inhibitor (NRTI) with chemical name (2R-cis)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. Tenofovir disoproxil fumarate is an HIV-1 nucleotide reverse transcriptase inhibitor prodrug with chemical name 9-[(R)-2-[[bis(isopropoxycarbonyl)oxy]methoxy] phosphinyl] methoxy]propyl]adenine fumarate (1:1). The chemical structures of DOR, 3TC, and TDF are shown below in [Figure 2.6.1: 1] through [Figure 2.6.1: 3].

Figure 2.6.1: 1 Chemical Structure of Doravirine



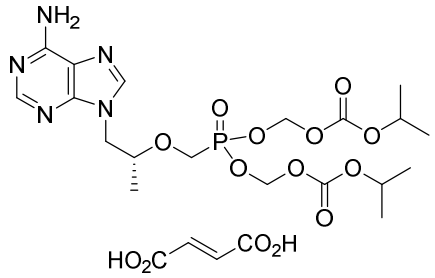
Molecular Formula: $C_{17}H_{11}ClF_3N_5O_3$

Figure 2.6.1: 2 Chemical Structure of Lamivudine



Molecular Formula: $C_8H_{11}N_3O_3S$

Figure 2.6.1: 3 Chemical Structure of Tenofovir Disoproxil Fumarate



Molecular Formula: $C_{19}H_{30}N_5O_{10}\ P \cdot C_4H_4O_4$

DOR is a potent NNRTI that exhibits a superior resistance profile compared to most widely used NNRTI, efavirenz, when tested against a broad array of clinically relevant NNRTI resistant viruses (>90 mutant viruses) in antiviral assays. In addition, non-B subtype viruses are also highly susceptible to DOR with EC_{50}s similar to that obtained with subtype B viruses. The antiviral activity of DOR versus WT virus (EC_{50}=12 nM) is more potent than many agents currently licensed for the treatment of HIV-1 infection, such as efavirenz EC_{50} of 30 nM.

Data from the nonclinical pharmacology, pharmacokinetic, and safety assessment evaluation, as well as the results of the clinical assessment, indicate that DOR has the efficacy and safety profile to fulfill a significant and growing medical need in HIV-1 treatment. DOR is a potent next generation NNRTI for the treatment of HIV-1 in treatment-naive adult patients, developed as a single entity to be part of anti-retroviral therapy or as part of a fixed dose combination (FDC) tablet with two nucleoside reverse transcriptase inhibitors, lamivudine and tenofovir disoproxil fumarate. The FDC is targeted for use as a complete regimen for the treatment of HIV-1 infection and offers advantages of both compliance and ease of use administration.

CTD 第 2 部

2.6　非臨床試験の概要文及び概要表

2.6.2　薬理試験の概要文

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LIST OF ABBREVIATIONS, ACRONYMS AND DEFINITION OF TERMS

Abbreviation/Acronym	Definition
3TC	Lamivudine
5-HT2B	5-hydroxytryptamine (serotonin) receptor 2B
AUC	Area Under the Curve
$AUC_{0\text{-}24\ hr}$	Area Under the Curve (0 to 24 hours)
CC_{50}	Cytotoxicity Concentration at 50% of Cell Viability
CHO	Chinese Hamster Ovary
CNS	Central Nervous System
C_{max}	Observed Maximum Concentration
DNA	Deoxyribonucleic Acid
DOR	Doravirine
EC_{50}	Concentration at which 50% Maximal Effect is Achieved
EC_{95}	Concentration at which 95% Maximal Effect is Achieved
ECG	Electrocardiogram
EFV	Efavirenz
ETR	Etravirine
EU	European Union
F	Female
FC	Fold Change
FBS	Fetal Bovine Serum
FOB	Functional Observational Battery
GLP	Good Laboratory Practice
hr	Hour
hERG	Human Ether-à go-go Related Gene
HIV-1	Human Immunodeficiency Virus Type 1
IC_{20}	Concentration at which 20% Inhibition is Achieved
IC_{50}	Concentration at which 50% Inhibition is Achieved
ICH	International Council on Harmonisation
M	Male
MOI	Multiplicity of Infection

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Abbreviation/Acronym	Definition
NHS	Normal Human Serum
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NOEL	No-Observed-Effect Level
RNA	Ribonucleic Acid
RPV	Rilpivirine
RT	Reverse Transcriptase
SC	Subcutaneous
SD	Standard Deviation
SW	Study Week
TDF	Tenofovir Disoproxil Fumarate
T_{max}	Time to Reach C_{max}

1 BRIEF SUMMARY

Doravirine (also referred to as DOR or MK-1439) is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). DOR displayed potent activity against wild-type (WT) virus and prevalent K103N and Y181C NNRTI mutants with EC_{50} values of 12 nM, 21 nM, and 31 nM respectively, in the presence of 100% serum. Because of its potential to offer important advantages over currently marketed NNRTIs, including safety, tolerability, activity against prevalent NNRTI-resistant mutants, limited drug-drug interactions and convenience of use, DOR was developed as a single entity to be co-administered with other anti-HIV agents and as part of a fixed dose combination (FDC) tablet. The FDC consists of DOR and two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), lamivudine (also referred to as 3TC) and tenofovir disoproxil fumarate (also referred to as TDF) for use as a complete regimen. The recommended human dose of DOR is 100 mg, as a single entity and in the FDC tablet: DOR (100 mg)/3TC (300 mg)/TDF (300 mg), for the treatment of HIV-1 infection in treatment-naive adult patients. Nonclinical exposure margin comparison of DOR to humans were based on population pharmacokinetics analysis from Phase 3 trials (P018 and 021), where a 100 mg QD DOR clinical dose resulted in a systemic geometric mean $AUC_{0\text{-}24hr}$ exposure of 37.8 µM•hr and a C_{max} of 2.26 µM. Nonclinical comparisons for 3TC and TDF are based on information from the US Prescribing Information and the EU Marketing Authorization of the respective marketed agents.

1.1 Doravirine

DOR is a pyridinone non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). DOR binds to a hydrophobic pocket in the p66 subunit of p66/p51 heterodimer near the polymerase active site. X-ray crystal structures of DOR with RT show that the compound binds to the classic NNRTI binding pocket. DOR displayed potent activity in the presence of 100% serum against wild-type (WT) virus and K103N and Y181C prevalent NNRTI mutants with EC_{50} values of 12 nM, 21 nM, and 31 nM, respectively. DOR potently inhibited 10 different subtype viruses with comparable EC_{50}s in the range from 1.2 nM to 10 nM. In the *in vitro* resistance selection studies, DOR displayed unique mutation development pathways where virus containing V106A substitution was the major mutant selected in the study, whereas E138K and L100I (followed by K103N) mutants represented the major viruses selected by RPV and EFV, respectively. In a two-drug combination study, DOR did not display antagonism with any of 18 licensed antiviral agents tested, including 3TC and TDF.

The cytotoxicity of DOR was evaluated with a number of different cell types, with CC_{50} >100 µM. No relevant off-target activities were observed with DOR or its major metabolite M9 when tested in biochemical assays against a broad panel of 110 enzymes and receptors, and human DNA polymerases (α, β, and γ). DOR was devoid of any effects of concern when evaluated for its potential effects on cardiovascular, neurological, and respiratory function in several in vivo and in vitro experimental nonclinical safety pharmacology models, consistent with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S7A and S7B guidances.

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1.2 Lamivudine, Tenofovir Disoproxil Fumarate

No pharmacology studies were conducted with 3TC and/or TDF by the Sponsor, with the exception of the evaluation of DOR antiviral activity in two-drug combination studies. An assessment of the nonclinical pharmacology profile of 3TC and TDF, as individual agents, was conducted using prescribing information, the scientific literature, and regulatory review documents available in the public domain to identify potential for synergistic adverse pharmacology. No significant concern regarding off-target effects or potential for synergistic or additive effects on cardiovascular, respiratory, or neurologic function was identified concerning DOR, 3TC and TDF co-administration.

1.2.1 Lamivudine (3TC)

For supporting nonclinical pharmacology data for 3TC assessed using ICH-compliant safety pharmacology studies, the Sponsor refers to EPIVIR US Prescribing Information [Ref. 4.3: 04P95N], the New Drug Application (NDA) 20-564 [Ref. 4.3: 03TKG7], and the EU Summary of Product Characteristics for EPIVIR [Ref. 4.3: 04664N].

Regulatory reviews reported that safety pharmacology studies with 3TC showed no effects of concern on cardiovascular, neurologic, or respiratory parameters, or on intestinal transport.

1.2.2 Tenofovir Disoproxil Fumarate (TDF)

For supporting nonclinical pharmacology data for TDF assessed using ICH-compliant safety pharmacology studies, the Sponsor refers to VIREAD US Prescribing Information [Ref. 4.3: 04P95P], the NDA 21-356 [Ref. 4.3: 0438FY] and the EU Summary of Product Characteristics for Viread [Ref. 4.3: 04N7D7].

