CTD 第 2 部

2.5　臨床に関する概括評価

MSD 株式会社

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
3TC	Lamivudine
ABC	Abacavir
AE	Adverse event or adverse experience
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ASaT	All subjects as treated
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
BID	Twice daily
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CP	Child-Pugh
CSR	Clinical study report
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-drug interaction(s)
DOR	Doravirine (MK-1439)
DRV	Darunavir
DRV+r	Darunavir boosted with ritonavir
EC50	Half maximal effective concentration
EFV	Efavirenz
EMA	European Medicines Agency
EPZICOM™/KIVEXA™	Alternative brand names for fixed dose combination of abacavir (ABC) plus lamivudine (3TC)
EU	European Union
FAS	Full analysis set (analysis population)
FCT	Film-coated tablet
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FFP	Fit-for-purpose
FMI	Final market image

Abbreviation/Term	Definition
FTC	Emtricitabine
GMR	Geometric least-squares mean ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV-1	Human immunodeficiency virus type 1
HPMCAS	Hypromellose acetate succinate
IAS-USA	International Antiviral Society-USA
ICH	International Council on Harmonisation
InSTIs	Integrase strand-transfer inhibitors
iPSP	Initial Pediatric Study Plan
iSAP	Integrated statistical analysis plan
LDL-C	Low-density lipoprotein cholesterol
MHLW	Ministry of Health, Labor and Welfare (Japan)
MSP	Main Safety Pool
NDA	New Drug Application
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOEL	No-observed-effect-level
NRTI	Nucleos(t)ide reverse transcriptase inhibitors
OCT	Oral compressed tablet
PBPK	Physiologically-based pharmacokinetic
PCR	Polymerase chain reaction
PDLC	Pre-Defined Limit of Change
PDVF	Protocol-defined virologic failure
P-gp	P-glycoprotein
PI	Protease inhibitor
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PMF	Premarket formulation
PP	Per Protocol
QD	Once daily
RNA	Ribonucleic Acid
RPV	Rilpivirine
RT	Reverse Transcriptase

Abbreviation/Term	Definition
SAE	Serious adverse event or serious adverse experience
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
SSP	Special Safety Pool
TDF	Tenofovir disoproxil fumarate
TLOVR	Time to loss of virologic response
TRUVADA	Brand name for fixed dose combination of emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF)

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Pharmacological Class

1.1.1 Doravirine (DOR)

Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by the Applicant as a once-daily (QD) oral treatment for Human immunodeficiency virus type 1 (HIV-1) infection. It is being developed as both the single agent DOR and as a fixed-dose combination (FDC) with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) (hereafter referred to as DOR/3TC/TDF). 3TC and TDF were selected as components of the FDC due the broad clinical use of these agents and recommended use of these agents as components in preferred regimens in HIV treatment guidelines.

1.1.2 Lamivudine (3TC)

Lamivudine (EPIVIR™, 3TC), hereafter referred to as 3TC, is a dideoxy analog of the nucleoside cytidine and, after phosphorylation, inhibits HIV reverse transcriptase and causes premature DNA chain termination. 3TC is approved by the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other health authorities for use in combination with other antiretroviral therapies (ARTs) for the treatment of HIV-1 infected adults and pediatric patients 3 months of age and older.

1.1.3 Tenofovir disoproxil fumarate (TDF)

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

1.2 Chemical and Pharmaceutical Properties

The formulation for DOR drug product is a film-coated tablet (dose strength of 100 mg DOR). The tablet is composed of [redacted] of DOR with hypromellose acetate succinate. [redacted] is further processed by [redacted] with other excipients and blending with [redacted] excipients prior to compression. Following compression, the final market image tablets are film-coated.

The formulation for DOR/3TC/TDF drug product is a bilayer, film-coated tablet (dose strength of 100 mg/300 mg/300 mg DOR/3TC/TDF). One layer consists of a DOR [redacted] while the other layer consists of a 3TC and TDF granulation. The DOR contains [redacted] of DOR with hypromellose acetate

succinate that is then [redacted] with other excipients. The 3TC and TDF granulation is manufactured by a roller compaction process with excipients. DOR [redacted] and 3TC/TDF granulation are compressed into bilayer tablets and then film-coated and the final market image tablets are film-coated.

1.3 Indications

DOR and DOR/3TC/TDF have not been licensed in any country.

DOR, in combination with other antiretroviral medicinal products, and DOR/3TC/TDF have been developed for the treatment of HIV-1 infection in adults. The recommended dosage of DOR in adults is one 100-mg tablet taken orally QD with or without food. The recommended dose of DOR/3TC/TDF is one tablet (containing 100 mg of DOR, 300 mg of 3TC, and 300 mg TDF) taken orally QD with or without food. The proposed indication text varies by country according to regulatory guidelines. For specific proposed indication, please refer to the proposed product labeling included with the application.

1.4 Scientific Background and Introduction

Since the development of the first ART for the treatment of HIV infection, there have been significant advances in HIV treatment. However, there remains an unmet medical need for new ARTs that are as highly effective and convenient as current ARTs with better tolerability and fewer side effects than currently available ARTs.

1.4.1 Epidemiology and Public Health Burden of HIV-1 Infection

HIV/acquired immunodeficiency syndrome (AIDS) is associated with significant morbidity and mortality. The World Health Organization (WHO) reported an estimated 36.7 million people around the world were living with HIV-1 infection in 2016 [Ref. 5.4: 04QL06]. Of these, approximately 1.8 million adults and children were newly infected and an estimated 1.0 million people died from AIDS-related illnesses. The majority of new infections and death (64% and 73%, respectively) occurred in sub-Saharan Africa. Approximately 2.1 million adults and children were living with HIV infection in western and central Europe and North America, with approximately 73,000 being newly infected.

To address this global public health challenge, the United Nations AIDS program has led global efforts to establish new targets for HIV treatment [Ref. 5.4: 04J04X]. The “90-90-90” goal for 2020 is that 90% of all people living with HIV will know their HIV status, 90% of all people diagnosed with HIV infection will receive sustained ART and 90% of all people receiving ART will have achieved viral suppression. Modeling suggests that if these targets are achieved, the HIV/AIDS epidemic can be controlled globally by 2030, resulting in profound health and economic benefits.

1.4.2 Current HIV-1 Treatment Landscape

Currently, more than 30 anti-retroviral drugs are commercially available for the treatment of HIV-1 infection in combination antiretroviral therapy (cART) worldwide. These drugs inhibit various stages of the HIV-1 lifecycle and belong to 6 classes: nucleos(t)ide reverse

transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors (PIs), integrase strand-transfer inhibitors (InSTIs), fusion inhibitors, and co-receptor antagonists. Treatment with cART (typically a combination of 3 antiretroviral drugs) has been shown to be effective in both reducing plasma HIV-1 ribonucleic acid (RNA) below the level of detection and restoring immune system function.

HIV-1 treatment guidelines have evolved in regard to which cART should be recommended as initial regimens vs. alternative regimens. NNRTI-based regimens had been previously recommended as first regimens, but are now on the alternative list for some guidelines, with recommendations differing slightly by region. Regimens including one of the existing NNRTIs were removed from the recommended list due to tolerability/safety and/or efficacy limitations (eg. the neuropsychiatric adverse event (AE) profile for efavirenz (EFV) and the suboptimal efficacy of rilpivirine (RPV) in patients with HIV-1 RNA >100,000 copies/mL).

- The US Department of Health and Human Services HIV-1 Treatment Guidelines (2016) [Ref. 5.4: 04QP95] recommend a regimen of either an InSTI or darunavir + ritonavir (DRV+r) in combination with 2 NRTIs.
- The International Antiviral Society-USA (IAS-USA) recommends initial regimens for most patients include 2 NRTIs plus an InSTI; other effective regimens include NNRTIs or boosted PIs with 2 NRTIs (2016 recommendations [Ref. 5.4: 04LMDF]).
- Other treatment guidelines such as the WHO (2016, [Ref. 5.4: 04MN5R]) and the European AIDS Clinical Society (EACS) (2017 [Ref. 5.4: 04MZSY]) include the NNRTI class (including EFV and RPV) as a recommended regimen in addition to InSTI- and PI-based regimens.

1.4.3 Rationale for DOR

As of 24-OCT-2017, 5 NNRTI medications are approved for use in the U.S.: delavirdine, EFV, etravirine, nevirapine, and RPV. As a class, NNRTIs have a long history of use (since 1996) and are generally highly efficacious against HIV-1 in treatment-naïve individuals [Ref. 5.4: 04PB3J]. However, these medications have various tolerability, safety, and efficacy limitations, some of which are specific to the NNRTI class, while some are specific to the individual NNRTI.

Efavirenz and RPV are among the most commonly prescribed anti-HIV-1 medications in the U.S. and in the EU. However, treatment-limiting neuropsychiatric AEs are associated with EFV use [Ref. 5.4: 04PB39] and efficacy in patients with HIV-1 RNA levels >100,000 copies/mL is suboptimal with RPV [Ref. 5.4: 04LK3B]. Delavirdine, etravirine, and nevirapine are less commonly prescribed than EFV and RPV primarily due to known side effects, lower efficacy, and/or a more complicated dosing schedule.

There is an unmet need for an NNRTI that can provide efficacy comparable to EFV without the neuropsychiatric side effects associated with EFV. There is also a need for an NNRTI that does not have the dyslipidemia side effects associated with other commonly used ART agents. Management of dyslipidemia is particularly important in HIV-1 infected individuals,

due to the known impact on serum lipids of various ART agents and due to the increased cardiovascular risk inherent to HIV-1 infection. Additionally there is a need for an NNRTI with a sufficient safety profile that demonstrates consistent efficacy across demographic and prognostic factors, including subjects with high baseline HIV-1 RNA (>100,000 copies/mL).

Availability of efficacious and well tolerated medications from multiple classes is important to provide multiple options for treatment, given various scenarios regarding patient co-morbidities, co-infections, concomitant treatments and potential for drug-drug interactions (DDIs), and pretreatment HIV-1 RNA and $CD4^+$ status.

Doravirine is a novel NNRTI that addresses many of the deficiencies of currently available NNRTIs that have caused them to be removed as recommended first-line regimens in some countries.

Doravirine has demonstrated:

- High and durable efficacy against to 2 well-established comparators.
- Consistent efficacy across demographic and prognostic factors, including subjects with high baseline HIV-1 RNA (>100,000 copies/mL) and low CD4+ T-cell count (<200 cells/mm^3).
- Low rate of viral drug resistance with a unique resistance pathway commonly requiring multiple substitutions to confer resistance.
- Excellent (superior) safety profile with:
    - a superior neuropsychiatric profile with significantly fewer neuropsychiatric AEs compared to EFV-based regimens;
    - a superior lipid profile (LDL-C and non-HDL-C) when compared with EFV and DRV+r; and
    - a lower rate of discontinuations due to AEs and SAEs when compared with EFV.
- Favorable drug-drug interaction profile with DOR not a perpetrator of clinically significant drug-drug interactions:
    - No dose adjustment necessary for patients with mild, moderate or severe renal or mild or moderate hepatic impairment; and
    - No interaction with proton pump inhibitors and other gastric acid-modifying agents and cation containing antacids.
- Available as a single-entity or fixed dose combination of DOR/3TC/TDF with once daily dosing without regard to food.

1.5 Overview of the Clinical Development Program

The clinical development program for DOR included parallel development of DOR as a single agent to be used in combination with other antiretroviral agents, and as an FDC (DOR/3TC/TDF) for the treatment of HIV-1 infection in adults aged 18 years and older.

The clinical development program for DOR and DOR/3TC/TDF includes 36 Phase 1 trials, 1 Phase 2b trial (P007) and 2 Phase 3 trials (P018, P021) that contribute data to this application; an additional 2 Phase 2 trials (P028, P030) and 1 Phase 3 trial (P024) are ongoing [Sec. 2.7.3.1.2-trtmtnve48wk].

Consistent with the formal guidance received from the FDA and the EMA Committee for Medicinal Products for Human Use (CHMP) as described in Section 2.5.1.6, the clinical development program for DOR and DOR/3TC/TDF proceeded as follows:

1. Demonstration of in vivo HIV-1 antiretroviral activity (P005): This Phase 1, placebo-controlled trial in 18 HIV-1-infected, treatment-naïve male subjects provided evidence of the short-term antiretroviral activity of DOR as monotherapy and supported continuation of the clinical program with larger trials using combination therapy.

2. In Phase 2b, P007, a multicenter, double-blind, randomized, dose-ranging trial in HIV-1-infected, treatment-naïve subjects was conducted to provide data supporting dose selection for subsequent Phase 2 and 3 trials and to provide 96-week efficacy and safety data for the selected dose. Assessment of safety included an evaluation of DOR at the final selected dose compared to EFV with respect to the proportion of subjects with CNS events at Week 8 and Week 24.

3. In Phase 3, the efficacy and safety of DOR and DOR/3TC/TDF were confirmed in trials P018 (DRIVE-FORWARD) and P021 (DRIVE-AHEAD) in HIV-1 infected treatment-naïve subjects. Both trials were designed to evaluate the non-inferior efficacy of DOR 100 mg:

   - In P018, DOR was evaluated as a single agent compared with the PI darunavir boosted with ritonavir (DRV+r). Doravirine was used in combination with either emtricitabine (FTC)/TDF (administered in the trial as TRUVADA™) or abacavir (ABC) plus 3TC (ABC/3TC; administered in this trial as either EPZICOM™ or KIVEXA™), as selected by the investigator.

   - In P021, DOR was evaluated as the fixed-dose combination DOR/3TC/TDF compared with the EFV-based regimen EFV/FTC/TDF (administered in this trial as ATRIPLA™).

The focus of this application is the complete 48-week data from P018 and P021. Subjects in each of these Phase 3 trials will continue blinded treatment through 96 weeks, with an optional open-label extension for an additional 96 weeks.

1.5.1 Overview of the Phase 1 Program

Thirty-six (36) Phase 1 trials were conducted to assess the safety, tolerability, PK, biopharmaceutics, and pharmacodynamics (PD) of DOR and DOR/3TC/TDF [Appendix 2.7.2: 1]. The following key trials were included:

- Two rising single and rising multiple dose trials (P001 and P006),
- One PD and PK trial in treatment-naïve male subjects with HIV-1 infection (P005),
- One single dose QT/QTc trial (P017) evaluating a supratherapeutic dose of DOR (1200 mg), which provided ~4-fold and ~3-fold the Cmax and AUC0-24, respectively, relative to the clinical dose,
- Intrinsic factor trials evaluating single-dose DOR PK in subjects with renal impairment (P051), subjects with hepatic impairment (P019), and in healthy elderly male and female subjects (P009),
- Sixteen drug-drug interaction (DDI) trials evaluating DOR as a victim and/or perpetrator of DDIs,
- A bioequivalence trial (P039) evaluating the PK of the uncoated (Phase 3 formulation) and coated DOR final market image (FMI) tablet,
- Two biopharmaceutics trials supporting development of DOR/3TC/TDF, that were conducted with the DOR/3TC/TDF FMI (P026 and P029), and
- Two trials evaluating the effect of food on DOR (P037) and DOR/3TC/TDF (P029) PK.

The clinical pharmacology trials were conducted primarily with DOR, administered as the single entity tablet. Following administration of the DOR/3TC/TDF FMI, the DOR, 3TC, and TDF components demonstrated similar PK compared to coadministration of each component administered as a single entity in a relative bioavailability trial (P026). Therefore the clinical pharmacology profile for each individual component administered as a single entity is applicable to the FDC of DOR/3TC/TDF [Sec. 2.7.1.2.1.2].

In Phase 1 trials, 700 subjects were enrolled, of which 678 subjects received at least one dose of DOR. The majority of subjects (~95%) were healthy adults; of these subjects, 12 were elderly (>65 years of age) male and 12 were elderly female. Other subject populations enrolled included 8 subjects with moderate hepatic impairment, 8 subjects with severe renal impairment, and 18 male HIV-1 infected subjects.

1.5.2 Overview of the Phase 2/3 Program

The results of P007, a Phase 2b dose-ranging trial of DOR plus FTC/TDF compared with EFV plus FTC/TDF in treatment-naïve HIV-1 infected adults (≥18 years of age) supported selection of the 100-mg dose of DOR for evaluation in the Phase 3 program. Two pivotal Phase 3 trials (P018, P021) evaluated the efficacy and safety of DOR and DOR/3TC/TDF in a global treatment-naïve HIV-1 infected adult population. Both Phase 3 trials are randomized, double-blind, active-controlled trials in which the comparator is a commonly-prescribed antiretroviral drug from either the PI class (DRV+r in P018) or the NNRTI class (EFV in P021).

Of the 979 subjects who received DOR or DOR/3TC/TDF in trials P007, P018, and P021, 855 received the 100-mg dose of DOR for the entire duration of the trial (for which the subject participated), either as DOR or DOR/3TC/FDC (the remaining received the 25, 50 or 200-mg dose of DOR in P007 [Table 2.5: 1]).

Table 2.5: 1

Summary of the Phase 2 and Phase 3 Clinical Trials Supporting the Current Application

Protocol	Phase	Location	Status	Primary Endpoints	Duration	DOR or DOR/3TC/TDF	N (Pts)	Comparator	N (Pts)
Treatment-Naïve Patients									
007	2b	Worldwide	Complete	Safety at Week 24	96 Weeks	DOR 25 mg†	40	EFV (600 mg)	108
						DOR 50 mg†	43		
						DOR 100 mg	108		
						DOR 200 mg†	41		
018	3	Worldwide	Ongoing (Pivotal; Week 48 CSR included in this application)	Efficacy and Safety at Week 48	96 weeks (optional extension for an additional 96 weeks)	DOR 100 mg	383	DRV (800 mg) +r (100 mg)	383
021	3	Worldwide	Ongoing (Pivotal; Week 48 CSR included in this application)	Efficacy and Safety at Week 48	96 weeks (optional extension for an additional 96 weeks)	DOR/3TC/TDF (100 mg/300 mg/300 mg)	364	EFV/FTC/TDF (600 mg/200 mg/300 mg)	364

Abbreviations: 3TC = lamivudine; DOR = doravirine; DRV = darunavir; EFV = efavirenz; FTC = emtricitabine; r = ritonavir (as used to boost darunavir); TDF = tenofovir disoproxil fumarate.

† Subjects randomized to DOR 25, 50 or 200 mg were switched to 100 mg dose between Weeks 36 and 72.

Source: [Ref. 5.3.5.1: P007V01MK1439, P018V01MK1439, P021V01MK1439A]

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Overall, the populations studied in the Phase 2b and Phase 3 trials in this application are diverse and representative of the worldwide target population. The 979 subjects treated with DOR or DOR/3TC/TDF in 29 countries allow a comprehensive evaluation of subjects with diverse racial, ethnic, and varied HIV disease characteristics (specifically, there was good representation of patients with high baseline viral load, and good proportion of viral subtypes B and non-B).

Efficacy and safety were evaluated in relevant demographic subgroups of the pooled populations in this Application, specifically age, gender, region, race and ethnicity. Efficacy was also evaluated in subgroups by the baseline prognostic factors of screening HIV-1 RNA, baseline HIV-1 RNA, baseline $CD4^+$ T-cell counts, chronic hepatitis B or C status, and viral subtype.

In addition to the trials that provide data to support this Application, an additional 2 Phase 2 trials and 1 Phase 3 trial of DOR/3TC/TDF are ongoing. These trials have not reached their primary analysis milestones and are not included in this application:

1. P028 is a Phase 2b trial to evaluate a switch from EFV/FTC/TDF (supplied as ATRIPLA™ or generic versions of this FDC) or its components [EFV, FTC plus TDF]) to DOR/3TC/TDF in virologically-suppressed, HIV-1 infected subjects.

2. P030 (Phase 2), in which treatment-naïve, HIV-1-infected subjects with selected transmitted NNRTI resistance mutations are treated with open-label DOR/3TC/TDF to assess antiretroviral activity.

3. P024 (Phase 3), in which HIV-1-infected subjects virologically suppressed on regimens that include ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir), cobicistat-boosted elvitegravir, or an NNRTI (specifically, EFV, nevirapine or RPV) each administered with two NRTIs are switched to DOR/3TC/TDF to assess antiretroviral activity.

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.

1.6 Regulatory Guidance and Advice

1.6.1 Regulatory Guidance

Regulatory agency advice was obtained at key points during the development program. Formal guidance received from the U.S. FDA and the EMA is summarized below.

1.6.2 FDA Regulatory Interactions

An [redacted] was held with the FDA on [redacted]-20[redacted] to seek agreement on [redacted] for DOR and DOR/3TC/TDF. Agreements were reached with the FDA that:

- The nonclinical data package, comprised of the completed, on-going, and planned non-clinical safety assessment program for DOR (and additionally for DOR/3TC/TDF, the public domain data available and reviewed from completed nonclinical safety assessment programs of 3TC and TDF as individual agents), was sufficient to support filing and registration of DOR and DOR/3TC/TDF.

- [redacted]

- [redacted]

- [redacted]

- [redacted]

- The proposed clinical data package, consisting of 48-week safety and efficacy data from the 2 Phase 3 clinical trials (P018 and P021), supported by 96-week safety and efficacy data from the Phase 2b trial (P007) would support filing and registration of DOR and DOR/3TC/TDF for the proposed indications.

- The size of the safety database, comprised of ~890 HIV-1 infected subjects who received the intended DOR dose of 100 mg (administered either as DOR plus 2 NRTIs or as the DOR/3TC/TDF FDC) for a minimum duration of 48 weeks, would be adequate to support filing and registration of DOR and DOR/3TC/TDF for the proposed indications.

- With regard to Merck's proposed safety endpoints in the Phase 3 trials in support of inclusion of comparative statements in the DOR and DOR/3TC/TDF labels:

  - For the dyslipidemia endpoint (P018 and P021): The FDA recommended using low-density lipoprotein cholesterol (LDL-C) as the comparative measure for lipid changes and agreed that non-high-density lipoprotein cholesterol (HDL-C) may also be clinically useful but should be compared either sequential to or in conjunction with LDL-C.

- For the neuropsychiatric AE endpoint (P021): Agreement was reached on the assessment of neuropsychiatric AEs at Week 48, with sequential testing in the categories of (1) dizziness, (2) sleep disorders and disturbances, (3) altered sensorium, (4) depression and suicide/self-injury, and (5) psychosis and psychotic disorders (in the order listed), with analysis to stop at the first category that fails to meet a two-sided p-value of 0.05. The FDA agreed to inclusion of AEs of all severities, noting that if the events were dominated by Grade 1 (mild) events, this may be reflected in the label.

- For the discontinuation due to AE endpoint (pooled data from P007 and P021): Merck proposed to include a hypothesis that DOR has a statistically significantly lower proportion of subjects who discontinued from study due to an AE compared to EFV (based on data pooled from P007 and P021 in a prospectively planned integrated statistical analysis plan), to support inclusion of a statement to that effect in the prescribing information. The Agency noted that the P007 results would be considered supportive, and that a final decision on inclusion of the pooled analysis of discontinuation due to AEs in the prescribing information would be a review issue.

On [redacted], the FDA agreed with Applicant's proposal [redacted]

[redacted] was agreed by the FDA on [redacted]. An [redacted] was agreed by the FDA on [redacted].

On [redacted], the FDA requested historical control data on skull malformations in Dutch-Belted rabbits, the strain used in the embryo-fetal development toxicity study where DOR was evaluated (TT #[redacted]-7050). Merck provided additional data on [redacted] and [redacted]. In a response dated [redacted], the FDA agreed with Merck's position that the highest dose of 300 mg/kg/day is the developmental no observed effect level (NOEL) in this study.

A [redacted] was held on [redacted]. Key agreements reached include the following:

- The nonclinical data package and the clinical efficacy and safety data package were considered adequate to support the DOR and DOR/3TC/TDF NDA submissions.
- The proposed approach to use a Simcyp physiologically-based pharmacokinetic (PBPK) model to simulate the effects of moderate CYP3A inhibitors on DOR exposure was deemed reasonable.
- The proposed content and timetable (approximately three months after submission of the initial New Drug Applications) for submission of the Safety Update Report were considered acceptable.

- [redacted]

1.6.3 European Regulatory Interactions

CHMP [redacted], summarized below, was obtained for DOR and DOR/3TC/TDF on [redacted]-20[redacted]:

- The completed, ongoing, and planned non-clinical safety pharmacology, genotoxicity, repeat dose toxicity, developmental and reproductive toxicity, and carcinogenicity studies were considered to be sufficient to support filing and registration of DOR, provided that no unexpected findings are detected during the evaluation. There was no need for combination studies. The toxicological follow-up of the metabolite M9 was identified as a potential concern.

- [redacted]

- The CHMP advised to perform a comparative bioavailability study using the final formulation of DOR/3TC/TDF in comparison with the administration of the individual components.

- The CHMP advised that a comparison of the exposure between healthy subjects and HIV-1 infected subjects should be made by a cross-trial comparison of non-compartmental PK analysis of plasma concentrations and from population PK analysis.

- The potential for interaction with OATP1B1 and 1B3 was noted: the CHMP encouraged the use of pitavastatin (more sensitive substrate) instead of atorvastatin for evaluation of this interaction.

- [redacted]

- [redacted]

- The CHMP [redacted]

- The proposed clinical data package, consisting of 48-week safety and efficacy data from the 2 Phase 3 clinical trials (P018 and P021), supported by 96-week safety and efficacy data from the Phase 2b trial (P007) was considered likely to provide sufficient data for assessment of the acceptability of the proposed indications of DOR and DOR/3TC/TDF.

- It was noted that superiority claims on safety endpoints, or comparative statements to other products, would not be accepted in the Summary of Product Characteristics (SmPC). The scope of the labelling and indication would only be determined after the data review.

- The proposed size of the safety database was considered to fulfill International Council on Harmonisation (ICH) criteria.

In [redacted] CHMP [redacted] obtained on [redacted] -20[redacted], the CHMP did not agree with the Applicant's proposal [redacted] The following is a summary of the recommendations provided in the Advice letter:

- [redacted]
- [redacted]
- [redacted]

A [redacted] was held with the European Medicines Agency on [redacted] -20[redacted].

[redacted] were agreed for DOR and DOR/3TC/TDF on [redacted] -20[redacted]. [redacted] for DOR and DOR/3TC/TDF were agreed on [redacted] -20[redacted] and [redacted] -20[redacted], respectively.

C Confidential

2 OVERVIEW OF BIOPHARMACEUTICS

2.1 Formulation Development (DOR and DOR/3TC/TDF)

DOR is a Biopharmaceutics Classification System (BCS) Class II compound (low solubility/high permeability) and is formulated as [redacted] based tablet. Two key formulations of DOR, a fit-for-purpose (FFP) oral compressed tablet (OCT) and a pre-market formulation (PMF) OCT, both containing [redacted]% DOR in hypromellose acetate succinate (HPMCAS) as [redacted], were used in the clinical development program. Differences between the FFP and PMF OCTs were minimal and were not anticipated to affect the bioavailability of DOR. The FMI is a film-coated tablet (FCT) that is identical to the PMF OCT used in the Phase 3 trial (P018), with the exception of film-coating. A bioequivalence trial [Sec. 2.7.1.2.1.1.1] established the bioequivalence of the PMF OCT to the FMI FCT intended for commercialization (P039).

DOR/3TC/TDF also utilized [redacted]% DOR in HPMCAS as [redacted]. BCS classifications of 3TC and TDF are well documented in the literature. TDF is widely considered as a BCS Class III compound (high solubility/low permeability) [Ref. 5.4: 04668S]. 3TC is also highly soluble but its permeability characteristics are less well defined; bioavailability of 3TC has been reported to be 80 - 86% [Ref. 5.4: 04P95N], [Ref. 5.4: 04N7XT]. While conservatively 3TC is classified as a BCS III compound, bioavailability does not appear to be limited by its permeability [Ref. 5.4: 03RL4N].

Two biopharmaceutics trials (P026 [Sec. 2.7.1.2.1.2.1] and P029 [Sec. 2.7.1.2.2.1.2]) were conducted with DOR/3TC/TDF. The DOR, 3TC, and TDF components of the DOR/3TC/TDF FMI demonstrated similar PK to coadministration of each individual component in a relative bioavailability trial (P026). Further, in a component interaction trial (P038) evaluating the PK of DOR, 3TC, and tenofovir when 3TC and TDF were administered in the presence or absence of 100 mg DOR, coadministration of DOR with 3TC and TDF had no meaningful impact on the PK of DOR, 3TC, or tenofovir [Sec. 2.7.2.2.3.1.8]. Thus, the clinical pharmacology, safety, and efficacy profile of DOR established following treatment with DOR/3TC/TDF can be applied to the DOR single entity tablet and the converse is also true; the clinical pharmacology, safety and efficacy profile of the single entity DOR tablet is also applicable to DOR/3TC/TDF.

2.2 Bioavailability and Food Effect

Absolute oral bioavailability of the FMI 100 mg DOR tablet was estimated using a population PK model-based approach with PK data following administration of a 100 µg IV microdose (P044) and following oral administration of the FMI in the trial establishing bioequivalence between the OCT and FMI (P039). The absolute oral bioavailability of the FMI 100 mg DOR tablet is ~64% [Sec. 2.7.1.3.1].

The effect of a standard high-fat meal on the PK of the DOR OCT and the FMI DOR/3TC/TDF was formally assessed in definitive food effect trials in healthy subjects (P037 for the DOR OCT, and P029 for FMI DOR/3TC/TDF) [Ref. 5.3.1.1: P029, P037]. Data from P037 demonstrated no clinically meaningful effect of food on the PK of DOR, and

the DOR tablet was administered without regard to food in Phase 3. Based on these data, the DOR tablet may be administered without regard to food. Data from P029 demonstrated there was no clinically meaningful effect of food on the PK of DOR, 3TC, and tenofovir when administered as DOR/3TC/TDF, and DOR/3TC/TDF was administered without regard to food in the Phase 3 trials. Based on these data, DOR/3TC/TDF may be administered without regard to food [Sec. 2.7.1.3.3].

3 OVERVIEW OF CLINICAL PHARMACOLOGY

3.1 Overview of Clinical Pharmacology

The PK of DOR has been extensively evaluated, both as a single entity and as DOR/3TC/TDF in healthy subjects. Following single dose oral administration, DOR is rapidly absorbed with a median time to maximum plasma concentration (Tmax) of 2 hours. Plasma concentrations of DOR decline in a monophasic manner. The terminal half-life ($t_{1/2}$) of DOR is 15 hours, which supports once daily (QD) dosing. The $t_{1/2}$ is comparable to 3TC and TDF and prevents a long PK tail of DOR if therapy is discontinued, minimizing the risk of resistance to DOR. Steady state is generally achieved by Day 2 of QD dosing, with accumulation ratios of 1.2 to 1.4 for AUC0-24, Cmax, and C24. Accumulation and time to steady state were consistent with the single-dose PK of DOR, indicating the PK of DOR is not time-dependent. DOR exposure and Cmax increase less than dose proportionally. Based on a population PK analysis, the steady state AUC0-24, C24, and Cmax of DOR following administration of 100 mg QD to HIV-1 infected subjects are 37.8 µM•hr (%CV: 29.2%), 930 nM (%CV: 63.1%), and 2.26 µM (%CV: 18.5%), respectively. DOR PK variability is moderate. The PK of DOR is similar in healthy subjects and in subjects with HIV-1 infection such that PK assessed in healthy subjects is representative of PK in subjects with HIV-1 infection.

DOR is eliminated primarily by oxidative metabolism by CYP3A. Excretion of unchanged drug via urinary or biliary excretion is minor. A summary of the DOR pharmacokinetic profile and ADME properties is provided in [Sec. 2.7.2.1.3.1].

3.2 Dose Selection and Comparability Bounds

3.2.1 Doravirine Dose Selection

Doses of 25 mg and 200 mg QD DOR were evaluated in a Phase 1b trial (P005) ([Sec. 2.7.2.2.4.1]) in HIV-1-infected subjects. In this trial, both the 25 mg and 200 mg QD doses achieved similar viral response (HIV-1 RNA placebo-corrected change from baseline) and were generally well tolerated. Consequently, DOR doses of 25, 50, 100, and 200 mg QD were selected for evaluation in a Phase 2b dose ranging trial (P007).

In the Phase 2b trial (P007) ([Sec. 2.7.3.2.1-trtmtnve48wk]), treatment-naïve subjects without NNRTI resistance mutations were randomized to receive DOR in doses of 25 mg, 50 mg, 100 mg, or 200 mg or EFV 600 mg in addition to FTC/TDF. DOR doses of 25 mg to 200 mg resulted in similar decreases in HIV-1 RNA over 24 and 48 weeks relative to EFV. These results indicate that the exposures achieved over the 25 mg to 200 mg doses are on the

plateau of the dose-response curve in this population. No safety concerns were identified over the 25 mg to 200 mg dose range.

Based on these data, a dose of 100 mg QD DOR was selected for evaluation in Phase 3 as it was projected to provide adequate C24 values in the setting of common NNRTI resistance mutations against which DOR is considered to be active in vitro (including the reverse transcriptase (RT) substitutions K103N, Y181C, Y190A, and K103N/Y181C) ([Sec. 2.6.2.2.1.2.1]). As similar decreases in HIV-1 RNA were observed over the 25 mg to 200 mg dose range, 100 mg provides a maximal response with no further efficacy advantage to dosing higher than 100 mg. The 100 mg dose also had the potential to provide adequate safety margins in the setting of factors that could result in increased DOR exposure such as concomitant administration of CYP3A inhibitors. Similarly the 100 mg dose had the potential to provide margins for decreases in DOR PK without impacting efficacy, such as in the setting of moderate CYP3A inducers. The appropriateness of the 100 mg QD dose with respect to benefit-risk balance is further demonstrated by data from the pivotal Phase 3 trials ([Sec. 2.7.3.3-trtmtnve48wk], [Sec. 2.7.4.2]).

