Integrated Review

Application Type	NDA
Application Number(s)	210806 and 210807
Priority or Standard	Standard
Submit Date(s)	October 21, 2017
Received Date(s)	October 23, 2017
PDUFA Goal Date	October 23, 2018
Division/Office	Division of Antiviral Products (DAVP)
Review Completion Date	See DARRTS electronic signature page
Established Name	Doravirine, DOR and doravirine/lamivudine/tenofovir disoproxil fumarate, DOR, 3TC, TDF, fixed-dose combination (FDC) tablet
(Proposed) Trade Name	PIFELTRO (DOR), DELSTRIGO (DOR, 3TC, TDF)
Pharmacologic Class	Non-nucleoside reverse transcriptase inhibitor
Code name	MK-1439 (DOR), and MK-1439A (DOR, 3TC, TDF)
Applicant	Merck
Dose Form/Formulation(s)	Doravirine 100-mg tablet and doravirine/lamivudine/tenofovir disoproxil fumarate 100-mg/300-mg/300-mg fixed-dose combination tablet
Dosing Regimen	One tablet taken orally once daily with or without food
Applicant Proposed Indication(s)/Population(s)	*Doravirine*: In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients *Doravirine/lamivudine/tenofovir disoproxil fumarate fixed-dose combination tablet:* is indicated as a complete regimen for the treatment of HIV-1 infection in treatment-naïve patients
Regulatory Action	Approval
Approved Indication(s)/Population(s) (if applicable)	PIFELTRO™ is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history. DELSTRIGO™ is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history

Table of Contents

Table of Tables

Table of Figures

Glossary

ABC	abacavir
ABC/3TC	fixed-dose combination tablet of 600 mg of abacavir and 300 mg of lamivudine
AC	active control
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atorvastatin
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
C_{24}	concentration at 24 hours postadministration
CCR5	C-C chemokine receptor type 5
$CD4^+$	positive for cluster of differentiation 4, a glycoprotein found on the surface of immune cells
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
Crl:WI	Charles River Wistar
CYP	cytochrome P450
DAIDS	Division of AIDS
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
DAVP	Division of Antiviral Products
DOR	doravirine (MK-1439)
DOR/3TC/TDF	(MK-1439A) fixed-dose combination tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate
DRV	darunavir
DRV+r	800 mg darunavir boosted with 100 mg ritonavir
DTG	dolutegravir
EC_{50}	effective concentration inhibiting 50% virus growth
EC_{95}	effective concentration inhibiting 95% virus growth
ECG	electrocardiogram
EFD	embryo-fetal development
EFV	efavirenz
EFV/FTC/TDF	fixed-dose combination tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate
ETR	etravirine
EVR	elbasvir
FAS	full analysis set

FC	fold change
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	fixed-dose combination
FTC	emtricitabine
GCP	good clinical practice
GFP	green fluorescent protein
GLP	good laboratory practice
GVR	grazoprevir
HDL-C	high-density lipoprotein cholesterol
HIV-1	human immunodeficiency virus type-1
HPMCAS	hydroxypropyl methylcellulose-acetate succinate
5-HT_{2B}	5-hydroxytryptamine (serotonin) receptor 2B
IC_{50}	concentration inhibiting 50% activity
IND	investigational new drug
INSTI	integrase strand transfer inhibitors
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
LDL-C	low-density lipoprotein cholesterol
LDP	ledipasvir
MATE	multi-antimicrobial extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MOI	multiplicity of infection
MT4 cells	T cell line derived from a human T cell leukemia
NDA	new drug application
NI	noninferiority
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NPE	neuropsychiatric event
NRTI	nucleos(t)ide reverse transcriptase inhibitor
OAP	Office of Antimicrobial Products
OATP	organic-anion-transporting polypeptide
OCS	Office of Computational Sciences
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PDUFA	Prescription Drug User Fee Act
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PND	postnatal day

popPK	population pharmacokinetics
PP	per protocol
QD	once daily
RHD	recommended human dose
RPV	rilpivirine
RSE	relative standard error
RT	reverse transcriptase
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SUR	Safety Update Report
3TC	lamivudine
TDF	tenofovir disoproxil fumarate
TDF/FTC	fixed-dose combination tablet of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine
TEAE	treatment-emergent adverse event
TFV	tenofovir
ULN	upper limit of normal
U.S.	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WT	wildtype

I. Executive Summary

1. Summary of Regulatory Action

These new drug applications (NDAs) for doravirine (DOR) and doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) fixed-dose combination tablets for oral use are submitted by Merck. DOR is a new non-nucleoside reverse transcriptase inhibitor (NNRTI), and lamivudine and tenofovir disoproxil fumarate are previously approved nucleos(t)ide reverse transcriptase inhibitors. These NDAs were reviewed by the multi-disciplinary review team. Each discipline has recommended approval of both NDAs, and I, the signatory authority for this application, concur with those recommendations. DOR will be approved in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in adult patients with no prior ARV treatment history and DOR/3TC/TDF will be approved as a complete regimen for the treatment of HIV-1 infection in adult patients with no prior ARV treatment history.

The Applicant has submitted two phase 3 adequate and well-controlled trials that provide substantial evidence of efficacy for the indications approved. DOR and DOR/3TC/TDF are safe for the intended use. The DOR development program demonstrated improved safety over protease inhibitor-based and efavirenz-based comparator regimens for certain prespecified analyses of fasting lipid laboratory measures (low-density lipoprotein cholesterol, LDL-C, and non-high-density lipoprotein cholesterol, non-HDL-C) and clinical neuropsychiatric endpoints (neuropsychiatric adverse events (AEs) of dizziness, sleep disorders and disturbances, and altered sensorium). These safety findings were considered a benefit for the use of DOR. The Statistical Review team concurs that appropriate statistical inference testing was conducted for these fasting lipid measures and neuropsychiatric AEs, but recommends inclusion of confidence intervals (CIs) and not p-values in labeling. Labeling will include both CIs and p-values based on precedent and related guidance (see Section II.6.4.2 for a more detailed discussion). We concur that identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance. The overall benefit-risk is favorable as described in the Benefit-Risk Assessment below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Interdisciplinary Assessment document and the separate Product Quality Review.

2. Benefit-Risk Assessment

Table 1. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HIV-1 is a transmissible viral infection that attacks $CD4^+$ cells and thereby weakens the body's immune system. Without effective treatment, HIV-1 leads to progressive destruction of the immune system, resulting in AIDS-defining illnesses and premature death in almost all cases. • In the U.S., 1.1 million people were living with HIV-1 at the end of 2015, and 39,782 people were diagnosed with HIV-1 in 2016.	HIV-1 continues to be a significant public health concern, both globally and domestically. Without effective treatment, HIV-1 leads to debilitating complications and therefore is a serious, life-threatening condition. With effective management, however, HIV-1 can be considered a controllable chronic condition.
Current Treatment Options	• The goal of HIV-1 treatment is to durably suppress HIV-1 viral load, preserve and restore the immune system, reduce associated morbidity, and ultimately improve long-term survival. An additional goal is to decrease HIV-1 transmission and reduce overall public health burden. • Standard of care treatment involves regimens of multiple antiretroviral (ARV) drugs from different mechanistic classes. – Current treatments are considered efficacious for most patients, but can vary by patient characteristics, e.g., baseline HIV-1 viral load, treatment history. – Safety profiles vary by mechanistic class. For example, the non-nucleoside reverse transcriptase inhibitor (NNRTI) class is associated with neuropsychiatric adverse events. The boosted protease inhibitor (PI) class is associated with dyslipidemia. • Identifying an optimal HIV-1 treatment regimen is further complicated by the development of drug resistance, which can affect a patient's use of other drugs in the future, and drug-drug interactions, which limit use of concomitant medications. • Consistent patient adherence is critical to sustaining HIV-1 viral load suppression. Fixed-dose combination products offer simpler and more convenient ARV regimens, increasing the likelihood of patient adherence.	Optimal management of HIV-1 is complex and must consider patients' individual needs. The treatment armamentarium would continue to benefit from additional effective ARV options—particularly as fixed-dose combinations—that are well-tolerated, have minimal drug-drug interactions, and are convenient to take. The armamentarium would also benefit from the availability of treatments with more favorable safety profiles.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of doravirine (DOR)-containing treatment of HIV-1 in patients with no prior ARV treatment history was evaluated in two main clinical trials: – PN018 “DRIVE-FORWARD” compared DOR versus darunavir boosted with ritonavir (DRV+r), a treatment from the PI class, both in combination with other ARVs. – PN021 “DRIVE-AHEAD” compared DOR as part of a fixed-dose combination versus efavirenz (EFV) (NNRTI class) combination treatment. – Together, the trials enrolled 1494 patients: 747 in DOR-containing arms and 747 in comparator arms. There were no significant issues with trial design, conduct, or analysis. • Both trials used an endpoint involving achieving a threshold measure of HIV-1 viral load (HIV-1 RNA <50 copies/mL). This endpoint is a well-established indicator of durable viral load suppression that results in clinical benefit. – In PN018, 83.8% of patients in the DOR treatment arm were below the threshold viral load at week 48 versus 79.9% of patients in the comparator arm. The results met the prespecified threshold for noninferiority. – In PN021, 84.3% of patients in the DOR combination treatment arm were below the threshold at week 48 versus 80.8% of patients in the comparator arm, meeting the prespecified threshold for noninferiority. – The results are consistent across various patient subgroups and robust to sensitivity analyses. • With the goal of demonstrating the superiority of DOR-containing treatment with respect to both unintended neuropsychiatric events and lipid elevations, the Applicant submitted prespecified analyses comparing DOR-containing treatment to the comparators. – Both PN018 and PN021 demonstrated statistically significant changes from baseline in two lipid parameters (LDL-C and non-HDL-C) compared to the active comparator arms at week 48. *(continued below)*	The submitted evidence shows durable viral load suppression in more than 80% of patients at 48 weeks. This clearly demonstrates a meaningful benefit in treating HIV-1 in treatment-naïve patients. This evidence further demonstrates that: • The efficacy of DOR-containing treatment is similar to both DRV+r- and EFV-containing regimens. • The studied DOR-containing treatments offer a safety advantage over the comparator treatments with regard to lipid elevations; however, the long-term clinical significance of the changes in lipids is unknown. • The DOR combination treatment offers a safety advantage over the EFV combination treatment with regard to neuropsychiatric adverse events. DOR-treated patients do experience neuropsychiatric adverse events; however, at lesser frequency than those receiving EFV. In light of study limitations, there remains important uncertainty about: 1. The comparable effectiveness or safety of DOR-containing regimens to integrase strand transfer inhibitor-containing (INSTI-containing) regimens, which are recommended agents for patients who have not received any treatment of their HIV-1 infection. 2. The effectiveness of DOR for treatment-experienced patients. The potential benefit of DOR for these patients will likely depend on a number of factors including baseline resistance profile and prior treatment history.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit ***(continued)***	– PN021 demonstrated statistically significantly lower proportions of patients experiencing neuropsychiatric AEs of dizziness, sleep disorders and disturbances, and altered sensorium in the DOR-containing arms compared to the active comparator arms. An additional trial, PN007, provided further supportive evidence. • None of the submitted clinical trials included comparison of DOR to a treatment from the INSTI class. INSTI-containing therapy is currently recommended in U.S. treatment guidelines as the initial regimen for most people with HIV-1. • There is no clinical evidence that DOR will be effective in those who have transmitted NNRTI resistance or in those with prior ARV treatment history who develop NNRTI resistance. If transmission of NNRTI resistant virus is suspected, resistance testing should guide the use of DOR.	*(See previous page)*
Risk and Risk Management	• The safety database included 855 patients who received the intended DOR dose for at least 48 weeks, exceeding the 300 to 500 subjects recommended for safety evaluations in the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015). Patient characteristics were adequately represented in terms of gender, age, race, and ethnicity. • The following adverse reactions occurred in at least five percent of DOR-treated patients: nausea, fatigue, headache, diarrhea, abdominal pain, abnormal dreams, and dizziness. Other issues assessed in depth: • More DOR-treated subjects experienced grade 1 and 2 increases in bilirubin, which were mostly isolated events without evidence of hepatotoxicity. Routine pharmacovigilance can adequately monitor related safety concerns. *(continued below)*	Overall, the safety evaluation is adequate to assess the safety of DOR and the DOR combination treatment for the proposed indication, dosage regimen, duration, and patient populations. The safety profile is well-characterized and none of the identified safety issues would preclude approval of DOR-containing treatment. The identified drug-drug interactions issues should be reflected in labeling, including: • Need for increased dosing of DOR when given with rifabutin, a CYP3A inducer. • Contraindication of DOR-containing treatment with a strong CYP3A inducer, due to the risk of developing resistance that can impede a patient's future use of other NNRTI-based regimens. *(continued below)*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management ***(continued)***	• DOR is primarily metabolized by cytochrome P450 3A (CYP3A) and DOR exposures increase when used with drugs that are strong inhibitors of CYP3A. However, the available safety data indicate that no DOR dose adjustment is needed when given with strong inhibitors of CYP3A. • Likewise, significant decreases of DOR plasma concentrations may occur when DOR is concomitantly used with strong inducers of CYP3A, which may decrease the effectiveness of DOR and lead to the development of resistance. Development of resistance can limit or eliminate the effectiveness of subsequent NNRTI-based regimens. – Rifabutin is a CYP3A inducer. The submitted evidence demonstrated that an additional dose of DOR can maintain effective DOR exposures when used with rifabutin; however, no evidence was provided to show that dose adjustments can maintain DOR's efficacy when used with strong inducers, such as rifampin. – M9 is the major metabolite of DOR and is eliminated via the kidneys. Based on modeling and simulation, concentrations of M9 are predicted to increase up to 4-fold when DOR is used with rifabutin. No human pharmacokinetic data are available for M9; however, the available data including human DOR exposure data, nonclinical DOR safety margin data, and negative prediction for M9 genetic toxicity, although not conclusive, did not establish adverse clinical impacts of concomitant use of DOR and rifabutin. • An imbalance in thyroid adenoma and carcinoma was observed at the highest studied dose (equivalent to approximately seven times the human dose) in a 2-year rat carcinogenicity study. This finding, however, was within the range observed in historical control rat studies. Further, no thyroid adenomas or carcinomas were reported in DOR-treated patients, making the clinical significance of this rat finding unclear. • Phase 3 trials are ongoing to provide safety data beyond 48 weeks.	Important uncertainties remain about the potential adverse effects of increased M9 concentrations when DOR at the recommended dose is coadministered with rifabutin, including in patients with renal impairment. Therefore, a postmarketing commitment (PMC) to conduct a drug-drug interaction trial in humans is recommended. Otherwise, no risk management beyond standard pharmacovigilance and ongoing phase 3 clinical trials is warranted based on this review.

Conclusions Regarding Benefit-Risk

HIV-1 continues to be a significant public health concern. Although the HIV-1 treatment armamentarium is robust, additional effective ARV treatment options that provide greater flexibility in meeting patients' individual needs and facilitating their tolerance for and adherence to lifelong HIV-1 treatment are needed. The submitted evidence clearly demonstrates that DOR-containing treatment is effective in treating HIV-1 in patients with no prior ARV treatment history. We can also conclude that DOR-containing treatments have similar efficacy to another NNRTI (EFV) and a PI (DRV+r), with the caveat that uncertainty remains about how these benefits compare to the most commonly used (INSTI) regimens. There is also uncertainty about how the benefits of DOR generalize to patients who have transmitted NNRTI resistance and in those with prior NNRTI treatment experience.

The safety evaluation for DOR was adequate, and the demonstrated safety profile of DOR-containing treatment in the treatment-naïve HIV-1 population is acceptable for the indicated dose and population of HIV-1 patients with no prior ARV treatment history. Moreover, DOR exhibits a safety advantage with respect to lipid elevations and neuropsychiatric adverse events over the two treatment regimens it was compared to, with the caveat that uncertainty remains about the comparable safety of DOR to the INSTI regimens. There are also important remaining uncertainties about the safety of DOR's metabolite (M9) when DOR is concomitantly used with rifabutin, which can be addressed through postmarketing studies. Other safety considerations, such as the identified drug-drug interactions and preclinical safety findings, can be adequately addressed in labeling.

With all factors considered, the benefits of DOR used in combination with other ARV treatments clearly outweigh the risks for HIV-1 infection in adult patients who have no prior history of ARV treatment. Its availability will give patients and providers one more safe and effective option to manage this complex disease. The uncertainties about extrapolating efficacy to patients with NNRTI resistance, however, justify limiting the indication to only the population of adult patients who have no prior ARV treatment history.

II. Interdisciplinary Assessment

3. Introduction

The Applicant submits these new drug applications (NDAs) for doravirine (MK-1439) (DOR) and doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) fixed-dose combination (FDC) seeking the following indications:

- DOR is indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in treatment-naïve patients
- DOR/3TC/TDF is indicated as a complete regimen for the treatment of HIV-1 infection in treatment-naïve patients

DOR is a new non-nucleoside reverse transcriptase inhibitor (NNRTI) that inhibits HIV-1 replication by noncompetitive binding of HIV-1 reverse transcriptase. DOR is the sixth NNRTI added to this mechanistic class. The other components of the FDC, 3TC and TDF, are previously approved nucleos(t)ide reverse transcriptase inhibitors. The regulatory history is summarized in Section III.13.

Standard HIV-1 treatment involves the administration of multiple antiretroviral drugs targeting different events in the viral life cycle. Approved drugs belong to seven mechanistic classes: nucleos(t)ide reverse transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), C-C chemokine receptor type 5 (CCR5) antagonists, fusion/entry inhibitors, and CD4-directed postattachment HIV-1 inhibitors. Currently, effective combination ARV treatment of HIV-1 infection for treatment-naïve or treatment-experienced patients without history of virologic failure is generally comprised of at least three ARV medications, two of which belong in the NRTI class and a third agent selected from the INSTI, PI, or NNRTI classes.

The key goal of the development program was to show noninferiority (NI) of DOR compared to efavirenz- and darunavir/ritonavir-based regimens. An additional goal was to show superiority with respect to two prespecified safety endpoints: lipid changes from baseline and neuropsychiatric events (NPE). The two phase 3 trials were conducted with treatment-naïve patients to support the use in treatment-naïve patients only. In order to seek an indication in treatment-experienced patients or for use in those patients with NNRTI acquired resistance, prospective, randomized clinical trials are needed. Given the concerns with cross-resistance among ARVs, clinical trials are needed to assess durability prior to approval for the treatment-experienced population, including those with NNRTI resistance.

Sections 6 and 7 of the review summarize the key review issues relating to evaluation of benefit and risk and risk management, respectively. The key review issues were addressed by an

interdisciplinary review team approach and each applicable discipline contributed to the overall team assessment and conclusions.

The review issues relating to the evaluation of benefit include:

- Acceptability of the prespecified safety analyses to show superiority of DOR over comparator to support proposed labeling
- Presentation of the prespecified and non-prespecified safety analyses in labeling with respect to treatment difference, 95% confidence interval (CI) and p-values

The review issues relating to risk and risk management include:

- Resistance:
  - Determination of emergent DOR-associated resistance in trials and impact of cross-resistance potential
  - Discrepancy in resistance data and resistance emergence between PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD
- Drug-drug interactions:
  - Reduction in DOR concentrations when administered with or following cessation of cytochrome P450 3A (CYP3A) inducers
  - Increased exposure of DOR M9 metabolite when DOR is administered with a CYP3A inducer
  - Increase in DOR concentrations when administered with a strong CYP3A inhibitor
- Imbalance in thyroid adenoma and carcinoma in 2-year carcinogenicity study
- Increases in bilirubin with DOR versus comparators

3.1. Approach to the Review

Table 2 provides an overview of the clinical trials important to the review of DOR and DOR/3TC/TDF efficacy and safety: two phase 3 trials, PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, and the supportive phase 2b dose-ranging trial, PN007.

Relative bioavailability studies showing similar DOR, TDF, and 3TC pharmacokinetics (PK) when administered individually or as part of DOR/3TC/TDF (PN014, PN015, and PN026) and Safety Update Report (SUR) data also contributed to the benefit-risk assessment of DOR-containing therapy.

Table 2. Summary of Clinical Trials Important to the Review of Efficacy and Safety

Study	Study Population	Trial Design	Study Treatment (drug, dose, N)	Primary Study Endpoints	No. of Subjects Enrolled*	Treatment Duration/ Follow Up	Centers and Count-ries
007	HIV-1-infected adults ≥18 years of age with HIV-1 RNA ≥1,000 copies/mL and $CD4^+$ cell counts ≥100 cells/mm^3 at screening	Phase 2b, MC, R, DB, AC, multipart, dose-ranging trial	Part 1 DOR 25 mg: 40 DOR 50 mg: 43 DOR 100 mg: 42 DOR 200 mg: 41 EFV 600 mg: 42 Part 2 DOR 100 mg: 66 EFV 600 mg: 66 All taken orally QD with FTC/TDF 200/300 mg	Efficacy: Proportion of subjects with HIV-1 RNA <40 copies/mL at week 24 in Part 1 and in Part 1/2 combined Safety: Proportion of subjects with central nervous system AEs by week 8 and by week 24 in Part 1/2 combined	Part 1 208 Part 2 132	Part 1 DOR: 24 weeks + 72 weeks on chosen DOR dose + 14 days follow-up EFV: 96 weeks + 14 days follow-up Part 2 96 weeks + 14 days follow-up	73 centers in 11 countries
018	HIV-1-infected adults ≥18 years of age with HIV-1 RNA ≥1,000 copies/mL at screening with no known resistance to any of the study drugs	Phase 3, MC, R, DB, AC, NI trial	DOR 100 mg: 383 DRV+r 800+100 mg: 383 All taken orally QD with FTC/TDF 200/300 mg or ABC/3TC 600/300 mg, based on investigator's selection	Efficacy: Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at week 48 Safety: Change from baseline in fasting LDL-C and non-HDL-C at week 48	766	96 weeks + 96 weeks open-label extension (all receive DOR 100 mg) + 14 days follow-up	133 sites in 15 countries

Study	Study Population	Trial Design	Study Treatment (drug, dose, N)	Primary Study Endpoints	No. of Subjects Enrolled*	Treatment Duration/ Follow Up	Centers and Count-ries
021	HIV-1-infected adults ≥18 years of age with HIV-1 RNA ≥1,000 copies/mL at screening with no known resistance to any of the study drugs	Phase 3, MC, R, DB, AC, NI trial	DOR/3TC/TDF 100/300/300 mg: 364 EFV/FTC/TDF 600/200/300 mg: 364 All taken orally QD	Efficacy: Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at week 48 Safety: - Proportion of subjects with AEs in the following categories: dizziness, sleep disorders and disturbances, and altered sensorium - Change from baseline in fasting LDL-C and non-HDL-C	728	96 weeks + 96 weeks open-label extension (all receive DOR/3TC/TDF 100/300/300 mg) + 14 days follow-up	126 sites in 22 countries

3TC = lamivudine; ABC = abacavir; AC = active control; AE = adverse event; DB = double-blind; DOR = doravirine (MK-1439); FTC = emtricitabine; HDL-C = high-density lipoprotein cholesterol; HIV-1 = human immunodeficiency virus type-1; LDL-C = low-density lipoprotein cholesterol; MC = multicenter; NI = noninferiority; PC = placebo-controlled; PG = parallel group; QD = once daily; R = randomized; TDF = tenofovir disoproxil fumarate

* Number reflects number of patients randomized and treated

4. Patient Experience Data

Table 3. Patient Experience Data That Informed Assessment of Benefit and Risk

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Appendix III.18 Clinical Safety Assessment Additional Information and Assessment
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data was submitted by Applicant, indicate here:**	
Data considered in the assessment (but not submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Pharmacologic properties of DOR that are relevant to the interpretation of benefit and risk are summarized in Table 4. The table includes minimal information about 3TC and TDF because the agents are approved in other formulations. The table includes 3TC and TDF information related to the DOR/3TC/TDF formulation and information relevant to therapeutic individualization.

Table 4. Summary of Pharmacologic Activity and Clinical Pharmacology

Characteristic	Drug Information
Pharmacologic Activity	
Mechanism of action	DOR is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). HIV-1 reverse transcriptase (RT) is essential for HIV-1 replication as it converts the linear, single-stranded RNA genome into linear, double-stranded DNA using its RT and RNase H activities. (See Section 5.1 and Appendix III.19.1)
Antiviral activity	DOR had EC_{50} values ranging from 0.6nM to 10nM against 10 different HIV-1 subtypes. The EC_{50} value of DOR against WT virus was 12nM when extrapolated to 100% normal human serum in MT4-gag-GFP T lymphoid cells. DOR EC_{50} values against mutant viruses with NNRTI substitutions K103N, Y181C and K103N/Y181C were 21nM, 31nM, and 33nM, respectively, in MT4-gag-GFP T lymphoid cells (See Section 5.1 and Appendix III.19.1;Table 122).
Active moieties	DOR: Parent is active and accounts for 75% of circulating radioactivity in plasma. 3TC: Intracellularly, 3TC is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP); Tenofovir: Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form active tenofovir diphosphate.
QT prolongation	DOR: At a dose of 1200 mg, which provides approximately four times the peak concentration observed following the recommended dose, DOR does not prolong the QT interval to any clinically relevant extent.
General Information	
Bioanalysis	Validated HPLC/MS/MS methods were used to determine the concentrations of DOR, 3TC, tenofovir (TFV), and coadministered drugs in human plasma, urine, and feces (as applicable to individual studies).
Healthy versus patients	DOR PK are similar in healthy subjects and HIV-1-infected subjects.
Drug exposure at steady state following the therapeutic dosing regimen	<table><tr><th>Parameter</th><th>DOR</th><th>3TC</th><th>TFV*</th></tr><tr><td>AUC (mcg*hr/mL)</td><td>16.7±4.51</td><td>8.87±1.83</td><td>2.29±0.69</td></tr><tr><td>C_{max} (mcg/mL)</td><td>0.98±0.18</td><td>2.04±0.54</td><td>0.30±0.09</td></tr><tr><td>C_{24}(mcg/mL)</td><td>0.44±0.18</td><td></td><td></td></tr></table>*Single 300-mg dose of TDF to HIV-1-infected subjects in the fasted state

Characteristic	Drug Information
Range of effective dose or exposure	The relationships between DOR exposure (AUC and C_{24}) and all efficacy endpoints in the phase 2 study were flat over the range of exposure achieved following doses of 25 to 200 mg QD (the full dose range studied).
Maximally tolerated dose or exposure	Not determined. No safety findings of concern were identified in the evaluated dose range (25 to 200 mg QD).
Dose proportionality	DOR AUC and C_{max} increase less than dose proportionally.
Accumulation	DOR: 1.2 to 1.5 (for DOR 30 to 240 QD)
Bridge between to-be marketed and clinical trial formulations	The to-be-marketed DOR formulation is a coated tablet, while an uncoated tablet was used in the pivotal phase 3 study (018). Based on a bioavailability study and supportive dissolution data, the two formulations are not substantially different. (See Appendix III.15.2.1) The DOR/3TC/TDF to-be-marketed formulation was used in the phase 3 trial, P021.
Absorption	
Bioavailability	Absolute bioavailability: DOR: 64%, 3TC: 86%, TDF: 25%
T_{max}	DOR: 2 hr; 3TC: 3.2 hr (fed) and 0.9 hr (fasted); TDF: 1 hr
Food effect (Fed/fasted) Geometric least square mean and 90% CI (continued below)	**DOR/3TC/TDF** (See Appendix III.15.2.1)

DOR $AUC_{0-\infty}$ 1.10 (1.01, 1.20)	DOR C_{max} 0.95 (0.80, 1.12)	DOR T_{max} T_{max} prolonged from 3 hr (fasted) to 6 hr (fed)
3TC $AUC_{0-\infty}$ 0.93 (0.84, 1.03)	3TC C_{max} 0.81 (0.65, 1.01)	3TC T_{max} T_{max} prolonged from 1 hr (fasted) to 3 hr (fed)
TFV $AUC_{0-\infty}$ 1.27 (1.17, 1.37)	TFV C_{max} 0.88 (0.74, 1.04)	TFV T_{max} T_{max} prolonged from 1 hr (fasted) to 3 hr (fed)
Fed state =30 minutes after start of high-fat, high-calorie breakfast		

Food effect (Fed/fasted) Geometric least square mean and 90% CI (continued)	**DOR Tablet** (See Appendix III.15.2.1)		
	$AUC_{0-\infty}$	C_{max}	T_{max}
	1.16 (1.06, 1.26)	1.0 (0.89, 1.19)	T_{max} prolonged from 2.5 hr (fasted) to 4.0 hr (fed)
	Fed state =30 minutes after start of high-fat, high-calorie breakfast		

Characteristic	Drug Information
Distribution	
Volume of distribution	DOR: V/F is 60.5 L
Plasma protein binding	DOR: 76% 3TC and TDF: low In MT4 cell, the EC_{95} values of DOR against WT HIV-1 increased 1.8- to 3.2-fold in the presence of 50% normal human serum compared to 10% normal human serum.
As substrate of transporters	DOR: no evidence that DOR is a substrate of transporters. (See Appendix III.15.1)
Elimination	
Mass balance results	DOR: 90.4% of the DOR dose was excreted in feces with the majority as unchanged drug (84.1%). The majority of the absorbed dose was excreted in urine both as unchanged drug (2.2%) and metabolites (7.2%). Thus, the predominant mechanism of elimination of the absorbed dose was metabolism (primarily forming the oxidative metabolite M9) (See Appendix III.15.2.1)
Apparent oral clearance	DOR: 106 mL/min 3TC: 398 mL/min TDF: 1044 mL/min
Terminal elimination half-life (median)	DOR: 15 hr 3TC: 5 to 7 hr TDF: 17 hr
Primary metabolic pathway(s)	DOR: CYP3A (See Appendix III.15.1) 3TC: minor metabolism TDF: minor metabolism
Primary excretion pathways (% dose) ±SD	DOR: 6% renal; biliary excretion is minor 3TC: 70% renal TDF: 70 to 80% renal
Drug Interaction Liability (Drug as Perpetrator) (See Appendix III.15.1)	
Inhibition/induction of metabolism	DOR, 3TC, and TDF do not inhibit or induce CYP enzymes or UGT1A1
Inhibition/induction of transporter systems	DOR, 3TC,and TDF are not expected to inhibit major transporters at the clinical dose.

3TC = lamivudine; AUC = area under the curve; C_{24} = concentration 24 hours after administration; CYP = cytochrome; DOR = doravirine (MK-1439); EC_{50} = effective concentration inhibiting 50% virus growth; GFP = green fluorescent protein; HIV-1 = human immunodeficiency virus type-1; MT4 = a T cell line derived from a human T cell leukemia; NNRTI = non-nucleoside reverse transcriptase inhibitor; PK = pharmacokinetic; QD = once daily; RT = reverse transcriptase; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; V/F = volume of distribution/bioavailability; WT = wildtype

[a] PK parameters are presented as mean ± standard deviation (SD) or median (minimum to maximum) unless otherwise noted;

[b] Approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical data support the potential effectiveness of DOR for the treatment of HIV-1 infection based on the following assessments:

- Structural, biochemical, and virologic studies support the mechanism of action, and DOR is an NNRTI of HIV-1.
- DOR shows good antiviral activity at concentrations that can be achieved in vivo without inducing toxic effects to cells.
- DOR has broad antiviral activity and is expected to have similar clinical antiviral activity as the other approved NNRTIs in the treatment-naive population.
- Based on cell culture data, antagonism is not a concern in a clinical setting and can be combined with other approved ARVs.

These data (summarized below) support the development program for DOR. However, based on the cross-resistance issue between DOR and with other NNRTIs, uncertainties exist regarding the activity of DOR against NNRTI-resistant viral strains in treatment-experienced patients and in patients with acquired NNRTI resistance.

Mechanism of Action

There are four other members in the NNRTI class of anti-HIV-1 drugs (efavirenz, etravirine, nevirapine and rilpivirine), and DOR has the same mechanism of action as the other drugs in this class. Co-crystallization of DOR and HIV-1 reverse transcriptase (RT) and the resultant X-ray structures showed that DOR binds to the classic NNRTI pocket of reverse transcriptase. Using an electrochemiluminescence RT biochemical assay and full-length recombinant HIV-1 RT proteins, the inhibitory concentration at 50% (IC_{50}) of DOR for RNA-dependent DNA polymerization of wildtype (WT) RT was 12.2nM. This was similar to mutant RTs expressing NNRTI resistance substitutions K103N (9.7nM) and Y181C (9.7nM).

Antiviral Activity in Cell Culture

The effective concentration inhibiting 50% virus growth (EC_{50}) value of DOR against WT virus was 12nM in T lymphoid cells when extrapolated to 100% normal human serum. DOR had no cytotoxicity at concentrations up to 100µM after ~72 hours of treatment in the following cell types: (1) stationary or activated peripheral blood mononuclear cells (PBMCs); (2) $CD4^+$ T cells, monocytes, and macrophages; and (3) proliferating MT4, SupT1, and HL60 cell lines treated for ~72 hours. In MT4 cells, DOR has a therapeutic index of >8,333. In addition, DOR had IC_{50} values of >100µM against purified human DNA polymerases α, β, and γ in biochemical assays showing it would be unlikely to inhibit these human DNA polymerases.

The antiviral activity of DOR was tested against 10 different subtypes of HIV-1 (Table 123) and had EC_{50} values ranging from 0.6nM to 10nM against these HIV-1 subtypes.

Cross-Resistance in Cell Culture

DOR had a similar antiviral activity profile in cell culture to rilpivirine and etravirine against mutant viruses with common NNRTI resistance substitutions (Table 122); however, this was highly dependent on the combination of NNRTI substitutions present. The common NNRTI resistance-associated substitutions (V106M, V108I, V179D, Y188C, Y188H, P236L) generally conferred less than 5-fold change in decreased susceptibility to DOR (Table 122). But, when in combination with multiple NNRTI resistance substitutions, these common substitutions could confer >10-fold to >100-fold decreased susceptibility to DOR.

Additional Cell Culture Data

The combination antiviral activity relationships of DOR with each of 18 FDA-approved anti-HIV-1 drugs (NNRTI: delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine; NRTI: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, zalcitabine, zidovudine; CCR5 coreceptor antagonist: maraviroc; gp41 fusion inhibitor: enfuvirtide; INSTI, raltegravir; PI: darunavir, indinavir) were tested against HIV-1_{IIIB} in CEM-SS cells (a human T-lymphoblastoid cell) and did not show antagonism on their combined antiviral activities (mean antagonism volume values <-50) (Table 125).

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Dose Selection and Potential Effectiveness

The doses selected for evaluation in phase 1b through phase 3 were acceptable based on virology, human PK, and exposure-response data. These studies were conducted in treatment-naïve HIV-infected patients, the indication sought in this application.

The phase 1b proof of concept study (P005) evaluated DOR doses of 25 mg (DOR: placebo, 6:3) and 200 mg once daily (QD; DOR: placebo, 6:3), administered as monotherapy for 7 days. The Applicant selected a concentration at 24 hours postadministration (C_{24}) ≥54nM as the PK target for the phase 1b study because that concentration is 95% effective against the NNRTI double-mutant K103N/Y181C. PK data from healthy subjects (P001) indicated a dose of 25 mg would achieve a mean C_{24} on day 1 of 213nM and >95% of the population was predicted to achieve C_{24} >148nM. The high dose of 200 mg was selected to minimize overlap of exposure between the doses and obtain study data from distinct exposures.

On day 8 of the phase 1b study, the mean placebo corrected HIV-1 RNA change from baseline was ~1.3 $\log_{10}$ copies/mL for both dose levels. Thus, the phase 2b trial (P007) evaluated DOR doses of 25, 50, 100, and 200 mg QD. No clinically meaningful association was found between DOR exposure and efficacy endpoints over the range of exposure achieved between 25- to 200-mg doses. DOR 100 mg QD was selected for phase 3 to accommodate exposure changes due to drug interactions. (See Appendix III.15.2.5)

Exposure-response information indicates the proposed DOR dose, 100 mg QD, is acceptable for the general patient population.

Exposure-response evaluations for efficacy in the phase 3 studies suggest the steady state DOR $AUC_{0\text{-}24}$ (area under the concentration-time curve over 24 hours) and C_{24} values achieved following the proposed 100 mg QD dose are associated with high levels of ARV activity and a low rate of virologic failure. The endpoint was HIV-1 RNA <50 copies/mL at week 48.

Exposure-response evaluations for safety in the phase 3 studies indicate the incidence rates of neuropsychiatric adverse events and the change in lipid profiles from baseline were similar across the exposure (AUC, C_{24}, C_{max}) range observed in the studies. (See Appendix III.15.2.5)

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Trial Design

Both PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD were randomized, double-blinded, active-controlled noninferiority trials. In this setting, the use of NI trials is acceptable to support the efficacy of DOR. Several drugs, including the active controls in both trials, have been approved for the treatment of HIV-1 infection in treatment-naïve patients and have "sufficiently well-described effects" of efficacy. The NI trials also allowed subjects randomized

to the control treatment to receive an active treatment for HIV-1 infection. Both trials utilized an NI margin of 10%. The trial designs for PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, as well as the use of a 10% NI margin, are consistent with the recommendations outlined in the *FDA HIV-1 Guidance for Industry* (2015).

At the time the phase 3 trials were designed in 2014, efavirenz (EFV) and darunavir boosted with ritonavir (DRV+r), both in combination with NRTIs, were recommended by the Department of Health and Human Services Adult and Adolescent Treatment Guideline panel as initial combination regimens for ARV-naïve patients. However, it is noted that the two trials lack an INSTI-containing active control comparison, which is currently recommended in the U.S. HIV-1 treatment guidelines as the initial regimen for most people with HIV-1. This limits comparability of the PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD DOR-containing treatment arm safety endpoint results to current standard of care, as it is unknown whether DOR-containing regimens would result in favorable lipid profiles or neuropsychiatric profiles versus INSTI-containing regimens.

Refer to Appendix III.16 for further details on the trial design for PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD.

6.2.2. Eligibility Criteria

Inclusion and exclusion criteria were generally similar for PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD: clinically stable adult subjects (≥18 years) with HIV-1 infection and no prior ARV treatment history, without documented or known resistance to DOR, EFV, 3TC, or TDF (both trials) or abacavir (ABC) (PN018 DRIVE-FORWARD only). See Table 97 and Table 98. The exclusion of subjects with documented or known resistance to DOR creates uncertainty about how the benefits of DOR generalize to patients who have transmitted NNRTI resistance and in those with prior NNRTI treatment experience.

6.2.3. Statistical Analysis Plan

The Applicant's statistical analysis plan (SAP) was considered acceptable. Below is a relevant summary of the SAP that informed the benefit review issues in Sections 6.4.1 and 6.4.2.

For both confirmatory trials, the primary efficacy endpoint was the proportion of subjects that achieve HIV-1 RNA <50 copies/mL at week 48. The primary efficacy endpoint is considered appropriate for the subject population, HIV-1 treatment-naïve patients, per the *FDA HIV-1 Guidance for Industry* (2015). The primary efficacy analysis population was the full analysis set (FAS) population, which included all randomized and treated subjects with baseline data.

Both confirmatory trials utilized secondary efficacy endpoints and secondary analyses of the primary efficacy endpoint. Refer to Appendices III.17.2 to III.17.4 for detailed information on the results.

Both PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD measured safety-related endpoints. For both trials, Tier 1 safety endpoints were prespecified for statistical testing and included in the testing hierarchy:

- Change from baseline in LDL-C and non-HDL-C at week 48 in both trials
- Proportion of subjects with neuropsychiatric AEs in the categories of dizziness, sleep disorders and disturbances, and altered sensorium by week 48 in PN021 DRIVE-AHEAD

Key secondary safety endpoints include:

- Change from baseline in total cholesterol, triglycerides, and HDL-C at week 48 in both trials
- Proportion of subjects with neuropsychiatric AEs in the categories of depression and suicide/self-injury and psychosis and psychotic disorders by week 48 in PN021 DRIVE-AHEAD

Refer to Appendix III.16 for the full list of trial endpoints.

The Applicant conducted both efficacy- and safety-related interim analyses. The Applicant allocated an alpha level of 0.00001 to an efficacy-related interim analysis conducted in PN018 DRIVE-FORWARD and three safety-related interim analyses conducted in PN021 DRIVE-AHEAD each. The lipid endpoints were assessed using ANCOVA (analysis of covariance), adjusted for baseline lipid value. The 95% CI for the neuropsychiatric events were calculated using Miettinen and Nurminen's method.

Refer to Appendix III.16 for further details on the endpoints and statistical analyses for PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD. Refer to Appendix III.17.1 for the trial design for PN007.

6.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

This section summarizes the demographics, baseline disease characteristics and primary efficacy results to support the benefit of DOR for the treatment of HIV-1 infection. The baseline demographics and disease characteristics are well-balanced between treatment arms within both trials and across the trials and are an adequate representation of adult patients with no prior ARV treatment history, including women (approximately 15%) and black/African American patients (approximately 20%).

Table 5 shows the disposition of all screened subjects for both confirmatory trials. The statistical review confirmed the numbers reported for both trials.

Table 5. Disposition of Subjects by Study Population and Study Arm

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Disposition	**DOR N=383 n (%)**	**DRV+r N=383 n (%)**	**DOR/3TC/TDF N=364 n (%)**	**EFV/FTC/TDF N=364 n (%)**
Patients screened	1027		992	
Screen failure	258		258	
Patients randomized	385	384	368	366
ITT population	383 (100%)	383 (100%)	364 (100%)	364 (100%)
Per protocol population	353 (92.2%)	341 (89.0%)	338 (92.9%)	339 (93.1%)
Safety population	383 (100%)	383 (100%)	364 (100%)	364 (100%)
Patients treated				
Completed treatment	327 (85.4%)	312 (81.5%)	313 (86.0%)	303 (83.2%)
Discontinued treatment	56 (14.6%)	71 (18.5%)	51 (14.0%)	61 (16.8%)
Primary reason for discontinuation				
Adverse event	4 (1.0%)	12 (3.1%)	10 (2.7%)	23 (6.3%)
Lack of efficacy	12 (3.1%)	14 (3.7%)	18 (4.9%)	10 (2.7%)
Applicant discontinued	3 (0.8%)	3 (0.8%)	2 (0.5%)	2 (0.5%)
Withdrew consent	10 (2.6%)	13 (3.4%)	8 (2.2%)	11 (3.0%)
Death	1 (0.3%)	0	1 (0.3%)	3 (0.8%)
Other	26 (6.8%)	29 (7.6%)	12 (3.3%)	12 (3.3)

DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; ITT = intent-to-treat

Table 6 contains information regarding demographic characteristics for each treatment arm for both trials. The slight differences observed in some demographic characteristics could be because a larger percentage of subjects in PN021 DRIVE-AHEAD enrolled in Latin America and Asia compared to PN018 DRIVE-FORWARD, which had a larger percentage of subjects enrolled in North America and Europe.

Table 7 contains information regarding baseline disease characteristics for each treatment arm for both trials.

Table 6. Demographic Characteristics: PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Demographic Characteristic	**DOR (N=383) n (%)**	**DRV+r (N=383) n (%)**	**DOR/3TC/TDF (N=364) n (%)**	**EFV/FTC/TDF (N=364) n (%)**
Sex				
Male	319 (83.3%)	326 (85.1%)	305 (83.8%)	311 (85.4%)
Female	64 (16.7%)	57 (14.9%)	59 (16.4%)	53 (14.6%)
Age (years)				
Mean (SD)	34.8 (10.5)	35.7 (10.7)	33.6 (10.5)	32.7 (9.9)
Median	33	34	32	30
Min, max	18, 68	18, 69	18, 70	18, 69
Age Group				
<65 years	381 (99.5%)	379 (99.0%)	362 (99.5%)	362 (99.5%)
≥65 years	2 (0.5%)	4 (1.0%)	2 (0.5%)	2 (0.5%)

Demographic Characteristic	PN018 DRIVE-FORWARD DOR (N=383) n (%)	PN018 DRIVE-FORWARD DRV+r (N=383) n (%)	PN021 DRIVE-AHEAD DOR/3TC/TDF (N=364) n (%)	PN021 DRIVE-AHEAD EFV/FTC/TDF (N=364) n (%)
Race				
White	280 (73.1%)	280 (73.1%)	177 (48.6%)	170 (46.7%)
Black or African American	86 (22.5%)	88 (23.0%)	67 (18.4%)	68 (18.7%)
Asian	7 (1.8%)	7 (1.8%)	59 (16.2%)	65 (17.9%)
American Indian or Alaska Native	3 (0.8%)	3 (0.8%)	10 (2.7%)	6 (1.6%)
Native Hawaiian or other Pacific Islander	1 (0.3%)	2 (0.5%)	0	0
Other	6 (1.6%)	3 (0.8%)	51 (14.0%)	55 (15.1%)
Ethnicity				
Hispanic or Latino	93 (24.3%)	86 (22.5%)	126 (34.6%)	120 (33.0%)
Not Hispanic or Latino	284 (74.2%)	290 (75.7%)	236 (64.8%)	238 (65.4%)
Not reported or unknown	6 (1.6%)	7 (1.8%)	2 (0.6%)	6 (1.6%)
Region				
United States	131 (34.2%)	135 (35.2%)	88 (24.2%)	87 (23.9%)
Canada	9 (2.3%)	11 (2.9%)	3 (0.8%)	7 (1.9%)
Latin America	38 (9.9%)	33 (8.6%)	89 (24.5%)	87 (23.9%)
Europe	170 (44.4%)	179 (46.7%)	88 (24.2%)	94 (25.8%)
Asia/Pacific	12 (3.1%)	3 (0.8%)	59 (16.2%)	62 (17.0%)
Australia	12 (3.1%)	3 (0.8%)	2 (0.5%)	1 (0.3%)
Africa	23 (6.0%)	22 (5.7%)	37 (10.2%)	27 (7.4%)

DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; SD = standard deviation

Table 7. Baseline Disease Characteristics: PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

Disease Characteristics	PN018 DRIVE-FORWARD DOR (n=383)	PN018 DRIVE-FORWARD DRV+r (n=383)	PN021 DRIVE-AHEAD DOR/3TC/TDF (n=364)	PN021 DRIVE-AHEAD EFV/FTC/TDF (n=364)
$CD4^+$ Cell Count ($cells/mm^3$)				
Mean (SD)	433 (208)	412 (230)	435 (218)	415 (211)
Median	410	393	413.5	388
Min, max	19, 1822	19, 1303	19, 1399	19, 1452
	n (%)	**n (%)**	**n (%)**	**n (%)**
$CD4^+$ Cell Count Group ($cells/mm^3$)				
≤50 $cells/mm^3$	6 (1.6%)	19 (5.0%)	9 (2.5%)	10 (2.7%)
51 – 200 $cells/mm^3$	36 (9.4%)	48 (12.5%)	35 (9.6%)	36 (9.9%)
>200 $cells/mm^3$	341 (89.0%)	316 (82.5%)	320 (87.9%)	318 (87.4%)
Baseline HIV-1 RNA				
≤100,000 copies/mL	300 (78.3%)	308 (80.4%)	291 (79.9%)	282 (77.5%)
>100,000 copies/mL	83 (21.7%)	74 (19.3%)	73 (20.1%)	82 (22.5%)
Unknown	0	1 (0.3%)	0	0
Screening HIV-1 RNA*				
≤100,000 copies/mL	290 (75.7%)	289 (75.5%)	275 (75.5%)	274 (75.3%)
>100,000 copies/mL	93 (24.3%)	94 (24.5%)	89 (24.5%)	90 (24.7%)

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Disease Characteristics	**DOR (n=383)**	**DRV+r (n=383)**	**DOR/3TC/TDF (n=364)**	**EFV/FTC/TDF (n=364)**
Screening HIV-1 RNA^				
≤100,000 copies/mL	292 (76.2%)	294 (76.8%)	286 (78.6%)	284 (78.0%)
>100,000 copies/mL	91 (23.8%)	89 (23.2%)	78 (21.4%)	80 (22.0%)
NRTI Background Therapy				
FTC/TDF	333 (86.9%)	335 (87.5%)	---	---
ABC/3TC	50 (13.1%)	48 (12.5%)	---	---
History of AIDS				
Yes	36 (9.4%)	37 (9.7%)	46 (12.6%)	53 (14.6%)
No	347 (90.6%)	346 (90.3%)	318 (87.4%)	311 (85.4%)
Baseline Hepatitis Status*				
Hepatitis B or C Positive	11 (2.9%)	18 (4.7%)	19 (5.2%)	18 (4.9%)
Hepatitis B & C Negative	372 (97.1%)	365 (95.3%)	345 (94.8%)	346 (95.1%)
Viral Subtype				
Clade B	266 (69.5%)	272 (71.0%)	232 (63.7%)	253 (69.5%)
Non-Clade B	117 (30.5%)	111 (29.0%)	130 (35.7%)	111 (30.5%)
Unknown	0	0	2 (0.5%)	0

* Based on number of subjects used to designate randomization strata
^ Based on actual number of subjects that meet the criteria
AIDS = acquired immunodeficiency syndrome; $CD4^+$ = cluster of differentiation 4, a glycoprotein found on the surface of immune cells; DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type-1; NRTI = nucleos(t)ide reverse transcriptase inhibitor; SD = standard deviation

Primary Efficacy Results

The review team was able to replicate the Applicant's analyses of the primary endpoint and agree in both trials, the lower bounds of the 95% CIs for the treatment difference was greater than -10%, leading to conclusions of NI for DOR and DOR/3TC/TDF compared to DRV+r and EFV/FTC/TDF (fixed-dose combination tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate), respectively. The primary, secondary and sensitivity analyses all show similar robust findings and demonstrated the efficacy of DOR and DOR/3TC/TDF in adult patients with no prior ARV treatment history. The basis for these conclusions is summarized below along with references to the appendices for further details.

Table 8 summarizes the primary efficacy analysis: the proportion of subjects in the FAS with HIV-1 RNA <50 copies/mL at week 48, defined using the FDA snapshot algorithm as outlined in the *FDA HIV-1 Guidance for Industry*. The treatment difference in PN018 DRIVE-FORWARD was 3.9% with a 95.001% CI of (-1.6%, 9.4%). The treatment difference in PN021 DRIVE-AHEAD was 3.5% with a 95% CI of (-2.0%, 9.0%).

Because the 95% CI from either trial did not exclude zero, the results do not support a conclusion of superiority.

Refer to Appendices III.17.2 and III.17.3 for secondary and sensitivity analyses of the primary efficacy endpoint.

Table 8. Summary of Primary Efficacy Analysis (Full Analysis Set): HIV-1 RNA Outcomes: PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Full Analysis Set	DOR N=383 n (%)	DRV+r N=383 n (%)	DOR/3TC/TDF N=364 n (%)	EFV/FTC/TDF N=364 n (%)
HIV-1 RNA <50 copies/mL	321 (83.8%)	306 (79.9%)	307 (84.3%)	294 (80.8%)
HIV-1 RNA ≥50 copies/mL	43 (11.2%)	50 (13.1%)	39 (10.7%)	37 (10.2%)
Discontinuation: AE or death	5 (1.3%)	11 (2.9%)	9 (2.5%)	24 (6.6%)
Discontinuation: other reasons	11 (2.9%)	15 (3.9%)	9 (2.5%)	8 (2.2%)
Missing RNA	3 (0.8%)	1 (0.3%)	0	1 (0.3%)
Treatment difference: HIV-1 RNA <50 copies/mL	3.9% 95.001% CI:* -1.6%, 9.4%		3.5% 95% CI: -2.0%, 9.0%	

AE = adverse event; DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type-1
* Level of significance adjusted from 95% to 95.001% to account for efficacy-related interim analysis

Secondary Endpoint Results: $CD4^+$ T-cell Count

Both PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD prespecified week 48 change from baseline in $CD4^+$ T-cell count as a secondary endpoint. The results did not provide evidence of a potentially statistically significant difference in the week 48 change from baseline in $CD4^+$ T-cell count. The review of the Applicant's analysis produced similar results as shown in Table 103. Refer to Appendix III.17.4 for detailed results of this secondary endpoint.

Additional Subgroup, Secondary and Sensitivity Analysis Results

Subgroup analyses of the primary efficacy endpoint produced treatment effects that were mostly favorable to the DOR-containing treatment (see Table 104 and Table 105). However, because the subgroup analyses are not controlled for multiple comparisons or powered for statistical inference, the results are considered exploratory. Refer to Appendix III.17.5 for detailed results of the subgroup analyses.

Secondary and sensitivity analyses of the primary efficacy endpoint as well as analyses of the secondary efficacy endpoints produced consistent findings of NI. The evidence of efficacy is consistent across various thresholds of viral suppression, methods of missing data imputation, and efficacy analysis populations. Refer to Appendices III.17.2 and III.17.3 for detailed results of the secondary and sensitivity analyses of the primary efficacy endpoint, and Appendix III.17.4 for the analyses of the secondary efficacy endpoints.

The findings are also supported by the efficacy results in PN007. Refer to Appendix III.17.1 for detailed efficacy results in PN007.

For PN018 and PN021, rates of virologic failure to DOR were similar in both trials and were comparable with virologic failure rates in the comparator arms. Additionally, emergence of

NRTI resistance substitutions was comparable between the DOR and comparator arms (see Section 7.7.1).

6.4. Review Issues Relevant to the Evaluation of Benefit

The review team concluded the results of the phase 3 trials support the efficacy of DOR in HIV-1-infected adults with no prior ARV treatment history. ***The review team did not identify any issues with assessing benefit of DOR with respect to the primary efficacy endpoint (HIV-1 RNA <50 copies/mL) or any secondary endpoints***; therefore, no further discussion is warranted in this subsection.

The review issues relevant to the evaluation of benefit focus on two prespecified safety endpoints for which DOR showed superiority (benefit) over two active comparators and include the acceptability of the prespecified safety analyses and presentation of prespecified and non-prespecified safety analyses in labeling. Please also refer to Appendix III.17 for additional details regarding the prespecified safety analyses.

6.4.1. Acceptability of Prespecified Safety Analyses to Show Superiority of DOR Over Comparator to Support Proposed Labeling

Issue: The acceptability of prespecified safety analyses demonstrating superiority of DOR-containing treatment over the relevant comparator is a review issue for this application, specifically phase 3 neuropsychiatric event (NPE) and lipid safety analyses and the Applicant's proposal for inclusion in Section 6 labeling. This Section describes the review team's reasoning for including NPE and lipid data in Section 6 of labeling, and Section 6.4.2 of this review describes the review team's recommendation for the presentation of prespecified and non-prespecified NPE and lipid safety analyses with respect to treatment differences, 95% CI, and p-values. While NPE and lipid laboratory parameters are distinct issues, the section below summarizes NPE and lipid safety together because the review team's recommendation was the same for both parameters regarding inclusion of the prespecified safety analyses and inclusion of the treatment difference, 95% CI, and p-values for these prespecified safety analyses in labeling.

Conclusion: The phase 3 NPE and lipid safety analyses demonstrating superiority of DOR-containing treatment over the respective comparator are acceptable and relevant based on prespecified analyses and are recommended for inclusion in DOR-containing Section 6 labeling. This recommendation is based on the following considerations:

Clinical relevance: NPEs have been identified as a safety signal for other NNRTIs, particularly with EFV, and unfavorable fasting lipid changes from baseline have been observed with other HIV-1 ARV treatments, particularly PIs. A goal of the DOR development program was to demonstrate improved safety over EFV- and DRV+r-containing regimens with prespecified analyses of clinical neuropsychiatric and fasting lipid laboratory endpoints. At the End-of-Phase 2 Meeting, the Applicant and FDA agreed on including NPEs and lipid changes from baseline as special safety endpoints in the phase 3 protocols; however, inclusion in labeling was a review issue.

Acceptable statistical methodology: All of the NPE and lipid safety endpoints prespecified for testing were tested in sequential order in order to control Type I error. Lipid sensitivity analyses,

which took into account baseline or on-treatment lipid-lowering therapy, produced the same information as the prespecified lipid analyses.

Team Assessment of NPE and Lipids

Neuropsychiatric Event Analyses

As stated above, a goal of the DOR development program was to demonstrate improved safety over EFV-containing regimens with prespecified analyses of clinical neuropsychiatric endpoints. This subsection presents relevant phase 2 PN007 trial NPE results, End-of-Phase 2 Meeting discussion, and phase 3 PN021 DRIVE-AHEAD NPE results.

End-of-Phase 2 Meeting

At the End-of-Phase 2 Meeting, FDA did not agree with the Applicant's original PN021 DRIVE-AHEAD proposal to pool NPEs for statistical analysis. FDA recommended subdividing the proposed PN021 DRIVE-AHEAD NPE analysis into clinically related, discrete categories and using week 48 timepoint for primary safety endpoint assessment. This latter recommendation to assess longer-term safety and tolerability (e.g. through week 48) was thought to be more clinically relevant in the context of HIV-1: while most NPEs with EFV may occur by week 8, it was unknown whether the same would be true for DOR-containing therapy.

FDA and the Applicant reached agreement on the revised PN021 DRIVE-AHEAD NPE safety endpoint approach to perform sequential testing of each NPE category in the following order: (1) dizziness, (2) sleep disorders and disturbances, (3) altered sensorium, (4) depression and suicide/self-injury, and (5) psychosis and psychotic disorders: this agreement was contingent upon FDA review of the complete protocol and statistical analysis plan. Labeling considerations are contingent on statistical superiority in sequence. Specifically, the finding of statistical superiority for a given safety endpoint was contingent on a finding of statistical superiority of all preceding safety endpoints.