As described in regulatory reviews, TDF did not reveal any effects of concern on the cardiovascular, respiratory, or neurological parameters. Consistent with the histomorphological adverse changes noted in the kidney in the repeat-dose rat toxicity studies with TDF, there was evidence of TDF-related effects on kidney function in a renal safety pharmacology study in rats at a dose of 500 mg/kg, but not at a dose of 50 mg/kg.

1.2.3 DOR/3TC/TDF Combination

Nonclinical testing of the combination of DOR, 3TC, and TDF has not been performed, with the exception of the evaluation of DOR antiviral activity in two-drug combination studies.

As reviewed below, DOR when evaluated for its potential effects on cardiovascular, neurological, and respiratory function in several in vitro or in vivo safety pharmacology models was without significant effects at systemic exposures exceeding those observed in humans at the clinical 100 mg dose.

In accordance with ICH M3(R2) guidance, combination safety pharmacology studies generally are not recommended to support clinical trials or registration if the individual agents have been tested according to current standards. In addition, no concern for potential

for additive or synergistic toxic effects was identified in the nonclinical safety programs of DOR, 3TC and TDF. All therapeutic agents target the non-mammalian HIV-1 reverse transcriptase enzyme with specificity, minimizing the potential for off-target activity. The approved marketed agents, TDF and 3TC, have been clinically used in combination with a large number of HIV antivirals for greater than 15 years (TDF) and greater than 22 years (3TC) with acceptable safety profiles. In addition, clinical experience with the DOR/3TC/TDF combination has not exhibited evidence of safety concern when DOR is added to the 3TC/TDF regimen.

2 PRIMARY PHARMACODYNAMICS

2.1 Primary Pharmacodynamics In Vitro

2.1.1 DOR Inhibition of HIV-1 Reverse Transcriptase Enzyme Activity in Vitro

Non-nucleoside reverse transcriptase inhibitors are allosteric inhibitors that bind to a site approximately 10 Å (angstrom) away from the polymerase active site. Upon binding to the NNRTI site, RT undergoes conformational changes including the displacement of a polymerase primer grip (β12-β13-β14 sheet) and alteration of active site geometry leading to the blockade of the chemical step of the polymerization reaction.

X-ray crystal structures of DOR with RT show that the compound binds to the classic NNRTI binding pocket. Biochemical assays were employed to measure potencies against purified recombinant WT RT and mutant RT with either K103N or Y181C substitution. DOR inhibited RNA-dependent DNA synthesis with IC_{50}s of 12.2 ± 2.0 nM (n=3), 9.7 ± 1.4 nM (n=3), and 9.7 ± 0.9 nM (n=3) against WT, K103N, and Y181C RTs, respectively (PD001) [Sec. 2.6.3.1].

2.1.2 Primary Pharmacodynamics Cell Culture Studies

2.1.2.1 DOR Antiviral Activity vs. WT and Mutant HIV-1 Laboratory Isolates

The RT mutations with K103N and Y181C substitutions account for much of the NNRTI resistance detected in patients who fail antiretroviral regimens, including first-generation NNRTIs, and these mutations can sometimes be found in circulating HIV-1. Therefore, DOR was tested in cell culture HIV-1 replication assays using a transformed human cell line and laboratory HIV-1 isolates including WT as well as the K103N and Y181C mutants. Since binding to serum proteins can reduce the efficacy of antiviral agents, the inhibitory potency of DOR was evaluated in the presence of 10% or 50% normal human serum (NHS) to determine the magnitude of the serum effect (PD002) [Sec. 2.6.3.1]. Marketed NNRTIs exhibit >99% plasma protein binding as compared to DOR, which has only 76% plasma protein binding. To mimic in vivo conditions more closely, the potency of DOR was also evaluated in the presence of 100% NHS (PD002) [Sec. 2.6.3.1]. The data obtained from 100% NHS are used as in vitro potency for DOR in the application.

A laboratory HIV-1 isolate (R8) in the MT4 human T-lymphoid cell line was employed to test the antiviral activity of DOR in the presence of 10% or 50% serum. The assay is a

multiple-cycle replication assay in which infections are initiated at a low multiplicity-of-infection (MOI) where the virus is allowed to spread through cells in culture over a period of 3 days. The extent of replication is quantified by measuring the amount of the major HIV-1 capsid antigen, p24, in culture supernatants using a commercial AlphaScreen assay, and EC_{95}s were reported for the results from this assay (PD002) [Sec. 2.6.3.1]. MT4-GFP reporter cells were used to monitor the level of infection for the assay in the presence of 100% serum. Infected cells were quantified at two time points, approximately 48hr and approximately 72hr post-infection, by counting the number of green cells in each well using an Acumen eX3 scanner. The ratio of the number of green cells between 48hr and 72hr was employed to determine the EC_{50}s (PD002) [Sec. 2.6.3.1].

In HIV-1 replication assays using MT4 cells infected in the presence of 10% NHS, DOR had an EC_{95} of 11.0 ± 2.6 nM (n=11) against WT virus and EC_{95}s of 13.4 ± 3.3 nM (n=11), 16.4 ± 3.2 nM (n=9), and 30.5 ± 3.0 nM (n=8) against K103N, Y181C, and K103N/Y181C mutant viruses, respectively [Table 2.6.2: 1] (A). These results indicated that DOR displayed less than 2-fold shift in potency against the two most prevalent mutants (K103N and Y181C). Under the same conditions, both etravirine (ETR) and rilpivirine (RPV) did not show any shift in potency versus K103N virus in comparison to WT virus [Table 2.6.2: 1] (A). However, ETR displayed more than 5- and 11-fold shift in potency in inhibiting the replication of Y181C and K103N/Y181C mutant viruses, respectively. Rilpivirine exhibited lower level of potency shift with 2- and 6-fold against the two mutant viruses, respectively. K103N mutant virus conferred greater than 40-fold of resistance to efavirenz (EFV), yet EFV had less than a 2-fold shift in potency with Y181C mutant virus (Lai M, 2014, [Ref. 4.3: 04LP04]).

In the presence of 50% serum, DOR displayed an EC_{95}s of 20 ± 6.7 nM (n=9), 43 ± 7.8 (n=7), 27 ± 14.2 (n=5), and 55 ± 13.9 nM (n=7) against WT virus as well as K103N, Y181C, and K103N/Y181C mutant viruses, respectively. As shown in [Table 2.6.2: 1] (B), all four NNRTIs showed that the fold-changes with mutant viruses relative to WT virus were similar to what was observed in the presence of 10% serum (Lai M, 2014, [Ref. 4.3: 04LP04]).

With respect to the effect of serum, DOR had a 2- to 3-fold shift in potency against WT and the three variants when the serum level increased from 10% to 50%. In contrast, serum content exhibited a larger impact on the potency of EFV and ETR with 6- to 10-fold and 7- to 12-fold increases in EC_{95}, respectively as the serum increased from 10% to 50%. Among the four NNRTIs, RPV displayed the biggest shift in potency (18- to 31-fold) when the serum increased from 10% to 50%.

Consistent with the results in 10% serum, viruses containing K103N mutation displayed significant resistance to EFV when tested in the presence of 50% serum. As shown in [Table 2.6.2: 1] (B), K103N and K103N/Y181C mutant viruses conferred greater than 30-fold resistance to EFV compared to WT virus. As a result, DOR was 34- and 54-fold more potent than EFV against K103N and K103N/Y181C mutants, respectively, and was only 2- to 3-fold more potent than EFV against WT and Y181C viruses under the same conditions. In comparison to ETR and RPV, DOR displayed approximately 2-fold better potency versus WT virus, and had a comparable potency against K103N mutant. DOR was 9- and 4-fold

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more potent than ETR and RPV in suppressing Y181C viruses, respectively. The K103N/Y181C mutant virus was 10- and 6-fold less susceptible to ETR and RPV compared to DOR, respectively (Lai M, 2014, [Ref. 4.3: 04LP04]).

Laboratory strains of HIV-1 harboring the common NNRTI-associated mutations K103N, Y181C, or K103N/Y181C substitutions in RT exhibit less than a 3-fold decrease in susceptibility to DOR compared to wild-type virus when evaluated in the presence of 100% NHS (as shown in [Table 2.6.2: 2]). The relative potencies of DOR to other NNRTIs determined in the presence of 100% NHS is similar to that determined in the presence of 50% NHS. DOR was 56- and 95-fold more potent than EFV against K103N and K103N/Y181C mutants, respectively, and was 2- to 3-fold more potent than EFV against WT and Y181C viruses under the same conditions. In comparison to ETR and RPV, DOR displayed approximately 5-fold better potency versus WT virus and K103N mutant. DOR was 12- and 5-fold more potent than ETR and RPV respectively in suppressing Y181C viruses. Compared to DOR, the K103N/Y181C mutant virus was 14- and 10-fold less susceptible to ETR and RPV, respectively (Feng M, 2016 [Ref. 4.3: 04LP05].