3.2.2 Doravirine Exposure Response for Efficacy

An efficacy exposure-response analysis was conducted to investigate the relationship between DOR PK and the proportion of subjects with HIV-1 infection achieving HIV-1 RNA < 50 copies/mL and < 40 copies/mL, and protocol defined virologic failure (PDVF), at Week 48 in the Phase 2b and Phase 3 trials [Sec. 2.7.2.1.5.2].

No statistically significant exposure-response relationships were identified between any of the DOR steady state PK parameters (AUC, C24, or Cmax) and efficacy endpoints over the range of exposures achieved at the 25 mg to 200 mg QD doses in the Phase 2b (P007) analysis. While statistically significant exposure-response relationships were identified between DOR PK and all efficacy endpoints evaluated in the Phase 3 analysis for exposures achieved at the 100 mg QD dose, the relationships were generally flat with a minimal decrease in efficacy in subjects with the lowest 10% of DOR PK values. The strongest exposure-response associations were observed for DOR steady state C24 compared to steady state AUC0-24 or Cmax. The exposure-response analyses for efficacy indicate that the exposure-response relationship is generally flat and that steady state DOR C24 values achieved at 100 mg QD in the Phase 3 trials or at the 25 mg to 200 mg dose range in the Phase 2b trial are associated with high levels of antiretroviral activity and low rate of virologic failure. Higher DOR exposures than those achieved with the 100 mg QD dose do not appear to lead to additional clinical benefit.

3.2.3 Doravirine Exposure Response for Safety

Results of safety analyses for the Phase 2b and Phase 3 trials indicate that the 100-mg QD dose of DOR is generally well tolerated ([Sec. 2.7.4.1]). No safety findings of concern have been identified in the clinical program. Nevertheless, given the incidence of neuropsychiatric AEs or unfavorable changes from baseline in fasting lipids for other HIV-1 antiretroviral treatments, the DOR exposure-response relationship for these endpoints was investigated [Sec. 2.7.2.1.5.3]. There was no association between the incidence of neuropsychiatric AEs

or fasting LDL-C levels and DOR exposure over the 25 mg to 200 mg QD dose range evaluated in the Phase 2b and Phase 3 trials. While a significant relationship was identified for DOR exposure and non-HDL-C, non-HDL-C levels over the range of exposures associated with the 100 mg QD dose were below baseline levels of non-HDL-C, consistent with an overall decrease in non-HDL-C levels relative to baseline. Therefore, the exposure-response relationship is not clinically meaningful.

3.2.4 Rationale for Doravirine Comparability Bounds

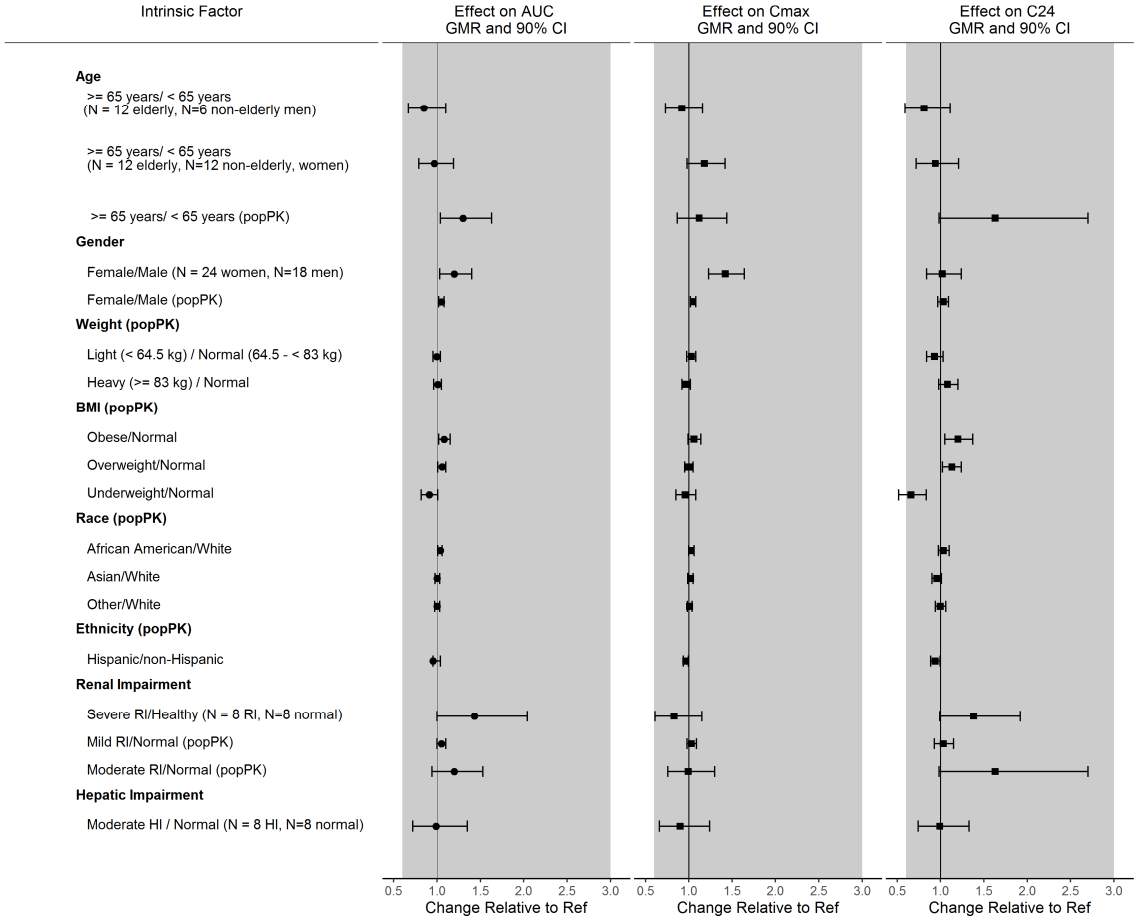
The bounds defining a clinically important change in DOR PK are (0.6, 3.0); the bounds define the range of change relative to the steady state C24 (lower bound) and AUC0-24 (upper bound) values associated with the 100 mg QD dose in subjects with HIV-1 infection where safety and efficacy are expected to be comparable to that of the recommended clinical dose of 100 mg QD DOR. The definition of a clinically important change in DOR exposure (comparability bounds) is based on preclinical safety data, the demonstrated efficacy in the Phase 2b and Phase 3 trials and the clinical and safety experience in the Phase 1, Phase 2b and Phase 3 trials. These clinical bounds are further supported by the exposure-efficacy relationships observed over the range of exposures achieved in Phase 2b and Phase 3, the lack of apparent association between AEs and increased dose or exposure, and efficacy and safety analyses for subpopulations [Sec. 2.7.2.1.5.4].

3.3 Intrinsic Factors and Special Populations

As determined from Phase 1 trials and/or population PK analyses, the effects of age, gender, weight, body mass index (BMI), race, ethnicity, mild, moderate or severe renal impairment, and mild or moderate hepatic impairment on DOR PK are not clinically meaningful, and no dose adjustments are needed [Sec. 2.7.2.1.3.1.2]. The effects of the intrinsic factors are summarized in the forest plot in Figure 2.5: 1.

Figure 2.5: 1

Effect of Intrinsic Factors on DOR Steady State C24 and AUC0-24



popPK GMR and 90% CI based on simulation of N = 1000 HIV-1 infected subjects per covariate subgroup for categorical covariates or total for continuous covariates
[Ref. 5.3.5.3: 04PPZ5], [Ref. 5.3.3.3: P009: 11], [Ref. 5.3.3.3: P019: 11], [Ref. 5.3.3.3: P051MK1439: 11]

Renal excretion of DOR is minor, with only 6% of the dose excreted unchanged in urine. The PK of DOR were evaluated in a dedicated Phase 1 trial in subjects with severe renal impairment (eGFR values <30 mL/min/1.73 m² and not on dialysis) compared to healthy subjects (P051) [Sec. 2.7.2.2.2.3]. Additionally, in the DOR population PK analysis, eGFR was not identified as a significant covariate impacting DOR PK. The change in DOR PK observed in subjects with severe renal impairment fell within the clinical bounds of (0.6, 3.0) and thus, dose adjustments of DOR for HIV-1 infected subjects with mild, moderate, and severe renal impairment are not needed.

The PK of DOR was evaluated in subjects with moderate hepatic impairment (CP-B score of 7-9) and compared with healthy subjects (P019) ([Sec. 2.7.2.2.2.2]). The changes in DOR PK observed in subjects with moderate hepatic impairment fell within the clinical bounds of

(0.6, 3.0); therefore, dose adjustments of DOR for HIV-1 infected subjects with mild and moderate hepatic impairment are not needed.

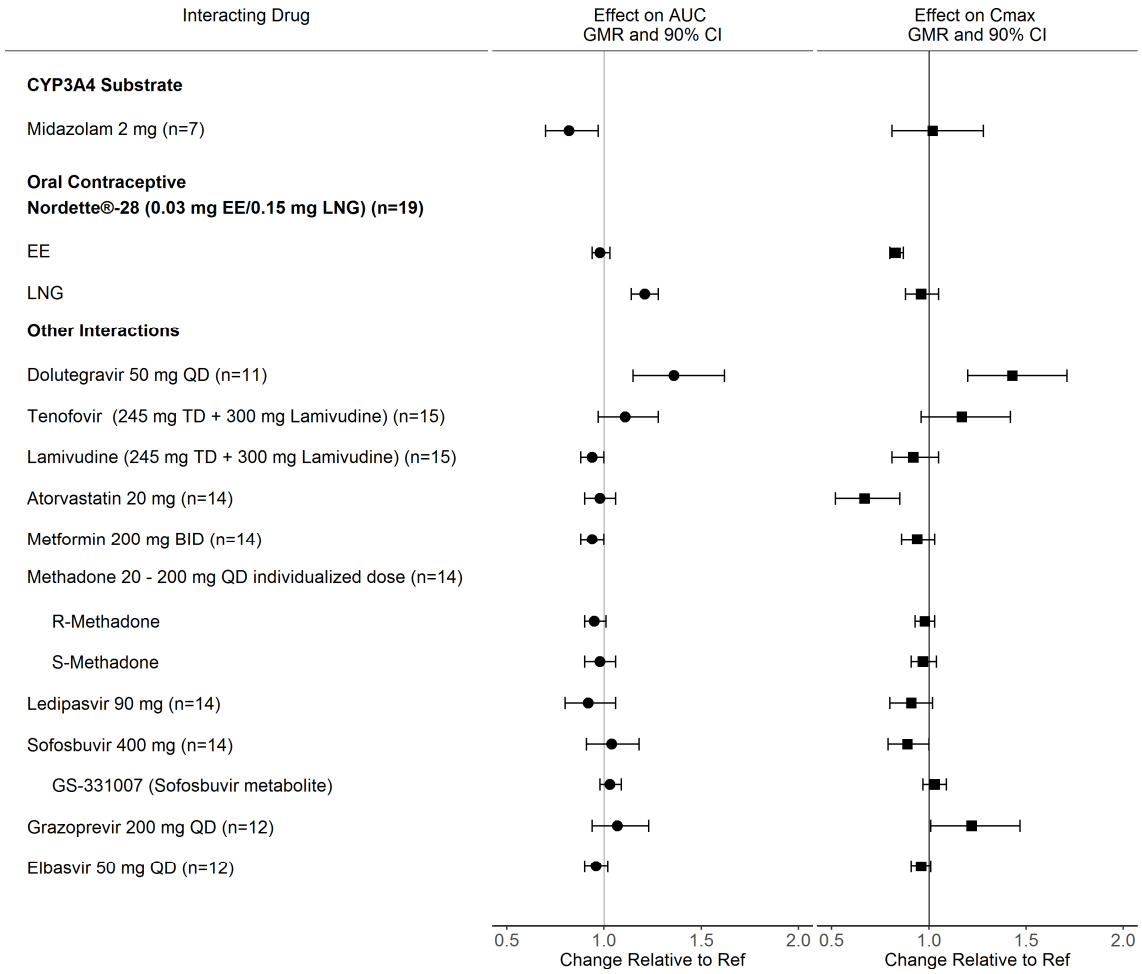
Based on the lack of effect of moderate hepatic impairment on DOR PK, clinically significant increases in exposure in patients with severe hepatic impairment are not anticipated; however, DOR has not been studied in this population in either a Phase 1 PK trial or in Phase 3 trials.

3.4 Drug-Drug Interactions

In vitro and clinical DDI trial data demonstrate that DOR is not expected to have a clinically meaningful effect on the PK of co-administered medications, including substrates of all major CYPs and drug transporters [Sec. 2.7.2.2.3.2]. The effect of DOR co-administration on the AUC and Cmax of co-administered drugs is summarized in the forest plot in [Figure 2.5: 2].

Figure 2.5: 2

Effect of DOR on the AUC and Cmax of Co-administered Drugs



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

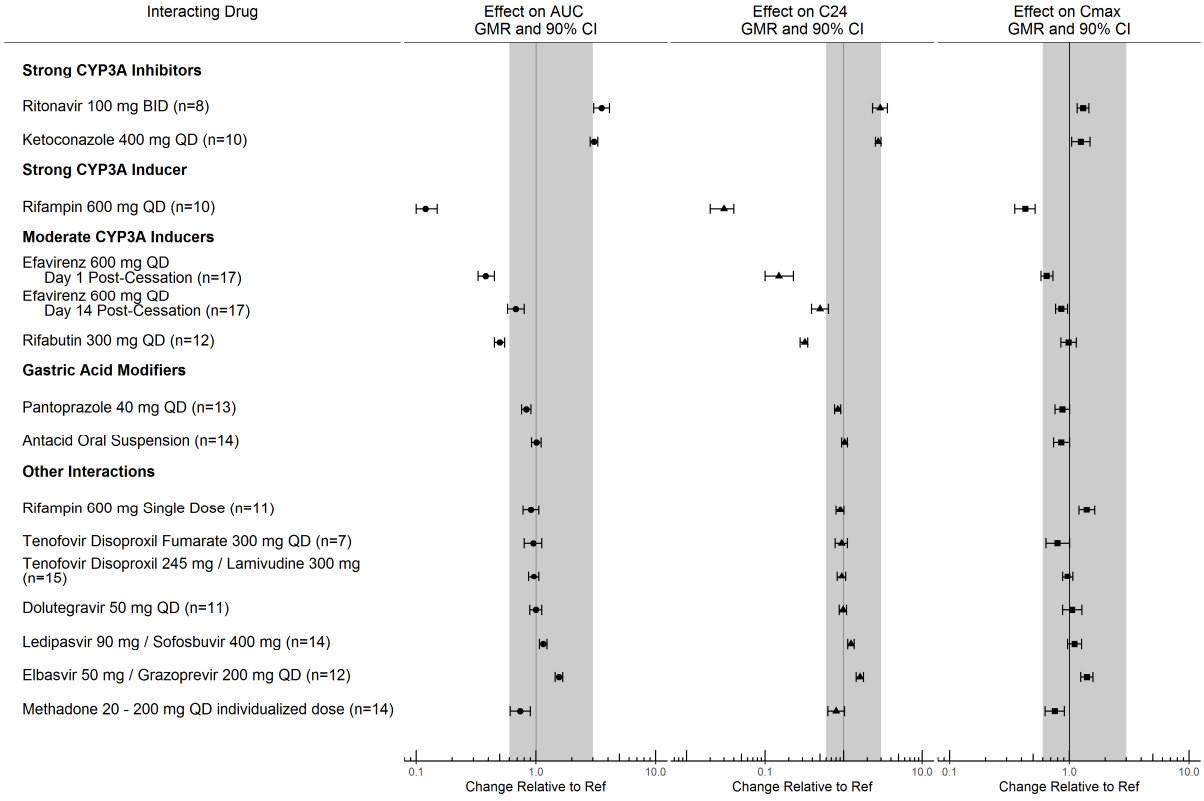
Preclinical data demonstrate that DOR is only a substrate for CYP3A metabolism and P-glycoprotein (P-gp) transport ([Sec. 2.7.2.1.4.2] [Sec. 2.7.2.1.4.4]). The effect of co-administered compounds on the AUC, C24, and Cmax of DOR are summarized in the forest plot in [Figure 2.5: 3]. CYP3A modulators may affect the PK of DOR. In trials, where DOR was co-administered with the strong CYP3A inhibitors ketoconazole (P010) [Sec. 2.7.2.2.3.1.3] [Figure 2.5: 3] and ritonavir (P002) [Sec. 2.7.2.2.3.1.2.] [Figure 2.5: 3], DOR AUC increased approximately 3-fold, with a smaller effect (25-40% increase) on Cmax. These increases are not considered clinically meaningful based on the bounds of clinical relevance (0.6, 3.0) [Sec. 2.7.2.1.5.4]. A clinical DDI trial with moderate CYP3A inhibitors has not been conducted. However, PBPK simulations of the interaction between DOR and the moderate CYP3A inhibitors, diltiazem and verapamil, with Simcyp® predict that moderate CYP3A inhibitors will have a more modest effect on DOR PK compared to strong inhibitors of approximately 2-fold increase in AUC [Sec. 2.7.2.3.1.1.6]. These data suggest that moderate inhibitors are not likely to lead to a clinically meaningful increase in DOR exposure.

Concomitant use of strong and moderate CYP3A inducers is likely to reduce DOR plasma concentrations leading to decreased efficacy. Therefore, the use of strong CYP3A inducers, such as rifampin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and St John's wort is contraindicated with DOR. However, based on non-parametric superposition projections of DOR plasma concentrations when co-administered with the more moderate inducer rifabutin, the administration of 100 mg BID (approximately every 12 hours) DOR with rifabutin is projected to maintain therapeutic exposures at steady state (ie, similar to those achieved with 100 mg QD DOR in the absence of inducers) [Sec. 2.7.2.3.1.1.6]. Individuals taking DOR/3TC/TDF with rifabutin should take the DOR single-entity tablet 12 hours apart from the DOR/3TC/TDF dose to maintain DOR plasma concentrations above the lower clinical bound. As the magnitude of induction associated with CYP3A moderate inducers varies across compounds (eg, EFV, etravirine, nevirapine, bosentan, nafcillin, modafinil), and is also dependent on the substrate, the effect of other CYP3A inducers on the PK of DOR cannot easily be predicted. Therefore the dose adjustment proposed for co-administration of rifabutin and DOR or DOR/3TC/TDF may not be sufficient for other moderate inducers which may be co-administered with DOR.

In addition, rifampin, when administered as a single dose, has the potential to inhibit OAT1B1 and P-gp. In the clinical trial evaluating the DDI between DOR and rifampin, the effect of single dose rifampin on DOR was also studied (P011) [Sec. 2.7.2.2.3.1.4]. Co-administration with single dose rifampin had a modest but not clinically meaningful increase in DOR Cmax (~40% increase) and no effect on DOR AUC [Sec. 2.7.2.2.3.1.4]. These results indicate that despite being a P-gp substrate, P-gp has minimal involvement in intestinal efflux of DOR. Furthermore, consistent with the high permeability of DOR and the in vitro OATP1B1 evaluation, these results also indicate that OATP1B1 inhibition has no meaningful effect on DOR PK [Figure 2.5: 3].

Figure 2.5: 3

Effect of Co-administered Compounds on the AUC, C24, and Cmax of DOR



Note: Different x-axis scale used for C24 panel

In conclusion, it is proposed that the use of DOR is contraindicated with strong CYP3A inducers (eg, rifampin, carbamezipine, oxcarbazepine, phenobarbital, phenytoin, St. John's wort) and DOR may be co-administered with the more moderate CYP3A inducer, rifabutin, if the DOR dose frequency is increased to 100 mg BID. The magnitude of effect of other moderate CYP3A inducers, which may be co-administered with DOR or DOR/3TC/TDF, on DOR PK is unknown.

DOR may be co-administered with moderate and strong CYP3A inhibitors without dose adjustment. Agents which inhibit OATP1B1 or modulate P-gp are not expected to have a clinically meaningful effect on the PK of DOR. Modulators of other CYPs or transporters are not anticipated to have a clinically meaningful effect on the PK of DOR.

Furthermore, as DOR is not anticipated to have a clinically meaningful effect on the PK of co-administered agents, few DDIs are anticipated with DOR, including other HIV-1 antiretrovirals.

3.5 Pharmacodynamics and Special Safety

Antiviral Activity

As suppression of HIV-1 RNA is a primary efficacy endpoint, HIV-1 RNA suppression data are discussed in detail in [Sec. 2.7.2.1.5.2], [Sec. 2.7.2.2.4.1], and [Sec. 2.7.3.3.3-trtmtnve48wk] and only the Phase 1b proof-of-concept (POC) trial (P005) is briefly summarized here. In the POC trial [Ref. 5.3.4.1: P005V01], which enrolled treatment-naïve HIV-1 infected male subjects, DOR doses of 25 mg and 200 mg administered once daily as monotherapy for 7 days, resulted in a robust reduction in HIV-1 RNA. On Day 8, 24 hours after the Day 7 dose, the mean placebo-corrected HIV-1 RNA change from baseline was ~1.3 log10 copies/ mL for both the 25 and 200 mg dose in treatment-naïve subjects with HIV-1 infection. There was no meaningful difference in HIV-1 RNA decline between the 25 and 200 mg dose groups [Sec. 2.7.2.1.3.2.1].

Safety- Effect on QTc Interval

In a thorough QT/QTc trial (P017) [Sec. 2.7.2.2.4.2], a supratherapeutic dose of 1200 mg of DOR, which provides 4.1-fold and 3.1-fold increases in Cmax and exposure, respectively, relative to the 100 mg dose, did not have a clinically meaningful effect on the QT interval corrected for heart rate by the population method (QTcP) [Sec. 2.7.2.1.3.2.2].

3.6 DOR/3TC/TDF Fixed Dose Combination

The marketed doses of 300 mg TDF and 300 mg 3TC are used in DOR/3TC/TDF. Efficacy for DOR/3TC/TDF was demonstrated in the Phase 3 trial P021 ([Sec. 2.7.3.2.3-trtmtnve48wk]). Additionally, no clinically meaningful differences in tenofovir or 3TC PK were observed in a relative bioavailability trial when TDF and 3TC were administered as part of DOR/3TC/TDF or co-administered as the individual components (P026) [Sec. 2.7.1.2.1.2.1]. Similarly, the PK of DOR is similar when administered as a single-entity or when administered as part of DOR/3TC/TDF (P029) [Sec. 2.7.1.1.3.2]. Moreover, in a component interaction trial (P038) evaluating the PK of tenofovir and 3TC when co-administered in the presence or absence of 100 mg DOR, co-administration of DOR with TDF and 3TC had no meaningful impact on the PK of tenofovir, 3TC, or DOR [Sec. 2.7.2.2.3.1.8]. Therefore, the clinical pharmacology profiles, dose, and dosing recommendations with respect to intrinsic and extrinsic factors described in the VIREAD and EPIVIR US [Ref. 5.4: 04P95P], [Ref. 5.4: 04P95N] and EU [Ref. 5.4: 04QHYF], [Ref. 5.4: 04QHYD] prescribing information, and summarized in [Sec. 2.7.2.3.1.2] and [Sec. 2.7.2.3.1.3], are applicable to TDF and 3TC, respectively, when administered as part of DOR/3TC/TDF. Similarly, the clinical pharmacology profile, proposed dose and dose recommendations for DOR with respect to intrinsic and extrinsic factors, as summarized in [Sec. 2.7.2.3.1.1.5] and [Sec. 2.7.2.3.1.1.6], are applicable to DOR when administered as part of DOR/3TC/TDF.

3.6.1 Intrinsic Factors

No dose adjustment is required for DOR/3TC/TDF based on age, gender, race, weight, BMI, or mild/moderate hepatic impairment. Dose adjustment is required for both 3TC and TDF in

patients with an estimated creatinine clearance below 50 mL/min [Sec. 2.7.2.3.2.1], [Sec. 2.7.2.3.1.3]; therefore, DOR/3TC/TDF should not be used in this population.

3.6.2 Extrinsic Factors

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

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

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

Due to the 3TC component which is predominantly eliminated in the urine by active organic cationic secretion, the possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system [Ref. 5.4: 04QHYD].

4 OVERVIEW OF EFFICACY

The Phase 2b and Phase 3 development program demonstrates that DOR 100 mg QD, as either the single entity in combination with other antiretroviral medications or as DOR/3TC/TDF, has potent and durable efficacy with respect to viral suppression and increase in $CD4^+$ T-cell counts in HIV-1-infected, treatment-naïve adults. The efficacy of DOR in combination therapy in this population is non-inferior to that of 2 well-established comparators – 1 from the NNRTI class (EFV) and 1 from the PI class (DRV+r) (both in combination with other antiviral medications).

4.1 Summary of Approach to Assessment of Efficacy

This overview summarizes efficacy data from 48 weeks of treatment in the 2 pivotal Phase 3 trials (P018 and P021) and supportive efficacy data from 96 weeks of treatment in the Phase 2b trial (P007).

This section is organized as follows: relevance of populations used in analyses of efficacy [Sec. 2.5.4.2]; methodology used for efficacy assessment [Sec. 2.5.4.3]; results of individual Phase 2b and 3 trials and pooled Phase 3 trials that support the proposed indications and regimens [Sec. 2.5.4.4.1] and [Sec. 2.5.4.4.2]; persistence of efficacy [Sec. 2.5.4.4.3]; rationale for applicability of foreign data to the United States [Sec. 2.5.4.5], and conclusions [Sec. 2.5.4.6].

Complete analyses of results from the individual trials are found in the respective clinical study reports [Ref. 5.3.5.1: P007V01MK1439], [Ref. 5.3.5.1: P018V01MK1439], [Ref. 5.3.5.1: P021V01MK1439A]. Additional pooled analyses are found in [Sec. 2.7.3-trtmtnve48wk] and the Integrated Summary of Efficacy [Sec. 5.3.5.3.2-trtmtnve48wk].

4.2 Relevance of the Patient Population

The subjects in the Phase 2b and 3 trials are representative of the HIV-1-infected population, thus supporting the proposed indication in patients from diverse geographic and ethnic backgrounds. Subjects studied in the Phase 2b and 3 trials include subjects with a broad range of baseline $CD4^+$ T-cell counts, with a broad range of baseline HIV-1 RNA levels, with and without a history of AIDS, and with and without hepatitis B/C co-infections.

4.3 Methods for Efficacy Assessment

4.3.1 Clinical Trial Design

The study designs of the Phase 2b trial, P007 (a 2-part dose ranging trial), and the Phase 3 trials, P018 and 021 (non-inferiority trials), are described in [Sec. 2.7.3.2.1.1-trtmtnve48wk, 2.7.3.2.2.1-trtmtnve48wk, 2.7.3.2.3.1-trtmtnve48wk] and in [Sec. 2.5.1].

4.3.2 Clinical Efficacy Endpoints

The primary efficacy endpoint in the 3 trials presented in this summary is virologic efficacy, as measured by proportions of subjects with HIV-1 RNA below a given threshold. In the 2 pivotal trials, P018 and P021, the primary endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. Secondary and exploratory endpoints included proportions of subjects with HIV-1 RNA <40 and <200 copies/mL at Week 48. Of note, proportions of subjects with HIV-1 RNA <40 copies/mL is the EMA primary endpoint.

In the supportive Phase 2b trial (P007), the primary endpoint was the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 24. Secondary endpoints included proportions of subjects with HIV-1 RNA <40 copies/mL at Weeks 48 and 96 as well as proportions of subjects with HIV-1 RNA <200 copies/mL at each of these time points. In order to support data from the pivotal trials, proportions of subjects in P007 with HIV-1 RNA <50 copies/mL were assessed as a post-hoc supportive analysis.

Immunologic efficacy was assessed by the change in $CD4^+$ T-cell count from baseline to various time points.

In addition to the virologic and immunologic endpoints, additional evaluations included assessment of protocol-defined virologic failure (PDVF), time to loss of virologic response (TLOVR) and development of viral drug resistance.

4.3.3 Statistical Methodology

The statistical approach to analyzing the efficacy of DOR and DOR/3TC/TDF in this application is consistent with current scientific and regulatory guidelines and is provided in detail in [Sec. 2.7.3.1.4.2-trtmtnve48wk].

Analysis Population

The Full Analysis Set (FAS) population was used as the primary population for the analysis of efficacy data in the individual trials and the integrated analyses. The FAS population consists of all randomized subjects who received at least one dose of study medication and had baseline data (for those analyses that require baseline data). In the FAS, subjects were included in the treatment group to which they were randomized.

Analysis of key efficacy endpoints in P018 and P021 was also carried out using the Per-Protocol (PP) population. The PP is defined in individual CSRs for each trial [Ref. 5.3.5.1: P018V01MK1439] [Ref. 5.3.5.1: P021V01MK1439A].

Missing Data Approach

Two approaches were used to address missing values in pivotal trials P018 and P021:

- The FDA Snapshot approach, in which all subjects with missing data were considered to be failures regardless of reason.
- The Observed Failure (OF) approach, in which subjects who prematurely discontinued assigned treatment due to lack of efficacy were considered to be failures thereafter; subjects with other types of missing data were excluded from the analysis.

The primary approach for the analysis of the proportion of subjects achieving virologic suppression (HIV-1 RNA <40 copies/mL, <50 copies/mL, and <200 copies/mL) was the FDA snapshot approach. The OF approach was applied as a sensitivity analysis.

The immunologic response endpoint (change from baseline to Week 48 in $CD4^+$ T-cell count) and efficacy by prognostic and demographic factors were analyzed using the OF approach.

Two other missing-data approaches were used in the Phase 2b trial P007 for the analysis of the virologic suppression endpoints: the Non-Completer=Failure (NC=F) approach, which is the protocol-specified primary approach, and the Treatment-Related Discontinuation=Failure (TRD=F) approach. In order to facilitate comparison with results from P018 and P021, post-hoc analyses were carried out using the FDA snapshot approach to missing data.

4.4 Efficacy Results

4.4.1 Efficacy Results in Individual Studies

4.4.1.1 Efficacy Results in P007

In the dose-finding phase (Part I) of this double-blind, active-controlled trial, 208 treatment-naïve HIV-1 infected subjects received DOR (plus FTC/TDF) at doses of either 25 mg (n=40), 50 mg (n=43), 100 mg (n=42), or 200 mg (n=41) QD, or received EFV (n=42) (plus FTC/TDF) at a dose of 600 mg once daily.

Following analysis of the 24-week data from the subjects in Part I, the 100-mg dose of DOR was selected for further study in Part II of P007 and in Phase 3 trials. In Part II, an additional 132 patients received either the 100-mg dose of DOR (n=66) or EFV (n=66), each in combination with FTC/TDF, for a total of 96 weeks of blinded treatment. Subjects who had received DOR at once-daily doses of 25, 50, or 200 mg in Part I were switched to the 100-mg dose of DOR at their next planned study visit while maintaining the study blind.

Virologic Efficacy at Week 24

The antiretroviral efficacy of each studied DOR dose (25, 50, 100, and 200 mg) in combination with FTC/TDF was robust and comparable to that observed for EFV 600 mg in combination with FTC/TDF at Week 24, whether the HIV-1 RNA cutoff was <40 copies/mL (primary endpoint), <50 copies/mL (supportive analysis), or <200 copies/mL (secondary endpoint), and regardless of the approach used for missing data ([Sec.2.7.3.2.1.2-trtmtnve48wk]).

Virologic Efficacy at Weeks 48 and 96

The antiretroviral efficacy of DOR 100 mg was sustained through Week 48 and durable through Week 96, comparable to that observed for EFV 600 mg. This was true regardless of HIV-1 RNA threshold (<40 [primary endpoint], <50 [supportive analysis], and <200 copies/mL [secondary endpoint]) or approach to missing data. Results presented below were calculated using data from subjects randomized to the DOR 100-mg group Parts I/II combined compared to the EFV group and using the FDA snapshot approach.

For Parts I and II combined:

- Week 48: 78.7% and 82.4% of subjects in the DOR 100-mg and EFV groups, respectively, achieved HIV-1 RNA <50 copies/mL; 77.8% and 78.7% of subjects, respectively, achieved HIV-1 RNA <40 copies/mL [Ref. 5.3.5.1: P007V01MK1439: Table 11-13], [Ref. 5.3.5.1: P007V01MK1439: Table 11-3].

- Week 96: 75.9% of subjects in both groups achieved HIV-1 RNA <50 copies/mL; 75.0% and 75.9% of subjects in the DOR 100-mg and EFV groups, respectively, achieved HIV-1 RNA <40 copies/mL [Ref. 5.3.5.1: P007V01MK1439: Table 11-14], [Ref. 5.3.5.1: P007V01MK1439: Table 11-4].

Antiretroviral efficacy was durable through Week 96, with comparable proportions of subjects with HIV-1 RNA <50 copies/mL in the DOR and EFV treatment groups.

Immunologic Efficacy: Change in $CD4^+$ T-Cell Count From Baseline

At Week 24, the immunologic efficacy of all doses of DOR, as measured by mean $CD4^+$ T-cell count increase, was robust and comparable to that of EFV 600 mg in both Part I (DOR-combined and EFV groups increased by 135 and 121 cells/mm^3, respectively) and Parts I/II combined (DOR 100-mg and EFV groups increased by 152 and 146 cells/mm^3, respectively). At Week 48 and Week 96, the immunologic efficacy of DOR 100 mg was sustained and comparable to that of EFV 600 mg [Ref. 5.3.5.1: P007V01MK1439: Table 11-9], [Ref. 5.3.5.1: P007V01MK1439: Table 11-10].

Protocol-Defined Virologic Failure and Development of Viral Drug Resistance

In P007, PDVF was defined as (with a 'confirmed' value being 2 consecutive measures at least 1 week apart):

- Non-responder: A subject who never achieved HIV-1 RNA <40 copies/mL by Week 24.

  OR

- Rebounder: A subject who, after an initial response of HIV-1 RNA <40 copies/mL, had confirmed HIV-1 RNA ≥40 copies/mL on or after Week 24.

The rates of PDVF for subjects treated with DOR were consistent with those observed for the EFV group through Week 96 (18.5% and 13.0%, respectively) ([Sec. 2.7.3.2.1.2.7-trtmtnve48wk]).