PN007

PN007 data were used to help inform the prespecified PN021 DRIVE-AHEAD NPE analyses. Overall, statistically significantly lower proportions of subjects in the DOR 100 mg arm experienced at least one NPE by weeks 8 and 24, compared to the EFV 600 mg arm. Below is a summary of the PN007 NPE results.

PN007 prespecified the proportion of subjects experiencing at least one protocol-defined NPE by weeks 8 and 24 for statistical testing of superiority as one of the primary objectives. To control Type I error, the week 24 hypothesis was tested only if the week 8 hypothesis was statistically significant. The subject proportions with NPEs in the DOR-containing arm at week 8 and week 24 were 24.1% and 26.9%, respectively, and in the EFV-containing arm at week 8 and week 24 was 44.4% and 47.2%, respectively. The observed treatment difference was -20.4% for both week 8 and week 24 endpoints, favoring DOR 100 mg.

PN021 DRIVE-AHEAD

The prespecified PN021 DRIVE-AHEAD NPE analyses support including the week 48 data in DOR and DOR/3TC/TDF labeling, as proposed by the Applicant. Section 6.4.2 discusses labeling of treatment difference, 95% CIs, and p-values.

PN021 DRIVE-AHEAD included NPEs as a prespecified co-primary endpoint, as agreed upon at the End-of-Phase 2 meeting, with the hypothesis that DOR/3TC/TDF is superior to EFV/FTC/TDF as measured by the subject proportion with all-cause and all grade NPEs by week 48 (superiority tested within category, sequentially, in the order indicated below):

- Dizziness
- Sleep Disorders and Disturbances
- Altered Sensorium

NPEs of Depression and Suicide/Self-Injury and Psychosis and Psychotic Disorders were predefined secondary endpoints. All five NPE categories were defined by Medical Dictionary for Regulatory Activities (MedDRA) groupings and included Division of Antiviral Products End-of-Phase 2 meeting input (see Appendices III.13 and III.17).

Section 6.2 provides PN021 DRIVE-AHEAD prespecified NPE analysis statistical methodology. PN021 DRIVE-AHEAD NPE analyses were conducted in the FAS, per subjects' actual treatment. Nevertheless, all subjects received his/her randomized treatment. All of the safety endpoints prespecified for testing were tested in sequential order in order to control Type I error. The testing of the NPE endpoints is considered acceptable due to the prespecification and the sequential order of the testing of the endpoints.

As shown in Table 9, the proportion of subjects that experienced each of the week 48 endpoints was lower in the DOR/3TC/TDF arm compared to the EFV/FTC/TDF arm. For the prespecified categories of dizziness, sleep disorders and disturbances, and altered sensorium, the analyses produced two-sided p-values less than 0.04997. Therefore, a statistically significantly lower proportion of subjects experienced dizziness, sleep disorders and disturbances, and altered sensorium in the DOR/3TC/TDF arm compared to the EFV/FTC/TDF arm. In addition, a lower proportion of subjects experienced depression and suicide/self-injury, psychosis and psychotic disorders, and one or more NPEs in the DOR/3TC/TDF arm compared to the EFV/FTC/TDF arm.

Table 9. Results of Neuropsychiatric AE Testing in PN021 DRIVE-AHEAD, Week 48

	DOR/3TC/TDF, N=364 n (%) (CI)	EFV/FTC/TDF, N=364 n (%) (CI)	Treatment Difference (95% CI)
Dizziness*	32 (8.8%) (6.1%, 12.2%)	135 (37.1%) (32.1%, 42.3%)	-28.3% (-34.0%, -22.5%) p<0.001
Sleep disorders and disturbances*	44 (12.1%) (8.9%, 15.9%)	93 (25.5%) (21.1%, 30.4%)	-13.5% (-19.1%, -7.9%) p<0.001
Altered sensorium*	16 (4.4%) (2.5%, 7.0%)	30 (8.2%) (5.6%, 11.6%)	-3.8% (-7.6%, -0.3%) p=0.033
Depression and suicide/self-injury^	15 (4.1%) (2.3%, 6.7%)	24 (6.6%) (4.3%, 9.7%)	
Psychosis and psychotic disorders^	1 (0.3%) (0%, 1.5%)	4 (1.1%) (0.3%, 2.8%)	
One or more neuropsychiatric AE^	86 (23.6%) (19.4%, 28.3%)	207 (56.9%) (51.6%, 62.0%)	

Source: statistical reviewer created
AE = adverse event; CI = confidence interval; DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate
*Prespecified categories for analysis
^Not prespecified for analysis. 95% CI provided as part of signal detection

Lipid Analyses

The phase 3 trial original prespecified lipid hypotheses to assess the superiority of DOR-containing therapy to the relevant comparator arms (i.e., DRV+r-containing therapy or EFV/FTC/TDF) were week 48 fasting serum LDL-C and non-HDL-C mean change from baseline. Other lipid-related hypotheses not prespecified for statistical testing were week 48 fasting triglycerides, total cholesterol, and HDL-C mean change from baseline. At the Pre-NDA meeting, the Division of Antiviral Products requested a sensitivity analysis for all lipid-related hypotheses to be consistent with other approved HIV-1 drug labels containing lipid information. Thus, the week 48 sensitivity analyses excluded subjects on baseline lipid-lowering agents, and subjects initiating lipid-lowering therapy postbaseline had their last fasted on-treatment values carried forward. The sensitivity analysis eliminates lipid-lowering therapy as a potential confounder of the treatment effect on the lipid-related endpoints.

Review of the distributions of the baseline characteristics found that they appear to be well-balanced between the DOR-containing arm and the active control arm in both trials. In addition, the distributions appear to be similar in the FAS population and the analysis population for the sensitivity analysis for all treatment arms. The findings do not suggest any measured confounding, but they do not guarantee balanced distribution of all variables between treatment arms within the trials.

Results from the protocol-specified and sensitivity analyses are almost identical for all lipid endpoints in both trials, and support including the sensitivity analyses data in labeling. Table 10 and Table 11 depict the results of the lipid protocol-specified and sensitivity analyses. Across the phase 3 trials, baseline lipid-lowering therapy use was 3% and on-treatment lipid-lowering

therapy initiation was 1%. Subjects in the DOR arm experienced a statistically significantly larger decrease in LDL and non-HDL cholesterol, compared to subjects in the DRV+r arm (see Table 10). Likewise, subjects in the DOR/3TC/TDF arm experienced a statistically significantly larger decrease in LDL and non-HDL cholesterol, compared to subjects in the EFV/FTC/TDF arm. Of note, the clinical benefit of these findings has not been demonstrated.

Table 10. Lipid Endpoints in PN018 DRIVE-FORWARD

		DOR			DRV+r			
Lipid	Analy-sis¥	N	Baseline Mean	Mean Change from Baseline (CI)	N	Baseline Mean	Mean Change from Baseline (CI)	Treatment Difference (CI)
LDL-C*	Orig	326	91.1	-4.5 (-6.8, -2.3)	318	91.7	9.9 (6.9, 12.9)	-14.6 (-18.2, -11.1) p<0.001
	Sens	317	91.4	-4.6 (-6.9, -2.3)	305	92.3	9.5 (6.4, 12.6)	-14.4 (-18.0, -10.8)
Non-HDL-C*	Orig	329	113.4	-5.3 (-7.8, -2.8)	325	114.4	13.8 (10.4, 17.1)	-19.3 (-23.3, -15.3) p<0.001
	Sens	320	113.6	-5.4 (-8.0, -2.9)	311	114.5	13.7 (10.4, 17.1)	-19.4 (-23.4, -15.4)
Total chol.^	Orig	329	156.9	-1.4 (-4.1, 1.4)	325	157.7	17.9 (14.2, 21.6)	
	Sens	320	157.2	-1.4 (-4.2, 1.4)	311	157.8	18.0 (14.3, 21.7)	
Triglycerides^	Orig	329	111.2	-3.1 (-10.6, 4.3)	325	117	22.0 (11.9, 32.1)	
	Sens	320	111	-3.1 (-10.7, 4.6)	311	113.7	24.5 (16.0, 33.1)	
HDL-C^	Orig	329	43.6	3.9 (2.8, 5.1)	325	43.3	4.2 (3.0, 5.4)	
	Sens	320	43.6	4.0 (2.8, 5.2)	311	43.3	4.3 (3.0, 5.5)	

CI = confidence interval; DOR = doravirine (MK-1439); DRV+r =800 mg darunavir boosted with 100 mg ritonavir; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

¥ Orig = original analysis; Sens = sensitivity analysis

* Prespecified categories for analysis

^ Not prespecified for analysis. 95% CI provided as part of signal detection

Table 11. Lipid Endpoints in PN021 DRIVE-AHEAD

		DOR			DRV+r			
Lipid	Analy-sis¥	N	Baseline Mean	Mean Change from Baseline (CI)	N	Baseline Mean	Mean Change from Baseline (CI)	Treatment Difference (CI)
LDL-C*	Orig	330	92	-1.6 (-4.0, 0.8)	305	90.7	8.7 (5.9, 11.6)	-10 (-13.5, -6.5) p<0.001
	Sens	317	91.7	-2.1 (-4.5, 0.3)	298	91.3	8.3 (5.4, 11.2)	-10.2 (-13.8, -6.7)
Non-HDL-C*	Orig	333	115.2	-3.8 (-6.3, -1.4)	314	114.8	13.3 (10.1, 16.5)	-17 (-20.9, -13.2) p<0.001
	Sens	320	114.7	-4.1 (-6.5, -1.7)	307	115.3	12.7 (9.5, 16.0)	-16.9 (-20.8, 13.0)
Total chol.^	Orig	333	157.4	-2.0 (-4.7, 0.8)	314	156.2	21.8 (18.4, 25.2)	-23.4 (-27.6, -19.3)
	Sens	320	156.8	-2.2 (-5.0, 0.5)	307	156.8	21.1 (17.7, 24.6)	-23.4 (-27.5, -19.2)
Triglycerides^	Orig	333	119.5	-12.4 (-19.7, -5.1)	314	123	22 (11.7, 32.3)	-36 (-47.1, -24.8)
	Sens	320	118.7	-12 (-19.4, -4.7)	307	122.6	21.6 (11.0, 32.1)	-35.3 (-46.6, -24.0)
HDL-C^	Orig	333	42.2	1.9 (0.8, 2.9)	314	41.4	8.5 (7.3, 9.7)	-6.5 (-8.0, -5.0)
	Sens	320	42.1	1.8 (0.8, 2.9)	307	41.6	8.4 (7.2, 9.6)	-6.4 (-7.9, -4.9)

CI = confidence interval; DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

¥ Orig. = original analysis; Sens. = sensitivity analysis

*Prespecified categories for analysis

^Not prespecified for analysis. 95% CI provided as part of signal detection

6.4.2. Presentation of Prespecified and Non-Prespecified Safety Analyses in Labeling With Respect to Treatment Difference, 95% CI and p-values

Issues 1 and 2: While Section 6.4.1 presents the reasoning for including NPE and lipid data in Section 6 of labeling, this section addresses the review issue regarding labeling considerations for how to present prespecified and non-prespecified NPE and lipid safety analyses with respect to:

(1) treatment difference, 95% CI, and

(2) p-values because statistical testing results are typically not included in Adverse Reactions, particularly when the test arm demonstrates improved safety over the comparator.

Conclusion 1: Alignment was reached between the review team, Division leadership and Signatory Authority to include in Section 6 of the DOR/3TC/TDF label the treatment difference and 95% CI information only for the NPE categories prespecified for statistical testing (i.e., dizziness, sleep disorders and disturbances, and altered sensorium) and the prespecified lipid parameters for statistical testing (i.e., LDL-C, non-HDL-C). The treatment difference and 95%

CI for the non-prespecified NPE and lipid parameter categories for statistical testing are not included in labeling.

Conclusion 2: Alignment was reached between the clinical team, Division leadership and Signatory Authority to include p-values in labeling for the three NPE categories prespecified for statistical testing and the two prespecified lipid parameters based on the following rationale which is also considered acceptable by the Clinical Reviewer:

(1) The three NPE categories (dizziness, sleep disorders and disturbances, and altered sensorium) and the two lipid parameters (LDL-C, non-HDL-C) were prespecified co-primary endpoints for statistical testing

(2) The FDA Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (2006) states a "confidence interval and a p-value provide complementary information, and both should usually be provided when describing uncertainty of the treatment effect.[1] A confidence interval provides a better numerical description of the uncertainty of the treatment effect and provides some information about its size. A p-value better conveys the strength of the finding (i.e., how likely it is that the observed treatment effect is a chance finding). However, it is generally better not to use a p-value alone."

While the NPE categories reflect safety information which is generally conveyed in the adverse reactions section of labeling, these categories nevertheless reflect a prespecified clinical outcome, and thus it is reasonable to extend the above clinical studies section of labeling guidance to this situation.

From a statistical perspective, the inclusion of p-values in the labeling for the three NPE categories prespecified for statistical testing is not recommended for the following reasons:

- P-values are tools of statistical inference that do not account or incorporate clinical benefit into its inference. Therefore, the p-values cannot be used to determine the clinical benefit of the observed treatment differences.
- P-values are used for making decisions regarding the statistical significance of a result. However, p-values are not designed to influence clinical decision-making at the patient level. Therefore, the p-values should not be used by prescribers to determine treatment choices.

While there is an FDA guidance regarding the clinical studies section of labeling (mentioned above), there is no FDA guidance that discusses the use of p-values in the adverse reactions section of labeling.

Additional labeling recommendations

The review team recommends inclusion of:

- Subject percentages in labeling text for the non-prespecified NPE category of depression and suicide/self-injury; labeling for psychosis and psychotic disorders is not recommended because of the small numbers (≤1.1% in both treatment arms).

[1] Guidance for Industry, *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006) https://www.fda.gov/media/72140/download

- Additional PN021 DRIVE-AHEAD NPE analyses include assessment of severity, treatment discontinuation, onset, and prevalence: the results are recommended for DOR/3TC/TDF labeling to provide further clinical context for prescribers (See Appendix III.22).
- Severity: Most NPEs through week 48 were mild or moderate in severity: DOR/3TC/TDF 97% (83/86) and EFV/FTC/TDF 96% (198/207). Week 48 NPE serious adverse events (SAEs) were reported in only one DOR-treated subject (sleep disorders and disturbances) and three EFV-treated subjects (depression and suicide/self-injury (two), altered sensorium).
- Treatment Discontinuation: NPEs led to treatment discontinuation in 1% of subjects in both the DOR/3TC/TDF (two subjects: sleep disorders and disturbances; depression and suicide/self-injury) and EFV/FTC/TDF groups (five subjects: sleep disorders and disturbances (two), depression and suicide/self-injury (two), sleep disorders and disturbances/dizziness).
- Onset: Most NPEs occurred within the first 4 weeks (DOR/3TC/TDF 72% (62/86), EFV/FTC/TDF 86% (177/207)) with median onset of 6 and 2 days in the DOR/3TC/TDF and EFV/FTC/TDF arms, respectively. Among the five NPE categories, median onset for both treatment groups was less than one week except for depression and suicide/self-injury (median onset 87 and 93.5 days in the DOR/3TC/TDF and EFV/FTC/TDF arms, respectively).
- Prevalence: The proportion of subjects who reported NPEs through week 4 was 17% (62/364) in the DOR/3TC/TDF group and 49% (177/364) in the EFV/FTC/TDF group. At week 48, the prevalence of NPEs was 12% (44/364) in the DOR/3TC/TDF group and 22% (81/364) in the EFV/FTC/TDF group. The numerically lower NPE proportion at week 48 compared with week 4 for both treatment arms, overall and for most NPE categories, suggest these defined NPEs may improve with continued therapy.
- Baseline mean and mean change from baseline for LDL-C, non-HDL-C, cholesterol, triglycerides, and HDL-C values.
- Grade 3 lipid information in Section 6 of DOR-containing labeling for consistency with other approved HIV-1 drug labels containing lipid information. See Table 20.

7. Risk and Risk Management (Assessment of the Safety of the Drug for its Intended Use)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

There were no nonclinical safety issues of significant concern as assessed by the general toxicology studies conducted during the development program. In specialized toxicology studies, DOR was nonphototoxic, nonirritating to the skin or eye, and showed no potential for sensitization. Two risk issues identified from nonclinical studies are further addressed under Section 7.7.4 (M9 metabolite) and Section 7.7.6 (thyroid adenoma and carcinoma). The overall documentation of the nonclinical program to support the safety of clinical development is summarized here. The nonclinical safety profile of DOR was evaluated in: safety pharmacology studies in rats, mice and dogs; repeat-dose toxicology studies in mice, rats and dogs for up to 12, 26, and 39 weeks, respectively; 12-week toxicology studies in rats to qualify impurities; phototoxicity studies in mouse fibroblasts and pigmented rats; juvenile, fertility and pre- and postnatal developmental studies in rats; embryo-fetal developmental studies in rats and rabbits; genetic toxicology studies (Ames, in vitro chromosomal aberration and in vivo rat micronucleus assays); and a 2-year carcinogenicity study in rats, as well as a 6-month study in transgenic mice. The data to support these conclusions are summarized below.

Safety Pharmacology and Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

No significant effects on neurologic (functional observational battery; rats and mice) or respiratory parameters (plethysmography; dogs) were observed following single oral doses of DOR up to 450 mg/kg in rats and mice, and up to 10 mg/kg in dogs. In addition, no significant cardiovascular effects on hemodynamic or electrocardiographic parameters were noted for up to 24 hours postdose in telemetry-monitored or vagotomized dogs given single oral doses of DOR up to 10 mg/kg. DOR did not significantly inhibit hERG current in vitro and the IC_{50} value was 88μM (approximately 150 times the unbound DOR levels at C_{max} measured at the recommended human dose; RHD).

To better understand human risk, numerous in vitro and in vivo nonclinical pharmacokinetic studies evaluating the absorption, distribution, metabolism and excretion of DOR were conducted in mice, rats, rabbits and dogs. DOR had moderate binding to plasma protein (0.24) in all species examined and had wide tissue distribution in the rat, except the brain. The highest concentrations of radioactively labeled DOR were observed in the alimentary canal, liver, and kidney, due to transit of the dose through the gastrointestinal tract and/or involvement in elimination. DOR did not display affinity for melanin and there was no preferential distribution of DOR into blood cells. DOR was eliminated primarily by oxidative metabolism in nonclinical species. The major metabolic pathway in nonclinical species and humans involved formation of M9, an oxidative metabolite resulting from cytochrome P (CYP)-mediated oxidation. In all species except rats, in which M9 underwent significant glucuronidation, the majority of M9 was eliminated without further modification, predominantly in urine. At pharmacologically relevant DOR exposures, M9 was the major metabolite circulating in mice and humans but not rats, rabbits, or dogs, where M9 was present in trace amounts or not detected. See Section 7.7.4 and Appendix III.14.

DOR was evaluated against a large panel of standard enzyme and other receptor assays to assess its specificity for off-target activities. DOR only showed moderate affinity to the 5-hydroxytryptamine (serotonin) receptor 2B (5-HT_{2B}) receptor in a ligand binding assay with an IC_{50} of 2.5µM, while in a subsequent cell based functional 5-HT_{2B} assay, no agonist or antagonist activity was observed by monitoring the accumulation of inositol-1-phosphate. Therefore, binding of DOR to 5-HT_{2B} does not impact 5-HT_{2B} receptor function.

General Toxicology

Repeat-dose toxicology studies assessed target organs of toxicity with potential relevance to humans. These studies were conducted in mice, rats and dogs with doses up to 450, 450 and 1000 mg/kg/day for up to 3, 6, and 9 months, respectively. In mice, non-adverse effects included mild decreases in weight gain. In the 6-month rat study, urinary crystals were observed in high dose (450 mg/kg/day) males and females and were later determined to be formed ex vivo and a result of supersaturation of DOR in the urine. Additional non-adverse test-article related findings included postdose salivation (at all dose levels), increased liver weight and various minimal changes in hematologic parameters. In the 9-month dog study, the only findings were mild gastrointestinal effects, postdose salivation and lacrimation and mild clinical chemistry changes. These effects were not considered adverse due to their intermittent nature and low magnitude.

DOR was not mutagenic or clastogenic as tested in the Ames assay up to 5000 µg/plate, the in vitro chromosomal aberration assay in Chinese hamster ovary cells up to 300µM, and the in vivo rat micronucleus assay up to day 14 at 450 mg/kg/day. A 6-month carcinogenicity transgenic rasH2 mouse study had no findings. A statistically significant increase in combined female thyroid adenoma and carcinoma was noted at the highest dose of 450 mg/kg/day (7 times the DOR AUC exposure at the RHD) in a 2-year rat carcinogenicity study. The clinical significance of this finding is unclear, and the finding was within the range observed in historical control studies. See Section 7.7.6.

DOR impurities and degradation products were qualified in either repeat dose toxicology studies with MK-1439 or in specific studies further detailed in Appendix III.14. All calculated safety margins from pivotal toxicology studies in three species were acceptable as identified in Table 12 below.

Table 12. Doravirine Safety Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (µM•hr)	Safety Margins*** (Multiples)
3-month mouse	450	196	5.5
6-month rat	450	279	7.5
9-month dog	1000	673	18

NOAEL = no observed adverse effect level

***Exposure multiples were based on population pharmacokinetics analysis from DOR phase 3 trials (P018 and P021), where a 100 mg QD DOR clinical dose resulted in systemic geometric mean exposures of $AUC_{0\text{-}24hr}$ of 37.8µM•hr.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

DOR belongs to the NNRTI class of ARV drugs. Hallmark NNRTI toxicities include neuropsychiatric symptoms, hepatotoxicity, rash, and severe skin and hypersensitivity reactions and are included as Boxed Warnings or Warnings and Precautions in labeling for certain NNRTIs. DOR's safety profile was favorable and did not warrant similar NNRTI labeling for the above events. DOR was superior to EFV, another NNRTI, with respect to neuropsychiatric symptoms and is discussed in Section 6.4.1, along with lipid parameters.

Additionally, there is significant cross-resistance among the NNRTI class and the assessment of resistance is critical to interpreting the overall benefit-risk of DOR and determining its role in the ARV armamentarium. For the discussion on the risk profile of DOR, see Section 7.7.1.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Neither DOR nor the FDC tablet DOR/3TC/TDF are available on the U.S. market or in any foreign market; therefore, no postmarketing experience is available for either DOR or DOR/3TC/TDF.

3TC has been approved for the treatment of HIV-1 infection since 1995, and TDF has been approved for the treatment of HIV-1 infection since 2001. Identified safety concerns described in the 3TC and TDF labels are included in the proposed labeling for DOR/3TC/TDF.

7.4. FDA Approach to the Safety Review

Approach to Assessment of Clinical Trial Data

Data from the two phase 3 trials in treatment-naïve HIV-1-infected subjects (PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD) were analyzed both individually and pooled for the DOR-containing arms to support safety for DOR 100 mg QD and for DOR/3TC/TDF FDC tablet QD. In general, the safety review was analyzed by trial, except in situations where pooling the data might help identify less common serious signals (discontinuations due to AEs and biliary SAEs). Pooling of the phase 3 trials for the DOR-containing arms is appropriate because the trial designs were similar with generally similar inclusion and exclusion criteria. In addition to a complete independent analysis of safety for the phase 3 trials, selected safety analyses from the phase 2 trial PN007 are included in this review when applicable. Treatment-emergent AEs (TEAEs) were protocol-defined as any AE occurring from the time of first study treatment dose until 14 days following cessation of study treatment. This safety review utilizes a modified TEAE definition (see Appendix III.18.3) which does not change the overall safety conclusions. Treatment-emergent adverse drug reactions are defined using investigator determination of causality as the basis for classification because of the active comparator trial design: the inaccuracies and potential biases of this type of classification are acknowledged.

The Applicant submitted a SUR 4 months after the original NDA submissions providing approximately 10 and 5 months' additional safety data for PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, respectively: no new PN007 safety data were included. Approximately

five months' additional safety data were also provided for the ongoing trials PN024, PN028, and PN030. Deaths, SAEs, and discontinuations due to AEs reported in the SUR are included in the relevant safety sections but are not included in any of the Section 7 tables.

Adequacy of Applicant's Clinical Safety Assessments

Clinical safety assessments included evaluations of AEs, vital sign measurements, and laboratory tests. In PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, key evaluations were performed at baseline, week 2 (PN018 only), and weeks 4, 8, 16, 24, and every 12 weeks thereafter, with a final follow-up visit 14 days post-study. Follow-up visits were also scheduled for subjects who discontinued treatment prematurely due to AEs. No major data quality or integrity issues were identified that would preclude performing a safety review for these NDAs. We did note missing electrocardiogram (ECG) data, missing alanine aminotransferase (ALT) values from most subjects enrolled in Australia, and missing MedDRA coding for several AEs; however, these issues were resolved early in the review and did not impact our overall safety assessment. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to MedDRA preferred terms for the events reported in PN018 DRIVE-FORWARD, PN021 DRIVE-AHEAD, and PN007 were reviewed and found to be acceptable.

All AEs in the reviewed trials were graded using a three-line grading scale, and are comparable within trials; however, the Applicant's AE grading scale has fewer toxicity grades than the toxicity grading scales used by most other companies, which have four or five toxicity grades. Consequently, AEs of a certain toxicity grade in these DOR-containing trials are not comparable to AEs of the same toxicity grade reported in trials performed by other companies, and as a result, further limit cross trial comparisons of AE data with other approved products.

7.5. Adequacy of the Clinical Safety Database

Overall, the safety database of over 1500 subjects is comprehensive and adequate to assess the safety of DOR and DOR/3TC/TDF for the proposed indication, dosage regimen, duration, and patient populations (Table 13 and Table 14). The 855 subjects in the safety database who received the intended DOR dose for at least 48 weeks exceeds the sample size recommended in the *FDA HIV-1 Guidance for Industry*. The Guidance recommends a sample size of 300 to 500 subjects for initial approval in treatment-naïve HIV-1-infected adult patients.

Table 13. Safety Population for DOR and DOR/3TC/TDF

Clinical Trial Groups[1]	DOR or DOR/3TC/TDF (N=1657)	Active Control (N=855)	Placebo (N=26)
Phase 3: 48-week data, HIV-1-infected population[2]	747	747	N/A
Phase 2: 96-week data, HIV-1-infected population	232[4]	108	N/A
Phase 1: various doses and durations, >95% healthy volunteers [3]	678	0	26

Source: Primary safety database for DOR
[1] Individuals exposed to DOR for the indication under review (there was no safety data submitted for DOR for other indications), either as a single tablet or as the FDC tablet DOR/3TC/TDF, N=1657
[2] to be used in product's labeling
[3] 650 of these subjects were healthy adults, 12 were subjects infected with HIV-1, 8 were subjects with moderate hepatic impairment, and 8 were subjects with severe renal impairment.
[4] 108 originally randomized to the 100 mg DOR daily dose, the others switched to the 100-mg dose after 24 weeks if continued in the study

Table 14. Duration of Exposure of DOR and DOR/3TC/TDF From PN007, PN018, and PN021

Cumulative exposure	DOR 25 mg	DOR 50 mg	DOR 100 mg	DOR 200 mg
Number of subjects exposed to ≥1 dose	42	44	952	97
≤4 weeks	3	4	20	56
>4 weeks	39	40	932	41
>24 weeks	36	38	882	38
>48 weeks	12	14	667	18

Source: Modified from Applicant Tables 2.7.4:5 and 2.7.4:6, Summary of Clinical Safety

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The safety evaluation for DOR was adequate, and the demonstrated safety profile of DOR-containing treatment in the treatment-naïve HIV-1 population is acceptable for the indicated dose and population of HIV-1 treatment-naïve patients. DOR-containing treatment arms had similar or less frequent overall treatment-emergent AEs versus the active comparators in the phase 3 trials. There was no clear pattern with reported deaths in the DOR-containing phase 2 and 3 trials that point to a specific safety concern. Rates of discontinuation due to AEs were low in the phase 3 trials. There were no trends or clustering of serious AEs identified in the individual trials. The most common treatment-emergent adverse drug reactions (ADRs) reported across the phase 3 trials in DOR-treated subjects were nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, and abnormal dreams: the majority of events were mild in severity.

Our overall safety assessment is based on data summarized in the following subsections.

7.6.1. Overall Adverse Event Summary

Reports of any AE and drug-related AEs occurred more frequently in the EFV/FTC/TDF group (91% and 63%, respectively) compared with the DOR, DRV+r, and DOR/3TC/TDF groups (78 to 83% and 31 to 32%, respectively). In addition, more AEs leading to discontinuation were

reported in the EFV/FTC/TDF group (7%) compared with the DOR, DRV+r, and DOR/3TC/TDF groups (2 to 3%). Reports of SAEs across treatment arms were similar.

Table 15. Overall Summary of Reported Adverse Events Through 48 Weeks for PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Subjects Experiencing Event	DOR & NRTIs N=383 n (%)	DRV+r & NRTIs N=383 n (%)	DOR/3TC/TDF N=364 n (%)	EFV/FTC/TDF N=364 n (%)
Any AE	308 (80.4%)	300 (78.3%)	302 (83.0%)	331 (90.9%)
Grade 1 (mild)*	188 (49.1%)	161 (42.0%)	164 (45.1%)	158 (43.4%)
Grade 2 (moderate)*	94 (24.5%)	112 (29.2%)	109 (29.9%)	132 (36.3%)
Grade 3 (severe)*	26 (6.8%)	27 (7.0%)	29 (8.0%)	41 (11.3%)
Drug-related AE	117 (30.5%)	123 (32.1%)	113 (31.0%)	229 (62.9%)
Drug-related grade 2 or 3 AE	25 (6.5%)	27 (7.0%)	38 (10.4%)	91 (25.0%)
SAE	19 (5.0%)	23 (6.0%)	14 (3.9%)	21 (5.8%)
Fatal SAE (treatment-emergent and posttreatment)	1 (<1%)	0	1 (<1%)	3 (<1%)
AE Leading to discontinuation^	6 (1.6%)	12 (3.1%)	11 (3.0%)	24 (6.6%)

Data Source: PN018 and PN021 subsets of the ISS (Integrated Summary of Safety) ADSL and ADAE datasets
AE = adverse event; DOR = doravirine (MK-1439); DOR/3TC/TDF = (MK-1439A) FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NRTI = nucleos(t)ide reverse transcriptase inhibitor; SAE = severe adverse event
* Maximum toxicity grade using Merck's AE Toxicity Grading Scale
^ AEs leading to discontinuation in this table were defined as any AE that began within the week 48 treatment period and led discontinuation, regardless of whether the discontinuation occurred within or outside the week 48 treatment period.

7.6.2. Deaths

Five deaths were reported among phase 3 subjects in the initial NDA submission (N=1 DOR/3TC/TDF, N=1 DOR+FTC/TDF, N=3 EFV/FTC/TDF), and no deaths were reported in PN007.

- Two deaths in DOR-treated subjects unfortunately do not have enough information to determine a cause of death, given the lack of autopsy. One subject may have died of an acute stroke or heart attack, which would fit with his cardiac risk factors of hypertension, smoking, and HIV-1 infection. (Of note, DOR did not have a noticeable effect on ECGs in PN007, nor did a supratherapeutic dose of DOR lead to QT prolongation in the thorough QT study). The other subject, whose $CD4^+$ count dropped shortly before death despite an undetectable viral load, may have had an undiagnosed infection.
- Three deaths in the subjects on EFV/FTC/TDF seem to be unrelated to treatment (traffic accident, suspected drug overdose, suicide), with the possible exception of the suicide which may have been exacerbated by EFV/FTC/TDF use.

In the SUR, five additional phase 3 deaths were reported, two occurring in DOR-treated subjects (leptospirosis, myocardial infarction), two occurring in DRV+r-treated subjects (pulmonary embolism, Hodgkin's disease), and one occurring in an EFV-treated subject ('natural causes').

One death was reported in the ongoing PN024 trial immediate switch group (possible drug overdose).

7.6.3. Serious Adverse Events

SAEs occurred in approximately 4 to 5% of subjects receiving DOR in both PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD through week 48, similar to rates in the active comparator groups (Table 16). Anogenital warts was the only SAE occurring in more than one DOR-treated subject in a single trial (N=2). Infections and infestations were the most frequently reported body system organ class with SAEs, though the rates were low and similar across all treatment arms. This finding is similar to other HIV-1 development programs and is likely due to an HIV-infected population that may be more susceptible to infections due to either immunosuppression or high risk behaviors (see Appendix III.18.5).

Table 16. SAE by Body System Organ Class in Weeks 0 to 48 of PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018		PN021	
Body System Organ Class	**DOR & NRTIs N=383 n (%)**	**DRV+r & NRTIs N=383 n (%)**	**DOR/3TC/ TDF N=364 n (%)**	**EFV/FTC/ TDF N=364 n (%)**
Any Subject with a SAE	20 (5.2%)	23 (6.0%)	14 (3.8%)	21 (5.8%)
Infections and infestations	7 (1.8%)	8 (2.1%)	6 (1.6%)	8 (2.2%)
Neoplasms benign, malignant and unspecified	1 (<1%)	3 (<1%)	3 (<1%)	1 (<1%)
Gastrointestinal disorders	3 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)
Injury, poisoning and procedural complications	1 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
General disorders and administration site conditions	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
Psychiatric disorders	2 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)
Nervous system disorders	1 (<1%)	3 (<1%)	0	1 (<1%)
Musculoskeletal and connective tissue disorders	2 (<1%)	3 (<1%)	0	0
Skin and subcutaneous tissue disorders	0	0	0	3 (<1%)
Respiratory, thoracic and mediastinal disorders	0 (<1%)	2 (<1%)	0	1 (<1%)
Metabolism and nutrition disorders	1 (<1%)	1 (<1%)	0	1 (<1%)
Hepatobiliary disorders	1 (<1%)	0	1 (<1%)	0
Cardiac disorders	0	0	1 (<1%)	0
Blood and lymphatic system disorders	0	0	1 (<1%)	0
Vascular disorders	0	0	0	1 (<1%)
Renal and urinary disorders	0	0	0	1 (<1%)
Pregnancy, puerperium and perinatal conditions	0	0	0	1 (<1%)
Social circumstances	1 (<1%)	0	0	0
Ear and labyrinth disorders	0	1 (<1%)	0	0

Data Source: PN018 and PN021 subsets of the ISS ADSL and ADAE datasets
DOR = doravirine (MK-1439); DRV+r =800 mg darunavir boosted with 100 mg ritonavir; NRTI = nucleos(t)ide reverse transcriptase inhibitor; SAE = serious adverse event

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Rates of discontinuation due to AEs were low in the phase 3 trials: 1.6% of subjects on DOR versus 3.1% of subjects on DRV+r in PN018 DRIVE-FORWARD, and 3.0% of subjects on DOR/3TC/TDF versus 6.6% of subjects on EFV/FTC/TDF in PN021 DRIVE-AHEAD. Within the combined DOR and DOR/3TC/TDF treatment groups from the two trials, no AEs leading to

discontinuation were reported in more than one subject except for nausea/vomiting, abdominal pain (or abdominal pain upper), fatigue/asthenia, rash, and renal disorders (see Table 17). However, even for these five types of AEs, rates of discontinuation were <1% in the combined DOR groups, and similar to or less than rates of discontinuations for these AEs in the active comparator groups. Additional discontinuations due to AE occurring in a single DOR-treated subject include depression, insomnia/nightmare, alopecia, adjustment disorder, disturbance in attention, esophageal obstruction, silicon granuloma, and pulmonary fibrosis (see Appendix III.18.6, Table 114).

Fatigue/asthenia, nausea, abdominal pain, insomnia, and rash are recommended to be included in the DOR and DOR/3TC/TDF Section 6 labeling as discussed in Section 7.6.5. Nightmare, a component of sleep disorders and disturbances, and depression and suicide are also both recommended for inclusion in the label as part of the proposed PN021 DRIVE-AHEAD NPE assessment. Other AEs leading to discontinuation in DOR treatment groups have likely alternative etiologies based on timing or comorbidities, including alopecia which is further discussed in Appendix III.18.13.

Table 17. Summary of Discontinuations Due to AEs in the Phase 3 Studies Seen in >1 Subject in the Combined DOR Group

Dictionary-Derived Term	Combined DOR and DOR/3TC/TDF N=747 n (%)	DRV+r & NRTIs N=383 n (%)	EFV/FTC/TDF N=364 n (%)
Nausea or vomiting	3 (<1%)	1 (<1%)	1 (<1%)
Abdominal pain (any type)	2 (<1%)	2 (<1%)	1 (<1%)
Fatigue or asthenia	2 (<1%)	0	1 (<1%)
Rash*	2 (<1%)	1 (<1%)	10 (2.7%)
Renal disorder (including acute kidney injury)	2 (<1%)	0	1 (<1%)

Data Source: PN018 and PN021 subsets of the ISS ADSL and ADAE datasets
AE = adverse event; DOR = doravirine (MK-1439); DOR/3TC/TDF = (MK-1439A) FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NRTI = nucleos(t)ide reverse transcriptase inhibitor
*Includes pooled terms: rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash, genital rash, viral rash, and drug eruption

7.6.5. Treatment-Emergent Adverse Drug Reactions

ADRs of any severity occurring ≥5% in any phase 3 trial treatment group are recommended for inclusion in Section 6 of the DOR-containing labels (Table 18). The recommendation for including ADRs in any treatment group is because of the phase 3 active control trial design. Similar preferred terms are pooled for the ADRs of fatigue, abdominal pain, and rash event, as specified in the table footnotes, to avoid splitting and thus underestimation of these ADRs.

The Applicant originally proposed labeling for moderate to severe ADRs occurring in ≥2% subjects in any treatment group; however, we recommend labeling ADRs of any severity in ≥5% subjects because of concerns regarding potential limitations of the Applicant's three-category grading scale (compared with four- or five-category detailed grading scales used by other companies).

- For example, in the PN018 DRIVE-FORWARD DRV+r arm, diarrhea was the only ADR that met the criteria of a moderate-to-severe event occurring in ≥2% subjects, whereas, in the currently approved DRV+r label in a trial in a similar population, seven ADRs met these criteria in the DRV+r group (abdominal pain, diarrhea, nausea, vomiting, anorexia, headache, and rash).

Table 18. Treatment-Emergent Adverse Drug Reactions Reported in ≥5% of Any Treatment Group, All Grades, PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, Week 48

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Dictionary-Derived Term	DOR & NRTIs N=383 n (%)	DRV+r & NRTIs N=383 n (%)	DOR/3TC/TDF N=364 n (%)	EFV/FTC/TDF N=364 n (%)
Any ADR	117 (31%)	123 (32%)	113 (31%)	229 (63%)
Nausea	25 (7%)	29 (8%)	18 (5%)	24 (7%)
Fatigue [*]	23 (6%)	11 (3%)	16 (4%)	16 (4%)
Headache	23 (6%)	10 (3%)	14 (4%)	16 (4%)
Diarrhea	21 (5%)	49 (13%)	12 (3%)	20 (5%)
Abdominal pain[^]	19 (5%)	9 (2%)	4 (1%)	9 (2%)
Dizziness	11 (3%)	7 (2%)	24 (7%)	116 (32%)
Rash event[#]	9 (2%)	12 (3%)	7 (2%)	44 (12%)
Abnormal dreams	4 (1%)	1 (<1%)	17 (5%)	34 (9%)
Insomnia	4 (1%)	6 (2%)	15 (4%)	18 (5%)
Somnolence	0	1 (<1%)	11 (3%)	24 (7%)

[*] Includes pooled terms: fatigue, asthenia, and malaise
[^] Includes pooled terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort, and gastrointestinal pain
[#] Includes pooled terms: rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash, genital rash, viral rash, and drug eruption
Data Source: PN018 and PN021 subsets of the ISS ADSL and ADAE datasets

Most ADRs in DOR-treated subjects were mild in severity: PN018 DRIVE-FORWARD DOR arm 79% (92/117), PN021 DRIVE-AHEAD DOR/3TC/TDF arm 65% (74/113). ADRs with a maximum intensity of moderate or severe reported in at least 2% of any treatment group (rounding up) are summarized in Table 19.

Table 19. Treatment-Emergent Adverse Drug Reactions Reported in ≥2% of Any Treatment Group, Moderate to Severe Intensity, PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, Week 48

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Dictionary-Derived Term	DOR & NRTIs N=383 n (%)	DRV+r & NRTIs N=383 n (%)	DOR/3TC/TDF N=364 n (%)	EFV/FTC/TDF N=364 n (%)
Any moderate or severe ADR	25 (7%)	27 (7%)	38 (10%)	91 (25%)
Rash event[#]	4 (1%)	4 (1%)	1 (<1%)	25 (7%)
Diarrhea	6 (2%)	7 (2%)	4 (1%)	3 (<1%)
Dizziness	1 (<1%)	1 (<1%)	5 (1%)	22 (6%)
Abnormal dreams	0	0	3 (<1%)	9 (2%)

[#] Includes pooled terms: rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash, genital rash, viral rash, and drug eruption
Data Source: PN018 and PN021 subsets of the ISS ADSL and ADAE datasets

7.6.6. Laboratory Findings

Phase 3 trial laboratory analyses did not reveal any imbalances apart from grade 1 and 2 bilirubin elevations in DOR-treated subjects. Laboratory findings recommended for DOR and DOR/3TC/TDF Section 6 labeling are listed in Table 20. For most parameters, laboratory findings are similar between the DOR and comparator groups, and grade 3 and 4 laboratory abnormalities were uncommon. Fewer graded fasting lipid elevations occurred in DOR-treated subjects versus comparators. Please see Sections 6.4.1 and 7.7.7 (subsections on lipid analysis and hepatobiliary analysis) for further analyses regarding differences in graded total bilirubin and fasting lipid abnormalities between treatment groups. The label inclusion rationale for liver enzymes, creatinine, creatine kinase, and lipase is to provide general consistency with other approved HIV-1 product labels.

Table 20. Subjects Meeting Chemistry Laboratory Abnormality Criteria, With a Grade Worsened From Baseline Through Week 48, in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Laboratory Abnormality^	**DOR & NRTIs n (%)**	**DRV+r & NRTIs n (%)**	**DOR/3TC/TDF n (%)**	**EFV/FTC/TDF n (%)**
ALT	N=380	N=378	N=363	N=359
Grade 2 (2.5 - <5.0 x ULN)	11 (2.9%)	7 (1.9%)	12 (3.3%)	13 (3.6%)
Grade 3 (5.0 - <10.0 x ULN)	5 (1.3%)	6 (1.6%)	2 (<1%)	5 (1.4%)
Grade 4 (≥10.0 x ULN)	0	3 (<1%)	1 (<1%)	1 (<1%)
Alkaline Phosphatase	N=380	N=378	N=363	N=359
Grade 2 (2.5 - <5.0 x ULN)	1 (<1%)	2 (<1%)	0	2 (<1%)
Grade 3 (5.0 - <10.0 x ULN)	0	0	0	1 (<1%)
AST	N=380	N=378	N=363	N=359
Grade 2 (2.5 - <5.0 x ULN)	17 (4.5%)	12 (3.2%)	6 (1.7%)	8 (2.2%)
Grade 3 (5.0 - <10.0 x ULN)	2 (<1%)	6 (1.6%)	1 (<1%)	5 (1.4%)
Grade 4 (≥10.0 x ULN)	0	0	1 (<1%)	2 (<1%)
Total Bilirubin	N=380	N=378	N=363	N=359
Grade 1 (1.1 - <1.6 x ULN)	19 (5.0%)	4 (1.1%)	13 (3.6%)	0
Grade 2 (1.6 - <2.6 x ULN)	6 (1.6%)	1 (<1%)	9 (2.5%)	0
Grade 3 (2.6 - <5.0 x ULN)	0	0	1 (<1%)	0
Grade 4 (≥5.0 x ULN)	0	0	1 (<1%)	1 (<1%)
Creatine Kinase	N=380	N=378	N=363	N=359
Grade 2 (6.0 - <10.0 x ULN)	9 (2.4%)	12 (3.2%)	9 (2.5%)	7 (1.9%)
Grade 3 (10.0 - <20.0 x ULN)	7 (1.8%)	7 (1.9%)	6 (1.7%)	7 (1.9%)
Grade 4 (≥20.0 x ULN)	6 (1.6%)	7 (1.9%)	2 (<1%)	4 (1.1%)
Creatinine*	N=380	N=378	N=363	N=359
Grade 2 (>1.3 - 1.8 x ULN)	10 (2.6%)	16 (4.2%)	8 (2.2%)	5 (1.4%)
Grade 3 (>1.8 - <3.5 x ULN)	5 (1.3%)	10 (2.6%)	7 (1.9%)	3 (<1%)
Grade 4 (≥3.5 x ULN)	1 (<1%)	0	0	1 (<1%)
Fasting Cholesterol	N=332	N=320	N=332	N=309
Grade 3 (≥300 mg/dl)	0	1 (<1%)	2 (<1%)	1 (<1%)
Fasting LDL Cholesterol	N=332	N=320	N=332	N=309
Grade 3 (≥190 mg/dL)	1 (<1%)	9 (2.8%)	1 (<1%)	5 (1.6%)
Fasting Triglyceride	N=335	N=327	N=336	N=318
Grade 3 (>500 - 1000 mg/dL)	2 (<1%)	2 (<1%)	2 (<1%)	8 (2.5%)
Grade 4 (>1000 mg/dL)	0	2 (<1%)	0	0

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Laboratory Abnormality^	**DOR & NRTIs n (%)**	**DRV+r & NRTIs n (%)**	**DOR/3TC/TDF n (%)**	**EFV/FTC/TDF n (%)**
Lipase	N=380	N=378	N=363	N=359
Grade 2 (1.5 - <3.0 x ULN)	14 (3.7%)	20 (5.3%)	19 (5.2%)	15 (4.2%)
Grade 3 (3.0 - <5.0 x ULN)	6 (1.6%)	6 (1.6%)	3 (<1%)	5 (1.4%)
Grade 4 (≥5.0 x ULN)	4 (1.1%)	3 (<1%)	1 (<1%)	2 (<1%)

Source: PN018 and PN021 Subset of ISS ADLB dataset. Each subject only included once per parameter at highest toxicity grade.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; DOR = doravirine (MK-1439); DOR/3TC/TDF = fixed-dose combination tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = fixed-dose combination tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NRTI = nucleos(t)ide reverse transcriptase inhibitor; ULN = upper limit of normal.
^ N = number of subjects with relevant laboratory data; n = number of subjects with laboratory abnormality.
* Grade 2 creatinine can also be an increase of 0.3 mg/dL above baseline, grade 3 creatinine can also be an increase of 1.5 to <2.0-fold above baseline, and grade 4 creatinine can also be an increase of >=2.0-fold above baseline.

7.7. Review Issues Relevant to the Evaluation of Risk

Overall, the safety evaluation is adequate to assess the safety of DOR and the DOR combination treatment for the proposed indication, dosage regimen, duration, and patient populations. The safety profile is well-characterized and none of the identified risk issues would preclude approval of DOR-containing treatment. The identified risk review issues relate to development of resistance and cross-resistance, drug-drug interactions, carcinogenicity, and clinical safety evaluation. During the review of clinical safety, we identified the two risk review issues: (1) increases in bilirubin with DOR versus comparators, and (2) imbalance in adverse events of alopecia with DOR versus comparators. The imbalance in alopecia events did not result in labeling or require a postmarketing requirement (PMR) or postmarketing commitment (PMC) and routine pharmacovigilance is recommended. The details of the alopecia analyses can be found in Appendix III.18.13. The other identified risk issues can be adequately addressed in labeling as summarized below. Two PMCs were issued to: (1) evaluate phenotypic resistance and (2) evaluate the PK of DOR and its primary metabolite (M9) when DOR is given with rifabutin as described below.

7.7.1. Resistance: Determination of Emergent DOR-Associated Resistance in Trials and Impact of Cross-Resistance Potential

Issue: The assessment of resistance is critical to interpreting the overall benefit-risk of DOR, specifically the development of DOR-associated resistance and impact on future NNRTI-based regimens. The key points on resistance from the DOR review include the following.

- The selection of resistance in cell culture provided data on key amino acid sites of interest in the reverse transcriptase to explore in clinical studies and confirmed the mechanism of action of DOR as an NNRTI.
- DOR does not appear to provide an advantage in resistance barrier over other approved NNRTIs.
- In comparison to DRV+r, DOR had more emergent resistance substitutions in DRIVE-FORWARD; DOR had similar rates of emergent resistance substitutions when compared to EFV in DRIVE-AHEAD.
- DOR resistance-associated substitutions can confer cross-resistance to the other approved NNRTIs.

- Failure on a DOR regimen with emergence of resistance to DOR has the consequence of limiting future NNRTI use because of significant cross-resistance to other NNRTIs.
- DOR-treated subjects also develop resistance to background regimen of NRTIs. This, too, can affect the selection of certain NRTIs in future regimens.

Conclusion: The emergence of DOR resistance substitutions does not preclude approval. In practice, resistance testing guides the selection of ARVs. Inclusion of clinical resistance data in labeling, including the specific DOR resistance associated substitutions and phenotypic changes, provide clinicians with the information needed to guide subsequent ARV regimens.

Team Assessment: The above key conclusions are supported by the following.

Cell Culture Selection

Selection of resistant viruses in cell culture can provide information on the resistance barrier of DOR and on resistance substitutions to anticipate clinically. DOR-resistant viruses were selected at 10X the effective concentration inhibiting 95% of virus growth (EC_{95}) value conducted at a fixed concentration and at 4X the EC_{95} value in escalating concentrations similar to the timing for resistance selection with EFV. DOR also selected for common NNRTI resistance substitutions associated with resistance to the approved NNRTIs. The predominant emergent HIV-1 DOR resistance-associated substitutions selected in cell culture were: RT V106A/I/M, V108I, H221Y, F227C/L/V, M230I, L234I, P236L, and Y318F. Based on the X-ray structure of DOR/RT complex, three residues (V106, V108, and F227) are in close proximity to DOR and, thus, may play an important role in the interactions between DOR and RT. The V106A and V108I mutant viruses conferred approximately 12- and 4-fold reductions in susceptibility to DOR, respectively. Emergence of additional substitutions likely further reduces the susceptibility of the mutant viruses to DOR. In the resistance selection with subtype A, B, and C viruses using MT4-GFP (green fluorescent protein) cells, viruses containing substitutions at V106 and F227 account for the majority of mutants in the breakthrough viruses under low multiplicity of infection (MOI) conditions. The double-mutant virus containing substitutions V106A+F227L confers >500-fold resistance to DOR.

Cross-Resistance

The common NNRTI resistance substitutions V106A, Y181V, Y181C, G190S and Y188L had greater than 5-fold reduced susceptibility to DOR. The greatest reductions in susceptibility to DOR were in HIV-1 variants encoding V106A (7.1- to 28.0-fold change) or Y188L (95- to >116-fold change). The highest levels of reduced susceptibility to DOR (>100-fold change) were observed in HIV-1 clinical isolates encoding a combination of Y188L+K103N (>124-fold change), Y188L+V106I (>110-fold change), E138K+Y181C+M230L (>111-fold change), and V106A+G190A+F227 (>106-fold change). HIV-1 variants encoding these combinations of NNRTIs resistance-associated substitutions were cross-resistant to efavirenz, etravirine, and rilpivirine. However, some common NNRTI resistance-associated substitutions (V106M, V108I, V179D, Y188C, Y188H, P236L) conferred less than 5-fold change in decreased susceptibility to DOR. Therefore, if transmission of NNRTI resistance virus is suspected, resistance testing should guide the use of DOR.

Clinical Resistance in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

The determination of the resistance substitutions that emerged in virologic failures in the clinical trials is important to understand how virologic failure on a DOR-containing regimen may impact future treatment options on other ARV drugs.

The Applicant determined the resistance subset of virologic failures differently than our analysis. Protocol-defined virologic failure was defined by the Applicant in both PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD as:

- Rebounder: A subject with confirmed (two consecutive measures at least 1 week apart) HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study;

OR

- Non-responder: A subject with confirmed (two consecutive measures at least 1 week apart) HIV-1 RNA ≥200 copies/mL at week 24 or week 36 OR with confirmed (two consecutive measures at least 1 week apart) HIV-1 RNA ≥50 copies/mL at week 48.

However, for the FDA resistance analyses, subjects were considered virologic failures if they had confirmed HIV-1 RNA ≥400 copies/mL after response of HIV-1 RNA <50 copies/mL at any time during the study OR if they discontinued with HIV-1 RNA ≥400 copies/mL at or after week 4. Subjects who discontinue while suppressed are censored from our resistance subset, because they have discontinued for adverse events and reasons other than virologic failure and resistance emergence. The confirmed ≥400 copies/mL of HIV-1 RNA cutoff is used to eliminate subjects who may have a temporary blip of increased viral load or aberrant results within the normal viral load assay variation. The resistance virologic failure determination differs from the primary endpoint (FDA snapshot algorithm), which considers virologic failure: HIV-1 RNA ≥50 copies/mL at week 48; missing RNA during week 48 window, but still on study drug; or study drug discontinuation due to AE, death, or other reasons. Thus, the FDA resistance subset has a different number of virologic failure subjects than the Applicants resistance subset and the primary endpoint determined by the FDA snapshot algorithm.

Testing for viral genotypic and phenotypic resistance to DOR and the ARVs used in each trial was performed by the Applicant for subjects with protocol-defined virologic failure and for subjects who discontinued the trial for any reason. Testing was done on the sample from the viral failure confirmation visit or, if not available, from the early discontinuation visit, if the subject's HIV-1 RNA level was >400 copies/mL. In some instances, samples from subjects with HIV-1 level <400 copies/mL were mistakenly sent for resistance testing, or subjects with HIV-1 >400 copies/mL did not have samples collected for such testing, due to site error. Postbaseline genotypic resistance to DOR was defined by the Applicant as any of the following substitutions in the reverse transcriptase (RT) gene: L100I, K101E, V106A, V106I, V106M, V108I, E138K, Y188L, G190A, G190S, H221Y, P225H, F227C, F227L, F227V, M230I, M230L, L234I, P236L, and Y318F. This list was acceptable because it contained the major NNRTI resistance substitutions as well as the resistance substitutions that were selected in cell culture.

In PN018 DRIVE-FORWARD, 21 subjects (21/383; 5.5%) in the DOR arm and 16 subjects (16/383; 4.1%) in the DRV+r arm were identified as meeting FDA virologic failure criteria by week 48 (Table 21). Thus, the rates of virologic failure were similar between the DOR and DRV+r treatment groups. Of the 21 virologic failure subjects in the DOR arm, 7 had postbaseline resistance data with 2 of them having DOR genotypic resistance emergence and one with phenotypic resistance. In addition, the subject with DOR genotypic and phenotypic resistance also had emergence of the M184V substitution and corresponding lamivudine/emtricitabine resistance. In the comparator DRV+r arm, 9 out of 16 subjects had postbaseline resistance data, but none of them showed genotypic or phenotypic resistance emergence to DRV+r, 3TC, FTC, ABC or TDF.

Table 21. Summary of Resistance Emergence in Virologic Failures From PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FOWARD		PN021 DRIVE-AHEAD	
	DOR N=383	DRV N=383	DOR N=364	EFV N=364
Virologic Failures[1,2]	21/383 (5.5%)	16/383 (4.2%)	22/364 (6%)	21/364 (6%)
Virologic Failures with Resistance Data[3,4]	7/21 (33%)	9/16 (56%)	20/22 (91%)	20/21 (95%)
With Genotypic Resistance Emergence[5]	2/7 (29%)	0/9 (0%)	9/20 (45%)	12/20 (60%)
With Phenotypic Resistance Emergence[5]	1/7 (14%)	0/9 (0%)	6/20 (30%)	12/20 (60%)

DOR = doravirine (MK-1439); DRV = darunavir; EFV = efavirenz.
[1] Confirmed HIV-1 RNA ≥400 copies/mL after response of HIV-1 RNA <50 copies/mL at any time during the study OR discontinued with HIV-1 RNA ≥400 copies/mL at or after week 4.
[2] Number and proportion. Denominator is number of subjects in treatment arm.
[3] Baseline and postbaseline resistance data.
[4] Number and proportion. Denominator is number of subjects with virologic failure.
[5] Number and proportion. Denominator is number of subjects with resistance data.

In PN021 DRIVE-AHEAD, rates of virologic failure were comparable in the DOR and EFV treatment groups: 22 subjects (22/364; 6%) and 21 subjects (21/364; 5.8%), respectively, were identified as meeting the FDA virologic failure resistance subset criteria by week 48 (Table 21). Of the 22 virologic failure subjects in the DOR arm, 20 had postbaseline resistance data with 9 of them having evidence of DOR genotypic resistance emergence and 6 having phenotypic reduced susceptibility to DOR.

In the comparator EFV arm, 20 had postbaseline resistance data with 12 of them having EFV phenotypic and/or genotypic resistance to EFV (Table 128 and Table 129). The predominant emergent NNRTI substitution in the EFV arm was the K103N substitution, which emerged in 83% (10/12) of the virologic failure subjects. In addition, one subject had emergent K65R as a mixture with 0.8-fold change in TDF susceptibility, five subjects had emergent M184V and FTC resistance, and two other subjects in the EFV arm had either emergent K103Q or baseline K101Q with no corresponding decrease in EFV susceptibility (1 to 1.5-fold).

Emergence of M184V or I was comparable between the DOR and EFV arms emerging in 42 to 44% of virologic failures (Table 129). The emergence of thymidine analog mutation substitutions (TAMS: M41L, D67N, or K70E) was also similar between the arms: one subject had emergent M41L in the DOR arm and one subject had emergent D67N/K70E in the EFV arm. Two subjects (22%) in the DOR arm had emergent K65R compared to one subject (8%) in the EFV arm.