The antiviral activity of DOR was also determined against the prevalent transmitted G190A mutant and RPV-associated mutant E138K with EC_{50} of 55.0 nM and 43.0 nM, respectively, in the presence of 100% NHS. When resistance selection was conducted at clinically relevant concentrations, DOR was shown to be able to suppress common NNRTI-associated mutants such as K103N, Y181C, K103N/Y181C, G190A, and E138K mutants (Feng M, 2016 [Ref. 4.3: 04LP05].

Table 2.6.2: 1 Antiviral Activity (EC_{95}, nM) of DOR, EFV, ETR, and RPV against HIV-1 Variants Assayed in the MT4 Cell Line in the Presence of 10% and 50% Serum (PD002)

A	10% NHS			
	WT	K103N	Y181C	K103N/Y181C
DOR	11	13	16	31
EFV	5.0	247	8.6	297
ETR	4.4	5.3	24	53
RPV	2.0	1.7	4.3	12.9

B	50% NHS			
	WT	K103N	Y181C	K103N/Y181C
DOR	20	43	27	55
EFV	41	1427	80	2943
ETR	38	36	263	653
RPV	37	48	120	407

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Table 2.6.2: 2 Antiviral Activity (EC_{50}, nM) of DOR, EFV, ETR, and RPV Against HIV-1 Variants Assayed in the MT4-GFP Cell Line in the Presence of 100% Serum (PD002)

	EC_{50} (nM)			
NNRTI	**WT**	**K103N**	**Y181C**	**K103N/Y181C**
DOR	12.0 ± 4.4 (61)	21 ± 6.8 (45)	31 ± 10 (44)	33 ± 4.2 (7)
EFV	30 ± 9.0 (93)	1173 ± 447 (70)	90 ± 21 (77)	3119 ± 506 (8)
ETR	67 ± 26 (73)	67 ± 23 (56)	382 ± 128 (55)	479 ± 192 (2)
RPV	56 ±16 (61)	56 ± 15 (37)	169 ± 45 (38)	318 ± 74 (7)

The antiviral activity of the NNRTIs was also evaluated against 10 different subtypes of viruses (PD002) [Sec. 2.6.3.1]. Several isolates from each subtype were selected for testing. As shown in [Table 2.6.2: 3], no virus from a total of 93 viruses displayed greater than a 2.5-fold shift in potency with DOR, compared to the control virus (EC_{50} = 4.2 nM) consisting of a drug sensitive reference strain (CNDO) with PR and RT sequence derived from laboratory HIV strain NL4-3. The inhibitory potency of DOR was in the range from 10 nM to 1.2 nM against these WT viruses. Among the 10 subtype viruses, subtype H virus appeared to be more susceptible to the NNRTIs with fold-changes from 0.17 to 0.3 (Lai M, 2014, [Ref. 4.3: 04LP04]).

Table 2.6.2: 3 The Fold-Change of Inhibitory Potency of NNRTIs Tested with Different HIV-1 Subtypes (PD002)

Subtype[a]	EFV	ETR	RPV	DOR
Subtype A (n=5)	0.81±0.34	0.76±0.36	0.84±0.45	0.84±0.33
Subtype A1 (n=13)	0.70±0.16	0.73±0.36	0.73±0.32	0.68±0.19
Subtype AE (n=5)	0.75±0.27	072±0.28	0.71±0.27	0.79±0.44
Subtype AG (n=18)	0.75±0.21	0.66±0.15	0.68±0.17	0.92±0.40
Subtype B (n=7)	1.02±0.52	0.79±0.22	0.75±0.20	0.99±0.42
Subtype BF (n=4)	1.02±0.39	1.02±0.37	0.92±0.32	1.44±0.73
Subtype C (n=22)	0.89±0.27	0.77±0.19	0.72±0.19	1.07±0.36
Subtype D (n=9)	0.91±0.16	0.74±0.12	0.71±0.15	0.94±0.29
Subtype G (n=8)	0.74±0.16	0.62±0.15	0.61±0.15	0.93±0.27
Subtype H (n=2)	0.29±0.01	0.18±0.08	0.17±0.07	0.30±0.01

a: A drug sensitive strain was employed as the control to calculate the fold-changes

2.1.2.2 The Effect of NNRTI-associated Mutations on DOR Antiviral Potency

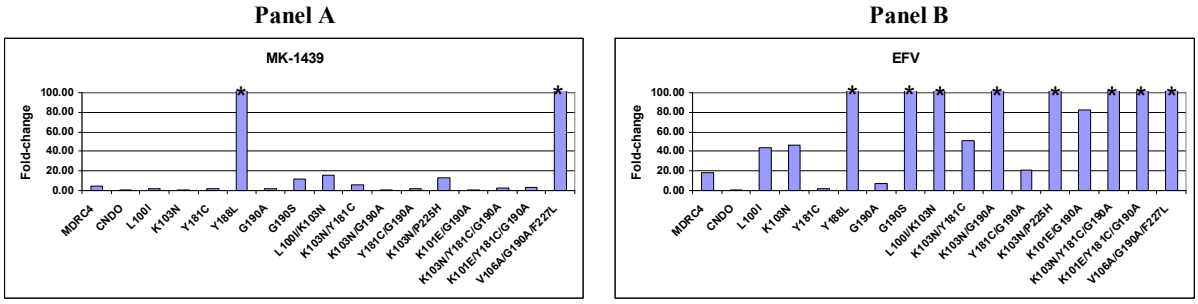
HIV-1 variants selected for resistance to NNRTIs either in cell culture or in the clinic harbor mutations in the NNRTI binding site such as K103N, Y181C, V106A, G190A, P236L, and K101E, (Das K, 2005 [Ref. 4.3: 03RHZV]). Various NNRTIs select for similar, but not

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identical, mutations in RT and confer resistance to NNRTIs. To test the effect of various known NNRTI resistance mutations on the potency, DOR was tested against wild type HIV-1 and a panel of viruses with defined mutations in NNRTI binding pocket in a single cycle infection assay (PD002) [Sec. 2.6.3.1].

Of the 15 resistant mutant viruses tested, only two mutant viruses (Y188L and V106A/G190A/F227L) displayed more than a 100-fold shift in potency against DOR [Figure 2.6.2: 1]. On the other hand, eight mutant viruses showed fold-changes of more than a 100 with EFV. For instance, virus with K103N/G190A double mutation conferred greater than 300-fold resistance versus EFV, but showed no resistance to DOR. Furthermore, the remaining mutant viruses also exhibited greater resistance to EFV than to DOR. One example is the K101E/G190A mutant, which conferred 83-fold resistance to EFV, yet the mutant virus was susceptible to DOR with a fold-change < 0.9.

Figure 2.6.2: 1 Comparison of the Mutant Profiles between DOR (MK-1439) and EFV in a Single Cycle Infection Assay (PD002)



HEK293 cells were employed for panel A and B experiments (Monogram data). In panels A and B, CNDO is a drug-sensitive reference standard that is used to determine the fold change in drug susceptibility relative to resistant viruses, where MDRC4 is a multi-drug resistant virus control that is used to evaluate and monitor assay performance.

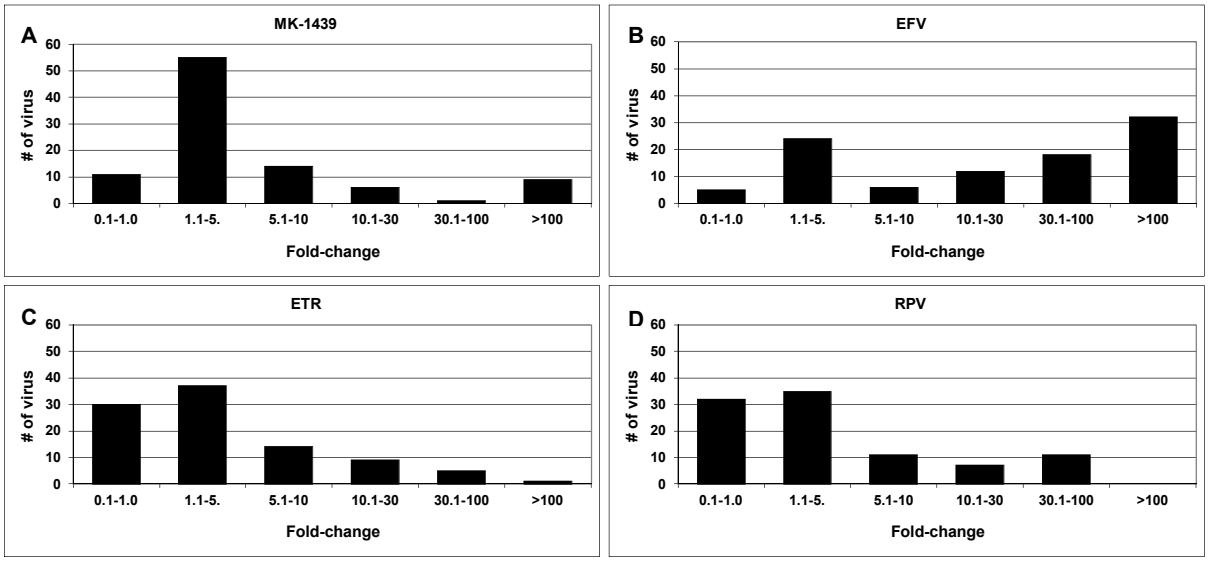
*Indicates EC_{50} was not reached at the highest concentration tested.