Three subjects who received DOR and 2 who received EFV developed NNRTI resistance-associated substitutions in RT. Phenotypic resistance to DOR was noted in only 1 of these subjects (in the DOR 25-mg group). The virus from this subject had 2 NNRTI resistance mutations, RT V106V/I and F227C, with a 66-fold higher IC_{50} relative to wild-type virus for DOR (compared with 2.2-fold at baseline). The two other subjects had the following NNRTI mutations identified, RT K101K/E and P236P/L for one subject and RT E138E/G and V179D for the other; neither of these two subjects had phenotypic resistance to DOR. Further details on resistance data for these and other subjects with PDVF, as well as brief descriptions for the subjects described above, are provided in the study report [Ref. 5.3.5.1: P007V01MK1439: 11.2].

4.4.1.2 Efficacy Results in Protocol 018

A total of 769 subjects were randomized 1:1 in P018 to receive DOR (n=385) or DRV+r (n=384) on a background of either FTC/TDF or ABC/3TC. A total of 766 subjects (383 in each treatment group) received at least 1 dose of study medication.

Efficacy Summary at Week 48

The antiretroviral efficacy of DOR 100 mg was noninferior to that of DRV+r, as assessed by the primary endpoint (proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 in the FAS) ([Table 2.5: 2]). Specifically, 83.8% and 79.9% of subjects in the DOR and DRV+r treatment groups, respectively, achieved HIV-1 RNA < 50 copies/mL using the FDA snapshot approach. The treatment difference (DOR – DRV+r) was 3.9% (95% CI: -1.6, 9.4). Because the lower bound of the 95% CI for treatment difference was above the predefined non-inferiority bound of -10 percentage points, it was concluded that the antiretroviral efficacy of DOR 100 mg was non-inferior to that of DRV+r. The antiretroviral efficacy of DOR 100 mg at Week 48, as measured by the proportion of subjects achieving the endpoint of HIV-1 RNA <40 copies/mL, also demonstrated efficacy comparable to that of DRV+r (83.3% and 79.9%, respectively). The treatment difference (DOR – DRV+r) was 4.2% (95% CI: -1.4, 9.7). Consistent antiretroviral efficacy results in the DOR and DRV+r groups were also observed for a threshold of <200 copies/mL (Table 2.5: 2). The antiretroviral efficacy of DOR 100 mg over time (timepoints prior to and through Week 48), is illustrated in [Sec. 2.7.3.2.2.2.3-trtmtnve48wk].

The key efficacy endpoints (proportions of subjects achieving HIV-1 RNA <50 copies/mL and <40 copies/mL at Week 48) were also analyzed for the PP population [Ref. 5.3.5.1: P018V01MK1439: Table 14.2-1]. These results are consistent with the results for the FAS population.

Of note, there was no noticeable difference in response in the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 with respect to background therapy (FTC/TDF or ABC/3TC) in the DOR group and in the DRV+r group.

The immunologic efficacy of DOR 100 mg, as measured by the change from baseline to Week 48 in $CD4^+$ T-cell count (OF approach), was comparable to that of DRV+r [Table 2.5: 2].

Table 2.5: 2

Protocol 018: Efficacy Analysis at Week 48

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (Doravirine - Darunavir)[‡]		Conclusion[§]
		Doravirine 100 mg QD n/N (%)	Darunavir/ritonavir 800/100 mg QD n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	321/383 (83.8)	306/383 (79.9)	3.913	(-1.590, 9.415)	Non-inferior
Secondary and Exploratory						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	321/364 (88.2)	306/355 (86.2)	1.880	(-3.072, 6.833)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	319/383 (83.3)	303/383 (79.1)	4.169	(-1.404, 9.743)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	319/364 (87.6)	303/355 (85.4)	2.160	(-2.898, 7.218)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	328/383 (85.6)	316/383 (82.5)	3.141	(-2.095, 8.378)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	328/364 (90.1)	316/355 (89.0)	1.068	(-3.504, 5.641)	
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	192.7 (171.5, 213.9)	185.6 (167.5, 203.6)	7.1	(-20.8, 35.0)	

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.
[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum. The 95% CI for mean difference in CD4 change was based on t-distribution.
[§] Doravirine 100 mg QD is concluded non-inferior to darunavir/ritonavir 800/100 mg QD if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.
Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.
Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.
n = Number of subjects in each subcategory.
N = Number of subjects in each treatment group.

Source: [P018V01MK1439: analysis-adsl; adcd4; adrna]

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Protocol-Defined Virologic Failure and Development of Viral Drug Resistance

In P018 (and P021), a subject with PDVF was defined as follows, with a 'confirmed' value being 2 consecutive measures at least 1 week apart:

- Non-responder: A subject with a confirmed HIV-1 RNA value of ≥200 copies/mL at Week 24 or Week 36, or a confirmed HIV-1 RNA value of ≥50 copies/mL at Week 48;

  OR

- Rebounder: A subject with a confirmed HIV-1 RNA value of ≥50 copies/mL after an initial response of HIV-1 RNA <50 copies/mL at any time during the trial.

PDVF rates were low and comparable for the DOR and DRV+r treatment groups at Week 48 (4.9% and 6.3%, respectively). Additional details are in [Sec. 2.7.3.2.2.2.6-trtmtnve48wk].

No resistance to DOR or DRV+r were seen among viral samples from the DOR- and DRV+r-treated subjects with PDVF. Among the subjects who discontinued for reasons other than PDVF, 1 subject in the DOR group with documented non-compliance developed resistance to DOR. The virus from this subject had 3 NNRTI resistance mutations – RT V106I, H221Y, F227C – and 1 NRTI resistance mutation – M184V - at the discontinuation visit, with evidence of phenotypic resistance (>96.6-fold higher IC_{50} relative to wild-type virus for DOR). No subjects in the DRV+r PDVF or early discontinuation groups developed resistance to any study drug. Further details on resistance data for these and other subjects with PDVF, as well as brief narratives for the subjects described above, are provided in the study report [Ref. 5.3.5.1: P018V01MK1439: 11.1.4.2.1].

4.4.1.3 Efficacy Results in Protocol 021

In this study, 734 subjects were randomized in a 1:1 ratio to receive either DOR/3TC/TDF (n=368) or EFV/FTC/TDF (n=366). A total of 728 subjects (364 in each treatment group) received at least 1 dose of study medication.

Efficacy Summary at Week 48

The antiretroviral efficacy of DOR/3TC/TDF at Week 48, as measured by the proportion of subjects in the FAS population with HIV-1 RNA <50 copies/mL, was non-inferior to that of EFV/FTC/TDF. Using the FDA snapshot approach, HIV-1 RNA <50 copies/mL was achieved by 84.3% and 80.8% of subjects in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, with a treatment difference (95% CI) of 3.5% (-2.0, 9.0). Because the lower bound of the 95% CI for the treatment difference was above the predefined non-inferiority bound of -10 percentage points, it was concluded that antiretroviral efficacy of DOR/3TC/TDF was non-inferior to that of EFV/FTC/TDF.

When using the more stringent endpoint of HIV-1 RNA <40 copies/mL (a secondary endpoint), DOR/3TC/TDF continued to demonstrate comparable antiretroviral efficacy to that of EFV/FTC/TDF at Week 48 (83.8% and 79.7%, respectively, with a treatment difference (95% CI) of 4.1% (-1.5, 9.7). Consistent antiretroviral efficacy results among subjects in the DOR/3TC/TDF and EFV/FTC/TDF groups were seen when using an HIV-1 RNA threshold of <200 copies/mL at Week 48 (Table 2.5: 3). The antiretroviral efficacy of DOR/3TC/TDF over time, through Week 48, is illustrated in [Sec. 2.7.3.2.3.2.3-trtmtnve48wk].

The key efficacy endpoints (proportions of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 and <40 copies/mL at Week 48 were also analyzed for the PP population, which excluded 51 subjects from the FAS population (26 in the DOR/3TC/TDF group and 25 in the EFV/FTC/TDF group). These PP results are consistent with the results for the FAS population [Ref. 5.3.5.1: P021V01MK1439A: Table 14.2-2]

The immunologic efficacy of DOR/3TC/TDF, as measured by the change from baseline to Week 48 in $CD4^+$ T-cell count (using the OF approach), was comparable to that of EFV/FTC/TDF [Table 2.5: 3].

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Table 2.5: 3

Protocol 021: Efficacy Analysis at Week 48

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (DOR/3TC/TDF - EFV/FTC/TDF)[‡]		Conclusion[§]
		DOR/3TC/TDF QD n/N (%)	EFV/FTC/TDF QD n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	307/364 (84.3)	294/364 (80.8)	3.537	(-1.951, 9.026)	Non-inferior
Secondary and Exploratory						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	307/346 (88.7)	294/331 (88.8)	-0.179	(-4.936, 4.578)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	305/364 (83.8)	290/364 (79.7)	4.084	(-1.493, 9.661)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	305/346 (88.2)	290/331 (87.6)	0.442	(-4.463, 5.346)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	313/364 (86.0)	301/364 (82.7)	3.274	(-2.012, 8.561)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	313/346 (90.5)	301/331 (90.9)	-0.523	(-4.943, 3.897)	
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	198.4 (180.2, 216.7)	188.4 (169.5, 207.2)	10.1	(-16.1, 36.3)	

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA ≤100,000 or >100,000 copies/mL). The 95% CI for mean difference in CD4 change was based on t-distribution.

[§] DOR/3TC/TDF QD is concluded non-inferior to EFV/FTC/TDF QD if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

n = Number of subjects in each subcategory.

N = Number of subjects in each treatment group.

Source: [P021V01MK1439A: analysis-adsl; adcd4; adrna]

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Protocol-Defined Virologic Failure and Development of Viral Drug Resistance

PDVF rates were low and comparable in the DOR/3TC/TDF and EFV/FTC/TDF treatment groups at Week 48 (6.0% and 3.8%, respectively). Additional details are in [Sec. 2.7.3.2.3.2.6-trtmtnve48wk]. (Note PDVF was defined identically in P021 and P018, see [Sec. 2.5.4.4.1.2] for details.)

In the DOR/3TC/TDF group, among subjects with PDVF, genotypic substitutions associated with DOR resistance were identified in virus samples from 7 subjects, with phenotypic resistance to DOR identified in 6 of these subjects. Five subjects also developed NRTI resistance (primarily RT M184Vor I with 2 subjects also with K65R). The majority of subjects who developed resistance to DOR required more than one substitution in RT through the V106 pathway, consistent with in vitro data. No subjects who discontinued early developed DOR resistance. In the EFV/FTC/TDF group, 12 subjects in the EFV/FTC/TDF PDVF and early discontinuation groups developed resistance to EFV, and 5 developed resistance to NRTIs. Further details on resistance data for these and other subjects with PDVF, as well as brief narratives for the subjects described above, are provided in the study report [Ref. 5.3.5.1: P021V01MK1439A: 11.1.4.2.1].

4.4.2 Efficacy Results in Pooled Population

This section presents efficacy data and analyses based on the pooled data from P018 and P021, in which the combined DOR group (n=747) is compared with both the DRV+r group from P018 (n=383) and the EFV/FTC/TDF group from P021 (n=364). The rationale for the pooling strategy for efficacy analysis can be found in [Sec. 2.7.3.1.3.1-trtmtnve48wk].

4.4.2.1 Study Population (Disposition and Baseline Subject Characteristics – Pooled Population)

The disposition of all subjects in the Phase 3 trials included in this submission is presented in [Sec. 2.7.3.3.2-trtmtnve48wk], including subjects whose data contributed to the efficacy analyses. Data from P018 and P021 represent subject status through the Week 48 window.

In the pooled efficacy analyses, comparable proportions of subjects across treatment groups discontinued from the trial by the Week 48 visit. The most common reason for discontinuation among subjects in the DOR Regimen group (DOR group in P018 and DOR/3TC/TDF group in P021) was lack of efficacy, in the DRV+r group it was loss to follow-up, while in the EFV/FTC/TDF group it was discontinuation due to AE followed by 'withdrawal by subject'. Approximately 3-fold higher proportions of subjects discontinued due to AEs in the EFV/FTC/TDF group compared with the DOR Regimen group.

Demographic and prognostic characteristics were comparable across the DOR Regimen group and both comparator groups, with the exception of various racial and regional subgroups; these differences reflect the worldwide enrollment of the pivotal trials [Table 2.5: 4]. Most subjects were male and white, and the proportion of enrolled women (14.6 to 16.5%) is consistent with that observed for other Phase 3 clinical trials in HIV-1 subjects. Approximately 75% of subjects in each treatment group were in the stratum of screening

HIV-1 RNA ≤100,000 copies/mL. The number of elderly (≥ 65 years of age) subjects and the number of subjects with hepatitis B or C co-infection was limited.

Table 2.5: 4

Subject Baseline Characteristics
Efficacy Pool (P018 and P021 Combined)

	DOR Regimen (P018, P021) (N = 747)	DRV+r (P018) (N = 383)	EFV/FTC/TDF (P021) (N = 364)
Gender n (%)			
Male	624 (83.5)	326 (85.1)	311 (85.4)
Female	123 (16.5)	57 (14.9)	53 (14.6)
Race n (%)			
American Indian or Alaska Native	13 (1.7)	3 (0.8)	6 (1.6)
Asian	66 (8.8)	7 (1.8)	65 (17.9)
Black or African American	153 (20.5)	88 (23.0)	68 (18.7)
Multiple	57 (7.6)	2 (0.5)	55 (15.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)	2 (0.5)	0 (0.0)
White	457 (61.2)	280 (73.1)	170 (46.7)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
Ethnicity n (%)			
Hispanic or Latino	219 (29.3)	86 (22.5)	120 (33.0)
Not Hispanic or Latino	520 (69.6)	290 (75.7)	238 (65.4)
Unknown	8 (1.1)	7 (1.8)	6 (1.6)
Region n (%)			
Africa	60 (8.0)	22 (5.7)	27 (7.4)
Asia/Pacific	71 (9.5)	3 (0.8)	62 (17.0)
Europe	258 (34.5)	179 (46.7)	94 (25.8)
Latin America	127 (17.0)	33 (8.6)	87 (23.9)
North America	231 (30.9)	146 (38.1)	94 (25.8)
Age (years)			
18 to 64	743 (99.5)	379 (99.0)	362 (99.5)
>=65	4 (0.5)	4 (1.0)	2 (0.5)
Mean (SD)	34.2 (10.5)	35.7 (10.7)	32.7 (9.9)
Median (min, max)	32.0 (18, 70)	34.0 (18, 69)	30.0 (18, 69)
Baseline CD4 Cell Count (cells/mm^3)			
N†	747	383	364
Mean (SD)	433.7 (212.9)	411.9 (229.6)	415.5 (210.6)
Median (min, max)	412.0 (19, 1822)	393.0 (19, 1303)	388.0 (19, 1452)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	15 (2.0)	19 (5.0)	10 (2.7)
>50 cells/mm^3 and <=200 cells/mm^3	71 (9.5)	48 (12.5)	36 (9.9)
>200 cells/mm^3	661 (88.5)	316 (82.5)	318 (87.4)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)			
N†	747	382	364
Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.5 (0.7)
Median (min, max)	4.4 (2.0, 6.4)	4.4 (2.4, 6.5)	4.5 (2.6, 6.4)

	DOR Regimen (P018, P021) (N = 747)	DRV+r (P018) (N = 383)	EFV/FTC/TDF (P021) (N = 364)
Baseline Plasma HIV-1 RNA (copies/mL)			
N[†]	747	382	364
Geometric Mean	25330.0	26630.5	29087.1
Median (min, max)	25406.0 (105, 2776658)	27357.0 (235, 3272236)	29732.5 (403, 2692740)
Baseline Plasma HIV-1 RNA n (%)			
<=100,000 copies/mL	591 (79.1)	308 (80.4)	282 (77.5)
>100,000 copies/mL	156 (20.9)	74 (19.3)	82 (22.5)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
Baseline Plasma HIV-1 RNA n (%)			
<=500,000 copies/mL	720 (96.4)	370 (96.6)	346 (95.1)
>500,000 copies/mL	27 (3.6)	12 (3.1)	18 (4.9)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
History of AIDS n (%)			
Yes	82 (11.0)	37 (9.7)	53 (14.6)
No	665 (89.0)	346 (90.3)	311 (85.4)
Stratum n (%)			
Screening HIV-1 RNA<= 100,000	565 (75.6)	289 (75.5)	274 (75.3)
Screening HIV-1 RNA> 100,000	182 (24.4)	94 (24.5)	90 (24.7)
Baseline Hepatitis Status[††]			
Hep B and/or C Positive	22 (2.9)	18 (4.7)	9 (2.5)
Hep B Positive Only	13 (1.7)	12 (3.1)	8 (2.2)
Hep C Positive Only	9 (1.2)	6 (1.6)	1 (0.3)
Hep B and C Negative	725 (97.1)	365 (95.3)	355 (97.5)
Viral Subtype n (%)			
Clade B	498 (66.7)	272 (71.0)	253 (69.5)
Non-Clade B	247 (33.1)	111 (29.0)	111 (30.5)
Missing	2 (0.3)	0 (0.0)	0 (0.0)

[†] Subjects with missing results excluded.
[††] Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C virus.
N = Number of subjects randomized and treated in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

Source: [ISE: analysis-adsl]

4.4.2.2 Efficacy Summary at Week 48: Virologic and Immunologic Responses

In the pooled efficacy analyses, virologic efficacy in the DOR Regimen group was consistent with that of each of the comparator groups for the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48) (primary endpoint), the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 48, and the proportion of subjects with HIV-1 RNA <200 copies/mL at Week 48, regardless of the missing-data approach (FDA snapshot or OF approach) [Table 2.5: 5]).

Immunologic efficacy was consistent across the DOR Regimen group, the DRV+r group and the EFV/FTC/TDF group at Week 48 with respect to increases from baseline in $CD4^+$ T-cell counts [Table 2.5: 5].

Table 2.5: 5

Efficacy Analysis at Week 48
Efficacy Pool (Protocols 018 and 021 Combined)

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		
		DOR Regimen (P018, P021) n/N (%)	DRV+r (P018) n/N (%)	EFV/FTC/TDF (P021) n/N (%)
Primary				
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	628/747 (84.1)	306/383 (79.9)	294/364 (80.8)
Secondary and Exploratory				
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	628/710 (88.5)	306/355 (86.2)	294/331 (88.8)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	624/747 (83.5)	303/383 (79.1)	290/364 (79.7)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	624/710 (87.9)	303/355 (85.4)	290/331 (87.6)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	641/747 (85.8)	316/383 (82.5)	301/364 (82.7)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	641/710 (90.3)	316/355 (89.0)	301/331 (90.9)
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	195.5 (181.5, 209.5)	185.6 (167.5, 203.6)	188.4 (169.5, 207.2)

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.
Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.
n = Number of subjects in each subcategory.
N = Number of subjects in each treatment group.

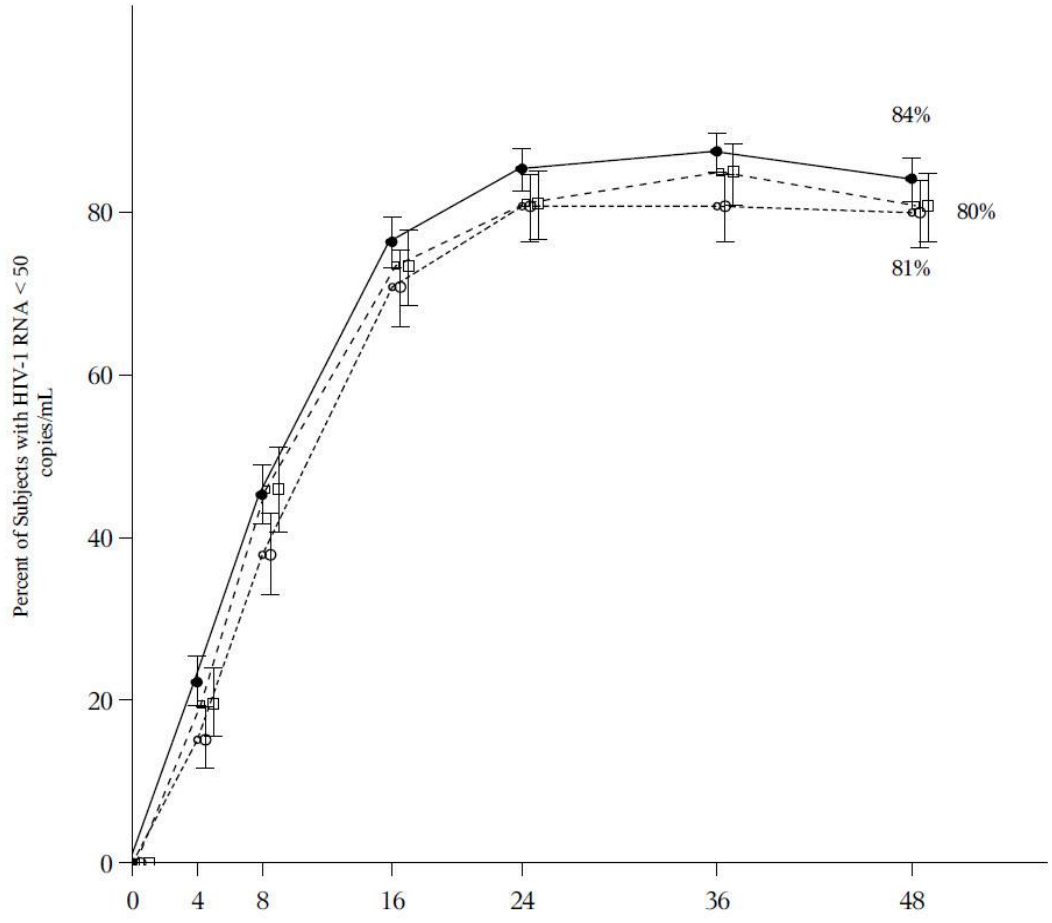
Source: [ISE: analysis-adsl; adcd4; adrna]

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The virologic response in all groups (using the threshold of HIV-1 RNA <50 copies/mL), was comparable and approached a plateau at Week 24 that was sustained through Week 48 ([Figure 2.5: 4]). A similar pattern was observed for the HIV-1 RNA thresholds of <40 and <200 copies/mL ([Sec. 5.3.5.3.2.3.3.2-trtmtnve48wk]).

Figure 2.5: 4

Proportion of Subjects With HIV-1 RNA < 50 copies/mL Over Time
Efficacy Pool (018 and 021 Combined)
FDA Snapshot Approach



Number of Contributing Subjects

● DOR	747	747	747	747	747	747	747
○ DRV	383	383	383	383	383	383	383
□ EFV	364	364	364	364	364	364	364

Source: [Figure 2.7.3-trtmtnve48wk: 12]

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Protocol-Defined Virologic Failure and Development of Viral Drug Resistance

Proportions of subjects who met the criteria for PDVF by Week 48 in P018 and P021 were low and consistent across the DOR Regimen group and the DRV+r group and EFV/FTC/TDF groups (5.5%, 6.3%, and 3.8%, respectively). It is notable that approximately two-thirds of subjects with PDVF in the DOR Regimen and DRV+r groups had low-level viremia, namely HIV-1 RNA between 50 and 200 copies/mL, at the time of virologic failure confirmation, compared with approximately half of subjects with PDVF in the EFV/FTC/TDF group [Table 2.7.3-trtmtnve48wk: 14]. Additional details are in [Sec. 2.7.3.3.3.5-trtmtnve48wk]. This observation is consistent with the possibility that the initial viremia meeting PDVF criteria was due to non-compliance with study medication, and that the subsequent lower viral load reflected increased compliance.

Among subjects treated with DOR or DOR/3TC/TDF in P018 and P021, 7 of 747 (0.9%) subjects developed genotypic and phenotypic resistance to DOR (30 subjects in the resistance analysis subset [subjects with HIV-1 RNA greater than 400 copies per mL at virologic failure or at early study discontinuation and having resistance data]). In the DRV+r treatment arm of the P018 (n = 383), no emergent darunavir-associated resistance substitutions were observed (11 subjects in the resistance analysis subset). In the EFV/FTC/TDF treatment arm of the P021, 12 of 364 (3.3%) subjects developed resistance to EFV (24 subjects in the resistance analysis subset). Treatment-emergent doravirine resistance -associated substitutions in RT included one or more of the following: A98G, V106I, V106A, V106M/T, Y188L, H221Y, P225H, F227C, F227C/R, and Y318Y/F with the majority requiring more than one substitution to confer DOR resistance (greater than 100-fold reduced susceptibility to doravirine). The most common substitution was at position V106 in combination with one or more substitutions. See [Sec. 2.7.3.3.3.5-trtmtnve48wk] for more detail. Treatment-emergent doravirine resistance-associated substitutions may confer cross-resistance to efavirenz, rilpivirine, nevirapine, and etravirine. Of the 7 subjects who developed doravirine resistance, 6 had phenotypic resistance to EFV and nevirapine, 3 had phenotypic resistance to nevirapine, and 2 had partial resistance to etravirine based on the Monogram Phenosense assay.

4.4.3 Persistence of Efficacy

Overall

Durable efficacy was demonstrated through 96 weeks of treatment in P007, and through 48 weeks of treatment in P018 and P021 as measured by: proportion of subjects with HIV-1 RNA <50, <40, and <200 copies/mL, and change from baseline in $CD4^+$ T-cell counts. Additionally, as seen in the TLOVR analyses in P018 and P021, the risk of loss-of-response was comparable in the DOR and DOR/3TC/TDF groups and their respective comparator groups.

Efficacy in Special Populations

The virologic and immunologic efficacy of DOR and DOR/3TC/TDF observed when assessed by various demographic and prognostic factors was consistent with the overall

population, to the extent possible given small sample sizes in some subpopulations. The subpopulations assessed were age, gender, region, race, ethnicity, screening HIV-1 RNA categories, baseline HIV-1 RNA categories, hepatitis B or C status, and viral subtype.

Subgroup analysis using the OF approach to missing data did not identify clinically meaningful differences in antiretroviral efficacy (proportion of subjects with HIV-1 RNA <50 copies/mL) across the 3 treatment groups for the subpopulations defined by these demographic and prognostic factors. This includes subjects with baseline HIV-1 RNA levels of >100,000 copies/mL at Week 48, the proportions of subjects in this subgroup with HIV-1 RNA <50 copies/mL were 81.1%, 76.4% and 80.8%, for the DOR Regimen, DRV+r and EFV/FTC/TDF groups, respectively. Among subjects with baseline $CD4^+$ T-cell counts of ≤200 cells/mm^3, the observed proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 was consistent across the DOR Regimen and DRV+r groups but slightly higher in the EFV/FTC/TDF group (75.9%, 72.1%, 83.7%, respectively). Similarly, there were no meaningful differences in immunologic efficacy observed across treatment groups across all demographic and prognostic factors [Table 5.3.5.3.2-trtmtnve48wk: 26]. See [Sec. 2.7.3.3.4-trtmtnve48wk].

4.5 Rationale for Applicability of Foreign Data to the United States Population

As highlighted in [Sec. 2.5.4.4.2.1], 30.9% of pooled population (P018 and P021) were from the North American region (the majority of subjects in the North American region were from the United States). In the integrated dataset, efficacy results were consistent among subjects from North America and subjects from other regions [Sec. 2.7.3.3.4-trtmtnve48wk]. In addition, DOR and DOR/3TC/TDF was generally well tolerated and had a safety profile that was similar among subjects from North America and subjects from other regions [Table 5.3.5.3.3-trtmtnve48wk: 79]. The Applicant considers foreign data to be applicable to the population in the United States.

4.6 Efficacy Conclusions for Doravirine and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

DOR 100 mg QD, as a single entity (administered in combination with other antiretroviral agents) and as a fixed-dose combination consisting of DOR/3TC/TDF, has been demonstrated in clinical trials enrolling HIV-1-infected, treatment-naïve patients to have robust efficacy with respect to both suppression of HIV-1 replication and increase in $CD4^+$ T-cell counts. This efficacy was non-inferior to that of two well-established HIV-1 therapies, one from the same NNRTI class as DOR (EFV) and another from the PI class (DRV+r). The following conclusions can be drawn from the pivotal Phase 3 trials (P018 and P021) and from additional data from the Phase 2b trial (P007):

- DOR and DOR/3TC/TDF are non-inferior to DRV+r and EFV with respect to the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48.

- DOR and DOR/3TC/TDF have comparable efficacy to DRV+r and EFV with respect to:

- Proportion of subjects with HIV-1 RNA <40 copies/mL and HIV-1 RNA < 200 copies/mL at Week 48.
- Increase from baseline in $CD4^+$ T-cell counts at Week 48.

- Sustained efficacy was seen with DOR and DOR/3TC/TDF through 48 weeks of treatment in P018 and P021; durable efficacy was seen through 96 weeks of treatment in P007, as evidenced by:
  - Proportion of subjects with HIV-1 RNA <50, <40, and <200 copies/mL.
  - Change from baseline in $CD4^+$ T-cell counts.
  - Time to loss of virologic response (TLOVR).

- Efficacy of DOR and DOR/3TC/TDF is consistent across subpopulations defined by age, gender, region, race/ethnicity, screening/baseline HIV-1 RNA [≤100,000 or >100,000 copies/mL], baseline $CD4^+$ T-cell count, chronic hepatitis B and C status, and viral subtype.

- DOR and DOR/3TC/TDF are associated with low rates of PDVF that are consistent with those observed for the comparators; development of treatment-emergent drug resistance was rare.
  - Approximately 1% of subjects treated with DOR developed genotypic resistance to DOR by Week 48, compared with 3% of subjects treated with EFV who developed genotypic resistance to EFV, and none of the subjects treated with DRV+r developed resistance to DRV

5 OVERVIEW OF SAFETY

The safety database reported in [Sec. 2.7.4] provides a comprehensive examination of the safety profile of DOR and DOR/3TC/TDF in 1657 individuals (979 treatment-naive subjects who received DOR or DOR/3TC/TDF in the Phase 2b/3 trials (P007, P018, P021) and 678 subjects received DOR and DOR/3TC/TDF in the Phase 1 trials). Overall, the results demonstrate that DOR, both as a single agent and as DOR/3TC/TDF, was generally well-tolerated at all doses studied. The safety profiles of DOR and DOR/3TC/TDF demonstrate safety benefits over DRV +r and EFV containing regimens, see [Sec. 2.5.6.2].

5.1 Summary of Approach to Assessment of Safety

This section will address safety in Phase 1, 2b, and 3 trials and is organized as follows: extent of exposure [Sec. 2.5.5.2]; analysis of AEs in Phase 1 trials, in Phase 2/3 trials, and in the integrated Phase 2/3 safety population pools [Sec. 2.5.5.3]; display of clinical laboratory results [Sec. 2.5.5.4]; safety in special groups and situations [Sec. 2.5.5.5]; and conclusions [Sec. 2.5.5.7].

Analysis Populations

Safety analyses were based on the All Subjects as Treated (ASaT) population (all randomized subjects who received at least 1 dose of study medication). Included in this application are analyses of safety data for 1657 individuals who received at least one dose of DOR, or DOR/3TC/TDF in 39 trials, including 36 Phase 1 trials, 1 Phase 2b trial (P007) and 2 Phase 3 trials (P018, P021). An overview of the Phase 2b/3 trials is provided in [Table 2.7.4: 1].

Integrated safety analyses were conducted on 2 pools of subjects in the Phase 2 and Phase 3 trials, the Main Safety Pool (MSP) and the Special Safety Pool (SSP).

- The MSP includes all treated subjects from P018 and P021 and those subjects in P007 initially randomized (either Part I or Part II) to the 100 mg DOR group. The MSP is the primary pool for the evaluation of all AEs.

- The SSP includes all randomized subjects from P021 and those subjects in P007 initially randomized (either Part I or Part II) to the DOR 100 mg and EFV groups. The SSP was primarily used to assess the proportion of participants discontinuing due to AEs by Week 48, the time to discontinuation due to AEs by Week 48, and neuropsychiatric events using pre-specified categories of AEs. The frequency of pre-specified neuropsychiatric events by Week 8 and by Week 48 in the SSP was a key safety endpoint in this analysis. A pre-defined list of neuropsychiatric AEs was examined in the following categories: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders.

See [Sec. 2.7.4.1.1.3] for more details regarding the MSP and SSP.

Assessment of Safety

AEs were assessed for the individual Phase 2b and Phase 3 trials and for the integrated safety data including review of common AEs, deaths, other SAEs, AEs leading to discontinuation, and AEs of special interest that consist of central nervous system (CNS)/neuropsychiatric AEs (comparison of DOR with EFV in trials P007 and P021). The frequency of pre-specified CNS events [Sec. 2.7.4.2.2.5.1] was assessed at Week 8 and by Week 24 in P007. The proportion of subjects with neuropsychiatric adverse events by Week 48 was assessed in the following categories (dizziness, sleep disorders and disturbances, altered sensorium, in that order) in P021. Evaluation of time to discontinuation due to AE was evaluated in P018 [Sec. 2.7.4.2.3.4], P021 [Sec. 2.7.4.2.4.4] individually, and in the SSP [Sec. 2.5.5.3.3.2.2].

Evaluations of laboratory values included review of Pre-Defined Limit of Change (PDLC) results, and assessment of change from baseline for laboratory parameters. The mean change from baseline in fasting lipids for the Phase 3 trials (P018 and P021) was evaluated at Week 48 in both studies; specifically a safety hypothesis tested superiority of the DOR regimen vs. the comparator with respect to LDL-C; if successful, subsequent testing for superiority with regard to fasting non-HDL-C at Week 48 would be performed.

5.2 Extent of Exposure

In the Phase 1 trials, 678 subjects received at least 1 dose of DOR or DOR/3TC/TDF. DOR has been administered as a single dose up to 1200 mg and as multiple doses up to 750 mg QD for 10 days. Across the Phase 1 program, 101 subjects received either DOR+3TC+TDF or DOR/3TC/TDF; of those 101 subjects, 86 received DOR/3TC/TDF [Appendix 5.3.5.3.1-trtmtnve48wk: 9] (Note: due to the nature of Phase 1 trials, subjects may have received more than 1 treatment in a given trial and therefore be counted in more than 1 category).