DOR was similarly effective to both DRV+r and EFV in the clinical trials based on the number of virologic failures. However, in comparison to DRV+r, DOR had more emergent resistance substitutions which, because of NNRTI cross-resistance, would likely negatively impact the ability of patients who fail with resistance to DOR to use other NNRTIs in the future. Based on the number of virologic failures and resistance emergence, DOR and EFV appear to have a similar barrier to resistance.

Overall, there were 11 virologic failures from clinical trials PN018 and PN021 who had emergent genotypic and phenotypic resistance. In PN018 and PN021 combined, the NNRTI resistance substitutions that emerged in more than one of the DOR virologic failures included V90I/G, A98G, V106I/A/M, E138G, H221Y, P225H/L/S, F227C/R, and the novel Y318F substitution (Table 22; See Appendix 0 for complete review of resistance analyses). Two other NNRTI substitutions that emerged were V108I and Y188L. The A98G, V106I/A/M, P225H/L/S, F227C/R and Y318F substitutions emerged most frequently in the virologic failures. The Y318F substitution is unique to DOR and was also selected in cell culture. The other substitutions also commonly emerge on treatment with the other approved NNRTIs and could confer cross-resistance to NNRTIs.

Table 22. Summary of Emerging DOR Resistance Substitutions

	PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD Combined	
	Emergence of DOR Resistance n/M^ (%)	Fold Change for DOR in Cell Culture
V90I/G	2/11 (18%)	1.6
A98G	3/11 (27%)	3.3
V106I/A/M*	5/11 (45%)	3.4 to 28
V108I*	1/11 (9%)	4.0
E138G	2/11 (18%)	Not assessed
Y188L	1/11 (9%)	95 to >116
H221Y*	2/11 (18%)	Selected at 4 X EC_{95}
P225H/L/S	4/11 (36%)	Not assessed
F227C*/R	5/11 (45%)	Selected at 10 X EC_{95}
Y318F*	2/11 (18%)	Not assessed

Source: FDA Analysis
DOR = doravirine (MK-1439)
^ n = number of subjects with resistance substitution; M = number of subjects with DOR resistance
*Substitutions that emerged in cell culture: V106A/I/M, V108I, H221Y, F227L/V/C/I, L234I, Y318F

Substitutions at V106, V108I, H221Y, F227 and Y318F were also selected in cell culture resistance selection experiments with DOR. The presence of the Y188L substitution conferred 95- to >116-fold change in DOR susceptibility in cell culture. The other substitutions individually conferred a 3- to 10-fold change in DOR susceptibility in cell culture. However, in the virologic failures from the clinical trials, multiple substitutions emerged in combination which conferred >90-fold decrease in DOR susceptibility. The data indicate that the combination of multiple NNRTI substitutions each conferring <10-fold decreased DOR susceptibility can result in higher level DOR resistance of >90-fold.

The mean and median fold change in DOR susceptibility was >141 and >110, respectively, (range >97 to >211) from the seven virologic failures with DOR genotypic and phenotypic resistance from both PN018 and PN021. Given the large range in DOR phenotypic susceptibilities of the small number of virologic failures, there are insufficient clinical phenotypic data to determine a definitive phenotypic breakpoint for DOR resistance. The shifts in susceptibility were one hundred-fold or greater for the virologic failures with genotypic changes at NNRTI resistance substitutions (V90I/G, A98G, V106I/A/M, E138G, H221Y, P225H/L/S, F227C/R) whereas the shifts were <2-fold for the virologic failures with other amino acid mixtures at NNRTI resistance sites.

Most DOR-resistant virologic failures were cross-resistant to efavirenz and about half were resistant to etravirine and rilpivirine: six of seven (86%) had resistance to EFV, three of seven (43%) had decreased susceptibility to etravirine (ETR), and four of seven (57%) had decreased susceptibility to rilpivirine (RPV). Comparatively, of the 11 virologic failure subjects resistant to EFV, 2 (18%) had decreased susceptibility to DOR (18- and 36-fold). Thus, failure on a DOR regimen with emergence of resistance to DOR has the consequence of limiting future NNRTI use because of significant cross-resistance to other NNRTIs.

The Applicant did not provide an assessment of phenotypic data on the Y318F resistance substitution, which was selected both in cell culture and in virologic failures in the DOR clinical trials. Thus, we are requesting the Applicant to analyze the phenotype of Y318F in cell culture as a PMC:

- Assess the phenotypic susceptibility in cell culture of DOR and approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) against Y318F alone and in combination with the following substitutions, which have been associated with DOR and/or other NNRTIs: K103N; Y181C; K103N/Y181C; L100I; L100I/K103N; V106A; P225H; V106A/P225H; H221Y; V106M; F227C; V108I.

7.7.2. Discrepancy in Resistance Data and Resistance Emergence Between PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

Issue: Rates of virologic failure to DOR were similar in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD; however, a lower rate of resistance was seen in PN018 DRIVE-FORWARD compared to PN021 DRIVE-AHEAD.

Conclusion: The lower rate of resistance seen with DOR in PN018 compared to PN021 is not indicative that DOR has a high genetic barrier to resistance. We determined the lack of collection of resistance samples for multiple subjects in PN018 appears to be the explanation for the lower number of subjects with resistance data and resistance emergence in this trial. DOR does not appear to provide an advantage in resistance barrier over other approved NNRTIs**.**

Team Assessment: As stated earlier, samples from subjects with HIV-1 level <400 copies/mL were mistakenly sent for resistance testing, or subjects with HIV-1 >400 copies/mL did not have samples collected for such testing, due to investigational site error. In PN018, six subjects did not have postbaseline resistance testing performed even though viral loads were >400 copies/mL. During the review of the protocol for PN021, the review team requested the inclusion of sample collection at every visit for potential resistance testing. This sampling scheme was not applied to protocol PN018, because it was already ongoing and partially enrolled. Therefore, resistance samples were not collected at each study visit in protocol PN018 as they were in protocol PN021, which explains the discrepancy in the number of subjects with postbaseline resistance data between the two trials and that development of DOR resistance is not less in PN018 (See Appendix III.19.3 for more details).

7.7.3. Reduction in DOR Concentrations When Administered With or Following Cessation of CYP3A Inducers

Issue: CYP3A inducers reduce DOR concentrations and may decrease the effectiveness of DOR and lead to the development of resistance. Development of resistance can limit or eliminate the effectiveness of subsequent future NNRTI-based treatment regimens. The potential impact of coadministration of CYP3A inducers on DOR efficacy and the impact of administration of DOR after cessation of a CYP3A inducer was also a key review issue.

Conclusions: DOR or DOR/3TC/TDF FDC is contraindicated with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers. If DOR is coadministered with rifabutin, increase DOR dosage to 100 mg twice daily. If DOR/3TC/TDF FDC is coadministered with rifabutin, take one tablet of DOR/3TC/TDF FDC once daily, followed by DOR 100 mg approximately 12 hours after the dose of DOR/3TC/TDF FDC. Prior to initiation of DOR, at least 4 weeks of a cessation period is needed following administration of a moderate or strong CYP3A inducer.

Team Assessment: The recommendations for dosage adjustments, contraindications and the amount of time needed between the cessation of a CYP3A inducer and beginning DOR therapy are based on the following information:

In a drug interaction study, administration of DOR with the strong CYP3A inducer rifampin (600 mg QD) reduced DOR concentrations. The geometric mean decreases were: 88% for AUC (area under the concentration versus time curve), 97% for C_{24}, and 57% for C_{max}. Based on these results, DOR should be contraindicated with strong CYP3A inducers. (See Appendix III.15.2.2.3)

In a drug interaction study, administration of DOR with the CYP3A inducer rifabutin (300 mg QD) reduced DOR concentrations to a lesser extent compared to rifampin. The geometric mean decreases were: 50% for AUC, 68% for C_{24}, and no change for C_{max}. Because of the importance of rifabutin in the HIV-1-infected population, a dose adjustment is recommended, to allow

administration of rifabutin to patients receiving DOR. PK projections indicate 100 mg twice daily DOR coadministered with 300 mg QD rifabutin achieves similar C_{24}, AUC_{0-24}, and C_{max} values to 100 mg QD DOR in the absence of a CYP3A inducer. (See Appendix III.15.2.2.3) The dose adjustment raised another issue (increase of DOR metabolite M9 exposure), which is addressed below.

Because of the importance of some CYP3A inducers in the HIV-1 population, the review team evaluated the amount of time needed between the cessation of a CYP3A inducer and beginning DOR therapy. The goal was to avoid subtherapeutic DOR concentrations at the beginning of therapy. The potential issue is illustrated by the results of the efavirenz (EFV) DDI study, in which DOR AUC is reduced by 62% when DOR administration starts the day after EFV administration ends, but is reduced by 32% when DOR administration starts 14 days after EFV administration ends.

The review team used Physiologic Based Pharmacokinetic modeling to determine the magnitude of DOR concentration reduction at various times following cessation of the strong CYP3A inducer, rifampin. Under the worst case scenario, 25% of the induction effect remains 4 weeks after cessation of rifampin. The magnitude of the DOR AUC reduction is acceptable based on the Phase 2 data. For simplicity of instructions, 4 weeks of cessation is recommended after any CYP3A inducer, prior to starting DOR.

7.7.4. Increased Exposure to DOR M9 Metabolite When DOR is Administered With a CYP3A Inducer

Issue: DOR is primarily metabolized by CYP3A, and M9 is the major metabolite. Administration with a CYP3A inducer is expected to increase M9 concentrations. Administration of DOR twice daily when coadministered with rifabutin will further increase M9 concentrations and could pose a safety concern. There are no human M9 plasma PK data that indicate the increase in patients who receive DOR 100 mg twice daily (BID) with rifabutin relative to concentrations in patients who receive DOR 100 mg QD without an inducer.

Conclusion: The limited available data do not indicate a safety concern related to the M9 metabolite when DOR 100 mg BID is administered with the CYP3A inducer rifabutin. However, there is uncertainty because the data are limited. Based on the findings summarized below, a PMC will be issued to address this uncertainty. The Applicant agreed to conduct a drug-drug interaction study to evaluate the pharmacokinetics of DOR and its primary metabolite (M9) when DOR 100 mg BID is coadministered with rifabutin as compared to the administration of DOR 100 mg QD alone in healthy subjects.

Team Assessment: The assessment of this issue included evaluation of nonclinical safety data and physiologically based pharmacokinetic (PBPK) modeling. (See Appendix III.15.2.6).

Exposures of M9 in plasma from patients administered the clinical dose (RHD; 100 mg once a day) were adequately covered in the chronic nonclinical safety studies. M9 was adequately assessed in the Ames assay (negative) and predicted to be negative in (Q)SAR analysis conducted by the FDA CDER Chemical Informatics Program. Coadministration of rifabutin (a CYP3A inducer) with DOR, may result in increased M9 exposure. Exposure margins were calculated based on estimated exposures of M9 in a three-month mouse study (study TT #12-6013) and estimated human exposures of M9 after rifabutin coadministration. Mouse levels of M9 in the 3-month study were estimated from a mass balance study in CD-1 mice, in which plasma exposures of M9 and MK-1439 were equivalent at 1- and 6-hour time-points after a single oral administration of 5 mg/kg MK-1439 (study PK013). The resulting safety margin was almost 10-fold (no observed adverse effect level (NOAEL) AUC 196µM; estimated maximum in humans 20µM.)

PBPK analysis was conducted to evaluate the maximum effect induction on the formation of the M9 metabolite, using the strong CYP3A inducer rifampin. The analysis shows that a strong CYP3A inducer may increase M9 AUC and Cmax by up to 2-fold and 4-fold, respectively. By increasing DOR dosing frequency from once daily to twice daily when coadministered with a moderate CYP3A inducer (rifabutin), M9 AUC is expected to increase approximately 4-fold, at maximum, by assuming a linear relationship between parent drug and production of M9 via CYP3A. The maximum levels of M9 after coadministration of DOR with rifabutin are anticipated to be 20µM or less. CYP3A inducers were not included in the phase 2/3 trials. The supporting clinical safety data for M9 are summarized as follows:

- Multiple doses of up to DOR 750 mg QD (n=6) for 10 days provided an exposure multiple (DOR and M9) of ~3.7-fold relative to the steady-state AUC following administration of 100 mg QD.
- Single doses of up to 1200 mg (n=6) provided an exposure multiple (DOR and M9) of 6.5-fold relative to the steady-state AUC following administration of 100 mg QD.

There are limited human safety data (n=6) from multiple doses of 750 mg QD (n=6) for 10 days, a regimen which may provide M9 exposures similar to coadministration of DOR and rifabutin. However, nonclinical data and (Q)SAR assessment for M9 indicate that there is likely not a significant safety concern with coadministration of DOR and rifabutin.

7.7.5. Increase in DOR Concentrations When Administered With a Strong CYP3A Inhibitor

Issue: Coadministration of DOR and drugs that inhibit CYP3A result in increased plasma concentrations of DOR which could pose a safety concern. (See Appendix III.15.2.2.2).

Conclusion: DOR dose does not need to be adjusted when DOR is administered with a strong CYP3A inhibitor.

Team Assessment: The findings below supported our overall conclusion.

The maximum effect was evaluated in a DDI study with the strong CYP3A inhibitor ketoconazole. Following administration of ketoconazole (400 mg QD) with DOR 100 mg, the geometric mean increases in DOR were: 3.06-fold for AUC (area under the concentration versus time curve), 1.25-fold for C_{max}, and 2.75-fold for C_{24}. In phase 2/3 trials, 12 subjects used a strong nontopical CYP3A inhibitor during treatment with DOR and no significant safety concerns were identified. In addition, DOR up to 750 mg for 10 days was studied in healthy volunteers with no safety concerns identified.

7.7.6. Imbalance in Thyroid Adenoma and Carcinoma in 2-Year Carcinogenicity Study

Issue: A nonclinical carcinogenicity study identified an imbalance in thyroid adenomas and carcinomas in female rats at the highest dose tested (450 mg/kg/day) following 2 years of daily dosing ($AUC_{0\text{-}24\ hr}$: 279µM•hr; approximately 7.5-fold above the DOR exposure at the RHD). No thyroid adenomas or carcinomas were reported in the phase 2 or 3 trials. The Applicant did not propose labeling because they did not consider the imbalance in thyroid adenoma and carcinomas relevant because these findings were within the range observed in historical control studies.

Conclusion: Labeling is proposed to state the clinical significance of this nonclinical finding is unclear and the finding was within the range observed in historical control studies.

Team Assessment: The decision for labeling is based on the following data.

In the 2-year oral carcinogenicity study in rats (study TT-136029), the rate of parafollicular cell adenoma in the high dose females was 13.5%, and the rate of parafollicular cell carcinoma was 2%, both of which were within the historical control ranges. The rate of parafollicular cell adenoma and carcinoma was also within the range of historical control data submitted by the Applicant from studies conducted in their own facilities. In an additional DOR 6-month oral carcinogenicity study in rasH2 transgenic mice (study TT #13-6005), there were no test article related neoplastic or non-neoplastic findings up to 300 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 228µM•hr; approximately 6-fold above the DOR exposure at the RHD).

The Executive Carcinogenicity Assessment Committee concurred that the combined incidence of drug related thyroid parafollicular cell adenomas and carcinomas in female rats was increased at 450 mg/kg/day and should be reflected in labeling for transparency and convey the uncertainties of these findings and human relevance. Additional nonclinical details are located in Appendix III.14 and final labeling that reflects this decision and historical control observations are included in Appendix III.22.

7.7.7. Increases in Bilirubin vs. Comparators

Issue: Numerically, more DOR-treated subjects developed increases in total bilirubin compared to the active comparators. Rates of graded total bilirubin abnormalities were higher in the DOR group (6.5%) versus the DRV+r group (1.3%) in PN018 DRIVE-FORWARD (treatment difference: 5.2%, 95% CI: 2.4%, 8.3% by the exact method), and also higher in the DOR group (6.6%) versus EFV group (<1%) in PN021 DRIVE-AHEAD (treatment difference: 6.3%, 95% CI: 3.8%, 9.3% by the exact method.

Conclusion: Our analyses do not suggest DOR has the potential for drug-induced liver injury, nor do they suggest a causal association with clinical AEs such as gallstones. The increases in bilirubin are not likely clinically meaningful. The team recommends including all graded total bilirubin laboratory information in the DOR and DOR/3TC/TDF labels. In addition, grade 2 to 4 ALT, aspartate aminotransferase (AST), and alkaline phosphatase laboratory information is recommended to provide general consistency with other approved HIV-1 product labels. Routine postmarketing pharmacovigilance is recommended for continued assessment of biliary events associated with DOR use.

Team Assessment: A detailed analysis was performed to evaluate the potential for hepatotoxicity from DOR because of numerical imbalances in bilirubin and biliary AEs between the DOR-containing and comparator groups, and because hepatotoxicity has been identified as a safety signal for other NNRTIs. Biliary AEs were defined by MedDRA preferred terms bile duct stone, biliary colic, biliary dyskinesia, cholecystitis, cholecystitis acute, and cholelithiasis. See Appendix III.18.9.

The following data support our conclusion:

- Preclinical animal toxicity data do not suggest a relationship between DOR and any changes in liver clinical chemistry parameters, including bilirubin, or adverse liver histopathology findings in either the rat or dog.
- Biliary excretion is not a significant pathway of elimination for DOR or its metabolites. DOR in vitro inhibition profile indicates increases of plasma unconjugated bilirubin via DOR inhibition of UGT1A1 or OATP1B1/3 are unlikely.
- Bilirubinemia in DOR-treated subjects was grade 1 or 2, not sustained, and not associated with graded abnormalities in other liver tests (ALT, AST, or alkaline phosphatase), and not associated with treatment discontinuation.
- No exposure-response was noted for changes in bilirubin.
- A numerical imbalance in clinical biliary AEs was noted for DOR compared to active comparators (eight events versus two events, respectively; see Table 119), including five DOR-treated subjects with biliary SAEs in PN007 and the phase 3 trials; however:
  - Among subjects who experienced biliary AEs, there was no evidence of elevated DOR PK parameters.
  - The dates of biliary AE onset were heterogeneous in relation to DOR initiation.
  - Most subjects experiencing a biliary AE had predisposing risk factors, including Hispanic ethnicity, obesity, hydrochlorothiazide use, and hyperlipidemia.
  - All had normal bilirubin levels prior to the biliary AE.

- The Division of Applied Regulatory Science consult concluded the chemical structure of DOR does not suggest a mechanism whereby DOR might cause biliary toxicity.
- No subjects met the complete definition for drug-induced liver injury[2] in the phase 3 trials or in PN007.

[2] Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a mortality of 10 to 50%. Hepatocellular injury sufficient to impair bilirubin excretion has been used by the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as an indicator of clinical concern for drug-induced liver injury includes the following: ALT or AST >3x upper limit of normal (ULN), total bilirubin >2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (for example, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury).

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

No dose adjustment of DOR is required in patients with mild, moderate, or severe renal impairment. In study 051, single dose DOR AUC was 43% higher in subjects with severe renal impairment compared to subjects without renal impairment. (See Appendix III.15.2.3)

DOR has not been studied in patients with end-stage renal disease or in patients undergoing dialysis.

DOR/3TC/TDF FDC is not recommended in patients with estimated creatinine clearance less than 50 mL/min, because the dosage regimen for 3TC and TDF need to be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with end-stage renal disease who require dialysis, but the dosing interval or dose cannot be modified for components of the FDC.

Hepatic Impairment

No dose adjustment of DOR is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. In study P019, single-dose DOR pharmacokinetics were not different for subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects without hepatic impairment. (See Appendix III.15.2.3)

DOR has not been studied in subjects with severe hepatic impairment (Child-Pugh score C).

Other Intrinsic Factors

The population pharmacokinetic analysis and an intrinsic factor study (P09) indicated sex, race, age (older versus younger adults), and body weight do not have a clinically significant effect on DOR pharmacokinetics. (See Appendices III.15.2.3 and III.15.2.4)

8.2. Drug Interactions

There are clinically significant DDIs when DOR is administered with CYP3A inducers (see Appendix III.15.2.2). The risks and management strategies are described in Section 7.7.3. The risk of coadministration with CYP3A inhibitors was evaluated, but deemed not clinically significant, as described in Section 7.7.5. There is no evidence that DOR has an effect on the pharmacokinetics of other drugs.

DOR as a Victim Drug

DOR is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of DOR. Coadministration of DOR and drugs that induce CYP3A result in decreased plasma concentrations of DOR. Coadministration of DOR and drugs that inhibit CYP3A result in increased plasma concentrations of DOR.

The table below includes results of DDI studies between DOR and CYP3A inhibitors and CYP3A inducers.

Table 23. Changes in Pharmacokinetic Parameter Values of DOR in the Presence of Coadministered Drug

Coadministered Drug	Regimen of Coadministered Drug	Geometric Mean Ratio (90% CI) of DOR Pharmacokinetics With/Without Coadministered Drug (No Effect=1.00)		
		AUC[1]	C_{max}	C_{24}
Ketoconazole	400 mg QD	3.06 (2.85, 3.29)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)
Rifampin	600 mg QD	0.12 (0.10, 0.15)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)
Rifabutin	300 mg QD	0.50 (0.45, 0.55)	0.99 (0.85, 1.15)	0.32 (0.28, 0.35)
Ritonavir[2]	100 mg BID	3.54 (3.04, 4.11)	1.31 (1.17, 1.46)	2.91 (2.33, 3.62)
Efavirenz[3]	600 mg QD[4]	0.38 (0.33, 0.45)	0.65 (0.58, 0.73)	0.15 (0.10, 0.23)
	600 mg QD[5]	0.68 (0.58, 0.80)	0.86 (0.77, 0.97)	0.50 (0.39, 0.64)

AUC = area under the curve; CI = confidence interval; QD = once daily; BID = twice daily; DOR = doravirine
[1] AUC_{inf} for single-dose, AUC_{0-24} for once daily.
[2] A single DOR 50-mg dose (0.5 times the recommended approved dose) was administered.
[3] Interaction was assessed following the cessation of efavirenz therapy.
[4] The first day following the cessation of efavirenz therapy and starting of DOR 100 mg QD
[5] 14 days following the cessation of efavirenz therapy and DOR 100 mg QD

DOR as a Perpetrator Drug

Based on in vivo studies, no clinically significant changes in exposure were observed for the following drugs when coadministered with DOR: midazolam, dolutegravir, lamivudine, tenofovir DF, elbasvir, grazoprevir, ledipasvir, sofosbuvir, GS-331007, ethinyl estradiol, levonorgestrel, atorvastatin, metformin, methadone (R-methadone), or methadone (S-methadone).

8.3. Pediatric Labeling/Plans for Pediatric Drug Development

No studies in the pediatric population have been submitted in the NDA applications. Because DOR is a new active ingredient, approval of DOR in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history triggers the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c). Per the Food and Drug Administration Safety and Innovation Act (FDASIA), the Applicant submitted an initial Pediatric Study Plan and agreed by the FDA on March 20, 2015. An amended initial Pediatric Study Plan was agreed by the FDA on May 24, 2017, which proposed a program of formulation development, clinical pharmacology, and clinical trials. The deferral and waiver requests listed below were presented to the Pediatric Review Committee on July 18, 2018, and the committee agreed with these requests (please refer to Pediatric Review Committee Meeting Minutes entered in DARRTS August 2, 2018 for complete details).

The Applicant had the following deferral requests for DOR:

A deferral of pediatric assessments of DOR in children aged 4 weeks to 23 months, on the grounds that:

- Additional safety and PK data in older children and in adults infected with virus harboring transmitted NNRTI resistance mutations are needed to support the initiation of studies in this age group;
- An age-appropriate formulation needs to be identified and shown to be biocomparable to the DOR tablet in adults prior to its administration in this age group.

A deferral of pediatric assessments of DOR in children aged at least 2 years and weighing less than 35 kg, on the grounds that:

- A benefit must first be established in the adult population in the setting of switch before administration to pediatric patients in this age/weight group;
- An age-appropriate formulation needs to be identified and shown to be biocomparable to the adult DOR tablet in adults prior to its administration in this age/weight group.

A deferral of pediatric assessments of DOR in children aged <18 years and weighing at least 35 kg.

The Applicant had the following deferral requests for DOR/3TC/TDF:

A deferral of pediatric assessments of DOR/3TC/TDF in children aged at least 2 years and weighing less than 35 kg, on the grounds that:

- A benefit must first be established in the adult population in the setting of switch before administration to pediatric patients in this age/weight group;
- An age-appropriate formulation needs to be identified and shown to biocomparable to the adult DOR/3TC/TDF tablet in adults prior to its administration in this age/weight group.

A deferral of pediatric assessments of DOR/3TC/TDF in children aged <18 years and weighing at least 35 kg, on the grounds that:

- Additional safety and PK data to support administration of the 100-mg dose of DOR in adolescents are needed to support initiation of studies of DOR/3TC/TDF in this age/weight group.

The Applicant requested (1) a waiver of pediatric assessments of DOR in children aged 0 to <28 days, on the grounds that there is no additional significant therapeutic benefit conferred by DOR in this segment of the pediatric population and, based on a lack of reliable/definitive diagnosis of HIV-1 infection in this age group, the product is unlikely to be used in a substantial number of patients in this category, and (2) a waiver of pediatric assessments of DOR/3TC/TDF in children aged less than 2 years, on the grounds that there is no additional significant therapeutic benefit conferred by DOR/3TC/TDF in this segment of the pediatric population.

8.4. Pregnancy and Lactation

Animal Data

The following nonclinical information was used in support of the indicated labeling sections. Additional nonclinical details are located in Appendix III.14 and final labeling is discussed in Appendix III.22.

Table 24. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	• Developmental toxicity studies were conducted in rats, with no adverse effects on maternal health or embryo-fetal development in rats. • In rabbits, administration of oral DOR at 300 mg/kg/day to pregnant females during organogenesis resulted in maternal toxicity (body weight loss) and concomitant fetal toxicity (skull malformations). Due to maternal toxicity at this dose, the malformations were not considered test article-related. • DOR maternal exposure was not associated with any adverse effects on pre- and postnatal development. DOR at doses up to 450 mg/kg/day in pregnant rats had no maternal or fetal effects on behavior or development. • DOR had no clear adverse effects on rats dosed daily from postnatal day (PND) 14 to PND 55, in a juvenile toxicity study.
8.2 Lactation	• In a rat pre- and postnatal study, DOR was detected in the plasma of neonates on lactation day 14, indicating transfer through milk; lactational transfer on lactation day 14 was up to 147%.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	• DOR exposure was not associated with effects on fertility. Daily oral doses of DOR to rats had no effects on male or female reproductive performance, on the estrous cycle or sperm, or on embryo/fetal viability.

DOR = doravirine (MK-1439); PND = postnatal day

All calculated safety margins from fertility and reproductive toxicology studies conducted in the rat and rabbit were acceptable as identified in Table 25 below.

Table 25. Doravirine Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg)	Nonclinical exposure (µM•hr)	Safety margins*** (multiples)
Fertility rat	450	279*	7.5
EFD rat	450	345	9
EFD rabbit	300	315	8.5
PPND rat	450	345**	9
Juvenile rat	300	333	9

EFD = embryo-fetal development; NOAEL = no observed adverse effect level; PPND = peri- and postnatal
*No PK data; based on 6 month study
**No PK data; based on EFD study
***Exposure multiples were based on population pharmacokinetics analysis from DOR phase 3 trials (PN018 and PN021), where a 100 mg QD DOR clinical dose resulted in systemic geometric mean exposures of $AUC_{0\text{-}24hr}$ of 37.8µM•hr.

Human Data

No adequate and well-controlled trials of DOR have been conducted in the pregnant population, and no adequate human data are available to establish whether or not DOR poses a risk to pregnancy outcomes.

Women who were pregnant and/or lactating were excluded from enrollment into DOR-containing clinical trials; however, six subjects became pregnant during the phase 2/3 trial period and discontinued due to pregnancy. The outcomes for these pregnancies were: a vaginal live birth with no congenital anomalies for two pregnancies (DOR 50 mg group in PN007, DOR group in PN018 DRIVE-FORWARD); spontaneous abortion considered not drug related for three pregnancies (one in the DOR group in PN018 DRIVE-FORWARD; one in the DOR/3TC/TDF group in PN021 DRIVE-AHEAD, one in the EFV/FTC/TDF group in PN021 DRIVE-AHEAD); and pending (pregnancy ongoing) for one pregnancy, (EFV/FTC/TDF group in PN021 DRIVE-AHEAD).

During the SUR period, there were five additional pregnant subjects. In PN018 DRIVE-FORWARD, three subjects (one subject in the DOR treatment group and two in the DRV/r treatment group) were pregnant. The subject in the DOR treatment group discontinued day 589, following an elective abortion on day 554. In PN021 DRIVE-AHEAD, two subjects (both in the DOR/3TC/TDF group) discontinued due to pregnancy: one subject discontinued day 327 (pregnancy outcome is pending), and one subject discontinued day 493 (pregnancy outcome was a spontaneous abortion on day 507; the investigator considered this outcome not related to study drug or study procedure).

9. Product Quality

Approval—The Office of Pharmaceutical Quality Review team has assessed NDAs 210806 and 210807 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable

10. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

Human Subjects Protections

The Applicant states the clinical trials were conducted in substantial conformance with International Conference on Harmonisation GCP (good clinical practice) requirements and applicable country and/or local statues and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The phase 3 trials were conducted according to FDA requirements, under investigational new drug applications (INDs) 112796 and 124997. Additionally, FDA clinical site inspections did not reveal evidence of GCP noncompliance at the inspected sites.

Clinical Site Inspections

Inspection sites were selected from PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD. A total of six sites, three from PN018 DRIVE-FORWARD and three from PN021 DRIVE-AHEAD, were selected using the BIMO site selection tool as a resource. Both domestic and foreign sites were selected because this approval would be the first of DOR and DOR/3TC/TDF, and because a substantial amount of the clinical trial experience with DOR and DOR/3TC/TDF has been at foreign sites. The clinical site inspection final reports were all classified as No Action Indicated.

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinic investigators as recommended in the guidance *Financial Disclosure by Clinical Investigators* (February 2013; see Appendix III.23), and by 21 CFR 54.4. None of the 280, 584, and 573 investigators for PN007, PN018, or PN021 respectively are employed by the Applicant, although three investigators are married to Merck employees. Two of the investigators (<1%) have financial interests or arrangements with the Applicant, three subinvestigators (all for PN018) did not return the requested information about financial disclosures, and the remaining investigators

(>99%) have no financial interests or arrangements with the Applicant, as defined in 21 CFR 54.2.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoint (proportion of subjects with HIV-1 RNA <50 copies/mL at week 48) is an objective laboratory measurement that is assessed centrally and not vulnerable to investigator bias. In addition, all three trials were randomized, active-controlled, and double-blind, which would minimize the potential for investigator bias to play a role. Finally, <1% of investigators had financial interests or arrangements with the Applicant, and these investigators with financial interests enrolled <1.5% of the subjects.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

DOR was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for DOR's drug class and there were no controversial issues that would benefit from advisory committee discussion.

12. Review Team Signatures Page

[This section will be used in the future for review team acknowledgements and signatures. The appendices will also include author acknowledgements and signatures.]

III. Appendices

13. Summary of Regulatory History

Table 26. Summary of Presubmission/Regulatory Activity

Date	Activity	Outcome
August 11, 2011	IND 112796 (DOR) was submitted in the United States	
June 24, 2014	Type B, End-of-Phase 2 meeting to discuss the proposed phase 3 clinical development plan including two proposed specified safety endpoints (lipid changes from baseline and neuropsychiatric events)	FDA and Merck agreed to the following: For PN018 DRIVE-FORWARD, LDL-C, as opposed to non-HDL-C alone, was agreed on as the primary comparative measure for lipid changes, with non-HDL-C measured either sequentially or in conjunction with LDL-C. Total cholesterol, HDL, and triglycerides were agreed on as acceptable supportive measures. For PN021 DRIVE-AHEAD, agreed NPEs would be analyzed in a sequential manner in the following order: 1) dizziness, 2) sleep disorders and disturbances, 3) altered sensorium, 4) depression and suicide/self-injury, and 5) psychosis and psychotic disorders. The sequential analysis would stop at the first category that fails to meet a p-value of 0.05. All severities would be included, and the analysis would be done at week 48
May 25, 2015	IND 124997 (DOR/3TC/TDF) was submitted in the United States	
January 17, 2017	Type C, CMC meeting to gain concurrence with Merck's selection of regulatory starting materials in the synthesis of MK-1439	Merck cancelled the meeting. The preliminary comments sent by the FDA were sufficiently clear. Agreement was reached on the selection of regulatory starting materials in the synthesis of MK-1439 drug substance for the planned NDA submissions
May 17, 2017	Type C, CMC meeting to obtain feedback regarding Merck's proposals for the product manufacturing and storage, commercial expiration date of the drug product, and dissolution method for DOR and the FDC	FDA agreed the proposed control strategy to (b) (4) drug product manufacturing and storage, and tablet expiry was acceptable. No agreement reached on the dissolution method and a full dissolution method development report was requested

Date	Activity	Outcome
August 8, 2017	Type B, Pre-NDA meeting agreeing on the phase 3 efficacy and safety analysis data along with the phase 2b data to support the NDA submission	FDA agreed to the efficacy and safety data from the phase 3 clinical trials (P018 and P021) along with the phase 2b data (PN007) are adequate to support the NDA submission.
October 23, 2017	NDAs submission complete	

DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; HDL-C = high-density lipoprotein cholesterol; IND = investigational new drug; LDL-C = low-density lipoprotein cholesterol; NDA = new drug application; NPE = neuropsychiatric event

14. Pharmacology Toxicology Assessment Additional Information and Assessment

14.1. Summary Review of Studies Submitted Under IND

14.1.1. Pharmacology

14.1.1.1. Primary pharmacology

Doravirine (DOR), a potent NNRTI of human immunodeficiency virus type 1 (HIV-1), has shown potent activity against wild-type (WT) virus and prevalent K103N and Y181C NNRTI mutants with EC_{50} values of 12nM, 21nM, and 31nM respectively.

14.1.1.2. Secondary Pharmacology

In Vitro Assessment of DOR in the (b) (4) – 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 (b) (4) screen with more than 110 enzymes and receptors. DOR only showed moderate affinity to the 5-hydroxytryptamine (serotonin) receptor 2B (5-HT_{2B}) in a ligand-binding assay with an IC_{50} of 2.5µM, while in a subsequent cell based functional 5-HT_{2B} assay, no agonist or antagonist activity was observed with monitoring of inositol-1-phosphate accumulation. Therefore, binding of DOR to 5-HT_{2B} does not impact 5-HT_{2B} receptor function.

DOR/3TC/TDF
Due to the low potential for off-target activity and cytotoxicity by each component, no additional secondary pharmacology studies were deemed necessary.

Table 27. Safety Pharmacology Studies

Study/ Study No.	Findings
TT #10-4716: Effect on hERG Current	A minor effect of MK-1439 on membrane K+ current was observed (IC_{50}=88μM) in hERG-transfected CHO cells in this GLP study. This effect is not considered to be of clinical concern.
TT #10-6029: Oral Functional Observational Battery Study in Rats Wistar Han Rats (10/sex/group) 0, 5, 75, or 450 mg/kg/day (oral)	A functional observational battery assay was conducted to evaluate potential nervous system effects in male rats after a single oral dose on study day 1 (conducted approximately 7 hours (±1 hour) postdose (expected T_{max})). There were no test article-related functional observational battery findings at all doses tested. The NOEL for nervous system function was ≥450 mg/kg (C_{max} of 15.2μM, approximately 6.5-fold DOR levels at the human C_{max} exposure). No significant neurobehavioral effects were observed for up to 24 hours postdose in an exploratory functional observational battery study in female mice given single oral doses of up to 750 mg/kg (study #TT-10-5262).
TT #10-5606: Oral Cardiovascular and Respiratory Telemetry Study in Dogs Beagle Dogs (2/sex) 0, 0.5, 2, or 10 mg/kg (oral gavage; ascending dose/ 3 day washout)	There were no test-article related effects on hemodynamic or electrocardiographic parameters or on body temperature. In addition, there were no test-article related effects on respiratory parameters [respiratory rate (breaths per minute) or depth of respiration (mm Hg)]. The NOEL was >10 mg/kg (C_{max}~12 (female) and 8 (male) μM; $AUC_{0\text{-}24\ hr}$=220 (female) and 161 (male) μM.hr at 10 mg/kg-taken from study #TT-10-6039; three-month toxicity study in dogs).
TT #10-5006: Cardiovascular Function in Anesthetized (Vagotomized) Dogs 1, 2, and 7 mg/kg (IV; three sequential 30-minute periods)	There were no test article-related effects on MAP, pulse, QRS, PR or QT/QTc intervals at any dose tested. Maximum average plasma concentrations of MK-1439 measured during the 30-minute infusions of 1, 2, and 7 mg/kg were 3, 6, and 14μM, respectively.

AUC = area under the curve; CHO = Chinese hamster ovary; DOR = doravirine (MK-1439); IC_{50} = concentration inhibiting 50% activity; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; MAP = mean arterial pressure; NDA = new drug application; NOEL = no observed effect level; NPE = neuropsychiatric event

14.1.2. ADME/PK

Absorption

Single Dose Pharmacokinetic Studies in Rabbits and Dogs (PK001, PKMK1439, PK011MK1439)

Table 28. IV and Oral Pharmacokinetic Parameters of Doravirine in Female Dutch-Belted Rabbits and Male Beagle Dogs

Study Number	[Ref. 4.2.2.2: PK011MK1439]	[Ref. 4.2.2.2: PK011MK1439]	[Ref. 4.2.2.2: PK001MK1439]	[Ref. 4.2.2.2: PK001MK1439]
Species / Strain	Rabbit/Dutch Belted	Rabbit/Dutch Belted	Dog/Beagle	Dog/Beagle
Gender / Number of animals	F/3	F/3	M/3	M/3
Feeding condition	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation	20% DMSO/60% PEG400/20%Water/Solution	0.5% Methyl cellulose/ 5mM HCL/Suspension	20% DMSO/60% PEG400/20%Water/Solution	0.5% Methyl cellulose/ 5mM HCL/Suspension
Method of administration	IV	P.O.	IV	P.O.
Dose (mg/kg)	1	5	1	5
Sample	Plasma	Plasma	Plasma	Plasma
Analyte	Doravirine	Doravirine	Doravirine	Doravirine
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
PK parameters (Mean ± SD):				
Total CL_p (mL/min/kg)	4.0 ± 0.50	NA	0.44 ± 0.04	NA
Vd_{ss} (L/kg)	2.67 ± 0.38	NA	0.9 ± 0.05	NA
$T_{1/2}$ (hr)	9.03 ± 0.51	NA	21.7 ± 2.1	NA
$AUC_{0-\infty}$ (µM•hr)	9.98 ± 1.26	20.53 ± 8.67	88.9 ± 8.73	205 ± 47
C_{max} (µM)	NA	1.78 ± 0.53	NA	5.7 ± 1.5
T_{max} (hr)	NA	3.5 ± 2.78	NA	0.8 ± 0.3
Bioavailability (%)	NA	41 ± 13	NA	47 ± 14

Additional Information:

- Abbreviations: SD = Standard Deviation; NA = Not Applicable.
- Spray-dried doravirine on HPMCAS-LG polymer at a drug load of 20% (w/w) was used for the oral suspension formulations.
- Bioavailability (F%) in dogs and rabbits were calculated in a crossover fashion using the $AUC_{0-\infty}$ value at 5 mg/kg P.O. relative to the $AUC_{0-\infty}$ at 1 mg/kg IV for each animal.

Distribution

Table 29. In vitro Protein Binding Determination of MK-1439 and M9 Metabolite (PK003MK1439, PK0012MK1439, PK015MK1439)

Compound	Species	Fraction Unbound[a]			
		0.1 µM	1.0 µM	3.0 µM	5.0 µM
DOR	Mouse	0.242 ± 0.025	0.238 ± 0.027	0.251 ± 0.020	0.262 ± 0.021
	Rat	0.349 ± 0.005	0.324 ± 0.012	0.282 ± 0.021	0.272 ± 0.014
	Rabbit	0.221 ± 0.012	0.240 ± 0.013	0.256 ± 0.029	0.279 ± 0.011
	Dog	0.241 ± 0.005	0.258 ± 0.003	0.187 ± 0.019	0.192 ± 0.009
	Human	0.257 ± 0.003	0.241 ± 0.009	0.233 ± 0.039	0.251 ± 0.032

[a] Values represent mean ± SD of 3-6 replicates.

Protein Binding of MK-1439 in Plasma from Different Species

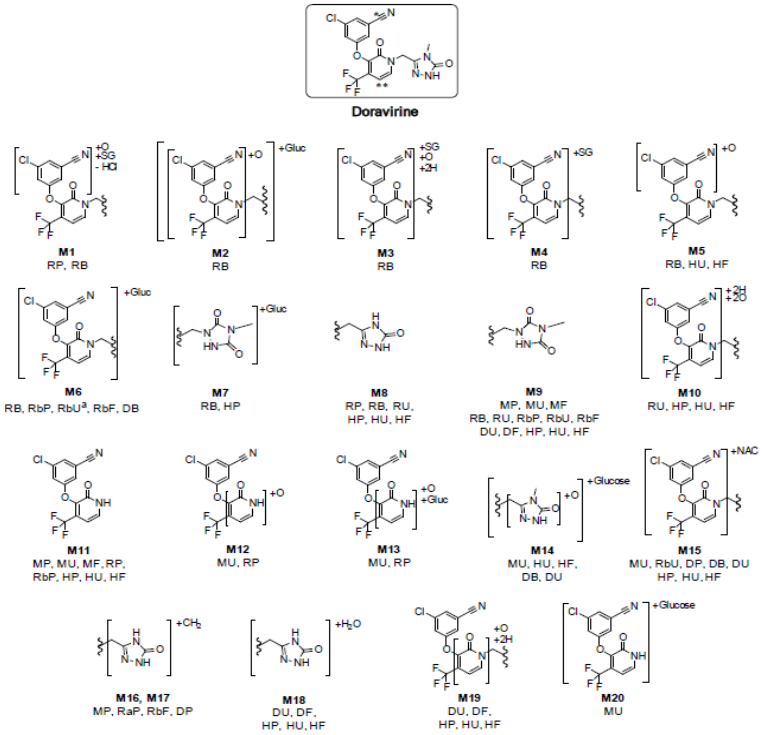
Concentrations of Radioactivity in Tissues of Male Long-Evans (Partially-Pigmented) Rats After a Single Oral Gavage Dose of [^{14}C]Doravirine at 5 mg/kg (PK005MK1439)

- Radioactivity was distributed to most tissues except central nervous system, eye lens and bone.
- Highest concentrations were found in the alimentary canal, bile and urine.
- Blood concentrations were maximal two hours postdose.
- Radioactivity remained up to 168 hours postdose.

Metabolism

Proposed Metabolic Pathways of Doravirine in Mice, Rats, Rabbits, Dogs and Humans (PK002MK1439, PK004MK1439, PK006MK1439 and PK013MK1439)

Figure 1. Proposed Structures of DOR Metabolites in Mice, Rats, Rabbits, Dogs, and Humans



* Indicates the position of ^{14}C and ** indicates the position of ^{3}H.

[a] Two metabolites identified in rabbit urine as doravirine glucuronides appeared to be different from M6 and were designated as M6a and M6b to differentiate from M6 observed in other species.

MP, RP, RbP, DP, HP=mouse, rat, rabbit, dog, human plasma; RB, DB=rat, dog bile; MU, RU, RbU, DU, HU=mouse, rat, rabbit, dog, human urine; MF, RF, RbF, DF, HF=mouse, rat, rabbit, dog, human feces.

Gluc=glucuronide, NAC=*N*-Acetylcysteine, SG=glutathione

Excretion and Metabolism of [^{14}C]MK-1439 in Male CD-1 Mouse and Female Dutch Belted Rabbit Following Oral Administration (PK013)

- The excretion and metabolism of [14C]MK-1439 was characterized in male CD-1 mice and female Dutch belted rabbits (5 mg/kg) following oral administration of a single 5 mg/kg dose.
- The major parent-related species circulating in mouse plasma were MK-1439 and M9, where levels of M9 were comparable to levels of MK-1439 (approximately 1:1 ratio) at the two time points with quantifiable levels of radioactivity (1 and 6 hr).
- The oxidative metabolite M9 was the major metabolite in rabbit urine, accounting for 19.5% of the dose.

M9 Metabolite Comments

- M9 was present in rat and dog plasma (at NOAEL doses) at levels that were respectively 52% and 51% relative to levels observed in plasma from healthy subjects who received multiple once daily 240-mg doses of DOR.
- The unbound fraction of M9 in rat and dog plasma was 2.2- and 2.8-fold higher, respectively, than in human plasma (Table 28).
- Unbound concentrations in the safety species, were approximately similar to the unbound concentrations in human plasma after administration of multiple once-daily administration of 240 mg DOR.
- Exposures of M9 in plasma from patients administered the clinical dose (RHD; 100 mg once a day) were adequately covered in the chronic safety studies.
- M9 was adequately assessed in the Ames assay (negative) and predicted to be negative in (Q)SAR analysis conducted by the FDA CDER Chemical Informatics Program.

Table 30. Fraction Unbound M9 Metabolite in Plasma from Different Species

Compound	Species	Fraction Unbound[a]	
		0.1 µM	1.0 µM
M9	Rat	0.18 ± 0.02	0.20 ± 0.01
	Dog	0.24 ± 0.01	0.25 ± 0.01
	Human	0.08 ± 0.003	0.09 ± 0.004

[a] Values represent mean ± SD of 3-6 replicates.

Coadministration of DOR and Rifabutin

- M9 is the primary metabolite resulting from DOR via CYP3A metabolism in humans.
- Coadministration of rifabutin (a CYP3A inducer) with DOR, may result in increased M9 exposure.
- An exposure margin of 4.5X was calculated by the Clinical Pharmacology reviewer. An exposure margin of 10X was calculated by the Applicant.
- Both margins were based on estimated exposures of M9 in a three-month mouse study (study TT #12-6013) and estimated human exposures of M9 (variable), after rifabutin coadministration.
- Mouse levels of M9 in the three-month study were estimated from a mass balance study in CD-1 mice, in which plasma exposures of M9 and MK-1439 were equivalent at 1- and 6-hour time-points after a single oral administration of 5 mg/kg MK-1439.

Excretion

Excretion of Total Radioactivity Following an Oral Dose of [^{14}C] Doravirine to Rats and Dogs (PK002MK1439, PK004MK1439)	• Overall recovery from bile duct cannulated rats: 93.4% Feces: 13% / Bile: 56.7% / Urine: 22.9% • Overall recovery from bile duct cannulated dogs: 73.6% Feces: 29.3% / Bile: 14.3% / Urine: 29.7% / incomplete recovery

Lactation

Oral Placental and Lactational Transfer Study in Rats/TT #15-7130	• MK-1439 was observed in maternal and fetal plasma at 2 and 24 hours postdose at 5 and 450 mg/kg/day on GD 20, and in maternal plasma and milk at 2 hours postdose on lactation day 14. • The placental transfer on GD 20 was similar at both doses and ranged between 48% and 52%. Lactational transfer on lactation day 14 was approximately 147% (LD) and 132% (HD) at 2 hours postdose.

CDER = Center for Drug Evaluation and Research; CYP = cytochrome P; DOR = doravirine (MK-1439); FDA = Food and Drug Administration; IV = intravenous; LD = low dose; HD = high dose; NOAEL = no observed adverse effect level; RHD = recommended human dose

Toxicokinetic data

Study/ Study No.	Major Findings
General Toxicology Studies	
TT#11-6019: Rat: 6-month repeat dose oral study Samples collected predose and 1, 2, 4, 6, 8 and 24 hrs postdose Accumulation: None Dose proportionality: Less than ***NOAEL: 450 mg/kg/day*** ***Safety Margin: 7.5***	**Table 31. Toxicokinetic Parameters for MK-1439 in Rat Plasma Week 13**

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
3	Female	25.2 ± 1.21	1.86 ± 0.0640	2.0 ± NC
	Male	13.0 ± 0.682	1.37 ± 0.102	1.0 ± NC
	All	19.1 ± 1.86	1.59 ± 0.136	1.0 ± NC
30	Female	108 ± 5.51	10.3 ± 1.49	1.0 ± NC
	Male	66.7 ± 2.19	7.24 ± 0.407	1.0 ± NC
	All	87.3 ± 5.67	8.76 ± 0.969	1.0 ± NC
450	Female	352 ± 14.8	28.1 ± 0.767	2.0 ± NC
	Male	206 ± 16.6	16.0 ± 1.77	2.0 ± NC
	All	279 ± 22.0	22.0 ± 2.84	2.0 ± NC

NC = Not Calculated

MK-1439 concentrations from all control group animals at 1 hour were below the lower limit of quantitation (LLQ = 0.029 µM) of the bioanalytical method.

TT#11-6019: Dog: 9-month repeat dose oral study

Samples collected predose and 1, 2, 4, 6, 8 and 24 hrs postdose
Accumulation: None
Dose proportionality: Less than

NOAEL: 1000 mg/kg/day
Safety Margin: 18

Table 32. Toxicokinetic Parameters for MK-1439 in Dog Plasma Week 13

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
1	Female	80.7 ± 9.03	4.14 ± 0.535	4.5 ± 0.96
	Male	83.8 ± 10.3	4.39 ± 0.522	4.5 ± 0.50
	All	82.2 ± 6.35	4.27 ± 0.349	4.5 ± 0.50
10	Female	365 ± 35.6	18.5 ± 1.69	2.8 ± 0.75
	Male	402 ± 14.5	19.9 ± 0.621	4.0 ± 0.82
	All	383 ± 19.1	19.2 ± 0.873	3.4 ± 0.56
1000	Female	643 ± 60.9	30.7 ± 2.57	3.3 ± 1.1
	Male	704 ± 9.28	34.8 ± 0.502	5.0 ± 0.58
	All	673 ± 30.8	32.7 ± 1.44	4.1 ± 0.67

MK-1439 concentrations in plasma from control animals were above the lower limit of quantitation (LLQ = 0.029 µM) at all time points for 3/8 animals, at 6 hours for 1/8 animal and at 24 hours for 1/8 animal. These values were less than 1.3% of the mean C_{max} of the low dose group and there is no impact on the quality and integrity of the study.

Reproductive Toxicology Studies	
TT #11-7040: MK-1439 Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats ***NOAEL: 450 mg/kg/day*** ***Safety Margin: 9***	**Table 33. Toxicokinetic Parameters for MK-1439 in Rat EFD Study; GD 15**

Summary Mean (± SE) Maternal Plasma MK-1439 Toxicokinetic Parameters in Rats Following Dosing of MK-1439: Gestation Day 15

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5	61.2 ± 2.50	5.08 ± 0.592	1.0 ± NC
45	243 ± 8.14	18.5 ± 0.222	2.0 ± NC
450	345 ± 16.3	26.1 ± 0.716	2.0 ± NC

NC = Not Calculated

Study/ Study No.	Major Findings
TT #11-7050: MK-1439 Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits ***NOAEL: 300 mg/kg/day*** ***Safety Margin: 8.5***	**Table 34. Toxicokinetic Parameters for MK-1439 in Rabbit EFD Study; GD 15**

Summary Mean (± SE) Maternal Plasma MK-1439 Toxicokinetic Parameters in Rabbits Following Dosing of MK-1439 : Gestation Day 15

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
2	13.8 ± 1.75	1.06 ± 0.0858	2.7 ± 0.67
15	80.7 ± 5.39	5.73 ± 0.420	2.3 ± 0.88
300	315 ± 32.8	20.1 ± 2.95	3.3 ± 0.67

TT #15-7140:MK-1439 Oral Toxicity and Toxicokinetic Study in Juvenile Rats ***NOAEL: 300 mg/kg/day*** ***Safety Margin: 9***	**Table 35. Toxicokinetic Parameters for MK-1439 in Rat Juvenile Study Postnatal Day 55**

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
10	Female	53.5 ± 2.24	5.40 ± 0.320	1.0 ± NC
	Male	43.7 ± 1.89	4.36 ± 0.135	2.0 ± NC
	All	48.5 ± 1.89	4.60 ± 0.134	2.0 ± NC
45	Female	159 ± 4.77	16.1 ± 0.486	1.0 ± NC
	Male	109 ± 4.39	11.5 ± 0.537	2.0 ± NC
	All	137 ± 7.97	13.6 ± 1.37	1.0 ± NC
300	Female	383 ± 16.1	35.3 ± 2.28	2.0 ± NC
	Male	283 ± 9.99	26.2 ± 0.548	2.0 ± NC
	All	333 ± 18.1	30.7 ± 2.30	2.0 ± NC

NC = Not calculated
MK-1439 was administered from Postnatal Day (PND) 14 to 55. MK-1439 concentrations in plasma from all control group animals at 1 hour post-dose were below the lower limit of quantitation (LLQ = 0.0291 µM) of the bioanalytical method.

Carcinogenicity Studies	
6-Month Oral Carcinogenicity Study in rasH2 Transgenic Mice ***NOAEL: 300 mg/kg/day*** ***AUC: 228µM·hr*** ***Safety Margin: 6***	**Table 36. Plasma DOR Toxicokinetic Parameters in Mice Following Dosing of DOR: Week 27**

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
10	Female	40.0 ± 3.98	10.8 ± 1.67	0.50 ± NC
	Male	33.5 ± 5.35	8.24 ± 0.861	0.50 ± NC
	All	36.7 ± 3.36	9.51 ± 1.01	0.50 ± NC
60	Female	123 ± 16.6	20.5 ± 3.50	0.50 ± NC
	Male	79.3 ± 7.13	18.9 ± 1.08	1.0 ± NC
	All	98.0 ± 10.7	19.2 ± 1.91	0.50 ± NC
300	Female	273 ± 24.2	40.1 ± 2.01	2.0 ± NC
	Male	182 ± 12.6	37.7 ± 1.83	1.0 ± NC
	All	228 ± 19.9	33.6 ± 2.15	1.0 ± NC

NC = Not calculated
DOR concentrations in plasma from all control mice at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.00935 µM) of the bioanalytical method.

Study/ Study No.	Major Findings
TT-136029: 2-Year Oral Carcinogenicity Study in Rats with a 6-Month Toxicokinetic Evaluation ***NOAEL: 450 mg/kg/day*** ***AUC: 279µM·hr (based on 6-month rat study)*** ***Safety Margin: 7.5***	**Table 37. Plasma MK-1439 Concentrations (µM) in Rats Following Dosing of MK-1439: Week 27**

			Time (hr)	
Week	Dose (mg/kg/day)	Sex	1	24
27	3	Female	3.23 ± 0.150	0.461 ± 0.0355
		Male	3.16 ± 0.0609	0.118 ± 0.00713
		All	3.20 ± 0.0740	0.290 ± 0.0783
	30	Female	15.9 ± 1.14	2.16 ± 0.139
		Male	13.0 ± 1.22	0.666 ± 0.146
		All	14.4 ± 0.992	1.41 ± 0.346
	450	Female	44.1 ± 1.72	3.08 ± 0.289
		Male	32.8 ± 1.15	2.33 ± 0.816
		All	38.4 ± 2.68	2.71 ± 0.421

MK-1439 concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.0287 µM) of the bioanalytical method.

AUC = area under the curve; DOR = doravirine (MK-1439); GD = on gestation days; NOAEL = no observed adverse effect level

14.1.3. Toxicology

14.1.3.1. General Toxicology

Nine-Month Oral Toxicity Study in Dogs / Study No. TT #11-6018

Key Study Findings

- The only clear test-article related findings were feces discoloration (in some low- and mid-dose and all high-dose animals due to the presence of unabsorbed MK-1439), postdose salivation (in a few animals at all dose levels) and lacrimation (in some mid- and high-dose animals).
- No adverse toxicological findings were observed. The NOAEL was 1000 mg/kg ($AUC_{0\text{-}24hr}$=673µM·hr; male and female combined at 13 weeks)

Conducting laboratory and location: Merck Research Laboratories, France
GLP compliance: Yes

Table 38. Methods of 9-Month Oral Toxicity Study in Dog

Parameter	Method details
Dose and frequency of dosing:	0, 1, 10, 1000 mg/kg/day; Daily
Route of administration:	Oral gavage
Formulation/vehicle:	Suspensions of MK-1439 in 10% polysorbate 80 in deionized water
Species/strain:	Dog/beagle
Number/sex/group:	4
Age:	25 to 29 weeks
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No Minor with no impact on study integrity

Table 39. Observations and Results: Changes from Control

Parameters	Major findings
Mortality	None due to test-article. HD: One female sacrificed on day 247 due to clinical signs as the result of an intubation accident.
Clinical signs	All dosed: Increased sporadic postdose salivation in a few animals at all dose levels. All dosed: Feces discoloration (pale brown or white), which appears to be due to unabsorbed test-article, observed almost every day starting at day 2 in all HD dogs. Also observed in 2/8 LD and 3/8 MD animals for a total of 1 to 3 days per animal; non-adverse MD and HD: Clear eye discharge (lacrimation) in 3/8 MD and 6/8 HD animals; non-adverse.
Body weights	HD: Weight loss of 0.2 kg (compared to pretest value) at week 36 in one out of four males. Animal gained 0.1 kg compared to an average 2.5 kg gain in controls over the 9-month study; non-adverse
Ophthalmoscopy	Unremarkable
Feed consumption	Unremarkable
ECG	Unremarkable
Hematology	Unremarkable
Clinical chemistry	HD: 123% increase in BUN at week 38 in 1/4 females (29 compared to 13 mg/dl at pretest). Finding not associated with other relevant observations but is outside the historical control range of 8 to 24 mg/dl and so could be test-article related.
Urinalysis	HD: 31% decrease in mean urinary volume at week 38; non-adverse
Gross pathology	Unremarkable
Organ weights	HD: 29% increase in liver weight (relative to body weight) 1/4 males; non-adverse
Histopathology Adequate battery: Yes	Unremarkable; Note: To better investigate lacrimation, the following additional samples were collected and assessed (bilateral): upper and lower eyelid, nictitating membrane with associated superficial gland (third eyelid) and the lacrimal gland. These tissues were also unremarkable.