The antiviral activity of DOR, EFV, ETR, and RPV was also evaluated against an extended panel of 96 NNRTI resistant clinical isolates by Monogram under the same assay format (PD002) [Sec. 2.6.3.1], (Lai M, 2014 [Ref. 4.3: 04LP04]).

Among the 96 viruses, 62 (65%), 16 (17%), 15 (16%), and 18 (19%) viruses displayed more than 10-fold resistance to EFV, DOR, ETR, and RPV, respectively [Figure 2.6.2: 2]. A majority of the mutant viruses with reduced susceptibility to DOR (>10-fold shift in EC_{50}) also displayed >10-fold resistance to EFV (15/16; 94%) and to RPV (12/16; 75%), whereas fewer than 50% (44%; 7/16) of the mutants were found to have reduced susceptibility to ETR. Viruses containing common NNRTI-associated mutations such as Y188C, Y188H, V179D, V108I, V106M, and P236L exhibited less than 5-fold resistance to DOR.

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Figure 2.6.2: 2 Susceptibility of a Panel of 96 Clinical NNRTI-associated Mutant Viruses to NNRTIs (PD002)

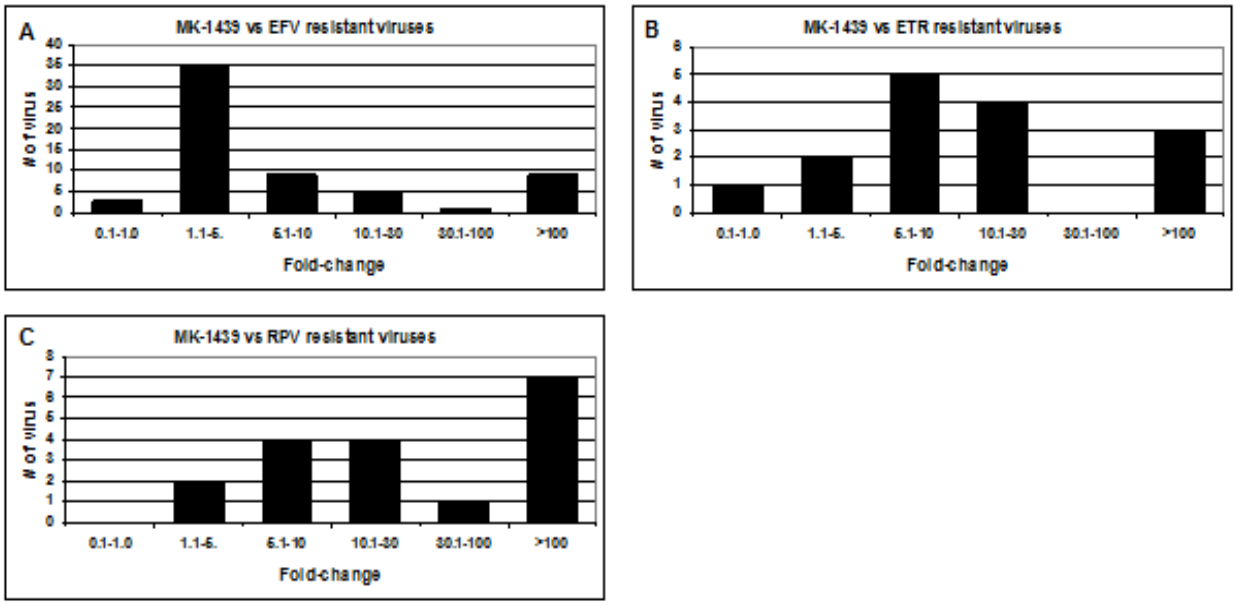


More than 30% of the mutant viruses exhibited greater than 100-fold resistance to EFV [Figure 2.6.2: 2] (B). On the other hand, the majority of the mutant viruses (>60%) displayed a fold-change of ≤ 5 when tested with the other three NNRTIs [Figure 2.6.2: 2] (A, C, and D).

Among 15 mutant viruses that showed greater than 10-fold shift in EC_{50} with ETR, seven of them exhibited reduced susceptibility to DOR. A majority of mutants (12/18; 67%) that exhibited >10-fold resistance to RPV also conferred >10-fold resistance to DOR. In contrast, more than 60% (38/62) of viruses that showed >10-fold resistance to EFV were susceptible to DOR with a ≤ 5-fold shift in EC_{50} [Figure 2.6.2: 3].

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Figure 2.6.2: 3 Susceptibility of EFV, ETR, and RPV Resistant Viruses to DOR (MK-1439) (PD002)



2.1.2.3 Cytotoxicity of DOR with Various Cell Types

DOR was tested for its cytotoxicity against resting and activated $CD4^+$ T cells, PBMCs, monocytes, and macrophages, and in proliferating transformed cell lines such as MT4, SupT1, and HL60 cell lines (PD004) [Sec. 2.6.3.1] with a previously identified cytotoxic compound used as a control.

As demonstrated in [Table 2.6.2: 4] and [Table 2.6.2: 5], DOR had no cytotoxicity in all cell types at the maximal tested concentration (CC_{50} > 100 µM).

Table 2.6.2: 4 Cytotoxicity of DOR on Proliferating and Stationary Human Cells (PD004)

	Proliferating cells			Stationary cells			
	MT4	HL60	SupT1	Monocyte	Macrophage	CD4	PBMC
CC_{50} (µM)	>100	>100	>100	>100	>100	>100	>100

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Table 2.6.2: 5 Cytotoxocity of DOR on Activated Cells (PD004)

	Activated cells			
Cells	Monocyte	CD4	Macrophage	PBMC
CC_{50} (µM)	>100	>100	>100	>100

2.1.3 Resistance Selection with DOR

Non-nucleoside reverse transcriptase inhibitors are an important component of antiretroviral therapy for the treatment of HIV-1 infected patients (Tarby C, 2004, [Ref. 4.3: 03RHZW]; Boone LR, 2006, [Ref. 4.3: 03RHZX]), but the efficacy of NNRTIs can be hampered by the development of resistant mutations, in particular, the mutations resulting in K103N and Y181C substitutions (DeClercq E, 1998, [Ref. 4.3: 03RHZY]). Consequently, there is a need for new NNRTIs that are effective against K103N and Y181C mutants, have distinct resistance profiles, and/or possess a higher barrier to resistance development (Janssen P, 2005, [Ref. 4.3: 03RHZZ]). To better understand how DOR may select for resistant viral variants, resistance selection studies were conducted in cell culture using subtype B virus under low MOI conditions using Sup T1 cells (PD003) [Sec. 2.6.3.1].

Resistance selection experiments were performed with escalating concentrations of DOR from 1x EC_{95} to 50x EC_{95}. No mutation was observed in the breakthrough viruses at 1x and 2x EC_{95}. As shown in [Table 2.6.2: 6], V108I was the mutation identified in the breakthrough viruses from experiment one at concentration of 4x EC_{95}, and V106A mutant virus started to emerge as DOR concentration increased (up to 50x EC_{95}). Both V108I and F227L mutations were detected in the breakthrough viruses at 4x EC_{95} in experiment two and co-existed throughout the experiment. A H221Y mutation was found in the breakthrough virus at 4x EC_{95} in experiment three. Additional mutations V106A and V108I emerged as the DOR concentration increased.

Resistance selection with EFV was also carried out under the same conditions to enable a direct comparison with DOR selection results. As shown in [Table 2.6.2: 6], known NNRTI-associated mutations (e.g., L100I, K101E) were found in breakthrough viruses.

Table 2.6.2: 6 Resistance Selection with DOR and EFV in Subtype B Virus Using Sup T1 Cells in the Presence of 10% FBS Under Low MOI Conditions (PD003)

			2xEC95		4xEC95		8xEC95		16xEC95		50xEC95
	n	T	Mutation	T	Mutation	T	Mutation	T	Mutation	T	Mutation
MK-1439	1	10	NM	7	V108(V/I)	8	V108(V/I) H221(H/Y)	12	V108(V/I) V106A		V108I V106A
	2	10	NM	7	V108(V/I) F227(F/L)	8	V108I F227(F/L)	10	V108I F227L	6	V108I F227L
	3	10	NM	11	H221(H/Y)	11	H221(H/Y) V106(V/A)	9	H221(H/Y) V106(V/A)	9	H221Y V106A V108I
EFV	1	14	NM	11	L100I	18	L100I	7	L100I Y188(Y/C)	4	L100I Y188(Y/C)
	2	10	NM	4	NM	11	K101E		NB		
	3	17	NM	7	K101(K/E)	11	K101E		NB		

T: duration time in unit of day; NM: no mutation was detected; NB: no breakthrough. Amino acids in parentheses indicate the mixture of wild type residue and the emerging mutation.