A total of 979 subjects received DOR in the Phase 2 and 3 trials: 232 subjects in P007 (108 received 100 mg QD for up to 96 weeks), 383 subjects in P018 (all received 100 mg for up to 48 weeks), and 364 subjects in P021 (as DOR/3TC/TDF [100 mg/300 mg/300 mg]) for up to 48 weeks) [Table 2.7.4: 2]. Both P018 and P021 are ongoing trials, and additional safety data may be provided in a supplemental application.

The integrated analysis of safety ([Sec. 2.7.4.1.1.3]) in the MSP includes data from a total of 1710 subjects in 3 groups: 855 subjects in the Main Combined DOR group, 472 in the Main Combined EFV group, and 383 subjects in the Main DRV+r group.

5.3 Analysis of Adverse Experiences

The overall safety evaluation plan is described in [Sec. 2.7.4.1.1.4]. Briefly, monitoring of AEs was performed by the investigator(s) at each trial visit. Treatment emergent AEs that occurred while on trial therapy or within the prespecified period following discontinuation of trial therapy were included in the safety analysis. Subjects were asked about any AEs during their trial visits and the information was recorded on AE case report forms. The investigator assessed the AE as to relationship to study medication and assessed the AE intensity as either mild, moderate, or severe. Serious AEs were to be reported within 24 hours to the Sponsor. Laboratory results were reviewed by the investigator for potential laboratory AEs. For Phase 2b/3 trials, guidelines for grading the severity of laboratory abnormalities were based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS Criteria) [Ref. 5.4: 04MB77].

5.3.1 Adverse Events in the Phase 1 Studies

In general, DOR and DOR/3TC/TDF given as single or multiple doses alone or co-administered with other therapies, were generally well-tolerated in the Phase 1 trials.

No deaths occurred in the Phase 1 trials. Three serious adverse events (SAEs) were reported following treatment with DOR, 2 were considered not related to trial drug by the investigator and 1 (spontaneous abortions) was considered related. (A brief narrative for the SAE of spontaneous abortion can be found in [Sec. 5.3.5.3.1.5.4-trtmtnve48wk] and the full narrative can be found in the individual CSR [Ref. 5.3.3.4: P050MK1439].)

Seven subjects discontinued study drug due to a drug-related AE in the Phase 1 trials; of these, 1 AE (headache) was considered to be related to DOR alone and 6 were considered to be related to other trial drugs. Most reported AEs were transient in nature and of mild to moderate intensity. No clear trends for dose-related increases in specific AEs were

identified. Two hundred two (28.9%) subjects reported at least one AE considered drug-related by the investigator. The most commonly reported drug-related AEs following administration of DOR, DOR/3TC/TDF and DOR + other trial drugs were headache (8.7%) and somnolence (5.0%) [Table 5.3.5.3.1-trtmtnve48wk: 15].

Refer to the Clinical Pharmacology Summary of Safety in [Sec. 5.3.5.3.1-trtmtnve48wk] for a detailed discussion of safety for the Phase 1 clinical pharmacology studies.

5.3.2 Adverse Events in the Individual Phase 2 and Phase 3 Studies

Analysis of AEs in individual Phase 2b and 3 trials can be found in [Sec. 2.7.4.2.2] for P007, [Sec. 2.7.4.2.3] for P018, and [Sec. 2.7.4.2.4] for P021. In general, in each of these trials, treatment with DOR and DOR/3TC/TDF was generally well tolerated with a favorable safety profile. Clinically meaningful and statistically significant advantages of the DOR Regimen were noted versus comparators with respect to central nervous system (CNS) events in P007 [Table 2.5: 6] and neuropsychiatric events (specifically in the categories of dizziness, sleep disorders and disturbances, and altered sensorium) in P021 [Table 2.5: 7].

Table 2.5: 6

Analysis of Subjects With Central Nervous System Adverse Events (CNS Events) by Week 8 and by Week 24
Part I/II Combined (Doravirine 100 mg vs. Efavirenz)
All Subjects as Treated (P007)

Treatment	Percent of Subjects With One or More Selected		Doravirine minus Efavirenz‡	
	n/N	%(95% CI)	Difference (95% CI)	p-Value
CNS Events† by Week 8				
Doravirine 100 mg	26/108	24.1 (16.4, 33.3)	-20.4 (-32.4, -7.8)	0.002
Efavirenz 600 mg	48/108	44.4 (34.9, 54.3)		
CNS Events† by Week 24				
Doravirine 100 mg	29/108	26.9 (18.8, 36.2)	-20.4 (-32.6, -7.5)	0.002
Efavirenz 600 mg	51/108	47.2 (37.5, 57.1)		

† Selected adverse events are from MedDRA terms of 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, concentration impaired.
‡ A negative value favors doravirine over efavirenz. The 95% CIs were calculated using Miettinen and Nurminen's method.
Subjects are counted once for each unique adverse event and may have had more than one unique adverse event.
n/N=Number of subjects included in a given category / number of subjects in each treatment group.
Note: Both doravirine and efavirenz were administered with TRUVADA™.

Source: [P007V01MK1439: analysis-adsl; adae]

Table 2.5: 7

Protocol 021: Analysis of Subjects with Neuropsychiatric Adverse Events by Week 48

	DOR/3TC/TDF QD (N=364)		EFV/FTC/TDF QD (N=364)		Treatment Difference (DOR/3TC/TDF - EFV/FTC/TDF)	2-Sided
	n	%	n	%	Estimate (95% CI)[†]	P-value[‡]
Subjects in population	364		364			
with one or more neuropsychiatric adverse events	86	(23.6)	207	(56.9)	-33.2 (-39.8, -26.4)	
with no neuropsychiatric adverse events	278	(76.4)	157	(43.1)	33.2 (26.4, 39.8)	
Dizziness	32	(8.8)	135	(37.1)	-28.3 (-34.0, -22.5)	<0.001
Sleep Disorders and Disturbances	44	(12.1)	93	(25.5)	-13.5 (-19.1, -7.9)	<0.001
Altered Sensorium	16	(4.4)	30	(8.2)	-3.8 (-7.6, -0.3)	0.033
Depression and Suicide/self-injury	15	(4.1)	24	(6.6)	-2.5 (-5.9, 0.8)	nps[*]
Psychosis and Psychotic Disorders	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)	nps[*]

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 19.1. Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a category is counted a single time for that category.

[†] The 95% CIs were calculated using Miettinen and Nurminen's method.

[‡] Superiority is tested sequentially for dizziness, sleep disorders and disturbances, and altered sensorium.

[*] Not pre-specified for statistical testing.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Source: [P021V01MK1439A: analysis-adsl; adcns]

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5.3.3 Adverse Events in the Integrated Safety Population Pool

5.3.3.1 Adverse Events in the Main Safety Pool (Protocols 007, 018 and 021)

By Week 48, the safety profile of DOR was comparable to or favorable relative to the Main DRV+r, and Main Combined EFV groups in the MSP. Compared with the Main Combined EFV treatment group, a lower proportion of subjects in the Main Combined DOR treatment group reported drug-related AEs, AEs that led to discontinuation, and drug-related AEs that led to discontinuation. The proportion of subjects reporting AEs, drug-related AEs, and SAEs were similar for the Main Combined DOR treatment group and the Main DRV+r treatment group [Table 2.5: 8]. Similar proportions of subjects reported SAEs in both treatment groups. The proportion of subjects discontinuing study medication due to AEs and drug-related AEs was also similar for these treatment groups.

Table 2.5: 8

Adverse Event Summary
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-48

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
with one or more adverse events	701	(82.0)	300	(78.3)	427	(90.5)
with no adverse event	154	(18.0)	83	(21.7)	45	(9.5)
with drug-related† adverse events	264	(30.9)	123	(32.1)	290	(61.4)
with serious adverse events	39	(4.6)	23	(6.0)	30	(6.4)
with serious drug-related adverse events	2	(0.2)	1	(0.3)	6	(1.3)
who died	1	(0.1)	0	(0.0)	2	(0.4)
discontinued‡ due to an adverse event	21	(2.5)	12	(3.1)	31	(6.6)
discontinued due to a drug-related adverse event	14	(1.6)	8	(2.1)	27	(5.7)
discontinued due to a serious adverse event	5	(0.6)	2	(0.5)	4	(0.8)
discontinued due to a serious drug-related adverse event	1	(0.1)	1	(0.3)	3	(0.6)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Main Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.
Main Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.
Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Source: [ISS: analysis-adsl; aeplus]

In the MSP, the most frequently reported AEs (incidence ≥5% in one or more treatment groups) for all treatment groups were headache, diarrhea, nausea, nasopharyngitis, upper respiratory tract infection, dizziness, and fatigue [Table 2.5: 9]. Dizziness, abnormal dreams, and rash were more frequently observed for subjects treated with EFV (35.4%, 12.9%, and 11.0%, respectively) compared with those treated with DOR (7.1%, 3.4%, and 3.0%,

respectively). Diarrhea was more frequently observed for subjects treated with DRV+r (22.5%) than among those treated with DOR (12.4%).

Table 2.5: 9

Subjects With Adverse Events
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-48

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
with one or more adverse events	701	(82.0)	300	(78.3)	427	(90.5)
with no adverse events	154	(18.0)	83	(21.7)	45	(9.5)
Gastrointestinal disorders	**298**	**(34.9)**	**162**	**(42.3)**	**179**	**(37.9)**
Diarrhoea	106	(12.4)	86	(22.5)	62	(13.1)
Nausea	81	(9.5)	46	(12.0)	45	(9.5)
Vomiting	33	(3.9)	10	(2.6)	31	(6.6)
General disorders and administration site conditions	**131**	**(15.3)**	**57**	**(14.9)**	**74**	**(15.7)**
Fatigue	57	(6.7)	20	(5.2)	28	(5.9)
Infections and infestations	**436**	**(51.0)**	**184**	**(48.0)**	**227**	**(48.1)**
Nasopharyngitis	81	(9.5)	39	(10.2)	41	(8.7)
Upper respiratory tract infection	78	(9.1)	23	(6.0)	30	(6.4)
Injury, poisoning and procedural complications	**50**	**(5.8)**	**20**	**(5.2)**	**51**	**(10.8)**
Investigations	**77**	**(9.0)**	**37**	**(9.7)**	**52**	**(11.0)**
Metabolism and nutrition disorders	**54**	**(6.3)**	**31**	**(8.1)**	**45**	**(9.5)**
Musculoskeletal and connective tissue disorders	**109**	**(12.7)**	**40**	**(10.4)**	**67**	**(14.2)**
Nervous system disorders	**211**	**(24.7)**	**73**	**(19.1)**	**223**	**(47.2)**
Dizziness	61	(7.1)	15	(3.9)	167	(35.4)
Headache	114	(13.3)	41	(10.7)	58	(12.3)
Somnolence	16	(1.9)	6	(1.6)	28	(5.9)
Psychiatric disorders	**144**	**(16.8)**	**51**	**(13.3)**	**170**	**(36.0)**
Abnormal dreams	29	(3.4)	3	(0.8)	61	(12.9)
Insomnia	42	(4.9)	18	(4.7)	35	(7.4)
Nightmare	21	(2.5)	5	(1.3)	27	(5.7)
Reproductive system and breast disorders	**34**	**(4.0)**	**10**	**(2.6)**	**27**	**(5.7)**
Respiratory, thoracic and mediastinal disorders	**107**	**(12.5)**	**36**	**(9.4)**	**47**	**(10.0)**

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Subjects With Adverse Events
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-48

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**141**	**(16.5)**	**62**	**(16.2)**	**124**	**(26.3)**
Rash	26	(3.0)	6	(1.6)	52	(11.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Main Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.
Main Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.
Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Source: [ISS: analysis-adsl; aeplus]

5.3.3.2 Pre-specified Safety Endpoints in the Special Safety Pool (SSP, P007 and P021)

The SSP is used for the analyses of the proportion of subjects who discontinued due to AEs from the P007 (100-mg group) and P021 trials combined due to AEs through Week 48 (pre-specified hypothesis in the iSAP), the time to discontinuation from the trials due to AEs through Week 48, and neuropsychiatric events using a pre-specified list of AEs.

5.3.3.2.1 Discontinuation and Time to Discontinuation Due to Adverse Events

In the SSP, a statistically significantly lower proportion of subjects discontinued the study due to AEs in the Special Combined DOR treatment group compared with the Special Combined EFV treatment group [Table 2.5: 10].

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Table 2.5: 10

Analysis of Proportion of Subjects Discontinuing from the Study Due to Adverse Event
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)
Weeks 0-48

	Special Combined DOR		Special Combined EFV		Treatment Difference (Special Combined DOR - Special Combined EFV)	
	n/N	(%)	n/N	(%)	Estimate (95% CI)[†]	2-sided p-value[†]
Discontinuation Due to an Adverse Event	13/472	(2.8)	29/472	(6.1)	-3.4 (-6.2, -0.8)	0.012

[†] Based on Miettinen & Nurminen method with weights proportional to the size of each protocol (P007, P021).
Special Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Special Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.
n = Number of subjects in each subcategory.
N = Number of subjects in each treatment group.

Source: [ISS: analysis-adsl; adtte]

The cumulative discontinuation rate over time is lower in the DOR group. Results of the log-rank test identified a treatment difference (nominal p = 0.010, unadjusted for multiplicity) by Week 48 in time to discontinuation due to AE [Figure 2.7.4: 4].

5.3.3.2.2 Neuropsychiatric Events

The proportions of subjects with neuropsychiatric events were lower in the DOR Regimen group compared with the EFV regimen group at Week 8 (20.3% vs. 50.6%) and at Week 48 (25.0% vs. 55.9%) ([Table 2.5: 11] and [Table 2.5: 12]). Most neuropsychiatric events in this analysis had been reported by Week 8. Dizziness (8.9 % for the DOR treatment group vs 35.4% for the EFV treatment group), and sleep disorders and disturbances (14.0% for the DOR treatment group vs 27.3% for the EFV treatment group) had substantially lower proportion of subjects reporting neuropsychiatric events in the Special Combined DOR treatment group compared to the Special Combined EFV treatment group.

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Table 2.5: 11

Analysis of Subjects with Neuropsychiatric Adverse Events by Week 8
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR (N=472)		Special Combined EFV (N=472)		Treatment Difference (Special Combined DOR - Special Combined EFV)
	n	%	n	%	Estimate (95% CI)[†]
Subjects in population	472		472		
with one or more neuropsychiatric adverse events	96	(20.3)	239	(50.6)	-30.3 (-36.0, -24.4)
with no neuropsychiatric adverse events	376	(79.7)	233	(49.4)	30.3 (24.4, 36.0)
Dizziness	37	(7.8)	159	(33.7)	-25.8 (-30.8, -20.9)
Sleep Disorders and Disturbances	53	(11.2)	114	(24.2)	-12.9 (-17.7, -8.2)
Altered Sensorium	15	(3.2)	28	(5.9)	-2.8 (-5.6, -0.1)
Depression and Suicide/self-injury	8	(1.7)	16	(3.4)	-1.7 (-3.9, 0.3)
Psychosis and Psychotic Disorders	2	(0.4)	6	(1.3)	-0.8 (-2.4, 0.4)

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 19.1. Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a category is counted a single time for that category.

[†] The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each protocol (P007, P021).

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Special Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Special Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; adcns]

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Table 2.5: 12

Analysis of Subjects with Neuropsychiatric Adverse Events by Week 48
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR (N=472)		Special Combined EFV (N=472)		Treatment Difference (Special Combined DOR - Special Combined EFV)
	n	%	n	%	Estimate (95% CI)[†]
Subjects in population	472		472		
with one or more neuropsychiatric adverse events	118	(25.0)	264	(55.9)	-30.9 (-36.8, -24.9)
with no neuropsychiatric adverse events	354	(75.0)	208	(44.1)	30.9 (24.9, 36.8)
Dizziness	42	(8.9)	167	(35.4)	-26.5 (-31.5, -21.4)
Sleep Disorders and Disturbances	66	(14.0)	129	(27.3)	-13.3 (-18.4, -8.3)
Altered Sensorium	18	(3.8)	32	(6.8)	-3.0 (-6.0, -0.1)
Depression and Suicide/self-injury	20	(4.2)	36	(7.6)	-3.4 (-6.6, -0.4)
Psychosis and Psychotic Disorders	4	(0.8)	7	(1.5)	-0.6 (-2.3, 0.9)

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 19.1. Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a category is counted a single time for that category.

[†] The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each protocol (P007, P021).

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Special Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Special Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; adcns]

5.4 Clinical Laboratory Evaluations

5.4.1 Clinical Laboratory Results in Phase 1 Studies

In all Phase 1 studies, descriptive summaries of laboratory safety data, if applicable to the protocol, were included in the individual clinical study reports. Within each trial, there were no clinically important trends for changes in laboratory safety parameter values for DOR in the clinical pharmacology trials.

5.4.2 Clinical Laboratory Results in the Individual Phase 2 and Phase 3 Studies

Results of clinical laboratory evaluations in individual Phase 2b and 3 trials can be found in [Ref. 5.3.5.1: P007V01MK1439] for P007; [Ref. 5.3.5.1: P018V01MK1439] for P018; and [Ref. 5.3.5.1: P021V01MK1439A] for P021. In general, in each of these trials, treatment with DOR and DOR/3TC/TDF was generally well tolerated. Few Grade 3 or 4 lab abnormalities were reported.

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Of note, in each of the individual Phase 2b and 3 trials, a higher proportion of subjects with Grade 1 and/or Grade 2 values for total bilirubin were observed for the DOR regimen compared with the comparator group. In P007, the proportion of Grade 1 bilirubin elevations were observed in 6.1% of the DOR group and 2.8%, of the EFV group. In P018, Grade 1 and/or Grade 2 bilirubin elevations were observed in 6.6% of the DOR group and 1.4% of the DRV+r group. In P021, Grade 1 and/or Grade 2 bilirubin elevations were observed in 6.1% of the DOR group and 0.0% of the EFV group. No subject in either treatment group met the criteria for DILI. The majority of elevations in the DOR group were Grade 1, single, transient elevations, with no pattern of the elevation occurring early or late relative to dosing.

Clinically meaningful differences of the DOR Regimen were noted versus comparators with respect to fasting lipid test results. For LDL-C, non-HDL-C, total cholesterol, and triglycerides, the differences in the mean change from baseline at Week 48 between DOR and DRV+r and DOR/3TC/TDF and EFV/FTC/TDF favored the doravirine-treatment group in P018 and P021, respectively. The LDL and non-HDL comparisons were pre-specified and the differences were statistically significant showing superiority for DOR for both parameters. See [Table 2.5: 13] for P018 results and [Table 2.5: 14] for P021 results.

Table 2.5: 13

Protocol 018: Change From Baseline in Fasting Lipids at Week 48

Treatment	N	Baseline Mean	Change from Baseline at Week 48		Difference Estimates (Doravirine - Darunavir)	
			Mean Change (SD)	95% CI†	Difference‡ 95% CI	2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	326	91.10	-4.51 (20.64)	(-6.76, -2.26)	-14.61 (-18.15, -11.06)	<0.0001
Darunavir/ritonavir 800/100 mg QD	318	91.76	9.92 (27.31)	(6.91, 12.94)		
Fasting Non-HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	113.34	-5.30 (23.28)	(-7.83, -2.78)	-19.34 (-23.33, -15.35)	<0.0001
Darunavir/ritonavir 800/100 mg QD	325	114.44	13.75 (31.08)	(10.36, 17.14)		
Fasting Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	156.92	-1.37 (25.47)	(-4.13, 1.39)	-19.50 (-23.82, -15.17)	nps*
Darunavir/ritonavir 800/100 mg QD	325	157.71	17.90 (33.95)	(14.20, 21.61)		
Fasting Triglyceride (mg/dL)						
Doravirine 100 mg QD	329	111.16	-3.14 (68.81)	(-10.61, 4.32)	-27.87 (-38.71, -17.02)	nps*
Darunavir/ritonavir 800/100 mg QD	325	117.02	21.97 (92.59)	(11.86, 32.07)		
Fasting HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	43.58	3.94 (10.66)	(2.78, 5.09)	-0.15 (-1.75, 1.45)	nps*
Darunavir/ritonavir 800/100 mg QD	325	43.27	4.15 (11.01)	(2.95, 5.36)		

The Last Observation Carry Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.

† Within group 95% CIs were based on t-distribution.

‡ The 95% CIs and 2-sided p-value for treatment difference were calculated from an ANOCOVA model with terms for baseline lipid level and treatment.

* Not pre-specified for statistical testing

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

N = Number of subjects with baseline and at least one postbaseline test result.

Source: [P018V01MK1439: analysis-adsl; adlpd]

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Table 2.5: 14

Protocol 021: Change From Baseline in Fasting Lipids at Week 48

Treatment	N	Baseline Mean	Change from Baseline at Week 48		Difference Estimates (DOR/3TC/TDF - EFV/FTC/TDF)	
			Mean Change (SD)	95% CI†	Difference‡ 95% CI	2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	330	92.03	-1.58 (22.12)	(-3.98, 0.81)	-10.01 (-13.53, -6.49)	<0.0001
EFV/FTC/TDF QD	305	90.75	8.74 (25.54)	(5.86, 11.62)		
Fasting Non-HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	115.23	-3.83 (22.59)	(-6.27, -1.40)	-17.02 (-20.89, -13.16)	<0.0001
EFV/FTC/TDF QD	314	114.84	13.26 (28.76)	(10.07, 16.45)		
Fasting Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	157.38	-1.97 (25.67)	(-4.74, 0.79)	-23.44 (-27.57, -19.32)	nps*
EFV/FTC/TDF QD	314	156.21	21.77 (30.74)	(18.35, 25.18)		
Fasting Triglyceride (mg/dL)						
DOR/3TC/TDF QD	333	119.45	-12.40 (67.30)	(-19.66, -5.15)	-35.96 (-47.10, -24.82)	nps*
EFV/FTC/TDF QD	314	122.97	22.01 (93.03)	(11.68, 32.34)		
Fasting HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	42.15	1.86 (9.59)	(0.83, 2.89)	-6.47 (-7.97, -4.96)	nps*
EFV/FTC/TDF QD	314	41.37	8.51 (10.66)	(7.32, 9.69)		

The Last Observation Carry Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.

† Within group 95% CIs were based on t-distribution.

‡ The 95% CIs and 2-sided p-value for treatment difference were calculated from an ANOCOVA model with terms for baseline lipid level and treatment.

* Not pre-specified for statistical testing

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

N = Number of subjects with baseline and at least one postbaseline test result.

Source: [P021V01MK1439A: analysis-adsl; adlpd]

5.4.3 Clinical Laboratory Results in the Integrated Main Safety Population Pool

In the MSP, the proportions of subjects with laboratory findings meeting Pre-Defined Limit of Change (PDLC) criteria at Week 48 for selected laboratory parameters was in general similar with few notable differences, in the 3 treatment groups [Table 2.7.4: 48].

- A higher proportion of subjects in the Main Combined DOR treatment group met PDLC criteria for total bilirubin Grade 1 and Grade 2 compared to the Main DRV+r and the Main Combined EFV treatment groups.
- A higher proportion of subjects in the Main DRV+r treatment group met PDLC criteria for Grade 2 and Grade 3 creatinine compared to the Main Combined DOR.
- A higher proportion of subjects in the Main Combined EFV group met PDLC criteria in both ALT and alkaline phosphatase for Grade 1 compared to the Main Combined DOR.

With regard to mean change in laboratory parameters from baseline at each time point by Week 48, other than the changes in fasting lipid parameters, there were no apparent differences between the treatment groups, and no apparent trends indicative of DOR related effects on clinical laboratory parameters. Change from baseline in fasting LDL-C, fasting non–HDL-C, fasting total cholesterol, fasting triglycerides, and fasting HDL-C were evaluated [Table 2.7.4: 49]. For fasting LDL-C, DOR was associated with a mean decrease of 3.69 mg/dL from baseline, while DRV+r and EFV were associated with mean increases of 9.92 mg/dL and 9.14 mg/dL, respectively, from baseline at Week 48. Similarly, for fasting non–HDL-C, fasting total cholesterol, fasting triglycerides, DOR was associated with mean decreases from baseline while DRV+r and EFV were associated with mean increases from baseline. The increases in fasting HDL-C were comparable in the 3 treatment groups.

5.5 Safety in Special Groups and Situations

The safety of DOR and DOR/3TC/TDF was assessed in the MSP based on examination of intrinsic [Sec. 2.7.4.5.1] and extrinsic factors [Sec. 2.7.4.5.2], as well as other situations (eg, overdose [Sec. 2.7.4.5.6] or use in pregnant or lactating women [Sec. 2.7.4.5.5]) likely to be encountered in the clinical practice of treating individuals with HIV-1 infection.

5.5.1 Intrinsic Factors

In the MSP, clinical and laboratory AEs were reviewed for subjects subgroups based on age, gender, race, ethnicity, hepatitis B and/or C infection status, and baseline CD4+ T-cell level. Overall, AEs and laboratory abnormality profiles were generally similar in subject subgroups based on gender, race/ethnicity, and age (<65 or ≥65 years; note that there were no subjects >75 years of age) [Sec. 2.7.4.5.1]. In all cases, differences between treatment groups were generally minimal within baseline subgroups. Although some differences were evident, the prevalence of AEs by SOC was similar for men and women overall. Similar findings were generally noted when AEs were evaluated by race and ethnicity, baseline hepatitis status, and $CD4^+$ T-cell count. Small sample sizes for subjects ≥65 years, females, some race categories, and subjects with chronic hepatitis B and/or C infection should be considered in the analysis and interpretation of data in these subgroups.

5.5.2 Extrinsic Factors and Drug-Drug Interactions

Safety by the extrinsic factor of geographical region (Africa, Asia/Pacific, Europe, Latin America, and North America) was evaluated, and the overall safety profiles for DOR and DOR/3TC/TDF were generally similar across geographic regions [Table 5.3.5.3.3-trtmtnve48wk: 79].

There were 16 Phase 1 trials conducted to investigate potential drug-drug interactions with DOR. Across all DDI trials, the safety profile was similar to that observed when DOR was not co-administered with another medication [Table 5.3.5.3.1-trtmtnve48wk: 14].

Only CYP3A modulators have the potential to affect the exposure of DOR to a clinically meaningful extent. The safety profile for subjects co-administered moderate or strong CYP3A inhibitors was similar to subjects without concomitant use of moderate or strong CYP3A inhibitors. Concomitant use of moderate or strong CYP3A inhibitors did not appear

to affect the incidence of AEs, drug-related AEs, SAEs, deaths, or discontinuations due to AEs [Table 5.3.5.3.3-trtmtnve48wk: 80], [Table 5.3.5.3.3-trtmtnve48wk: 81], [Table 5.3.5.3.3-trtmtnve48wk: 82], and [Table 5.3.5.3.3-trtmtnve48wk: 83].

Although the proportions of subjects with 1 or more AEs were similar for subjects in the Main Combined DOR group with concomitant use of moderate or strong CYP3A inhibitors and subjects without concomitant use of moderate or strong CYP3A inhibitors, the incidence of a few specific AEs differed. The proportions of subjects with diarrhea, nausea, and cough were higher in subjects with concomitant use of moderate or strong CYP3A inhibitors compared to the subjects without concomitant use of moderate or strong CYP3A inhibitors (25.1% vs 11.3%, 19.4% vs 8.6%, and 13.4% vs 3.6%, respectively) [Table 5.3.5.3.3-trtmtnve48wk: 81]. However, the proportions of subjects with drug-related diarrhea, nausea, and cough were similar in these same subgroups (4.5% vs 3.9%, 9.0% vs 5.7%, 1.5% vs 0%, respectively).

5.5.3 Overdose

In the Phase 2b/3 trials, there were 3 reports of overdose of the DOR regimen in the MSP. The duration of the overdoses ranged from 24 hours to 2 days. The highest number of 100-mg tablets taken (accidental overdose) was 3 (300 mg/day). No AEs were reported with any of the overdoses.

5.5.4 Use in Pregnancy and Lactation

Females who were pregnant and/or lactating were excluded from enrollment into any of the clinical trials; however, 6 subjects became pregnant during the trail period and discontinued from the Phase 2b/3 trials due to pregnancy. The outcomes for these pregnancies were as follows: a vaginal live birth with no congenital anomalies for 2 pregnancies (DOR 50 mg group in P007 and DOR group in P018); spontaneous abortion considered not drug related for 3 pregnancies (1 in the DOR group in P018; 1 in the DOR/3TC/TDF group in P021 and 1 in the EFV/FTC/TDF group in P021); and pending (pregnancy ongoing) for 1 pregnancy, (EFV/FTC/TDF group in P021). Additional information is in [Section 2.7.4.5.5]. The use of DOR and DOR/3TC/TDF in pregnancy and lactation is not recommended. Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission.

5.6 Limitations of the Safety Database

No specific safety issues were identified that would preclude the approval of DOR and/or DOR/3TC/TDF for the proposed indications. However, the following may be considered to be limitations/missing information of the safety database in this application with no/insufficient safety data for the following populations: treatment experienced subjects, pediatric subjects, subjects above the age of 65; and pregnant or nursing women. Additionally, in the population examined, potential long term safety signals may not be known as there is limited safety date beyond 48 weeks of therapy. The Phase 3 trials (P018, P021) will continue through 96 weeks of therapy, and additional safety findings from this longer duration of follow-up will be provided in a future submission. These limitations of

the safety database are appropriately acknowledged in the corresponding sections in the proposed Product Circular.

5.6.1 Risk Management Plan

A comprehensive Risk Management Plan is provided in this Application [1.16.1].

5.7 Safety Conclusions for Doravirine and Doravirine/Lamivudine/Tenofovir disoproxil fumarate

DOR and DOR/3TC/TDF were generally well tolerated in 855 HIV-1 infected treatment-naïve subjects treated with the 100 mg dose of DOR for at least 48 weeks.

In P021, a statistically significantly lower proportion of DOR/3TC/TDF-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric AEs by Week 48 in the three pre-specified categories (Tier 1 – Adverse Events of Special Interest): dizziness, sleep disorders and disturbances, and altered sensorium:

- Dizziness (8.8% vs. 37.1% [-28.3; p<0.001])
- Sleep disorders and disturbances (12.1% vs. 25.5% [-13.5; p<0.001])
- Altered sensorium (4.4% vs. 8.2% [-3.8; p= 0.033])

With regard to LDL- and non-HDL-cholesterol, total cholesterol, and triglycerides, the differences in the mean change from baseline at Week 48 (DOR – DRV+r and DOR/3TC/TDF - EFV/FTC/TDF) favored the DOR-treatment group in both Phase 3 studies (P018, P021). The LDL and non-HDL comparisons were pre-specified and the differences were statistically significant showing superiority for DOR for both parameters:

- LDL-C: P018 (-4.51 vs. 9.92 mg/dL [-14.61; *p<0.0001*]); P021 (-1.58 vs. 8.74 mg/dL [-10.01; *p<0.001*])
- Non-HDL-C: P018 (-5.30 vs. 13.75 mg/dL [-19.34; *p<0.001*]); P021 (-3.83 vs. 13.26 mg/dL [-17.02; *p<0.001*])

In a pooled analysis combining data from P007 and P021, a statistically significantly lower proportion of subjects who discontinued due to an adverse event by Week 48 was seen for the combined DOR and DOR/3TC/TDF group (2.8%) compared with the combined EFV/FTC/TDF group (6.1%) [treatment difference -3.4%, p-value 0.012].

The results of the individual Phase 1-3 trials and pooled analyses demonstrated that the 100-mg dose of DOR (given alone or in combination with other antiretroviral agents) and DOR/3TC/TDF have a favorable safety profile when compared with DRV+r and EFV/FTC/TDF.

6 BENEFITS AND RISKS CONCLUSIONS

DOR and DOR/3TC/TDF have positive benefit/risk profiles that support the recommended dose regimens.

6.1 Therapeutic Context

6.1.1 Disease or Condition

Background information regarding HIV-1 infection including the epidemiology and public health burden of HIV-1 infection can be found in [Sec. 2.5.1.4.1] of this document. Lifelong ART is needed for HIV-1 infected patients and as people living with HIV age, they commonly have multiple co-morbidities.

6.1.2 Current Therapies

Background information regarding the current HIV-1 therapies for treatment naive subjects can be found in [Sec. 2.5.1.4.2] of this document.

Medical Need

There continues to be a need for HIV-1 therapy options that are efficacious, safe, well tolerated, convenient for patients (coformulated and administered once daily), and without significant food effect or drug-drug interactions.

6.2 Benefits

The clinical benefits of treatment with DOR or DOR/3TC/TDF of HIV-1 infected treatment-naïve patients are clearly supported by the robust clinical trial data in a diverse population:

DOR and DOR/3TC/TDF showed:

- robust and non-inferior efficacy as compared to DRV+r and EFV, respectively, through Week 48 in Phase 3 trials and as compared to EFV through Week 96 in the Phase 2b trial as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL;
- consistent efficacy across demographic and prognostic factors, including subjects with high baseline HIV-1 RNA (>100,000 copies/mL) and low CD4+ T-cell count (<200 cells/mm^3) in Phase 2 and 3 trials; and
- a robust immunological response with increases in $CD4^+$ T-cell counts from baseline similar to DRV+r and EFV in Phase 2 and Phase 3 trials.

DOR and DOR/3TC/TDF demonstrated the following excellent (superior) safety profile with:

- a superior neuropsychiatric profile with significantly fewer neuropsychiatric AEs compared to EFV-based regimens;

- a superior lipid profile when compared with EFV and DRV+r; and
- a lower rate of discontinuations due to AEs when compared with EFV.

DOR and DOR/3TC/TDF showed a favorable resistance profile with the following aspects:

- Potent in vitro antiviral activity against wild-type and the most common NNRTI resistant variants: In 100% normal human serum, wild-type HIV-1 had EC50 of 12nM, with similarly low EC50s of 21, 31, and 55 nM against HIV-1 mutants containing the most frequently transmitted NNRTI mutations RT K103N, Y181C, and G190A, respectively.

- Low rate of resistance in Phase 2 and 3 trials with a unique resistance pathway that commonly requires more than 1 substitution to confer DOR resistance.