All dosed = all MK-1439-dosed animals; BUN = blood urea nitrogen; HD = high dose; LD = low dose; MD = middle dose

Six-Month Oral Toxicity Study in Rats/ Study No. TT #11-6019

Key Study Findings

- Urinary crystals were observed in high-dose males and females at both 3 and 6-month timepoints. Additional non-adverse test-article related findings at the high dose included postdose salivation, increased liver weight (up to ~16%) and various minimal changes in hematologic parameters (mid and high dose).
- No adverse toxicological findings were observed. The NOAEL was 450 mg/kg (AUC_{0-24}=279µM·h; male and female combined at 13 weeks).

Conducting laboratory and location: Merck Research Laboratories, France
GLP compliance: Yes

Table 40. Methods of 6-Month Oral Toxicity Study in Rats

Parameter	Method details
Dose and frequency of dosing:	0, 3, 30, 450 mg/kg/day; Daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) [redacted]
Species/strain:	Rat/Wistar Han
Number/sex/group:	15
Age:	5 weeks
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No Minor with no impact on study integrity

Table 41. Observations and Results: Changes from Control

Parameters	Major findings
Mortality	MD: One male was found dead on study day 85 without relevant clinical signs observed prior to death. The main histopathology findings were observed in kidneys (pelvis dilatation, papilla necrosis, and mineralization), urinary bladder (dilatation, inflammation, and mineralization), prostate and seminal vesicle (inflammation). Mineralization also observed in heart, aorta, and stomach. Changes correlated with gross observations (kidney discoloration and pelvic dilatation, urinary bladder dilatation and discoloration, prostate discoloration) and supported urinary obstruction as a cause of death (considered to be unrelated to test article). Mineralization was also consistent with uremia secondary to urinary obstruction. C: One female found dead on study day 165, following blood sampling for hematological and serum biochemical examinations, considered to be related to anesthesia accident.
Clinical signs	HD: Increased sporadic postdose salivation in all animals starting on study week 3.
Body weights	Unremarkable
Ophthalmoscopy	Unremarkable
Feed consumption	Unremarkable
Hematology	MD and HD: +10% prothrombin time and activated partial thromboplastin time at 26 weeks; non-adverse HD: 7% increase in mean platelet volume at 12 weeks (male); non-adverse HD: 17 to 33% increase in WBCs, lymphocytes, and neutrophils at 12 and 24 weeks (M) HD: 4 to 6% decrease in RBCs/hemoglobin/hematocrit at 12 and 24 weeks (male). Note: Although statistically significant, change is minimal, within the historical control range and not adverse. HD: 15% decrease in reticulocytes at 24 weeks (female); non-adverse
Clinical chemistry	Unremarkable

Parameters	Major findings
Urinalysis	HD: Decrease in mean urine volume (-56%) associated with increased specific gravity and low urine pH in 3 animals (pH=5.5) at week 12 only (female). Note: Animals with low pH did not have crystals present. The relationship of this finding to the test-article is uncertain. HD: One female urine described as "grossly bloody" at 12 weeks. Animal also had significant amount of protein in the 1 ml of urine collected at 24 weeks (in the absence of occult blood). HD: Microscopic examination of urinary sediments revealed the presence of yellow-brown needle-like crystals in urchin-shaped or bundle-shaped clusters in four females and one male at week 12 and in four females and five males at week 24. Urinary crystals were observed in the absence of histopathological effects on the urinary bladder or kidney and were considered non-adverse. Based on NMR and LC-MS analyses of urine sediment, the primary component of the urine crystals was MK-1439. Proton NMR spectra of urine sediments revealed one major component with spectral characteristics identical to the MK-1439 standard analyzed under the same conditions. Accurate mass and CID fragmentation data obtained by LC-MS confirmed the identification of MK-1439.
Gross pathology	Unremarkable
Organ weights	HD: 14 to 16% increase in liver weight (abs; male and female); non-adverse
Histopathology Adequate battery: Yes	Unremarkable

BUN = blood urea nitrogen; C = control; CID = collision-induced dissociation; HD = high dose; LC-MS = liquid chromatography coupled mass spectrometry; LD = low dose; MD = middle dose; NMR = nuclear magnetic resonance; RBC = red blood cells; WBC = white blood cells

General Toxicology; Additional Studies

Three-Month Oral Toxicity Study in Rats /TT #10-6040

Ten males and female Crl:WI(Han) rats per group were dosed with vehicle (b) (4) or 3, 30 or 450 mg/kg/day MK 1439 (b) (4)

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined in all groups. Test article-related antemortem changes at ≥30 mg/kg/day were limited to postdose salivation in both sexes at 450 mg/kg/day, and the presence of urinary crystals in the urine of the majority of females at 450 mg/kg/day, and in a single female at 30 mg/kg/day. The urinary crystals were shown to be formed ex vivo in the exploratory ten-day oral-dose urine examination study in female rats (TT #14-1095; reviewed in additional studies). The NOAEL for this study was 450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 253µM•hr; approximately 6.5-fold above the DOR exposure at the RHD).

Three-Month Oral Toxicity Study in Dogs /TT #10-6039

Three female and male Beagle dogs per group received the vehicle, or 1, 10 or 1000 mg/kg/day MK-1439 in 10% polysorbate 80 in deionized water. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic and electrocardiographic examinations, and clinical and anatomic pathology evaluations. Plasma

DOR concentrations were determined in all samples. Discoloration of the feces (likely from the non-absorbed MK-1439) was observed the high dose in both sexes. The NOAEL for this study was 1000 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 683µM•hr, approximately 18-fold above the DOR exposure at the RHD).

MK-1439 3-Month Oral Range-Finding and Toxicokinetic Study in CD1 Mice/TT #12-6013

MK-1439 was administered once daily, by oral gavage, to male and female CD1 mice daily for approximately 3 months at up to 450 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weights, and clinical and anatomic pathology evaluations. Plasma MK-1439 concentrations were determined in MK-1439-treated groups from the toxicokinetic arm. Antemortem test article-related findings were limited to mild decreases in body weight gain in both sexes at 450 mg/kg/day (compared to controls, -16% in females in study week 13 and -22% to -37% in males from study week 8 onward). This was not considered adverse since the changes were relatively small. AUC increased less than dose proportionally, indicating saturation. Although M9 levels were not directly measured in this study, DOR and M9 levels were anticipated to be similar in CD-1 mice, based on a mass balance study (1:1 ratio). The NOAEL was 450 mg/kg/day ($AUC_{0\text{-}24\ hr}$=196µM.hr/mL), approximately 5.5 times the exposure at the RHD.

Table 42. Genetic Toxicology

Study/ Study No.	Key Study Findings
In Vitro Reverse Mutation Assay in Bacterial cells/TT #10-8021, 10-8099 and 10-8113 GLP compliance: Yes Study is valid: Yes	*Salmonella typhimurium* (TA1535, TA97a, TA98, and TA100) and *Escherichia coli* (WP2 uvrA pKM101) treated for 48 hours with up to 5000 µg/plate with and without S-9 metabolic activation. MK-1439 did not produce any 2-fold or greater increases in revertants relative to solvent control (DMSO) in any study. The positive control (2-aminoanthracene) and diagnostic mutagens (sodium azide, 4-nitroquinoline-N-oxide, 2-nitrofluorene and ICR-191) showed appropriate S-9- and strain-dependent increases in revertants.
Assay for Chromosomal Aberrations In Vitro in Chinese Hamster Ovary Cells/TT #11-8662 and 11-8666 GLP compliance: Yes Study is valid: Yes	Chinese hamster ovary cells; up to 300µM; +/-S9 There was no increase in structural chromosome aberrations in MK-1439 treated cells and the assay was negative. The positive controls (cyclophosphamide and mitomycin C) induced significant increases in aberrations over the solvent controls (DMSO).
Assay for Micronucleus Induction in Rat Bone Marrow From a 2-Week Oral Toxicity Study/TT #10-8725 GLP compliance: Yes Study is valid: Yes	Rat, bone marrow micronuclei; single oral doses of 5 to 450 mg/kg/day MK-1439 for 13 days. No effects on the proportion of polychromatic erythrocytes among total erythrocytes in the bone marrow were observed. Additionally, frequencies of micronuclei-polychromatic erythrocytes for all MK-1439 treated groups were similar to concurrent controls and consistent with the historical control range.
Other Genetic Toxicology Studies	None

DMSO = dimethyl sulfoxide; GLP = good laboratory practice; ICR-191 = acridine mutagen

14.1.3.2. Carcinogenicity

Six-Month Oral Carcinogenicity Study in rasH2 Transgenic Mice /TT #13-6005

Jic:CB6F1-TgrasH2@Jcl mice were assigned to five groups of 25 females and 25 males each that received 10, 60, and 300 mg/kg/day of DOR or control article only (two control groups of 25 mice/sex/group). The amount of HPMCAS administered to the control groups (1200 mg/kg/day) was equivalent to the amount of polymer present in the high-dose group formulation. In addition, a positive control group of 10 females and 10 males was given urethane in 0.9% sodium chloride at 1000 mg/kg, by the intraperitoneal route, once a day, on study days 1, 3, and 5. Assessment of toxicity or carcinogenicity was based on mortality, clinical observations (including palpation for presence of masses except in the positive control group), body weights, and anatomic pathology evaluations. DOR concentrations in plasma samples from DOR-treated and control animals were determined.

There were no test article-related unscheduled deaths and no test article-related findings in clinical observations or body weights. There was no test article-related increase in mortality and no evidence of a carcinogenic potential in any sex up to 300 mg/kg/day. The incidence of adenomas of the Harderian gland was 2 out of 25 in males of the 300-mg/kg/day group. None were present in males of the low- and mid-dose or the concurrent control groups.

The FDA Statistical Reviewer's tumor analysis showed a statistically significant increasing trend for adenoma in the Harderian glands in male mice (p=0.0343). The pairwise comparisons did not show statistically significant increased tumor incidence in any treated group compared to the combined control. Per the final Applicant report, similar or higher incidences of this tumor type have been found in 5/34 vehicle-treated male rasH2 historical control groups. As such, there were no test article related neoplastic or non-neoplastic findings in this study at up to 300 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 228µM•hr; approximately 6-fold above the DOR exposure at the RHD) after 6 months of daily oral administration of DOR.

Two-Year Oral Carcinogenicity Study in Rats with a Six-Month Toxicokinetic Evaluation/ TT-136029

The carcinogenicity potential of MK-1439 was tested in an oral 2-year rat carcinogenicity study. Wistar Han rats were administered 3, 30, or 450 mg/kg/day of MK-1439 provided as a (b) (4) (b) (4) suspended in vehicle equivalent to that in the formulation administered to the 450-mg/kg/day MK-1439 dose group.

There were no variations of tumor incidences considered related to administration of MK-1439. A statistically significant increase of Leydig cell tumors was observed in high dose males and an increased incidence of combined parafollicular adenoma and parafollicular carcinoma in the thyroid was observed in high dose females, by the FDA statistical reviewer. However, these numbers were within the range or close to those observed in historical control animals ((b) (4)), as outlined below.

According to historical control data for 104 week studies in Wistar Han male rats (b) (4)), the range of interstitial cell adenoma in male testes was between 0.89 and 6.67%. Seven percent of males (3/43) at the high dose were found with Leydig cell tumors in the current carcinogenicity study, which is just slightly above the historical control maximum (6.67%).

In the current carcinogenicity study, the rate of parafollicular cell adenoma in the high dose females was 13.5%, which was within the historical control range of 1.22% to 22% ((b) (4) ; supplier). Likewise, the rate of parafollicular cell carcinoma was 2%, which was also within the historical control range of 1.33% and 8.93% ((b) (4) supplier). The rate of parafollicular cell adenoma (13.5%) and carcinoma (2%) was also within the range of historical control data submitted by the Applicant from studies conducted in their own facilities; i.e., 0 to 16% for adenomas and 0 to 2% for carcinomas. The thyroid findings were observed at 450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 279µM•hr; approximately 7.5-fold above the DOR exposure at the RHD) after 2 years of daily oral administration of DOR.

The Executive Carcinogenicity Assessment Committee concurred that the combined incidence of drug related thyroid parafollicular cell adenoma and carcinoma in females was increased at 450 mg/kg/day. As such, the label reflects this decision and the historical control observation.

14.1.3.3. Reproductive and Developmental Toxicology

14.1.3.3.1. Fertility and Early Embryonic Development

Oral Fertility Study in Female and Male Rats/ TT 13-7300

Key Study Findings

- No adverse toxicological findings were observed. The NOAEL for general toxicity and reproductive and fertility parameters in males and females was 450 mg/kg/day, the highest dose level evaluated.

Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources
Merck Research Laboratories
West Point, Pennsylvania 19486 U.S.A.

GLP compliance: Yes

Table 43. Methods of Oral Fertility Study in Female and Male Rats

Parameter	Method Details
Dose and frequency of dosing:	Untreated, 0 (vehicle), 5, 30, 450 mg/kg; daily
Route of administration:	Oral
Formulation/vehicle:	MK-1439 provided as a (b) (4)
Species/strain:	Rat, Wistar Han, Crl:WI(Han)
Number/sex/group:	20/sex/group
Satellite groups:	None
Study design:	Females: 15 days prior to cohabitation, during cohabitation and through GD7; Males: 15 days prior to cohabitation, during cohabitation and until prior to scheduled sacrifice (6 weeks total)

Parameter	Method Details
Dose and frequency of dosing:	Untreated, 0 (vehicle), 5, 30, 450 mg/kg; daily
Route of administration:	Oral
Deviation from study protocol affecting interpretation of results:	No

w/v = weight/volume

Table 44. Observations and Results

Parameters	Major findings
Mortality	Unremarkable
Clinical signs	Unremarkable
Body weights	Unremarkable
Sperm count	HD: Low sperm count as compared to control; not considered toxicologically significant because only 1 male (out of 20) was lower than the historical control.
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]*	HD: Percent peri-implantation loss was 50% higher in the highest dose females, as compared to controls (24.2% high dose versus 16% controls). This number was also higher than the highest historical control value (24.2% high dose versus 21.7% highest historical control value). However, due to a lack of dose response and one high dose female being out of the range of the concurrent control group, this was not considered toxicologically significant.

LD = low dose; MD = mid dose; HD = high dose

14.1.3.3.2. Embryo-Fetal Development

MK-1439 Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats/ TT #11-7040

Key Study Findings

- The no observed effect level (NOEL; maternal and developmental) in this study was 450 mg/kg/day, with a maternal $AUC_{0\text{-}24}$ value of 345µM·h.

Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources
Merck Research Laboratories
West Point, Pennsylvania 19486 U.S.A.

GLP compliance: Yes

Table 45. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 5, 45, 450 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	MK-1439 (b) (4)
Species/strain:	Rat/Wistar Han
Number/sex/group:	25 females per group; 15 for cesarean and 10 for TK sampling
Satellite groups:	None

Parameter	Method Details
Study design:	Dosing GD 6 to GD 20
Deviation from study protocol affecting interpretation of results:	No

GD = gestation day; TK = toxicokinetic

Table 46. Observations and Results

Parameters	Major findings
Mortality	Unremarkable
Clinical signs	Unremarkable
Body weights	Unremarkable
Necropsy findings Cesarean section data	Unremarkable
Necropsy findings Offspring	LD: Unremarkable MD: Unremarkable HD: The litter mean incidence (1.8%) for incomplete ossification of thoracic vertebrae in the 450-mg/kg/day group was slightly above the historical control range for this laboratory (average =0.26%; range =0 to 0.88%). However, it was not considered test article-related because 1) this finding occurred in isolation from any other finding, 2) there was no evidence of an effect on the overall ossification of the skeleton and the finding occurred in only 2 additional fetuses out of 188 fetuses in the 450-mg/kg/day group (1 fetus out of 175 fetuses total in the control versus 3 fetuses out of 188 fetuses total, in the 450 mg/kg/day group). Additionally, although no maternal toxicity was observed, the study was deemed acceptable given that the maximum feasible dose, based on maximum feasible concentration and dose volume, was evaluated.

HD = high dose; LD = low dose; MD = middle dose

MK-1439 Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits/TT #11-7050

Key Study Findings

- The NOAEL in this study was 300 mg/kg/day for maternal and developmental toxicity. The AUC_{0-24} value for the maternal NOAEL at 300 mg/kg was 315µM·h.

Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources
Merck Research Laboratories
West Point, Pennsylvania 19486 U.S.A.

GLP compliance: Yes

Table 47. Methods of Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing:	0, 2, 15, 300 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4)
Species/strain:	Rabbit/Dutch Belted
Number/sex/group:	22 females per group; 14 for cesarean section and 9 for TK sampling
Satellite groups:	None

Parameter	Method Details
Study design:	Daily dosing from GD 7 to GD 20 for cesarean section and GD 7 through GD 15 for toxicokinetic sampling
Deviation from study protocol affecting interpretation of results:	No

GD = gestation day; TK = toxicokinetic; w/w = weight/weight

Table 48. Observations and Results

Parameters	Major findings
Mortality	HD: One female aborted on GD 25. There were no abortions in the exploratory oral range-finding toxicity study in pregnant rabbits (TT #11-7055) with this compound at comparable exposure levels and abortions have been observed in control rabbits on occasion in this laboratory. For these reasons, the abortion at 300 mg/kg/day was not considered test article-related.
Clinical signs	Unremarkable
Body weights	HD: Test article-related decreases in mean maternal body weight gain from GD 7 to 21 (12% below control) and from GD 7 to adjusted GD 28 (62% below control) were observed. These were not considered adverse.
Necropsy findings Cesarean section data	Unremarkable
Necropsy findings Offspring	LD: Unremarkable MD: Unremarkable HD: There were two skull bone malformations that were associated with the two fetuses from two litters at the highest dose of 300 mg/kg/day. These fetuses had multiple external abnormalities of the head. This incidence is consistent with higher skull malformations in this rabbit strain.[1] The Applicant also provided historical control data which demonstrated a very low incidence of skull malformations. However due to maternal toxicity at this dose, these malformations were not considered test article-related.

HD = high dose; LD = low dose; MD = middle dose; GD = gestation day

[1] Posobiec, LM, EM Cox, HM Solomon, EM Lewis, KF Wang, and D Stanislaus, 2016, A Probability Analysis of Historical Pregnancy and Fetal Data from Dutch Belted and New Zealand White Rabbit Strains from Embryo-Fetal Development Studies, Birth Defects Res B Dev Reprod Toxicol, 107(2):76-84.

14.1.3.3.3. Prenatal and Postnatal Development

MK-1439 Oral Pre- and Postnatal Developmental Toxicity Study in Rats/ TT #11-7010

Key Study Findings

- The NOAEL in this study was 450 mg/kg/day.

Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources
Merck Research Laboratories
West Point, Pennsylvania 19486 U.S.A.

GLP compliance: Yes

Table 49. Methods of Oral Pre- and Postnatal Developmental Toxicity Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 5, 45, 450 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4)
Species/strain:	Rat/ Wistar Han
Number/sex/group:	20 females per group
Satellite groups:	None
Study design:	The potential effects of MK-1439 on development, growth, behavior, reproductive performance, and fertility of the F1 generation in rats following oral administration to F0 females from GD 6 through lactation day 20 were evaluated.
Deviation from study protocol affecting interpretation of results:	No

GD = gestation day

Table 50. Observations and Results

Generation	Major Findings
F0 dams	Unremarkable
F1 generation	MD/HD: Compared to concurrent gender controls, slightly higher mean motor activity in F1 females in the 45 and 450 mg/kg/day groups was observed (38% and 41% above concurrent controls, respectively). However, only a few MK-1439-treated females had basic movements that exceeded historical controls. In addition, there was no dose-response, the finding was not observed in males, and there were no other toxicological findings.
F2 generation	Unremarkable

HD = high dose; LD = low dose; MD = middle dose

MK-1439 Oral Toxicity and Toxicokinetic Study in Juvenile Rats/TT #15-7140

Male and female Wistar Han rats were dosed with 10, 45 or 300 mg/kg/day MK-1439 from postnatal day (PND) 14 to PND 55. An interim necropsy was conducted on PND 56 to 58 and a final necropsy was conducted after a 4-week recovery period.

The only significant finding was a dose-related increase in the incidence of MK-1439-treated rats with urine crystals (brown, needle-like, appearing in clusters) observed ex vivo following overnight urine collection in all test article-treated groups in postnatal week 8 with increasing frequency at 300 mg/kg/day; this finding was not correlated with any other clinical pathology observation or any anatomic pathology finding. The urine crystals were no longer present after a 4-week treatment-free period (postnatal week 13) and in another study were found to be formed ex vivo. The NOAEL in this study was 300 mg/kg/day, with an $AUC_{0\text{-}24}$ value of 333 uM·h (males and females combined).

14.1.3.4. Other Toxicology Studies

Exploratory Ten-Day Oral-Dose Urine Examination Study in Female Rats/Study # TT 14-1095

The purpose of this study was to investigate urine crystal formation in vivo and ex vivo using various urine collection methods in female rats orally dosed with MK-1439 daily for 10 days. Sixteen female Crl:WI(Han) rats received 450 mg/kg/day of MK-1439 (base compound) formulated as a (b) (4) , at a dose volume of 10 mL/kg. Control animals were not included. Assessment of toxicity was based on mortality, clinical observations, body weights, and gross examinations of urinary bladder and kidney. Overnight urine collections via metabolism caging (ex vivo collection) were performed on all rats on study days 3 and 9. Urine collections via cystocentesis (in vivo collection) were performed on all rats on study days 4 and 10. Urine chemistry and microscopic examinations were performed to evaluate crystal formation. Drug concentrations in plasma, urine supernatant, and urine sediment were measured. Urine crystal precipitation was only seen following ex vivo overnight metabolism cage collection (9/16 urine samples on day 3 and 16/16 urine samples on day 9). Crystals were not present after in vivo urine collection (cystocentesis), indicating crystal formation due to changes in external environment (temperature, volume decrease, protein precipitation etc.). Also, the concentration of MK-1439 in urine of overnight cystocentesis collection were 6 to 10 times fold higher than the measured solubility in FaSSIF (fasted state simulating intestinal fluid) or in vitro urine, indicating facilitation of solubility by urine proteins.

Phototoxicity, Irritation and Sensitization Studies

In a local lymph node assay conducted in mice, DOR at 5% to 25% administered by topical application to the dorsum of each mouse ear for three consecutive days, was not considered a dermal sensitizer since there was no test-article related increase in the stimulation index compared to the vehicle control group (study TT #13-7859). DOR was a non-irritant in a bovine corneal opacity and permeability test in which five pig corneas were dosed with a 20% suspension of DOR (study TT #13-7857). DOR was also non-irritating to skin in the MatTek EpiDerm MTT Viability Assay in which tissue samples were treated with 100 mg DOR for up to 24 hours (study TT #13-7858). Lastly, there were no skin reactions or ocular observations (confirmed by histopathology of the eye tissues) indicative of phototoxicity in a three-day oral gavage phototoxicity study in male pigmented rats dosed with up to 450 mg/kg DOR and exposed to ultraviolet radiation thereafter (study TT #11-9011).

Impurity Studies

DOR impurities and degradation products were qualified in either repeat dose toxicology studies with MK-1439 or in specific studies reviewed below (TT #13-6035, TT #14-6017 and TT #16-6010). A summary of DOR impurities, dose multiples and qualification details are provided in the Applicant table below.

Table 51. DOR Impurities and Dose Multiples

Impurity	Specification Limits	Impurity Level %	Rodent Total Daily Intake of Impurity (mg/kg)	Human Total Daily Intake of Impurity (mg/kg)[a]	Dose Multiple based on mg/kg[c]	Rodent Total Daily Intake of Impurity (mg/m^2)[d]	Human Total Daily Intake of Impurity (mg/m^2)[d]	Dose Multiple based on mg/m^2[e]
Drug Substance Impurities								
(b) (4)								
Drug Product Impurities								
(b) (4)								

a Based upon a total daily DOR dose of 100 mg and presuming a 60 kg patient

b Based upon a total daily TDF dose of 300 mg and presuming a 60 kg patient

c Dose multiple was calculated as a ratio of total daily intake in rats (mg/kg) divided by the total daily intake in humans (mg/kg).

d Based upon a mg/kg to mg/m^2 conversion factor of 6 for rat, 3 for mouse, and 37 for an adult human e.g. mg/kg X 37 equals adult human dose on basis of mg/m^2.

e Dose multiple was calculated as a ratio of total daily intake in rodents (mg/m^2) divided by the total daily intake in humans (mg/m^2).

f Based on the nonclinical Batch/Lot # L-002447553-006H004 (b) (4) (b) (4) used in the GLP 3 month oral toxicity study in rats TT #13-6035 [Sec. 2.6.7.17].

g Impurities tested in DOR batch #L-002447553-000V027 and (b) (4) Lot # L-006151920-000V002 used in the GLP 3 month oral toxicity study in rats TT#16-6010 [Sec. 2.6.7.17].

h Impurities tested in DOR batch # L-002447553-009P002 (b) (4) (b) (4) used in the GLP three-month oral range-finding and toxicokinetic study in CD1 mice TT #12-6013 [Sec. 2.6.7.7A].

Three-Month Oral Toxicity Study in Rats/TT #13-6035

The purpose of this study was to determine the potential toxicity and toxicokinetic profile of a new DOR batch lot (to qualify impurities (b) (4)) when administered once daily by oral gavage to rats for approximately 3 months. Crl:WI(HAN) rats were assigned to two groups of 10 females and 10 males each that received 0 or 115 mg/kg/day of DOR or control article only. The test article form was a (b) (4) in vehicle was administered to the control group at 460 mg/kg/day. (b) (4) administered to the 115 mg/kg/day dose group.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations in the test article-treated and control groups were determined. There were no test article-related unscheduled deaths. There were no test article-related clinical signs, changes in body weight or food consumption, or ophthalmic findings. Serum triglyceride levels at 115 mg/kg/day in females and males were decreased (-26% and -40%, respectively) compared to mean control values at study week 12. These isolated decreases in triglycerides were

considered of minimal toxicological significance because of the small magnitude of the changes. There were no test article-related postmortem changes. The mean plasma DOR toxicokinetic parameters for males and females combined in study week 13 were: AUC_{0-24} of 202µM·h, C_{max} of 21.4µM and T_{max} of 1 hr.

Three-Month Oral Toxicity Study in Rats/TT #14-6017

The purpose of this study was to determine the potential toxicity of a new batch lot of DOR containing an induced (b) (4), and the toxicokinetic profile of DOR when this batch lot is administered orally, once daily, to rats for approximately 3 months. Crl:WI(Han) rats were assigned to two groups, one test article-treated and one control) of 10 females and 10 males each. The test article-treated group received 30 mg/kg/day of DOR, supplied as a (b) (4)

(b) (4)

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations in the test article-treated and control groups were determined. There were no unscheduled deaths. There were no test article-related clinical signs, changes in body weight or food consumption, clinical pathology or ophthalmic findings. There were no test article-related postmortem findings. The mean plasma DOR toxicokinetic parameters for males and females combined in study week 13 were: AUC_{0-24} of 140µM·h, C_{max} of 14.5µM and T_{max} of 1 hr.

Three-Month Oral Toxicity Study in Rats with a Micronucleus Assay/TT #16-6010

The purpose of this study was to determine the potential toxicity profile of a new DOR batch lot and to determine the potential toxicity profile and micronucleus induction potential of Tenofovir Disoproxil Fumarate degradant G (also known as (b) (4)) when each test article formulation is individually administered orally once daily to rats for approximately 3 months. Crl:WI(Han) rats were assigned to three groups of 10 females and 10 males each that received 30 mg/kg/day of DOR (free base form) in 10% polysorbate 80 in deionized water, 0.3 mg/kg/day of tenofovir disoproxil fumarate degradant G ((b) (4)) in 10% polysorbate 80 in deionized water or vehicle only, at a dose volume of 5 mL/kg.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Bone marrow was collected from the humerus at necropsy for micronucleus evaluation (in the Tenofovir Disoproxil Fumarate degradant G dose group only). All animals survived to scheduled termination. There were no test article-related antemortem findings, clinical pathology changes or ophthalmic findings. There were no test article-related postmortem findings for both test articles. The micronucleus assay was negative for Tenofovir Disoproxil Fumarate degradant G at 0.3 mg/kg/day. Based on the absence of findings, the NOELs were ≥30 mg/kg/day and ≥0.3 mg/kg/day, for DOR and Tenofovir Disoproxil Fumarate degradant G, respectively.

Additional Impurities

The Applicant was asked to provide additional information for the safety of, (b) (4) at (b) (4) (limit of detection) in the DOR drug substance and justification for (b) (4) classification as a class (b) (4) solvent (controlled at a level of ≤ (b) (4) weight %). In both cases, sufficient justification was provided to support safety at the proposed levels.

In addition, DOR (b) (4) and (b) (4) impurities in the (b) (4) were negative for mutagenicity potential (*in silico* evaluation) and were qualified in the three-month mouse study (TT #12-6013).

Referenced NDAs, BLAs, DMFs

Some MK-1439 nonclinical safety studies, including safety pharmacology, absorption, distribution, metabolism, excretion (ADME), repeat-dose toxicology, genetic toxicology have been reviewed by Dr. Christopher Ellis and Dr. Janice Lansita under IND 112796 and are summarized (as appropriate) in sections of this review. Complete reviews of all pivotal studies for DOR are included within the review text. 3TC and TDF have been fully reviewed under NDA-020564 and NDA-021356.

14.2. Individual Reviews of Studies Submitted to the NDA

15. Clinical Pharmacology Assessment: Additional Information

15.1. In Vitro studies

Plasma Protein Binding

The binding of [^{3}H]DOR to plasma proteins was determined by equilibrium dialysis. [^{3}H]DOR was added to rat, dog, and human plasma at final concentrations of 0.1 and 1μM. Binding was independent of concentration between 0.1 and 1μM where mean unbound fractions were 24.9%, 25.0, and 33.7 for humans, rats, and dogs, respectively. The protein binding (human plasma) of the M9, did not vary between 0.1 and 1μM M9. The unbound fraction of M9 (8% to 9%) was 3-fold lower than that of DOR.

Blood-to-Plasma Partitioning

The distribution of [^{3}H]DOR between red blood cells and plasma of rats, dogs, and humans was determined in freshly drawn blood at concentrations of 0.1, 1.0, and 10μM. The observed blood to plasma concentration ratios ranged from 0.90 to 1.10 and showed no clear concentration dependence. The blood-to-plasma partitioning ratio for metabolite M9 was in general lower across species compared to MK-1439, with values of 0.7 to 0.9 in rats, dogs, and humans (human: 0.7).

Metabolism of [^{3}H]DOR

The metabolism of [^{3}H]DOR was investigated in vitro in liver microsomes and hepatocytes from humans. Relatively low turnover was observed. The major metabolite identified in human liver microsomes (M9) resulted from oxidative metabolism of the triazole. No significant antiviral activity was observed for M9. M9 was not metabolized in human hepatocytes following a 2-hr incubation.

Incubation of DOR (10μM) with recombinant human CYPs (CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9*1, 2C9*2, 2C9*3, 2C18, 2C19, 2D6*1, 2E1, 2J2, 3A4, 3A5, and 3A7) demonstrated oxidation of DOR was carried out primarily by CYP3A4/5. Studies using an inhibitory anti-CYP3A monoclonal antibody indicated DOR oxidative metabolism was mainly catalyzed by CYP3A4 and CYP3A5 (Applicant's nonclinical report PK003).

The kinetic constants for the oxidation of DOR to the metabolite M9 were determined using recombinant CYP3A4 and CYP3A5. K_m values for one-site and two-site binding models were determined for both enzymes. The one-site binding K_m was similar for both enzymes (20.9 and 31.1μM). The high affinity, low capacity K_m of the two-site binding model (K_{m1}) was similar for both enzymes (3.6 and 5.4μM). The V_{max} was approximately 15- to 20-fold higher for CYP3A4 using either model, so that the intrinsic clearance (Cl_{int}) ranges for rhCYP3A4 and rhCYP3A5were 0.110 to 0.142 and 0.0048 to 0.0049 μL/min/pmol CYP, respectively (Applicant's nonclinical report PK017).

No glucuronidation products were detected after 2 hrs incubation DOR with liver microsomes fortified with UPDGA for all species.

Inhibition of CYP Isozymes by DOR

The reversible inhibitory effects of MK-1439 on human liver microsomal activity was evaluated in pooled human liver microsomes. The CYPs (substrate) evaluated were: CYP1A2 (phenacetin),

2B6 (bupropion), 2C8 (amodiaquine), 2C9 (diclofenac), 2C19 (S-mephenytoin), 2D6 (dextromethorphan), and 3A4 (midazolam and testosterone). The IC_{50} was >100μM for all CYPs (see nonclinical report PK003).

Time-dependent inhibition of CYP3A4 was evaluated in pooled human liver microsomes (1 mg/mL) that were preincubated for 5 to 45 min at 37°C with DOR (10 and 50μM). DOR did not cause time-dependent inhibition of CYP3A4 activity at either concentration.

15.1.1. Induction of CYP3A4 and CYP1A2-

The potential for DOR to up-regulate the activity of drug metabolizing enzymes and transporters via ligand-activated nuclear receptors, including the arylhydrocarbon receptor (AhR), the constitutive androstane receptor (CAR) and the pregnane x receptor (PXR), was evaluated in cryopreserved plated human hepatocytes from 3 donors. Hepatocytes were treated for 48 hours with vehicle control, DOR (0.1 to 20μM), or positive control inducers omeprazole (50μM), phenobarbital or rifampicin (10μM) for AhR, CAR, and PXR, respectively. Results indicate DOR does not induce mRNA or enzyme activity for CYP1A2 or 2B6. DOR did not induce CYP3A4 mRNA or enzyme activity at 0.1 to 5μM. An increase in CYP3A4 mRNA was observed at 10μM (1.2- to 4.0-fold) and 20μM (1.4- to 4.2-fold). This effect was small and had no corresponding effect on CYP3A4 enzyme activity. These in vitro results indicated that DOR is not likely to cause drug interactions via activation of AhR, CAR, or PXR.

Inhibition of UGT1A1- An experiment in pooled human liver microsomes, using 20μM estradiol as the substrate, DOR was not an inhibitor of UGT1A1 (IC_{50} >100μM).

15.1.2. Evaluation of Drug Transporters Involved in the Disposition of DOR

BCRP

Bi-directional transport of [^{3}H] DOR (0.1 to 1μM) was measured across monolayers of MDCKII and MDCKII cells stably expressing human BCRP (MDCKII-BCRP) at 37°C, in the absence and presence of the BCRP inhibitor Ko143 (2μM). Results indicate that DOR is not a substrate for BCRP.

P-gp

Bi-directional transport of DOR (0.1 to 1μM) was measured across monolayers of porcine renal epithelial cells (LLC-PK1) and LLC-PK1 cells stably expressing human MDR1 (LLC-MDR1) at 37°C. Results indicate DOR is not a P-gp (P-glycoprotein) substrate.

OATP1B1 and OATP1B3

[^{3}H]DOR (1μM) was evaluated as a substrate of OATP1B1 and OATP1B3 in MDCKII cells stably expressing OATP1B1 or OATP1B3. Results indicated DOR was not a substrate of either transporter.

15.1.3. Evaluation of Inhibition of Drug Transporters by DOR

Table 52. Table Effect of DOR on the Activity of Human Uptake and Efflux Transporters

Transporter	IC_{50} (μM)	Maximum Concentration Tested (μM)
BCRP	51±4	75
P-gp	>100 (0%)	100
BSEP	>50 (2%)	50
OATP1B1	39±2	75
OATP1B3	31±4	75
OAT1	>75 (13%)	75
OAT3	16±0.7	75
OCT2	67±9	75
MATE1	>50 (28%)	50
MATE2	>50 (39%)	50

BCRP = breast cancer resistance protein; DOR = doravirine (MK-1439); MATE = multi-antimicrobial extrusion protein; OATP = organic-anion-transporting polypeptide; P-gp = P-glycoprotein

BCRP

The ATP-dependent uptake of [^{3}H]methotrexate ([^{3}H]MTX; 10μM) was measured in membrane vesicles containing human BCRP in the absence or presence of DOR (0 to 75μM) The in vitro IC_{50} value (51μM) was more than 50-fold above DOR free concentrations in plasma Therefore, systemic drug interactions via this transporter are unlikely. However, DOR could inhibit the intestinal efflux of BCRP substrates. The theoretical gut lumen concentrations of DOR (940μM, assuming complete dissolution of the 100-mg dose in 250 mL of intestinal fluid) at the therapeutic dose exceed 10-fold of the in vitro IC_{50}. However, the solubility of DOR is limited. In vitro, the solubility of DOR was 120 μg/mL (282μM), so the actual concentrations in the gut lumen are unlikely to exceed this value.

P-gp

Inhibition of intestinal P-gp was not adequately tested. Attempts to test DOR inhibition of P-gp at 300μM in vitro resulted in 8.7% inhibition; however, DOR precipitated in the assay media. Thus, although inhibition of gut P-gp cannot be excluded, it is likely to be limited by DOR's solubility (282μM) and be of no clinical relevance.

BSEP

The ATP-dependent uptake of [^{3}H]taurocholic acid ([^{3}H]TCA; 1μM) was measured in membrane vesicles containing human bile salt export pump (BSEP) in the absence or presence of DOR (0 to 50μM). DOR did not inhibit BSEP at concentrations up to 50μM in vitro.

OATP1B1

Uptake of [^{3}H]pitavastatin (0.1μM) was measured in MDCKII and MDCKII cells stably expressing human OATP1B1(MDCKII-OATP1B1)) cells in the absence or presence of DOR (0 to 75μM). Results indicated that DOR inhibited OATP1B1 with an IC_{50} value of 39μM. Based on a bioavailability of approximately 64%, a mean unbound C_{max} of 0.54μM and an unbound hepatic inlet concentration ($I_{max,u}$) of approximately 1.1μM, DOR is unlikely to inhibit OATP1B1 in vivo (R<1.1).

OATP1B3

Uptake of [^{3}H]sulfobromophthalein (0.1μM) was measured in MDCKII and MDCKII cells stably expressing human OATP1B3(MDCKII-OATP1B3) cells in the absence or presence of DOR (0 to 75μM). With an $I_{max,u}$ of approximately 1.1μM, R<1.1. Therefore, DOR is unlikely to inhibit OATP1B3 in vivo.

OAT1, OAT3, and OCT2

Uptake of [^{3}H]cidofovir (1μM) was measured in MDCKII cells and MDCKII cells stably expressing human OAT1 (MDCKII-OAT1) in the absence or presence of MK-1439 (0 to 75μM). Uptake of [^{3}H]estrone sulfate (1μM) was measured in MDCKII cells and MDCKII cells stably expressing human OAT3 (MDCKII-OAT3) in the absence and presence of DOR (0 to 75μM). Uptake of [^{14}C]metformin ([10μM) was measured in CHO-K1 and CHO-K1 cells stably expressing human OCT2 (CHO-K1-OCT2) cells in the absence or presence of DOR (0 to 75μM). Results indicate, drug interactions via OAT1, OAT3 or OCT2 are unlikely.

MATE1 and MATE2K

The inhibitory effect of DOR on the uptake of 5μM [^{14}C]metformin was evaluated in CHO-K1 cells transfected with MATE1 and in MDCK-II cells transfected with MATE2K. At 50μM, the highest concentration tested, 28 and 39% inhibition was observed for MATE1 and MATE2K, respectively. Because the $I_{max,u}/IC_{50}$ value is <0.02, the risk for interaction of DOR with substrates of these transporters is low.

15.2. In Vivo Studies

15.2.1. ADME Studies

Mass Balance

Study P008 was a single-dose, one-period study with six healthy adult male subjects. On day 1, a single oral capsule dose of approximately 351 mg (~211 μCi) $^{[14C]}$DOR (actual doses ranged from 349 mg to 353 mg) was administered to each subject with 240 mL of water after an overnight fast. A dose of 350 mg was used to approximate exposures from a 100- to 150-mg tablet dose. Blood, urine, and fecal samples were collected to measure total radioactivity (plasma, urine, and fecal), DOR concentrations (plasma only), and metabolic profiling (plasma, urine, and fecal) for at least 168 hours postdose.

Total mean recovery of radioactivity was approximately 101% (95% CI: 97.5% to 105%), with approximately 10.8% excreted in urine and 90.4% in feces (84.1% as unchanged drug). 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 circulating component of total radioactivity in plasma, accounting for approximately 76% plasma total radioactivity AUC_{0-48}. The primary components in urine were M9 (6.7% of the dose) and DOR (2.2% of the radioactive dose). M8, M10, and M18 were detected in urine, but combined represented approximately 0.5% of the dose. The mean plasma DOR to total radioactivity AUC ratio was approximately 0.77. Total radioactivity in plasma was below the LLOQ of 94 ng equivalents/g (221nM equivalents) in all subjects by 120 hours postdose, and plasma DOR concentrations fell below the LLOQ of 1.00 ng/mL (2.35nM) in half the subjects (3) by 168 hours postdose. Total radioactivity in urine

and feces samples was present at quantifiable levels up to the last collection interval for each subject.

PK of IV Microdose of DOR

Study P044 was a single-dose, single period trial in 11 healthy male and female subjects. Each subject received an IV dose of 100 μg DOR administered via infusion syringe over 15 minutes. Seventeen blood samples were collected predose and from 5 minutes to 72 hrs after start of the infusion.

Table 53. DOR PK Following IV Dose of 100 μg Over 15 Minutes

	Min	Max	Geo Mean	Geo %CV
$AUC_{0-\infty}$ (nM*hr)	46.3	93.6	63.1	28.3
C_{max} (nM)	5.14	14.4	8.47	30.1
$T_{1/2}$ (hr)	8.42	17.75	12.16	25.3
CL (L/hr)	2.51	5.08	3.73	28.3
V_{dss} (L)	45.0	75.8	60.5	18.5

%CV = percent coefficient of variation; AUC = area under the curve; DOR = doravirine (MK-1439); IV = intravenous; PK = pharmacokinetic

Plasma concentrations of DOR declined in a bi-exponential manner.

Single and Multiple Ascending Dose

Study P006 was a double-blind, randomized, placebo-controlled, single-rising and multiple dose study in healthy male subjects. The DOR oral (b) (4) tablet was administered under fasting conditions. Two panels of eight subjects each received DOR or matching placebo in a 3:1 ratio. There was at least a 7-day washout period between study drug administration at the beginning of each period. Plasma PK samples were collected up to 120 hrs postdose. Urine was collected on days 1 and 2.

- Panel A: period 1- Single 600 mg; period 2- Single 800 mg; period 3- 450 mg QD x10
- Panel B: period 1- Single 1000 mg; period 2- Single 1200 mg: period 3- 750 mg QD x10

Table 54. Single dose DOR PK – Geo Mean (90% CI); $T_{1/2}$- Geo Mean (% Geo CV)

	600 mg	800 mg	1000 mg	1200 mg
$AUC_{0-\infty}$ (μM*hr)	146 (126, 169)	179 (154, 208)	216 (186, 250)	246 (212, 286)
C_{max} (nM)	7420 (6380, 8630)	8180 (7030, 9520)	10100 (8670, 11700)	10800 (9270, 12600)
$T_{1/2}$ (hr)	13.58 (14.10)	16.45 (26.97)	15.42 (10.97)	18.88 (34.23)

CV = coefficient of variation; AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); PK = pharmacokinetic

Table 55. Multiple Dose DOR PK – Geo Mean (90% CI)

	450 mg day 1	450 mg day 10	750 mg day 1	750 mg day 10
AUC_{0-24} (μM*hr)	82.0 (70.2, 95.7)	100 (85.7, 117)	99.1 (84.9, 116)	138 (118, 161)
C_{max} (nM)	5580 (4810, 6460)	7590 (6550, 8790)	6980 (6020, 8080)	10500 (8910, 12400)
C_{24} (nM)	1940 (1520, 2470)	2090 (1640, 2670)	2370 (1850, 3020)	2850 (2220, 3670)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); PK = pharmacokinetic

- Accumulation ratio- 450 mg- 1.22 (1.13, 1.32) for AUC and 1.36 (1.15, 1.61) for C_{max}; 750 mg- 1.39 (1.28, 1.51) for AUC and 1.50 (1.26, 1.79) for C_{max}
- Time to achieve steady state was 2 to 3 days.

Food effect for DOR/3TC/TDF tablet

Study P029 was a single-dose, randomized, 2-period, 2-treatment, crossover, comparative fed and fasted bioavailability study using the same tablet formulation of DOR/3TC/TDF 100/300/300 mg that was used in phase 3 trials. 14 healthy subjects enrolled and 13 completed both periods. Plasma PK samples were collected up to 72 hrs postdose.

- Treatment A- 1 FDC tablet 30 minutes after the start of a high-fat, high-calorie breakfast
- Treatment B- 1 FDC tablet after an overnight fast of at least 10 hours.

The washout between drug administration was 7 days (3 hours). The content of the high-fat meal was: 997 total kcal with 50.6% from fat, 34.1% from carbohydrates, and 14.4% from protein.

Table 56. Effect of Food on DOR/3TC/TDF: Fed/Fasted Geometric Mean Ratio (90% CI)

	DOR	3TC	TFV
$AUC_{0-\infty}$	1.10 (1.01, 1.20)	0.93 (0.84, 1.03)	1.27 (1.17, 1.37)
C_{max}	0.95 (0.80, 1.12)	0.81 (0.65, 1.01)	0.88 (0.74, 1.04)

3TC = lamivudine; AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); TFV = tenofovir

There were no clinically significant differences in PK for DOR, 3TC, or TFV after administration of DOR/3TC/TDF tablets with or without food.

Food effect for DOR tablet

Study P037 was a single-dose, randomized, 2-period, 2-treatment, crossover, comparative fed and fasted bioavailability study using the DOR 100-mg tablet. 14 healthy subjects participated. Plasma PK samples were collected up to 72 hrs postdose.

- Treatment A- 1 DOR tablet after an overnight fast of at least 10 hours
- Treatment B- 1 DOR tablet 30 minutes after the start of a high-fat, high-calorie breakfast

The washout between drug administration was 7 days (3 hours). The content of the high-fat meal was: 997 total kcal with 50.6% from fat, 34.1% from carbohydrates, and 14.4% from protein.

Fed/fasted geometric mean ratio and 90% CI: $AUC_{0-\infty}$ 1.16 (1.06, 1.26); C_{max} 1.03 (0.89, 1.19)

There were no clinically significant differences in PK for DOR after administration of the tablet with or without food.

Comparative Bioavailability: DOR/3TC/TDF tablet vs. individual components

Study P026 was a single-dose, randomized, two-period, two-treatment, two-sequence, crossover study in 24 healthy male and female volunteers. Drugs were administered after an overnight fast (at least 10 hours). The washout period was 7 days. PK samples were collected for 72 hours postdose.

- Treatment A: 100 mg DOR/300 mg 3TC/300 mg TDF fixed dose combination (FDC)
- Treatment B: one DOR 100-mg tablet, one 3TC (Epivir®) 300-mg tablet and one Viread® 245-mg tablet (Note: The Applicant used Viread® in the form of tenofovir disoproxil (as fumarate) as distributed in Europe. Per EMA's Summary of Product Characteristics, each film-coated tablet containing 245 mg of tenofovir disoproxil (as fumarate) is equivalent to 300 mg of tenofovir disoproxil fumarate (TDF).

Table 57. DOR PK Following Administration as FDC vs. Individual Components

	FDC Geo Mean (95% CI)	Individual components Geo Mean (95% CI)	FDC/Individual Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	38.1 (33.1, 43.7)	37.7 (32.4, 43.7)	1.01 (0.94, 1.08)
C_{max} (nM)	1780 (1540, 2050)	1790 (1580, 2030)	0.99 (0.91, 1.09)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); FDC = fixed dose combination; PK = pharmacokinetic

Table 58. 3TC PK Following Administration as FDC vs. Individual Components

	FDC Geo Mean (95% CI)	Individual components Geo Mean (95% CI)	FDC/Individual Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	13600 (12400, 14800)	13000 (11800, 14300)	1.04 (1.00, 1.09)
C_{max} (ng/mL)	2730 (2420, 3090)	2750 (2410, 3130)	1.00 (0.91, 1.09)

3TC = lamivudine; AUC = area under the curve; CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic

Table 59. Tenofovir PK Following Administration as FDC vs. Individual Components

	FDC Geo Mean (95% CI)	Individual components Geo Mean (95% CI)	FDC/Individual Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	2400 (2180, 2640)	2450 (2180, 2750)	0.98 (0.93, 1.03)
C_{max} (ng/mL)	244 (214, 279)	282 (239, 331)	0.87 (0.78, 0.97)

AUC = area under the curve; CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic

DOR, 3TC, and TFV exposures are similar after administration as the individual components or the DOR/3TC/TDF combination tablet.

Comparative Bioavailability: DOR Coated and Uncoated

Study P039 was a single-dose, randomized, two-period, two-treatment, two-sequence, crossover study in 24 healthy male and female volunteers. Drugs were administered after an overnight fast (at least 10 hours). The washout period was 7 days. PK samples were collected for 72 hours postdose.

- Uncoated DOR 100-mg tablet: used in phase 2 and phase 3
- Coated DOR 100-mg tablet: final market image

Table 60. DOR PK Following Administration as Coated vs. Uncoated Tablets

	Coated tablet Geo Mean (95% CI)	Uncoated tablet Geo Mean (95% CI)	Coated/uncoated Geo Mean Ratio(90% CI)
$AUC_{0-\infty}$ (μM*hr)	41.0 (35.2, 47.7)	39.7 (34.1, 46.1)	1.03 (0.99, 1.08)
C_{max} (nM)	2080 (1840, 2350)	1890 (1710, 2080)	1.10 (1.01, 1.20)

AUC = area under the curve; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

The two tablet formulations are bioequivalent.

15.2.2. Drug-Drug Interactions

15.2.2.1. Interactions Among Components of DOR/3TC/TDF

All three components: Study P038 evaluated the interaction among the three components of DOR/3TC/TDF in healthy volunteers. This was an open-label, single-dose, randomized, three-period, three-treatment, six-sequence, crossover study. In each period, subjects (15) received one

of the following three treatments after an overnight fast of at least 10 hrs, with a washout period of at least 7 days between periods.

- Treatment A: 100 mg DOR
- Treatment B: 300 mg 3TC (Epivir®) and 300 mg TDF (Viread®)
- Treatment C: 100 mg DOR, 300 mg 3TC, and 300 mg TDF

Table 61. DOR PK Following Administration Alone and After Coadministration With 3TC and TDF

	DOR+3TC+TDF Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+3TC+TDF)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	37.7 (28.7, 49.4)	39.1 (31.5, 48.6)	0.96 (0.87, 1.06)
C_{max} (nM)	2030 (1720, 2400)	2090 (1810, 2420)	0.97 (0.88, 1.07)

3TC = lamivudine; AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

Table 62. 3TC PK Following Administration as 3TC+TDF and After Coadministration of DOR, 3TC, and TDF

	DOR+3TC+TDF Geo Mean (95% CI)	3TC and TDF Geo Mean (95% CI)	(DOR+3TC+TDF)/(3TC+TDF) Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	14200 (12400, 16200)	15000 (13800, 16500)	0.94 (0.88, 1.00)
C_{max} (ng/mL)	2910 (2460, 3450)	3150 (2760, 3600)	0.92 (0.81, 1.05)

3TC = lamivudine; AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

Table 63. Tenofovir PK Following Administration as 3TC+TDF and After Coadministration of DOR, 3TC, and TDF

	DOR+3TC+TDF Geo Mean (95% CI)	3TC and TDF Geo Mean (95% CI)	(DOR+3TC+TDF)/(3TC+TDF) Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	2790 (2470, 3150)	2500 (2090, 2990)	1.11 (0.97, 1.28)
C_{max} (ng/mL)	338 (286, 400)	289 (237, 352)	1.17 (0.96, 1.42)

3TC = lamivudine; AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

Coadministration does not significantly alter the PK of DOR, 3TC, and TDF.

Effect of TDF on DOR

Study P003 was a two-period, fixed sequence study in eight healthy males.

- Period 1: DOR 100 mg single dose alone, fasted
- Period 2: TDF 300 mg QD for 18 days; DOR 100 mg on day 14. All doses of TDF alone were administered within 30 minutes prior to or after a meal. However, on day 14 TDF was coadministered with DOR in the fasted state.

Table 64. DOR PK Following Administration Alone And After Coadministration With Multiple Dose TDF

	DOR+TDF Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+TDF)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	33.4 (25.9, 43.2)	35.3 (27.5, 45.3)	0.95 (0.80, 1.12)
C_{max} (nM)	1310 (965, 1780)	1630 (1210, 2190)	0.80 (0.64, 1.01)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

Multiple-dose TDF did not have a clinically meaningful effect on DOR PK.

15.2.2.2. DDI Studies Evaluating Effect of Other Drugs on DOR PK (CYP3A Inhibitors)

Ketoconazole

Study P010 was an open-label, fixed-sequence, two-period study in ten healthy subjects. There was a washout of at least 7 days between drug administration in periods 1 and 2.

- Period 1: 100 mg single dose of DOR (100 mg premarket formulation oral (b) (4) tablet)
- Period 2: 400 mg ketoconazole QD for 10 days, with coadministration of a single oral dose of 100 mg DOR on day 2.

Subjects were required to fast for at least 10 hours before dosing on day 1 of period 1 and day 2 of period 2, and for at least 4 hours thereafter. In period 2 (except on the morning of day 2, when DOR was coadministered with ketoconazole following an overnight fast), subjects were required to fast for at least 1 hour prior to and at least 2 hours post ketoconazole dosing. DOR plasma PK samples were collected predose and up to 72 hrs postdose in period 1 and up to 216 hrs postdose in period 2.

Table 65. DOR PK Following Administration Alone and After Coadministration With Multiple Dose Ketoconazole

	DOR+ketoconazole Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+ketoconazole)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	91.47 (76.36, 109.56)	29.88 (26.61, 33.56)	3.06 (2.85, 3.29)
C_{max} (nM)	1759 (1460, 2118)	1402 (1160, 1695)	1.25 (1.05, 1.49)
C_{24} (nM)	1180 (991, 1405)	429 (382, 482)	2.75 (2.54, 2.98)
$T_{1/2}$ (hr)	32.37 (geometric mean)	15.23 (geometric mean)	

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

Ritonavir

Study P002 was a, fixed-sequence, two-period study in eight healthy male subjects. There was a washout of at least 7 days between drug administration in period 1 and period 2.

- Period 1: 50 mg single dose of DOR (10 mg fit-for-purpose oral (b) (4) tablets)
- Period 2: 100 mg of ritonavir BID for 20 days. On day 14, subjects received the morning ritonavir with a single oral dose of 50 mg DOR. Subjects consumed a meal within 30 minutes prior to or after drug administration except the day 1 dose of DOR and day 14 morning dose of ritonavir and DOR, when the drug products were administered under fasted conditions. DOR plasma PK samples were collected predose and up to 120 hrs postdose in period 1 and up to 168 hrs postdose in period 2.

Table 66. DOR PK Following Administration Alone and After Coadministration With Multiple Dose Ritonavir

	DOR+ritonavir Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+ritonavir)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	73.5 (62.0, 87.1)	20.8 (17.5, 24.6)	3.54 (3.04, 4.11)
C_{max} (nM)	1260 (1080, 1470)	963 (825, 1120)	2.91 (2.33, 3.62)
C_{24} (nM)	935 (772, 1130)	322 (266, 390)	1.31 (1.17, 1.46)
$T_{1/2}$ (hr)	35.16 (geometric mean)	13.97 (geometric mean)	

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

15.2.2.3. DDI Studies Evaluating Effect of Other Drugs on DOR PK (CYP3A Inducers)

Rifampin (Single Dose- OATP1B1/3 Inhibitor, Multiple Dose- CYP3A Inducer)

Study P011 was a two-period, fixed-sequence study conducted in 11 healthy non-tobacco using male subjects. The study assessed the effects of single and multiple doses of rifampin on the single-dose pharmacokinetics of DOR.

- Period 1: 100-mg dose single dose of DOR (100 mg premarket formulation oral (b) (4) tablets)
- Period 2: 600 mg single dose of rifampin plus 100 mg single dose of 100 mg DOR on day 1. 600 mg rifampin QD for 15 days (days 4 to 18) plus a single 100-mg dose DOR on day 17.

The washout period was at least 7 days between dosing in period 1 and first dosing in period 2. Study medications were administered under fasted conditions. DOR plasma PK samples were collected predose and up to 72 hrs postdose in period 1, predose and up to 72 hrs post day 1 dose in period 2, and up to 48 hrs post day 17 dose in period 2.