To evaluate potential mutations that would be selected by DOR with non-subtype B viruses, resistance selection was also conducted with subtype A and C viruses in addition to subtype B virus (Feng M, 2015, [Ref. 4.3: 04LP06]). The resistance selection experiments were conducted in 96-well format using MT4-GFP with CCR5 co-receptor that is controlled by LTR transcription. Under low MOI conditions, supernatant from wells with lower concentration of DOR was distributed to wells containing higher concentration of the compound during each passage. As a result, small portions of mutant viruses that broke through at low concentration of DOR would be transferred to wells containing higher concentration of the compound, which can facilitate viral breakthrough under higher selective pressure. Under these conditions, viral breakthrough was observed even with compound concentration as high as 1000x EC_{95}.

The plates were scanned by Acumen EX3 after each passage during the resistance selection process; detection of green fluorescence was found to progress gradually from column 11 to column 1 as viral breakthrough started from column 11 containing lowest concentration of DOR (1x EC_{95}). Breakthrough viruses were harvested and subjected to sequence analyses. Mutation data were collected from two independent experiments with total of 16 repeats (two plates, eight rows each). The results from resistance selection with subtype B virus is shown in [Table 2.6.2: 7], two major mutation development pathways were associated with DOR in this study. V106A was the first mutation identified in breakthrough viruses at lower concentration of DOR. As compound concentration increased, an additional mutation emerged such as F227L or L234I to give double mutants V106A/F227L or V106A/L234I.

V106A/F227L mutant virus conferred significant resistance to DOR with fold-change (FC) in potency greater than 500 compared to wild type virus. Conversely, V106A/L234I displayed 170-fold resistance to DOR. As a result, at higher compound concentrations, F227L further evolved along with V106A/L234I to give a triple mutant to overcome the selection pressure. Other minor mutation development pathways were also identified, such as starting with V108I mutant followed by the emergence of V106A and L234I substitutions sequentially or starting with L234I mutant virus followed by sequentially evolution of V108I and V106A substitutions. In addition, some other minor mutations are also identified in the resistance selection studies such as V106I, H221Y, F227V, M230I, P236L, and Y318F. These results are also consistent with the resistance selection performed with Sup T1 cells where V106A, F227L, and V108I mutants were selected under low MOI conditions (Feng M, 2015, [Ref. 4.3: 04LP06]).

Resistance selection with benchmark compound EFV was also conducted under the same conditions to serve as a comparator. As shown in [Table 2.6.2: 7], three mutation development pathways were identified. Two of them were started from L100I mutant followed by the substitutions of K103N or V179D. L100I/K103N containing virus was highly resistant to EFV with FC greater than 500. L100I/V179D mutant showed FC of 94 to EFV. At compound concentration greater than 163-fold of EC_{95}, additional substitutions P225H or M230L emerged with L100I/V179D mutant to give a triple mutant to circumvent the selection pressure. The third mutation pathway was initiated by K103N mutant followed by the addition of L100I substitution. These mutation development pathways are consistent with literature reports and clinical findings (Feng M, 2015, [Ref. 4.3: 04LP06]).

Table 2.6.2: 7 Resistance Selection with DOR and EFV with Subtype B Virus Using MT4-GFP Cells in the Presence of 10% FBS (PD003)

MK-1439	a	V106A →V106A/F227L
	b	V106A → V106A/L234I → V106A/L234I/F227L
EFV	a	L100I → L100I/K103N
	b	L100I → L100I/V179D → L100I/V179D/P225H or M230L
	c	K103N → K103N/L100I

Resistance selection with subtype B virus using MT4-GFP cells was also conducted under high MOI conditions at DOR and EFV concentrations of 3x, 10x, and 30x EC_{95}. For DOR, most viral breakthroughs were observed at 3x EC_{95} (n=24). Population sequencing analysis indicated that the mutations selected under these conditions are similar to the mutations observed under low MOI conditions. The most frequent identified mutant viruses contain mutations that gave V106A, L234I, F227L, and V108I substitutions. Although V108I mutant was not listed as the major mutation pathway under low MOI conditions, it is involved in several minor mutation pathways. Similarly, the majority of viral breakthrough occurred at 3x EC_{95} concentration in the selection with EFV. The mutations selected under

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these conditions are also consistent with the results from low MOI conditions, where K103N, L100I and V179D are the major mutants identified in the breakthrough viruses.

In the resistance selection with subtype A virus in the presence of DOR using MT4-GFP/CCR5 cells, the major mutation pathway started with V106A mutant at low concentration of the compound (minor population was found with V106M substitution) followed by the development of F227L mutant (minor population with C or V substitution). A minor mutation pathway also emerged in this selection study with V108I as the first mutant identified in the breakthrough virus. As the compound concentration increased, L234I and V106A(I) substitutions was sequentially developed to give a triple mutant. The results are shown in [Table 2.6.2: 8]. For the resistance selection with EFV, there were also two mutation pathways identified where L100I and V106M mutants led each of the pathways followed by the emergence of Y188H(C) or V179D and Y188C or L100I substitutions, respectively (Feng M, 2015, [Ref. 4.3: 04LP06]).

The resistance selection results with subtype C virus are shown in [Table 2.6.2: 9]. Two mutation pathways were identified in the selection with DOR. V106A mutant again led the first selection pathway followed by the emergence of F227I substitution. The other pathway was led by V106M mutant followed by the evolvement of F227C substitution. As to EFV, similar to the results from the resistance selection with subtype A virus, L100I and V106M led the two mutation pathways. L100I mutant was followed by V106M and Y188C (or F227C) substitutions at higher concentrations of EFV instead of Y188H or V179D with subtype A virus. The V106M pathway was followed by Y188C substitution as compound concentration increased (Feng M, 2015, [Ref. 4.3: 04LP06]).

In conclusion, DOR-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes, as well as NNRTI-resistant HIV-1. Observed emergent amino acid substitutions in RT included: V106A, V106M, V106I, V108I, F227L, F227C, F227V, H221Y, M230I, L234I, P236L, and Y318F.

Table 2.6.2: 8 Resistance Selection with DOR and EFV with Subtype A Virus Using MT4-GFP/CCR5 Cells in the Presence of 10% FBS (PD003)

MK-1439	a	V106A(M) → V106A(M)/F227L(C/V) -- Major
	b	V108I → V108I/L234I → V108I/L234I/V106A(I) -- Minor
EFV	a	L100I → L100I/Y188H(C) or V179D
	b	V106M → V106M/Y188C or L100I

Amino acid in the parentheses represents minor population.

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Table 2.6.2: 9 Resistance Selection with DOR and EFV with Subtype C Virus Using MT4-GFP/CCR5 Cells in the Presence of 10% FBS (PD003)

MK-1439	a	V106A → V106A/F227I
	b	V106M → V106M/F227C
EFV	a	L100I → L100I/V106M →L100I/V106M/Y188C or F227C
	b	V106M → V106M/Y188C

In addition, resistance selections were conducted with K103N, Y181C, G190A, and E138K mutants at clinically relevant concentrations of DOR. Results suggested that DOR was able to suppress the following NNRTI-associated substitutions: K103N, Y181C, G190A, and E138K mutants under clinically relevant concentrations (Feng M, 2016, [Ref. 4.3: 04LP05]).

2.1.4 Biochemical Activity of DOR Against Human DNA Polymerases α, ß, and γ

The potential for off-target activity of DOR against mechanistically similar enzymes was evaluated by assessing the inhibitory activity of DOR with human cellular DNA polymerases α, β, and mitochondrial DNA polymerase γ (PD005) [Sec. 2.6.3.1]. DOR exhibited greater than 10,000-fold selectivity with respect to the cellular DNA polymerases α, β, and γ with IC_{50}s >100 μM. Therefore, DOR does not inhibit the human cellular DNA polymerases α, ß, and mitochondrial DNA polymerase γ.

2.1.5 Combination Study of DOR

The necessity of combination therapy for the treatment of HIV-1 infection often presents the potential that the effect of one component in the combination therapy may have impact on the antiviral activity of other component(s), which could be synergistic, additive or antagonistic.

Therefore, the anti-HIV-1 activity of DOR was evaluated in two-drug combination studies with any of 18 different licensed anti-HIV inhibitors (PD006) [Sec. 2.6.3.1], including 3TC and TDF. Each two-drug combination experiment was tested three times in CEM-SS cells or MAGI-CCR5 cells acutely infected with HIV-1_{IIIB} or HIV-1_{Ba-L}, respectively. Viral growth/inhibition was evaluated by measuring virus-induced cytopathic effects (CPE) in CEM-SS cells or by β-galactosidase reporter gene induction in MAGI-CCR5 cells at the experimental endpoint. The cytotoxicity of each two-drug combination was also evaluated in parallel with the antiviral evaluations. The concentrations of DOR used in these evaluations were selected in order to test a broad range of concentrations and to provide a complete set of dose response curves as possible under the limitations of eight total concentrations. Similarly, the concentrations of other antiviral agents used in this study were selected to provide as complete of dose response curves as possible under the limitations of five total concentrations. The "positive antagonism control" of stavudine in combination with

ribavirin was tested in parallel with each of the assays that were performed. Analysis of drug interactions for each of the two-drug combinations was performed using the Prichard and Shipman MacSynergy II three-dimensional model for statistical evaluation of combination assays.