Dosing of DOR and DOR/3TC/TDF will be convenient to patients given the following characteristics:

- Favorable drug-drug interaction profile with DOR not a perpetrator of clinically significant drug-drug interactions:
    - No dose adjustment necessary for patients with mild, moderate or severe renal or mild or moderate hepatic impairment.
    - No interaction with proton pump inhibitors and other gastric acid-modifying agents and cation containing antacids
- Available as a single-entity or fixed dose combination of DOR/3TC/TDF with once daily dosing without regard to food

6.3 Risks

Overall the clinical development program demonstrated a favorable safety and tolerability profile for DOR and DOR/3TC/TDF, and no specific safety issues were identified that would preclude the approval of DOR and DOR/3TC/TDF for the proposed indications. However, it is acknowledged that the safety database has the following limitations:

- Limited safety data beyond 48 weeks (potential long term safety signals may not be known)
- No clinical data in subjects who are pregnant/lactating.
- Minimal efficacy data in subjects ≥65 years of age.

Additionally, the efficacy database has the following limitations:

- Limited information regarding durability of response (Phase 3 data available to 48 weeks)

6.4 Benefit Risk Assessment

DOR in combination with other ARTs and DOR/3TC/TDF have been shown to be efficacious in treatment-naïve HIV-1 infected patients. Integrated safety analysis of DOR and DOR/3TC/TDF demonstrates that DOR is generally well tolerated and has a favorable safety profile with no untoward risks identified. Risks have been extensively analyzed and were found to be limited and appear to be safely manageable by clinicians.

DOR is not expected to have many of the safety concerns associated with EFV (treatment-limiting neuropsychiatric AEs and dyslipidemia) and/or DRV+r (dyslipidemia). In addition, DOR is not expected to have major drug-drug interactions that would limit its utility in clinical practice. Additionally, the fixed-dose-combination DOR/3TC/TDF is a simple regimen that could result in good adherence, thereby potentially decreasing the risk of virologic failure. A table summarizing the favorable and unfavorable effects in the Phase 2b/3 trials is provided in [Appendix 2.5: 1].

Given the continued need for new HIV-1 therapy options with robust efficacy and favorable safety profiles, the efficacy and safety profile for DOR and DOR/3TC/TDF to date show sufficient benefit to seek marketing authorization for DOR and DOR/3TC/TDF.

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Appendix 2.5: 1

Summary of Favorable and Unfavorable Effects in Doravirine Phase 2b and 3 Studies (P007, P018 and P021) in this Application

Effect	Short Description	Unit	DOR Regimen	Comparator	Uncertainties / Strength of evidence	References
Favorable						
Proportion of subjects achieving HIV-1 RNA <50 copies/mL	Robust and non-inferior efficacy as compared to DRV+r and EFV through Week 48 in Phase 3 trials	%	84.1	79.9 (DRV + r); 80.8 (ETV/FTC/TDF)		[Table 2.5: 5]
Proportion of subjects achieving HIV-1 RNA <40 copies/mL	Robust and non-inferior efficacy as compared to DRV+r and EFV through Week 48 in Phase 3 trials	%	83.5	79.1 (DRV + r); 79.7 (ETV/FTC/TDF)		[Table 2.5: 5]
Increase in $CD4^+$ T-cell counts from baseline	A robust immunological response in Phase 3 trials		195.5	185.6 (DRV + r); 188.4 (ETV/FTC/TDF)		[Table 2.5: 5]
Proportion of subjects with neuropsychiatric AEs	Fewer neuropsychiatric AEs compared to EFV-based regimens in the Special Safety Population	%	20.3, at Week 8; 25.0 at Week 48	50.6, at Week 8 (EFV Group); 55.9 at Week 48 (EFV Group)		[Sec. 2.5.5.3.3.2]
	Fewer neuropsychiatric AEs in the DOR regimen compared to EFV-based regimens in P021	%	23.6	56.9 (EFV/FTC/TDF)		[Sec. 2.5.5.3.2]
Change in baseline fasting lipids at Week 48	More favorable lipid profile and superior LDL-C and non-HDL-C profile when compared against EFV and DRV+r :					[Sec. 2.5.5.4.2]
	Fasting LDL Cholesterol	mg/dL	-4.51 (DOR) -1.58 (DOR/3TC/TDF)	9.92 (DRV+r); 8.74 (EFV/FTC/TDF)		
	Fasting non-LDL Cholesterol	mg/dL	-5.30 (DOR) -3.83 (DOR/3TC/TDF)	13.75 (DRV+r); 13.26 (EFV/FTC/TDF)		
	Fasting Cholesterol	mg/dL	-1.37 (DOR) -1.97 (DOR/3TC/TDF)	17.90 (DRV+r); 21.77 (EFV/FTC/TDF)		
	Fasting Triglyceride	mg/dL	-3.14 (DOR) -12.40 (DOR/3TC/TDF)	21.97 (DRV+r) 22.01 (EFV/FTC/TDF)		
Rate of discontinuations due to AEs	A lower rate of discontinuations due to AEs and SAEs when compared against EFV	%	2.8	6.1 (EFV Group)		[Sec. 2.5.5.3.3.1]
Unfavorable						
Not Applicable						

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The following tables summarize the efficacy results from the main studies supporting the present application.

Table 1 Summary of Efficacy for Trial P018

<table>
<tr><td colspan="4">Title: 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</td></tr>
<tr><td rowspan="4">Study identifier</td><td colspan="2">Protocol Number:</td><td>018</td></tr>
<tr><td colspan="2">Clinical Phase:</td><td>3</td></tr>
<tr><td colspan="2">EudraCT Number:</td><td>2014-001127-69</td></tr>
<tr><td colspan="2">Other Codes:
IND Number:
ClinicalTrials.gov identifier:</td><td>
112,796
NCT02275780</td></tr>
<tr><td rowspan="4">Design</td><td colspan="3">Multicenter, double-blind (with in-house blinding), randomized, active-comparator-controlled trial to evaluate the safety, efficacy, and pharmacokinetics (PK) 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, who had 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.</td></tr>
<tr><td colspan="2">Planned duration of main phase:</td><td>96 weeks; Week 48 is the primary time point.</td></tr>
<tr><td colspan="2">Duration of run-in phase:</td><td>Not applicable</td></tr>
<tr><td colspan="2">Planned duration of extension phase:</td><td>96 weeks</td></tr>
<tr><td>Hypothesis (EU-specific)</td><td colspan="3">DOR 100 mg QD is noninferior to DRV+r (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 48; the superiority of MK-1439 100 mg QD to darunavir/ritonavir (800 mg/100 mg) QD was to be assessed if noninferiority was established.</td></tr>
<tr><td rowspan="2">Treatment groups</td><td>DOR
(doravirine; MK-1439)</td><td colspan="2">Doravirine 100-mg oral compressed 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</td></tr>
<tr><td>DRV+r
(darunavir + ritonavir)</td><td colspan="2">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</td></tr>
</table>

Endpoints and definitions	Primary efficacy endpoint (EU-specific)	HIV-1 RNA <40 copies/mL at Week 48	Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL
	Secondary efficacy endpoints	HIV-1 RNA <50 copies/mL	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 48 and Week 96
		HIV-1 RNA <40 copies/mL at Week 96	Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL
		$CD4^+$ T-cell count	Change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96
	Exploratory efficacy endpoints	HIV-1 RNA <200 copies/mL	Proportion of subjects achieving plasma HIV-1 RNA level <200 copies/mL at Week 48 and Week 96
		TLOVR	Time to loss of virologic response (TLOVR)
		PDVF	Protocol-defined virologic failure (PDVF)
		Viral drug resistance	Viral drug resistance
Last subject's last visit for primary endpoint analysis:	29-Sep-2016; the study is ongoing.		
Database lock:	[redacted]-20[redacted]		

RESULTS AND ANALYSIS	
Analysis description	**Primary Analysis** Proportion of Subjects With HIV-1 RNA <40 copies/mL at Week 48 *Statistical Methodology*: The EU-specific primary hypothesis on antiretroviral activity was assessed by the percentage of subjects achieving plasma HIV-1 RNA <40 copies/mL at Week 48 using the Abbott RealTime HIV-1 Assay. A margin of 10 percentage points was used to define noninferiority: DOR (100 mg QD) was concluded to be noninferior 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 <40 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 <40 copies/mL): all missing data were treated as failures regardless of the reason.
	Secondary Efficacy Analysis Proportion of Subjects With HIV-1 RNA <50 copies/mL at Week 48 *Statistical Methodology*: Same as for primary 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 time point; 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 (OF) 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 time point 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 The primary time point is Week 48.

Efficacy at Week 48	Treatment Group		Treatment Difference †	
	DOR n/N (%)	DRV+r n/N (%)	Estimated Difference	95% CI
Primary				
Proportion of subjects with HIV-1 RNA <40 copies/mL (*FDA Snapshot*)	319/383 (83.3)	303/383 (79.1)	4.169	(-1.404, 9.743)
Secondary and Exploratory				
Proportion of subjects with HIV-1 RNA <40 copies/mL (*OF approach*)	319/364 (87.6)	303/355 (85.4)	2.160	(-2.898, 7.218)
Proportion of subjects with HIV-1 RNA <50 copies/mL (*FDA Snapshot*)	321/383 (83.8)	306/383 (79.9)	3.913	(-1.590, 9.415)
Proportion of subjects with HIV-1 RNA <50 copies/mL (*OF approach*)	321/364 (88.2)	306/355 (86.2)	1.880	(-3.072, 6.833)
Proportion of subjects with HIV-1 RNA <200 copies/mL (*FDA Snapshot*)	328/383 (85.6)	316/383 (82.5)	3.141	(-2.095, 8.378)
Proportion of subjects with HIV-1 RNA <200 copies/mL (*OF approach*)	328/364 (90.1)	316/355 (89.0)	1.068	(-3.504, 5.641)
	Mean (95% CI)	**Mean (95% CI)**	**Mean Difference**	**95% CI**
Change from baseline in CD4 cell count (cells/mm^3) (*OF approach*)	192.7 (171.5, 213.9)	185.6 (167.5, 203.6)	7.1	(-20.8, 35.0)

OF = Observed Failure approach.

n = Number of subjects in each subcategory; N = Number of subjects in each treatment group.

† The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum. The 95% CI for mean difference in CD4 change was based on t-distribution.

Analysis of postbaseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

Summary	The proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 (FDA Snapshot approach; EU-specific primary endpoint) was 83.3% in the DOR group and 79.1% in the DRV+r group, with a treatment difference (DOR − DRV+r) (95% CI) of 4.2% (-1.4, 9.7), demonstrating noninferiority of DOR 100 mg QD versus DRV+r (800 mg/100 mg QD), each in combination with FTC/TDF or ABC/3TC. The proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 (FDA Snapshot approach; secondary efficacy endpoint) was 83.8% (321/383) in the DOR group and 79.9% (306/383) in the DRV+r group, with a treatment difference of 3.9% (-1.6, 9.4). Analysis results for these endpoints using the OF approach were consistent with those of the FDA snapshot approach. With respect to the secondary efficacy analysis of change from baseline in CD4$^+$ T-cell count, the DOR group had a similar mean change from baseline (193 cells/mm^3) compared with the DRV+r group (186 cells/mm^3), with a treatment difference (95% CI) of 7.1 (-20.8, 35.0). In addition, the proportion of subjects achieving HIV-1 RNA <200 copies/mL at Week 48 (using both missing-data approaches) was supportive of the results for the primary and key secondary endpoints.

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Analysis description	**Supportive Efficacy Analysis** Virologic Outcome *Statistical methodology*: In addition to the analysis of proportion of subjects achieving virologic success (HIV-1 RNA <50 copies/mL) at Week 48, subjects who were not classified as virologic success were further categorized as HIV-1 RNA ≥50 copies/mL or no virologic data in the time window with reasons of 1) discontinued study due to AE or death, 2) discontinued study for other reasons (including loss to follow-up, noncompliance with study drug, etc), or 3) on study but missing data in window.

Virologic Outcome at Week 48	**Treatment Group**			
	DOR (N=383)		**DRV+r (N=383)**	
	n	(%)	n	(%)
OUTCOME (*FDA Snapshot*)				
HIV-1 RNA <50 copies/mL	321	(83.8)	306	(79.9)
HIV-1 RNA ≥ 50 copies/mL†	43	(11.2)	50	(13.1)
No virologic data at Week 48 window	19	(5.0)	27	(7.0)
Reasons				
Discontinued study due to AE or death‡	5	(1.3)	11	(2.9)
Discontinued study for other reasons§	11	(2.9)	15	(3.9)
On study but missing data in window	3	(0.8)	1	(0.3)

† Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (Relative Day 295-378).

‡ Includes subjects who discontinued because of AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

§ Other Reasons includes: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, withdrawal by subject.

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

Summary:	The virologic outcomes of the DOR group were similar to those of the DRV+r group. In addition to the similarity between treatment groups with respect to the proportion of subjects with HIV-1 RNA <50 copies/mL described above, similar proportions of subjects in the DOR and DRV+r groups were categorized as having HIV-1 RNA ≥50 copies/mL (11.2% and 13.1%, respectively), and similar proportions of subjects were categorized as having no virologic data at Week 48 window (5% and 7% of subjects, respectively).

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Analysis description	**Supportive Analysis**: Subgroup Efficacy Statistical methodology: To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the efficacy endpoint was calculated within each category of the subgroup factors.
Summary	Across all subgroups defined by baseline prognostic and demographic factors, the DOR group showed antiretroviral efficacy comparable to that of the DRV+r group (based on 95% CIs that included 0), consistent with the findings seen for the DOR and DRV+r treatment groups overall. Of note, among subjects with a high baseline HIV-1 RNA level (>100,000 copies/mL), similarly high proportions of subjects achieved HIV-1 RNA <40 copies/mL at Week 48 in the DOR and DRV+r treatment groups (79.7% and 75.0%, respectively). Similarly, among subjects with baseline $CD4^+$ T-cell counts ≤50 cells/mm^3 or >50 and ≤200 cells/mm^3, the proportion of subjects who achieved HIV-1 RNA <40 copies/mL at Week 48 was at least as high in the DOR group (83.3% and 82.9%) as in the DRV+r group (66.7% and 72.1%). Within both treatment groups, trends of lower efficacy were seen with high baseline HIV-1 RNA (>100,000 and >500,000 copies/mL) and low pre-treatment $CD4^+$ T-cell counts; these trends were less pronounced for the DOR group than for the DRV+r group.
Analysis description	**Supportive 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 could also be applied to this time-to-event data.
Summary	Kaplan-Meier analysis and analyses using the log-rank test and the Cox model demonstrate that the DOR and DRV+r groups were similar with respect to the risk of loss-of-virologic-response events; such events were infrequently noted among subjects in either treatment group through Week 48.
Analysis description	**Exploratory Analysis**: Protocol-Defined Virologic Failure (PDVF) and Viral Drug Resistance *Statistical methodology*: The proportion of subjects with protocol-defined virologic failure was summarized by treatment group. The protocol definition of virologic failure is (1) rebounder: subject with confirmed HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; or (2) non-responder: subject with confirmed (2 consecutive measures at least 1 week apart) HIV-1 RNA ≥200 copies/mL at Week 24 or Week 36 OR confirmed HIV-1 RNA ≥50 copies/mL at Week 48.
Summary	Rates of PDVF by Week 48 were low and comparable among subjects in the DOR (4.9%) and DRV+r (6.3%) treatment groups. Development of viral drug resistance was rare: no primary genotypic resistance was seen among subjects who met PDVF criteria in either the DOR or DRV+r group, while virus from 1 DOR-treated subject who discontinued due to noncompliance was found to have genotypic and phenotypic resistance to both DOR and FTC.

Table 2 Summary of Efficacy for Trial P021

Title: A Phase 3 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		
Study identifier	Protocol Number:	021
	Clinical Phase:	3
	EudraCT Number:	2014-003382-17
	Other Codes: IND Number: ClinicalTrials.gov identifier:	 124,997 NCT02403674
Design	Multicenter, multinational, randomized, double-blind, active-controlled trial designed to evaluate the safety and efficacy of DOR/3TC/TDF (MK-1439A) once daily (QD) compared with efavirenz (EFV)/emtricitabine (FTC)/TDF QD (ATRIPLA) in HIV-1-infected, treatment-naïve adults ≥18 years of age, who had plasma HIV-1 RNA ≥1000 copies/mL at screening and no known resistance to DOR or any other study drug.	
	Planned duration of Main phase:	96 weeks; Week 48 is the primary time point.
	Duration of Run-in phase:	Not applicable
	Planned duration of Extension phase:	96 weeks
Hypothesis (EU-specific)	DOR/3TC/TDF QD is noninferior to EFV/FTC/TDF QD as assessed by the proportion of subjects with HIV-1 RNA <40 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48; a margin of 10 percentage points was used to define noninferiority. DOR/3TC/TDF QD is superior to EFV/FTC/TDF 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.	
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 (EU-specific)	HIV-1 RNA <40 copies/mL at Week 48	Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at Week 48
	Secondary efficacy endpoints	HIV-1 RNA <50 copies/mL	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 48 and Week 96
		HIV-1 RNA <40 copies/mL at Week 96	Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL
		$CD4^+$ T-cell count	Change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96
	Exploratory efficacy endpoints	HIV-1 RNA level <200 copies/mL	Proportion of subjects achieving plasma HIV-1 RNA level <200 copies/mL at Week 48 and Week 96
		PDVF	Protocol-defined virologic failure (PDVF)
		TLOVR	Time to loss of virologic response (TLOVR)
		Viral drug resistance	Viral resistance for subjects who meet viral failure criteria and whose virus can be amplified.
Last subject's last visit for primary endpoint analysis	20-Mar-2017; the study is ongoing		
Database lock	[redacted]-20[redacted]		
RESULTS AND ANALYSIS			
Analysis description	**Primary Analysis** Proportion of Subjects With HIV-1 RNA <40 copies/mL at Week 48 *Statistical Methodology*: The primary EU-specific hypothesis on antiretroviral activity was assessed by the proportion of subjects achieving plasma HIV-1 RNA <40 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% CI for the difference in the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 48 (DOR/3TD/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 <50 copies/mL at Week 48 and Week 96 *Statistical Methodology*: The proportion of subjects achieving HIV-1 RNA <50 copies/mL were analyzed using the same approach as described above for the proportion of subjects achieving HIV-1 RNA <40 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 OF 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.
Analysis population and time point description	The primary population for efficacy analyses was the 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. The primary time point is Week 48.

Efficacy at Week 48	Treatment Group		Treatment Difference †	
	DOR/3TC/TDF n/N (%)	EFV/FTC/TDF n/N (%)	Estimated Difference	95% CI
Primary				
Proportion of subjects with HIV-1 RNA <40 copies/mL (*FDA Snapshot*)	305/364 (83.8)	290/364 (79.7)	4.084	(-1.493, 9.661)
Secondary and Exploratory				
Proportion of subjects with HIV-1 RNA <40 copies/mL (*OF approach*)	305/346 (88.2)	290/331 (87.6)	0.442	(-4.463, 5.346)
Proportion of subjects with HIV-1 RNA <50 copies/mL (*FDA Snapshot*)	307/364 (84.3)	294/364 (80.8)	3.537	(-1.951, 9.026)
Proportion of subjects with HIV-1 RNA <50 copies/mL (*OF approach*)	307/346 (88.7)	294/331 (88.8)	-0.179	(-4.936, 4.578)
Proportion of subjects with HIV-1 RNA <200 copies/mL (*FDA Snapshot*)	313/364 (86.0)	301/364 (82.7)	3.274	(-2.012, 8.561)
Proportion of subjects with HIV-1 RNA <200 copies/mL (*OF approach*)	313/346 (90.5)	301/331 (90.9)	-0.523	(-4.943, 3.897)
	Mean (95% CI)	**Mean (95% CI)**	**Mean Difference**	**95% CI**
Change from baseline in CD4 cell count (cells/mm^3) (*OF approach*)	198.4 (180.2, 216.7)	188.4 (169.5, 207.2)	10.1	(-16.1, 36.3)

OF = Observed Failure approach.

n = Number of subjects in each subcategory; N = Number of subjects in each treatment group.

† The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA ≤100,000 or >100,000 copies/mL). The 95% CI for mean difference in CD4 change was based on t-distribution.

Analysis of postbaseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

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Summary	The proportion of subjects achieving the EU-specific primary endpoint of HIV-1 RNA <40 copies/mL (FDA snapshot approach) was 83.8% and 79.7% in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, with a treatment difference (95% CI) of 4.1% (-1.5, 9.7). The proportion of subjects achieving the secondary endpoint of HIV-1 RNA <50 copies/mL at Week 48 (FDA snapshot approach) was 84.3% (307/364) in the DOR/3TC/TDF group and 80.8% (294/364) in the EFV/FTC/TDF group with a treatment difference (95% CI) of 3.5% (-2.0, 9.0). Analysis results for these endpoints using the OF approach were consistent with those of the FDA snapshot approach. In addition, the proportion of subjects achieving HIV-1 RNA <200 copies/mL at Week 48 (using both missing data approaches) were supportive of the results for the primary and key secondary endpoints. Analysis of the change from baseline in $CD4^+$ T-cell count indicated similar results for both treatment groups, with a mean increase from baseline at Week 48 of 198 cells/mm^3 in the DOR/3TC/TDF group and 188 cells/mm^3 in the EFV/FTC/TDF group.
Analysis description	**<u>Supportive Efficacy Analysis</u>** Virologic Outcome *Statistical methodology*: In addition to the analysis of proportion of subjects achieving virologic success (HIV-1 RNA <50 copies/mL) at Week 48, subjects who were not classified as virologic success were categorized as virologic failure (HIV-1 RNA ≥50 copies/mL) or as having no virologic data in the time window with reasons of: 1) discontinued study due to an AE; 2) discontinued study for other reasons (includes withdraw consent, loss to follow-up, moved); or 3) on study but missing data in window. The full categorization of virologic outcome at Week 48 was summarized by treatment group.

	Virologic Outcome at Week 48	Treatment Group			
		DOR/3TC/TDF (N=364)		EFV/FTC/TDF (N=364)	
		n	(%)	n	(%)
OUTCOME (*FDA Snapshot*)					
HIV-1 RNA <50 copies/mL		307	(84.3)	294	(80.8)
HIV-1 RNA ≥ 50 copies/mL†		39	(10.7)	37	(10.2)
No virologic data at Week 48 window		18	(4.9)	33	(9.1)
Reasons					
Discontinued study due to AE or death‡		9	(2.5)	24	(6.6)
Discontinued study for other reasons§		9	(2.5)	8	(2.2)
On study but missing data in window		0	(0.0)	1	(0.3)

† Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (Relative Day 295-378).

‡ Includes subjects who discontinued because of AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

§ Other Reasons includes: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject.

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Summary	The virologic outcomes of DOR/3TC/TDF are comparable to those of EFV/FTC/TDF, in regard to proportion of participants with HIV-1 RNA <50 copies/mL (84.3% vs. 80.8%, respectively) and HIV-1 RNA ≥50 copies/mL (10.7% vs. 10.2%, respectively). A higher proportion of participants in the EFV/FTC/TDF group (9.1%) than in the DOR/3TC/TDF group (4.9%) had no virologic data at Week 48 window, driven by a higher proportion of subjects in the EFV/FTC/TDF group discontinuing from the trial due to an AE.

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Analysis description	**Supportive Analysis**: Subgroup Efficacy *Statistical methodology*: To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the efficacy endpoint was calculated within each category of the subgroup factors.
Summary	Similar results (based on 95% CI for treatment difference that includes 0) were found for the DOR/3TC/TDF and EFV/FTC/TDF groups across most of the subgroups defined by baseline prognostic and demographic factors. The overall trend of antiretroviral efficacy for subjects with HIV-1 RNA <40 copies/mL, <50 copies/mL, and <200 copies/mL was consistent and similar in the two treatment groups, regardless of baseline prognostic and demographic factors. Specifically, similar results for both treatment groups were seen for the proportions of subjects who achieved HIV-1 RNA <40 copies/mL at Week 48 among subjects with a high baseline HIV-1 RNA level (>100,000 copies/mL). Among subjects with baseline $CD4^+$ T-cell counts ≤50 cells/mm^3, the proportions of subjects who achieved HIV-1 RNA <40 copies/mL at Week 48 were similar in the DOR/3TC/TDF and EFV/FTC/TDF groups (62.5% and 66.7%, respectively), while among subjects with baseline $CD4^+$ T-cell counts >50 and ≤200 cells/mm^3, a larger proportion in the EFV/FTC/TDF group achieved HIV-1 RNA <40 copies/mL at Week 48 (64.7% and 85.3% [95% CI: -41.2, -0.1]), although the numbers of subjects in each of these baseline-$CD4^+$ subgroups were too small to be clinically meaningful. The proportions of subjects with HIV-1 RNA <40 copies/mL, <50 copies/mL, and <200 copies/mL at Week 48 by prognostic and demographic factors for combined baseline $CD4^+$ subgroups, using the OF approach, show an overall trend of antiretroviral efficacy that was similar in the treatment groups for these analyses, with no meaningful differences at Week 48 identified.
Analysis description	**Exploratory 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.
Summary	The risk of loss of virologic response was observed at similar rates for both treatment groups. Based on the Kaplan-Meier plot for TLOVR and analyses using the log-rank test and the Cox model, the DOR/3TC/TDF and EFV/FTC/TDF groups were similar with respect to risk of loss of virologic response.
Analysis description	**Exploratory Analysis**: 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.

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Summary	Rates of PDVF were low in both the DOR/3TC/TDF and EFV/FTC/TDF treatment groups: a total of 22 subjects (6.0%) in the DOR/3TC/TDF group and 14 subjects (3.8%) in the EFV/FTC/TDF group were identified as meeting PDVF criteria by Week 48. Subjects with PDVF generally had low-level viremia at the time of failure. Ten of the 16 subjects in the DOR/3TC/TDF group who met the rebound definition of PDVF had HIV-1 RNA between 50 and 200 copies/mL at the viral failure confirmation visit (as did 4 of 10 in the EFV/FTC/TDF group). Seven subjects who met PDVF criteria in the DOR/3TC/TDF group had genotypic and/or phenotypic resistance to DOR (as did 9 subjects in the EFV/FTC/TDF group with genotypic and phenotypic resistance to EFV) and 7 subjects had genotypic and/or phenotypic resistance to NRTIs (as did 5 subjects in the EFV/FTC/TDF group). Three subjects in the EFV/FTC/TDF group who discontinued for reasons other than PDVF had both genotypic and phenotypic resistance to EFV; in comparison, none of the subjects in the DOR/3TC/TDF group who discontinued for reasons other than PDVF had both genotypic and phenotypic resistance to EFV.

Table 3 Summary of Efficacy for Trial P007

Title: Multicenter, Double-Blind, Randomized, 2-Part, Dose Ranging Study to Compare the Safety, and Antiretroviral Activity of MK-1439 Plus TRUVADA™ Versus Efavirenz Plus TRUVADA™ in Antiretroviral Treatment-Naïve, HIV-1 Infected Patients		
Study identifier	Protocol Number:	PN007
	Clinical Phase:	2b
	EudraCT Number:	2012-001573-93
	US IND Number	112,796
	ClinicalTrials.gov Identifier:	NCT01632345
Design	Multicenter, double-blind (with in-house blinding), randomized, 2-part dose-ranging Phase 2b trial in approximately 320 antiretroviral- naïve HIV-1 infected subjects, with randomization being stratified by subject initial (Screening) HIV-1 RNA (≤ or >100,000 copies/mL).	
	Duration of main phase:	Part I: 96 weeks of treatment and 14 days of follow-up Part II: 96 weeks of treatment and 14 days of follow-up
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypotheses	Doravirine at the final selected dose is superior to efavirenz, each in combination therapy with TRUVADA™, as measured by proportion of subjects with CNS events by Week 8. If superiority is established at Week 8, the same hypothesis will be tested at Week 24.	
Treatment groups	Part I – Doravirine 25 mg	Doravirine 25 mg once daily + TRUVADA™ once daily 41 subjects randomized, 40 treated
	Part I – Doravirine 50 mg	Doravirine 50 mg once daily + TRUVADA™ once daily. 43 subjects randomized and treated
	Part I – Doravirine 100 mg	Doravirine 100 mg once daily + TRUVADA™ once daily. 42 subjects randomized and treated
	Part I – Doravirine 200 mg	Doravirine 200 mg once daily + TRUVADA™ once daily. 41 subjects randomized and treated
	Part I – Efavirenz 600 mg	Efavirenz 600 mg once daily + TRUVADA™ once daily. 43 subjects randomized, 42 treated
	Note: After dose selection, all doravirine-treated subjects in Part I were switched to doravirine 100 mg for the remainder of their 96 weeks of total study medication.	

	Part II – Doravirine 100 mg		Doravirine 100 mg once daily + TRUVADA™ once daily. 66 subjects randomized and treated
	Part II – Efavirenz 600 mg		Efavirenz 600 mg once daily + TRUVADA™ once daily. 66 subjects randomized and treated
	Primary efficacy endpoint	HIV-1 RNA <40 copies/mL	Proportion of subjects with HIV-1 RNA <40 copies/mL at Week 24 in Part I and in Part I/II combined.
	Secondary efficacy endpoints	HIV-1 RNA <40 copies/mL	Proportion of subjects with HIV-1 RNA <40 copies/mL at Week 48 or Week 96 in Part I and in Part I/II combined.
		HIV-1 RNA <200 copies/mL	Proportion of subjects with HIV-1 RNA <200 copies/mL at Weeks 24, 48, and 96 in Part I and in Part I/II combined.
		$CD4^+$ T-cell count	Change from baseline in $CD4^+$ T-cell counts at Weeks 24, 48, and 96 in Part I and in Part I/II combined.
Database lock	[redacted]-20[redacted]		
RESULTS AND ANALYSIS			
	Part I was an estimation trial intended to provide preliminary data on antiviral activity and general tolerability. Part I randomized approximately 200 subjects to the 4 dose groups of doravirine and the efavirenz group. There were approximately 100 subjects per group who received the final selected dose of doravirine or efavirenz after pooling data from Parts I and II.		
Analysis description	**<u>Primary Efficacy Analysis</u>** Proportion of subjects with virologic response HIV-1 RNA <40 copies/mL at Week 24 in Part I and Part I/II combined *Statistical methodology*: The difference in proportion of subjects with virologic responses between treatment groups and the associated 95% CI were calculated using Miettinen and Nurminen's method with stratification by screening HIV-1 RNA ≤100,000 or >100,000 copies/mL. The Non-Completer=Failure (NC=F) approach was used as the primary approach to handle missing data. All missing values were considered as failures unless intermittent missing flanked by 2 successes. (Note: at the primary time point of Week 24 in Parts I/II combined, the number of subjects in the doravirine 100-mg arm is 107 subjects as 1 subject satisfied this criterion.)		

Analysis population and time point description	The primary population for analysis of the primary analysis of efficacy data was the FAS population, consisting of all randomized subjects who received at least 1 dose of blinded study medication and had baseline data for those analyses that required baseline data. The primary time point is Week 24. For Part I, the FAS population included a total of 208 subjects (166 for all doravirine groups; and 42 for efavirenz). For Part I/II, the FAS population included a total of 340 subjects (232 for all doravirine groups, 108 for efavirenz). The key cohort of 215 subjects (107 on doravirine 100 mg; 108 on efavirenz) from Part I/II combined provided data to confirm the overall safety and efficacy of doravirine 100 mg versus efavirenz at Week 24.

PART I: Proportion of Subjects with HIV-1 RNA <40 copies/mL at Week 24 (Doravirine All Doses vs. Efavirenz)

Missing data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <40 copies/mL		Difference in Percent Response (DOR – EFV)†
		n/N	% (95% CI)	(95% CI)‡
Non-Complete=Failure	Doravirine 25 mg	32/40	80.0 (64.4, 90.9)	15.7 (-4.1, 34.4)
	Doravirine 50 mg	32/43	74.4 (58.8, 86.5)	10.0 (-9.6, 29.1)
	Doravirine 100 mg	30/42	71.4 (55.4, 84.3)	6.6 (-13.2, 26.0)
	Doravirine 200 mg	33/41	80.5 (65.1, 91.2)	15.9 (-3.4, 34.4)
	Doravirine Combined	127/166	76.5 (69.3, 82.7)	11.9 (-2.5, 28.2)
	Efavirenz 600 mg	27/42	64.3 (48.0, 78.4)	
Treatment-Related Disc.=Failure	Doravirine 25 mg	32/38	84.2 (68.7, 94.0)	19.9 (0.3, 38.0)
	Doravirine 50 mg	32/43	74.4 (58.8, 86.5)	10.0 (-9.6, 29.1)
	Doravirine 100 mg	30/42	71.4 (55.4, 84.3)	6.6 (-13.2, 26.0)
	Doravirine 200 mg	33/40	82.5 (67.2, 92.7)	18.0 (-1.1, 36.2)
	Doravirine Combined	127/163	77.9 (70.8, 84.0)	13.4 (-1.0, 29.6)
	Efavirenz 600 mg	27/42	64.3 (48.0, 78.4)	
Observed Failure	Doravirine 25 mg	32/37	86.5 (71.2, 95.5)	18.8 (-0.3, 37.0)
	Doravirine 50 mg	32/41	78.0 (62.4, 89.4)	10.4 (-8.9, 29.3)
	Doravirine 100 mg	30/41	73.2 (57.1, 85.8)	4.8 (-14.7, 24.2)
	Doravirine 200 mg	33/40	82.5 (67.2, 92.7)	14.5 (-4.4, 32.9)
	Doravirine Combined	127/159	79.9 (72.8, 85.8)	11.9 (-2.0, 28.3)
	Efavirenz 600 mg	27/40	67.5 (50.9, 81.4)	
FDA Snapshot Approach	Doravirine 25 mg	32/40	80.0 (64.4, 90.9)	15.7 (-4.1, 34.4)
	Doravirine 50 mg	32/43	74.4 (58.8, 86.5)	10.0 (-9.6, 29.1)
	Doravirine 100 mg	30/42	71.4 (55.4, 84.3)	6.6 (-13.2, 26.0)
	Doravirine 200 mg	33/41	80.5 (65.1, 91.2)	15.9 (-3.4, 34.4)
	Doravirine Combined	127/166	76.5 (69.3, 82.7)	11.9 (-2.5, 28.2)
	Efavirenz 600 mg	27/42	64.3 (48.0, 78.4)	

† A positive value favors doravirine over efavirenz

‡ The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screening HIV-1 RNA >100,000 copies/mL or ≤100,000 copies/mL)

For each treatment group, n/N = (number of responders) / (number of subjects).