Table 67. DOR PK Following Administration Alone and After Coadministration With Single Dose Rifampin

	DOR+rifampin Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+rifampin)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	33.1 (28.2, 38.9)	36.5 (26.7, 49.8)	0.91 (0.78, 1.06)
C_{max} (nM)	2160 (1890, 2470)	1540 (1230, 1920)	1.40 (1.21, 1.63)
C_{24} (nM)	459 (347, 608)	511 (360, 725)	0.90 (0.80, 1.01)
$T_{1/2}$ (hr)	5.50 (geometric mean)	18.60 (geometric mean)	

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

Single-dose administration of rifampin with single dose of DOR results in a 40% increase in C_{max} but no significant effect on the AUC and C_{24hr} of DOR. These results suggest that a single dose of rifampin decreased DOR volume of distribution. Thus, the effect of single dose rifampin on DOR C_{max} may be due to OATP1B1/3 inhibition.

Table 68. DOR PK Following Administration Alone and After Coadministration With Multiple Dose Rifampin

	DOR+rifampin (mult. dose) Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+rifampin)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	4.47 (3.87, 5.01)	36.5 (26.7, 49.8)	0.12 (0.10, 0.15)
C_{max} (nM)	661 (562, 778)	1540 (1230, 1920)	0.43 (0.35, 0.52)
C_{24} (nM)	16.4 (11.6, 23.2)	511 (360, 725)	0.03 (0.02, 0.04)
$T_{1/2}$ (hr)	6.30 (geometric mean)	18.60 (geometric mean)	

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

The reduction in DOR AUC and C_{24} (88% and 97%, respectively) when DOR is administered with multiple doses of rifampin, confirms DOR is a sensitive CYP3A and P-gp substrate.

Rifabutin

Study P035 was a two-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. There was a 7-day washout between periods.

- Period 1: 100-mg dose single dose of DOR (100-mg tablets)
- Period 2: 300 mg rifabutin QD on day 1 through day 16. On day 14, a single dose of 100 mg DOR was administered with rifabutin.

DOR was administered under fasted conditions. With the exception of period 2, day 14 (DOR PK day), rifabutin was administered 30 minutes after a meal. On day 14, rifabutin was administered under fasted conditions. DOR plasma PK samples were collected predose and up to 72 hrs postdose in periods 1 and 2.

Table 69. DOR PK Following Administration Alone and After Coadministration With Multiple-Dose Rifabutin

	DOR+rifabutin (mult dose) Geo Mean (95% CI) N=12	DOR alone Geo Mean (95% CI) N=18	(DOR+rifabutin)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	19.7 (17.7, 21.8)	39.5 (34.3, 45.5)	0.50 (0.45, 0.55)
C_{max} (nM)	1730 (1470, 2030)	1740 (1560, 1950)	0.99 (0.85, 1.15)
C_{24} (nM)	197 (169, 230)	625 (530, 737)	0.32 (0.28, 0.35)
$T_{1/2}$ (hr)	9.39 (geometric mean)	15.7 (geometric mean)	

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic
Note: Six out of 18 subjects were not included in DOR PK analysis for period 2. The six subjects were discontinued prior to DOR administration in period 2 due to adverse events related to rifabutin.

Rifabutin is a moderate inducer of CYP3A. Coadministration of DOR with rifabutin at steady-state reduced the AUC and C_{24} of DOR by approximately 50% and 68%, respectively. The peak concentrations of DOR were not affected. Nonparametric superposition (NPS) was used to determine the effect of doubling the DOR dose when administered with rifabutin. The NPS indicated 100 mg BID DOR coadministered with 300 mg QD rifabutin achieves similar C_{24}, AUC_{0-24}, and C_{max} values to a dose of 100 mg QD DOR in the absence of a CYP3A inducer.

Efavirenz (CYP3A inducer) Stopped Prior to DOR Administration

Study P020 was a three-period, fixed-sequence, multiple-dose study to investigate the effect of switching from efavirenz therapy to DOR on the PK of DOR. Twenty healthy male and female subjects were enrolled.

- Period 1: 100 mg DOR QD from days 1 to 5 (100-mg tablet)
- Period 2: 600 mg efavirenz QD from days 1 to 14
- Period 3: 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. All drugs were administered under fasted conditions.

- Period 1- DOR plasma PK samples were collected predose on days 1 to 5 and at specified time points up to 24 hours postdose on days 1 and 5.
- Period 2- EFV PK samples were collected predose on day 1.
- Period 3- DOR plasma PK samples were collected for 24 hours on days 1 and 14, and predose samples for DOR and EFV were collected on days 1 to 14. Blood samples for CYP2B6 genotype determination were obtained from consented subjects. (EFV is metabolized by and induced CYP2B6.)

Table 70. DOR PK Following Single Dose (Day 1) Administration Alone and After Pretreatment With Multiple Dose Efavirenz

	DOR+EFV (mult dose) Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+EFV)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	10.7 (9.00, 12.8)	28.0 (24.9, 31.6)	0.38 (0.33, 0.45)
C_{max} (nM)	1350 (1160, 1570)	2080 (1810, 2380)	0.65 (0.58, 0.73)
C_{24} (nM)	93.3 (56.5, 154)	625 (528, 740)	0.15 (0.10, 0.23)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); EFV = efavirenz; Geo = geometric; PK = pharmacokinetic

Table 71. DOR PK Following Multiple Dose (Day 14) Administration Alone and After Pretreatment with Multiple-Dose Efavirenz

	DOR+EFV (mult dose) Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+EFV)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	28.0 (23.9, 33.0)	41.1 (35.3, 47.9)	0.68 (0.58, 0.80)
C_{max} (nM)	2490 (2230, 2780)	2880 (2470, 3360)	0.86 (0.77, 0.97)
C_{24} (nM)	449 (331, 610)	902 (730, 1120)	0.50 (0.39, 0.64)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); EFV = efavirenz; Geo = geometric; PK = pharmacokinetic

Following multiple-dose efavirenz pretreatment relative to no pretreatment, DOR C_{24} was initially reduced by ~85% after a single dose, and gradually recovered, but was still reduced by ~50% after 14 days of DOR dosing. Efavirenz concentrations decreased steadily following cessation of dosing but remained detectable in all subjects for 9 days following cessation of therapy.

15.2.2.4. DDI Studies Evaluating Effect of Other Drugs on DOR PK (Acid Reducing Agents)

Study P042 was a single-dose and multiple-dose, three-period, three-treatment, fixed-sequence study in 14 healthy subjects.

- Period 1-single 100-mg DOR tablet
- Period 2- single 100-mg DOR tablet with a single 20-mL antacid oral suspension containing 1600 mg aluminum hydroxide, 1600 mg magnesium hydroxide, and 160 mg simethicone
- Period 3- 40-mg pantoprazole sodium delayed-release tablet QD with a single 100-mg DOR tablet on day 5)

All three treatments were administered under fasting conditions. In each period, DOR plasma PK samples were collected predose and 72 hrs postdose.

Table 72. DOR PK Following Administration Alone and With Antacid

	DOR + antacid Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR +antacid)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	43.9 (36.3, 52.7)	43.5 (37.4, 50.6)	1.01 (0.92, 1.11)
C_{max} (nM)	1840 (1480, 2290)	2130 (1860, 2440)	0.86 (0.74, 1.01)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

Table 73. DOR PK Following Administration Alone and With Pantoprazole

	DOR + pantoprazole Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR +pantoprazole)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	36.1 (30.3, 43.1)	43.5 (37.4, 50.6)	0.83 (0.76, 0.91)
C_{max} (nM)	1870 (1550, 2260)	2130 (1860, 2440)	0.88 (0.76, 1.01)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

Administration of DOR with an antacid oral suspension or pantoprazole does not have a clinically meaningful effect on DOR PK.

15.2.2.5. DDI Studies Evaluating Effect of DOR on Other Drugs

Midazolam (3A substrate)

Study P001V01 included a single sequence evaluation of the effect of multiple doses of DOR on midazolam PK in 8 healthy male subjects.120 mg DOR was administered QD on days 1 to 14. On days -1 and 13, 2-mg of midazolam syrup was administered orally. Drugs were administered in the fasted state. Plasma PK samples for midazolam were collected up to 24 hours postdose.

Table 74. Midazolam (MDZ) PK Following Administration Alone and With DOR

	MDZ + DOR Geo Mean (95% CI)	MDZ alone Geo Mean (95% CI)	(MDZ +DOR)/MDZ Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	27.0 (15.9, 45.8)	32.9 (19.4, 55.7)	0.82 (0.70, 0.97)
C_{max} (nM)	10.1 (6.9, 14.9)	9.97 (6.83, 14.6)	1.02 (0.81, 1.28)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; MDZ = midazolam; PK = pharmacokinetic

Results suggest that DOR is not a clinically meaningful inducer or inhibitor of CYP3A, consistent with in vitro results.

Atorvastatin

Study P036 was a two-period, fixed sequence trial in 16 male and female subjects. In period 1, subjects received a single dose of 20 mg atorvastatin. In period 2 subjects received 100 mg DOR QD (100-mg tablets) 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. Subjects fasted from 8 hours prior to and until

at least 4 hours after atorvastatin administration. Atorvastatin plasma PK samples were collected predose and up to 60 hours postdose.

Table 75. Atorvastatin (ATV) PK Following Administration Alone and With DOR

	ATV + DOR (n=14) Geo Mean (95% CI)	ATV alone (n=16) Geo Mean (95% CI)	(ATV +DOR)/ATV Geo Mean Ratio (90% CI)
$AUC_{0\text{-}t}$ (ng*hr/mL)	38.2 (30.4, 48.0)	39.2 (31.4, 49.0)	0.97 (0.90, 1.06)
C_{max} (ng/mL)	5.25 (3.54, 7.78)	7.87 (5.93, 10.4)	0.67 (0.52, 0.85)

ATV = atorvastatin; AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic
Note: Two subjects did not complete period 2 because of AEs not considered related to study drugs.

Atorvastatin is a substrate of CYP3A, OATP1B1, MDR1, BCRP and P-gp. The study shows that DOR has minimal impact on the disposition of atorvastatin, which is consistent with in vitro studies and other in vivo DDI studies. It is not clear why C_{max} is lower when DOR is coadministered with atorvastatin. It may be partially due to a greater variability associated with C_{max} ratio as compared to the ratios of other PK parameters. Ten of 14 subjects had atorvastatin C_{max} ratios [(ATV +DOR)/ATV] of 0.8 or lower.

Methadone

Study P045 evaluated the effect of DOR in methadone in 14 male and female subjects who remained on stable oral methadone maintenance therapy 20 to 180 mg QD. The effect of methadone on DOR was also evaluated, using a cross study comparison. Subjects received their usual oral maintenance dose of methadone on days 1 through 7. On days 2 through 6, subjects received DOR 100 mg QD (100 mg (b) (4) tablet) immediately after methadone administration. On days 1 and 6, subjects fasted until 4 hrs postdose. DOR plasma PK samples were collected predose on days 2 to 6 and for 24 hrs postdose on day 6. Methadone PK plasma PK samples were collected predose on days 1 to 6 and for 16 hrs postdose on day 1 and 24 hrs postdose on day 6.

Table 76. R-Methadone PK (Dose Normalized) Following Maintenance Dose Administration Alone and With Multiple Dose DOR

	Meth + DOR Geo Mean (95% CI)	Meth alone Geo Mean (95% CI)	(Meth + DOR)/meth Geo Mean Ratio (90% CI)
$AUC_{0\text{-}24}$/D (ng*hr/ML/mg)	53.2 (44.6, 63.5)	55.8 (46.4, 67.1)	0.95 (0.90, 1.01)
C_{max}/D (ng/ML/mg)	3.33 (2.83, 3.91)	3.41 (2.89, 4.01)	0.98 (0.93, 1.03)
C_{24}/D (ng/mL/mg)	1.82 (1.45, 2.27)	1.91 (1.56, 2.34)	0.95 (0.88, 1.03)

AUC = area under the curve; CI = confidence interval; /D = per dose; DOR = doravirine (MK-1439); Geo = geometric; Meth = methadone; PK = pharmacokinetic

Table 77. S-Methadone PK (Dose Normalized) Following Maintenance Dose Administration Alone and With Multiple Dose DOR

	Meth + DOR Geo Mean (95% CI)	Meth alone Geo Mean (95% CI)	(Meth + DOR)/meth Geo Mean Ratio (90% CI)
$AUC_{0\text{-}24}$/D (ng*hr/ML/mg)	50.8 (37.5, 68.8)	52.0 (38.3, 70.4)	0.98 (0.90, 1.06)
C_{max}/D (ng/ML/mg)	3.67 (2.87, 4.68)	3.77 (2.95, 4.82)	0.97 (0.91, 1.04)
C_{24}/D (ng/mL/mg)	1.47 (0.97, 2.21)	1.51 (1.03, 2.22)	0.97 (0.91, 1.04)

AUC = area under the curve; CI = confidence interval; /D = per dose; DOR = doravirine (MK-1439); Geo = geometric; Meth = methadone; PK = pharmacokinetic

DOR does not alter methadone PK.

DOR PK: Compared to DOR PK from study PN020 (period 1, day 5), AUC_{24}, C_{max}, and C_{24} were 28%, 24%, and 20% lower when DOR was administered in subjects taking methadone. The difference may be due to the cross-study comparison or delayed gastric emptying. The lower exposure is not clinically significant, based on phase 2 efficacy data for 25 mg DOR.

Metformin

Study P048 was a two-period, two-treatment, fixed-sequence study in 14 healthy male and female subjects.

- Period 1: 1000 mg single oral dose of metformin immediate release tablet.
- Period 2: DOR 100 mg QD (100-mg tablet) from day 1 to day 7 and 1000 mg metformin single dose on day 5. There was a washout of at least 3 days between metformin administration in period 1 and the first DOR dose in period 2. A standardized breakfast was given within 25 minutes prior to metformin. On days 1 to 4 and days 6 to 7, light breakfast was given approximately 30 minutes before DOR. Metformin plasma PK samples were collected predose and up to 72 hours post.

Table 78. Metformin PK Following Administration Alone and With DOR

	Metformin + DOR Geo Mean (95% CI)	Metformin alone Geo Mean (95% CI)	(metformin +DOR)/metformin Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	9660 (8290, 11300)	10300 (8740, 12200)	0.94 (0.88, 1.00)
C_{max} (ng/mL)	1270 (1130, 1420)	1350 (1150, 1570)	0.94 (0.86, 1.03)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

DOR does not affect metformin PK, thus it is not likely to affect OCT-1 or OCT-3 substrates.

Oral Contraceptive (Ethinyl estradiol and levonorgestrel)

Study P012 was a, two-period, fixed-sequence study in 20 healthy postmenopausal or oophorectomized adult females.

- Period 1-single dose Nordette®-28 (0.15 mg levonorgestrel (LN), 0.03 mg ethinyl estradiol (EE))
- Period 2- DOR 100 mg QD (tablet) for 17 consecutive days, with a single dose of Nordette®-28 coadministered on day 14. Subjects fasted prior to dosing. There was a washout of at least 7 days between dosing in period 1 and the first dose in period 2. Plasma PK samples for LN and EE were collected for 96 hrs postdose.

Table 79. Levonorgestrel and Ethinyl Estradiol PK Following Administration Alone and With DOR

	LN/EE + DOR (n=19) Geo Mean (95% CI)	LN/EE alone (n=20) Geo Mean (95% CI)	(LN/EE +DOR)/(LN/EE) Geo Mean Ratio (90% CI)
EE			
$AUC_{0-\infty}$ (pg*hr/mL)	832.32 (750.20, 923.43)	845.66 (758.43, 942.92)	0.98 (0.94, 1.03)
C_{max} (pg/mL))	55.12 (49.30, 61.63)	66.03 (59.09, 73.78)	0.83 (0.80, 0.87)
LN			
$AUC_{0-\infty}$ (ng*hr/mL)	45.59 (36.39, 57.12)	37.72 (30.77, 46.23)	1.21 (1.14, 1.28)
C_{max} (ng/mL))	2.47 (2.02, 3.01)	2.57 (2.13, 3.09)	0.96 (0.88, 1.05)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); EE = ethinyl estradiol; Geo = geometric; LN = levonorgestrel; PK = pharmacokinetic

One subject discontinued before period 2.

Multiple-dose DOR does not alter the PK of EE or LN significantly.

15.2.2.6. DDI Studies Evaluating Effect of DOR on Other Drugs and Effect of Other Drugs on DOR

Dolutegravir

Study P016 was a three-period, fixed-sequence trial. Twelve healthy male and female subjects enrolled. (One discontinued after period 1 due to positive cotinine screen.

- Period 1- 50 mg dolutegravir (DTG) QD for 7 days
- Period 2- 200-mg DOR QD for 7 days (2 x 100-mg tablets)
- Period 3- 50 mg DTG + 200 mg DOR 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.

Dosing in the morning of day 7 was following a fasting period of ≥10 hours. On days 1 to 6, standardized meals (including breakfast approximately 1 hour after dosing) was served. Plasma PK samples for DOR and DTG were collected predose and up to 24 hrs postdose on day 7.

Table 80. DOR PK Following Administration Alone and With DTG

	DOR+DTG (n=11) Geo Mean (95% CI)	DOR alone (n=11) Geo Mean (95% CI)	(DOR+DTG)/DOR Geo Mean Ratio (90% CI)
AUC_{0-24} (μM*hr)	47.6 (39.7, 57.1)	47.6 (40.1, 56.4)	1.00 (0.89, 1.12)
C_{max} (nM)	3760 (3080, 4590)	3540 (2900, 4330)	1.06 (0.88, 1.28)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); DTG = dolutegravir; Geo = geometric; PK = pharmacokinetic

Table 81. DTG PK Following Administration Alone and With DOR

	DOR+DTG (n=11) Geo Mean (95% CI)	DTG alone (n=12) Geo Mean (95% CI)	(DOR+DTG)/DTG Geo Mean Ratio (90% CI)
AUC_{0-24} (ng*hr/mL))	58500 (48600, 70500)	42900 (37000, 49600)	1.36 (1.15, 1.62)
C_{max} (ng/mL)	4400 (3810, 5070)	3070 (2590, 3640)	1.43 (1.20, 1.70)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); DTG = dolutegravir; Geo = geometric; PK = pharmacokinetic

DTG had no effect on DOR. DOR increased DTG concentrations by 35 to 45%, which is not clinically significant. Of note, DOR dose used in this study is 2-fold higher than the proposed to-be-marketed dose (100 mg).

DTG is metabolized primarily by UGT1A1 with some contribution from CYP3A. It is a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. DOR is not expected to inhibit UGT1A1, CYP3A, or P-gp. In vitro, DOR inhibits BCRP with an IC_{50} value of 51μM, above DOR plasma C_{max} (<4μM), thus inhibition of BCRP at the systemic level is not anticipated. However, there is potential for inhibition of BCRP at the gut level ($[I2]/IC_{50}$ >10, where [I2] is defined as the (molar dose of DOR)/250 mL), which may be the cause of the increases in DTG exposure observed in this trial.

Elbasvir and grazoprevir

Study P050 was a nonrandomized, fixed-sequence, single-site, three-period trial in 12 healthy male and female subjects.

- Period 1- 100 mg DOR QD days 1 to 5

- Period 2- 50 mg elbasvir (EVR) and 200 mg grazoprevir (GVR) QD days 1 to 10
- Period 3- 100 mg DOR, 50 mg EVR, and 200 mg GVR QD days 1 to 5

There was a 5 day washout after the last dose in period 1 and no washout after period 2. Plasma PK samples for DOR were collected predose and for 24 hrs postdose on day 5 of periods 1 and 3. Plasma PK samples for EVR and GVR were collected predose and for 24 hrs postdose on day 10 of period 2 and day 5 of period 3.

Table 82. DOR PK Following Administration Alone and With EVR/GVR

	DOR+EVR/GVR Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+EVR/GVR)/DOR Geo Mean Ratio (90% CI)
AUC_{0-24} (μM*hr)	64.6 (54.1, 77.3)	41.3 (35.5, 48.1)	1.56 (1.45, 1.68)
C_{max} (nM)	4770 (4080, 5590)	3400 (2950, 3910)	1.41 (1.25, 1.58)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); EVR = elbasvir; Geo = geometric; GVR = grazoprevir; PK = pharmacokinetic

Table 83. EVR PK Following Administration With GVR and With GVR and DOR

	EVR/GVR + DOR Geo Mean (95% CI)	EVR/GVR alone Geo Mean (95% CI)	(EVR/GVR/DOR)/(EVR/GVR)R Geo Mean Ratio (90% CI)
AUC_{0-24} (μM*hr)	3.73 (3.00, 4.63)	3.89 (3.24, 4.67)	0.96 (0.90, 1.02)
C_{max} (nM)	287 (222, 370)	298 (238, 373)	0.96 (0.91, 1.01)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); EVR = elbasvir; Geo = geometric; GVR = grazoprevir; PK = pharmacokinetic

Table 84. GVR PK Following Administration With EVR and With EVR and DOR

	EVR/GVR + DOR Geo Mean (95% CI)	EVR/GVR alone Geo Mean (95% CI)	(EVR/GVR/DOR)/(EVR/GVR)R Geo Mean Ratio (90% CI)
AUC_{0-24} (μM*hr)	6.05 (4.12, 8.87)	5.64 (3.68, 8.66)	1.07 (0.94, 1.23)
C_{max} (nM)	2190 (1400, 3410)	1800 (1090, 2950)	1.22 (1.01, 1.47)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); EVR = elbasvir; Geo = geometric; GVR = grazoprevir; PK = pharmacokinetic

The 40 to 60% increase in DOR concentrations is not clinically significant. The mechanism may be through inhibition of CYP3A in the gut by GVR. GVR is a weak CYP3A inhibitor. DOR did not alter PK of EVR or GVR.

Ledipasvir/Sofosbuvir

Study P053 was a randomized, three-period, crossover trial. On day 1 of each period, subjects received a single dose of either DOR alone, ledipasvir (LDP)/sofosbuvir (SOF) alone, or DOR administered with LDP/SOF in a randomized manner. There was a washout of 14 days between each dose. Plasma PK samples were collected predose and for 168 hrs (LDP), 120 hrs (SOF and metabolite GS-331007), or 72 hrs (DOR).

Table 85. DOR PK Following Administration Alone and With LDP/SOF

	DOR+LDP/SOF Geo Mean (95% CI)	DOR alone Geo Mean (95% CI)	(DOR+LDP/SOF)/DOR Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	41.8 (36.2, 48.3)	36.3 (30.2, 43.7)	1.15 (1.07, 1.24)
C_{max} (nM)	1850 (1550, 2210)	1670 (1400, 1990)	1.11 (0.97, 1.27)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; LDP = ledipasvir; PK = pharmacokinetic; SOF = sofosbuvir

Table 86. LDP PK Following Administration of LDP/SOF and DOR+LDP/SOF

	LDP/SOF + DOR Geo Mean (95% CI)	LDP/SOF alone Geo Mean (95% CI)	(LDP/SOF/DOR)/(LDP/SOF) Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	7450 (5470, 10100)	8080 (6060, 10800)	0.92 (0.80, 1.06)
C_{max} (ng/mL)	225 (165, 308)	248 (182, 339)	0.91 (0.80, 1.02)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; LDP = ledipasvir; PK = pharmacokinetic; SOF = sofosbuvir

Table 87. SOF PK Following Administration of LDP/SOF and DOR+LDP/SOF

	LDP/SOF + DOR Geo Mean (95% CI)	LDP/SOF alone Geo Mean (95% CI)	(LDP/SOF/DOR)/(LDP/SOF) Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	1170 (949, 1440)	1130 (886, 1440)	1.04 (0.91, 1.18)
C_{max} (ng/mL)	1060 (829, 1350)	1190 (949, 1500)	0.89 (0.79, 1.00)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; LDP = ledipasvir; PK = pharmacokinetic; SOF = sofosbuvir

Table 88. GS-331007 PK Following Administration of LDP/SOF and DOR+LDP/SOF

	LDP/SOF + DOR Geo Mean (95% CI)	LDP/SOF alone Geo Mean (95% CI)	(LDP/SOF/DOR)/(LDP/SOF) Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (ng*hr/mL)	16400 (14400, 18600)	15800 (13900, 18000)	1.03 (0.98, 1.09)
C_{max} (ng/mL)	1010 (877, 1160)	981 (866, 1110)	1.03 (0.97, 1.09)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; LDP = ledipasvir; PK = pharmacokinetic; SOF = sofosbuvir

Single dose administration of DOR with LDP/SOF did not alter PK of DOR, LDP, SOF, or GS-331007.

15.2.3. Intrinsic Factors

Gender and Age

Study P09 was a one-period, parallel-group study in healthy elderly male and female subjects and healthy young female subjects. 12 subjects per group enrolled in the study. Group 2 consisted of healthy elderly female subjects, aged between 65 and 80 years (inclusive), Group 3 consisted of healthy young female subjects, aged between 18 and 50 years (inclusive). Subjects received a single oral 100-mg dose of DOR (one phase I tablet) with 240 mL of water after fasting overnight for at least 8 hours. Healthy young male data from study PN001 were included as a comparator.

Table 89. Summary of DOR PK (Arithmetic Mean (Standard Deviation)) After Single Dose Administration

	Elderly male	Elderly female	Young female	Young male (PN001)
AUC_{0-24} (μM*hr)	20.8 (4.35)	29.0 (5.74)	27.3 (7.30	22.9 (5.50)
C_{max} (nM)	1520 (387)	2420 (602)	2050 (521)	1670 (459)
C_{24} (nM)	500 (133)	535 (156)	606 (294)	610 (136)
$T_{1/2}$ (hr)	17.5 (6.75) (n=11)[1]	14.5 (4.2)	17.7 (7.16)	16.6 (8.75)

AUC = area under the curve; DOR = doravirine (MK-1439); PK = pharmacokinetic

[1] $T_{1/2}$ not determined for one elderly male because extrapolated AUC was greater than 25% of $AUC_{0-\infty}$

The C_{max} of DOR was 42% higher for female compared to male subjects. It is not expected to be clinically significant. No difference was observed between elderly male and young male or elderly female and young female subjects.

Hepatic Impairment

Study P019 was a non-randomized, single-dose study. Eight subjects with moderate hepatic insufficiency (Child-Pugh 7 to 9) and eight healthy matched control subjects enrolled. DOR 100 mg single dose (100 mg oral (b) (4) tablet formulation) was administered following an overnight fast. Plasma PK samples were collected predose and up to 72 hrs postdose.

Table 90. Summary of DOR PK After Single Dose Administration: Moderate Hepatic Impairment and Controls

	Moderate Hepatic Impairment Geo Mean (95% CI)	Healthy Controls Geo Mean (95% CI)	Moderate Hepatic/Healthy Control Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	53.9 (41.5, 70.0)	54.6 (42.1, 71.0)	0.99 (0.72, 1.35)
C_{max} (nM)	1850 (1420, 2420)	2050 (1570, 2680)	0.90 (0.66, 1.24)
C_{24} (nM)	842 (658, 1080)	847 (662, 1080)	0.99 (0.74, 1.33)
$T_{1/2}$ (hr) geo mean (%CV)	17.97 (30.8)	18.12 (30.5)	

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

Moderate hepatic insufficiency does not affect DOR PK.

Renal Impairment

Study P051 was a non-randomized, single-dose study. Eight subjects with severe renal impairment (eGFR ≤ 30 mL/min/1.73 m^2 not on dialysis) and eight healthy matched control subjects enrolled. DOR 100 mg single dose (100 mg FCT formulation) was administered following an overnight fast. Plasma PK samples were collected predose and up to 72 hrs postdose. A 96-hr sample was collected from renal impaired subjects.

Table 91. Summary of DOR PK After Single Dose Administration: Severe Renal Impairment and Controls

	Severe Renal Impairment Geo Mean (95% CI)	Healthy Controls Geo Mean (95% CI)	Severe Renal/Healthy Control Geo Mean Ratio (90% CI)
$AUC_{0-\infty}$ (μM*hr)	64.5 (47.4, 87.8)	45.1 (33.2, 61.4)	1.43 (1.00, 2.04)
C_{max} (nM)	1580 (1210, 2080)	1900 (1450, 2500)	0.83 (0.61, 1.15)
C_{24} (nM)	943 (710, 1250)	684 (515, 908)	1.38 (0.99, 1.92)
$T_{1/2}$ (hr) geo mean (%CV)	25.02 (36.4)	684 (515, 908)	

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); Geo = geometric; PK = pharmacokinetic

The magnitude of the increase of DOR concentrations in severe renal impairment subjects versus controls is not considered clinically significant.

15.2.4. Population PK Analysis

The goal of the population PK analysis (popPK) was to develop a popPK model to assess sources of variability (intrinsic and extrinsic covariates) of DOR.

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 oral doses of DOR as a single entity or as DOR/3TC/TDF. The PK of DOR was characterized with a one-compartment model described by first-order absorption (K_a), volume of distribution (V/F), and linear clearance (CL/F) from the central compartment. The less than dose-proportional increases in DOR exposure were described by estimation of two relative bioavailability (F1) for the dose ranges of <30 mg and >120 mg in comparison to the dose range of 30 to 120 mg. An additive residual

error model was employed for log-transformed data. Separate residual errors were estimated for the phase 1 data versus the phase 2b/3 data, and within the phase 1 data for the first 0.5 h postdose versus the remaining time points.

Table 92. Parameter Estimates of Final Model With Significant Covariates

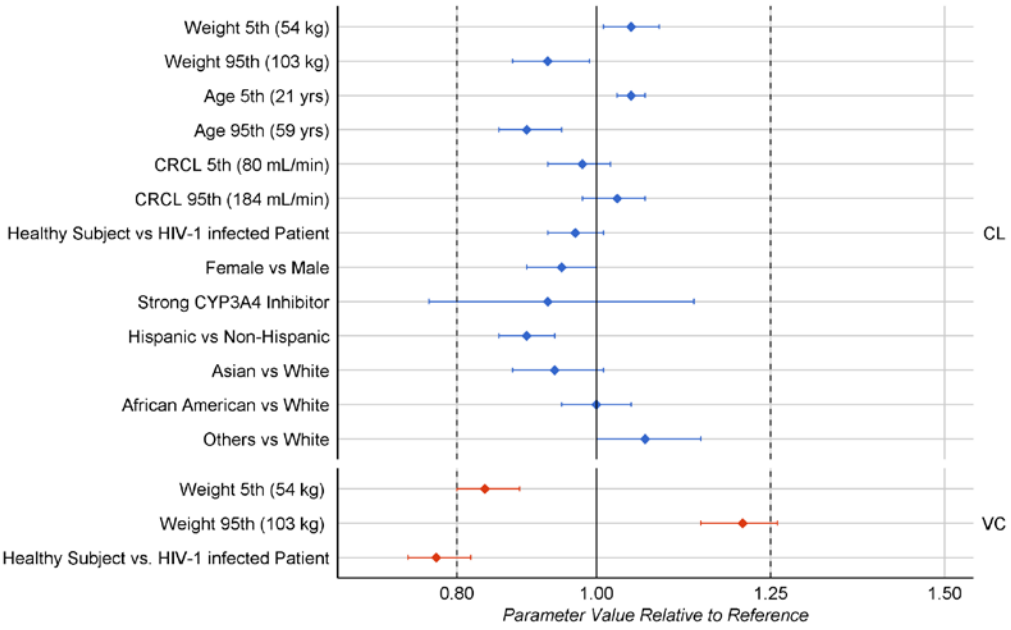
Fixed effects						
	Final Estimate	**%RSE**	**%CV**	**95% LBound**		**95% UBound**
CL/F (L/h)	6.34	1.37	--	6.1		6.51
V/F (L)	162	3.17	--	152		172
K_a (1/h)	1.40	4.57	--	1.28		1.53
F1 <30 mg	1.20	5.87	--	1.06		1.34
F1 30 to 120 mg (ref)	1	-	--	--		--
F1 >120 mg	0.895	9.32	--	0.732		1.06
Age on CL	-0.00508	16.6	--	-0.00673		-0.00343
Subject status on V	-0.220	12.3	--	-0.273		-0.167
Weight on V	0.00788	15.4	--	0.00551		0.0102
Interindividual Variability						
	Final Estimate	**%RSE**	**%CV**	**95% LBound**	**95% UBound**	**η-shrinkage**
CL/F	0.117	7.93	35.2	0.0986	0.135	11.4
V/F	0.101	8.26	32.6	0.0848	0.118	38.7
	Final Estimate	**%RSE**	**%CV**	**95% LBound**	**95% UBound**	**ε-shrinkage**
SD phase 1 ≤ 0.5 hr	0.224	3.77	22.4	0.207	0.241	7.37
SD phase 1 >0.5 hr	1.25	6.89	125	1.08	1.42	7.37
SD phase 2b/3	0.521	4.01	52.1	0.48	0.562	7.37

CL/F = linear clearance; %CV = percent coefficient of variation; RSE = relative standard error; SD = standard deviation; V/F = volume of distribution

No signs of model misspecification were identified. Prediction-corrected visual predictive check showed the final model adequately described the observed PK profile of DOR. Bootstrap analyses demonstrated consistency in parameter estimates and indicated robustness of the model.

Automated stepwise covariate model building was applied to select significant covariates. The final population PK model included statistically significant effects of body weight and HIV-1 infection status on apparent volume of distribution and age on apparent clearance. In addition, the effects of all evaluated covariates on the DOR PK parameters were determined forest plot based on 1000 bootstrap results of full covariate model. The effects of continuous covariates on PK parameters were illustrated though comparing the PK parameter in a patient with extreme (5^{th} or 95^{th} percentile) covariate value relative to the parameter in a patient with the median covariate value. Overall the effects of these covariates on PK parameters were modest. Statistically significant covariates age, body weight and healthy status were not expected to result in a greater than 25% change in DOR PK parameters. PopPK analysis indicated no significant effect of concomitant administration of strong CYP3A4 inhibitors on CL. However, this analysis was limited by the small number of subjects who received strong CYP3A4 inhibitors (N=8) in the phase 2/3 trials.

Figure 2. Covariate Effects on DOR Pharmacokinetic Parameters



Source: Reviewer's Analysis based on popPK dataset "mk-doravirine-pkxxpsm01-20170616.csv"
Reference: Weight (70kg), Age (34 years old), CRCL (121 mL/min).

$AUC_{0\text{-}24}$, C_{max}, and C_{24} at steady-state were simulated from post hoc compartmental parameter estimates of the final model for each subject in the phase 2b and 3 trials.

Table 93. Summary Statistics of DOR Steady-state $AUC_{0\text{-}24}$, C_{max} and C_{24} Following Administration of 25 mg, 50 mg, 100 mg, or 200 mg QD DOR in the Phase 2b (P007) and Phase 3 (P018, P021) Trials

Study	Dose	$AUC_{0\text{-}24}$ (nM*hr)	C_{max} (nM)	C_{min} (nM)
7	25	11401 (30)	675 (20.9)	281 (45.8)
	50	19432 (27.1)	1162 (16.8)	445 (41.3)
	100	32222 (27.9)	2027 (16.2)	676 (45.6)
	200	55673 (28.9)	3534 (17.4)	1167 (48)
18	100	38985 (26.5)	2291 (18.6)	971 (40.7)
21	100	37190 (26.7)	2233 (18.1)	889 (42.3)

Source: Reviewer's Analysis to confirm Table 11 in Applicant's popPK report
AUC = area under the curve; DOR = doravirine; popPK = population pharmacokinetics

The absolute bioavailability of the final market image DOR film-coated tablet was estimated via a popPK model. The analysis was based on PK data from 24 healthy fasted subjects receiving a single oral of 100 mg final market image FCT DOR (trial P039) and 11 healthy subjects receiving a single IV infusion of 100 mcg DOR (trial P044). A two-compartment model with first order absorption was used to fit the data. Between-subject variability on CL and V was described by exponential error models and residual variability was captured by a proportional model. No covariate was included in this analysis as the focus was to estimate absolute BA. Based on this analysis, the absolute bioavailability of the 100 mg final market image tablet of DOR is estimated to be 64% (with 8.2 % RSE). Estimates (%RSE) of other parameters are CL 0.919 L/hr (18.3%), central compartment CL 3.67 L/hr (7.9%), central compartment volume (V2) 22.8 L (13.1%), intercompartmental CL (Q) 51.9 L/hr (17.2%), and peripheral compartment volume (V3) 43 L (9%).

15.2.5. Dose/Exposure Response Relationships

Relationships between DOR dose or exposure and efficacy and safety were characterized based on 1 phase 2b trial (P007) and 2 phase 3 trials (P018 and P021). The phase 2b trial (P007) was a dose ranging trial (DOR 25, 50, 100, and 200 mg QD) in treatment-naïve HIV-1 infected subjects. Two phase 3 trials were conducted in treatment-naïve HIV-1 infected subjects, both with DOR at 100 mg QD doses. The dose/exposure response evaluations included 947 HIV-1 infected subjects receiving DOR as a single entity or DOR/3TC/TDF. Efficacy was assessed as the proportion of subjects achieving HIV-1 RNA levels at two cut-offs: <50 copies/mL, and <40 copies/mL. Additionally, occurrence of protocol defined virologic failure (PDVF) was included as an efficacy endpoint in the evaluation. safety endpoints included neuropsychiatric adverse events through week 8 and 48, and lipid profiles (fasting LDL-C and fasting non-HDL-C) at week 48.

Phase 2b Dose Response for Efficacy:

- Efficacy was similar across the 25 to 200-mg dose groups.

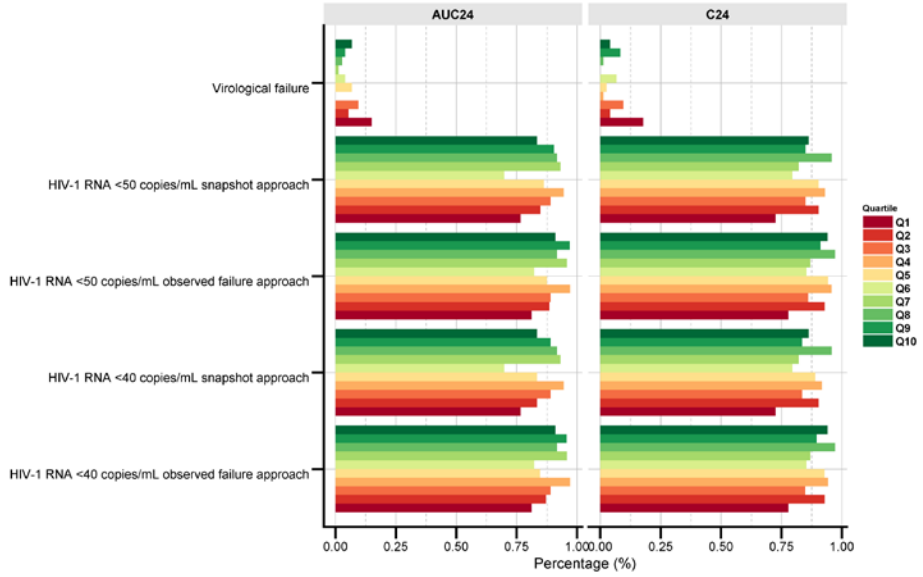
Phase 2b Dose Response for Safety:

- No statistically significant differences in neuropsychiatric AE incidence rates were found among 25 mg, 100 mg and 200 mg. A higher rate of neuropsychiatric AEs was found with 50 mg compared to 100 mg. This was likely due to chance because of small sample size as no difference in incidences rate was found when comparing other doses. The distribution of change in lipid profiles was similar across dose groups.

Exposure Response for Efficacy:

- (Phases 2b) Virologic response and virologic failure were similar across the exposure quartiles. Logistic regression results indicated log-transformed baseline viral load was the only significant predictor of response. The exposure-response relationships between DOR PK (AUC and C_{24}) and efficacy endpoints were flat over the range of exposure achieved over the 25- to 200-mg doses.
- (Phase 3) The observed proportion of subjects achieving HIV-1 RNA levels at two cut-offs: <50 copies/mL, and <40 copies/mL and occurrence of protocol defined virologic failure stratified by 10 DOR exposure quartiles in the phase 3 showed a trend of lower response and higher virologic failure in the lowest exposure quartile.

Figure 3. Observed Efficacy Endpoints Across Exposure Quartiles in Phase 3 Trials P018 and P021



Statistically significant exposure-response relationships were identified between DOR PK (AUC and C_{24}) and nearly all evaluated efficacy endpoints over the exposures achieved at the 100 mg QD dose. A visualization of the predicted exposure-response relationships for each of the four HIV-1 RNA efficacy endpoints and virologic failure based on final models with DOR steady state PK (C_{24} and AUC_{0-24}) indicated that although slopes were statistically different from zero, the ER relationships were generally flat with a minimal decrease in efficacy in subjects with low DOR exposure. Even in the lowest exposure quartile, more than 80% response rate and about 10% virologic failure were predicted.

Exposure Response for Safety

Neuropsychiatric AEs- The observed incidence rate of neuropsychiatric AEs was comparable across different DOR exposure quartiles. The logistic regression results for DOR exposure and the occurrence of neuropsychiatric AEs did not indicate a trend of strong association between neuropsychiatric AEs and DOR PK over the dose range of 25 to 200 mg QD.

Lipid Profiles- The change in lipid profiles from baseline appears similar across DOR exposure quartiles. Predicted relationships between DOR PK and change in lipids based on final logistic regression model indicated that lower DOR exposure was associated with slightly larger decreases in lipids from baseline.

Table 94. Predicted Change in LDL-C and Non-HDL-C from Baseline at Week 48 at different Quantiles of DOR PK distribution

AUC_{0-24} Metrics	LDL-C		Non-HDL-C	
	AUC_{0-24} µM*hr	Prediction (95% CI)	AUC_{0-24} µM*hr	Prediction (95% CI)
5th Percentile	16.15	-4.35 (-6.8, -1.91)	16.19	-6.83 (-9.45, -4.22)
Median	36.72	-2.72 (-4.01, -1.43)	36.74	-4.59 (-6.01, -3.18)
95th Percentile	59.56	-0.91 (-3.41, 1.6)	59.53	-2.11 (-4.88, 0.66)

Source: Reviewer's Analysis based on Dataset "mk1439-er-lipids-20170622.xpt".
AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density

An exploratory analysis investigated whether concomitant administration with a strong CYP3A4 inhibitor would affect the safety profile. The incidence rates of neuropsychiatric AE and change in lipid profiles from baseline were compared between patients who took strong CYP3A4 inhibitors and those who did not. Among five patients who took strong CYP3A4 inhibitors during treatment in study P007 and P021, three experienced neuropsychiatric AEs. Although this was higher compared to 31% of neuropsychiatric AE in patients without concomitant strong CYP3A4 inhibitor, the confidence intervals overlapped because of the small sample size. Similarly, although the median decrease in LDL-C and non-HDL-C at week 48 from baseline in 9 patients with concomitant strong CYP3A4 inhibitors was smaller compared to the median decrease in all other patients, this difference is not statistically significant. Both comparisons were limited by the small number of subjects who took strong CYP3A4 inhibitors for at least 7 days.

15.2.6. Physiologic Based Pharmacokinetic Modeling Review

Physiologic Based Pharmacokinetic (PBPK) modeling was used to address two questions:

(1) What duration of cessation period is needed after discontinuation of a CYP3A inducer, before starting DOR administration?
(2) What is the anticipated systemic exposure of M9 metabolite when rifabutin is coadministered and DOR dose is doubled to 100 mg BID?

DOR PBPK model: The Applicant developed a PBPK model for DOR using SimCYP® version 16. The model was built with physicochemical and in vitro data, clinical IV data, single oral dose PK data, and human absorption, metabolism, excretion data.

Table 95. Table Summary of DOR PBPK Model Input Parameters

Parameter	Input Value	Source
Molecular weight	425.7	Predicted (ACD/LogD Suite, Ver. 10.03)
LogP	3.0	
Compound type	Monoprotic base	
pK_a	9.47	Measured
Plasma free fraction	0.24	Measured
Blood to plasma ratio	1.0	Measured
Absorption model	First order	Measured
P_{app} (x 10^{-6} cm/s)	25	
P_{eff} (x 10^{-4} cm/s)	3.11	Calculated in SimCYP®
Ka (hr^{-1})	1.36	Based on Population PK analysis
Fa	0.664	Estimated from preliminary PopPK model of F =0.637[†]
Distribution model	Minimal PBPK, 1 compartment	Clinical IV data
V_{ss} (L/kg)	0.73	
Elimination model	Enzyme kinetics	SimCYP®'s retrograde calculator with CLIV =3.85 L/hr
CYP3A4 CL_{int} (µL/min/pmol)	0.026	
CL_{renal} (L/hr)	0.566	

CL = clearance; DOR = doravirine; IV = intravenous; PBPK = physiologic based pharmacokinetic; V_{ss} = apparent volume of distribution at steady state
[†] Final PopPK model absolute bioavailability estimate was F =0.638 [Ref. 5.3.5.3: 04NVZG]

The DOR PBPK model was further verified by comparison of simulated and observed AUC, C_{max}, and C_{24} ratios for drug-drug interactions.

Table 96. Simulated and Observed Drug Interaction Results

		DOR + perpetrator/DOR alone (90% CI)		
Treatment	**Data**	**AUC**	**C_{max}**	**C_{24}**
400 mg ketoconazole QD, DOR 100 mg day 2	simulated	3.33 (3.13, 3.53)	1.18 (1.17, 1.19)	3.23 (2.89, 3.60)
	observed	3.06 (2.85, 3.29)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)
600 mg rifampin QD. DOR 100 mg day 14	simulated	0.26 (0.25, 0.28)	0.71 (0.68, 0.73)	0.008 (0.005, 0.014)
	observed	0.12 (0.10, 0.15)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)
600 mg efavirenz QD x 14d. Day 1 of DOR 100 mg QD post efavirenz cessation	simulated	0.49 (0.47, 0.52)	0.81 (0.80, 0.83)	0.08 (0.06, 0.11)
	observed	0.38 (0.33, 0.45)	0.65 (0.58, 0.73)	0.15 (0.10, 0.23)
600 mg efavirenz QD x 14d. Day 14 of DOR 100 mg QD post efavirenz cessation	simulated	0.66 (0.63, 0.70)	0.81 (0.79, 0.83)	0.38 (0.33, 0.44)
	observed	0.68 (0.58, 0.80)	0.86 (0.77, 0.97)	0.50 (0.39, 0.64)

AUC = area under the curve; CI = confidence interval; DOR = doravirine (MK-1439); QD = once daily

The impact of coadministration of rifampin (SimCyp built-in model) on AUC and C_{max} was under-predicted, although the model did capture a significant decrease in exposure caused by rifampin. To address this concern, the reviewer conducted a sensitivity analysis on the maximal induction effect (Ind_{max}) of rifampin, and observed that increasing the parameter Ind_{max} from 16-fold to 40-fold for rifampin improved the prediction of the effect of rifampin on DOR to within 20% of the observed values.

Duration Of Cessation Period is Needed After Discontinuation of a CYP3A Inducer, Before Starting DOR Administration

The reviewer used the optimized Ind_{max} to predict the effect of pretreatment of rifampin with various cessation periods prior to the DOR treatment to determine the required cessation period for patients who take a CYP3A inducer prior to the DOR treatment. The cessation period allows the CYP3A induction effect to subside.

The effect of the number of days of rifampin therapy (600 mg QD) cessation prior to initiation of DOR therapy on DOR concentrations was evaluated with Ind_{max} of 16 and 40. Using an Ind_{max} of 16, following 21 days (3 weeks) of rifampin cessation, 13% of the reduction effect remains. Using an Ind_{max} of 40, following 28 days (4 weeks) of rifampin cessation, 13% of the reduction effect remains. Because rifampin 900 mg QD may be used off-label in the HIV population, the period of rifampin cessation required prior to initiation of DOR therapy following rifampin 900 mg QD for 4 weeks was also evaluated as maximum effect. The analysis shows that increasing the rifampin dose from 600 mg QD to 900 QD 25% of the induction effect remains following 4 weeks of rifampin cessation. The magnitude of the DOR AUC reduction is acceptable based on the phase 2 data. For simplicity of instructions, 4 weeks of cessation is recommended after any CYP3A inducer, prior to starting DOR.

Anticipated Systemic Exposure of M9 Metabolite When Rifabutin is Coadministered and DOR Dose is Doubled to 100 Mg BID

During the review, we considered the potential for significantly increased M9 concentrations when DOR is coadministered with a CYP3A inducer. There will a further increase when DOR dose is doubled 100 mg BID when administered with rifabutin. The Applicant added the M9 model to the PBPK analysis to evaluate the effect of a CYP3A inducer on M9 concentrations.

The Applicant incorporated M9 into the DOR PBPK model to evaluate the effect of rifabutin on the M9 concentrations, with the following assumptions:

- Formation rate of M9: Based on the mass balance study (P008), 55% of the absorbed dose of DOR is excreted as M9, 12.9% is recovered in urine as DOR, and any remaining DOR is converted to other metabolites. As a result, the rate of M9 formation via CYP3A4 was specified as 55% of the total clearance of DOR, corresponding to 65% of the hepatic clearance. As DOR is primarily metabolized by CYP3A4, the remaining 35% of hepatic clearance was assigned to CYP3A4 metabolism (inducible) that does not lead to the formation of M9.
- Distribution of M9: The volume of distribution of M9 was assumed to be one compartment and a minimal PBPK model was used. M9 V_{ss} was predicted from the plasma free fraction, determined in vitro, and the predicted pK_a and logP.
- Elimination of M9: Based on mass balance data, M9 is primarily cleared intact in urine and feces, with a minor amount converted to secondary metabolites. Therefore, M9 elimination was parameterized as renal clearance and additional systemic clearance to represent the excretion in feces, with 10% assigned to non-inducible metabolism. In the absence of plasma concentration-time data for M9 in humans, the total clearance in the model was fit to match the M9/DOR AUC ratio observed in the mass balance trial.

Although there are no human PK data for M9 to verify the effect, the model is generally reasonable. The analysis shows that a strong CYP3A inducer may increase M9 AUC and C_{max} by up to 2-fold and 3-fold, respectively. By increasing DOR dosing frequency from once daily to twice daily when coadministered with a moderate CYP3A inducer, rifabutin, M9 AUC is expected to increase approximately 4-fold, at maximum.

16. Trial Design Assessment Additional Information and Assessment

Table 97. PN018 DRIVE-FORWARD Protocol Synopsis

Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
Compound name	MK-1439, doravirine 100-mg oral (b) (4) tablet	
Indication	Treatment of HIV-1 infection	
Design	A phase 3 Multicenter, Double-Blind, Randomized, Active Comparator- Controlled Clinical Trial to Evaluate the Safety and Efficacy of Doravirine (MK-1439) 100 mg Once Daily Versus Darunavir 800 mg Once Daily Plus Ritonavir 100 mg Once Daily, Each in Combination with TRUVADA™ or EPZICOM™/ KIVEXA™, in Treatment-Naïve HIV-1 Infected Subjects	
Trial identifiers	Protocol Number: Clinical phase: EudraCT Number: Other Codes: IND Number: ClinicalTrials.gov identifier:	018 3 2014-001127-69 112,796 NCT02275780
Ethics	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.	
Trial centers	This trial was conducted at 133 sites: 40 sites in the United States, 12 in Germany, 11 in the Russian Federation, 11 in the United Kingdom, 10 in Spain, 8 in France, 6 each in Australia and Romania, 5 each in Canada and Chile, 4 each in Argentina and Austria, 4 in Puerto Rico, 3 each in Denmark and South Africa, and 1 in Italy. (An additional site was opened in Mexico; however, no subjects were screened or randomized at that site.)	
Design	Multicenter, double-blind (with in-house blinding), randomized, active comparator-controlled trial to evaluate the safety, efficacy, and pharmacokinetics of doravirine (DOR; MK-1439) compared with ritonavir-boosted darunavir (DRV+r), each given in combination with emtricitabine plus tenofovir disoproxil fumarate (FDC/TDF) (supplied as TRUVADA™) or abacavir plus lamivudine (ABC/3TC) (supplied as EPZICOM™ or KIVEXA™), in human immunodeficiency virus type 1 (HIV-1)-infected, treatment-naïve adults ≥18 years of age, with plasma HIV-1 RNA ≥1000 copies/mL at screening (within 45 days of randomization [first day of treatment]) and no known resistance to DOR or any other study drug. An external Data Monitoring Committee provides ongoing monitoring of safety data. In addition, an interim safety analysis was performed at week 8, and an interim efficacy analysis was performed when complete week 24 data were available for approximately 340 subjects for the purpose of stopping the study if there was a lack of efficacy as prespecified (futility). **Planned duration of main phase (base study):** 96 weeks; week 48 is primary timepoint. (Data from week 96 will be presented in a future report.) **Planned duration of extension phase:** 96 weeks	
Objectives in base study	Primary Objective: To evaluate the antiretroviral activity of MK-1439 (DOR) 100 mg once daily (QD), compared with DRV+r (800 mg/100 mg) QD, each in combination	

	with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at week 48 Secondary Objectives: To evaluate MK-1439 (DOR) 100 mg QD, compared with DRV+r (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, with respect to: 1. safety and tolerability, as assessed by review of the accumulated safety data at week 48 and week 96. 2. effect on fasting serum lipids, as measured by mean change from baseline in fasting serum lipids at week 48. 3. safety and tolerability, as measured by the time to discontinuation from study due to an adverse experience (AE). 4. immunologic effect, as measured by the change from baseline in $CD4^+$ T-cell count at week 48 and week 96. 5. antiretroviral activity, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at week 96. 6. antiretroviral activity, as measured by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at week 48 and week 96.
Selection of trial population	**Key Inclusion Criteria** • At least 18 years of age • HIV-1 infected • ARV treatment-naïve • At screening, alkaline phosphatase <3.0 x ULN, AST and ALT <5.0 X ULN, and creatinine clearance >50 mL/min by the Cockcroft-Gault equation • Clinically stable with no sign of active infection • Unlikely to become pregnant or to impregnate a partner (either not of reproductive potential or agrees to use of acceptable contraception methods) **Key Exclusion Criteria** • Use of illicit drugs or recent history of abuse of illicit drugs or alcohol • History of treatment for another viral infection with an agent that is also active against HIV-1 (such as adefovir, TDF, entecavir, FTC, or 3TC) • Documented or known resistance to DOR, EFV, FTC, 3TC, and/or TDF • Use of systemic immunosuppressive therapy or immune modulators within 30 days prior to study treatment, or anticipated use during the study • Current diagnosis of acute hepatitis • Pregnant or breastfeeding, or expecting to become pregnant during the study • Documented or known resistance to ABC
Hypotheses	• MK-1439 100 mg QD is non-inferior to darunavir/ritonavir (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48. Superiority of MK-1439 100 mg QD to darunavir/ritonavir (800 mg/100 mg) QD will be assessed if non-inferiority is established. • MK-1439 100 mg QD is superior to darunavir/ritonavir (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the mean change from baseline in fasting low-density lipoprotein cholesterol (LDL-C) at week 48. If superiority is established with respect to LDL-C, the following subsequent hypothesis will be tested: MK-1439 100 mg QD is superior to darunavir/ritonavir (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the mean change from baseline in fasting non-high-density lipoprotein cholesterol (HDL-C) at week 48. • MK-1439 100 mg QD is non-inferior to darunavir/ritonavir (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at week 96. Superiority of MK-1439 100 mg QD to darunavir/ritonavir (800 mg/100 mg) QD will be assessed if non-inferiority is established.

Treatment groups	**DOR (doravirine; MK-1439)** Doravirine 100-mg oral (b) (4) tablet, in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; supplied as TRUVADA™) or abacavir/lamivudine (ABC/3TC; supplied as EPZICOM™ or KIVEXA™), administered QD for 96 weeks 385 subjects randomized, 383 treated
	DRV+r (darunavir + ritonavir) [Note: appears in results tables as 'Darunavir/ritonavir'] Darunavir 800-mg tablet, in combination with ritonavir 100-mg tablet and with either FTC/TDF (supplied as TRUVADA™) or ABC/3TC (supplied as EPZICOM™ or KIVEXA™), administered QD for 96 weeks 384 subjects randomized, 383 treated
Endpoints and definitions	**Primary efficacy endpoint** Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at week 48
	Secondary efficacy endpoints • Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at week 96 • Change from baseline in $CD4^+$ T-cell count at week 48 and week 96 • Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at week 48 and week 96
	Exploratory efficacy endpoints • Time to loss of virologic response (TLOVR) • Protocol-defined virologic failure (PDVF) Viral drug resistance
	Tier 1 safety endpoint • Change from baseline in fasting LDL-C and non-HDL-C at week 48
	Tier 2 safety endpoints • Change from baseline in total cholesterol, triglycerides, and HDL-C at week 48 • Broad categories of AEs through week 48 (any AE, serious AE [SAE], drug-related AE, drug-related SAE, discontinuation due to AE) • Time to discontinuation from study due to AE AEs (preferred term and system organ class) with incidence ≥4 subjects in any treatment group • Predefined limits of change in laboratory parameters with incidence ≥4 subjects in any treatment group
	Tier 3 safety endpoints • AEs (preferred term and system organ class) and predefined limits of change in laboratory parameters with incidence <4 subjects in both treatment groups • Change from baseline in laboratory parameters and vital signs
	Pharmacokinetics endpoint • Descriptive statistics for doravirine plasma concentrations collected over 48 weeks.
Trial status	The trial is ongoing; the current report contains complete data through week 48 for the primary endpoint analysis.
Database lock	23-Nov-2016
Results and analysis	With 340 subjects planned for each treatment arm, the trial has 90% power to demonstrate the primary hypothesis that DOR (MK-1439) 100 mg QD is non-inferior to DRV+r (800 mg/100 mg) QD, each in combination with FTC/TDF or ABC/3TC, at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at week 48. This assumes a true response rate of 80% at week 48 for both arms, using the Food and Drug Administration (FDA) "Snapshot" approach.