Results suggest that the antiviral activity of DOR was not antagonistic when combined with the NNRTIs delavirdine, efavirenz, etravirine, nevirapine, or rilpivirine; the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, zalcitabine or zidovudine; the PIs darunavir or indinavir; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc; or the integrase strand transfer inhibitor raltegravir. In contrast, the positive antagonism control of stavudine in combination with ribavirin exhibited a highly antagonistic interaction in all experiments. Therefore, the overall interpretation of these data suggest that antagonism of the antiviral effects of the 18 licensed antiretroviral drugs evaluated in this study should not be an issue associated with the use of DOR in a clinical setting (Lai M, 2014, [Ref. 4.3: 04LP04]).

2.2 Primary Pharmacodynamics In Vivo

Consistent with guidances, including FDA *Guidance for Industry Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment, November 2015, Revision 1*, demonstration of anti-HIV activity in an animal model is not required; therefore no in vivo primary pharmacodynamic studies were conducted.

3 SECONDARY PHARMACODYNAMICS

3.1 Secondary Pharmacodynamics In Vitro

3.1.1 In Vitro Assessment of DOR in the [redacted] – Pharmacology Screen (PD001)

DOR was evaluated against a large panel of standard enzyme and other receptor assays to assess its specificity for off-target activities. In a [redacted] screen with more than 110 enzymes and receptors (PD001) [Sec. 2.6.3.1], DOR only showed moderate affinity to the 5-HT2B receptor in a ligand binding assay with an IC_{50} of 2.5 µM, while in a subsequent cell based functional 5-HT2B assay, no agonist or antagonist activity was observed by monitoring the accumulation of inositol-1-phosphate. Therefore, binding of DOR to 5-HT2B does not impact 5-HT2B receptor function. The major circulating metabolite in human plasma (M9) was also evaluated in the in vitro screening panel for off-target activities and there was no significant activity at concentrations up to 10 µM [Sec. 2.6.4].

3.2 Secondary Pharmacodynamics In Vivo

Apart from safety pharmacology studies further reviewed in [Sec. 2.6.2.4], specific studies evaluating in vivo secondary pharmacodynamics have not been conducted.

4 SAFETY PHARMACOLOGY

DOR was evaluated for its potential effects on cardiovascular, neurological, and respiratory function in several experimental safety pharmacology models [Table 2.6.2: 10]. All pivotal safety pharmacology studies were conducted in accordance with the principles of Good Laboratory Practice (GLP). Unless otherwise indicated, all studies were conducted at Merck Research Laboratories, West Point, Pennsylvania, U.S.A. or Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France. The U.S.A. and France are members of the Organisation for Economic Co-operation and Development (OECD) and therefore part of the OECD Mutual Acceptance of Data system. GLP compliance statements are included in all GLP study reports. Based on population pharmacokinetics analysis from Phase 3 trials (P018 and 021), a 100 mg QD DOR clinical dose results in a systemic geometric mean $AUC_{0\text{-}24hr}$ exposure of 37.8 µM•hr and a C_{max} of 2.26 µM.

Table 2.6.2: 10 Safety Pharmacology Studies with DOR

Studies to Support ICH S7A and S7B Recommendations		
Study No. (GLP Status)	**Study Title**	**Dose Levels (mg/kg)**
TT #[redacted]-4716 (GLP)	MK-1439: Electrophysiological Evaluation on hERG Channel Current Stably Expressed in CHO Cells	N/A
TT #[redacted]-5006 (Non-GLP)	MK-1439: Effect of MK-1439 on Cardiovascular Function in Anesthetized, Vagotomized Dogs	0, 1, 3, 10 (cumulative dose)
TT #[redacted]-5606 (GLP)	MK-1439: Oral Cardiovascular and Respiratory Telemetry Study in Dogs	0, 0.5, 2, 10
TT #[redacted]-5262 (Non-GLP)	MK-1439: Exploratory Neurological Study in Mice	0, 10, 100, 750
TT #[redacted]-6029 (GLP)	MK-1439: Two-Week Oral Toxicity Study in Rats with a Functional Observational Battery Assay	0, 5, 75, 450
Other Pharmacology Studies		
TT #[redacted]-1080 (Non-GLP)	MK-1439: Exploratory Oral Pharmacology Study in Dogs	20 (SD 1), 2 (SD 8); 200 (SD 1), 750 (SD 8)[a]
a 6-day washout period between doses		

DOR inhibited hERG current with an IC_{50} value of 88 µM and an IC_{20} value of 19 µM (TT #[redacted]-4716) [Sec. 2.6.3.4], approximately 162-fold and 35-fold respectively the unbound DOR levels at the human C_{max} exposure at the therapeutic dose of 100 mg [Sec. 2.4.3.3.3]. There were no test-article related effects on cardiovascular parameters in anesthetized, vagotomized dogs up to 10 mg/kg of cumulative dose (plasma concentrations up to14 µM, approximately 6-fold DOR levels at the human C_{max} exposure) (TT #[redacted]-5006) [Sec. 2.6.3.4]. In conscious dogs (TT #[redacted]-5606) [Sec. 2.6.3.4], the no-observed-effect level (NOEL) for cardiovascular and respiratory function was ≥10 mg/kg (expected $C_{max} \geq 8.24$ µM, approximately 3.5-fold DOR levels at the human C_{max} exposure) based on C_{max} attained at 10 mg/kg in an oral dog toxicity study (TT #[redacted]-6030) [Sec. 2.6.7.6]. Repeat dose toxicity

studies in dogs of up to nine month duration were conducted at DOR doses up to 1000 mg/kg/day [Sec. 2.6.7.7E] [Sec. 2.6.7.7F], and were without findings upon ECG assessment (C_{max} of 32.7 µM, approximately 14-fold the DOR levels at the human C_{max} exposure). There were no effects on neurological function in mice (TT #[redacted]-5262) and rats (TT #[redacted]-6029) at single doses up to 750 and 450 mg/kg (exposures not evaluated in mice; in rats, C_{max} of 15.2 µM at 450 mg/kg was approximately 6.5-fold DOR levels at the human C_{max} exposure) [Sec. 2.6.3.4].

Individual study summaries are detailed below.

4.1 Effect on hERG Current (TT #[redacted]-4716)

DOR was tested for its effect on hERG channels heterologously expressed in CHO-K1 cells using standard whole-cell voltage-clamp techniques. Doravirine inhibited hERG current with an IC_{50} value of 88 µM and an IC_{20} value of 19 µM (TT #[redacted]-4716) [Sec. 2.6.3.4]. The IC_{50} and IC_{20} values are higher by approximately 162-fold and 35-fold, respectively, to the unbound DOR levels at the human C_{max} exposure at the therapeutic dose of 100 mg [Sec. 2.4.3.3.3].

4.2 Cardiovascular Function in Anesthetized (Vagotomized) Dogs (TT #[redacted]-5006)

DOR was administered intravenously during three sequential 30-minute periods at 1, 2, and 7 mg/kg (1, 3, and 10 mg/kg, cumulative dose) in a vehicle of 100% DMSO to determine its effects on cardiovascular function in dogs (three females). These effects were compared to the effects of vehicle alone (100% DMSO) previously tested in a separate set of three dogs. Heart rate, arterial pressure, and electrocardiographic parameters (PR, QRS, and QT/QTc intervals) were monitored during each 30-minute infusion period. There were no test article-related effects on cardiovascular parameters at all doses tested. Average DOR plasma concentrations measured following the 30-minute infusions of 1, 2, and 7 mg/kg were 2.7 ± 0.4, 6.3 ± 1.9, and 14.0 ± 1.3 µM (Mean ± SD), respectively (TT #[redacted]-5006) [Sec. 2.6.3.4]. There were no test-article related effects on cardiovascular parameters in anesthetized, vagotomized dogs up to 10 mg/kg of cumulative dose (plasma concentrations up to 14 µM, approximately 6-fold DOR levels at the human C_{max} exposure).

4.3 Oral Cardiovascular and Respiratory Telemetry Study in Dogs (TT #[redacted]-5606)

DOR at 0.5, 2, and 10 mg/kg and vehicle (10% polysorbate 80 in deionized water) alone were administered as single doses by oral gavage using an ascending dose administration regimen to determine potential effects on cardiovascular and respiratory function in conscious dogs (2 male and 2 female). Heart rate, arterial pressure, electrocardiographic parameters (PR, QRS, QT and RR intervals), rate and depth of respiration, and body temperature were monitored via telemetry for approximately 24 hours post-dose. QT interval was corrected for changes in heart rate (QTc) using an individual animal correction method. There were no test article-related effects on cardiovascular and respiratory parameters at all doses tested. The NOEL for cardiovascular and respiratory function in this study was

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≥10 mg/kg (TT #[redacted]-5606) [Sec. 2.6.3.4]. The expected C_{max} of 8.24 µM at 10 mg/kg was approximately 3.5-fold DOR levels at the human C_{max} exposure.