Note: Both doravirine and efavirenz were administered with TRUVADA™.

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Summary	**Results of Part I**: - All doravirine treatment groups demonstrated potent and similar antiviral efficacy compared to efavirenz, with 71.4%-80.5% versus 64.3% achieving HIV-1 RNA <40 copies/mL, respectively, at Week 24 - There was no dose differentiation among doravirine treatment groups.

PARTS I and II Combined:
Proportion of Subjects with HIV-1 RNA <40 copies/mL at Week 24 (Doravirine 100 mg vs. Efavirenz)

Missing data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <40 copies/mL		Difference in Percent Response (DOR – EFV)†
		n/N	% (95% CI)	(95% CI)‡
Non-Complete=Failure	Doravirine 100 mg	78/107	72.9 (63.4, 81.0)	-0.5 (-12.3, 11.2)
	Efavirenz 600 mg	79/108	73.1 (63.8, 81.2)	
Treatment-Related Disc.=Failure	Doravirine 100 mg	78/105	74.3 (64.8, 82.3)	0.2 (-11.4, 11.8)
	Efavirenz 600 mg	79/107	73.8 (64.4, 81.9)	
Observed Failure	Doravirine 100 mg	78/104	75.0 (65.6, 83.0)	-3.4 (-14.8, 8.0)
	Efavirenz 600 mg	79/101	78.2 (68.9, 85.8)	
FDA Snapshot Approach	Doravirine 100 mg	78/108	72.2 (62.8, 80.4)	-1.2 (-13.0, 10.5)
	Efavirenz 600 mg	79/108	73.1 (63.8, 81.2)	

† A positive value favors doravirine over efavirenz

‡ The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screening HIV-1 RNA >100,000 copies/mL or ≤100,000 copies/mL)

For each treatment group, n/N = (number of responders) / (number of subjects).

Note: Both doravirine and efavirenz were administered with TRUVADA™.

Summary	**Results of Parts I/II Combined**: Doravirine at selected dose of 100 mg demonstrated potent and similar antiviral efficacy compared to efavirenz, with 72.9% versus 73.1% achieving HIV-1 RNA <40, respectively, at Week 24.
Analysis description	**Secondary Efficacy Analysis** *Statistical methodology*: For the analysis of the secondary endpoints of the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 48 or Week 96 in Part I and Part I/II combined and the proportion of subjects with virologic response HIV-1 RNA <200 copies/mL at Weeks 24, 48, or 96 in Part I and Part I/II combined, the same methodology as described for the primary efficacy analyses was used. Missing data was handled using the NC=F approach. For the analysis of the secondary endpoint of change from baseline in $CD4^+$ T-cell counts at Weeks 24, 48, or 96 in Part I (Week 24 only) or Part I/II combined, descriptive statistics including 95% CIs were provided. Missing data were handled using the OF approach. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.
Analysis population and time point description	The primary population for the secondary efficacy analyses was the FAS population.

Summary	The proportion of subjects with virologic response HIV-1 RNA <40 copies/mL at Weeks 48 or 96 in Part I/II combined showed potent, durable, and similar antiretroviral efficacy between doravirine 100 mg compared with efavirenz 600 mg. In Part I/II combined, at 48 weeks, the proportions of subjects with HIV-1 RNA <40 copies/mL were 77.8% of subjects randomized to doravirine 100 mg and 79.4% of subjects randomized to efavirenz (difference [95% CI]: -1.9% [-12.9, 9.2]). In Part I/II combined, at 96 weeks, the proportions of subjects with HIV-1 RNA <40 copies/mL were 75.0% of subjects randomized to doravirine 100 mg and 75.9% of subjects randomized to efavirenz (difference [95% CI]: -0.8% [-12.4, 10.7]). The proportion of subjects with virologic response HIV-1 RNA <200 copies/mL at Weeks 24, 48, or 96 in Part I and Part I/II combined showed potent and similar efficacy across treatment groups. All secondary efficacy analyses showed similar results when comparing doravirine treatment groups (individually and combined) versus the efavirenz group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following terms may be used interchangeably within the document:

- Participant / subject
- Study / trial

Abbreviation/Term	Definition
3TC	Lamivudine
AE	Adverse event or adverse experience
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
AUC0-24	Area under the DOR plasma concentration time curve between 0 h – 24 h
ASaT	All Subjects as Treated
ATRIPLA™	Fixed-dose combination of efavirenz plus emtricitabine and tenofovir disoproxil fumarate
ATV	Atazanavir
C24	DOR concentrations 24 h post dose
cART	Combination antiretroviral therapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum (Peak) DOR plasma concentration
CSR	Clinical Study Report
DAIDS	Division of Acquired Immunodeficiency Syndrome
DOR	Doravirine (MK-1439)
DOR/3TC/TDF	Fixed-dose combination of doravirine plus lamivudine and tenofovir disoproxil fumarate
DRV	Darunavir
DRV+r	Darunavir boosted with ritonavir
DSG	Delayed switch group
EACS	European AIDS Clinical Society
EFV	Efavirenz
EMA	European Medicines Agency
EVG	Elvitegravir
EU	European Union
FAS	Full analysis set (analysis population)
FDA	Food and Drug Administration
FDC	Fixed-dose combination

Abbreviation/Term	Definition
FTC	Emtricitabine
HDL-C	High-density lipoprotein cholesterol
HIV-1	Human immunodeficiency virus type 1
IAS-USA	International Antiviral Society-USA
InSTI	Integrase strand-transfer inhibitor
ISG	Immediate switch group
LDL-C	Low-density lipoprotein cholesterol
LOQ	Limit of quantitation
LPV	Lopinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitors
NVP	Nevirapine
OF	Observed Failure
PDLC	Pre-Defined Limit of Change
PDVF	Protocol-defined virologic failure
PI	Protease inhibitor
PK	Pharmacokinetic(s)
QD	Once daily
RNA	Ribonucleic Acid
RPV	Rilpivirine
SAE	Serious adverse event or serious adverse experience
SAP	Statistical Analysis Plan
TDF	Tenofovir disoproxil fumarate
UNAIDS	United Nations Programme on HIV and AIDS
US	United States
WHO	World Health Organization
WT	Wild-Type

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Pharmacological Classes

Doravirine (DOR, also known as MK-1439) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) active against human immunodeficiency virus type 1 (HIV-1) infection.

DOR is available as a single agent (PIFELTRO™) and as a fixed-dose combination (FDC) with the 2 nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) (DELSTRIGO™) (DOR/3TC/TDF, also known as MK-1439A).

1.2 Approved Indications and Purpose of this Supplemental Application

DOR, as a single agent used in combination with other antiretroviral agents, or as part of the FDC DOR/3TC/TDF, has been approved in the United States (U.S.), European Union (EU), and Canada for the treatment of HIV-1 infection in adults. The recommended dosage of DOR in adults is one 100 mg tablet taken orally once daily (QD), with or without food. The recommended dose of DOR/3TC/TDF is one tablet (containing 100 mg of DOR, 300 mg of 3TC, and 300 mg TDF) taken orally QD, with or without food.

The original marketing applications, which supported the registrations of the DOR single agent and the FDC, provided: 1) chemistry, manufacturing and control data; 2) non-clinical pharmacology, pharmacokinetic (PK) data, and toxicology data 3) clinical pharmacology data (including PK and Phase 1 safety data) and modeling and simulation data; and 4) safety and efficacy data in Phase 2b/3 studies to support the use of DOR in HIV-1-infected adults. The clinical development program for DOR and DOR/3TC/TDF that contributed data to the original marketing applications included 2 pivotal Phase 3 trials (P018, P021) in treatment-naive adults, a single Phase 2b trial (P007) in treatment-naïve adults, and 36 Phase 1 trials. The approved indication text varies by country, in accordance with each country's regulatory guidelines. Please refer to the approved product labeling for country-specific indication.

The objective of this supplemental application (Switch Application) is to update the prescribing information to include data from a single Phase 3 trial (P024) in HIV-1-infected, virologically suppressed participants switching from a stable antiretroviral regimen to DOR in combination with other antiretroviral agents or DOR/3TC/TDF. The data support switching to a DOR-containing regimen in patients whose HIV-1 RNA was virologically suppressed on a stable antiretroviral regimen for at least 3 months. Although P024 required at least 6 months of viral suppression on a stable antiretroviral regimen prior to study entry, no difference in efficacy is expected for a patient who is virologically suppressed for either 3 months or 6 months on a stable regimen as long as the patient is virologically suppressed at the time of switch and has no history of virologic failure or viral drug resistance. Recent clinical trials requiring participants to be virologically suppressed on a stable ART regimen for at least 3 months have demonstrated continued durable virologic suppression similar to that observed in trials that required at least 6 months of virologic suppression on a stable ART regimen.

1.3 Chemical and Pharmaceutical Properties

The formulation for the single agent DOR drug product is a film-coated tablet (dose strength of 100 mg DOR). The tablet is composed of [redacted] of DOR with hypromellose acetate succinate. [redacted] is further processed by [redacted] with other excipients and blending with [redacted] excipients prior to compression. Following compression, the final market image tablets are film-coated.

The formulation for the DOR/3TC/TDF drug product is a bilayer, film-coated tablet containing 100 mg of DOR, 300 mg of 3TC, and 300 mg of TDF equivalent to 245 mg of tenofovir disoproxil. One layer consists of a DOR [redacted] and the other layer consists of a 3TC and TDF granulation. The DOR [redacted] contains [redacted] of DOR with hypromellose acetate succinate that is then [redacted] with other excipients. The 3TC and TDF granulation is manufactured by a roller compaction process with excipients. DOR [redacted] and 3TC/TDF granulation are then compressed into bilayer tablets and the final market image tablets are film-coated.

There are no changes to the formulation for DOR/3TC/TDF relative to the approved original marketing application.

1.4 Scientific Background and Introduction

Epidemiology and Public Health Burden of HIV-1 Infection

HIV/acquired immunodeficiency syndrome (AIDS) is associated with significant morbidity and mortality. The Joint United Nations Programme on HIV and AIDS (UNAIDS) reported that an estimated 36.9 million people around the world were living with HIV-1 infection in 2017 [Ref. 5.4: 04ZQBB]. Of these, approximately 1.8 million adults and children were newly infected in 2017 and an estimated 940,000 people died from AIDS-related illnesses that year. The majority of new infections and deaths (65% and 70%, respectively) occurred in sub-Saharan Africa (central, eastern, western, and southern regions). Approximately 2.2 million adults and children were living with HIV in western and central Europe and North America in 2017, with approximately 70,000 being newly infected that year.

To address this global public health challenge, UNAIDS has led global efforts to establish new targets for HIV treatment. The "90-90-90" goal for 2020 is that 90% of all people living with HIV will know their HIV status, 90% of all people diagnosed with HIV infection will receive sustained antiretroviral therapy (ART) and 90% of all people receiving ART will have achieved viral suppression. Modeling suggests that if these targets are achieved, the HIV/AIDS epidemic can be globally controlled by 2030, resulting in profound health and global economic benefits.

Significant advances in HIV treatment have been achieved over the last 30 years. However, new therapies that are at least as efficacious as current therapies, with improved safety and tolerability profiles, convenient dosing, and a different resistance profile are still needed.

Current HIV-1 Treatment Landscape

Currently, more than 30 antiretroviral drugs are commercially available worldwide for use in combination antiretroviral therapy (cART) for the treatment of HIV-1 infection. These drugs inhibit various stages of the HIV-1 lifecycle and belong to 7 classes: NRTIs, NNRTIs, protease inhibitors (PIs), integrase strand-transfer inhibitors (InSTIs), attachment inhibitors, co-receptor antagonists, and fusion inhibitors. Treatment with cART (typically a combination of 3 antiretroviral drugs) has been shown to be effective in reducing both plasma HIV-1 RNA to a level below detection and restoring immune system function with an increase in $CD4^+$ T cell counts.

- The US Department of Health and Human Services HIV-1 Treatment Guideline (2018) [Ref. 5.4: 05084L] recommends a regimen of an InSTI in combination with 2 NRTIs for most patients with HIV-1; other regimens including a boosted PI or NNRTI may be preferred in certain clinical situations.

- The International Antiviral Society-USA (IAS-USA) recommends an InSTI plus 2 NRTIs as initial regimens for most patients; other effective regimens include NNRTIs or boosted PIs with 2 NRTIs (2018 recommendations [Ref. 5.4: 0508DT].

- Other treatment guidelines such as the World Health Organization (WHO) (2018, [Ref. 5.4: 05084L]) and the European AIDS Clinical Society (EACS) (2017 [Ref. 5.4: 04MZSY]) include the NNRTI class (including efavirenz [EFV] and rilpivirine [RPV]) as a recommended regimen in addition to InSTI- and PI-based regimens.

The expanding number of antiretroviral drugs and drug combinations have made it possible for patients to consider switching from one effective regimen to another. The fundamental principle of regimen switching is to maintain viral suppression without risking future treatment options. Several factors that may warrant a change in therapy include: simplification of regimens by reducing pill burden or dosing frequency, tolerability, safety, prevention or mitigation of drug-drug interactions, and elimination of food requirements. The use of three-drug regimens, either within-class or between-class, is generally recommended and patients with no resistance mutations can likely switch to a regimen that has been shown to be effective in treatment-naïve patients. The advances in antiretroviral drugs and improved understanding of HIV drug resistance make it possible for patients to switch to another regimen that address one or more of the situations listed above.

Rationale for DOR

As a class, NNRTIs have been commercially available since 1996 and are highly efficacious against HIV-1 in treatment-naïve individuals [Ref. 5.4: 04PB3J]. However, most NNRTIs have various tolerability, safety, and efficacy limitations, some of which are specific to the whole NNRTI class, while some are specific to the individual NNRTI.

EFV and RPV are commonly prescribed in the U.S. and in the EU. However, EFV is associated with treatment-limiting neuropsychiatric adverse events (AEs) [Ref. 5.4: 04PB39] and RPV's efficacy is suboptimal in individuals with baseline HIV-1 RNA >100,000 copies/mL or $CD4^+$ T-cell counts < 200 cells/mm^3 [Ref. 5.4: 04LK3B].Etravirine and nevirapine (NVP) are less commonly prescribed, primarily due to specific side effects, lower efficacy, and/or a more complicated dosing schedule. Management of dyslipidemia is particularly important in HIV-1-infected individuals, due to the known impact of various agents on serum lipids and the increased cardiovascular risk inherent to HIV-1 infection. Viral drug resistance is another limitation of many NNRTIs. Because a single viral mutation may confer resistance against one or several currently available NNRTIs, there is an ongoing need to continue development of NNRTIs with differing resistance profiles.

DOR addresses many of the limitations of other currently available NNRTIs. As presented in the original marketing applications, DOR and DOR/3TC/TDF provide robust efficacy, a favorable safety and resistance profile, and convenient treatment options for HIV-1-infected adults. In addition, the profile of DOR allows patients who are virologically suppressed on other regimens to switch to a DOR regimen by potentially reducing pill burden, mitigating drug-drug interactions, and eliminating food requirements. The data provided in this Supplemental Application demonstrate that DOR/3TC/TDF has durable efficacy and a favorable safety and resistance profile in virologically suppressed adults who switched their baseline ART regimens to DOR/3TC/TDF through 48 weeks of treatment. These data support an update of the current prescribing information to reflect the efficacy and safety results for DOR and DOR/3TC/TDF in adults with suppressed HIV-1 RNA at baseline who switch to a DOR-containing regimen (see [Sec. 2.5.4-switch48wk], and [Sec. 2.5.5-switch48wk]).

1.5 Overview of the Clinical Development Program

Overview of the Phase 3 Program

The clinical development program for DOR and DOR/3TC/TDF that contributed data to the original marketing applications included 2 ongoing pivotal Phase 3 trials (P018, P021), a single completed Phase 2b trial (P007), and 36 completed Phase 1 trials.

One ongoing, global, Phase 3 trial (P024) was designed to evaluate a switch to DOR/3TC/TDF in HIV-1-infected adults who are virologically suppressed (HIV-1 RNA <40 copies/mL) on a stable (minimum 6 months at baseline) ART regimen. The antiretroviral regimen included a ritonavir- or cobicistat-boosted PI (specifically, atazanavir [ATV], darunavir [DRV], or lopinavir [LPV]), or cobicistat-boosted elvitegravir (EVG) (an InSTI), or an NNRTI (specifically EFV, NVP, or RPV), each administered with 2 NRTIs.

Participants were stratified in the base study (through Study Week 48) by their baseline regimen at screening (one of the PIs specified above boosted with ritonavir vs. one of the PIs specified above boosted with cobicistat vs. EVG boosted with cobicistat or one of the NNRTIs specified above); participant in the ritonavir-boosted PI stratum were further stratified by use of lipid-lowering therapy at Study Day 1 (yes/no). Participants who were eligible and consented to enter the base study were randomized in a 2:1 ratio to either the Immediate Switch Group (ISG) who received DOR/3TC/TDF on Study Day 1 or to the Delayed Switch Group (DSG) who started DOR/3TC/TDF at Study Week 24. The primary efficacy endpoint evaluated the non-inferior antiretroviral activity of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of their baseline regimen for 24 weeks, as measured by the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the ISG and at Study Week 24 in the DSG.

Of the 673 participants randomized to the ISG and DSG treatment groups, 670 were treated (447 in the ISG, 223 in the DSG), and 656 (447 in the ISG, 209 in the DSG) received DOR/3TC/TDF [Table 2.5-switch48wk: 1].

Table 2.5-switch48wk: 1
Summary of the Phase 3 Clinical Trial Supporting the Current Application

Protocol / Phase / Location	Population	Status	Primary Endpoint	Design and Duration	DOR/3TC/TDF Regimens	N Treated	Comparator
024 / 3 / Global	Virologically suppressed HIV-1-infected adults (ages 21-71 years)	Base Study (through Week 48) complete; open label study extensions ongoing. (Week 48 results from CSR included in this Supplemental Application)	Proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the ISG and Study Week 24 in the DSG	Base Study= 1st 48 weeks.	DOR/3TC/TDF ISG: DOR/3TC/TDF QD for 48 weeks from Study Day 1 to Study Week 48 (n=447) DOR/3TC/TDF DSG: DOR/3TC/TDF QD for 24 weeks from Study Week 24 to Study Week 48 (n=209)	Total N= 670: (DOR/3TC/TDF ISG [n=447] and DOR/3TC/TDF DSG [n=223])	Baseline regimen[a] for the DSG from Study Day 1 to Study Week 24 (n=223)

[a] Ritonavir- or cobicistat-boosted PI (specifically, ATV, DRV, or LPV) or cobicistat-boosted EVG, or an NNRTI (specifically, EFV, NVP, or RPV) each administered with 2 NRTIs
3TC = lamivudine, ATV= atazanavir, CSR = Clinical Study Report, DOR = doravirine, DRV= darunavir, DSG= delayed switch group, EFV= efavirenz, EVG= elvitegravir, HIV-1= Human immunodeficiency virus type 1, ISG= immediate switch group, LPV= lopinavir, NVP= nevirapine, NRTI= nucleos(t)ide reverse transcriptase inhibitors, NNRTI= non-nucleoside reverse transcriptase inhibitor, PI= protease inhibitor, RNA = ribonucleic acid, RPV= rilpivirine, TDF= tenofovir disoproxil fumarate

Source: [Ref. 5.3.5.1: P024MK1439A]

Enrollment of participants across 23 countries in P024 allowed for a comprehensive evaluation of DOR/3TC/TDF in a population with diverse racial, ethnic, and regional demographic characteristics, and varied prior treatment regimens.

Efficacy and safety were evaluated for the overall trial population and for relevant subgroups, specifically age, gender, race, ethnicity, region, hepatitis B and/or C infection status, and baseline $CD4^+$ T-cell count. Efficacy was also evaluated for subgroups by baseline prognostic factors, specifically history of selected NNRTI mutations in participants on PI and InSTI regimens, ART class in baseline regimen at randomization and by ART class in baseline regimen received, and duration of ART regimen prior to enrollment.

In addition, safety narratives are provided for participants in 4 ongoing Phase 2/3 trials of DOR or DOR/3TC/TDF (P018, P021, P028, and P030) who experienced an AE leading to discontinuation of study medication or serious adverse event (SAE) as of the data cut-offs for this supplemental application [Table 2.7.4-switch48wk: 2] . Narratives for these trials are included in [Sec. 2.7.4-switch48wk: 2.2]:

1. P018 is a Phase 3 trial to evaluate the safety and efficacy of DOR 100 mg QD versus darunavir 800 mg QD plus ritonavir 100 mg once daily, each in combination with emtricitabine (FTC)/TDF or ABC/3TC, in treatment-naïve, HIV-1-infected adults

2. P021 is a Phase 3 trial to evaluate the safety and efficacy of DOR/3TC/TDF QD versus EFV/FTC/TDF QD in treatment-naïve, HIV-1-infected adults.

3. P028 is a Phase 2b trial to evaluate a switch from EFV/FTC/TDF (supplied as ATRIPLA™ or generic versions of this FDC) or its components [EFV, FTC plus TDF]) to DOR/3TC/TDF in virologically-suppressed, HIV-1-infected adults.

4. P030 is a Phase 2a trial to assess antiretroviral activity in treatment-naïve, HIV-1-infected adults with selected transmitted NNRTI resistance mutations treated with open-label DOR/3TC/TDF.

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials, including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the trials were performed.

1.6 Regulatory Guidance and Advice

Regulatory agency advice was obtained at key points during the development program. Formal guidance on the proposed Phase 3 clinical development program for DOR and DOR/3TC/TDF was received from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The advice relevant to the original marketing applications was summarized in those applications, and advice relevant to P024 and the proposed switch indications for DOR and DOR/3TC/TDF are summarized below.

1.6.1 FDA Regulatory Interactions

- At an [redacted] held on [redacted]-20[redacted] the following agreements were reached with the FDA:

  - The proposed clinical data package, consisting of 48-week safety and efficacy data from P024 would support filing and registration of the proposed indications for both DOR and DOR/3TC/TDF in adults on a stable antiretroviral regimen, to replace the third agent in their current ART containing 2 NRTIs (DOR), or as a complete regimen to replace their current ART (DOR/3TC/TDF).

  - [redacted]

- In an [redacted]-20[redacted] communication in follow-up to [redacted], the Agency:

  - [redacted]

  - [redacted]

  - [redacted]

- On -20 , the Agency agreed with the Sponsor's proposal
- On -20 , the Agency communicated to the Sponsor that
- On -20 the Agency noted that
- On -20 the Agency agreed with the Sponsor's proposal to submit a single safety update report under NDA 210806 and NDA 210807 to support the Agency's safety review of the switch supplemental NDAs for both PIFELTRO™ and DELSTRIGO™, as well as the planned supplemental NDAs to provide Week 96 data from P018 and P021.

1.6.2 European Regulatory Interactions

In obtained on N-20 (also summarized in the original marketing applications, as noted above) the Committee for Medicinal Products for Human Use (CHMP):

- The CHMP
- The CHMP

In CHMP obtained on -20 (as also summarized in the original marketing application), the CHMP did not agree with the Applicant's proposal The CHMP

[redacted]

2 OVERVIEW OF BIOPHARMACEUTICS

There is no new biopharmaceutics information since the original marketing applications. The biopharmaceutics program that contributed data to the original marketing applications included 4 trials:

- A bioequivalence trial (P039) evaluating the PK of DOR for the uncoated (Phase 3 formulation) and coated final market image tablet,
- One relative bioavailability trial (P026) was conducted with the DOR/3TC/TDF final market image, and
- Two trials evaluating the effect of food on the PK of DOR (P037) and DOR/3TC/TDF (P029).

3 OVERVIEW OF CLINICAL PHARMACOLOGY

There is no new clinical pharmacology data since the original marketing applications. Thirty-six Phase 1 trials were conducted to assess the safety, tolerability, PK (including drug-drug interactions and the effect of intrinsic and extrinsic factors on PK), biopharmaceutics and pharmacodynamics of DOR and DOR/3TC/TDF and contributed data to the Original Marketing Applications.

The clinical pharmacology trials were conducted primarily with DOR, administered as the single entity tablet. Following administration of the DOR/3TC/TDF final market image, the DOR, 3TC, and TDF components demonstrated similar PK compared to coadministration of each component administered as a single entity in a relative bioavailability trial (P026). Therefore the clinical pharmacology profile for each individual component administered as a single entity is applicable to the FDC of DOR/3TC/TDF.

Population PK, and exposure response analyses, based on P024, were updated in this supplemental application. These analyses confirmed that the PK and exposure response of DOR were unchanged in the switch population compared to the treatment naïve populations.

3.1 Pharmacokinetics Assessment

The population PK model presented in the original marketing applications [Ref. 5.3.5.3: 04PPZ5] was updated for this supplemental application to evaluate the consistency of DOR PK in P024's switch population (in the ISG) with that of the treatment-naïve population. The population PK parameters were re-estimated with the additional PK data from the ISG arm of P024 and the final model was used to estimate individual PK (post-hoc) parameter values for switch and treatment-naïve populations.

DOR plasma concentrations by protocol at different nominal weeks and nominal times were plotted to compare the available PK data from prior Phase 3 studies in treatment-naïve participants (P018 and P021) to P024 (ISG and DSG). As expected, these plots suggest a very similar range of DOR steady state concentrations between the studies across different time points, as shown in [Figure 2.5-switch48wk: 1] below. Moreover, model predicted DOR Cmax, C24, and AUC0-24 from P024 ISG were comparable to the corresponding values in the treatment-naïve population [Figure 2.5-switch48wk: 2]. These results indicate that DOR PK exposures are consistent between the two populations, and therefore the clinical pharmacology findings from the treatment-naïve population are also applicable to the switch population.

Figure 2.5-switch48wk: 1
Exploratory PK Analysis Comparing Available Phase 3 PK Data from Treatment-Naïve (P018, P021) and Switch Population (P024) (N = 443 [ISG]; 201 [DSG])

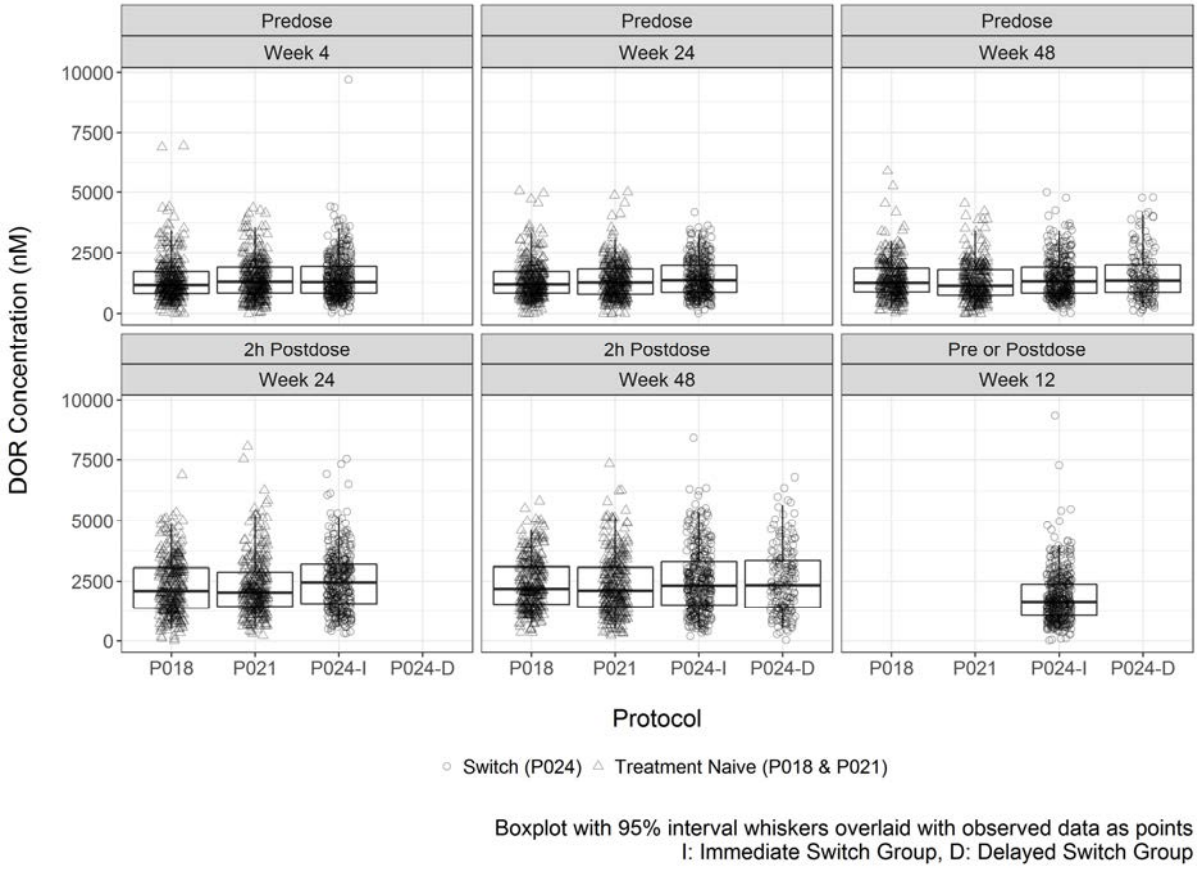
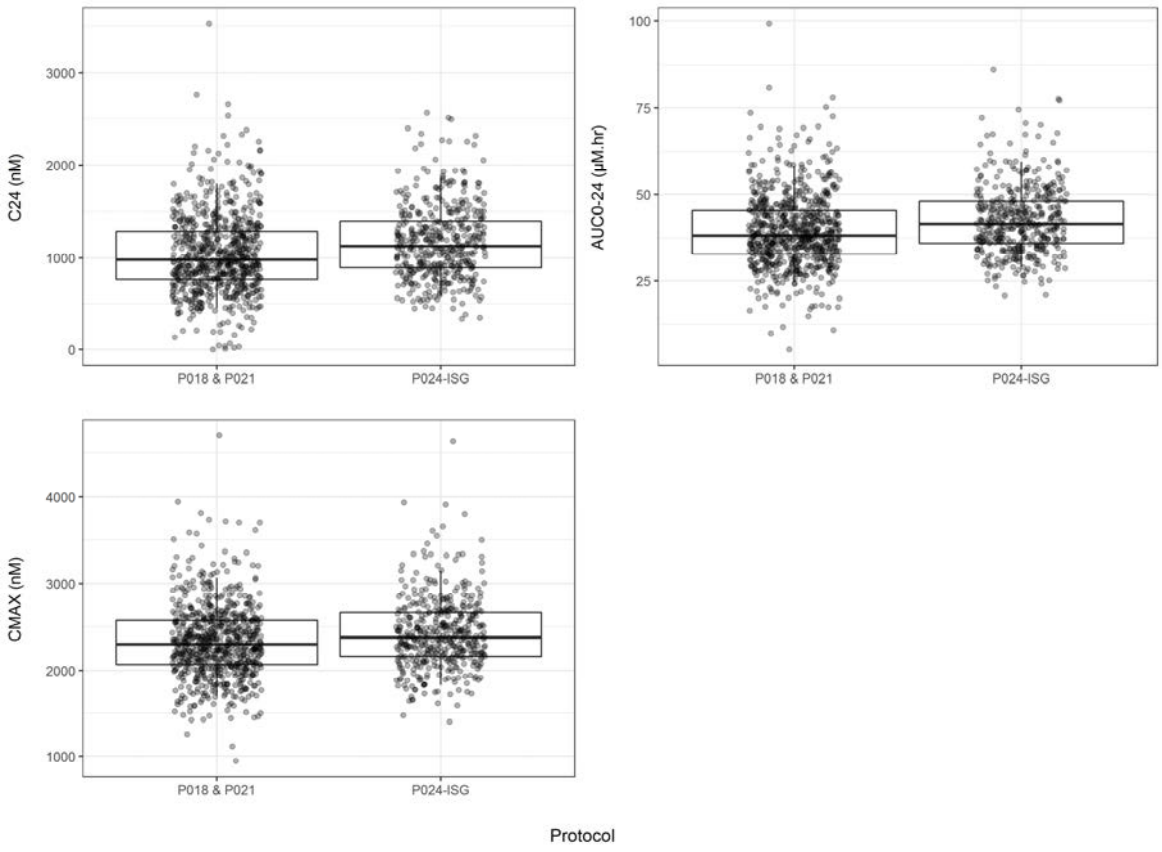


Figure 2.5-switch48wk: 2
Comparison of Steady-State DOR C24, AUC0-24, and Cmax Following Administration of 100 mg QD DOR Between Treatment Naïve (P018 & P021) and Switch Population (P024 ISG)



4 OVERVIEW OF EFFICACY

The efficacy data reported in this supplemental application and in [Sec. 2.7.3-switch48wk] provide results of the Phase 3 trial, P024, and demonstrate that DOR/3TC/TDF, provides continued viral suppression and maintenance of baseline $CD4^+$ T-cell counts in HIV-1-infected, virologically suppressed adults.

Key efficacy results include the following:

- An immediate switch to DOR/3TC/TDF on Study Day 1 is non-inferior when compared to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks as assessed by the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the ISG and at Study Week 24 in the DSG [Table 2.5-switch48wk: 4].