Analysis description	**Primary Efficacy Analysis: Proportion of Subjects With HIV-1 RNA <50 copies/mL at week 48** Statistical Methodology: The primary hypothesis on antiretroviral activity was assessed by the percentage of subjects achieving plasma HIV-1 RNA <50 copies/mL at week 48 using the Abbott RealTime HIV-1 Assay. A margin of 10 percentage points was used to define non-inferiority: DOR (100 mg QD) was concluded to be non-inferior to DRV+r (800 mg/100 mg QD) if the lower bound of the two-sided 95% CI for the difference in the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48 (DOR – DRV+r) was greater than −10 percentage points. The FDA Snapshot approach was used as the primary approach to analysis with respect to the proportion of subjects with virologic response (HIV-1 RNA <50 copies/mL): all missing data were treated as failures regardless of the reason. **Secondary Efficacy Analysis: Proportion of Subjects With HIV-1 RNA <40 copies/mL at week 48** Statistical Methodology: The same methodology used for the primary endpoint was used for this endpoint. **Secondary Efficacy Analysis: Change from baseline in $CD4^+$ T-cell count at week 48** Statistical Methodology: The difference between the treatment groups in change from baseline in $CD4^+$ T-cell count was estimated at each timepoint. However, these estimates were not subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference is dependent upon the absolute value at baseline, and the magnitude and direction of the $CD4^+$ T-cell changes seen in each treatment arm. The observed failure approach was used for calculations of change from baseline in $CD4^+$ T-cell count. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.
Analysis population and timepoint description	The primary population for efficacy analyses was the Full Analysis Set (FAS) population. The FAS population consisted of all randomized subjects who received at least one dose of study drug and had baseline data for those analyses that require baseline data.

Source: Applicant Clinical Study Report P018V01MK1439
3TC = lamivudine; ABC = abacavir; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DOR = doravirine (MK-1439); DRV+r =800 mg darunavir boosted with 100 mg ritonavir; FAS = full analysis set; FDA = Food and Drug Administration; FDC = fixed dose combination; HDL-C = high-density lipoprotein cholesterol; HIV-1 = human immunodeficiency virus type-1; LDL-C = low-density lipoprotein cholesterol; PDVF = protocol-defined virologic failure; QD = once daily; SAE = serious adverse event; TDF = tenofovir disoproxil fumarate; TLOVR = time to loss of virologic response; ULN = upper limit of normal

Table 98. PN021 DRIVE-AHEAD Protocol Synopsis

Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Compound name:	MK-1439A, fixed-dose combination (FDC) oral tablet of doravirine (DOR) 100 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg
Indication	Treatment of HIV-1 infection
Protocol title	A Phase III Multicenter, Double-Blind, Randomized, Active Comparator- Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A Once-Daily Versus ATRIPLA™ Once-Daily in Treatment-Naïve HIV-1 Infected Subjects
Trial identifiers	Protocol Number: 021 Clinical Phase: 3 EudraCT Number: 2014-003382-17 Other Codes: IND Number: ClinicalTrials.gov identifier: 124997 NCT02403674
Ethics	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Trial centers	This trial was conducted at 126 sites: 33 in the United States; 9 in South Africa; 8 in Russia; 7 in the United Kingdom; 7 in Peru; 6 in Germany; 6 in Taiwan; 6 in Thailand; 5 in Portugal; 4 in Canada; 4 in Chile; 4 in Guatemala; 4 in Spain; 3 in Belgium; 3 in Colombia; 3 in Puerto Rico; 3 in Switzerland; 3 in Mexico; 2 in Australia; 2 in Denmark; 2 in Israel; 1 in Honduras; and 1 in New Zealand.
Design	This is an ongoing, phase 3, multicenter, multinational, randomized, double-blind, active-controlled trial designed to evaluate the safety and efficacy of DOR/3TC/TDF once daily (QD) (MK-1439A) compared with efavirenz (EFV)/emtricitabine (FTC)/TDF QD (ATRIPLA) in HIV-1- infected, treatment-naïve adults ≥18 years of age, with plasma HIV-1 RNA ≥1000 copies/mL at screening (within 45 days of randomization [first day of treatment]) and no known resistance to DOR or any other study drug. Safety data during the base study (through week 96 of treatment plus the 14-day follow-up period) are monitored by an external Data Monitoring Committee, with reviews approximately every 6 months. **Planned duration of main phase (base study):** 96 weeks; week 48 is primary time point. (Data from week 96 will be presented in a future report.). **Planned duration of extension phase:** 96 weeks
Objectives in base study	**Primary Objectives:** In HIV-1 positive, treatment-naïve subjects with pretreatment HIV-1 RNA ≥1000 copies/mL: 1. To evaluate the noninferior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 assay) at week 48. 2. To evaluate the safety and tolerability of MK-1439A QD compared with ATRIPLA QD as measured by the proportion of subjects with neuropsychiatric adverse events (AEs) in the following categories: dizziness, sleep disorders and disturbances, and altered sensorium. **Secondary Objectives:** In HIV-1 positive, treatment-naïve subjects with pretreatment HIV-1 RNA ≥1000 copies/mL: 1. To evaluate the safety and tolerability of MK-1439A QD compared to ATRIPLA QD as assessed by review of the accumulated safety data by week 48 and week 96. 2. To evaluate the effect of MK-1439A QD compared to ATRIPLA QD on fasting low-density lipoprotein cholesterol (LDL-C) as measured by the mean change from baseline at week 48. 3. To evaluate the effect of MK-1439A QD compared to ATRIPLA QD on fasting non–high-density lipoprotein cholesterol (HDL-C) as measured by the mean change from baseline at week 48. 4. To evaluate the safety and tolerability of MK-1439A QD compared with ATRIPLA QD as measured by the proportion of subjects with neuropsychiatric AEs in the following categories: depression and suicide/self-injury, and psychosis and psychotic disorders. 5. To evaluate the safety and tolerability of MK-1439A QD compared with ATRIPLA QD as measured by the proportion of subjects with at least one neuropsychiatric AE across the 5 categories of: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders. 6. To evaluate the safety and tolerability of MK-1439A QD compared to ATRIPLA QD as measured by the time to discontinuation from study due to an AE. 7. To evaluate the immunologic effect of MK-1439A QD compared to ATRIPLA QD as measured by the change from baseline in $CD4^+$ T-cell count at week 48 and week 96. 8. To evaluate the superior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 assay) at week 48.

	9. To evaluate the noninferior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 assay) at week 96. 10. To evaluate the superior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 assay) at week 96. 11. To evaluate the antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA below the limit of quantification (BLoQ) of the Abbott RealTime HIV-1 Assay (<40 copies/mL) at week 48 and week 96. 12. To evaluate the pharmacokinetics of MK-1439, when administered as a component of MK-1439A, and the pharmacokinetic-pharmacodynamic association, if supported by the data. **Exploratory Objectives:** In HIV-1 positive, treatment-naïve subjects with pretreatment HIV-1 RNA ≥1000 copies/mL: 1. To evaluate the antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <200 copies/mL at week 48 and week 96. 2. To evaluate the antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the Time to Loss of Virologic Response (TLOVR). 3. To assess the development of resistance to MK-1439A in subjects who have virologic failure. 4. To describe the outcomes for work productivity and activity impairment related to general health during the study in MK-1439A relative to ATRIPLA QD. 5. To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.
Selection of trial population	**Key Inclusion Criteria** • At least 18 years of age • HIV-1 infected • ARV treatment-naïve • At screening, alkaline phosphatase <3.0 x ULN, AST and ALT <5.0 X ULN, and creatinine clearance >50 mL/min by the Cockcroft-Gault equation • Clinically stable with no sign of active infection • Unlikely to become pregnant or to impregnate a partner (either not of reproductive potential or agrees to use of acceptable contraception methods) • At screening, have hemoglobin >9.0 g/dL (if female) or >10.0 g/dL (if male) **Key Exclusion Criteria** • Use of illicit drugs or recent history of abuse of illicit drugs or alcohol • History of treatment for another viral infection with an agent that is also active against HIV-1 (such as adefovir, TDF, entecavir, FTC, or 3TC) • Documented or known resistance to DOR, EFV, FTC, 3TC, and/or TDF • Use of systemic immunosuppressive therapy or immune modulators within 30 days prior to study treatment, or anticipated use during the study • Current diagnosis of acute hepatitis • Pregnant or breastfeeding, or expecting to become pregnant during the study • Evidence of decompensated or advanced liver disease, or liver cirrhosis with a Child-Pugh Class C score or a Pugh-Turcotte score >9

Hypotheses	**Primary Objectives:** MK-1439A QD is noninferior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at week 48. A margin of 10 percentage points is used to define noninferiority. MK-1439A QD is superior to ATRIPLA QD as measured by the proportion of subjects with neuropsychiatric AEs in the following categories by week 48 (superiority will be tested within category, sequentially, in the order indicated below): dizziness, sleep disorders and disturbances, and altered sensorium. **Secondary Objectives:** MK-1439A QD is superior to ATRIPLA QD as assessed by the mean change from baseline in LDL-C at week 48. MK-1439A QD is superior to ATRIPLA QD as assessed by the mean change from baseline in non-HDL-C at week 48. MK-1439A QD is superior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV- 1 Assay) at week 48. MK-1439A QD is noninferior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at week 96. A margin of 10 percentage points is used to define noninferiority. MK-1439A QD is superior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV- 1 Assay) at week 96.
Treatment groups	**DOR/3TC/TDF (MK-1439A)** DOR/3TC/TDF single oral tablet FDC containing DOR 100 mg, 3TC 300 mg, and TDF 300 mg, administered QD for 96 weeks. 368 subjects randomized, 364 treated
	EFV/FTC/TDF (ATRIPLA) EFV/FTC/TDF is a single oral tablet FDC containing EFV 600 mg, FTC 200 mg, and TDF 300 mg (equivalent to 245 mg of tenofovir disoproxil), administered QD for 96 weeks. 366 subjects randomized, 364 treated
Endpoints and definitions	**Primary efficacy endpoint** • Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at week 48
	Secondary efficacy endpoints • Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at week 48 and week 96 • Change from baseline in $CD4^+$ T-cell count at week 48 and week 96
	Exploratory efficacy endpoints • Proportion of subjects achieving plasma HIV-1 RNA level <200 copies/mL at week 48 and week 96 • Time to loss of virologic response (TLOVR) • Viral resistance for subjects who meet viral failure criteria and whose virus can be amplified.
	Tier 1 safety endpoint • Proportion of subjects with neuropsychiatric AEs in the following categories: dizziness, sleep disorders and disturbances, and altered sensorium • Change from baseline in fasting LDL-C and non-HDL-C.

	Tier 2 safety endpoint • Proportion of subjects with neuropsychiatric AEs in the following categories: depression and suicide / self-injury, and psychosis and psychotic disorders • Proportion of subjects with one or more neuropsychiatric AEs • Change from baseline in fasting lipids not classified as Tier 1 • Modified lipid-lowering therapy • Any AE • Any Serious AE (SAE) • Any Drug-Related AE • Any Serious and Drug-Related AE • Discontinuation due to AE • Specific AEs, system organ classes (SOCs), or Pre-Defined Limit of Changes (PDLCs) (incidence ≥4 subjects in at least one of the treatment groups).
	Tier 3 safety endpoint • Specific AEs, SOCs, or PDLCs (incidence <4 subjects in all of the treatment groups) Change from Baseline Results (Labs, Vital Signs).
	Pharmacokinetics endpoint Descriptive statistics for DOR plasma concentrations collected over 48 weeks.
	Patient-reported outcome endpoints Subjects to complete a Work Productivity and Activity Impairment Questionnaire (WPAI) at day 1, week 4, week 8, week 16, and week 48 (or the discontinuation visit). This patient-reported outcome questionnaire is designed to assess the quantitative impact of health conditions on loss of time and impaired productivity for functional activities such as work-for-pay, school work, and work around the house.
Trial status	The trial is ongoing; the current report contains complete data through week 48 for the primary endpoint analysis.
Database lock	26-Apr-2017 (Last subject's last visit for 48-week analysis: 20-Mar-2017.)
Results and analysis	With 340 subjects planned for each treatment arm, the trial has 90% power to demonstrate the primary hypothesis that DOR/3TC/TDF (MK-1439A) QD is noninferior to ATRIPLA (EFV/FTC/TDF) QD at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at week 48. This assumes a true response rate of 80% at week 48 for both arms, using the United States Food and Drug Administration (FDA) "snapshot" approach.
Analysis description	**Primary Efficacy Analysis: Proportion of Subjects With HIV-1 RNA <50 copies/mL at week 48** *Statistical Methodology:* The primary hypothesis on antiretroviral activity was assessed by the proportion of subjects achieving plasma HIV-1 RNA <50 copies/mL at week 48 using the Abbott RealTime HIV-1 Assay. A margin of 10 percentage points was used to specify the criterion for noninferiority: DOR/3TC/TDF was concluded to be noninferior to EFV/FTC/TDF if the lower bound of the two-sided 95% confidence interval (CI) for the difference in the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48 (DOR/3TC/TDF – EFV/FTC/TDF) was greater than −10 percentage points. The FDA Snapshot approach was used as the primary approach for this analysis: all missing data were treated as failures regardless of the reason. **Secondary Efficacy Analysis: Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at week 48 and week 96** *Statistical Methodology:* The proportion of subjects achieving HIV-1 RNA <40 copies/mL were analyzed using the same approach as described above for the proportion of subjects achieving HIV-1 RNA <50 copies/mL. **Secondary Efficacy Analysis: Change from baseline in $CD4^+$ T- cell count at week 48 and week 96** *Statistical Methodology:* The treatment difference in changes from baseline in $CD4^+$ T cell count at each time point was estimated with a key interest at week 48; however, these estimates were not subject to an absolute criterion for similarity. The clinical

	interpretation of the treatment difference was dependent upon the absolute value at baseline, and the magnitude and direction of the $CD4^+$ T-cell changes seen in each treatment arm. The observed failure approach was used for the calculations of change from baseline in $CD4^+$ T-cell count. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy. **Exploratory Efficacy Analysis: Proportion of subjects achieving plasma HIV-1 RNA level <200 copies/mL at week 48 and week 96** *Statistical Methodology:* The proportion of subjects achieving HIV-1 RNA <200 copies/mL were analyzed using the same approach as described above for the proportion of subjects achieving HIV-1 RNA <50 copies/mL. **Exploratory Efficacy Analysis: Time to Loss of Virologic Response** *Statistical Methodology:* TLOVR was estimated using Kaplan-Meier product-limit estimates and graphically displayed. Log-rank tests and Cox Proportional Hazards models were also applied to these time-to-event data.
Analysis population and time point description	Protocol-Defined Virologic Failure (PDVF) and Viral Drug Resistance *Statistical Methodology:* The number of subjects with PDVF was summarized for each treatment group. Genotypic and phenotypic resistance data from subjects with protocol-defined virologic failure were summarized. The primary population for efficacy analyses was the Full Analysis Set (FAS) population. The FAS population consisted of all randomized subjects who received at least one dose of study drug.

Source: Applicant Clinical Study Report P021V01

3TC = lamivudine; ABC = abacavir; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DOR = doravirine (MK-1439); DRV+r =800 mg darunavir boosted with 100 mg ritonavir; FAS = full analysis set; FDA = Food and Drug Administration; FDC = fixed dose combination; HDL-C = high-density lipoprotein cholesterol; HIV-1 = human immunodeficiency virus type-1; LDL-C = low-density lipoprotein cholesterol; PDVF = protocol-defined virologic failure; QD = once daily; SAE = serious adverse event; TDF = tenofovir disoproxil fumarate; TLOVR = time to loss of virologic response; ULN = upper limit of normal

17. Efficacy Assessment Additional Information and Assessment

This appendix provides further detail and information regarding the benefit data and results from the confirmatory trials PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD as well as the dose-ranging phase 2 trial PN007. This appendix also include the additional analyses regarding the prespecified safety analyses which were outlined as part of the assessment of benefit.

17.1. PN007

Trial PN007 was a two-part, phase 2 dose-ranging trial to compare the safety and efficacy of various doses of DOR to efavirenz (EFV) 600 mg in HIV-1-infected, treatment-naïve subjects.

In Part 1 of the trial, subjects were randomized in a 1:1:1:1:1 ratio to one of five treatment arms: DOR 25 mg, DOR 50 mg, DOR 100 mg, DOR 200 mg, and EFV 600 mg, all taken QD. Based on results from Part 1, a single dose of DOR was chosen for Part 2. Subjects receiving DOR at any dose in Part 1 switched to the chosen dose, DOR 100 mg, for Part 2 of the trial. Subjects randomized to EFV 600 mg in Part 1 continued to receive EFV 600 mg in Part 2. Part 2 of the trial enrolled additional subjects and randomized them in a 1:1 ratio to DOR 100 mg and EFV 600 mg. Along with the randomized study drug, subjects received Truvada QD (FTC/TDF 200/300 mg). Randomization was stratified by screening HIV-1 RNA (≤100,000 copies/mL, >100,000 copies/mL).

The efficacy endpoints for Part 1 include the proportion of subjects that achieve HIV-1 RNA <40 copies/mL at week 24 and the proportion of subjects that achieve HIV-1 RNA <50 copies/mL at week 24. The efficacy endpoints for Part 2 include the proportion of subjects that achieve HIV-1 RNA <40 copies and HIV-1 RNA <50 copies/mL, both measured at weeks 24, 48, and 96. HIV-1 RNA was quantified using the Abbott RealTime HIV-1 Assay, which has a lower limit of quantification of 40 copies/mL. The trial was not designed to conduct statistical testing on the primary efficacy endpoint. However, it did prespecify the Tier 1 safety endpoints in Part 2 for statistical testing.

All the aforementioned endpoints were assessed by calculating the difference in proportions between the DOR arm and the EFV arm. The 95% confidence interval (CI) for the difference in proportion was calculated using Miettinen's and Nurminen's method to adjust for the randomization strata.

Subject dispositions and baseline characteristics were relatively balanced across treatment arms, considering the limited sample sizes for each arm.

Given the similarity of the results and to be consistent with the other trials in the NDA submissions, only the results for the proportion of subjects that achieve HIV-1 RNA <50 copies/mL are presented. Table 99 contains the proportion of subjects that achieve HIV-1 RNA <50 copies/mL at week 24 in Part 1, as measured by the FDA-defined snapshot algorithm. The observed proportions are similar across the DOR arms and higher than the proportion in the EFV arm.

Table 99. Proportion of Subjects With HIV-1 RNA <50 Copies/mL at Week 24 in Part 1

Part 1: Week 24	DOR 25 mg (n=40)	DOR 50 mg (n=43)	DOR 100 mg (n=42)	DOR 200 mg (n=41)	EFV 600 mg (n=42)
HIV-1 RNA <50 copies/mL	32 (80.0%) (64.4%, 90.9%)	34 (79.1%) (64.0%, 90.0%)	32 (76.2%) (60.5%, 87.9%)	34 (82.9%) (67.9%, 92.8%)	29 (69.0%) (52.9%, 82.4%)
HIV-1 RNA ≥50 copies/mL	5 (12.5%)	7 (16.3%)	9 (21.4%)	5 (12.2%)	11 (26.2%)
Discontinuation: Adverse Events	1 (2.5%)	2 (4.7%)	1 (2.4%)	0	2 (4.8%)
Discontinuation: Other Reasons	2 (5.0%)	0	0	2 (4.9%)	0
Missing	0	0	0	0	0
Difference versus EFV	11.0% (-8.4%, 29.8%)	9.9% (-9.0%, 28.6%)	6.8% (-12.5%, 26.0%)	13.7% (-5.0%, 32.0%)	

DOR = doravirine (MK-1439); EFV = efavirenz

Table 100 contains the proportion of subjects that achieve HIV-1 RNA <50 copies/mL at week 24 in Part 1/2. The proportions are similar between DOR 100 mg and EFV 600 mg.

Table 100. Proportion of Subjects With HIV-1 RNA <50 Copies/mL at Week 24 in Part 1/2

Part 2: Week 24	DOR 100 mg (n=107)	EFV 600 mg (n=108)
HIV-1 RNA <50 copies/mL	83 (77.6%)	84 (77.8%)
HIV-1 RNA ≥50 copies/mL	21 (19.6%)	17 (15.7%)
Discontinuation: Adverse Events	1 (0.9%)	6 (5.6%)
Discontinuation: Other Reasons	2 (1.9%)	1 (0.9%)
Missing	0	0
Treatment Difference	-0.3% (95% CI: -11.6%, 10.9%)	

DOR = doravirine (MK-1439); EFV = efavirenz

The results generated from PN007 suggest that DOR has similar efficacy across treatment doses and that DOR 100 mg has a similar level of efficacy to EFV 600 mg.

17.2. Secondary Analyses of Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint included using the observed failure method to assess the effect of missing data and using the per-protocol (PP) set as the analysis population for the primary efficacy analysis. The PP set is a subset of the FAS that excludes subjects that commit “important deviations from the protocol that could substantially affect or confound the results of the primary efficacy endpoint(s)” (PN021 DRIVE-AHEAD Study Report).

Per-Protocol Population

Table 101 summarizes the proportion of subjects in the per-protocol (PP) population with HIV-1 RNA <50 copies/mL at week 48. As in the FAS, the lower bound of the confidence interval for the treatment difference was above the prespecified margin of -10% for both trials. The results in the PP population support the previous conclusion of NI of DOR and DOR/3TC/TDF to the active controls, particularly in the presence of minimal protocol violations.

Table 101. Proportion of Subjects in PP Population with HIV-1 RNA<50 Copies/mL At Week 48

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Per-Protocol	DOR (n=353)	DRV+r (n=341)	DOR/3TC/TDF (n=338)	EFV/FTC/TDF (n=339)
HIV-1 RNA <50 copies/mL	316 (89.5%)	298 (87.4%)	302 (89.3%)	291 (85.8%)
HIV-1 RNA ≥50 copies/mL	31 (8.8%)	32 (9.4%)	28 (8.3%)	26 (7.7%)
Discontinuation: AE or death	3 (0.8%)	10 (2.9%)	8 (2.4%)	21 (6.2%)
Discontinuation: other reasons	3 (0.8%)	0	0	0
Missing RNA	0	1 (0.3%)	0	1 (0.3%)
Treatment difference: HIV-1 RNA <50 copies/mL	2.1% 95% CI: -2.7%, 6.9%		3.5% 95% CI: -1.4%, 8.5%	

DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type-1

Observed Failure Approach

Table 102 summarizes the results of the primary efficacy analysis under the observed failure approach. While the observed treatment differences decrease in both trials and even changes direction in PN021 DRIVE-AHEAD, the lower bound of the 95% CI is greater than the NI margin of -10% for both trials. This result suggests that exclusion of missing data does not affect the NI of DOR and DOR/3TC/TDF compared to DRV+r and EFV/FTC/TDF, respectively.

Table 102. Primary Efficacy Analysis: Observed Failure

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Observed Failure	**DOR n=364**	**DRV+r n=355**	**DOR/3TC/TDF n=346**	**EFV/FTC/TDF n=331**
HIV-1 RNA <50 copies/mL	321 (88.2%)	306 (86.2%)	307 (88.7%)	294 (88.8%)
HIV-1 RNA ≥50 copies/mL	43 (11.8%)	49 (13.8%)	39 (11.3%)	37 (11.2%)
Treatment difference: HIV-1 RNA <50 copies/mL	1.9% 95.001% CI: -3.1%, 6.8%		-0.2% 95% CI: -4.9%, 4.6%	

DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type-1

17.3. Sensitivity Analyses: Misclassification of Randomization Strata

The Applicant reported that a number of subjects in both trials were randomized using the incorrect screening HIV-1 RNA stratum. In order to evaluate whether the incorrect assignments influenced the results of NI, the statistical reviewer repeated the primary efficacy analysis using the correct screening HIV-1 RNA stratum for all subjects as a sensitivity analysis. Using the correct screening HIV-1 RNA stratum does not change the primary efficacy endpoint result for subjects. However, it may affect the estimated treatment difference and its corresponding 95% CI because both account for the size of the randomization strata.

PN021 DRIVE-AHEAD also misclassified 12 subjects in the DOR/3TC/TDF arm and 13 subjects in the EFV/FTC/TDF arm into the wrong hepatitis randomization strata. However, the primary efficacy analysis did not adjust for the hepatitis randomization strata. As a result, the misclassifications for hepatitis status did not affect the primary efficacy analysis.

The incorrect assignments regarding screening HIV-1 RNA do not appear to alter the results of NI of DOR and DOR/3TC/TDF to DRV+r and EFV/FTC/TDF, respectively. Using subjects' actual screening HIV-1 RNA stratum in PN018 DRIVE-FORWARD, the observed treatment effect was 4.0% with a 95% CI of (-1.5%, 9.5%), compared to the observed treatment effect of 3.9% with a 95% CI of (-1.6%, 9.4%) in the primary efficacy analysis. In PN021 DRIVE-AHEAD, the sensitivity analysis produced a treatment effect of 3.5% with a 95% CI of (-2.0%, 9.0%), the same result as in the primary analysis.

17.4. Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints included achieving HIV-1 RNA <40 copies/mL, achieving HIV-1 RNA <200 copies/mL, and change from baseline in $CD4^+$ cell count at week 48, all measured at week 48. The analyses of the RNA-related secondary endpoints produced consistent results to the primary efficacy analysis.

Change from Baseline in $CD4^+$ Cell Count at Week 48

In addition to analyzing viral suppression using HIV-1 RNA, the Applicant prespecified the change from baseline in $CD4^+$ T-cell count at week 48 as a secondary efficacy endpoint in both trials. Additionally, the Applicant also presented results for the change from baseline in $CD4^+$ T-cell count at weeks 8 and 24. The analysis was conducted in the FAS but used the observed failure approach so the analysis includes only subjects with $CD4^+$ T-cell counts at baseline and at the specified time point. The treatment difference was modeled using ANCOVA and adjusted for baseline $CD4^+$ T-cell count. The review of the Applicant's analysis produced similar results as shown in Table 103.

Since neither of the 95% CIs for week 48 changes from baseline include zero, they do not provide evidence of a potentially statistically significant difference in the week 48 change in $CD4^+$ T-cell count from baseline between the DOR-containing arm and the active control. In addition, the estimated treatment differences at weeks 8 and 24 do not suggest a relationship between time and treatment difference.

Table 103. Change from Baseline in CD4⁺ Cell Count at Week 48

PN018 DRIVE-FORWARD							
	DOR			DRV+r			
Week	N	Baseline Mean	Mean Change from Baseline	N	Baseline Mean	Mean Change from Baseline	Treatment Difference
8	375	430.1	101.0 (85.4, 116.6)	372	412.8	106.6 (93.9, 119.4)	-5.6 (-25.7, 14.5)
24	374	431.4	171.9 (152.3, 191.5)	364	410.0	160.3 (144.8, 175.8)	11.6 (-13.4, 36.6)
48	363	433.2	192.7 (171.5, 213.9)	353	409.6	185.6 (167.5, 203.6)	7.1 (-20.7, 34.9)
PN021 DRIVE-AHEAD							
	DOR/3TC/TDF			EFV/FTC/TDF			
Week	N	Baseline Mean	Mean Change from Baseline	N	Baseline Mean	Mean Change from Baseline	Treatment Difference
8	359	434.8	125.7 (111.6, 139.8)	347	414.5	97.3 (83.3, 111.3)	28.4 (8.6, 48.2)
24	357	433.5	158.6 (142.0, 175.3)	338	414.8	155.0 (138.2, 171.7)	3.6 (-20.0, 27.2)
48	344	433.9	198.4 (180.2, 216.7)	329	414.3	188.4 (169.5, 207.2)	10.1 (-16.2, 36.3)

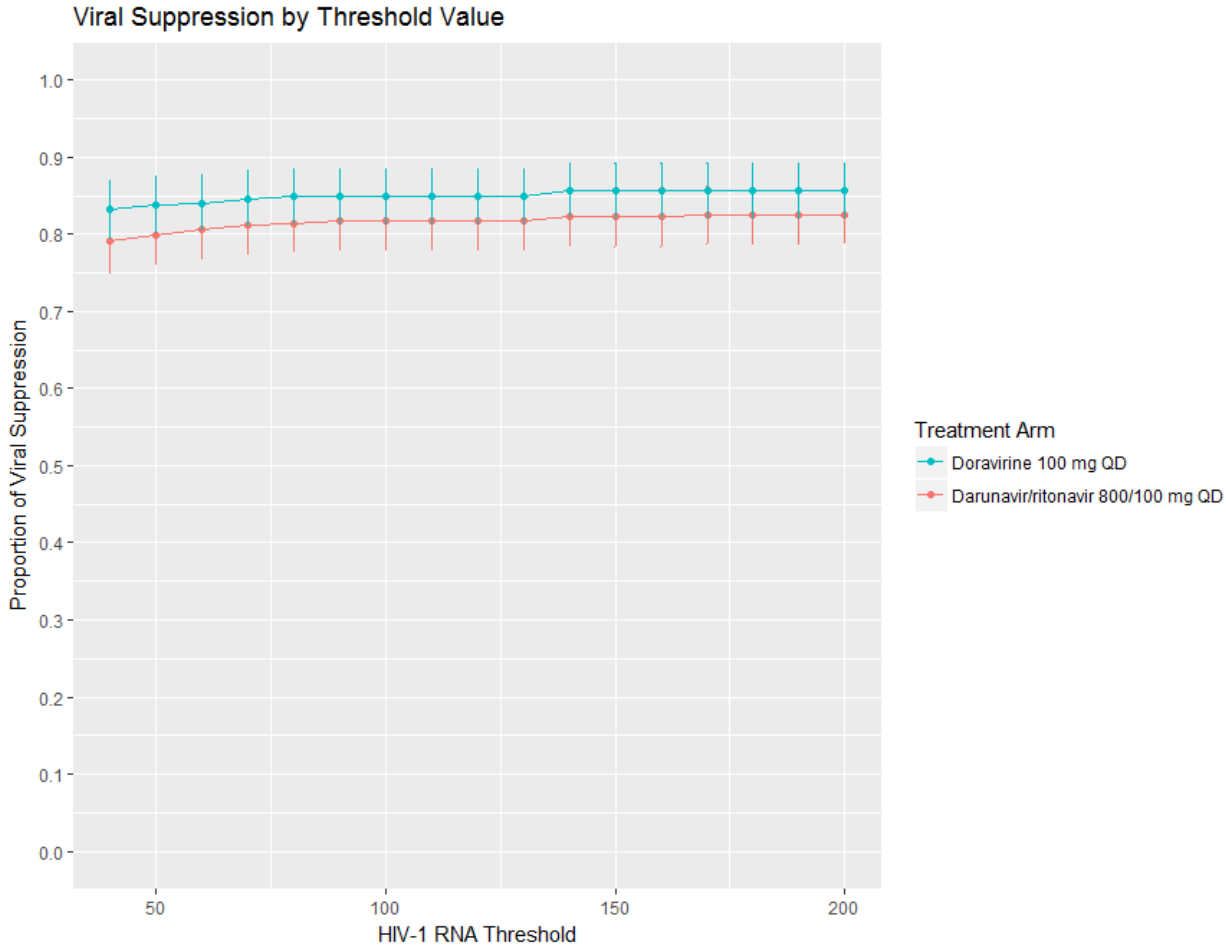
DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate

Additional Analyses Conducted by Statistical Reviewer

Proportion of Viral Suppression Across Threshold Values

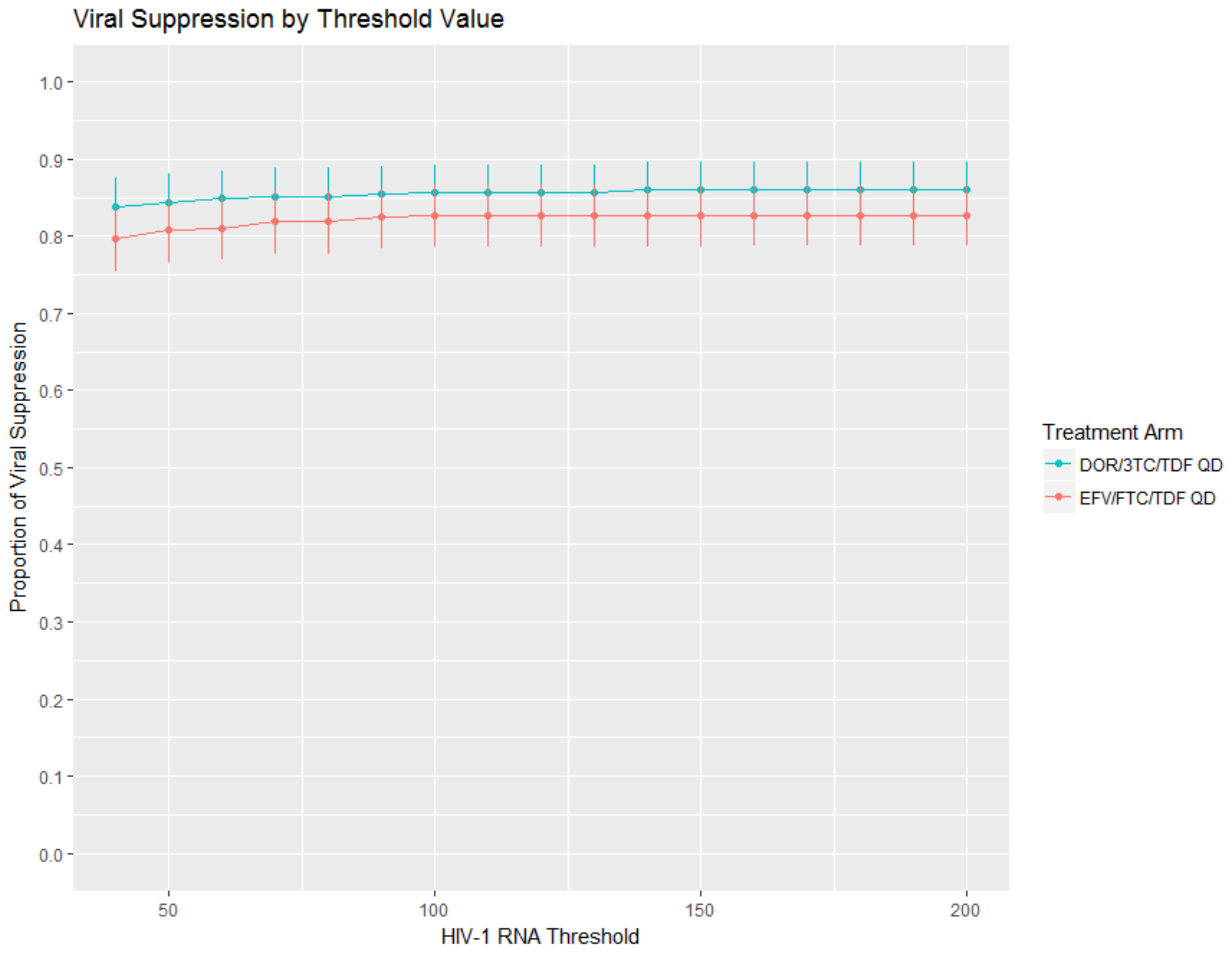
Figure 4 depicts the proportion of subjects in each treatment arm that achieve viral suppression, defined using various thresholds, in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, respectively. In both trials, the percentage of subjects in the DOR-containing arm that achieved viral suppression was higher than the percentage in the active control arm across the chosen thresholds, all multiples of ten from 40 to 200. While the treatment difference and corresponding 95% CI was not calculated for every threshold depicted in the figures, the trends in the figures suggest that the evidence of efficacy for DOR and DOR/3TC/TDF is consistent across the various thresholds of viral suppression.

Figure 4. Proportion of Subjects Achieving Viral Suppression by HIV-1 Threshold and Treatment Arm



Source: Data from PN018

Figure 5. Proportion of Subjects Achieving Viral Suppression by HIV-1 Threshold and Treatment Arm



Source: Data from PN021
DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate

17.5. Subgroup Analyses

The Applicant conducted subgroup analyses for the primary efficacy endpoint of HIV-1 RNA <50 copies/mL at week 48 and the secondary efficacy endpoints of HIV-1 RNA <40 copies/mL and week 48 change from baseline in $CD4^+$ T-cell count. The statistical reviewer repeated the subgroup analyses. In the statistical reviewer's analyses, three of the subgroups were redefined:

- Race (Asian, black or African-American, white, other)
- Geographic region (United States, other)
- Baseline $CD4^+$ T-cell count ($\leq$200 cells/mm^3, >200 cells/mm^3)

Because the results of the analyses for HIV-1 RNA <50 copies/mL and HIV-1 RNA <40 copies/mL are very similar, only the results for HIV-1 RNA <50 copies/mL will be presented.

The Applicant used the observed failure approach, while the statistical reviewer used the FDA-defined snapshot algorithm to define success for HIV-1 RNA <50 copies/mL. In addition, the

statistical reviewer conducted interaction testing using the Breslow-Day test to assess whether efficacy may differ between values of a demographic or disease characteristic.

HIV-1 RNA <50 copies/mL

Table 104 presents the subgroup analyses by demographic characteristics and treatment arm for the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48. Table 105 also presents the subgroup analyses by baseline disease characteristics and treatment arm for the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48.The tables also present the treatment difference between the treatment arms and the corresponding 95% CI.

Several of the subgroups had sample sizes too small to provide stratum-adjusted results. Thus, Table 104 and Table 105 provide unadjusted results. The reliance on unadjusted results is more prevalent in PN018 DRIVE-FORWARD because its analyses accounted for four randomization strata, compared to two randomization strata for PN021 DRIVE-AHEAD. In addition, several subgroups had zero subjects with screening HIV-1 RNA >100,000 copies/mL and who used ABC/3TC as the NRTI background therapy. The lack of such subjects in those subgroups may affect the generalizability of the results.

The Breslow-Day test did not produce any evidence of differing treatment effects between the values of the demographic variables. According to the test, the treatment effect of the DOR-containing treatment on viral suppression compared to the active control appears to be consistent across the values of the demographic variables.

All conducted subgroup analyses for this review are considered exploratory. However, among subjects with baseline $CD4^+$ T-cell count $\leq$200 cells/mm^3, the observed treatment differences between the DOR-containing arm and the active control arm was inconsistent between the two confirmatory trials. In PN018 DRIVE-FORWARD, the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48 was higher for the DOR arm than the DRV+r arm. However, in PN021 DRIVE-AHEAD, the proportion subjects with HIV-1 RNA <50 copies/mL was lower in the DOR/3TC/TDF arm than the EFV/FTC/TDF arm.

The Breslow-Day test to assess the treatment effect of the DOR-containing treatment compared to the active control between baseline $CD4^+$ T-cell count $\leq$200 cells/mm^3 and >200 cells/mm^3 produced p-values of 0.167 in PN018 DRIVE-FORWARD and 0.043 in PN021 DRIVE-AHEAD. Therefore, the efficacy of DOR according to baseline $CD4^+$ T-cell count may warrant further exploration in future trials to determine if any consistent trends exist.

Table 104. Subgroup Analyses by Demographic Characteristic and Treatment Arm

		PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Characteristic		**DOR**	**DRV+r**	**DOR/3TC/TDF**	**EFV/FTC/TDF**
Age					
<65 years	n/N	319/381 (83.7%)	302/379 (79.9%)	305/362 (84.3%)	293/362 (80.9%)
	Diff	3.8% (-1.7%, 9.3%)		3.3% (-2.2%, 8.8%)	
≥65 years	n/N	2/2 (100%)	3/4 (75.0%)	2/2 (100%)	1/2 (50.0%)
	Diff	25.0% (-64.6%, 100%)*		50.0% (-72.2%, 100%)*	
Gender					
Male	n/N	269/319 (84.3%)	268/326 (82.2%)	257/305 (84.3%)	250/311 (80.4%)
	Diff	2.1% (-3.7%, 8.0%)		3.7% (-2.3%, 9.6%)	
Female	n/N	52/64 (81.4%)	38/57 (66.7%)	50/59 (84.7%)	44/53 (83.0%)
	Diff	14.6% (-1.2%, 30.3%)*		1.2% (-13.1%, 15.5%)	
Race					
White	n/N	244/280 (87.1%)	232/280 (82.9%)	149/177 (84.2%)	138/170 (81.2%)
	Diff	4.1% (-1.9%, 10.0%)		3.3% (-4.4%, 11.1%)	
Black	n/N	61/86 (70.9%)	63/88 (71.6%)	54/67 (80.6%)	51/68 (75.0%)
	Diff	-0.3% (-14.3%, 13.6%)		5.9% (-8.2%, 20.1%)	
Asian	n/N	7/7 (100%)	6/7 (85.7%)	56/59 (94.9%)	54/65 (83.1%)
	Diff	14.3% (-22.5%, 51.0%)*		12.3% (0.8%, 23.8%)	
Other	n/N	9/10 (90.0%)	5/8 (62.5%)	48/61 (78.7%)	51/61 (83.6%)
	Diff	27.5% (-15.0%, 70.0%)*		-4.9% (-19.2%, 9.5%)	
Ethnicity					
Non-Hispanic	n/N	233/284 (82.0%)	230/290 (79.3%)	200/236 (84.7%)	189/238 (79.4%)
	Diff	2.8% (-3.8%, 9.3%)		5.0% (-1.9%, 11.9%)	
Hispanic	n/N	82/93 (88.2%)	70/86 (81.4%)	105/126 (83.3%)	101/120 (84.2%)
	Diff	6.5% (-4.7%, 17.6%)		-0.5% (-9.9%, 8.9%)	
Geographic region					
United States	n/N	99/131 (75.6%)	102/135 (75.6%)	67/88 (76.1%)	63/87 (72.4%)
	Diff	0.0% (-10.4%, 10.4%)*		4.8% (-7.9%, 17.5%)	
Other	n/N	222/252 (88.1%)	204/248 (82.3%)	240/276 (87.0%)	231/277 (83.4%)
	Diff	5.8% (-0.5%, 12.1%)		3.4% (-2.5%, 9.4%)	

DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate

* Result is unadjusted for randomization strata

Table 105. Subgroup Analyses by Disease Characteristic and Treatment Arm

		PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Characteristic		**DOR**	**DRV+r**	**DOR/3TC/TDF**	**EFV/FTC/TDF**
Baseline HIV-1 RNA					
≤100,000 copies/mL	n/N	257/300 (85.7%)	250/308 (81.2%)	251/291 (86.3%)	235/282 (83.3%)
	Diff	4.5% (-1.5%, 10.5%)		2.9% (-3.0%, 8.8%)	
>100,000 copies/mL	n/N	64/83 (77.1%)	55/74 (74.3%)	56/73 (76.7%)	59/82 (72.0%)
	Diff	2.8% (-10.8%, 16.4%)*		5.6% (-8.3%, 19.5%)	
Screening HIV-1 RNA					
≤100,000 copies/mL	n/N	249/290 (85.9%)	233/289 (80.6%)	241/275 (87.6%)	229/274 (83.6%)
	Diff	5.3% (-0.9%, 11.4%)		4.1% (-1.8%, 10.0%)	
>100,000 copies/mL	n/N	72/93 (77.4%)	73/94 (77.7%)	66/89 (74.2%)	65/90 (72.2%)
	Diff	-0.2% (-12.4%, 12.0%)		1.9% (-11.2%, 15.0%)	
NRTI background therapy					
FTC/TDF	n/N	278/333 (83.5%)	270/335 (80.6%)	N/A	
	Diff	2.9% (-3.0%, 8.7%)			
ABC/3TC	n/N	43/50 (86.0%)	36/48 (75.0%)	N/A	
	Diff	11.0% (-5.3%, 27.2%)			
Baseline $CD4^+$ T-cell count					
≤200 cells/mm^3	n/N	34/42 (81.0%)	44/67 (65.7%)	29/44 (65.9%)	36/46 (78.3%)
	Diff	15.3% (-1.5%, 32%)*		-12.1% (-31.1%, 6.9%)	
>200 cells/mm^3	n/N	287/341 (84.2%)	262/316 (82.9%)	278/320 (86.9%)	258/318 (81.1%)
	Diff	1.3% (-4.4%, 7.1%)		5.7% (0.0%, 11.3%)	
HIV-1 subtype					
Clade B	n/N	224/266 (84.2%)	222/272 (81.6%)	195/232 (84.1%)	202/253 (79.8%)
	Diff	2.2% (-4.3%, 8.7%)		4.4% (-2.4%, 11.2%)	
Non-Clade B	n/N	97/117 (82.9%)	84/111 (75.7%)	112/132 (84.8%)	92/111 (82.9%)
	Diff	6.2% (-4.6%, 16.9%)		1.7% (-7.8%, 11.2%)	
Hepatitis B and/or C co-infection (actual)					
Yes	n/N	9/11 (81.8%)	13/18 (72.2%)	8/11 (72.7%)	8/9 (88.9%)
	Diff	9.6% (-23.5%, 42.7%)*		-16.2% (-53.7%, 21.3%)*	
No	n/N	312/372 (83.9%)	293/365 (80.3%)	299/353 (84.7%)	286/355 (80.6%)
	Diff	3.6% (-2.0%, 9.2%)		4.0% (-1.5%, 9.6%)	

3TC = lamivudine; ABC = abacavir; DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type-1; NRTI = nucleos(t)ide reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate

$CD4^+$ T-cell Count

For the week 48 change from baseline in $CD4^+$ T-cell count, the statistical reviewer obtained results consistent with the Applicant's results. Only black subjects in PN021 DRIVE-AHEAD had a treatment difference with a 95% CI that excluded zero. Table 106 summarizes the results of the subgroup analysis in black subjects enrolled in PN021 DRIVE-AHEAD. A possible explanation for this finding is lower baseline mean $CD4^+$ T-cell count for black subjects compared to non-black subjects, particularly in the EFV/FTC/TDF arm. However, for reasons previously mentioned, this analysis is considered exploratory and was not included in the labeling for DOR/3TC/TDF.

Table 106. PN021 DRIVE-AHEAD: Black or African-American Subjects

	DOR/3TC/TDF			EFV/FTC/TDF			
Week	N	Baseline Mean	Mean Change from Baseline (CI)	N	Baseline Mean	Mean Change from Baseline (CI)	Treatment Difference (CI)
48	63	356.8	196.6 (152.3, 241.0)	63	370.9	136.0 (98.0, 174.0)	60.6 (2.8, 118.4)

DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate

17.6. Analyses of Prespecified Safety Endpoints to Assess the Benefit of DOR

17.6.1. Lipid Analyses

The week 48 lipid sensitivity analyses excluded subjects on baseline lipid-lowering agents, and subjects initiating lipid-lowering therapy postbaseline had their last fasted on-treatment valued carried forward (see section II.6.4.1). The sensitivity analysis eliminates lipid-lowering therapy as a potential confounder of the treatment effect on the lipid-related endpoints. Table 107 summarizes Phase 3 trial subjects with baseline and on-treatment lipid-lowering therapy.

Table 107. Baseline and On-Treatment Lipid-Lowering Therapy, Week 48

	n (%)			
	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Medication Class	DOR & NRTIs N=383	DRV+r + NRTIs N=383	DOR/3TC/TDF N=364	EFV/FTC/TDF N=364
Any baseline lipid-lowering therapy	12 (3%)	14 (4%)	15 (4%)	10 (3%)
Any on-treatment lipid-lowering therapy	6 (2%)	4 (1%)	3 (1%)	8 (2%)

Source: ISS ADLPD, CMPLUS, and ADSL datasets, PN018 and PN02
DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NRTI = nucleos(t)ide reverse transcriptase inhibitor

Table 108. Comparison of FAS and Labeling Population for Lipid Analysis in PN018 DRIVE-FORWARD

	FAS Population		Labeling Population	
PN018 DRIVE-FORWARD	**DOR (n=383)**	**DRV+r (n=383)**	**DOR (n=320)**	**DRV+r (n=311)**
Sex				
Male	319 (83.3%)	326 (85.1%)	263 (82.2%)	267 (85.9%)
Female	64 (16.7%)	57 (14.9%)	57 (17.8%)	44 (14.1%)
Age (years)				
Mean (SD)	34.8 (10.5)	35.7 (10.7)	34.1 (10.1)	35.3 (10.4)
Median	33	34	32	34
Min, max	18, 68	18, 69	18, 63	18, 69
Age Group				
<65 years	381 (99.5%)	379 (99.0%)	320 (100%)	309 (99.4%)
≥65 years	2 (0.5%)	4 (1.0%)	0	2 (0.6%)
Race				
White	280 (73.1%)	280 (73.1%)	237 (74.1%)	232 (74.6%)
Black or African American	86 (22.5%)	88 (23.0%)	69 (21.6%)	67 (21.5%)
Asian	7 (1.8%)	7 (1.8%)	4 (1.2%)	6 (1.9%)
American Indian or Alaska Native	3 (0.8%)	3 (0.8%)	3 (0.9%)	3 (1.0%)
Native Hawaiian or other Pacific Islander	1 (0.3%)	2 (0.5%)	1 (0.3%)	2 (0.6%)
Other	6 (1.6%)	3 (0.8%)	6 (1.9%)	1 (0.3%)
Ethnicity				
Hispanic or Latino	93 (24.3%)	86 (22.5%)	80 (25.0%)	70 (22.5%)
Not Hispanic or Latino	284 (74.2%)	290 (75.7%)	234 (73.1%)	236 (75.9%)
Not Reported or Unknown	6 (1.6%)	7 (1.8%)	6 (1.9%)	5 (1.6%)
Region				
United States	131 (34.2%)	135 (35.2%)	104 (32.5%)	98 (31.5%)
Canada	9 (2.3%)	11 (2.9%)	8 (2.5%)	8 (2.6%)
Latin America	38 (9.9%)	33 (8.6%)	36 (11.2%)	30 (9.6%)
Europe	170 (44.4%)	179 (46.7%)	146 (45.6%)	155 (49.8%)
Asia/Pacific	12 (3.1%)	3 (0.8%)	7 (2.2%)	2 (0.6%)
Australia	12 (3.1%)	3 (0.8%)	7 (2.2%)	2 (0.6%)
Africa	23 (6.0%)	22 (5.7%)	19 (5.9%)	18 (5.8%)
Baseline LDL-C count				
N (%)	326	318	324	312
Mean (SD)	91.1 (28.6)	91.8 (30.4)	91.1 (28.5)	91.2 (30.1)
Median	87.5	88.0	87.5	88.0
Min, Max	25, 184	30, 228	25, 184	30, 228
Baseline non-HDL-C count				
N (%)	329	325	320	311
Mean (SD)	113.3 (34.3)	114.4 (35.0)	113.6 (34.3)	114.5 (34.4)
Median	109	110	109	110
Min, Max	36, 302	40, 270	36, 302	40, 270

DOR = doravirine (MK-1439); DRV+r =800 mg darunavir boosted with 100 mg ritonavir; FAS = full analysis set; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation

Table 109. Comparison of FAS and Labeling Population for Lipid Analysis in PN021 DRIVE-AHEAD

	FAS Population		Labeling Population	
PN021 DRIVE-AHEAD	**DOR/3TC/TDF (n=364)**	**EFV/FTC/TDF (n=364)**	**DOR/3TC/TDF (n=320)**	**EFV/FTC/TDF (n=307)**
Sex				
Male	305 (83.8%)	311 (85.4%)	272 (85.0%)	263 (85.7%)
Female	59 (16.4%)	53 (14.6%)	48 (15.0%)	44 (14.3%)
Age (years)				
Mean (SD)	33.6 (10.5)	32.7 (9.9)	33.3 (10.1)	31.9 (9.3)
Median	32	30	31	30
Min, max	18, 70	18, 69	18, 68	18, 69
Age Group				
<65 years	362 (99.5%)	362 (99.5%)	319 (99.7%)	306 (99.7%)
≥65 years	2 (0.5%)	2 (0.5%)	1 (0.3%)	1 (0.3%)
Race				
White	177 (48.6%)	170 (46.7%)	153 (47.8%)	146 (47.6%)
Black or African American	67 (18.4%)	68 (18.7%)	57 (17.8%)	49 (16.0%)
Asian	59 (16.2%)	65 (17.9%)	57 (17.8%)	59 (19.2%)
American Indian or Alaska Native	10 (2.7%)	6 (1.6%)	7 (2.2%)	6 (2.0%)
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	51 (14.0%)	55 (15.1%)	46 (14.4%)	47 (15.3%)
Ethnicity				
Hispanic or Latino	126 (34.6%)	120 (33.0%)	113 (35.3%)	107 (34.9%)
Not Hispanic or Latino	236 (64.8%)	238 (65.4%)	206 (64.4%)	196 (63.8%)
Not Reported or Unknown	2 (0.6%)	6 (1.6%)	1 (0.3%)	4 (1.3%)
Region				
United States	88 (24.2%)	87 (23.9%)	71 (22.2%)	66 (21.5%)
Canada	3 (0.8%)	7 (1.9%)	3 (0.9%)	5 (1.6%)
Latin America	89 (24.5%)	87 (23.9%)	83 (25.9%)	77 (25.1%)
Europe	88 (24.2%)	94 (25.8%)	75 (23.4%)	82 (26.7%)
Asia/Pacific	59 (16.2%)	62 (17.0%)	56 (17.5%)	55 (17.9%)
Australia	2 (0.5%)	1 (0.3%)	1 (0.3%)	0
Africa	37 (10.2%)	27 (7.4%)	32 (10.0%)	22 (7.2%)
Baseline LDL count				
N (%)	330	305	317	298
Mean (SD)	92.0 (32.5)	90.7 (30.3)	91.7 (30.8)	91.3 (30.0)
Median	88	89	88	89
Min, Max	9, 240	18, 183	9, 214	18, 183
Baseline non-HDL count				
N (%)	333	314	320	307
Mean (SD)	115.2 (34.7)	114.8 (33.3)	114.7 (33.4)	115.3 (33.2)
Median	112	113	112	113
Min, Max	13, 267	39, 216	13, 245	39, 216

DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; FAS = full analysis set; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation

17.6.2. Neuropsychiatric Event Analyses

PN021

The PN021 DRIVE-AHEAD predefined NPE preferred term list is provided below, using MedDRA version 19.1, by category:

Dizziness: Dizziness

Sleep Disorders and Disturbances: Behavioral insomnia of childhood; hyposomnia; initial insomnia; insomnia; middle insomnia; terminal insomnia; breathing-related sleep disorder; dyssomnia; hypnagogic hallucination; hypnopompic hallucination; sleep attacks; abnormal dreams; abnormal sleep-related event; confusional arousal; loss of dreaming; nightmare; parasomnia; rapid eye movements sleep abnormal; sleep inertia; sleep sex; sleep talking; sleep terror; sleep-related eating disorder; somnambulism; sleep disorder due to a general medical condition; sleep disorder due to general medical condition, hypersomnia type; sleep disorder due to general medical condition, insomnia type; sleep disorder due to general medical condition, mixed type; sleep disorder due to general medical condition, parasomnia type; hypersomnia-bulimia syndrome; sleep disorder; sopor; hypersomnia related to another mental condition; insomnia related to another mental condition; rapid eye movement sleep behavior disorder

Altered Sensorium: Altered state of consciousness; apallic syndrome; consciousness fluctuating; depressed level of consciousness; hyperglycemic unconsciousness; lethargy; loss of consciousness; neonatal oversedation; postinjection delirium sedation syndrome; postictal state; preictal state; sedation; somnolence; somnolence neonatal; stupor; syncope; hypoglycemic unconsciousness; psychogenic pseudosyncope; disturbance in attention

Depression and Suicide/Self Injury: Activation syndrome; adjustment disorder with depressed mood; adjustment disorder with mixed anxiety and depressed mood; agitated depression; anhedonia; antidepressant therapy; childhood depression; decreased interest; depressed mood; depression; depression postoperative; depressive symptom; dysphoria; electroconvulsive therapy; feeling guilty; feeling of despair; feelings of worthlessness; major depression; menopausal depression; post stroke depression; postictal depression; completed suicide; depression suicidal; intentional overdose; intentional self-injury; poisoning deliberate; self-injurious ideation; suicidal behavior; suicidal ideation; suicide attempt; helplessness; perinatal depression; persistent depressive disorder; Columbia suicide severity rating scale abnormal; suicide threat

Psychosis and Psychotic Disorders: Acute psychosis; alcoholic psychosis; Alice in Wonderland syndrome; brief psychotic disorder with marked stressors; brief psychotic disorder without marked stressors; brief psychotic disorder, with postpartum onset; Charles Bonnet syndrome; childhood psychosis; Clang associations; Cotard's syndrome; delusion; delusion of grandeur; delusion of reference; delusion of replacement; delusional disorder, erotomanic type; delusional disorder, grandiose type; delusional disorder, jealous type; delusional disorder, mixed type; delusional disorder, persecutory type; delusional disorder, somatic type; delusional disorder, unspecified type; delusional perception; dementia of the Alzheimer's type, with delusions; depressive delusion; derailment; epileptic psychosis; erotomanic delusion; flight of ideas; hallucination; hallucination, auditory; hallucination, gustatory; hallucination, olfactory; hallucination, synaesthetic; hallucination, tactile; hallucination, visual; hallucinations, mixed; hypnagogic hallucination; hypnopompic

hallucination; hysterical psychosis; ideas of reference; illusion; jealous delusion; loose associations; neologism; paranoia; paranoid personality disorder; Parkinson's disease psychosis; paroxysmal perceptual alteration; persecutory delusion; postictal psychosis; postinjection delirium sedation syndrome; posturing; psychosis postoperative; psychotic behavior; psychotic disorder; psychotic disorder due to a general medical condition; reactive psychosis; rebound psychosis; schizoaffective disorder; schizoaffective disorder bipolar type; schizoaffective disorder depressive type; schizophrenia; schizophreniform disorder; schizotypal personality disorder; senile psychosis; shared psychotic disorder; somatic delusion; somatic hallucination; substance-induced psychotic disorder; tangentiality; thought blocking; thought broadcasting; thought insertion; thought withdrawal; transient psychosis; waxy flexibility; mixed delusion; neuroleptic-induced deficit syndrome

Individual PTs within each PN021 DRIVE-AHEAD NPE category are listed in Table 110. This analysis highlights the PTs that drove the NPE category results. PTs with observed treatment differences >2% between the DOR/3TC/TDF and EFV/FTC/TDF groups are bolded and include:

- Sleep Disorders and Disturbances: abnormal dreams, insomnia
- Altered Sensorium: somnolence

Note that the Dizziness category was defined by the single MedDRA PT ‘Dizziness’.