4.4 Exploratory Neurological Study in Mice (TT #[redacted]-5262)

A functional observational battery (modified Irwin method) was performed following a single oral dose of DOR (10, 100 and 750 mg/kg) or vehicle (10% polysorbate 80 in Deionized Water) to assess nervous system function in female CD-1 mice (5 animals/dose group). Neurological assessments such as general behavior, neural reflexes, and motor function were conducted at 0.5, 1, 2, 5, and ~24 hours postdose; body temperature was measured at 2 hours postdose. There were no test-article related effects observed up to 24 hours postdose. The NOEL for nervous system function in this study was ≥750 mg/kg (TT #[redacted]-5262) [Sec. 2.6.3.4].

4.5 Oral Functional Observational Battery Study in Rats (TT #[redacted]-6029)

On Day 1 of a two-week toxicity study in male Wistar Han rats, a functional observational battery (FOB) was performed to assess nervous system function following administration by oral gavage of DOR at 5, 75, and 450 mg/kg prepared as a [redacted] formulation (consisting of [redacted]% DOR base form and [redacted]% of hydroxypropylmethylcellulose acetate succinate [HPMCAS]) in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water or control article alone (HPMCAS at 180 mg/ml in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water) (TT #[redacted]-6029) [Sec. 2.6.3.4]. The assessment, consisting of home cage, hand-held, and open-field observations, stimulus activity responses, grip-strength, foot splay, latency on the hot plate, and body temperature, was conducted approximately 7 hours (± 1 hour) post-dose (expected T_{max}). There were no test article-related FOB findings at all doses tested. The NOEL for nervous system function was ≥450 mg/kg (C_{max} of 15.2 µM, approximately 6.5-fold DOR levels at the human C_{max} exposure).

4.6 Other Pharmacology Study

4.6.1 Oral Pharmacology Study in Dogs (TT #[redacted]-1080)

An additional study was conducted to determine the DOR serum biochemical and pharmacokinetic profile in dogs when administered in a rising dose paradigm with a 6-Day washout period between doses. Two groups of dogs consisting of one female and one male per group were administered DOR suspended in 10% polysorbate 80 in deionized water. One group received 20 mg/kg on Study Day 1 and 2 mg/kg on Study Day 8 while the second group received 200 mg/kg on Study Day 1 and 750 mg/kg on Study Day 8. Assessments consisted of mortality and physical signs along with hematological and serum biochemistry evaluations (samples collected approximately 24 hours post dose on Study Day 2 and 9). Toxicokinetic evaluation was performed on samples collected at 0 (predose) and at approximately 1, 2, 4, 7, and 24 hours post-dose on Study Days 1 and 8 (TT #[redacted]-1080) [Sec. 2.6.3.4].

All animals survived until the scheduled study termination and were returned to the animal colony upon completion of the final toxicokinetic/clinical pathology blood sample collection. Presence of white substance (resembling test article) in the feces was observed post-dose in animals administered 750 mg/kg. Slight decreases (-60 to 65% decrease from pre-test) in reticulocytes were observed on Study Days 2 and 9 in the female (Animal#10-0143) dosed at 200 and 750 mg/kg. There were no test article-related changes in serum biochemical parameters. Plasma concentrations of DOR were determined by protein precipitation followed by liquid chromatography-tandem mass spectrometry. Toxicokinetic parameters are presented in [Table 2.6.2:11].

Table 2.6.2:11 Plasma DOR (MK-1439) Toxicokinetic Parameters in Dogs (TT #[redacted]-1080) - Study Days 1 and 8

	DOR (MK-1439) (mg/kg)			
	Female #10-0141		Male #10-0140	
	20	2[a]	20	2[a]
$AUC_{0\text{-}24\ hr}$ (μM·hr)	112.5	60.95	127.3	51.42
C_{max} (μM)	5.60	3.30	7.70	3.30
T_{max}	7	2	4	2
	Female #10-0143		Male #10-0142	
	200	750[a]	200	750[a]
$AUC_{0\text{-}24\ hr}$ (μM·hr)	161.0	166.4	238.9	224.8
C_{max} (μM)	8.10	8.20	13.0	10.3
T_{max}	24	24	4	24

[a] DOR (MK-1439) (≤ 0.25 μM) was observed in the pre-dose (T0) sample on Study Day 8.

DOR concentrations observed in the pre-dose samples obtained on Study Day 8 were considered due to persistence of test article exposure in study animals from Study Day 1 dose administration.

5 PHARMACODYNAMIC DRUG INTERACTIONS

As reviewed in [Sec. 2.6.2.2.1.5], the anti-HIV-1 activity of DOR was evaluated in two-drug combination studies with any of 18 different licensed anti-HIV inhibitors. Combination study suggested that DOR should not have antagonistic interaction with the same or different classes of antiviral agents, including 3TC and TDF.

DOR did not exhibit effects on cardiovascular or respiratory systems in dogs, and no neurobehavioral changes were observed in rats or mice. Based on the absence of changes in these safety pharmacology studies, the established pharmacology profiles of 3TC and TDF, and in accordance with ICH M3(R2) guidance which states that combination safety pharmacology studies generally are not recommended to support clinical trials or marketing

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if the individual agents have been tested according to current standards, no safety pharmacology studies were conducted where DOR, 3TC or TDF were co-administered.

6 DISCUSSION AND CONCLUSIONS

DOR is a next generation NNRTI that potently suppresses HIV-1 replication. DOR's lower level potency shift, compared to the other NNRTIs tested (when serum concentration is increased from 10% to 50%), is directly related to differences in protein binding between DOR and the other three marketed NNRTIs (EFV, ETR, and RPV). These marketed NNRTIs exhibit >99% plasma protein binding as compared to DOR, which has only 76% plasma protein binding. As a result, in the presence of 50% serum, DOR exhibited better antiviral activity than EFV against WT virus and the two prevalent mutant viruses (K103N and Y181C mutant viruses). Under the same conditions, DOR displayed better antiviral activity than ETR and RPV in suppressing the replication of WT virus and Y181C containing virus, and had similar potency to the two NNRTIs against K103N mutant virus. When the antiviral activity was evaluated in the presence of 100% serum, DOR displayed better potency than EFV, ETR, and RPV versus WT and the two mutant viruses, which may be ascribed to greater potency shift for EFV, ETR, and RPV in the presence of 100% serum.

The mutant profile of DOR is superior to EFV, and similar to ETR and RPV, when potencies were evaluated against a broad panel of NNRTI-associated mutants. In the test with 96 NNRTI-associated mutant viruses, more than 60% of viruses exhibited greater than 10-fold resistance to EFV, whereas more than 60% of viruses had a fold-change ≤ 5 when tested with DOR, ETR, and RPV.

Although viruses containing Y188L mutation exhibited significant resistance to DOR, the mutation was not selected by DOR during in vitro resistance selection. While Y188L mutant virus also shows greater than 100-fold resistance to EFV, it only represents 5% of the patients who failed in treatment with the EFV-containing regimen. The lack of prevalent Y188L mutation may have been due to the fact that two base changes are required for the Y188L mutation.

Resistance selection of subtype B virus with DOR was conducted under both high and low MOI conditions using SupT1 cells. Viruses containing V106A, V108I, and L234I mutations represented the most frequently selected mutants under both conditions. Additional mutation with F227 variants often emerged at higher concentration of DOR. The V106A, V108I, and L234I mutant viruses confer approximately 12-, 4-, and 11-fold resistance to DOR, respectively. Emergence of additional mutations such as F227L or F227C further reduces the susceptibility of the mutant viruses to DOR. Based on the X-ray structure of DOR /RT, all three residues (V106, V108, and F227) are in close proximity to the molecule and may play an important role in the interactions between DOR and RT. In the resistance selection with subtype A, B, and C viruses using MT4-GFP cells, viruses containing substitutions at the position of V106, V108, L234, and F227 also account for the majority of mutants identified in the breakthrough viruses under low MOI conditions. Mutations selected under high MOI

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conditions with subtype B virus using MT4-GFP cells are consistent with the mutations selected under low MOI conditions.

The two-drug antiviral antagonism combination study indicated that DOR should not have antagonistic interaction with the same or different classes of antiviral agents; thus antagonism of the antiviral effects, including 3TC and TDF, is unexpected.

Doravirine had no cytotoxicity in any cell types tested (CC_{50} > 100 μM). When evaluated for off-target activities against a large panel of enzyme and receptor assays, including DNA polymerases, DOR showed only moderate affinity to the 5-HT2B receptor in a ligand binding assay and was determined to have no agonist or antagonist effects on this receptor in a subsequent functional cell assay. The major metabolite M9 also had no identified off-target activity.