- An immediate switch to DOR/3TC/TDF on Study Day 1 met the criteria for non-inferiority (not adjusted for multiplicity) when compared to continuation of the baseline regimen for 24 weeks as assessed by the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 24 for both groups [Table 2.5-switch48wk: 5].
- An immediate switch to DOR/3TC/TDF is comparable to continuation of the baseline regimen based on the proportion of participants with HIV-1 RNA <40 copies/mL at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG [Table 2.5-switch48wk: 4], [Table 2.5-switch48wk: 5].
- An immediate switch to DOR/3TC/TDF met the criteria for non-inferiority (not adjusted for multiplicity) when compared to continuation of the baseline regimen based on the proportion of participants with HIV-1 RNA ≥50 copies/mL at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG [Table 2.5-switch48wk: 4], [Table 2.5-switch48wk: 5].
- No treatment emergent resistance was observed for DOR or any of the components of the FDC in either treatment group through Study Week 48 (Study Weeks 0-48 for ISG, Study Weeks 24-48 for DSG).

4.1 Summary of Approach to Assessment of Efficacy

This overview summarizes efficacy data from 48 weeks of treatment in P024 from the base study. Complete results from P024 are presented in the CSR [Ref. 5.3.5.1: P024MK1439A].

4.2 Relevance of the Patient Population

P024 includes participants with a range of baseline $CD4^+$ T-cell counts, with and without a history of AIDS, with and without hepatitis B/C co-infection, and with varied prior treatment regimens [Table 2.5-switch48wk: 2]. As such, the trial population is representative of participants who are stably suppressed and choose to switch from their current antiretroviral regimen.

4.3 Methods for Efficacy Assessment

4.3.1 Clinical Trial Design

The trial design of P024 is described in [Sec. 2.5.1.5-switch48wk].

Clinical Efficacy Endpoints

Primary efficacy endpoints:

- For the U.S. FDA, the primary efficacy endpoint in P024 was the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG [Sec. 2.5.1.6.1-switch48wk].

- For the EMA, the primary efficacy endpoint in P024 was the proportion of participants with HIV-1 RNA <40 copies/mL at Study Week 48 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG [Sec. 2.5.1.6.2-switch48wk].

Secondary efficacy endpoints:

- Proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 24 in both groups
- The proportion of participants maintaining HIV-1 RNA <40 copies/mL at Study Week 24 in both groups
- The proportion of participants with HIV-1 RNA ≥50 copies/mL at Study Week 24 in both groups
- The proportion of participants with HIV-1 RNA ≥50 copies/mL at Study Week 48 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG
- Immunologic efficacy was assessed by the change in $CD4^+$ T-cell count from baseline to Study Week 24 in both groups
- Immunologic efficacy was assessed by the change in $CD4^+$ T-cell count from baseline to Study Week 48 in the DOR/3TC/TDF ISG and Study Week 24 in the Baseline Regimen DSG

Additional evaluations:

- Number of participants experiencing protocol-defined virologic failure (PDVF, defined as participants who have 2 consecutive measurements of HIV-1 RNA ≥50 copies/mL at least 1 week apart) in both groups, and
- Assessment of viral drug resistance for participants who met PDVF criteria and discontinued or discontinued the study without PDVF, and had HIV-1 RNA >400 copies/mL at the discontinuation visit.

For this trial, the primary timepoints for the analysis of efficacy were Study Week 48 for the ISG compared with Study Week 24 for the DSG [Table 2.5-switch48wk: 4]. The secondary timepoint for the analysis of efficacy was Study Week 24 for the ISG compared with Study Week 24 for the DSG [Table 2.5-switch48wk: 5].

4.3.2 Statistical Methodology

Analysis Population

The Full Analysis Set (FAS) population was used as the primary population for the analysis of efficacy data in P024. The FAS population consisted of all randomized participants who received at least 1 dose of study medication (note that for participants who were randomized to the DSG, study treatment also included their ongoing baseline regimen during Study

Week 0 to Study Week 24), and had baseline data (for those analyses that require baseline data). Participants were included in the treatment group to which they were randomized.

Missing Data Approach

Two approaches were used to address missing values:

- The FDA Snapshot approach, which considered participants with missing data to be failures regardless of reason, and
- The Observed Failure (OF) approach, which considered participants who prematurely discontinued assigned treatment due to lack of efficacy to be failures. Participants with other types of missing data were excluded from the analysis in this approach.

The FDA Snapshot approach was the primary approach for the analysis of the proportion of participants maintaining virologic suppression (HIV-1 RNA <40 copies/mL and <50 copies/mL) or who had HIV-1 RNA ≥50 copies/mL. The OF approach was applied as a sensitivity analysis.

The immunologic response endpoint (change from baseline in $CD4^+$ T-cell count) was analyzed using the OF Approach and efficacy by subgroups was analyzed using both the OF and FDA Snapshot approaches.

The methods for assessment of each endpoint in P024 are described in Table 9 in the protocol for the CSR [Ref. 5.3.5.1: P024MK1439A: 16.1.1].

Multiplicity

The following hypotheses were tested sequentially at the one-sided Type 1 error rate of 2.5% in the following order:

1) Primary efficacy hypothesis testing non-inferiority for the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 for the ISG vs Study Week 24 for the DSG

2) Secondary safety hypothesis testing superiority for the mean change from baseline in fasting low-density lipoprotein cholesterol (LDL-C) at Study Week 24 in each treatment group. Primary analyses of lipid endpoints were performed only for participants whose regimen at screening was a ritonavir-boosted PI.

3) Secondary safety hypothesis testing superiority for the mean change from baseline in fasting non- high-density lipoprotein cholesterol (non-HDL-C) at Study Week 24 in each treatment group. Primary analyses of lipid endpoints were performed only for participants whose regimen at screening was a ritonavir-boosted PI.

4) Secondary efficacy hypothesis testing superiority for the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 for the ISG vs Study Week 24 for the DSG.

Testing stopped with the first of these tests failing to reach statistical significance and all subsequent tests were not considered for statistical significance.

The secondary efficacy hypotheses testing non-inferiority and superiority between treatment groups at Study Week 24 were supportive to the primary efficacy hypothesis and were not subject to a prespecified multiplicity adjustment. The ≥50 copies/mL endpoint was recommended as the primary endpoint for HIV switch trials as in the latest FDA guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (November 2015), which was issued after the trial began. This endpoint was included as a secondary endpoint for assessing non-inferiority in the analysis plan as a measure of strength of evidence, and was not included in the multiplicity control strategy in this trial.

Efficacy and safety data were collected through Study Week 48 for both ISG and DSG groups. Efficacy and safety analyses at Study Week 48 were also conducted for participants who switched to DOR/3TC/TDF QD at Study Week 24 for the DSG group. To assess the overall safety profile of DOR, safety data from ISG Study Weeks 0 to 48 and DSG Study Weeks 24 to 48 were pooled and summarized.

4.4 Efficacy Results

The results presented here are from the Week 48 base study of P024.

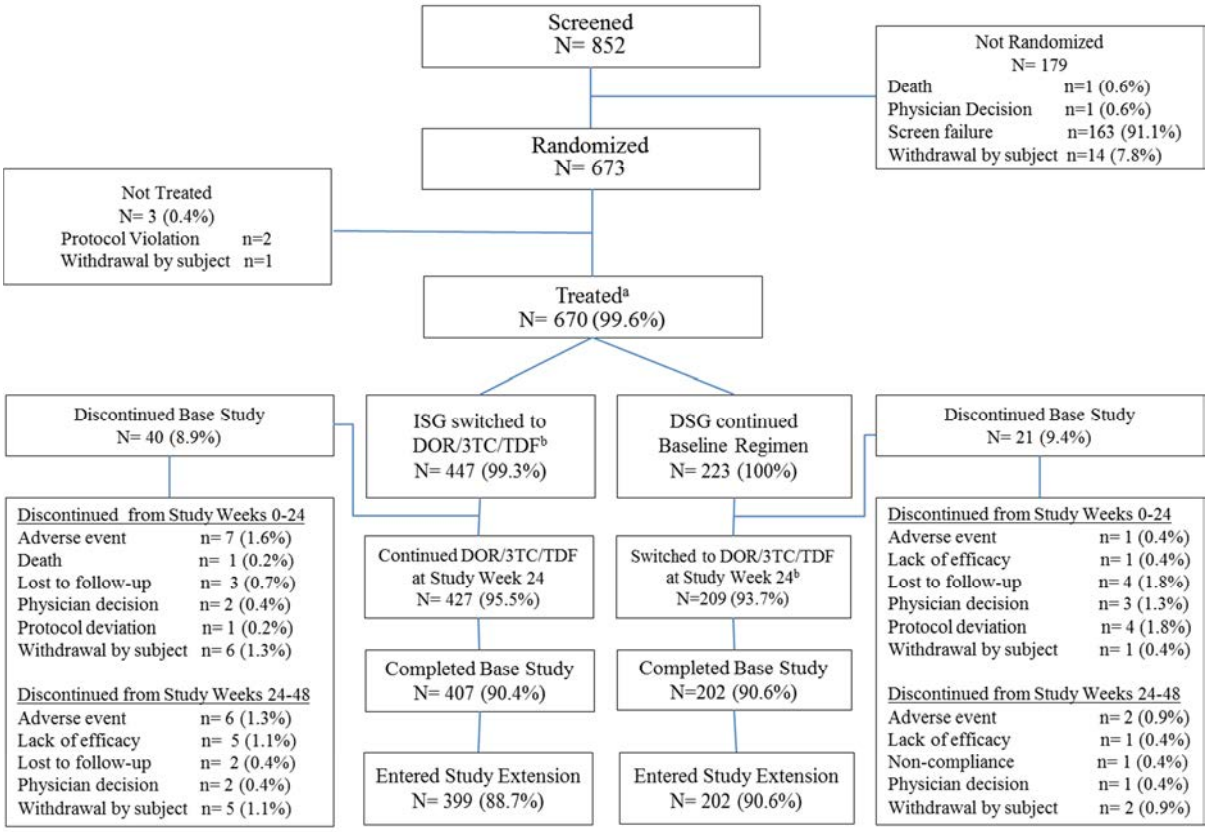
4.4.1 Study Population (Disposition and Baseline Characteristics)

A total of 673 participants were randomized to study treatment, and 670 were treated. Three randomized participants (all in the ISG) did not receive study drug due to protocol violation (n=2) or withdrawal from trial (n=1). Of the 223 DSG participants who continued their baseline regimen, 209 (93.7%) switched to DOR/3TC/TDF at Study Week 24. Most participants in both groups (90.4% and 90.6% in the ISG and DSG groups, respectively) completed their treatment regimen through Week 48. The number of participants who discontinued the trial was comparable in both treatment groups [Figure 2.5-switch48wk: 3].

Baseline demographic and disease characteristics were comparable in both the ISG and DSG; no clinically meaningful differences were observed between the groups [Table 2.5-switch48wk: 2].

The ART classes for the baseline regimen received by participants are summarized in [Table 2.5-switch48wk: 3].

Figure 2.5-switch48wk: 3
Disposition of Participants by Treatment Group



[a] The number receiving at least one dose of study treatment in the base study (N=670).
[b] The number receiving at least one dose of DOR/3TC/TDF in the base study included all treated ISG participants (N=447) from Study Weeks 0-48 and DSG participants (N=209) from Study Weeks 24-48.

Source: [Ref. 5.3.5.1: P024MK1439A: Table 14.1-1, 14.1-2, 14.1-3] and [Ref. 5.3.5.1: P024MK1439A: 16.1.7.4].

Table 2.5-switch48wk: 2
Subject Baseline Characteristics by Treatment Group

	ISG (N = 447)	DSG (N = 223)	Total (N = 670)
Gender n (%)			
Male	372 (83.2)	194 (87.0)	566 (84.5)
Female	75 (16.8)	29 (13.0)	104 (15.5)
Race n (%)			
American Indian or Alaska Native	5 (1.1)	2 (0.9)	7 (1.0)
Asian	17 (3.8)	8 (3.6)	25 (3.7)
Black or African American	56 (12.5)	34 (15.2)	90 (13.4)
Multiple	24 (5.4)	11 (4.9)	35 (5.2)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.0)	1 (0.1)
White	344 (77.0)	168 (75.3)	512 (76.4)
Ethnicity n (%)			
Hispanic or Latino	99 (22.1)	45 (20.2)	144 (21.5)
Not Hispanic or Latino	341 (76.3)	175 (78.5)	516 (77.0)
Unknown	7 (1.6)	3 (1.3)	10 (1.5)
Region n (%)			
Asia/Pacific	19 (4.3)	12 (5.4)	31 (4.6)
Europe	268 (60.0)	137 (61.4)	405 (60.4)
Latin America	49 (11.0)	24 (10.8)	73 (10.9)
North America	111 (24.8)	50 (22.4)	161 (24.0)
Age (years)			
18 to 64	438 (98.0)	214 (96.0)	652 (97.3)
≥65	9 (2.0)	9 (4.0)	18 (2.7)
Mean (SD)	43.1 (10.1)	43.7 (10.6)	43.3 (10.3)
Median (min, max)	43.0 (21, 71)	42.0 (22, 71)	43.0 (21, 71)
Baseline $CD4^+$ T-Cell Count (cells/mm^3)			
N[†]	439	220	659
Mean (SD)	664.9 (295.3)	649.9 (279.2)	659.9 (289.9)
Median (min, max)	633.0 (82, 1928)	624.5 (140, 1687)	628.0 (82, 1928)
Baseline $CD4^+$ T-Cell Counts n (%)			
<200 cells/mm^3	13 (2.9)	4 (1.8)	17 (2.5)
≥200 cells/mm^3	426 (95.3)	216 (96.9)	642 (95.8)
Missing	8 (1.8)	3 (1.3)	11 (1.6)
Baseline Plasma HIV-1 RNA n (%)			
<50 copies/mL	436 (97.5)	222 (99.6)	658 (98.2)
<40 copies/mL	436 (97.5)	220 (98.7)	656 (97.9)
≥40 copies/mL	11 (2.5)	3 (1.3)	14 (2.1)
≥50 copies/mL	11 (2.5)	1 (0.4)	12 (1.8)
History of AIDS n (%)			
Yes	80 (17.9)	35 (15.7)	115 (17.2)
No	367 (82.1)	188 (84.3)	555 (82.8)

Subject Baseline Characteristics by Treatment Group

	ISG (N = 447)	DSG (N = 223)	Total (N = 670)
Stratum n (%)			
Ritonavir-boosted PI	312 (69.8)	155 (69.5)	467 (69.7)
Lipid-lowering therapy	31 (6.9)	12 (5.4)	43 (6.4)
Non-Lipid-lowering therapy	281 (62.9)	143 (64.1)	424 (63.3)
Cobicistat-boosted PI	4 (0.9)	2 (0.9)	6 (0.9)
Cobicistat-boosted elvitegravir or an NNRTI	131 (29.3)	66 (29.6)	197 (29.4)
Duration of ART Regimen Prior to Enrollment (%)			
<1 year	26 (5.8)	12 (5.4)	38 (5.7)
≥1 year	421 (94.2)	211 (94.6)	632 (94.3)
Duration of ART Regimen Prior to Enrollment (months)			
N[†]	447	223	670
Mean (SD)	56.6 (38.4)	58.6 (37.0)	57.3 (37.9)
Median (min, max)	48.4 (6.9, 264.9)	50.5 (7.2, 181.1)	49.3 (6.9, 264.9)
Baseline Hepatitis Status[††]			
Hep B and/or C Positive	14 (3.1)	9 (4.0)	23 (3.4)
Hep B Positive Only	12 (2.7)	7 (3.1)	19 (2.8)
Hep C Positive Only	2 (0.4)	2 (0.9)	4 (0.6)
Hep B and C Negative	433 (96.9)	214 (96.0)	647 (96.6)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen			
N	340 (76.1)	168 (75.3)	508 (75.8)
K103N, Y181C, and/or G190A	11 (2.5)	13 (5.8)	24 (3.6)

[†] Subjects with missing results excluded.

[††] Evidence of hepatitis B surface antigen or evidence of hepatitis C virus (HCV) RNA by polymerase chain reaction (PCR) quantitative test for HCV.

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.

N = Number of subjects randomized and treated in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

Source: [P024MK1439A: adam-adsl]

Table 2.5-switch48wk: 3
Subject Baseline Antiretroviral Therapy Received by Treatment Group

	ISG (N=447)	DSG (N=223)	Total (N=670)
ART Class in Baseline Regimen† n (%)			
Ritonavir-boosted PI	311 (69.6)	155 (69.5)	466 (69.6)
ATV	96 (21.5)	43 (19.3)	139 (20.7)
DRV	161 (36.0)	81 (36.3)	242 (36.1)
LPV	54 (12.1)	31 (13.9)	85 (12.7)
Cobicistat-boosted PI	5 (1.1)	1 (0.4)	6 (0.9)
DRV	5 (1.1)	1 (0.4)	6 (0.9)
Cobicistat-boosted elvitegravir	25 (5.6)	12 (5.4)	37 (5.5)
NNRTI	106 (23.7)	55 (24.7)	161 (24.0)
EFV	78 (17.4)	36 (16.1)	114 (17.0)
NVP	17 (3.8)	12 (5.4)	29 (4.3)
RPV	11 (2.5)	7 (3.1)	18 (2.7)
Co-administered NRTIs n(%)			
TDF/FTC	330 (73.8)	154 (69.1)	484 (72.2)
TAF/FTC	22 (4.9)	11 (4.9)	33 (4.9)
ABC/3TC	61 (13.6)	28 (12.6)	89 (13.3)
ZDV/3TC	23 (5.1)	19 (8.5)	42 (6.3)
TDF/3TC	10 (2.2)	10 (4.5)	20 (3.0)
Others††	1 (0.2)	1 (0.4)	2 (0.3)

†Based on the baseline regimen received, each administered with two NRTIs.
††Other NRTIs includes: 1 for TDF/FTC/ZDV and 1 for ABC/TDF.
ISG= Immediate Switch Group; DSG=Delayed Switch Group.
Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.
N = Number of subjects randomized and treated in each treatment group; n (%) = Number (percent) of subjects in each sub-category.

Source: [P024MK1439A: adam-adsl; adbase]

4.4.2 Efficacy Summary at Week 48

In all assessments of primary and secondary timepoints, the efficacy of DOR/3TC/TDF in the ISG is non-inferior or comparable to that observed in the DSG, using either the FDA Snapshot or OF approach, or both. For the endpoints below other than the primary endpoint, results by chronological order at the secondary timepoint are presented first followed by results at the primary timepoints.

Proportion of Participants With HIV-1 RNA<50 copies/mL

The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA <50 copies/mL (FDA Snapshot approach), in the DOR/3TC/TDF ISG at Study Week 48 is non-inferior to that observed in the Baseline Regimen DSG at Study Week 24 [Table 2.5-switch48wk: 4].

Because the lower bound of 95% CI for the treatment difference was not greater than zero, it could not be concluded that efficacy in the DOR/3TC/TDF ISG is superior to that in the Baseline Regimen DSG at the primary timepoints [Table 2.5-switch48wk: 4].

The primary and key secondary objectives compared efficacy of the ISG at Study Week 48 to the DSG at Study Week 24, thereby potentially biasing the outcomes against the ISG arm which followed participants for twice the duration of the DSG baseline regimen for the primary endpoint.

The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA <50 copies/mL (FDA Snapshot approach), in the DOR/3TC/TDF ISG at Study Week 24 met the criteria for non-inferiority (not adjusted for multiplicity) as compared to that observed in the Baseline Regimen DSG at Study Week 24 [Table 2.5-switch48wk: 5].

Consistent results for this endpoint were also observed using the OF approach at the specified timepoints [Table 2.5-switch48wk: 4], [Table 2.5-switch48wk: 5].

Proportion of Participants With HIV-1 RNA<40 copies/mL

The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA <40 copies/mL (FDA Snapshot approach), was comparable at Study Week 24 for both groups [Table 2.5-switch48wk: 5].

The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA <40 copies/mL (FDA Snapshot approach), in the DOR/3TC/TDF ISG at Study Week 48 was comparable to that observed in the Baseline Regimen DSG at Study Week 24 [Table 2.5-switch48wk: 4].

The analysis of the proportion of participants with HIV-1 RNA <40 copies/mL by FDA Snapshot approach was consistent with the primary analysis. Consistent results for this endpoint were also observed using the OF approach at the specified timepoints [Table 2.5-switch48wk: 4], [Table 2.5-switch48wk: 5].

Proportion of Participants With HIV-1 RNA≥50 copies/mL

The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA ≥50 copies/mL (FDA Snapshot approach), in the DOR/3TC/TDF ISG at Study Week 24 met the criteria for non-inferiority (not adjusted for multiplicity) to that observed in the Baseline Regimen DSG at Study Week 24 using the pre-defined non-inferiority bound of 4 percentage points [Table 2.5-switch48wk: 5].

The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA ≥50 copies/mL (FDA Snapshot approach), at Study Week 48 in the DOR/3TC/TDF ISG group met the criteria for non-inferiority (not adjusted for multiplicity) to the Baseline Regimen DSG at Study Week 24 using the pre-defined non-inferiority bound of 4 percentage points [Table 2.5-switch48wk: 4].

Change from Baseline in $CD4^+$ T-cell Count

The efficacy of DOR/3TC/TDF, as assessed by the change from baseline in $CD4^+$ T-cell count (OF approach), in the DOR/3TC/TDF ISG at Study Week 24 was comparable to that observed in the Baseline Regimen DSG at Study Week 24 [Table 2.5-switch48wk: 5].

The efficacy of DOR/3TC/TDF, as assessed by the change from baseline in $CD4^+$ T-cell count (OF approach), in the DOR/3TC/TDF ISG at Study Week 48 was comparable to that observed in the Baseline Regimen DSG at Study Week 24 [Table 2.5-switch48wk: 4].

Table 2.5-switch48wk: 4
Efficacy Analysis at Primary Timepoints
Base Study

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[‡]		Conclusion[§]
		DOR/3TC/TDF QD ISG at Study Week 48 n/N (%)	Baseline Regimen DSG at Study Week 24 n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	406/447 (90.8)	211/223 (94.6)	-3.784	(-7.877, 0.310)	Non-inferior[§]
Secondary and Exploratory						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	406/413 (98.3)	211/215 (98.1)	0.169	(-2.241, 2.580)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	401/447 (89.7)	208/223 (93.3)	-3.556	(-7.977, 0.864)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	401/413 (97.1)	208/215 (96.7)	0.355	(-2.681, 3.391)	
Proportion of Subjects with HIV-1 RNA ≥50 copies/mL	Snapshot	7/447 (1.6)	4/223 (1.8)	-0.232	(-2.529, 2.064)	Non-inferior[*]
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Change from Baseline in $CD4^+$ T-Cell Count (cells/mm^3)	OF	13.9 (-2.6, 30.4)	18.0 (-3.6, 39.5)	-4.0	(-31.6, 23.5)	

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs.cobicistat-boosted elvitegravir or NNRTI). The 95% CI for mean difference in $CD4^+$ T-Cell change was based on t-distribution.

[§] DOR/3TC/TDF QD ISG was determined to be non-inferior to Baseline Regimen DSG for the endpoint of HIV-1 RNA <50 copies/mL since the lower bound of the 95% CI for the difference in percent response was above -8 percentage points.

[*] DOR/3TC/TDF QD ISG met the criterion for non-inferiority (not adjusted for multiplicity) to Baseline Regimen DSG for the endpoint of HIV-1 RNA ≥50 copies/mL since the upper bound of the 95% CI for the difference in percent response was below 4 percentage points.

Analysis of post-baseline data includes laboratory records collected after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.

n = Number of subjects in each subcategory.

N = Number of subjects in each treatment group.

Source: [P024MK1439A: adam-adsl; adeff1; adeff2]

Table 2.5-switch48wk: 5
Efficacy Analysis at Secondary Timepoint
Base Study

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[‡]		Conclusion[§]
		DOR/3TC/TDF QD ISG at Study Week 24 n/N (%)	Baseline Regimen DSG at Study Week 24 n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	419/447 (93.7)	211/223 (94.6)	-0.877	(-4.706, 2.952)	Non-inferior[§]
Secondary and Exploratory						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	419/427 (98.1)	211/215 (98.1)	-0.012	(-2.444, 2.419)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	415/447 (92.8)	208/223 (93.3)	-0.427	(-4.591, 3.738)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	415/427 (97.2)	208/215 (96.7)	0.446	(-2.564, 3.456)	
Proportion of Subjects with HIV-1 RNA ≥50 copies/mL	Snapshot	8/447 (1.8)	4/223 (1.8)	-0.003	(-2.343, 2.337)	Non-inferior[*]
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Change from Baseline in $CD4^+$ T-Cell Count (cells/mm^3)	OF	5.1 (-11.8, 22.1)	18.0 (-3.6, 39.5)	-12.8	(-41.1, 15.4)	

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs.cobicistat-boosted elvitegravir or NNRTI). The 95% CI for mean difference in $CD4^+$ T-Cell change was based on t-distribution.

[§] DOR/3TC/TDF QD ISG met the criterion for non-inferiority (not adjusted for multiplicity) to Baseline Regimen DSG for the endpoint of HIV-1 RNA <50 copies/mL since the lower bound of the 95% CI for the difference in percent response was above -8 percentage points.

[*] DOR/3TC/TDF QD ISG met the criterion for non-inferiority (not adjusted for multiplicity) to Baseline Regimen DSG for the endpoint of HIV-1 RNA ≥50 copies/mL since the upper bound of the 95% CI for the difference in percent response was below 4 percentage points.

Analysis of post-baseline data includes laboratory records collected after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.

n = Number of subjects in each subcategory.

N = Number of subjects in each treatment group.

Source: [P024MK1439A: adam-adsl; adeff1; adeff2]

PDVF and Development of Viral Drug Resistance:

The resistance analysis population consisted of participants who met the criteria for PDVF and discontinued (n=8), and those who discontinued the trial without PDVF (n=53).

Rates for PDVF were low and comparable between treatment groups in the base study. Three participants with PDVF (2 in DOR/3TC/TDF ISG and 1 in Baseline Regimen DSG) and 3 participants who discontinued early (1 in DOR/3TC/TDF ISG and 2 in Baseline Regimen DSG) had samples with HIV-1 RNA>400 copies/mL available for resistance testing.

No drug resistance to DOR or any of the components of the FDC was identified in ISG or DSG participants who received DOR/3TC/TDF and met the criteria for resistance testing.

One participant with PDVF in the Baseline Regimen DSG receiving ritonavir-boosted DRV, FTC and TDF had genotypic resistance associated mutation to 3TC and FTC [RT M184M/I] and phenotypic resistance to 3TC (>106.75 fold compared to Wild-Type [WT]) and FTC (>44.0 fold compared to WT) that was identified at the Week 12 (Day 84) visit at which viral failure was identified (thus, the participant discontinued from the trial before the switch to DOR/3TC/TDF).

None of the 24 participants (11 ISG [Day 1], 13 DSG [Week 24]) on PI and InSTI regimens who had virus with baseline NNRTI mutations (RT K103N, G190A, or Y181C) experienced virologic failure through Study Week 48 or at the time of discontinuation.

Further details are provided in the CSR [Ref. 5.3.5.1: P024MK1439A: 11.2].

Subgroup Analysis:

Analysis of subgroups with respect to the proportion of participants with HIV-1 RNA <50 copies/mL and <40 copies/mL (OF and FDA Snapshot Approaches) revealed comparable antiretroviral and immunologic results for both treatment groups at primary and secondary timepoints regardless of baseline prognostic and demographic factors and consistent with the overall population, to the extent possible given small sample sizes in some subpopulations. Analysis of subgroups with respect to the proportion of participants with HIV-1 RNA≥50 copies/mL (OF and FDA Snapshot Approaches) was comparable for the 2 groups. The proportion of participants with virologic and immunologic responses at primary and secondary timepoints by ART class of baseline regimens received were consistent with results of previous analyses. There were no clinically meaningful differences in antiretroviral or immunologic efficacy observed between treatment groups across all subgroups.

Further details are provided in the CSR [Ref. 5.3.5.1: P024MK1439A: 11.1.4.3, 11.1.4.4].

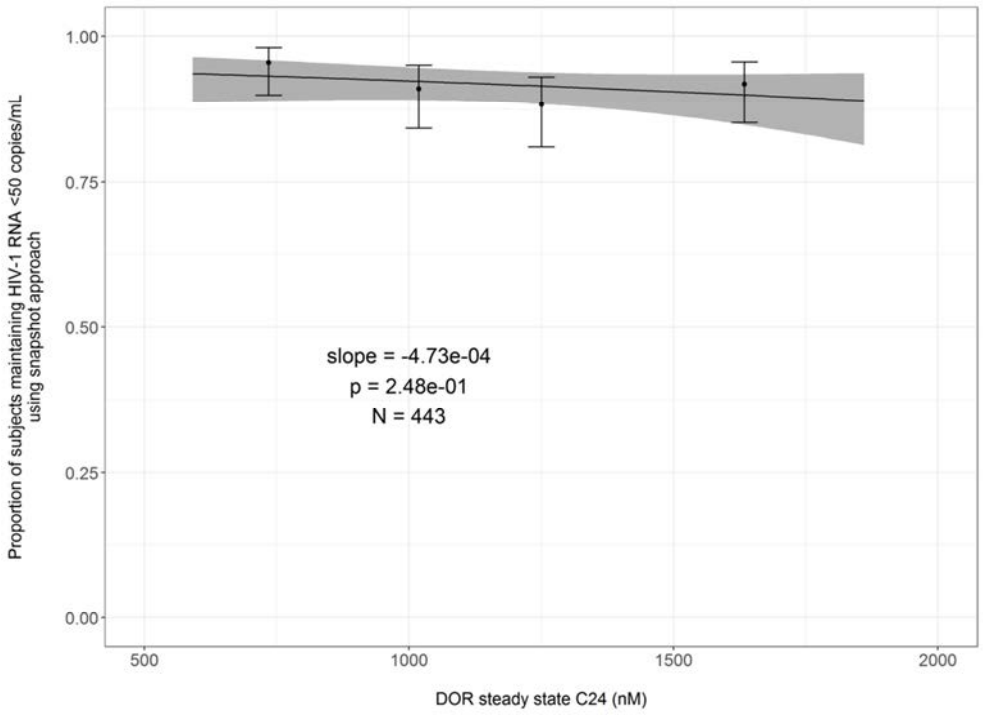
PK/PD and Other Analysis Results:

The exposure-response relationship of DOR, based only on data from the P024 ISG, was explored graphically for signs of clear differences in response at different quartiles of PK exposure in switch participants. Graphical and logistic regression analysis of the primary pharmacodynamics endpoint, i.e., proportion of participants maintaining <50 copies/mL,

versus quartiles of steady-state DOR C24 from ISG of P024 showed a flat exposure-response relationship as seen in [Figure 2.5-switch48wk: 4]. The 100 mg dose was previously selected based on dose-ranging evaluations in the treatment-naïve population and confirmed in Phase 3 treatment-naïve trials. There is no reason to expect a differing dose- or exposure-response relationship in the switch population and therefore the Phase 3 switch trial (P024) was conducted using this 100 mg dose. The results from this exposure-response analysis indicate that the responses observed at the 100 mg dose lack exposure-dependency and hence support appropriateness of the selected dose in the switch population. Additional details about the analysis including secondary endpoints are presented in the modeling and simulation report [Ref. 5.3.5.3: 04ZHL5].

Figure 2.5-switch48wk: 4

Predicted and Observed Proportion of Participants Maintaining HIV-1 RNA <50 copies/mL Using Snapshot Approach as a Function of DOR Steady-State C24 Quartiles Following Administration of 100 mg DOR (P024 ISG, N=443)



4.4.3 Applicability of Efficacy Results to Single Agent Doravirine

The Applicant considers that the efficacy results from P024 support an indication for switching to DOR, either as a single entity in combination with other antiretroviral agents or as DOR/3TC/TDF. In the treatment-naïve trials, P018 and P021, DOR in combination with ABC/3TC, FTC/TDF, or 3TC/TDF demonstrated similar and potent efficacy at the primary endpoint of each trial at Week 48. It would be expected that these NRTI background regimens when combined with DOR would have similar efficacy in a switch population since they are already virologically suppressed. Thus, the efficacy results from P024 with DOR/3TC/TDF would be applicable to DOR in combination with other NRTI background regimens and support the switching of patients who are virologically suppressed on a stable regimen to a DOR-containing regimen.

4.5 Rationale for Applicability of Foreign Data to the United States Population

As observed in [Table 2.5-switch48wk: 2], 24.0% of the population (P024) were from the North American region (the majority of participants in the North American region were from the U.S.). Overall, the efficacy of DOR/3TC/TDF was consistent among participants from North America and participants from other regions [Ref. 5.3.5.1: P024MK1439A: Table 11-7, 11-8, 11-9], [Ref. 5.3.5.1: P024MK1439A: Table 14.2-15, Table 14.2-16, Table 14.2-18, Table 14.2-19, Table 14.2-21]. In addition, DOR/3TC/TDF was generally well tolerated and had a safety profile that was comparable among participants from North America and participants from other regions [Ref. 5.3.5.1: P024MK1439A: Table 14.3-21]. The Applicant considers foreign data to be applicable to the population in the U.S.

4.6 Efficacy Conclusions for Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

In this clinical trial that enrolled HIV-1-infected, virologically suppressed participants, a switch to DOR/3TC/TDF demonstrated non-inferior virologic efficacy and similar increases in $CD4^+$ T-cell counts compared to continuation of a baseline regimen consisting of either a boosted PI, EVG, or NNRTI + 2 NRTIs.

Based on the results from this study, the following efficacy conclusions can be made:

- A switch to DOR/3TC/TDF is non-inferior to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG and observed to be non-inferior (not adjusted for multiplicity) at Study Week 24 for both groups.

The following key efficacy results were also observed:

- A switch to DOR/3TC/TDF was observed to be non-inferior (not adjusted for multiplicity) to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of participants maintaining HIV-1 RNA ≥50 copies/mL at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG compared to Study Week 24 in the Baseline Regimen DSG.

- A switch to DOR/3TC/TDF was comparable to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of participants maintaining HIV-1 RNA <40 copies/mL at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG compared to Study Week 24 in the Baseline Regimen DSG.

- A switch to DOR/3TC/TDF was comparable to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the change from baseline in $CD4^+$ T cell count at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG compared to Study Week 24 in the Baseline Regimen DSG.