Table 110. Neuropsychiatric AE Testing by Preferred Term in PN021 DRIVE-AHEAD, Week 48

	n (%)	
AEDECOD	**DOR/3TC/TDF N=364**	**EFV/FTC/TDF N=364**
Dizziness	32 (8.8%)	135 (37.1%)
Sleep Disorders and Disturbances		
Abnormal dreams	17 (4.7%)	42 (11.5%)
Insomnia	19 (5.2%)	32 (8.8%)
Hyposomnia	0	1 (<1%)
Initial insomnia	0	1 (<1%)
Nightmare	12 (3.3%)	17 (4.7%)
Sleep disorder	4 (1.1%)	11 (3.0%)
Somnambulism	1 (<1%)	0
Altered Sensorium		
Somnolence	12 (3.3%)	27 (7.4%)
Altered state of consciousness	0	1 (<1%)
Lethargy	2 (<1%)	0
Syncope	2 (<1%)	2 (<1%)
Depression and Suicide/self-injury		
Adjustment disorder with depressed mood	1 (<1%)	2 (<1%)
Completed suicide	0	1 (<1%)
Depressed mood	4 (1.1%)	7 (1.9%)
Depression	8 (2.2%)	12 (3.3%)
Intentional overdose	0	1 (<1%)
Major depression	1 (<1%)	0
Persistent depressive disorder	1 (<1%)	0
Suicidal ideation	1 (<1%)	1 (<1%)
Suicide attempt	0	1 (<1%)

	n (%)	
AEDECOD	**DOR/3TC/TDF N=364**	**EFV/FTC/TDF N=364**
Psychosis and Psychotic Disorders		
Hallucination	1 (<1%)	3 (<1%)
Paranoia	0	1 (<1%)

Source: JReview Output, ISS ADAM ANCNS Dataset, PN021
DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate

Most NPEs through week 48 were mild or moderate in severity: DOR/3TC/TDF 97% (83/86) and EFV/FTC/TDF 96% (198/207). Week 48 NPE SAEs were reported in only one DOR-treated subject (subject (b) (6), sleep disorders and disturbances) and three EFV-treated subjects [depression and suicide/self-injury (two), altered sensorium]. NPEs led to treatment discontinuation in 1% of subjects in both the DOR/3TC/TDF (two subjects: subject (b) (6), sleep disorders and disturbances; subject (b) (6) depression and suicide/self-injury) and EFV/FTC/TDF groups [five subjects: sleep disorders and disturbances (two), depression and suicide/self-injury (two), sleep disorders and disturbances/dizziness].

Most NPEs in PN021 DRIVE-AHEAD occurred within the first 4 weeks [DOR/3TC/TDF 72% (62/86), EFV/FTC/TDF 86% (177/207)] with median onset of 6 and 2 days in the DOR/3TC/TDF and EFV/FTC/TDF arms, respectively (Table 111). Among the five NPE categories, median onset for both treatment groups was less than one week except for depression and suicide/self-injury (median onset 87 and 93.5 days in the DOR/3TC/TDF and EFV/FTC/TDF arms, respectively).

Table 111. Neuropsychiatric AEs Onset in PN021 DRIVE-AHEAD, Week 48

Adverse Event Category	DOR/3TC/TDF	EFV/FTC/TDF
Any Subject with NPE - N	86	207
Median onset – days (min, max)	6 (1, 325)	2 (1, 367)
Occurred by week 4* - n (%)	62 (72.1%)	177 (85.5%)
Dizziness - N	32	135
Median onset – days (min, max)	4 (1, 251)	2 (1, 310)
Occurred by week 4* - n (%)	26 (81.3%)	123 (91.1%)
Sleep disorders and disturbances - n	44	93
Median onset – days (min, max)	5 (1, 316)	2 (1, 345)
Occurred by week 4* - n (%)	37 (84.1%)	82 (88.2%)
Altered sensorium – n	16	30
Median onset – days (min, max)	5 (1, 191)	2 (1, 140)
Occurred by week 4* - n (%)	13 (81.3%)	24 (80.0%)
Depression and suicide/self-injury - n	15	24
Median onset – days (min, max)	87 (2, 325)	93.5 (1, 367)
Occurred by week 4* - n (%)	4 (26.7%)	15 (62.5%)
Psychosis and psychotic disorders - n	1	4
Median onset – days (min, max)	2	1.5 (1, 258)
Occurred by week 4* - n (%)	1 (100%)	4 (100%)

Source: JReview and JMP Outputs, ISS ADAM ANCNS and ADSL datasets, PN021
AE = adverse event; DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NPE = neuropsychiatric event
* Defined as NPE onset by day 42 (the ISS SAP upper limit of the week 4 window)

Additional PN021 DRIVE-AHEAD NPE analyses support the conclusion DOR/3TC/TDF has a lower proportion of subjects experiencing NPEs compared with EFV/FTC/TDF (Table 112). The

proportion of subjects with overall NPEs observed through week 4, defined as NPE onset by day 42 (the ISS SAP upper limit of the week 4 window), was 17% in the DOR/3TC/TDF arm and 49% in the EFV/FTC/TDF arm. The proportion of subjects with overall NPEs at week 48, defined as NPEs present between day 211 and day 378 (the ISS SAP lower and upper limits of the week 36 and week 48 windows, respectively), was 12% in the DOR/3TC/TDF arm group and 22% in the EFV/FTC/TDF arm. The numerically lower NPE proportion at week 48 compared with week 4 for both treatment arms, overall and for most NPE categories, suggest these defined NPEs may improve with continued therapy.

Table 112. Neuropsychiatric AE Analyses in PN021 DRIVE-AHEAD, Proportion up to Week 4* and Proportion at Week 48^

	n (%)	
Adverse Event Category	**DOR/3TC/TDF N=364**	**EFV/FTC/TDF N=364**
Week 4*: Any NPE	62 (17.0%)	177 (48.6%)
Dizziness	25 (6.9%)	121 (33.2%)
Sleep Disorders and Disturbances	32 (8.8%)	76 (20.9%)
Altered Sensorium	12 (3.3%)	24 (6.6%)
Depression and Suicide/self-injury	2 (<1%)	9 (2.5%)
Psychosis and Psychotic Disorders	1 (<1%)	3 (<1%)
Week 48^: Any NPE	44 (12.1%)	81 (22.3%)
Dizziness	11 (3.0%)	35 (9.6%)
Sleep Disorders and Disturbances	23 (6.3%)	38 (10.4%)
Altered Sensorium	6 (1.6%)	9 (2.5%)
Depression and Suicide/self-injury	11 (3.0%)	15 (4.1%)
Psychosis and Psychotic Disorders	0	1 (<1%)

Source: JReview and JMP Outputs, ISS ADAM ANCNS and ADSL datasets, PN021
AE = adverse event; DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NPE = neuropsychiatric event
* Defined as NPE onset by day 42 (the ISS SAP upper limit of the week 4 window)
^ Defined as NPEs present between day 211 and day 378 (the ISS SAP lower and upper limits of the week 36 and week 48 windows, respectively)

Hallmark NNRTI toxicities include depression and suicidal events as well as sleep disorder events; focused PN021 DRIVE-AHEAD analyses were performed to examine the relationship between having a psychiatric medical history and these NPE categories. As presented below, less than 50% of subjects reporting either depression and suicide/self-injury NPEs or sleep disorder and disturbances NPEs had a history of psychiatric illnesses and no clear imbalance in AEs, SAEs, or discontinuations due to AEs is identified between treatment arms based on having a history of psychiatric illnesses.

- PN021 DRIVE-AHEAD subjects with **depression and suicide/self-injury** NPEs:

DOR/3TC/TDF

- 40% (6/15) with psychiatric history
  - N=1 history of depression
- No SAEs
- 1 discontinuation due to AE
  - Severe depression in subject without known psychiatric history

EFV/FTC/TDF

- 29% (7/24) with psychiatric history
  - N=4 history of depression
- 2 SAEs
  - Completed suicide in subject without known psychiatric history ([(b) (6)])
  - Suicide attempt in subject without known psychiatric history ([(b) (6)])
- 2 discontinuations due to AE: neither subject with known psychiatric history

- PN021 DRIVE-AHEAD subjects with **sleep disorder and disturbances** NPEs:

DOR/3TC/TDF

- 23% (10/44) with psychiatric history
  - N=4 insomnia/sleep disorder history
- 1 SAE
  - Insomnia/nightmare leading to discontinuation in a subject with history of depression ([redacted])
- 1 discontinuation due to AE (above)

EFV/FTC/TDF

- 19% (18/93) with psychiatric history
  - N=7 insomnia/sleep disorder history
- No SAEs
- 3 discontinuations due to AE: none of subjects with known psychiatric history

PN018

For completeness, similar week 48 analyses were performed for PN018 DRIVE-FORWARD using the same PN021 DRIVE-AHEAD predefined NPE category MedDRA PTs. Neuropsychiatric AEs were not a prespecified analysis for PN018 DRIVE-FORWARD. Overall there was an approximate 10% increase in overall NPEs in the PN021 DRIVE-AHEAD DOR arm (24%) compared with the PN018 DRIVE-FORWARD DOR arm (13%), with similar trends generally observed in the individual NPE categories: NPEs overall and by individual category were similar between the PN018 DRIVE-FORWARD DOR- and DRV+r-containing arms as expected (Table 113). We hypothesize the increased PN021 DRIVE-AHEAD DOR arm NPEs is because of increased AE reporting in the EFV-containing protocol.

Focused PN018 DRIVE-FORWARD analyses of depression and suicide/self-injury NPEs and sleep disorder and disturbances NPEs and history of psychiatric illnesses were similar to PN021 DRIVE-AHEAD conclusions: no clear imbalance in AEs, SAEs, or discontinuations due to AEs is identified between treatment arms based on having a history of psychiatric illnesses.

Table 113. Neuropsychiatric AEs in PN021 DRIVE-AHEAD, PN018 DRIVE-FORWARD by Week 48

	n (%)			
	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
	DOR & NRTIs N=383	DRV+r + NRTIs N=383	DOR/3TC/TDF N=364	EFV/FTC/TDF N=364
Any subject with predefined NPE	51 (13.3%)	60 (15.7%)	86 (23.6%)	207 (56.9%)
Dizziness	19 (5.0%)	15 (3.9%)	32 (8.8%)	135 (37.1%)
Sleep disorders and disturbances	28 (7.3%)	25 (6.5%)	44 (12.1%)	93 (25.5%)
Depression and suicide/self-injury	8 (2.1%)	13 (3.4%)	15 (4.1%)	24 (6.6%)
Altered sensorium	5 (1.3%)	17 (4.4%)	16 (4.4%)	30 (8.2%)
Psychosis and psychotic disorders	1 (<1%)	1 (<1%)	1 (<1%)	4 (1.1%)

Source: JReview and JMP Outputs, ISS ADAM ANCNS and ADSL datasets, PN021, PN018
AE = adverse event; DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NPE = neuropsychiatric event; NRTI = nucleos(t)ide reverse transcriptase inhibitor

PN007

The phase 2 trial PN007 prespecified the proportion of subjects experiencing at least one NPE by weeks 8 and 24 for statistical testing of superiority as one of the primary objectives reviewed in section II.6.4.1. The following selected MedDRA preferred terms were pooled and categorized

as a NPE (defined as central nervous system event in the protocol): depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, hallucination auditory, hallucination visual, completed suicide, suicidal behavior, major depression, depressed mood, depressive symptom, insomnia, disturbance in attention, somnolence, dizziness, or concentration impaired.

The results of the analysis of prespecified neuropsychiatric events are presented in section II.6.4.1. In addition, a somewhat higher proportion of discontinuations due to AE were observed in the EFV arms than in the DOR arms, although the occurrence of such discontinuations was low.

18. Clinical Safety Assessment Additional Information and Assessment

18.1. Information to Support Section 7.4 FDA Approach to the Safety Review

Data from two phase 3 trials in treatment-naïve HIV-1 infected subjects (PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD) were analyzed both individually and pooled for the DOR-containing arms to support safety for DOR 100 mg QD and for DOR/3TC/TDF FDC tablet QD. In general, the safety review was analyzed by trial, except in situations where pooling the data might help identify less common serious signals (discontinuations due to AEs and biliary SAEs). Pooling of the phase 3 trials for the DOR-containing arms is appropriate because the trial designs were similar with generally similar inclusion and exclusion criteria, except that PN018 DRIVE-FORWARD had an extra inclusion criterion for hemoglobin above a certain threshold and an extra exclusion criterion for advanced or decompensated liver disease. In addition to a complete independent analysis of safety for the phase 3 trials, selected safety analyses from the phase 2 trial PN007 are included in this review when applicable.
Clinical trial data were independently analyzed in JMP, JMP Clinical, MAED, and JReview. All the safety assessments and conclusions are those of the FDA reviewer unless otherwise specified. Certain safety tables exported from JReview include calculated percentages with decimal places; therefore, some percentages may be different compared to labeled safety information which rounds to whole numbers.
The Applicant submitted a SUR 4 months after the original NDA submission providing approximately 10 and 5 months of additional safety data for PN018 DRIVE-FORWARD (data cutoff date 7/14/2017) and PN021 DRIVE-AHEAD (data cutoff date 8/21/2017), respectively (no new PN007 safety data were included). Approximately 5 months of additional safety data were also provided for the ongoing trials PN024, PN028, and PN030 (data cutoff date 8/21/2017):

- PN024: Phase 3 trial evaluating a switch from a boosted PI, NNRTI, or integrase inhibitor based regimen to DOR/3TC/TDF for 48 weeks in virologically-suppressed subjects with HIV-1 infection. Subjects randomized 2:1 to an immediate or delayed (week 24) switch.
- PN028: Phase 2b trial evaluating a switch from EFV/FTC/TDF to DOR/3TC/TDF in virologically-suppressed, HIV-1 infected subjects for a 36 week total duration. Subjects randomized 1:1 to an immediate or deferred (week 36) switch.
- PN030: Phase 2 trial evaluating the safety and efficacy of DOR/3TC/TDF in ARV treatment-naïve subjects with HIV-1 infection with selected NNRTI-transmitted resistance mutations.

Deaths, SAEs, and discontinuations due to AEs reported in the SUR are included in the relevant safety sections.

18.2. Issues Regarding Data Integrity and Submission Quality

Data integrity and quality of the initial submission in combination with subsequent submissions were adequate to perform the safety review for DOR and DOR/3TC/TDF. The OCS Jump Start service also analyzed data fitness and found no major issues that would preclude performing a safety review. We did note missing ECG data, missing ALT values from most subjects enrolled

in Australia, and missing MedDRA coding for several AEs; however, these issues were resolved early in the review and did not impact our overall safety assessment.

18.3. Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) versions 19.0 (PN007) and 19.1 (PN018 DRIVE-FORWARD, PN021 DRIVE-AHEAD, ISS) were used for AE coding. Other than issues identified in the Applicant's TEAE definition and those concerning Merck's AE toxicity grading scale (discussed below), there were no identified issues with respect to recording, coding, and categorizing AEs. The Applicant categorized SAEs in accordance with standard, regulatory definitions and grouped AEs using the standard MedDRA hierarchy. The Applicant's translations of verbatim terms to preferred terms for the events reported in PN018 DRIVE-FORWARD, PN021 DRIVE-AHEAD, and PN007 were reviewed and found to be acceptable. Laboratory toxicities were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004; Clarification August 2009.

TEAEs were defined as any AE that occurred from the time the first dose of study treatment was taken until 14 days following cessation of study treatment. Cessation of study treatment relied on review of treatment diaries and, using the Applicant's definition, AEs occurring >14 days after treatment diaries were last reviewed were counted as "poststudy", even if the subject was presumed to still be on treatment.

- For example, two deaths that occurred >14 days after the last study visit were counted as "poststudy" and not included as TEAEs, even though the two subjects were presumed to still be taking study medication at the time of death.

This safety review utilizes a modified TEAE definition that defines the last day of study treatment as the earliest of the following: 1) the day of death, 2) the last day of study treatment if confirmed by the subject at a discontinuation study visit, or 3) the day the subject would have run out of study treatment if fully compliant after the last study visit. Using this modified method adds a total of 22 TEAEs: 3 to PN018 DRIVE-FORWARD, 12 to PN021 DRIVE-AHEAD, and 7 to PN007. Thus, while some numbers from our safety analyses may be slightly different than the numbers provided in the Applicant's analyses, the differences are very small and do not change the overall safety conclusions.

Merck's AE toxicity grading scale uses a three-line grading table with the following toxicity grades:

- Mild (grade 1): awareness of signs or symptoms, but easily tolerated
- Moderate (grade 2): discomfort enough to cause interference with usual activity
- Severe (grade 3): incapacitating with inability to work or do usual activity

All AEs in the reviewed trials were graded using this same scale, and so are comparable within the trials; however, Merck's AE grading scale has fewer toxicity grades than the toxicity grading scales used by most other companies, which have 4 to 5 toxicity grades. Consequently, AEs of a certain toxicity grade in these DOR-containing trials are not comparable to AEs of the same toxicity grade reported in trials performed by other companies.

18.4. Routine Clinical Tests

Routine clinical evaluations for safety included medical history taking for assessment of symptoms of adverse events, vital sign measurements and physical examinations for assessment of signs of adverse events, and laboratory evaluations. In the phase 2 study PN007, ECGs were also performed at screening, week 24, and week 48. In the pivotal trials PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, key evaluations were performed at baseline, week 2 (PN018 only), and weeks 4, 8, 16, 24, and every 12 weeks thereafter, with a final follow-up visit 14 days poststudy. Follow-up visits were also scheduled for subjects who discontinued treatment prematurely due to adverse events.

18.5. Serious Adverse Events

Only one DOR-recipient in each study had an SAE that was judged to be related to study treatment by the investigator. Causality assessment of both these SAEs are confounded by timing and comorbidities, and neither is convincing for a causal association. In the first case, the SAEs of nausea and vomiting occurred three days after a single dose of study medication, and in the setting of preexisting acute kidney injury of unclear etiology. In the second case, the SAEs of asthenia, nightmare, and insomnia occurred eight months after initiating study treatment, and in the setting of preexisting depression. These two cases are described below:

PN018 DRIVE-FORWARD

- DOR+TDF/FTC, SAE nausea and vomiting: 49-year-old man with medical history including HIV-1. Baseline CD4 544 cells/mm^3, HIV-1 RNA 663 copies/mL. The subject received one study drug dose because he was found to have acute kidney injury on predose labs (creatinine 2.76 mg/dL), and thus discontinued for safety reasons. On day 4 developed nausea and vomiting, judged related to study medication, and day 6 was hospitalized for continued nausea and vomiting, acute kidney injury, and hypovolemia. These AEs resolved within a few days except for acute kidney injury, classified as resolving at the day 9 discontinuation visit (creatinine 1.88 mg/dL).

PN021 DRIVE-AHEAD

- DOR/3TC/TDF, SAEs asthenia, nightmare, insomnia: 38-year-old woman with medical history including HIV-1, depression, renal disorder, hypertension, and hypercholesterolemia. Baseline CD4 442 cells/mm^3, HIV-1 RNA 13,356 copies/mL. On day 265 experienced severe asthenia, nightmare, and insomnia, judged related to study medication. Creatinine increased from baseline 0.78 mg/dL to 1.00 on day 169, associated with moderate renal disorder and vitamin D deficiency. The investigator assessed asthenia and vitamin D deficiency as caused by renal insufficiency worsened by TDF use, and on day 272 the subject discontinued study medication.

Similar to the phase 3 trials, no PN007 SAEs were reported in more than one subject in the same treatment arm. Compared to the phase 3 trials, more subjects overall in PN007 had SAEs [10% (11/108) in subjects initially randomized to DOR 100 mg, and 12% (13/108) in subjects initially randomized to EFV]; however, PN007 data were for 96 weeks of treatment rather than 48 weeks in the phase 3 trials, which likely explains this discrepancy. No SAEs in PN007 DOR-treated subjects were judged related to study medication.

In the SUR no additional phase 3 drug-related SAEs were reported. In the ongoing trials PN024, PN028, and PN030, drug-related SAEs were reported in four PN024 DOR-treated subjects in the immediate switch group: these cases report AEs which are proposed for labeling (depression, asymptomatic increased lipase, asymptomatic increased AST/ALT) or lack information to assess causality (pancreatitis).

18.6. Discontinuations due to Adverse Events

DOR-treated subjects who discontinued due to AEs in PN018 DRIVE-FORWARD or PN021 DRIVE-AHEAD are described in Table 17 and Table 114.

Table 114. Discontinuations Due to an AE in Subjects on DOR or DOR/3TC/TDF, 0 to 48 Weeks, in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

Subject	Age/Sex/ Race	AE	Serious	Severity	Related	AE Onset Day	DOR Last Day*	Outcome
PN018 DRIVE-FORWARD (all below subjects on DOR)								
(b) (6)	26/M/B	Abdominal pain nausea	N N	Mild Mild	Y Y	169	198/ 253	Resolved in 6 days
	32/M/W	Rash erythematous	N	Moderate	Y	4	148/ 149	Not resolved
	35/M/W	Rash macular	N	Severe	Y	13	14/ 29	Resolved in 6 days
	49/M/B	Acute kidney injury	N	Mild	Y	1	1	Resolving
	25/F/W	Nausea	N	Mild	Y	362	399	Not resolved
	41/M/O	Death	Y	Severe	N	222	222	Fatal
PN021 DRIVE-AHEAD (all below subjects on DOR/3TC/TDF)								
(b) (6)	26/M/W	Depression	N	Severe	Y	325	406	Not resolved
	32/F/W	Abdominal pain upper	N	Severe	Y	3	20/ 58	Resolved in 18 days
	25/M/W	Adjustment Disorder	N	Moderate	Y	1	348/ 349	Not resolved
	34/M/W	Disturbance in Attention	N	Severe	Y	90	169	Resolved in 90 days
	38/M/W	Vomiting (3d episode)	N	Moderate	Y	309	336/ 337	Resolved in 11 days
	18/M/W	Fatigue	N	Severe	Y	25	77/ 78	Resolved in 56 days
	58/M/W	Silicon granuloma	N	Mild	N	311	315/ 455	Resolved in 9 days
	38/W/F	Asthenia Insomnia Nightmare renal disorder Vit D deficiency	Y Y Y N N	Severe Severe Severe Moderate Moderate	Y Y Y Y Y	265 265 265 266 266	272	Resolving Not resolved Resolved Resolving Resolving
	63/M/W	Esophageal obstruction	Y	Severe	N	171	191/ 218	Sequelae
	51/M/W	Alopecia	N	Moderate	Y	122	203/ 228	Resolved in 97 days
	42/M/B	Pulmonary tuberculosis	N	Moderate	N	272	274/ 275	Not resolved

M = male; F = female; B = black; W = white; O = other race; N = no; Y = yes; DOR = doravirine; DOR/3TC/TDF = (MK-1439A) FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; AE = adverse event.

* DOR last day is descr bed as one day if the last day DOR was taken is documented, and descr bed as 2 days if not documented and there is a discrepancy between the last reported dose (Applicant definition) and the last possible dose if the subject continued to take the drug as directed (FDA definition).

18.7. Treatment-Emergent Adverse Events

The most common TEAEs reported across the phase 3 trials in DOR-treated subjects were diarrhea, headache, nausea, and nasopharyngitis. The majority of events were grade 1 in severity. Table 115 summarizes common TEAEs irrespective of severity and causality.

Table 115. Treatment-emergent AEs Reported in ≥5% of DOR-Treated Subjects, All Grades and All Causality, Phase 3 Population, Week 48

	n (%)			
	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Dictionary Derived Term	DOR & NRTIs N=383	DRV+r & NRTIs N=383	DOR/3TC/TDF N=364	EFV/FTC/TDF N=364
Diarrhea	54 (14%)	86 (22%)	39 (11%)	49 (13%)
Headache	53 (14%)	41 (11%)	47 (13%)	45 (12%)
Nausea	41 (11%)	46 (12%)	28 (8%)	39 (11%)
Upper respiratory tract infection	36 (9%)	23 (6%)	33 (9%)	23 (6%)
Fatigue	31 (8%)	20 (5%)	21 (6%)	22 (6%)
Nasopharyngitis	30 (8%)	39 (10%)	39 (11%)	31 (9%)
Back pain	21 (5%)	8 (2%)	9 (2%)	15 (4%)
Cough	19 (5%)	6 (2%)	16 (4%)	14 (4%)
Abdominal pain upper	19 (5%)	10 (3%)	8 (2%)	2 (1%)
Dizziness	19 (5%)	15 (4%)	32 (9%)	135 (37%)
Insomnia	14 (4%)	18 (5%)	19 (5%)	32 (9%)
Pharyngitis	7 (2%)	10 (3%)	20 (5%)	15 (4%)
Vomiting	12 (3%)	10 (3%)	15 (4%)	27 (7%)

Data Source: PN018 and PN021 subsets of the ISS ADSL and ADAE datasets

18.8. Laboratory Findings

A summary of the grade 1 to 4 laboratory abnormalities reported during week 0 to 48 of the phase 3 trials is shown below in Table 116 and Table 117. For most parameters, laboratory findings are similar between the DOR and comparator groups, and grade 3 and 4 laboratories are uncommon.

Table 116. Subjects Meeting Chemistry Laboratory Abnormality Criteria, With a Grade Worsened From Baseline through Week 48, in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Laboratory Abnormality	DOR & NRTIs N=383	DRV+r & NRTIs N=383	DOR/3TC/TDF N=364	EFV/FTC/TDF N=364
ALT				
Grade 1 (1.25 - <2.5 x ULN)	33/380 (8.7%)	27/378 (7.1%)	47/359 (13.1%)	
Grade 2 (2.5 - <5.0 x ULN)	11/380 (2.9%)	7/378 (1.9%)	12/363 (3.3%)	13/359 (3.6%)
Grade 3 (5.0 - <10.0 x ULN)	5/380 (1.3%)	6/378 (1.6%)	2/363 (<1%)	5/359 (1.4%)
Grade 4 (≥10.0 x ULN)	0	3/378 (<1%)	1/363 (<1%)	1/359 (<1%)
Alkaline Phosphatase				
Grade 1 (1.25 - <2.5 X ULN)	3/380 (<1%)	8/378 (2.1%)	13/363 (3.6%)	28/359 (7.8%)
Grade 2 (2.5 - <5.0 x ULN)	1/380 (<1%)	2/378 (<1%)	0	2/359 (<1%)
Grade 3 (5.0 - <10.0 x ULN)	0	0	0	1/359 (<1%)

Laboratory Abnormality	PN018 DRIVE-FORWARD DOR & NRTIs N=383	PN018 DRIVE-FORWARD DRV+r & NRTIs N=383	PN021 DRIVE-AHEAD DOR/3TC/TDF N=364	PN021 DRIVE-AHEAD EFV/FTC/TDF N=364
AST				
Grade 1 (1.25 - <2.5 x ULN)	30/380 (7.9%)	26/378 (6.9%)	29/363 (8.0%)	36/359 (10.0%)
Grade 2 (2.5 - <5.0 x ULN)	17/380 (4.5%)	12/378 (3.2%)	6/363 (1.7%)	8/359 (2.2%)
Grade 3 (5.0 - <10.0 x ULN)	2/380 (<1%)	6/378 (1.6%)	1/363 (<1%)	5/359 (1.4%)
Grade 4 (≥10.0 x ULN)	0	0	1/363 (<1%)	2/359 (<1%)
Total Bilirubin				
Grade 1 (1.1 - <1.6 x ULN)	19/380 (5.0%)	4/378 (1.1%)	13/363 (3.6%)	**0**
Grade 2 (1.6 - <2.6 x ULN)	6/380 (1.6%)	1/378 (<1%)	9/363 (2.5%)	**0**
Grade 3 (2.6 - <5.0 x ULN)	0	0	1/363 (<1%)	0
Grade 4 (≥5.0 x ULN)	0	0	1/363 (<1%)	1/359 (<1%)
Creatine Kinase				
Grade 1 (3.0 - <6.0 x ULN)	22/380 (5.8%)	22/378 (5.8%)	17/363 (4.7%)	17/359 (4.7%)
Grade 2 (6.0 - <10.0 x ULN)	9/380 (2.4%)	12/378 (3.2%)	9/363 (2.5%)	7/359 (1.9%)
Grade 3 (10.0 - <20.0 x ULN)	7/380 (1.8%)	7/378 (1.9%)	6/363 (1.7%)	7/359 (1.9%)
Grade 4 (≥20.0 x ULN)	6/380 (1.6%)	7/378 (1.9%)	2/363 (<1%)	4/359 (1.1%)
Creatinine*				
Grade 1 (1.1 – 1.3 x ULN)	1/380 (0.3%)	0	0	0
Grade 2 (>1.3 - 1.8 x ULN)	10/380 (2.6%)	16/378 (4.2%)	8/363 (2.2%)	5/359 (1.4%)
Grade 3 (>1.8 - <3.5 x ULN)	5/380 (1.3%)	10/378 (2.6%)	7/363 (1.9%)	3/359 (<1%)
Grade 4 (≥3.5 x ULN)	1/380 (<1%)	0	0	1/359 (<1%)
Fasting Glucose				
Grade 1 (110 - 125 mg/dL)	23/335 (6.9%)	26/327 (8.0%)	12/336 (3.6%)	13/318 (4.1%)
Grade 2 (>125 - 250 mg/dL)	7/335 (2.1%)	9/327 (2.8%)	6/336 (1.8%)	5/318 (1.6%)
Grade 3 (>250 - 500 mg/dl)	4/335 (1.2%)	1/327 (<1%)	0	2/318 (<1%)
Fasting Cholesterol				
Grade 1 (200 - <240 mg/dL)	33/335 (9.8%)	48/327 (14.7%)	21/336 (6.3%)	44/318 (13.8%)
Grade 2 (240 - <300 mg/dl)	4/335 (1.2%)	32/327 (9.8%)	2/336 (<1%)	24/318 (7.5%)
Grade 3 (≥300 mg/dl)	0	1/327 (<1%)	2/336 (<1%)	1/318 (<1%)
Fasting LDL Cholesterol				
Grade 1 (130 - <160 mg/dL)	23/332 (6.9%)	34/320 (10.6%)	15/332 (4.5%)	22/309 (7.1%)
Grade 2 (160 - <190 mg/dL)	1/332 (<1%)	23/320 (7.2%)	3/332 (<1%)	15/309 (4.9%)
Grade 3 (≥190 mg/dL)	1/332 (<1%)	9/320 (2.8%)	1/332 (<1%)	5/309 (1.6%)
Fasting Triglyceride				
Grade 1 (150 - 300 mg/dL)	41/335 (12.2%)	71/327 (21.7%)	32/336 (9.5%)	51/318 (16.0%)
Grade 2 (>300 - 500 mg/dL)	9/335 (2.7%)	13/327 (4.0%)	13/336 (3.9%)	19/318 (6.0%)
Grade 3 (>500 - 1000 mg/dL)	2/335 (<1%)	2/327 (<1%)	2/336 (<1%)	8/318 (2.5%)
Grade 4 (>1000 mg/dL)	0	2/327 (<1%)	0	0
Amylase				
Grade 1 (1.1 - <1.5 x ULN)	16/380 (4.2%)	16/378 (4.2%)	9/363 (2.5%)	14/359 (3.9%)
Grade 2 (1.5 - <3.0 x ULN)	8/380 (2.1%)	9/378 (2.4%)	2/363 (<1%)	5/359 (1.4%)
Grade 3 (3.0 - <5.0 x ULN)	0	2/378 (<1%)	0	0
Lipase				
Grade 1 (1.1 - <1.5 x ULN)	20/380 (5.3%)	23/378 (6.1%)	18/363 (5.0%)	18/359 (5.0%)
Grade 2 (1.5 - <3.0 x ULN)	14/380 (3.7%)	20/378 (5.3%)	19/363 (5.2%)	15/359 (4.2%)
Grade 3 (3.0 - <5.0 x ULN)	6/380 (1.6%)	6/378 (1.6%)	3/363 (<1%)	5/359 (1.4%)
Grade 4 (≥5.0 x ULN)	4/380 (1.1%)	3/378 (<1%)	1/363 (<1%)	2/359 (<1%)

Source: PN018 and PN021 Subset of ISS ADLB dataset. Each subject only included once per parameter at highest toxicity grade.
ULN = upper limit of normal.
* Grade 2 creatinine can also be an increase of 0.3 mg/dL above baseline, grade 3 creatinine can also be an increase of 1.5 to <2.0-fold above baseline, and grade 4 creatinine can also be an increase of ≥2.0-fold above baseline.

Table 117. Subjects Meeting Hematology Laboratory Abnormality Criteria, With a Grade Worsened From Baseline Through Week 48, in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
Hematology Laboratory Abnormality	**DOR & NRTIs N=383**	**DRV+r & NRTIs N=383**	**DOR/3TC/TDF N=364**	**EFV/FTC/TDF N=364**
Hemoglobin				
Grade 1 (male 10.0-10.9 g/dL; female 9.5 - 10.4 g/dL)	7/380 (1.8%)	8/378 (2.1%)	9/362 (2.5%)	5/359 (1.4%)
Grade 2 (male 9.0 - <10.0 g/dL; female 8.5 - <9.5 g/dL)	3/380 (<1%)	6/378 (1.6%)	3/362 (<1%)	1/359 (<1%)
Grade 3 (male 7.0 - <9.0 g/dL; female 6.5 - <8.5 g/dL)	1/380 (<1%)	0	1/362 (<1%)	1/359 (<1%)
Neutrophils				
Grade 1 (0.800 - 1.000 x 10^9/L)	6/379 (1.6%)	3/378 (<1%)	2/362 (<1%)	2/359 (<1%)
Grade 2 (0.600 - 0.7999 x 10^9/L)	1/379 (<1%)	4/378 (1.1%)	2/362 (<1%)	3/359 (<1%)
Grade 3 (0.400 - 1.599 x 10^9/L)	0	1/378 (<1%)	0	1/359 (<1%)
Grade 4 (<0.400 x 10^9/L)	1/379 (<1%)	2/378 (<1%)	3/362 (<1%)	2/359 (<1%)
Platelets				
Grade 1 (100 - <124.999 x 10^9/L)	3/379 (<1%)	4/376 (1.1%)	2/359 (<1%)	2/357 (<1%)
Grade 2 (50 - <100 x 10^9/L)	1/379 (<1%)	2/376 (<1%)	2/359 (<1%)	0
Grade 4 (<25 x 10^9/L)	1/379 (<1%)	0	0	0

Data Source: PN018 and PN021 Subsets of ISS ADLB dataset. Each subject only included once per parameter at highest toxicity grade

18.9. Hepatobiliary Analysis

A detailed hepatobiliary analysis was performed to evaluate the potential for hepatotoxicity from DOR because of numerical imbalances in bilirubin and biliary AEs between the DOR-containing and comparator groups, and because hepatotoxicity has been identified as a safety signal for other NNRTIs. This section summarizes the following analyses: 1) review of hepatic laboratory abnormalities, including total bilirubin and an overview of potential drug-induced liver injury and Hy's Law cases; 2) review of hepatobiliary AEs; and 3) hepatic events in subjects coinfected with Hepatitis B or C.

Review of Hepatic Laboratory Abnormalities, Bilirubinemia

As noted in the section on laboratory findings (sections II.7.7.7) rates of graded total bilirubin abnormalities were higher in the DOR group (6.5%) versus the comparator group (1.3%) in PN018 DRIVE-FORWARD (treatment difference: 5.2%, 95% CI: 2.4%, 8.3% by the exact method), and also higher in the DOR group (6.6%) versus the comparator group (<1%) in PN021 DRIVE-AHEAD (treatment difference: 6.3%, 95% CI: 3.8%, 9.3% by the exact method). This bilirubinemia was primarily unconjugated, not associated with graded abnormalities in other liver tests (ALT, AST, or alkaline phosphatase), and not associated with treatment discontinuation.

As shown in Table 118, 95% of subjects with graded total bilirubin abnormalities had a maximum toxicity grade of 1 or 2, and 62% had graded abnormalities isolated to one study visit. The two grade 4 abnormalities had plausible alternative etiologies; acute hepatitis A virus infection (EFV/FTC/TDF) and bile duct stone (DOR/3TC/TDF). Accounting for relative frequency of study visits and blood draws, the graded total bilirubin abnormalities occurred throughout the study without an apparent temporal pattern in relation to start of therapy. Subjects with graded total bilirubin abnormalities from either the DOR or comparator treatment groups in

the phase 3 trials were disproportionately male (1/233 [<1%] female versus 54/1261 [4.3%] male subjects): the clinical relevance of this observation is unclear.

Table 118. Maximum Total Bilirubin Toxicity Grade, Increased From Baseline, From 0 to 48 Weeks in the Pivotal Studies

	n (%)			
	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
	DOR & NRTIs N=383	DRV+r & NRTIs N=383	DOR/3TC/TDF N=364	EFV/FTC/TDF N=364
Any Grade				
Overall	25 (6.5%)	5 (1.3%)	24 (6.6%)	1 (<1%)
Isolated	15 (3.9%)	3 (<1%)	16 (4.4%)	1
Transient	2 (<1%)	1 (<1%)	4 (1.1%)	0
Sustained	8 (2.1%)	1 (<1%)	4 (1.1%)	0
Grade 1				
Overall	19 (5.0%)	4 (1.0%)	13 (3.6%)	0
Isolated	13	2	10	0
Transient	2	1	2	0
Sustained	4	1	1	0
Grade 2				
Overall	6 (1.6%)	1 (<1%)	9 (2.5%)	0
Isolated	2	1	4	0
Transient*	0	0	2	0
Sustained*	4	0	3	0
Grade 3				
Overall	0	0	1 (<1%)	0
Isolated	0	0	1	0
Transient	0	0	0	0
Sustained	0	0	0	0
Grade 4				
Overall	0	0	1 (<1%)	1 (<1%)
Isolated	0	0	1	1
Transient	0	0	0	0
Sustained	0	0	0	0

DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NRTI = nucleos(t)ide reverse transcriptase inh bitor

Graded events by isolated (1 study visit only), transient (more than one study visit but separated by time and not at consecutive visits) and sustained (2 or more consecutive study visits).

* Transient and sustained grade 2 events had a maximum toxicity grade of 2, with transient or sustained events that were an increased grade from baseline but not necessarily all grade 2.

Mean bilirubin levels beginning 2 weeks after starting treatment were higher in subjects receiving DOR than in subjects receiving DRV+r (difference of ~0.1 mg/dL) or EFV (difference of ~0.2 mg/dL); however, this finding appears to be due to mean bilirubin levels decreasing after treatment initiation in the DRV+r and EFV groups, rather than mean bilirubin levels increasing after treatment initiation in the DOR groups. Analysis of bilirubin levels in subjects who received different daily doses of DOR in PN007 did not show any dose association with bilirubin levels.

Review of Hepatobiliary AEs and Biliary AEs

TEAEs through week 48 in the hepatobiliary disorders body system class in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD were initially reviewed. Rates of week 48 hepatobiliary disorder system organ class (SOC) AEs were low and similar between treatment

groups [<1% (2/383) among both DOR and DRV+r recipients in PN018 DRIVE-FORWARD; 1.1% (4/364) versus <1% (3/364) among DOR/3TC/TDF and EFV/FTC/TDF recipients, respectively, in PN021 DRIVE-AHEAD]. However, across trials there was a numerical difference in biliary SAEs (five in the pooled DOR group, versus zero in the active comparator groups). Consequently, a specific biliary AE analysis to fully evaluate any potential biliary signals was conducted, using the following preferred terms to define a biliary AE: bile duct stone, biliary colic, biliary dyskinesia, cholecystitis, cholecystitis acute, and cholelithiasis. The safety pool was expanded to include the phase 2 study PN007 and to include TEAEs that occurred after 48 weeks.

The identified biliary AEs are described in Table 119. DOR-treated subjects accounted for 8 of 10 subjects with biliary AEs, all five subjects with biliary SAEs, all six subjects with moderate to severe biliary AEs, and all five subjects requiring cholecystectomy. It is notable that at least one DOR-treated subject had a biliary SAE in each trial. None of the eight DOR-treated subjects with biliary TEAEs had graded bilirubin abnormalities except one subject with a bile duct stone (who had a single elevated bilirubin level of 12.3 at the time the stone was diagnosed), and none were considered related to study drug by the investigator.

Table 119. Biliary Treatment Emergent AEs in PN007, PN018 DRIVE-FORWARD, and PN021 DRIVE-AHEAD

Trial/ Subject	Treatment	Age/Sex/Race/ Ethnicity	AE	Serious	Severity (Grade)	AE Days	Comment
DOR-Containing Treatment							
PN007/ (b) (6)	200 mg DOR +TDF/FTC	26/M/W/NH	Biliary dyskinesia	Y	Moderate (2)	123-134	AE resolved after cholecystectomy. Treatment discontinued on day 110 for prior AE (Nausea/Vomiting from cryptosporidium).
PN007/ (b) (6)	100 mg DOR + TDF/FTC	44/M/ W/NH	Cholecystitis Cholecystitis	N Y	Moderate (2) Moderate (2)	118-127; 235-262	AE resolved after cholecystectomy.
PN007/ (b) (6)	25 mg DOR + TDF/FTC	49/M/W/NH	Acute cholecystitis	Y	Severe (3)	67	AE resolved after cholecystectomy.
PN018/ (b) (6)	DOR + TDF/FTC	25-26/M/B/NH	Biliary colic Biliary colic Cholelithiasis	N N N	Moderate (2) Severe (3) Mild (1)	412 451 451-	Biliary colic resolved, cholelithiasis not resolved at data cutoff.
PN018/ (b) (6)	DOR + TDF/FTC	54/M/W/H	Acute cholecystitis	Y	Severe (3)	232-237	AE resolved after cholecystectomy.
PN018/ (b) (6)	DOR + TDF/FTC	30/M/W/H	Cholelithiasis	N	Mild (1)	330-	Recovering at data cutoff.

Trial/ Subject	Treatment	Age/Sex/Race/ Ethnicity	AE	Serious	Severity (Grade)	AE Days	Comment
DOR-Containing Treatment							
PN021/ (b) (6)	DOR/3TC/TDF	46/M/W/H	Bile duct stone	Y	Severe (3)	160-170	AE resolved after cholecystectomy with stone extraction.
PN021/ (b) (6)	DOR/3TC/TDF	36/F/Multiple/H	Biliary colic	N	Mild (1)	41	Resolved
Comparator Treatment							
PN007/ (b) (6)	EFV + TDF/FTC	45/M/W/NH	Cholelithiasis	N	Mild (1)	299-674+	Not resolved at end of study
PN021/ (b) (6)	EFV/FTC/TDF	30/F/W/H	Biliary colic	N	Mild (1)	84-304	Resolved

AE = adverse event; DOR = doravirine (MK-1439); EFV = efavirenz; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; TDF/FTC = FDC tablet of 300 mg TDF and 200 mg FTC; M = male; F = female; W = white; B = black; H = Hispanic; NH = non-Hispanic

18.10. Rash and Hypersensitivity Reactions

A detailed analysis of rash and hypersensitivity reactions was performed to evaluate the potential for skin reactions from DOR because rash and severe skin and hypersensitivity reactions have been identified as safety signals for other NNRTIs. Of note, the active comparator labels include WARNINGS AND PRECAUTIONS rash information.

Rash Events

Rash events were analyzed by pooling the preferred term of “drug eruption” and the preferred terms that contained the word “rash”, as specified in the table legend below, and similar to how rash events were pooled in the dolutegravir label.

DOR recipients in PN018 DRIVE-FORWARD had similar rates of overall rash events and rash ADRs (8% and 2%) as DRV+r recipients (9% and 3%), but DOR/3TC/TDF recipients in PN021 DRIVE-AHEAD had one third the rate of rash events and rash ADRs (6% and 2%) as EFV/FTC/TDF recipients (18% and 12%, Table 120). No DOR-treated subject had a rash SAE, and there were no reported severe drug eruptions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, or DRESS syndrome (drug reaction with eosinophilia and systemic symptoms). Two DOR recipients in PN018 DRIVE-FORWARD discontinued treatment due to a rash event. One subject developed a severe, generalized, macular rash day 13. Study treatment was stopped the next day, and the rash resolved by day 19. The second subject developed a moderate, generalized, erythematous rash day 4 treated with loratadine and diphenhydramine. The rash did not resolve, study treatment was stopped on day 149, and the rash had not resolved by day 163.

A longer median rash onset time was observed in the DOR groups (median 38 to 40 days) versus the active comparator groups (median 11 to 13 days); however, rash events in both the DOR and active comparator groups usually developed within 50 days of treatment initiation.

Table 120. Rash Events in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD, Week 48

	n (%)			
	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
	DOR & NRTIs N=383	DRV+r & NRTIs N=383	DOR/3TC/TDF N=364	EFV/FTC/TDF N=364
Any Subject with rash event*	32 (8.4%)	33 (8.6%)	22 (6.0%)	65 (17.9%)
Rash SAEs	0	0	0	3 (<1%)
D/C due to rash AEs	2 (<1%)	1 (<1%)	0	10 (2.7%)
Maximum Toxicity grade				
1	25 (6.5%)	28 (7.3%)	18 (4.9%)	38 (10.4%)
2	6 (1.6%)	5 (1.3%)	4 (1.1%)	23 (6.3%)
3	1 (<1%)	0	0	4 (1.1%)
Related Rash Event	9 (2.3%)	12 (3.1%)	7 (1.9%)	44 (12.1%)

Data Source: PN018 and PN021 subsets of the ISS ADSL and ADAE datasets
AE = adverse event; D/C = discontinuation; DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NRTI = nucleos(t)ide reverse transcriptase inhibitor; SAE = serious adverse event
*Includes pooled terms: rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash, genital rash, viral rash, and drug eruption

18.11. Hypersensitivity Reactions

Hypersensitivity reactions in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD were analyzed using the MedDRA-based adverse event diagnostics tool hypersensitivity SMQ narrow search; however, most identified hypersensitivity reaction events were rash events [64% (132/205)], including 88% (14/16) of hypersensitivity reaction ADRs in DOR-treated subjects. The two non-rash hypersensitivity reaction ADRs in DOR-treated subjects were not suggestive of a causal DOR relationship: (1) moderate urticaria in PN021 DRIVE-AHEAD days 11 to 19 with negative rechallenge; and (2) mild allergic dermatitis in PN018 DRIVE-FORWARD days 19 to 26 without study treatment interruption. No DOR-treated subjects reported angioedema or erythema multiforme or had a hypersensitivity SAE. One DOR-treated subject experienced a severe non-rash hypersensitivity reaction AE to concomitant medication (Levaquin).

18.12. Rash and Hypersensitivity Reaction Analysis Conclusions

Rash events occurred at similar rates in the DOR and DOR/3TC/TDF groups compared to the DRV+r group, but at substantially lower rates than the EFV/FTC/TDF group. Rash ADRs occurred >5% among phase 3 trial subjects in the EFV/FTC/TDF group; therefore, rash is recommended for DOR and DOR/3TC/FDC Section 6 ADVERSE REACTIONS labeling.

No specific hypersensitivity reaction events were identified in phase 3 DOR-treated subjects: rash events comprised most identified hypersensitivity reaction narrow SMQ AEs.

Because no SAEs due to rash or hypersensitivity have been reported with DOR or DOR/3TC/TDF to date, neither rash or hypersensitivity reaction is currently recommended for the WARNINGS AND PRECAUTIONS section of the label. Routine postmarketing pharmacovigilance is recommended for continued assessment of rash and hypersensitivity associated with DOR use.

18.13. Alopecia

An imbalance in adverse events of alopecia was noted for DOR compared to the comparators: eight DOR-treated subjects (1%, 8/747) reported alopecia versus three subjects in the combined comparator groups (<1%, 3/747) (see Table 121).

Among the DOR-treated subjects with alopecia, four subjects (50%) had moderate or severe alopecia, three subjects (38%) had alopecia considered related to study treatment, six subjects (75%) had alopecia that did not completely resolve while still on study treatment, and one subject discontinued treatment due to the alopecia. Onset ranged day 1 to 371, with no clear temporal pattern. Alopecia AEs resolved or were resolving while still on a DOR-containing regimen (N=3), and these may reflect U.S. background rates of alopecia. Alopecia was not observed as a drug related effect in any nonclinical study conducted in dog, rat or mouse study at exposure multiples up to 18-fold above the DOR exposure at the RHD. Based on the data to date, alopecia is not considered a safety signal, and labeling is not warranted due to the low frequency and lack of a temporal pattern. Routine postmarketing pharmacovigilance is recommended for continued assessment of alopecia events associated with DOR use.

Table 121. Alopecia in PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	n (%)			
	PN018 DRIVE-FORWARD		PN021 DRIVE-AHEAD	
	DOR & NRTIs N=383	DRV+r & NRTIs N=383	DOR/3TC/TDF N=364	EFV/FTC/TDF N=364
Any subject with alopecia*	1 (<1%)	1 (<1%)	7 (1.9%)	2 (<1%)
Alopecia SAEs	0	0	0	0
D/C due to alopecia	0	0	1 (<1%)	0
Maximum toxicity grade				
1	0	1 (<1%)	4 (1.1%)	1 (<1%)
2	1 (<1%)	0	2 (<1%)	1 (<1%)
3	0	0	1 (<1%)	0
Related alopecia	0	0	3 (<1%)	0

Data Source: PN018 and PN021 subsets of the ISS ADSL and ADAE datasets
AE = adverse event; D/C = discontinuation; DOR = doravirine (MK-1439); DOR/3TC/TDF = FDC tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV/FTC/TDF = FDC tablet of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate; NRTI = nucleos(t)ide reverse transcriptase inhibitor; SAE = serious adverse event
*Includes preferred terms alopecia and alopecia areata

18.14. Safety Analyses by Demographic Subgroups

Safety analyses by gender, race, ethnicity, and age (less than or ≥65 years of age) were performed for safety events among DOR recipients through 48 weeks in PN018 DRIVE-FORWARD, PN021 DRIVE-AHEAD, and subjects originally randomized to 100 mg DOR in PN007. Of note, only five DOR recipients were ≥65 years of age, which compromised a meaningful interpretation of AE findings by age. No concerning patterns were identified in the safety analyses by race, gender, ethnicity, or age. The following findings are described in more detail because they were identified either in the context of specific safety analyses (graded

bilirubin abnormalities) or because of numerical differences among demographic subgroups (dizziness, cardiovascular disorders):

- Graded total bilirubin abnormalities were observed more frequently in male versus female subjects, as described previously in section II.7.7.7 and 18.9 (subsection on hepatobiliary analysis).
- The TEAE of dizziness was reportedly disproportionately in Asian subjects both in the combined DOR group and the combined EFV group. The majority (207/251, 82.5%) of subjects with a TEAE of dizziness reported a maximum toxicity grade of 1 (mild).
    - In the combined DOR group, 12/56 (21.4%) Asian versus 6/131 (4.6%) black versus 33/455 (7.3%) white subjects reported dizziness.
    - In the combined EFV group, 41/62 (66.0%) Asian versus 17/76 (22.4%) black versus 78/231 (33.7%) white subjects reported dizziness.
    - Of note, Asian subjects did not have higher DOR exposures versus other races to explain this difference.
- In Section 2.7.4 of the NDA submission (Summary of Clinical Safety), the Applicant reported that there was a higher proportion of AEs in the Cardiovascular Disorders SOC in Asian subjects compared to other races, for both the combined DOR group and combined EFV group.
    - Among Asian subjects in the phase 2 and 3 trials, 7% (5/71) in the combined DOR group and 3% (2/67) in the EFV group reported cardiovascular disorder TEAEs. These events in DOR-treated Asian subjects were mild [palpitations (3), sinus bradycardia, tachycardia] and none were SAEs, considered related to study treatment, or led to discontinuation.
    - Among white and black or African American subjects in the phase 3 trials, 1% (7/543) and 2% (3/169) in the combined DOR group and 1% (3/257) and 2% (2/85) in the EFV group reported cardiovascular TEAEs, respectively.

While there is a numerical increased proportion of cardiovascular disorder SOC events reported in Asian DOR-treated subjects, the totality of the available information including small numbers, mild and non-serious nature of the reported TEAEs, and lack of higher DOR exposures in Asian subjects versus other races does not support additional DOR or DOR/3TC/TDF labeling at this time. Routine postmarketing pharmacovigilance is recommended for continued assessment of any cardiovascular events associated with DOR use.

18.15. Patient-Reported Outcome Endpoints

In PN021 DRIVE-AHEAD, subjects completed a WPAI at day 1, week 4, week 8, week 16, and week 48 (or the discontinuation visit). The WPAI has been used in studies of HIV-1-infected patients and utilizes a one week recall period. As HIV-1 infection has been shown to have an impact on productivity, the WPAI: General Health Questionnaire (WPAI:GH) was included as an exploratory measurement to describe the impact of these treatments. This patient-reported outcome questionnaire was designed to assess the quantitative impact of health conditions on loss of time and impaired productivity for functional activities such as work-for-pay, school work, and work around the house. There were no statistically significant treatment differences between the DOR/3TC/TDF and EFV/FTC/TDF treatment groups in regard to absenteeism,

presenteeism, overall work productivity impairment due to health, or activity impairment due to health across all study time points. Because the WPAI:GH was an exploratory endpoint, the study was not specifically powered to detect a treatment difference and is not proposed to be included in labeling.

19. Mechanism of Action / Drug Resistance Additional Information and Assessment

19.1. Mechanism of Action

DOR is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). HIV-1 reverse transcriptase (RT) is essential for HIV-1 replication as it converts the linear, single-stranded RNA genome into linear, double-stranded DNA using its reverse transcription and RNase H activities.

The Applicant conducted numerous structural, biochemical and virologic studies to support the mechanism of action. Co-crystallization of DOR and HIV-1 RT and the resultant X-ray structures showed that DOR binds to the classic NNRTI pocket of reverse transcriptase (data not shown, Study Report PD001mk1439, page 3). To examine the inhibition activity of wildtype (WT) and variant RTs with NNRTI resistance-associated substitutions K103N or Y181C, the Applicant produced the full-length recombinant HIV-1 RT proteins in *Escherichia coli* and quantified the incorporation of ruthenium-conjugated-dUMP into the minus strand DNA in the presence or in the absence of added drug using an electrochemiluminescence RT biochemical assay. The inhibitory concentration at 50% (IC_{50}) of DOR for RNA-dependent DNA polymerization of WT RT (12.2±2.0nM, n=3) was similar to NNRTI mutant RTs expressing K103N (9.7±1.4nM, n=3), and Y181C (9.7±0.9nM, n=3) resistance substitutions. The IC_{50} value of DOR for WT RT (12.2nM) was higher than the corresponding IC_{50} values for WT RT with efavirenz (0.42nM), etravirine (0.64nM), and rilpivirine (1.1nM).

The Applicant evaluated the inhibitory activity of DOR (assayed at concentrations from 1 to 100 µM) with purified human DNA polymerases α, β, and γ activities in biochemical assays using gapped fish sperm DNA as a template. Aphidicolin was used as a control inhibitor for DNA polymerase α, and ddATP as a control inhibitor for polymerases β and γ. DOR inhibited DNA polymerases α, β, and γ with an IC_{50} value >100µM. Therefore, the selectivity index of DOR for HIV-1 RT (IC_{50} value =12.2nM, Study Report PD001mk1439, page 4) compared to cellular DNA polymerases (>100µM) is >8,197-fold.

19.1.1. Antiviral Activity in Cell Culture

The antiviral activity of DOR was tested using the HIV-1 isolate R8 grown in MT4-gag-GFP T lymphoid cells (Table 122)**.**

Table 122. Antiviral Activity of DOR, EFV, ETR, and RPV Against HIV-1 Variants (EC_{50} Value (nM))

	EC_{50} Value nM (N)			
NNRTI	**WT**	**K103N**	**Y181C**	**K103N/Y181C**
DOR	12±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)

Source: Applicant's Table 2 in Study Report PD002mk1439, page 10; EFV, efavirenz; ETR, etravirine; RPV, rilpivirine.
DOR = doravirine (MK-1439); EC_{50} = effective concentration inhibiting 50% virus growth; EFV = efavirenz; ETR = etravirine; HIV-1 = human immunodeficiency virus type-1; NNRTI = non-nucleoside reverse transcriptase inh bitor; RPV = rilpivirine; WT = wildtype HIV-1 isolate R8 grown in MT4-gag-GFP T lymphoid cells

In addition, the antiviral activity of DOR was tested against 10 different subtypes of HIV-1 (Table 123).

Table 123. Antiviral Activity of DOR and Other NNRTIs Against 10 Different HIV-1 Subtypes* (Fold Change)

Subtype	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

Source: Applicant's Table 3 in Study Report PD002mk1439, page 10
DOR = doravirine (MK-1439); EFV = efavirenz; ETR = etravirine; RPV = rilpivirine
* A drug sensitive reference strain (HIV-1 CNDO) was employed as the control to calculate the fold changes.