DOR, when evaluated for its potential effects on cardiovascular, neurological, and respiratory function in several in vitro or in vivo safety pharmacology models, was without significant effects at exposures exceeding those observed in humans at the clinical 100 mg dose. Doravirine inhibited hERG current with an IC_{50} value of 88 μM and an IC_{20} value of 19 μM, approximately 162-fold and 35-fold respectively the unbound DOR levels at the human C_{max} exposure at the therapeutic dose of 100 mg [Sec. 2.4.3.3.3]. There were no test article-related effects on cardiovascular parameters in anesthetized, vagotomized dogs up to 10 mg/kg of cumulative dose (plasma concentrations up to 14 μM, approximately 6-fold DOR levels at the human C_{max} exposure). In conscious dogs orally administered DOR, the NOEL for cardiovascular and respiratory function was ≥10 mg/kg (expected C_{max} ≥ 8.24 μM, approximately 3.5-fold DOR levels at the human C_{max} exposure); repeat dose toxicity studies of up to nine month duration at DOR doses up to 1000 mg/kg/day were without ECG findings (C_{max} of 32.7 μM, approximately 14-fold DOR levels at the human C_{max} exposure). There were no effects on neurological function in mice and rats at single oral doses up to 750 mg/kg and 450 mg/kg, respectively (exposure not evaluated in mice at this dose; in rats, C_{max} of 15.2 μM at 450 mg/kg, approximately 6.5-fold DOR levels at the human C_{max} exposure).

Based on the absence of changes of concern in the DOR safety pharmacology studies, the established known pharmacology profile of 3TC and TDF, and in accordance with ICH M3(R2) guidance which states that combination safety pharmacology generally are not recommended to support registration if the individual agents have been tested according to current standards, no safety pharmacology studies were conducted with co-administration of DOR, 3TC and TDF.

In conclusion, the pharmacological profile of DOR supports the safe and effective use of DOR (100 mg) as a single entity and in the DOR/3TC/TDF FDC tablet for the treatment of HIV-1 infection in treatment-naive adult patients.

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2.6　非臨床試験の概要文及び概要表

2.6.3　薬理試験概要表

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Sec. 2.6.3.1 Pharmacology: Overview

Test Article: DOR

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol. Section
Primary Pharmacodynamics					
Antiviral Activity/Potency	NA	In vitro	MRL-WP	PD002	[Ref. 4.2.1.1: PD002MK1439]
Resistance Selection	NA	In vitro	MRL-WP	PD003	[Ref. 4.2.1.1: PD003MK1439]
Cytotoxicity	NA	In vitro	MRL-WP	PD004	[Ref. 4.2.1.1: PD004MK1439]
Biochemical Activity	NA	In vitro	MRL-WP	PD005	[Ref. 4.2.1.1: PD005MK1439]
Combination Study	NA	In vitro	MRL-WP	PD006	[Ref. 4.2.1.1: PD006MK1439]
Secondary Pharmacodynamics					
Biochemical Activity (Enzyme Activity & Merck Screen Study)	NA	In vitro	MRL-WP	PD001	[Ref. 4.2.1.2: PD001MK1439]

Sec. 2.6.3.1 Pharmacology: Overview (Continued)

Test Article: DOR

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol. Section
Safety Pharmacology					
hERG Assay[a]	hERG channels stably expressed in Chinese hamster ovary (CHO-K1) cells	In vitro	MRL-WP	TT #[redacted]-4716	[Ref. 4.2.1.3: TT[redacted]4716FIN]
Cardiovascular Function	Dog/Beagle (anesthetized, vagomotized, ventilated)	IV	MRL-WP	TT #[redacted]-5006	[Ref. 4.2.1.3: TT[redacted]5006FIN]
Cardiovascular & Respiratory Function[a]	Dog/Beagle	Oral	MRL-WP	TT #[redacted]-5606	[Ref. 4.2.1.3: TT[redacted]5606FIN]
Behavioral and CNS Function	Mouse/CD-1	Oral	MRL-WP	TT #[redacted]-5262	[Ref. 4.2.1.3: TT[redacted]5262FIN]
Behavioral & CNS Function (FOB)[a]	Rat/Wistar Han	Oral	MRL-FR	TT #[redacted]-6029	[Ref. 4.2.3.2: TT[redacted]6029FIN]
Pharmacology with Toxicokinetics	Dog/Beagle	Oral	MRL-WP	TT #[redacted]-1080	[Ref. 4.2.1.3: TT[redacted]1080FIN]

a Report contains a GLP compliance statement.
CNS = Central Nervous System; FOB = Functional Observational Battery; IV = Intravenous; M = Male; MRL–WP = Merck Research Laboratories, West Point, Pennsylvania, USA; MRL-FR = Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France.

Sec. 2.6.3.2 Primary Pharmacodynamics

See Primary Pharmacodynamics [Sec. 2.6.2.2].

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Sec. 2.6.3.3 Secondary Pharmacodynamics

See Secondary Pharmacodynamics [Sec. 2.6.2.3].

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Sec. 2.6.3.4 Safety Pharmacology

Test Article: DOR

Organ Systems Evaluated	Species/ Strain	Method of Admin-istration	Dose/Concen-tration Level[a]	Gender and No. per Group	Noteworthy Findings	GLP Compli-ance	Study Number
hERG Assay	CHO-hERG cell line (Chinese hamster ovary cells)	In vitro	10, 30, 100 µM	NA	IC_{50} value of 88 µM; IC_{20} value of 19 µM	Yes	TT #[redacted]-4716 [Ref. 4.2.1.3: TT[redacted]4716FIN]
Cardiovascular Function	Dog/Beagle (anesthetized, vagomotized, ventilated)	IV	Doses administered were 1, 2, 7 mg/kg, yielding cumulative doses of 1, 3, and 10 mg/kg	3F	No test article-related findings. Peak Average Plasma Concentrations: 1 mg/kg: 3 µM 3 mg/kg: 6 µM 10 mg/kg: 14 µM	No	TT #[redacted]-5006 [Ref. 4.2.1.3: TT[redacted]5006FIN]
Cardiovascular & Respiratory Function	Dog/Beagle	Oral	0, 0.5, 2, 10 mg/kg	2F, 2M	No effects.	Yes	TT #[redacted]-5606 [Ref. 4.2.1.3: TT[redacted]5606FIN]
Behavioral and CNS Function	Mouse/CD-1	Oral	0, 10, 100, 750 mg/kg/day	5F/group	No effects.	No	TT #[redacted]-5262 [Ref. 4.2.1.3: TT[redacted]5262FIN]
Behavioral and CNS Function (FOB)	Rat/Wistar Han	Oral	0, 5, 75, 450 mg/kg/day[b]	6M/group	No effects.	Yes	TT #[redacted]-6029 [Ref. 4.2.3.2: TT[redacted]6029FIN]

2.6.3.4 Safety Pharmacology (Continued)

Test Article: DOR

Organ Systems Evaluated	Species/ Strain	Method of Admin-istration	Dose/Concen-tration Level[a]	Gender and No. per Group	Noteworthy Findings	GLP Com-pliance	Study Number
Pharmacology with Toxicokinetics	Dog/ Beagle	Oral	GRP1: 20 mg/kg (SD 1), 2 mg/kg (SD 8) GRP2: 200 mg/kg (SD 1), 750 mg/kg (SD 8)	1F, 1M/group	Antemortem Findings: White substance (resembling test article) in feces at 750 mg/kg. Slight decreases (-60 to 65% from pretest) in reticulocytes on SD2 and SD9 in female dosed at 200 and 750 mg/kg. No changes in serum biochemical parameters. Plasma Pharmacokinetic Parameters:	No	TT #[redacted]-1080 [Ref. 4.2.1.3: TT[redacted]1080FIN]

	MK-1439 (mg/kg)			
	Female #10-0141		Male #10-0140	
	20	2[a]	20	2[a]
$AUC_{0\text{-}24\ hr}$ (μM•hr)	112.5	60.95	127.3	51.42
C_{max} (μM)	5.60	3.30	7.70	3.30
T_{max} (hr)	7	2	4	2
	Female #10-0143		Male #10-0142	
	200	750[a]	200	750[a]
$AUC_{0\text{-}24\ hr}$ (μM•hr)	161.0	166.4	238.9	224.8
C_{max} (μM)	8.10	8.20	13.0	10.3
T_{max} (hr)	24	24	4	24

[a] MK-1439 (≤ 0.25μM) was observed in the pre-dose (T0) sample.
Drug Metabolism Notebook Reference: 0285509/0041

DOR observed in the pre-dose samples obtained on SD 8 could potentially be due to persistence of test article exposure in study animals from SD 1 dose administration.

a Single dose unless specified otherwise.
b FOB performed at approximately 7 hours postdose on SD 1.
F = Female; FOB = Functional Observation Battery; GRP = Group; M = Male; NA = Not Applicable; SD = Study Day

Sec. 2.6.3.5 Pharmacodynamic Drug Interactions

See Pharmacodynamic Drug Interactions [Sec. 2.6.2.5].