19.1.2. Antiviral Activity in Cell Culture in the Presence of Serum and Serum Proteins

To determine if serum proteins affect the antiviral activity of DOR, the antiviral activity of DOR was determined against the HIV-1 R8 isolate in MT4 cells in the presence of 50% normal human serum compared to 10% normal human serum (Table 124).

Table 124. Antiviral Activity of DOR, EFV, ETR, and RPV Against HIV-1 Variants Assayed in MT4 Cell Line in the Presence of 10% or 50% Normal Human Serum

EC_{95} (nM) in the Presence of 10% Normal Human Serum				
NNRTI	**WT**	**K103N**	**Y181C**	**K103N/Y181C**
DOR	11.0±2.6 (n=11)	13.4±3.3 (n=11)	16.4±3.2 (n=9)	30.5±3.9 (n=8)
EFV	5.0±3.2 (n=203)	247±83 (n=152)	8.6±4.5 (n=45)	297±129 (n=41)
ETR	4.4±2.1 (n=29)	5.3±3.9 (n=28)	23.5±12 (n=11)	52.5±23.9 (n=11)
RPV	2.0±1.0 (n=8)	1.7±1.0 (n=5)	4.3±3.1 (n=6)	12.9±9.9 (n=6)
EC_{95} (nM) in the Presence of 50% Normal Human Serum				
NNRTI	**WT**	**K103N**	**Y181C**	**K103N/Y181C**
DOR	20±6.7 (n=9)	43±7.8 (n=7)	27±14 (n=5)	55±14 (n=7)
EFV	41±24 (193)	1427±53 (n=22)	80±34 (n=25)	2943±903 (n=12)
ETR	38±22 (n=42)	36±9.8 (n=24)	263±191 (n=19)	653±216 (22)
RPV	37±16 (n=11)	48±18 (n=7)	120±26 (n=6)	407±153 (6)

Source: Applicant's Table 1 in Study Report PD002mk1439, page 9.
DOR = doravirine (MK-1439); EC_{95} = effective concentration inhibiting 95% virus growth; EFV = efavirenz; ETR = etravirine; NNRTI = non-nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; WT = wildtype

19.1.3. Cytotoxicity, Mitochondrial Toxicity and Therapeutic Index

The Applicant tested the cytotoxicity of DOR in stationary and activated human peripheral blood mononuclear cells (phytohemagglutinin P-treated PBMCs), $CD4^+$ T helper cells (phytohemagglutinin P-treated), human monocytes (treated first with interferon γ and then with phorbol myristate acetate), human monocyte-derived macrophages, and in proliferating cells such as MT4 (human T cell leukemia cells), SupT1 (human T cell lymphoblastic lymphoma

cells), and HL60 (human acute myeloid leukemia cells) cell lines (Study Report PD004mk1439). Cell viability was tested using AlamarBlue™ Cell Viability Reagent (Invitrogen) following incubation of the cells with DOR or with a known cytotoxic control compound (L-001898133-001N003) for ~3 days.

DOR had no cytotoxicity up to a concentration of 100µM in stationary or in activated PBMCs, $CD4^+$ T cells, monocytes, and macrophages as well as in proliferating MT4, SupT1, and HL60 cell lines treated for ~72 hours. The EC_{50} values were determined with infected cells treated with DOR for 48 or 72 hours. DOR displayed no more cytotoxicity than its dissolvent DMSO in cell cultures. A therapeutic index of >8,333 was calculated from the cytotoxicity value (concentration inhibiting 50 percent cell growth; CC_{50}) and antiviral activity value (EC_{50}) in MT4 cells (therapeutic index = >100,000nM/12nM).

19.1.4. Combination Antiviral Activity in Cell Culture

The combination antiviral activity relationships of DOR with each of 18 FDA-approved anti-HIV-1 drugs (NNRTIs: delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine; NRTIs: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, zalcitabine, zidovudine; CCR5 coreceptor antagonist: maraviroc; gp41 fusion inhibitor: enfuvirtide; INSTI, raltegravir; PIs: darunavir, indinavir) were tested by (b) (4) (PD006mk1439). The known antagonistic combination of ribavirin and stavudine was used as a positive control for antagonism.

All the combinations were tested three times in CEM-SS cells (a human T-lymphoblastoid cell line) with $HIV\text{-}1_{IIIB}$, except for the combination of DOR with maraviroc, where $HIV\text{-}1_{Ba\text{-}L}$ was evaluated in MAGI-CCR5 (HeLa cells expressing high levels of CD4 and CCR5 coreceptor and the HIV-1 LTR driving β-galactosidase expression) cells. The combination antiviral relationships were analyzed using the MacSynergy II program and the Bliss Independence Model. The combinations of DOR with any of the 18 FDA-approved anti-HIV-1 drugs tested did not show antagonistic activity on their combined antiviral activities (mean antagonism volume values <-50) (Table 125).

Table 125. Interpretation of the MacSynergy Analysis for the Antiviral Efficacy of DOR in Combination with 18 FDA Approved Antiretroviral Drugs

Antiretroviral Drug	Mean Synergy/Antagonism Volume (nM^2%, μM^2% or nM·µM%; n=3)*	Interpretation of Antiviral Results in Combination with DOR
Nucleoside Reverse Transcriptase Inhibitors (NRTI)		
Lamivudine	32.4 / -0.15	Non-antagonistic
Abacavir	43.9 / -2.13	Non-antagonistic
Zidovudine	20.6 / -7.06	Non-antagonistic
Stavudine	43.7 / -3.90	Non-antagonistic
Zalcitabine	15.1 / -3.43	Non-antagonistic
Didanosine	11.4 / -0.70	Non-antagonistic
Emtricitabine	19.6 / 0	Non-antagonistic
Tenofovir DF	26.7 / -6.46	Non-antagonistic

Antiretroviral Drug	Mean Synergy/Antagonism Volume (nM^2%, μM^2% or nM·μM%; n=3)*	Interpretation of Antiviral Results in Combination with DOR
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)		
Delavirdine	18.6 / -11.4	Non-antagonistic
Efavirenz	4.81 / -4.05	Non-antagonistic
Etravirine	36.6 / -11.4	Non-antagonistic
Nevirapine	3.79 / -3.04	Non-antagonistic
Rilpivirine	6.78 /-3.33	Non-antagonistic
Protease Inhibitors		
Darunavir	40.9 / -4.54	Non-antagonistic
Indinavir	5.13 / -5.93	Non-antagonistic
Entry Inhibitors		
Maraviroc	35.7 / -0	Non-antagonistic
Enfuvirtide	14.4 / -20.4	Non-antagonistic
Integrase Inhibitor		
Raltegravir	60.8 / -7.27	Additive/slightly synergistic
Positive Antagonism Control (CEM-SS Cells)		
Stavudine/Ribavirin	1.50 / -298	Highly antagonistic at expected concentrations
Positive Antagonism Control (MAGI-CCR5 Cells)		
Stavudine/Ribavirin	27.2 / -412	Highly antagonistic at expected concentrations

Source: Applicant's Table 1 from Study Report PD006mk1439, page 8
CEM-SS = a human T-lymphoblastoid cell; DOR = doravirine (MK-1439); NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleos(t)ide reverse transcriptase inh bitor
*The Antiviral Synergy Plot (95%) datasets from multiple experiments (n=3) are combined and arithmetic means are calculated for each drug-drug concentration. The positive and negative values are individually summed to respectively give Mean Volumes for Synergistic and Antagonistic interactions.

19.1.5. Resistance Development in Cell Culture

DOR-resistant HIV-1 (subtype B, isolate R8) variants were selected in Sup T1 cells infected at low and at high MOIs using fixed doses of DOR (10x, 50x and 250x EC_{95}) (Study Report PD003mk1439). At high MOIs and 10x DOR EC_{95} value drug concentration, a single F227C substitution was detected in emerging HIV-1 resistant variants.

At low MOIs with escalating DOR concentrations (1x to 50x EC_{95}), the Applicant selected HIV-1 variants carrying known NNRTI resistance-associated substitutions, V106A, V108I, H221Y, and F227L. Other known NNRTI resistance-associated substitutions (L100I and K101E) were selected in parallel experiments with efavirenz treatment of HIV-1 subtype B cultures.

In addition, resistance selection was performed with HIV-1 subtypes A, B and C viruses. MT4 cells carrying an HIV-1 LTR-GFP fusion gene (MT4-GFP for subtype B) and MT4-GFP stably expressing the CCR5 gene (MT4-GFP/CCR5 for subtypes A and C) were infected at low MOIs and used to select DOR-resistant HIV-1 variants. V106A was the first substitution selected at low DOR concentrations in HIV-1 subtype B resistant variants. With increasing DOR concentrations, HIV-1 with double resistance-associated substitutions, V106A/F227L (fold change (FC) values >500), V106A/L234I (FC value =150) and V106A/F227L/L234I triple substitutions emerged. V108I was also selected followed by emergence of V106A and L234I. In parallel efavirenz-treated cultures, HIV-1 variants carrying the single (L100I) followed by double (L100I/K103N, L100I/V179D or triple (L100I/V179D/P225H or M230L) resistance-

associated substitutions were selected. HIV-1 variants carrying K103N, followed by L100I/K103N, were also selected by efavirenz treatment. L100I, K103N and V179D were the predominant efavirenz resistance-associated substitutions identified in the subtype B studies.

In DOR selection of HIV-1 subtype A variants in MT4-GFP/CCR5 cells, V106A/M was selected followed by selection of double resistance-associated substitutions (V106A(M)/F227L(C/V). Efavirenz selected HIV-1 variants carrying L100I with secondary emergence of L100I/Y188H/C or V179D and V106M followed by secondary selection of Y188C or L100I.

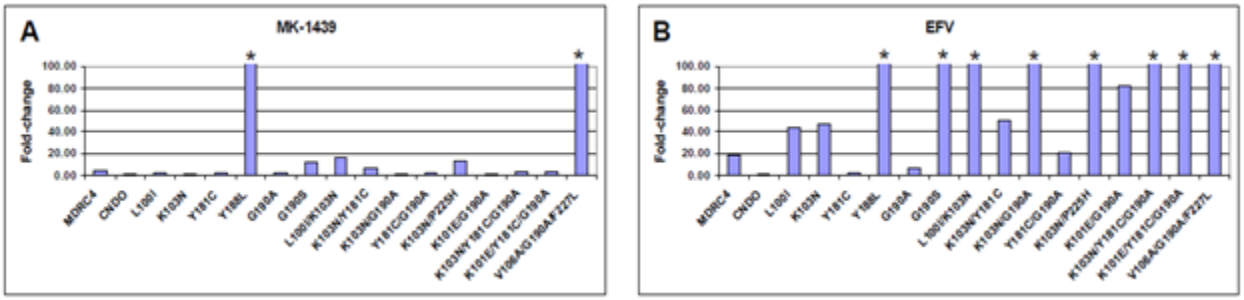
In HIV-1 subtype C studies, DOR treatment selected HIV-1 variants carrying V106A followed by secondary emergence of F227I or V106M followed by emergence of F227C. Efavirenz selected L100I and V106M variants followed by substitutions of Y188C or F227C.

In summary, the predominant emergent HIV-1 DOR resistance-associated substitutions selected in cell culture were: RT V106A/I/M, V108I, H221Y, F227C/L/V, M230I, L234I, P236L, and Y318F. Based on the X-ray structure of DOR/RT complex, 3 residues (V106, V108, and F227) are in close proximity to DOR and, thus, may play an important role in the interactions between DOR and RT. The V106A and V108I mutant viruses conferred approximately 12- and 4-fold reductions in susceptibility to DOR, respectively. Emergence of additional substitutions likely further reduces the susceptibility of the mutant viruses to DOR. In the resistance selection with subtype A, B, and C viruses using MT4-GFP cells, viruses containing substitutions at V106 and F227 account for the majority of mutants in the breakthrough viruses under low MOI conditions. The double mutant virus containing substitutions V106A/F227L confers >500-fold resistance to DOR.

To determine EC_{50} values of DOR against circulating HIV-1 variants, a PhenoSense GT™ assay (performed by (b) (4)) was used. The protease and RT genes from HIV-1 present in patient plasma samples were amplified and inserted into a resistance test vector, which contains a luciferase gene. HIV-1 stocks carrying the patient specimen-derived sequences were generated and tested for susceptibility to DOR, efavirenz, etravirine, and rilpivirine. Data were analyzed by plotting inhibition of luciferase activity versus log10 drug concentration and EC_{50} values were calculated by nonlinear least squares and bootstrapping (Study Report PD002mk1439).

The Applicant highlighted the single Y188L and the triple (V106A/G190A/F227L) resistance-associated substitutions, which conferred >100-fold decreases in susceptibility to DOR (Figure 6, panel A). However, another single substitution (G190S) and two double resistance-associated substitutions, L100I/K103N and K103N/P225H, conferred ~12-fold, ~15-fold, and ~12-fold reductions in susceptibility to DOR, respectively. K103N/Y181C also conferred 7-fold decreased susceptibility to DOR. In contrast, efavirenz susceptibility was decreased by >100-fold by multiple NNRTI resistance-associated substitutions. Single (Y188L, G190S), double (L100I/K103N, K103N/G190A, K103N/P225H) and triple (K103N/Y181C/G190A, K101E/Y181C/G190A, and V106A/G190A/F227L) resistance-associated substitutions conferred >100-fold reduction in susceptibility to efavirenz (Figure 6, panel B). Similar patterns in the relative frequencies and magnitude of DOR and efavirenz resistance phenotypes were observed using a panel of clinical NNRTI resistance-associated mutant viruses (below).

Figure 6. Comparison of the Mutant Profiles Between DOR and Efavirenz (EFV) in a Single Cycle Infection Assay



Source: Applicant's Figure 1 (Study Report PD002mk1439, page 12)
DOR = doravirine (MK-1439); EFV = efavirenz
HEK293 cells were employed for panel A and B experiments (b) (4) data). In panels A and B, HIV-1 CNDO is a drug-sensitive reference standard that is used to determine the FC in drug susceptibility relative to resistant viruses, and MDRC4 is a multi-drug resistant virus control that is used to evaluate and monitor assay performance.
*Indicates the EC_{50} value was not reached at the highest concentration tested.

19.1.6. Resistance and Cross-Resistance in a Panel of 96 Clinical NNRTI Resistance-Associated Mutant Viruses

The susceptibilities of a panel of 96 clinical NNRTI resistance-associated mutant viruses to DOR and efavirenz, etravirine, and rilpivirine were examined by (b) (4) (summarized in Table 126). The Applicant analyzed the data using an arbitrary 10-fold cutoff for drug resistance to all the NNRTIs including DOR (Study Report PD002mk1439, page 12). However, we reanalyzed the data using various cutoffs (0 to <5, ≥5 to 30, >30) for DOR susceptibility and using the (b) (4) cutoffs for EFV (≥3-fold), ETR (≥2.9-fold), and RPV (≥2.0-fold). In the FDA analyses, DOR showed antiviral activity with EC_{50}-fold change <5 against 62 of the 96 (65%) clinical HIV-1 isolates encoding RT NNRTI resistance-associated substitutions including the most commonly found K103N. Of the remaining 34 of the 96 (35%) clinical HIV-1 isolates with ≥5-fold reduced susceptibility to DOR, 33 (97%), 23 (68%), and 27 (79%) had ≥5-fold reduced susceptibility to efavirenz, etravirine, and rilpivirine, respectively.

Overall, in the panel of 96 mutant viruses, 78 mutant viruses (81%) were resistant to efavirenz (≥3-fold reduction in susceptibility). Of these, 57 (73%) had <5-fold reduction in susceptibility to DOR. Of the 63 viruses with ≥10-fold shift in EC_{50} value with efavirenz, 17 (27%) were reduced in susceptibility to DOR (≥10 fold).

Forty-one percent (n=39) of the 96 HIV-1 isolates encoding NNRTI resistance-associated substitutions were resistant to etravirine (≥3-fold reduction in susceptibility) and, of these, 59% (n=23) were also resistant to DOR (≥5-fold reduced susceptibility). Of the 15 mutant viruses that had ≥10 reduction in susceptibility to etravirine, eight (53%) were also resistant to DOR.

Almost half (47%; n=45) of the mutant viruses were reduced in susceptibility to rilpivirine (≥2-fold reduction) and of these 60% (n=27) were also reduced in susceptibility to DOR. Of the RPV-resistant viruses with a ≥10-fold shift, thirteen (13/19; 68%) also conferred resistance to DOR.

The common NNRTI resistance-associated substitutions (V106M, V108I, V179D, Y188C, Y188H, P236L) conferred less than 5-fold change in decreased susceptibility to DOR. Notably, however, the resistance-associated substitutions V106M and V108I emerged in RT of DOR-

resistant HIV-1 variants selected in cell culture resistance selection experiments (Study Report PD003mk1439).

Furthermore, the HIV-1 RT single amino acid substitutions V106A, Y181V, Y181C, G190S and Y188L had ≥5-fold reduced susceptibility to DOR. The greatest reductions in susceptibility to DOR were in HIV-1 variants encoding V106A (7.1 to 28.0 FC values) or Y188L (95- to >116 FC values). HIV-1 variants encoding a single NNRTI resistance-associated substitution, V106A or G190S, were cross-resistant to DOR and efavirenz; whereas, HIV-1 encoding the single NNRTI resistance-associated substitution of Y181V, Y181C, or Y188L were cross-resistant to DOR and efavirenz, etravirine, and rilpivirine.

HIV-1 variants encoding a combination of K103N with L100I, Y181C, P225H, and/or V108I conferred reductions in susceptibility to DOR in the range of 2.0 to 27-fold change (Table 126). HIV-1 clinical isolates encoding a combination of Y181C with K101E, K103N, K103R, V108I, V108V/I, V179D and/or G190S conferred 2.0 to 18-fold decreased susceptibility to DOR. The highest levels of reduced susceptibility to DOR were observed in HIV-1 clinical isolates encoding a combination of Y188L + K103N (>124-FC), Y188L + V106I (>110-FC), and E138K + Y181C + M230L (>111-FC). HIV-1 variants encoding these combinations of NNRTIs resistance-associated substitutions were cross-resistant to efavirenz, etravirine, and rilpivirine. HIV-1 isolates encoding the combination of V106A+G190A+F227 were highly resistant to DOR (>106 FC values) and were cross resistant to efavirenz.

Table 126. DOR Susceptibility of HIV-1 Carrying NNRTIs Resistance-Associated Substitutions

Substitution(s)	Fold Changes*	Cross-Resistance
Medium fold change values (Range: 5 to <30-fold)		
V106A	7.1-28.0	EFV
Y181V	1.0, 9.2	EFV, ETR, RPV
Y181C	1.2-1.5, 6.0	EFV, ETR, RPV
G190S	1.5, 4.6-11.0	EFV
K103N/P225H	5.7, 10.0	EFV
K103N/V108I	3.7, 5.5	EFV, RPV
K103N/Y181C	2.6, 3.9, 5.0-5.7	EFV, ETR, RPV
L100I/K103N	2.7, 4.5-19	EFV, ETR, RPV
V108I/Y181C	6.0, 7.8	EFV, ETR, RPV
K101E/Y181C/G190S	18.0	EFV, ETR, RPV
K103N/V108I/Y181C	2.0, 4.8-5.6	EFV, ETR, RPV
L100I/K103N/V108I	27.0	EFV, ETR, RPV
K103R/V108V/I/V179D/Y181C	4.9	EFV, ETR, RPV
Large fold change values (Range: ≥30-fold)		
Y188L	95 to >116	EFV, ETR, RPV
K103N/Y188L	>124	EFV, ETR, RPV
V106I/Y188L	>110	EFV, ETR, RPV
V106A/G190A/F227L	>106	EFV
E138K/Y181C/M230L	>111	EFV, ETR, RPV

Source: FDA generated summary table based upon results presented in Applicant's Table 4, Study Report PD002mk1439, pages 14-16

EFV = efavirenz; ETR = etravirine; HIV-1 = human immunodeficiency virus type-1; NNRTI = non-nucleoside reverse transcriptase inh bitor; RPV = rilpivirine

* Included are some FC values are <5, because isolates with the same resistance-associated substitution(s) had fold change values >5. Therefore, the substitution(s) and all the corresponding fold change values were included in the summary table.

19.2. Clinical Virology

19.2.1. Methodology

See section II.7.7.1.

19.2.2. Resistance Analyses in Treatment-Naïve Clinical Trials

Clinical Trial PN018

In PN018, 21 subjects (21/383; 5.5%) in the DOR arm and 16 subjects (16/383; 4.1%) in the DRV+r arm were identified as meeting FDA virologic failure criteria by week 48. Thus, the rates of virologic failure were similar between the DOR and DRV+r treatment groups. Of the 21 virologic failure subjects in the DOR arm, 7 had postbaseline resistance data, with 2 of them having DOR genotypic resistance emergence (Table 127). Subject (b) (6) had NNRTI resistance-associated substitution E138G emerge as a mixture with other RT substitutions (V60I R83K, K173T, V245E, V293I) after viral load rebound at week 48. Subject (b) (6) had NNRTI resistance-associated substitutions V90I/V, V106I, H221Y, F227C and lamivudine/emtricitabine resistance substitution, M184V, emerge after discontinuation due to non-compliance at week 24. The presence of the E138E/G mixture and other substitutions in Subject (b) (6) did not confer decreased susceptibility to DOR (FC=0.98). However, in Subject (b) (6), the V90I/V, V106I, H221Y and F227C substitutions conferred >97-fold decreased susceptibility to DOR and the M184V conferred resistance to emtricitabine (>58-fold).

In the DRV+r arm, 9 out of 16 subjects had postbaseline resistance data, but none of them showed genotypic or phenotypic resistance emergence to DRV+r, 3TC, FTC, ABC or TDF.

Table 127. Summary of Virologic Failures for FDA Resistance Analysis in PN018 (n=37; n=21 in DOR Arm and n=16 in DRV+r Arm)

Subject ID	Arm	Timepoint	Viral Load	PI RAS[1,2,3]	RT RAS[1,2,3]	Phenotype at Failure
(b) (6)	DOR +FTC TDF	WK24	31,896	NONE	A98S	DOR 1.11 FTC 0.86 TFV 1.0
	DOR +FTC TDF	WK48	847	NONE	NONE	DOR 0.69 FTC 1.05 TFV 0.78
	DOR +FTC TDF	WK48 Rebound	16,499	NONE	V60I R83K E138E/G K173T G196E V245E V293I	DOR 0.98 FTC 1.1 TFV 0.66 (EFV 0.7) (ETR 0.6) (RPV 0.8)
	DOR +FTC TDF	WK24	14,980	L89M	A62V V90I	DOR 2.47 FTC 1.0 TFV 1.1
	DOR +FTC TDF	WK24	13,417	M36I L89M	K104K/R	DOR 0.75 FTC 0.97 TFV 0.78
	DOR +FTC TDF	WK24	9,016	M36I R57K V77I L89M	**E194K**	NO POST BASELINE SAMPLE

Subject ID	Arm	Timepoint	Viral Load	PI RAS[1,2,3]	RT RAS[1,2,3]	Phenotype at Failure
(b) (6)	DOR +FTC TDF	WK48	24,002	V82I L89M	NONE	DOR 1.0 FTC 0.75 TFV 0.84
	DOR +FTC TDF	WK24 DC Noncompliant	55,708	M36I/M	K49K/R V90I/V V106I M184V H221Y F227C	DOR >97 FTC >58 TFV 0.42 (EFV 1.7) (ETR 1.5) (RPV 1.2)
	DRV +FTC TDF	WK36	32,792	NONE	NONE	DRV 0.56 FTC 0.87 TFV 0.8
	DRV +FTC TDF	WK4	12,200	NONE	NONE	DRV 0.53 FTC 1.08 TFV 1.03
	DRV +FTC TDF	WK16	1,182	M36I/M		DRV 0.91 FTC 1.12 TFV 0.76
	DRV +FTC TDF	WK8	712	NONE	NONE	DRV 2.7 FTC 1.16 TFV 0.83
	DRV +FTC TDF	WK24	3,397	M36I F53F/L L89M	NONE	DRV 0.7 FTC 0.92 TFV 0.83
	DRV + ABC 3TC	WK24	16,957	M36I V77I L89M	NONE	DRV 0.56 ABC 0.94 3TC 2.8
	DRV +FTC TDF	WK36	493	V77I	K104R E138S	DRV 0.43 FTC 1.15 TFV 0.7
	DRV +FTC TDF	WK36	55,646	E35INS M36L L38NL V77I V82I		DRV 1.54 FTC 0.93 TFV 0.9
	DRV +FTC TDF	WK24	489	E35D M36I L89M	S68G V179I	DRV 1.05 FTC 1.32 TDF 0.71

Source: FDA Analysis
3TC = lamivudine; ABC = abacavir; DOR = doravirine (MK-1439); DRV = darunavir; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; FTC = emtricitabine; PI = protease inhibitor; RT = reverse transcriptase; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; RAS = resistance-associated substitution
[1] Substitutions present at baseline are not bolded.
[2] Emergent substitutions are bolded.
[3] Resistance-associated substitutions are bolded and underlined.
Subjects with no postbaseline sample: DOR arm: (b) (6) ; DRV arm: (b) (6),

19.2.3. Clinical Trial PN021

In PN021, rates of virologic failure were comparable in the DOR and EFV treatment groups: 22 subjects (22/364; 6%) and 21 subjects (21/364; 5.8%), respectively, were identified as meeting FDA virologic failure criteria by week 48 (confirmed >400 copies/mL at discontinuation or at

virologic failure timepoint ≥ week 4). Of the 22 virologic failure subjects in the DOR arm, 20 had postbaseline resistance data, with 9 of them having evidence of DOR genotypic resistance emergence and 6 having phenotypic reduced susceptibility to DOR (Table 128). The nine subjects are summarized briefly below:

- Subject (b) (6) had emergent E138G as a mixture at week 36 with no decrease in DOR susceptibility (fold change =0.79).
- Subject (b) (6) had emergent Y188L at week 48 with corresponding >182-fold decrease in DOR susceptibility, emergent M184V with corresponding >102-fold resistance to 3TC and emergent M41L with no change in TDF susceptibility.
- Subject (b) (6) had emergent Y318F as a mixture at week 48 with no decrease in DOR susceptibility (fold change =0.35)
- Subject (b) (6) had emergent V90V/G, V106I, F227C at week 24 with >105-fold decreased DOR susceptibility and 3.1-fold change in 3TC susceptibility.
- Subject (b) (6) had emergent A98G, V106V/I, H221H/Y, P225P/L, and F227C at week 24 with >110-fold decrease in DOR susceptibility and emergent M184V with a decrease in 3TC susceptibility of >116-fold.
- Subject (b) (6) had emergent P225P/S and A355A/T mixtures at week 48 with a 1.8-fold change in DOR susceptibility.
- Subject (b) (6) had emergent A98A/G, P225L and F227C with >176-fold decrease in DOR susceptibility and emergent M184V with >104-fold decrease in 3TC susceptibility.
- Subject (b) (6) had emergent A98A/G, V106A, P225H, and Y318Y/F with >211-fold decrease in DOR susceptibility and emergent K65R with a 1.6-fold decrease in TDF susceptibility and 12-fold decrease in 3TC susceptibility.
- Subject (b) (6) had emergent V106M, V108V/I, and F227F/C/R with >103-fold decrease in DOR susceptibility and emergent K65R/K mixture and M184V with >97-fold decrease in 3TC susceptibility.

Table 128. Summary of Virologic Failures for FDA Resistance Analysis in PN021 (n=43; n=22 in DOR Arm and n=21 in EFV Arm) (n=9 in DOR Arm and n=12 in EFV Arm With Resistance Emergence)

Subject ID	Arm	Timepoint	Viral Load	RT Resistance Associated Substitution[1,2,3]	Phenotype at Failure
(b) (6)	DOR 3TC TDF	WK24	10,232	NONE	DOR 1.0 3TC 1.1 TDF 0.8
	DOR 3TC TDF	WK8	7,469	G196E	DOR 0.4 3TC 0.7 TDF 0.6
	DOR 3TC TDF	WK36	32,952	A62V K104K/R K122K/E E138E/G G196G/E K385K/R	DOR 0.79 3TC 1.3 TDF 1.0
	DOR 3TC TDF	WK48	1,256	M41L M184V Y188L V189I	DOR >182 3TC >102 TDF 0.8 (EFV >120) (ETR 3.4) (RPV 11)

Subject ID	Arm	Timepoint	Viral Load	RT Resistance Associated Substitution[1,2,3]	Phenotype at Failure
(b) (6)	DOR 3TC TDF	WK16	6,938	I257I/V	DOR 0.9 3TC 1.3 TDF 0.8
	DOR 3TC TDF	WK48	7,498	A62V Y318Y/F	DOR 0.3 3TC 0.7 TDF 0.8
	DOR 3TC TDF	WK48	788	E44E/G S68G T69T/A R72R/K K104Q K122K/R	DOR 0.6 3TC 1.1 TDF 1.0
	DOR 3TC TDF	WK24	12,691	V90V/G V106I T165K G196E F227C A288S	DOR >105 3TC 3.1 TDF 0.3 (EFV 3.1) (ETR 4) (RPV 3.4)
	DOR 3TC TDF	WK48	9,631	G196E	DOR 0.9 3TC 1.0 TDF 0.8
	DOR 3TC TDF	WK8	2,849	A98S G196E	DOR 1.6 3TC 1.1 TDF 0.9
	DOR 3TC TDF	WK24	13,901	NONE	DOR 0.8 3TC 1.2 TDF 1.
	DOR 3TC TDF	WK60	110,949	NONE	DOR 1.4 3TC 1.2 TDF 0.8
	DOR 3TC TDF	WK24	33,250	A98G V106V/I A158T M184V H221H/Y P225P/L F227C	DOR >110 3TC >116 TDF 0.6 (EFV 30) (ETR 7.9) (RPV 10)
	DOR 3TC TDF	WK24	221,864	NONE	DOR 1.1 3TC 1.1 TDF 0.8
	DOR 3TC TDF	WK48	172,105	P225P/S A355A/T	DOR 1.8 3TC 1.1 TDF 1.0 (EFV 1.2) (ETR 1.2) (RPV 0.8)
	DOR 3TC TDF	WK48	2,551	NO POST BASELINE SAMPLE	NO POST BASELINE SAMPLE
	DOR 3TC TDF	WK24	7,527	N57N/I A98A/G T107T/S M184V P225L F227C	DOR >176 3TC >104 TDF 0.5 (EFV 12) (ETR 2.8) (RPV 3.8)

Subject ID	Arm	Timepoint	Viral Load	RT Resistance Associated Substitution[1,2,3]	Phenotype at Failure
(b) (6)	DOR 3TC TDF	WK24	80,038	K65R S68S/G A98A/G V106A G196E P225H Y318Y/F	DOR >211 3TC 12 TDF 1.6 (EFV 4.8) (ETR 0.7) (RPV 1.0)
	DOR 3TC TDF	WK24	246,237	V179D L368L/S	DOR 0.8 3TC 1.1 TDF 1.0
	DOR 3TC TDF	WK4	410	A62A/V K104N V254V/I	DOR 1.3 3TC 1.4 TDF 1.0
	DOR 3TC TDF	WK24	71,727	K65K/R V106M V108V/I M184V F227F/C/R	DOR >103 3TC >97 TDF 0.4 (EFV 11) (ETR 0.8) (RPV 0.6)
	DOR 3TC TDF	WK8	742	NO POST BASELINE SAMPLE	NO POST BASELINE SAMPLE
	EFV, FTC, TDF	WK24	1,610	K103N	EFV 32 FTC 1.0 TDF 0.7
	EFV, FTC, TDF	WK16	22,634	NONE	FAILED
	EFV, FTC, TDF	WK16		K103N R277K G335A	EFV 20 FTC 0.9 TDF 0.9
	EFV, FTC, TDF	WK24	13,437	NONE	EFV 1.2 FTC 0.9 TDF 1.0
	EFV, FTC, TDF	WK8	1,551	NONE	EFV 2.3 FTC 0.9 TDF 0.8
	EFV, FTC, TDF	WK48	407	K103N K104R V179I G196E R284R/K	EFV 6.4 FTC 1.1 TDF 0.8
	EFV, FTC, TDF	WK24	2,329	K103Q	EFV 1.0 FTC 0.9 TDF 1.0
	EFV, FTC, TDF	WK48	31,823	S68G E89E/G V90I K103N E138E/G	EFV 11 FTC 1.1 TDF 0.9
	EFV, FTC, TDF	WK36	3,459	A98A/G K103N	EFV 5.3 FTC 0.9 TDF 0.9
	EFV, FTC, TDF	WK24	16,960	K103N	EFV 11 FTC 0.7 TDF 0.8

Subject ID	Arm	Timepoint	Viral Load	RT Resistance Associated Substitution[1,2,3]	Phenotype at Failure
(b) (6)	EFV, FTC, TDF	WK48	9,566	L74L/V V75M L109L/M V118I M184V G190E S191S/F V292I Q334Q/K R356R/K	FAILED
	EFV, FTC, TDF	WK48	480	NO POST BASELINE SAMPLE	NO POST BASELINE SAMPLE
	EFV, FTC, TDF	WK4	1,994	NONE	EFV 0.4 FTC 1.1 TDF 0.6
	EFV, FTC, TDF	WK24	4,017	K103N M184V G196E Y232Y/H	EFV 6.8 FTC >90 TDF 0.6
	EFV, FTC, TDF	WK24	2,649	V90I K103N L109M M184V M230L K263R	EFV >92 FTC >93 TDF 0.6
	EFV, FTC, TDF	WK16	1,496	K311K/Q T369T/I V381V/I	EFV 1.2 FTC 0.8 TDF 0.9
	EFV, FTC, TDF	WK4	996	NONE	EFV 0.7 FTC 0.9 TDF 0.8
	EFV, FTC, TDF	WK24	87,443	D67D/G K70E V90I M184I G190E K219K/E V245E V293I	EFV >112 FTC >90 TDF 0.4
	EFV, FTC, TDF	WK36	11,224	K65K/R K103N V108V/I M184M/I R356R/K E399E/G	EFV 22 FTC 81 TDF 0.8
	EFV, FTC, TDF	WK4	434,48	A98S	EFV 0.9 FTC 1.3 TDF 1.1
	EFV, FTC, TDF	WK36	136,633	K101K/N K103N V179I G196E P225P/H	EFV 24 FTC 1.3 TDF 1.0 (DOR 2.2)

Source: FDA Analysis
3TC = lamivudine; DOR = doravirine (MK-1439); DRV = darunavir; DRV+r =800 mg darunavir boosted with 100 mg ritonavir; EFV = efavirenz; ETR = etravirine; FTC = emtricitabine; RPV = rilpivirine; RT = reverse transcriptase; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; RAS = resistance-associated substitution
[1] Substitutions present at baseline are not bolded.
[2] Emergent substitutions are bolded.
[3] Resistance-associated substitutions are bolded and underlined.

Of the 21 virologic failure subjects in the EFV arm, 20 had postbaseline resistance data with 12 of them having EFV phenotypic and/or genotypic resistance to EFV (Table 128 and Table 129). Of these 12 subjects, 10 had emergent K103N substitution, 1 had emergent K65R as a mixture with 0.8-fold change in TDF susceptibility, and 5 had emergent M184V and FTC resistance. In addition, 2 other subjects in the EFV arm had either emergent K103Q or baseline K101Q with no corresponding decrease in EFV susceptibility (1 to 1.5-fold).

In PN021, emergence of M184V or I was comparable between the DOR and EFV arms emerging in 42 to 44% of virologic failures (Table 127). The emergence of thymidine analog mutation substitutions (TAMS: M41L, D67N, or K70E) was also similar between the arms: one subject

had emergent M41L in the DOR arm and one subject had emergent D67N/K70E in the EFV arm. Two subjects (22%) in the DOR arm had emergent K65R compared to one subject (8%) in the EFV arm. The predominant emergent NNRTI substitution in the EFV arm was the K103N substitution, which emerged in 83% (10/12) of the virologic failure subjects.

19.2.4. Combined Clinical Trials PN018 and PN021

For PN018 and PN021, rates of virologic failure to DOR were similar in both trials and were comparable with virologic failure rates in the comparator arms (Table 129). We also note that in PN018, 7/21 (33%) of the virologic failures had baseline viral loads >100,000 in the DOR arm compared to 3/15 (20%) in the DRV+r arm and in PN021, 9/22 (41%) of the DOR virologic failures had baseline viral loads >100,000 compared to 7/21 (33%) in the EFV arm.

However, the number of virologic failures with resistance data was higher in PN021 compared to PN018: (>90% compared to 33 to 56%) (Table 129). In the DOR arms of both trials, there were 11 total virologic failures with evidence of resistance emergence; 2 subjects in PN018 and 9 subjects in PN021. Seven of the 11 virologic failures with evidence of genotypic resistance emergence to DOR had decreased susceptibility to DOR (>97-fold to >211-fold).

Table 129. Summary of Resistance Emergence in Virologic Failures From PN018 and PN021

	PN018		PN021	
	DOR	DRV	DOR	EFV
Virologic Failures	21/383 (5.5%)	16/383 (4.2%)	22/364 (6%)	21/364 (6%)
Virologic Failures with Resistance Data	7/21 (33%)	9/16 (56%)	20/22 (91%)	20/21 (95%)
With Genotypic Resistance Emergence	2/7 (29%)	0/9 (0%)	9/20 (45%)	12/20 (60%)
With Phenotypic Resistance Emergence	1/7 (14%)	0/9 (0%)	6/20 (30%)	12/20 (60%)

	PN018		PN021	
	DOR	DRV	DOR	EFV
RT Substitutions				
K103N				10/12 (83%)
M184V/I	1/2		4/9 (44%)	5/12 (42%)
L74V				1/12 (8%)
K65R			2/9 (22%)	1/12 (8%)
D67N K70E				1/12 (8%)
M41L			1/9 (11%)	
T69S/G			1/9 (11%)	
A62V			1/9 (11%)	
V75M				1/12 (8%)
V118I				1/12 (8%)
E138G/K	1/2		1/9 (11%)	1/12 (8%)
V90I/G	1/2		1/9 (11%)	3/12 (25%)
A98G			3/9 (33%)	
K101N				1/12 (8%)
V106I/A/M	1/2		4/9 (44%)	
V108I			1/9 (11%)	1/12 (8%)
Y188L			1/9 (11%)	
G190E				2/12 (17%)
H221Y	1/2		1/9 (11%)	
P225H/L/S			4/9 (44%)	1/12 (8%)
F227C/R	1/2		4/9 (44%)	1/12 (8%)
M230L				1/12 (8%)
Y318F			2/9 (22%)	

Source: FDA Analysis
DOR = doravirine (MK-1439); DRV = darunavir; EFV = efavirenz

In PN018 and PN021 combined, the NNRTI resistance substitutions that emerged in more than one of the DOR virologic failures included V90I/G, A98G, V106I/A/M, E138G, H221Y, P225H/L/S, F227C/R, and the novel Y318F substitution (Table 22). Two other NNRTI substitutions that emerged were V108I and Y188L. The A98G, V106I/A/M, P225H/L/S, F227C/R and Y318F substitutions emerged most frequently in the virologic failures.

Substitutions at V106, V108I, H221Y, F227 and Y318F were also selected in cell culture resistance selection experiments. The presence of the Y188L substitution conferred 95- to >116-fold change in DOR susceptibility in cell culture. The other substitutions individually conferred a 3- to 10-fold change in DOR susceptibility in cell culture. However, in the virologic failures from the clinical trials, multiple substitutions emerged in combination which conferred >90-fold decrease in DOR susceptibility. The data indicate that the combination of multiple NNRTI substitutions each conferring <10-fold decreased DOR susceptibility can result in higher level DOR resistance of >90-fold.

19.2.5. Phenotypic Data and Cross-Resistance

There were no screening/baseline phenotypic data of DOR for the responder subjects in PN018. In PN021, there was only screening/baseline phenotypic data for 23 responder subjects (6 of whom were in the DOR arm). The fold change in DOR susceptibility for these subjects ranged from 0.29 to 3.69 with a median of 0.97 and mean of 1.05.

For the 20 virologic failures in PN021, the phenotypes ranged from 0.35 to >211 with a median of 1.3. However, the mean and median fold change in susceptibility to DOR of the nine virologic failures with evidence of DOR genotypic and/or phenotypic resistance from PN021 was considerably higher at 90 and >103, respectively (range 0.35 to >211). Three of the nine virologic failures who had only amino acid mixtures of NNRTI resistance substitutions showed DOR phenotypic fold changes of <2-fold. However, the mean and median fold change in susceptibility to DOR of the other 6 virologic failures with DOR phenotypic resistance was >148 and >143, respectively (range >103 to >211). All six of these virologic failures with resistance to DOR were also cross-resistant to EFV (>3-fold) (Table 130).

The mean and median fold change in DOR susceptibility was >141 and >110, respectively, (range >97 to >211) from the seven virologic failures with DOR genotypic and phenotypic resistance from both PN018 and PN021. Given the large range in DOR phenotypic susceptibilities of the small number of virologic failures, there are insufficient clinical phenotypic data to determine a definitive phenotypic breakpoint for DOR resistance. The shifts in susceptibility were hundred-fold or greater for the virologic failures with genotypic changes at NNRTI resistance substitutions (V90I/G, A98G, V106I/A/M, E138G, H221Y, P225H/L/S, F227C/R) whereas the shifts were <2-fold for the virologic failures with amino acid mixtures at NNRTI resistance sites.

Of the virologic failures with decreased susceptibility to DOR, 6/7 (86%) had resistance to EFV, 3/7 (43%) had decreased susceptibility to ETR, and 4/7 (57%) had decreased susceptibility to RPV.

Table 130. Cross-Resistance of DOR Virologic Failures With Reduced Susceptibility

Subject ID	Trial	Visit	DOR Phenotype	EFV Phenotype	RPV Phenotype	ETR Phenotype
(b) (6)	21	Week 48	>182	>120	11	3.4
	21	Week 24	>105	3	3.4	4.0
	21	Week 24	>110	30	10	7.9
	21	Week 24	>176	9	3.8	2.8
	21	Week 36	>211	4.8	1.0	0.7
	21	Week 24	>103	11	0.6	0.8
	18	Week 24	>97	1.7	1.2	1.5

Source: FDA Analysis
DOR = doravirine (MK-1439); EFV = efavirenz; ETR = etravirine; RPV = rilpivirine
PhenoSense® suscept bility cutoffs for EFV (3.0), RPV (2.5), ETR (2.9)
Bolded numbers indicate reduced susceptibility

Of the 11 virologic failure subjects resistant to EFV, 2 (18%) had decreased susceptibility to DOR (18- and 36-fold) (Table 131).

Table 131. Cross-Resistance of EFV-Resistant Virologic Failures in PN021

Subject ID	Visit	EFV Phenotype	DOR Phenotype
(b) (6)	Week 24	32	2.9
	Week 16	20	1.6
	Week 48	6.4	0.95
	Week 48	11	1.95
	Week 36	5.3	0.96
	Week 24	11	1.1
	Week 24	6.8	0.9
	Week 36	>92	36
	Week 24	>112	18
	Week 36	22	2.3
	Week 36	24	2.2

Source: FDA Analysis
DOR = doravirine (MK-1439); EFV = efavirenz
Bolded numbers indicate reduced susceptibility

19.3. Discrepancy in Resistance Data Between PN018 and PN021

For PN018 and PN021, rates of virologic failure to DOR were similar in both trials and were comparable with virologic failure rates in the comparator arms. However, the number of virologic failures with resistance data was higher in PN021 compared to PN018: (>90% compared to 33 to 56%). The lack of collection of resistance samples for multiple subjects in PN018 appears to be the explanation for the lower number of subjects with resistance data and resistance emergence in this trial.

An examination of the virologic failures in PN018 showed that several subjects did not have postbaseline resistance testing performed even though viral loads were >400 copies/mL. A request was sent to the Applicant for additional resistance information on these six subjects: (b) (6) (week 60), (b) (6) (week 36 or 48), (b) (6) (week 24), (b) (6) (week 8), (b) (6) (week 16), and (b) (6) (week 8). The Applicant's response stated that protocol PN021 was the trial included in the original Investigational New Drug application for DOR/3TC/TDF (MK-1439A, IND 124,997), which was submitted on March 23, 2015. In the Agency's Study May Proceed letter dated April 24, 2015, the Agency requested that Merck revise protocol PN021 to include collection of samples at every visit for potential resistance testing if virologic failure occurs and if confirmed. Protocol PN021 was amended accordingly, prior to initiation of the trial. However, because protocol PN018 was already ongoing and partially enrolled at that time, this change was not applied to protocol PN018. Therefore, per protocol, resistance samples were not collected at each study visit in protocol PN018 as they were in protocol PN021, which explains the discrepancy in the number of subjects with postbaseline resistance data between the two trials. No resistance samples were collected or available for Subject (b) (6) The resistance sample from week 24 for Subject (b) (6) was sent to (b) (4) and analyzed after the database lock. This subject was sensitive to all drugs in the PhenoSense® assay and GenoSure® assay with no recognized resistance associated substitutions in RT or protease. In addition, as stated earlier, samples from subjects with HIV-1 level <400 copies/mL were mistakenly sent for resistance testing, or subjects with HIV-1 >400 copies/mL did not have samples collected for such testing, due to investigational site error.

19.3.1. Summary of Virologic Failures in Phase 2 Trial 007

The DOR resistance emergence data from phase 2 trial 007, showing emergence of NNRTI resistance substitutions V106I, E138G and F227C, support the data obtained in the two phase 3 trials.

There were three virologic failure subjects from trial 007 summarized below:

- Subject (b) (6) (DOR 25 mg group): At screening and baseline, HIV-1 RNA was 93,083 and 47,556 copies/mL, respectively, <40 copies/mL at week 16 and 498 copies/mL at week 24 with protocol-defined virologic failure (PDVF) (rebound) at week 36 (HIV-1 RNA 17,814 copies/mL) and week 72 (time of resistance test). Discontinued from study medication at week 60 (last laboratory visit was at week 72) due to non-compliance with study medication. K101K/E and P236P/L genotypic resistance substitutions were found at week 36 with no evidence of phenotypic decrease in DOR susceptibility; no genotypic or phenotypic resistance was found for emtricitabine or tenofovir.
- Subject (b) (6) (DOR 25 mg group): At screening and baseline, HIV-1 RNA was 95,653 and 123,695 copies/mL, respectively, <40 copies/mL at weeks 8, 12, 16, and 24, 663 copies/mL at week 36 and 44 copies/mL at week 48. At week 60, HIV-1 RNA was 533 copies/mL (VF confirmation). The subject completed the trial and reported being 100% compliant with study medication. The following genotypic resistance substitutions were found: V106V/I and F227C and M184V (emtricitabine-associated substitution); 66-fold decrease in susceptibility to DOR and a greater than 91-fold decrease in susceptibility to emtricitabine noted. No genotypic or phenotypic resistance for tenofovir.
- Subject (b) (6) (DOR 100 mg group): At screening and baseline, HIV-1 RNA was 209,326 and 111,344 copies/mL, respectively. A V179D genotypic resistance substitution was found at screening. At week 24, HIV-1 RNA was 46,213 copies/mL (VF confirmation) and subject discontinued due to non-compliance. At week 24, V179D and E138E/G and A62V (emtricitabine- and tenofovir-associated substitution) were found. No evidence of phenotypic decrease in susceptibility to DOR, emtricitabine, or tenofovir was noted.

20. Other Drug Development Considerations Additional Information

Not applicable

21. Data Integrity Related Consults (OSI, Other Inspections)

[This section will be used in the future for the actual inspection reports – to be determined.]

22. Labeling Considerations and Recommendations Additional Information

22.1. Overview of Major Labeling Changes

- Information highlighted below are significant changes made to the full prescribing information from the Applicant proposed label submitted on October 23, 2017 for PIFELTRO and DELSTRIGO labels.
- HIGHLIGHTS and TABLE OF CONTENTS were revised for consistency with the rest of the Prescribing Information.
- "Treatment-naïve" was revised to "no prior antiretroviral treatment history" throughout the PI for consistency with newer HIV-1 labels.
- DELSTRIGO label was updated with information from 3TC and TDF labels for consistency. (b) (4) ,
- (b) (4)

22.2. Summary of Major Changes

Below is a summary of the major changes in the Prescribing Information with references to the respective review sections for further details.

4 CONTRAINDICATIONS

Enzalutamide and mitotane were added as examples of strong CYP3A inhibitors that are contraindicated to be coadministered with PIFELTRO and DELSTRIGO.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Common Adverse Reactions:

PIFELTRO: Table 1, which displays (b) (4) , was modified to display adverse reactions for all grades in at least 5% of subjects in both DRIVE-FORWARD and DRIVE-AHEAD.

DELSTRIGO: Table 1 was modified to include adverse reactions for all grades in at least 5% of subjects in DRIVE-AHEAD. The adverse reactions listed in Table 1 for both PIFELTRO and DELSTRO labels differ as PIFELTRO also included adverse reactions from DRIVE-FORWARD.

For the rationale to include all grades, refer to section II.7.6.

The Applicant proposed to include [redacted] (b) (4)

PIFELTRO: The revised labeling contains the discontinuation rate of study drug due to adverse events for each arm in DRIVE-FORWARD and DRIVE-AHEAD.

DELSTRIGO: The revised labeling contains the discontinuation rate of study drug due to adverse events for DRIVE-AHEAD.

For rationale on discontinuation rates, refer to section II.7.6.

Neuropsychiatric Adverse Events:

PIFELTRO and DELSTRIGO: Table 2, which displays neuropsychiatric adverse events (NPE) in DRIVE-AHEAD, was revised to include the prespecified NPEs of sleep disorders and disturbances, dizziness, and altered sensorium with treatment difference displayed with confidence interval. Subjects who reported one or more NPE and subjects who reported depression and suicide/self-injury NPEs are described in text without treatment difference because these events were not prespecified for statistical testing. Information about DRIVE-AHEAD NPEs characterized by severity, onset, and those leading to treatment discontinuation was added as well. For rationale for labeling with respect to display of NPE, treatment difference, 95% CI and p-value for the prespecified and non-prespecified NPEs, refer to section II.6.4.1 and section II.6.4.2.

Similarly, refer to section II.6.4.1 and section II.6.4.2 for rationale for labeling with respect to display of prespecified and non-prespecified lipid parameters.

Laboratory Abnormalities:

PIFELTRO and DELSTRIGO: Table 3, which displays laboratory abnormalities, was revised to [redacted] (b) (4) etained ULN cutoff pertaining to grade 2 to 4 events and to include total bilirubin with limit 1.1 to <1.6 ULN and fasted lipid values for cholesterol, LDL, and triglycerides corresponding to grade ≥3 limits.

Table 4, which displays [redacted] (b) (4), was revised to add baseline and change in lipid levels and included treatment difference and confidence interval for prespecified lipid levels for LDL and non-HDL cholesterol. For rationale, refer to section II.6.4.1 and section II.6.4.2.

6.2 Postmarketing Experience

Postmarketing events from 3TC and TDF labels were added, as subsection 6.2 should include adverse reactions that are identified from domestic and foreign spontaneous reports for each component of the drug.

7 DRUG INTERACTIONS

Changes to **7.1, Effects of Other Drugs on PIFELTRO**, and **7.2, Effects of Other Drugs on DELSTRIGO**, were based on Physiologic Based Pharmacokinetic modeling of the persistence

of the CYP3A induction effect. A recommendation to allow at least 4 weeks of cessation of drug prior to initiation of PIFELTRO or DELSTRIGO was added for enzalutamide, anticonvulsants, antimycobacterials, mitotane, and St. John's wort.

Concomitant drugs from Table 5, "Drug interactions with PIFELTRO or DELSTRIGO," where no clinically relevant changes were observed were (b) (4) included as text.

For **7.2, Effect of PIFELTRO on Other Drugs**, and **7.3, Effects of DELSTRIGO on Other Drugs**, the list of drugs with no clinically significant changes in concentration was updated to include those drugs for which: 1) it was empirically studied drug interaction and no clinically significant changes in DOR were observed, or 2) it is an ARV drug and no significant drug interactions are anticipated based on mechanistic understanding of all drugs involved.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Statement that no exposure-response relationship for efficacy was identified for DOR in dose range trial of 0.25 to 2 times the recommended dose of PIFELTRO or DELSTRIGO was added.

12.3 Pharmacokinetics

Results summarizing negative clinical drug interaction studies for DOR was added to include in vitro data on inhibition and induction of CYP enzymes, and inhibition of UGT1A1 and major efflux and update transporters.

Table 7, which displays clinically significant drug interactions, was modified (b) (4) ketoconazole and ritonavir. Although the AUC for DOR increased approximately 3- to 3.5-fold when coadministered with ketoconazole and ritonavir, the increase in DOR exposure was not considered clinically significant. The available safety data from phase 2 and 3 trials was sufficient to support the increased DOR exposures.

12.4 Microbiology

Updates to subsection 12.4 were based on the criteria for FDA resistance analysis. For rationale, refer to section II.7.7.1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Following statement was added: "A statistically significant incidence of thyroid parafollicular cell adenoma and carcinoma seen only in female rats at the high dose was within the range observed in historical controls." For rationale, refer to section II.7.7.6.

14 CLINICAL STUDIES

PIFELTRO: Table 8, which displays virologic outcomes in DRIVE-FORWARD and DRIVE-AHEAD, was revised to include "n's" for subgroup demographics.

DELSTRIGO: Table 8, which displays virologic outcomes in DRIVE-AHEAD, was revised to include "n's" for subgroup demographics.

Patient Labeling

Patient labeling was updated for consistency with changes to the package insert and for consistency with other labels for the treatment of HIV-1 infection.

23. Postmarketing Requirements and Commitments

23.1. PMR/PMCs for DOR

The following postmarketing requirements (PMRs) and postmarketing commitments (PMCs) apply to DOR.

Pediatric Research Equity Act PMRs

- Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of doravirine in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg. The safety and antiviral activity of doravirine in pediatric subjects must be evaluated for a minimum of 24 weeks.
- Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of doravirine in HIV-1 infected pediatric subjects at least 2 years of age and weighing less than 35 kg. The study participants must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of doravirine
- Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of doravirine in HIV-1 infected pediatric subjects 4 weeks of age to 23 months of age. The study participants must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of doravirine.

PMCs

- Assess the phenotypic susceptibility in cell culture of doravirine and approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) against Y318F alone and in combination with the following substitutions, which have been associated with doravirine and/or other NNRTIs: K103N; Y181C; K103N/Y181C; L100I; L100I/K103N; V106A; P225H; V106A/P225H; H221Y; V106M; F227C; V108I.
- Conduct a drug-drug interaction study to evaluate the pharmacokinetics of doravirine and its primary metabolite (M9) when doravirine 100 mg BID is coadministered with rifabutin as compared to the administration of doravirine 100 mg QD alone in healthy subjects.

23.2. PMR/PMCs for DOR/3TC/TDF

The following PMRs and PMCs apply to the fixed-dose combination tablet of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate (DOR/3TC/TDF).

Pediatric Research Equity Act PMRs

- Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of doravirine/lamivudine/tenofovir disoproxil fumarate fixed dose combination (FDC) product in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg. Subjects must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of doravirine/lamivudine/tenofovir disoproxil fumarate FDC product. A clinical trial in pediatric subjects weighing at least 35 kg may not be required

if dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products.

- Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of doravirine/lamivudine/tenofovir disoproxil fumarate fixed dose combination (FDC) product in HIV-1 infected pediatric subjects age 2 years and older, and weighing less than 35 kg. The study participants must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of the FDC product, doravirine/lamivudine/tenofovir disoproxil fumarate. A clinical trial in pediatric subjects 2 years and older and weighing less than 35 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials conducted with the individual drug products.

PMCs

- Assess the phenotypic susceptibility in cell culture of doravirine and approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) against Y318F alone and in combination with the following substitutions, which have been associated with doravirine and/or other NNRTIs: K103N; Y181C; K103N/Y181C; L100I; L100I/K103N; V106A; P225H; V106A/P225H; H221Y; V106M; F227C; V108I

24. Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinic investigators as recommended in the guidance for industry, Financial Disclosure by Clinical Investigators,[4] and by 21 CFR 54.4. None of the 280, 584, and 573 investigators for PN007, PN018, or PN021 respectively are employed by the Applicant, although three investigators are married to Merck employees. Two of the investigators (<1%) have financial interests or arrangements with the Applicant, three subinvestigators (all for PN018) did not return the requested information about financial disclosures, and the remaining investigators (>99%) have no financial interests or arrangements with the Applicant, as defined in 21 CFR 54.2.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoint (proportion of subjects with HIV-1 RNA <50 copies/mL at week 48) is an objective laboratory measurement that is assessed centrally and not vulnerable to investigator bias. In addition, all three trials were randomized, active-controlled, and double-blind, which would minimize the potential for investigator bias to play a role. Finally, <1% of investigators had financial interests or arrangements with the Applicant, and these investigators with financial interests enrolled <1.5% of the subjects.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

Covered Clinical Study (Name and/or Number): PN007, PN018 "DRIVE-FORWARD", and PN021 "DRIVE-AHEAD"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 280 (58 principal investigators) for PN007, 584 (125 principal investigators) for PN018, and 573 (126 principal investigators) for PN021		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 investigators, but 3 investigators are married to Sponsor employees: (b) (6): a principal investigator for PN007 (b) (6) subjects enrolled), for PN018 (b) (6) subject enrolled), and for PN021 ((b) (6) subjects enrolled) (b) (6): a sub-investigator for PN018 (b) (6) subjects enrolled) and for PN021 (b) (6) subjects enrolled) (b) (6): a principal investigator for PN021 (b) (6) subjects enrolled)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2 investigators: (b) (6)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1 (by wife)		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)