- No participant who received DOR/3TC/TDF in the ISG or DSG and met the criteria for resistance testing had genotypic or phenotypic resistance to any of the components.

- None of the 24 participants (11 ISG [Day 1], 13 DSG [Week 24]) on PI and InSTI regimens who had virus with baseline NNRTI mutations (RT K103N, G190A, or Y181C) experienced virologic failure on DOR/3TC/TDF through Study Week 48 or at the time of discontinuation.

- DOR PK exposures were consistent between treatment-naïve and switch populations.

- A flat exposure-response relationship between the proportion of participants maintaining HIV-1 RNA<50 copies/mL and steady-state DOR C24 at a 100 mg once-daily dose in the switch population was observed.

Compared to continuing a baseline regimen, DOR/3TC/TDF demonstrated non-inferior virologic efficacy and comparable increases in $CD4^+$ T-cell counts. These findings support switching from a stable antiretroviral regimen to a DOR-containing regimen as clinically appropriate.

5 OVERVIEW OF SAFETY

The original marketing applications provided a comprehensive evaluation of the safety profile of DOR and DOR/3TC/TDF in 1657 individuals (979 treatment-naïve participants who received DOR or DOR/3TC/TDF in the Phase 2b/3 trials [Ref. 5.3.5.1: P007V01MK1439, P018V01MK1439, P021V01MK1439A] and 678 participants who received DOR and DOR/3TC/TDF in the Phase 1 trials). Overall, the results demonstrated that DOR, both as a single agent and as DOR/3TC/TDF, was generally well-tolerated at all doses studied.

The safety data reported in [Sec. 2.7.4-switch48wk] in this supplemental application provides an evaluation of the safety profile of DOR/3TC/TDF in 656 virologically suppressed participants who received DOR/3TC/TDF in a Phase 3 switch trial (P024). Overall, the results in P024 demonstrate that DOR/3TC/TDF was generally well-tolerated in this trial population, with a similar safety profile to that of the treatment-naïve population.

Key safety results include the following:

- Participants who switched to DOR/3TC/TDF immediately had a higher incidence of AEs and drug-related AEs through Study Weeks 0-24 when compared with the incidence of these events among participants who remained on their baseline regimen through Study Weeks 0-24 in this open-label trial. The open-label switch study design may have contributed to the difference in reported AE rates. The higher reported rates of AEs and drug-related AEs in the ISG are not unexpected since these participants switched to a new regimen, whereas participants in the DSG continued on their baseline regimen, which they were on for at least 6 months prior to study entry. The majority of the reported AEs were of mild to moderate intensity and considered by the investigator to be unrelated to study medication.

- The safety profile of DOR/3TC/TDF demonstrates a favorable lipid profile compared to ritonavir-boosted PI-based regimens after 24 weeks of treatment; see [Sec. 2.5.6.2-switch48wk]. A switch to DOR/3TC/TDF is superior to the continuation of a baseline ritonavir-boosted PI regimen for 24 weeks, as assessed by the difference in mean change from baseline in fasting LDL-C and fasting non-HDL-C at Study Week 24 in each treatment group.

5.1 Summary of Approach to Assessment of Safety

This section will address safety in P024. Complete analyses of results from the P024 trial are presented in the CSR [Ref. 5.3.5.1: P024MK1439A].

Analysis Populations

Safety analyses were based on the All Subjects as Treated (ASaT) population (all randomized participants who received at least 1 dose of study medication). In the ASaT, participants were included in the treatment group corresponding to the treatment they

actually received. Included in this supplemental application are analyses of safety data for 670 individuals in the ASaT population in P024.

Assessment of Safety

AEs were assessed for P024 including review of common AEs, drug-related AEs, AEs leading to discontinuation, drug-related SAEs, and deaths. The change from baseline in fasting lipids (LDL-C, non-HDL-C, total cholesterol, HDL-C, and triglycerides) was analyzed, with LDL-C and non-HDL-C assessed according to pre-specified hypotheses. Primary analyses of these lipid endpoints were performed only for participants whose regimen at screening was a ritonavir-boosted PI.

Evaluations of laboratory values included review of Pre-Defined Limit of Change (PDLC) results, and assessment of change from baseline for laboratory parameters and vital signs.

5.2 Extent of Exposure

A total of 656 participants received DOR/3TC/TDF in the base study. The ISG participants (n=447) received DOR/3TC/TDF on Study Day 1 and continued through Study Week 48 whereas the DSG participants (n=209) switched from their baseline regimens to DOR/3TC/TDF at Study Week 24 [Ref. 5.3.5.1: P024MK1439A: 10.6]. P024 is an ongoing trial, and additional safety data will be provided in a subsequent safety update report.

5.3 Analysis of Adverse Experiences

The overall safety evaluation plan is described in [Ref. 5.3.5.1: P024MK1439A: 12]. For P024, safety and tolerability were assessed by clinical and statistical review of safety parameters, including clinical and laboratory AEs, abnormal laboratory values as per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse events, version 2.0 (DAIDS criteria) and vital signs.

5.3.1 Adverse Events in P024

Data for AEs in P024 can be found in [Sec. 2.7.4-switch48wk: 2]. Overall, treatment with DOR/3TC/TDF was generally well tolerated.

AEs

ISG Study Weeks 0 to 24 (DOR/3TC/TDF), DSG Study Weeks 0 to 24 (Baseline Regimen)

A higher proportion of participants in the DOR/3TC/TDF ISG compared to the Baseline Regimen DSG reported AEs (68.9% versus 52.5%, respectively) and drug-related AEs (19.5% versus 2.2%) in this open-label trial [Table 2.5-switch48wk: 6], [Table 2.5-switch48wk: 7]. Nasopharyngitis and headache were the only AEs reported by ≥5% of participants in either treatment group during Study Weeks 0-24 [Ref. 5.3.5.1: P024MK1439A: Table 12-3].

The incidences of SAEs, drug-related SAEs, and discontinuation due to AE were low (<4%) and occurred with similar frequency in both groups through Study Week 24 [Table 2.5-switch48wk: 7].

The majority of the AEs were of mild to moderate intensity and considered by the investigator to be unrelated to study medication [Ref. 5.3.5.1: P024MK1439A: 12.1.3.1, 12.1.3.2].

ISG Study Weeks 0 to 24 (DOR/3TC/TDF), DSG Study Weeks 24 to 48 (DOR/3TC/TDF)

A similar safety profile was observed for participants following their switch to DOR/3TC/TDF, regardless of whether the switch was immediate (ISG: Study Weeks 0-24) or delayed (DSG: Study Weeks 24-48) [Table 2.5-switch48wk: 6].

Overall DOR/3TC/TDF: ISG Study Weeks 0 to 48 + DSG Study Weeks 24 to 48

Participants who received DOR/3TC/TDF (pooled data from ISG: Study Weeks 0 to 48 and DSG: Study Weeks 24 to 48) experienced a low incidence of discontinuations due to AEs (2.9%), discontinuations due to drug-related AEs (2.0%), SAEs (4.0%), and drug-related SAEs (0.8%); the most frequently reported AEs for participants who received DOR/3TC/TDF during the base study were nasopharyngitis (8.2%), headache (8.1%), and diarrhea (6.1%). [Table 2.5-switch48wk: 6] [Ref. 5.3.5.1: P024MK1439A: Table 12-3].

The most common drug-related AE reported during treatment with DOR/3TC/TDF (pooled data from ISG Study Weeks 0 to 48 and DSG Study Weeks 24 to 48) was increased ALT, occurring in 2.2% of participants in the ISG, and 1.9% of participants in the DSG following the switch [Table 2.5-switch48wk: 6] [Ref. 5.3.5.1: P024MK1439A: Table 12-5]. Drug-related AEs of increased ALT were generally mild or moderate in severity, rarely led to discontinuation (n=2 [0.3%]), and generally resolved despite continuation of DOR/3TC/TDF.

No randomized participant died during the base study. One participant died during the screening period-the cause of death was recorded as intoxication, and in the opinion of the investigator, was not related to study medication. Two participants, both in the ISG, died in the post-study period (>14 days after the last dose of study medication, as reported by the participant at the time of the last visit) (1 participant who died from myocardial infarction 108 days after last reported dose, and 1 participant who died from suspected illicit drug overdose 82 days after last reported dose). [Ref. 5.3.5.1: P024MK1439A: 12.2.1.1].

Table 2.5-switch48wk: 6
Adverse Event Summary
Study Weeks 0-48; Base Study

	DOR/3TC/TDF QD ISG Study Weeks 0-24		Baseline Regimen DSG Study Weeks 0-24		DOR/3TC/TDF QD DSG Study Weeks 24-48		DOR/3TC/TDF QD ISG Study Weeks 0-48		DOR/3TC/TDF QD ISG(Study Weeks 0-48) + DSG(Study Weeks 24-48)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	447		223		209		447		656	
with one or more adverse events	308	(68.9)	117	(52.5)	126	(60.3)	359	(80.3)	485	(73.9)
with no adverse event	139	(31.1)	106	(47.5)	83	(39.7)	88	(19.7)	171	(26.1)
with drug-related[†] adverse events	87	(19.5)	5	(2.2)	29	(13.9)	100	(22.4)	129	(19.7)
with serious adverse events	13	(2.9)	8	(3.6)	4	(1.9)	22	(4.9)	26	(4.0)
with serious drug-related adverse events	2	(0.4)	0	(0.0)	1	(0.5)	4	(0.9)	5	(0.8)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	11	(2.5)	1	(0.4)	4	(1.9)	15	(3.4)	19	(2.9)
discontinued drug due to a drug-related adverse event	7	(1.6)	0	(0.0)	4	(1.9)	9	(2.0)	13	(2.0)
discontinued drug due to a serious adverse event	4	(0.9)	1	(0.4)	1	(0.5)	6	(1.3)	7	(1.1)
discontinued drug due to a serious drug-related adverse event	2	(0.4)	0	(0.0)	1	(0.5)	3	(0.7)	4	(0.6)

[†] Determined by the investigator to be related to the drug.

Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.

Source: [P024MK1439A: adam-adsl; adae]

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Table 2.5-switch48wk: 7
Analysis of Adverse Event Summary
Study Weeks 0-24; Base Study

	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		Difference in % vs Baseline Regimen DSG
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	447		223		
with one or more adverse events	308	(68.9)	117	(52.5)	16.4 (8.6, 24.2)
with no adverse event	139	(31.1)	106	(47.5)	-16.4 (-24.2, -8.6)
with drug-related[‡] adverse events	87	(19.5)	5	(2.2)	17.2 (13.0, 21.5)
with serious adverse events	13	(2.9)	8	(3.6)	-0.7 (-4.2, 2.0)
with serious drug-related adverse events	2	(0.4)	0	(0.0)	0.4 (-1.3, 1.6)
who died	0	(0.0)	0	(0.0)	0.0 (-1.7, 0.9)
discontinued drug due to an adverse event	11	(2.5)	1	(0.4)	2.0 (-0.2, 4.0)
discontinued drug due to a drug-related adverse event	7	(1.6)	0	(0.0)	1.6 (-0.1, 3.2)
discontinued drug due to a serious adverse event	4	(0.9)	1	(0.4)	0.4 (-1.7, 1.9)
discontinued drug due to a serious drug-related adverse event	2	(0.4)	0	(0.0)	0.4 (-1.3, 1.6)

[†] Based on Miettinen & Nurminen method.

[‡] Determined by the investigator to be related to the drug.

Estimated differences are provided in accordance with the statistical analysis plan.

Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.

Source: [P024MK1439A: adam-adsl; adae]

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5.4 Clinical Laboratory Evaluations in P024

Results of clinical laboratory evaluations in P024 can be found in [Ref. 5.3.5.1: P024MK1439A: 12.3.2]. In general, treatment with DOR/3TC/TDF was well tolerated. Few Grade 3 or 4 laboratory abnormalities were reported.

In participants who were receiving a stable antiretroviral regimen of a ritonavir-boosted PI + 2 NRTIs at screening, DOR/3TC/TDF had a superior lipid profile in participants in the DOR/3TC/TDF ISG compared to that observed in the Baseline Regimen DSG with respect to change from baseline to Study Week 24 in fasting LDL-C and non HDL-C. The differences between these two groups in mean changes from Study Weeks 0-24 in fasting LDL-C and non-HDL C were statistically significant [Table 2.5-switch48wk: 8].

Results for the change from baseline in fasting lipids for all treated participants including other baseline regimens were comparable to the results for participants on a ritonavir-boosted PI at Study Week 24 [Ref. 5.3.5.1: P024MK1439A: Table 14.3-46].

An imbalance in favor of the DSG was noted among participants in both groups for elevations of Grade 1 and 2 ALT/AST and Grade 1 lipase. A comprehensive review of the imbalance showed these elevations were generally transient, asymptomatic, and not associated with clinical AEs. Nearly all resolved with continued therapy, and rarely led to discontinuation. Most were not attributed to study drug and not considered clinically significant [Ref. 5.3.5.1: P024MK1439A: 12.3.2.2.1]. The incidence of Grade 1 bilirubin elevations among participants in both groups was low and comparable during the base trial and there were no concurrent ALT/AST elevations [Ref. 5.3.5.1: P024MK1439A: Table 12-10] [Ref. 5.3.5.1: P024MK1439A: Table 14.3-53]. No participant in either treatment group met the criteria for DILI [Ref. 5.3.5.1: P024MK1439A: 16.2.8].

Table 2.5-switch48wk: 8
Change From Baseline in Fasting Lipids at Study Week 24
Subjects in Ritonavir-boosted PI Strata; Base Study

Treatment	N	Baseline Mean	Change from Baseline: Mean Change (SD)	Change from Baseline: 95% CI†	Difference Estimates (ISG - DSG): Difference‡ 95% CI	Difference Estimates (ISG - DSG): 2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
ISG	256	108.82	-16.54 (23.10)	(-19.38, -13.70)	-14.65 (-18.92, -10.38)	<0.0001
DSG	125	109.00	-1.94 (25.74)	(-6.50, 2.61)		
Fasting Non-HDL Cholesterol (mg/dL)						
ISG	266	139.14	-24.74 (29.26)	(-28.27, -21.20)	-23.03 (-28.00, -18.05)	<0.0001
DSG	133	137.99	-1.31 (28.45)	(-6.19, 3.57)		
Fasting Cholesterol (mg/dL)						
ISG	266	188.66	-26.21 (30.26)	(-29.87, -22.56)	-25.80 (-30.93, -20.67)	nps*
DSG	133	186.41	0.51 (28.68)	(-4.41, 5.43)		
Fasting Triglyceride (mg/dL)						
ISG	266	155.83	-43.15 (99.18)	(-55.12, -31.18)	-42.90 (-59.13, -26.67)	nps*
DSG	133	152.85	0.94 (114.56)	(-18.71, 20.59)		
Fasting HDL Cholesterol (mg/dL)						
ISG	266	49.52	-1.48 (9.85)	(-2.67, -0.29)	-2.99 (-4.80, -1.18)	nps*
DSG	133	48.41	1.82 (8.34)	(0.39, 3.25)		
Total Cholesterol to HDL Ratio						
ISG	266	4.07	-0.44 (1.09)	(-0.57, -0.30)	-0.33 (-0.57, -0.08)	nps*
DSG	133	4.59	-0.57 (5.50)	(-1.52, 0.37)		

The Last Observation Carried Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.

† Within group 95% CIs were based on t-distribution.

‡ The 95% CIs and 2-sided p-value for treatment difference were calculated from an ANCOVA model with terms for baseline lipid level, use of lipid-lowering therapy at Study Day 1 and treatment.

*Not pre-specified for statistical testing

Analysis of post-baseline data includes laboratory records collected after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.

N = Number of subjects whose regimen at screening is a ritonavir-boosted PI and with baseline and at least one postbaseline test result.

Source: [P024MK1439A: adam-adsl; adlpd]

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5.5 Safety in Special Groups and Situations in P024

5.5.1 Intrinsic Factors

In P024, clinical and laboratory AEs were reviewed for participant subgroups based on age, gender, race, and ethnicity, hepatitis B and/or C infection status, and baseline $CD4^+$ T-cell level through Study Week 24. Overall, AEs and laboratory abnormality profiles were generally comparable in participant subgroups based on gender, race/ethnicity, region, and age (<65 or ≥65 years) [Sec. 2.7.4-switch48wk: 2.1.4]. Subgroup analyses did not identify clinically significant differences in the safety profile of DOR/3TC/TDF between subgroups through Week 24. In all cases, differences between treatment groups were generally minimal within baseline subgroups. Where sufficient sample sizes were present for meaningful comparison, the incidences of drug-related AEs and discontinuations due to AEs was higher among participants in the ISG than in the DSG, regardless of baseline subgroup categorization. Small sample sizes for participants ≥65 years, females, some race categories, and participants with chronic hepatitis B and/or C infection should be considered in the analysis and interpretation of data in these subgroups.

5.5.2 Extrinsic Factors

Specific analysis of extrinsic factors was not applicable.

5.5.3 Overdose

In P024, there were no reports of overdose of the DOR/3TC/TDF regimen.

5.5.4 Use in Pregnancy and Lactation

Females who were pregnant and/or lactating were excluded from enrollment into any of the clinical trials. No participants became pregnant during the trial period. The use of DOR and DOR/3TC/TDF in pregnancy and lactation is not recommended. Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission.

5.5.5 Applicability of Safety Results to Single Agent Doravirine

In the DOR clinical development program, no unique safety issues have emerged for DOR either in trials in treatment-naïve study participants with different NRTI background regimens or in participants who were virologically suppressed and received DOR/3TC/TDF. The Applicant considers that the safety results from P024 support the indication for switching to DOR, either as a single entity in combination with other antiretroviral agents or as DOR/3TC/TDF. In the treatment-naïve trials, P018 and P021, DOR in combination with ABC/3TC, FTC/TDF, or 3TC/TDF demonstrated similar safety profiles at the primary endpoint of each study at Week 48. The safety profile for DOR/3TC/TDF in the switch population through 48 weeks in the ISG and from 24-48 weeks in the DSG was also similar to what was observed in the treatment-naïve population with no additional safety findings. The safety findings in the P024 trial support use of single agent DOR used in combination with an NRTI regimen in a switch setting.

5.6 Limitations of the Safety Database

No specific safety issues were identified that would preclude the approval of DOR/3TC/TDF and/or DOR for use in a switch setting. However, the following may be considered limitations/missing information of the safety database in this supplemental application with no/insufficient safety data for the following populations: participants above the age of 65; and pregnant or nursing women. Although data are available through Week 48 in the switch population, the safety profile is not expected to be different from the treatment-naïve trial in which 96 week data are available. Participants in P024 will continue treatment with DOR/3TC/TDF beyond Week 48 through trial extensions. Additional safety findings from this follow-up will be provided in a safety update report.

5.6.1 Risk Management Plan

A Risk Management Plan is provided in this supplemental application, as applicable.

All published clinical literature about DOR/3TC/TDF was reviewed for consistency with the safety findings reported in this marketing application. References are provided in Module 5 [Ref. 5.4: 050XCL].

5.7 Safety Conclusions for Doravirine/Lamivudine/Tenofovir disoproxil fumarate

DOR/3TC/TDF was generally well tolerated in 656 virologically suppressed participants who received DOR/3TC/TDF in P024 for at least 24 weeks and up to 48 weeks.

Based on the results from this study, the following safety conclusions can be made:

- A switch to DOR/3TC/TDF in virologically suppressed individuals is generally well tolerated, with a favorable safety profile when compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by review of the accumulated safety data for 24 weeks.
- A switch to DOR/3TC/TDF is superior to the continuation of a ritonavir-boosted PI regimen for 24 weeks, as assessed by the mean change from baseline in fasting LDL-C and non-HDL-C at Study Week 24.

The following key safety results were also observed:

- Participants had a similar safety profile following their switch to DOR/3TC/TDF, regardless of whether the switch was immediate (ISG: Study Weeks 0-24) or delayed (DSG: Study Weeks 24-48).

- Participants who switched to DOR/3TC/TDF immediately had a higher incidence of AEs and drug-related AEs through Study Weeks 0-24 when compared with the incidence of these events among participants who remained on their baseline regimen through Study Weeks 0-24 in this open-label trial. The majority of the reported AEs were of mild to moderate intensity and considered by the investigator to be unrelated to study medication.

Compared to continuing a ritonavir-boosted, PI-based baseline regimen, DOR/3TC/TDF demonstrated a superior lipid profile and a favorable safety profile. These findings provide further support for switching to a DOR-containing regimen in this patient population.

6 BENEFITS AND RISKS CONCLUSIONS

DOR and DOR/3TC/TDF have positive benefit/risk profiles that support the recommended dose regimens.

6.1 Therapeutic Context

6.1.1 Disease or Condition

Background information regarding HIV-1 infection can be found in [Sec. 2.5.1.4-switch48wk] of this document. Lifelong cART is needed for HIV-1-infected patients and as people living with HIV age, they commonly develop multiple co-morbidities and often require different co-medications that may limit their ability to take certain antiretroviral medications.

6.1.2 Current Therapies

Background information regarding the current HIV-1 therapies can be found in [Sec. 2.5.1.4-switch48wk] of this document.

6.1.3 Medical Need

There continues to be a need for HIV-1 therapy options that are efficacious, safe, well tolerated, convenient for patients, with a distinct resistance profile, and without significant food effect or drug-drug interactions. The profile of DOR addresses many of these concerns by providing another efficacious and safe treatment option that allows patients who are virologically suppressed on other regimens to switch to a DOR regimen by potentially reducing pill burden, mitigating drug-drug interactions, and eliminating food requirements.

6.2 Benefits

Overall, the clinical development program demonstrates favorable benefits of treatment with DOR and DOR/3TC/TDF in HIV-1-infected adults that are supported by the clinical trial data:

A switch to DOR/3TC/TDF was efficacious in virologically suppressed participants compared to continuation of a baseline regimen consisting of either a boosted PI, EVG, or NNRTI + 2 NRTIs. Specifically:

- The antiretroviral response among those who switched to DOR/3TC/TDF is non-inferior to the response among those who continued the baseline regimen for 24 weeks as measured by:
  - the proportion of participants with HIV-1 RNA <50 copies/mL at Study Week 48 in the ISG and at Study Week 24 in the DSG;
  - the proportion of participants with HIV-1 RNA <50 copies/mL at Study Week 24 in each group; and
  - the proportion of participants with HIV-1 RNA ≥50 copies/mL at Study Week 24 in each group;
- The antiretroviral response among those who switched to DOR/3TC/TDF was comparable to the response among those who continued the baseline regimen for 24 weeks as measured by:
  - the proportion of participants with HIV-1 RNA <40 copies/mL at Study Week 48 in the ISG and at Study Week 24 in the DSG;
  - the proportion of participants with HIV-1 RNA <40 copies/mL at Study Week 24 in each group;
  - changes in $CD4^+$ T-cell counts from baseline at Study Week 48 in the ISG and at Study Week 24 in the DSG; and
  - changes in $CD4^+$ T-cell counts from baseline at Study Week 24 in each group.
- Consistent efficacy was observed across prespecified demographic and prognostic factors.

In addition, DOR/3TC/TDF demonstrated a favorable safety profile with:

- A superior lipid profile among individuals who switched as compared to the profile in those who continued a ritonavir-boosted PI-based regimen, as assessed by the mean change from baseline in fasting LDL-C and non-HDL-C at Study Week 24 in each group; and
- A favorable safety profile over 24 weeks of treatment among individuals who switched when compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen as assessed by the accumulated safety data by Week 24 (including few discontinuations due to AEs).

DOR/3TC/TDF showed a favorable resistance profile with the following aspects:

- Low rates of PDVF and no treatment emergent resistance observed for DOR in either treatment group through Week 48 in P024.

- None of the 24 participants (11 ISG [Day 1], 13 DSG [Week 24]) on PI and InSTI regimens who had virus with baseline NNRTI mutations (RT K103N, G190A, or Y181C) experienced virologic failure through Week 48 or at the time of discontinuation.

Overall, based on the P024 trial and other DOR trials, DOR and DOR/3TC/TDF are efficacious, generally safe, well tolerated and constitute important treatment options for patients given the following characteristics:

- Favorable drug-drug interaction profile with DOR not a perpetrator of clinically significant drug-drug interactions.
  - No dose adjustment necessary for patients with mild, moderate or severe renal or mild or moderate hepatic impairment.
  - No interaction with proton pump inhibitors and other gastric acid-modifying agents and cation containing antacids.

- Available as a single-entity or FDC of DOR/3TC/TDF for QD dosing without regard to food.

6.3 Risks

Overall, the clinical development program demonstrates a favorable safety and tolerability profile for DOR and DOR/3TC/TDF, and no specific safety issues were identified. The data support the use of DOR and DOR/3TC/TDF for the treatment of HIV-1 infection in both treatment-naïve and virologically suppressed switch populations. However, it is acknowledged that the safety database has the following limitations:

- Limited safety data beyond 48 weeks in the switch population.

- Participants who switched to DOR/3TC/TDF immediately had a higher incidence of AEs and drug-related AEs through Study Weeks 0-24 when compared with the incidence of these events among participants who remained on their baseline regimen through Study Weeks 0-24 in this open-label trial. The open-label switch study design may have contributed to the difference in reported AE rates. The higher reported rates of AEs and drug-related AEs in the ISG are not unexpected since these participants switched to a new regimen, whereas participants in the DSG continued on their baseline regimen, which they were on for at least 6 months prior to study entry. Similar findings have been observed in other studies comparing a switch to a new drug with continuing a baseline regimen [Ref. 5.4: 0529CQ], [Ref. 5.4: 0528SS], [Ref. 5.4: 0528SR]. The majority of the reported AEs were of mild to moderate intensity and considered by the investigator to be unrelated to study medication.

- No clinical data in participants who are pregnant/lactating.

- Minimal efficacy data in participants ≥65 years of age.

Additionally, the efficacy database has the following limitations:

- Limited information regarding durability of response.

6.4 Benefit-risk Assessment

DOR/3TC/TDF has been shown to be efficacious in a virologically suppressed HIV-1-infected population and both DOR and DOR/3TC/TDF have been shown to be efficacious in the treatment-naïve population. Safety analysis of DOR and DOR/3TC/TDF demonstrates that they are generally well tolerated and have a favorable safety profile with no untoward risks identified. The data from the switch study are consistent with the data submitted for the original marketing applications. Risks have been extensively analyzed and were found to be limited and can be safely managed by clinicians.

A table summarizing the favorable and unfavorable effects in the Phase 3 trial for P024 is provided in [Table 2.5-switch48wk: 9].

The robust efficacy and favorable safety and resistance profile for DOR and DOR/3TC/TDF to date show sufficient benefit to allow switching from a stable antiretroviral regimen to a DOR-containing regimen as clinically appropriate.

6.5 Appendix

Table 2.5-switch48wk: 9
Summary of Favorable and Unfavorable Effects in DOR/3TC/TDF Phase 3 Trial (P024) in this Supplemental Application

Effect	Short Description	Unit	DOR/3TC/TDF QD ISG at Study Week 24	DOR/3TC/TDF QD ISG at Study Week 48	Baseline Regimen DSG at Study Week 24 n/N (%)	Uncertainties / Strength of evidence	References
Favorable							
Proportion of participants with HIV-1 RNA <50 copies/mL (Snapshot)	Robust and non-inferior efficacy for an immediate switch to DOR/3TC/TDF as compared to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks in the Phase 3 trial	%	93.7	90.8	94.6		[Table 2.5-switch48wk: 4, Table 2.5-SWITCH48WK: 5]
Proportion of participants with HIV-1 RNA <40 copies/mL (Snapshot)	Robust efficacy response in P024	%	92.8	89.7	93.3		[Table 2.5-switch48wk: 4, Table 2.5-switch48wk: 5]
Proportion of participants with HIV-1 RNA ≥50 copies/mL (Snapshot)	Robust and non-inferior efficacy for an immediate switch to DOR/3TC/TDF as compared to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks in the Phase 3 trial	%	1.8	1.6	1.8		[Table 2.5-switch48wk: 4, Table 2.5-switch48wk: 5]
Increase in $CD4^+$ T-cell counts from baseline (OF)	Immunological response in P024		5.1	13.9	18		[Table 2.5-switch48wk: 4, Table 2.5-switch48wk: 5]
Change in baseline fasting lipids at Week 48	More favorable lipid profile and superior LDL-C and non-HDL-C profile for an immediate switch to DOR/3TC/TDF as compared to continuation of a ritonavir-boosted PI-based for 24 weeks:						[Table 2.5-switch48wk: 8]
	Fasting LDL Cholesterol	mg/dL	-16.54		-1.94		
	Fasting non-HDL Cholesterol	mg/dL	-24.74		-1.31		
	Fasting Cholesterol	mg/dL	-26.21		0.51		
	Fasting Triglyceride	mg/dL	-43.15		0.94		
	Fasting HDL Cholesterol	mg/dL	-1.48		1.82		

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Effect	Short Description	Unit	DOR/3TC/TDF QD ISG at Study Week 24	DOR/3TC/TDF QD ISG at Study Week 48	Baseline Regimen DSG at Study Week 24 n/N (%)	Uncertainties / Strength of evidence	References
Unfavorable							
Rate of AEs and drug-related AEs	A numerically higher percentage of participants in the ISG reported AEs, including drug-related AEs, than in the DSG						[Table 2.5-switch48wk: 6]
	AEs	%	68.9		52.5		[Table 2.5-switch48wk: 6]
	Drug-related AEs	%	19.5		2.2		[Table 2.5-switch48wk: 6]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
cART	combination antiretroviral therapy
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
CSR	clinical study report
DOR	doravirine
DRV; DRV+r	darunavir; darunavir in combination with ritonavir
EFV	efavirenz
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
HIV-1	human immunodeficiency virus type 1
InSTI	integrase strand-transfer inhibitor
MAA	marketing authorization application
MSP	Main Safety Pool
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleos(t)ide reverse transcriptase inhibitor
NVP	nevirapine
OF	observed failure (approach to missing data)
PDVF	protocol-defined virologic failure
PI	protease inhibitor
QD	once daily
RPV	rilpivirine
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SSP	Special Safety Pool
TDF	tenofovir disoproxil fumarate

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Pharmacologic Classes

Doravirine (DOR; also known as MK-1439) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) active against HIV-1 infection.

DOR is available as a single agent (PIFELTRO™) and as a fixed-dose combination (FDC) (DOR/3TC/TDF) with the nucleoside analogue reverse transcriptase inhibitors (NRTIs) lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) (DOR/3TC/TDF; also known as MK-1439A).

1.2 Approved Indications and Purpose of This Supplemental Application

DOR, as a single agent used in combination with other antiretroviral agents, or as part of the FDC DOR/3TC/TDF, has been approved in the United States, Canada, and the European Union for the treatment of HIV-1 infection in adults. The recommended dosage of DOR is one 100-mg tablet taken orally QD with or without food. The recommended dosage of DOR/3TC/TDF is one tablet (containing 100 mg of DOR, 300 mg of 3TC, and 300 mg TDF) taken orally QD with or without food.

The objective of this Week 96 Treatment-Naïve Supplemental Application is to provide 96-week data on the efficacy and safety of DOR, in combination with other antiretroviral agents or as DOR/3TC/TDF, in HIV-1-infected treatment-naïve adult patients. The data within this Supplemental Application, through 96 weeks of treatment, provide the basis for updates to the 48-week data in the clinical efficacy and safety sections of the Prescribing Information. No revision is proposed to the approved indication.

1.3 Chemical and Pharmaceutical Properties

The formulation for the single-agent DOR drug product is a film-coated tablet (dose strength of 100 mg DOR). The tablet is composed of [redacted] of DOR with hypromellose acetate succinate. [redacted] is further processed by [redacted] with other excipients and blending with [redacted] excipients prior to compression. Following compression, the final market image tablets are film-coated.

The formulation for the DOR/3TC/TDF drug product is a bilayer, film-coated tablet (dose strength of 100 mg/300 mg/300 mg DOR/3TC/TDF; 300 mg of TDF is equivalent to 245 mg of tenofovir disoproxil). One layer consists of a DOR [redacted], and the other layer consists of a 3TC and TDF granulation. The DOR [redacted] contains [redacted] of DOR with hypromellose acetate succinate that is then [redacted] with other excipients. The 3TC and TDF granulation is manufactured by a roller-compaction process with excipients. DOR [redacted] and 3TC/TDF granulation are compressed into bilayer tablets, and the final market image tablets are then film-coated.

1.4 Scientific Background and Introduction

Epidemiology and Public Health Burden of HIV-1 Infection

HIV/AIDS is associated with significant morbidity and mortality. The Joint United Nations Programme on HIV and AIDS (UNAIDS) reported that an estimated 36.9 million people around the world were living with HIV-1 infection in 2017 [Ref. 5.4: 04ZQBB]; approximately 1.8 million adults and children were newly infected in 2017, and an estimated 940,000 died from AIDS-related illnesses that year. The majority of new infections and deaths (65% and 70%, respectively) occurred in sub-Saharan Africa. Approximately 2.2 million adults and children were living with HIV in western and central Europe and North America in 2017, with approximately 70,000 being newly infected that year.

To address this global public health challenge, UNAIDS has led global efforts to establish new targets for HIV treatment. Modeling suggests that if these targets (the "90-90-90" goals for 2020) are achieved, the HIV/AIDS epidemic can be globally controlled by 2030, resulting in profound health and economic benefits.

Current HIV-1 Treatment Landscape

Currently, more than 30 antiretroviral drugs are commercially available worldwide for use in combination antiretroviral therapy (cART) for the treatment of HIV-1 infection. These drugs inhibit various stages of the HIV-1 lifecycle and belong to 7 classes: nucleos(t)ide reverse transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors (PIs), integrase strand-transfer inhibitors (InSTIs), attachment inhibitors, co-receptor antagonists, and fusion inhibitors. Treatment with cART (typically a combination of 3 antiretroviral drugs) has been shown to be effective in both reducing plasma HIV-1 RNA to a level below detection and restoring immune system function with an increase in $CD4^+$ T-cells.

- The US Department of Health and Human Services HIV-1 Treatment Guideline (2018) [Ref. 5.4: 053CRN] recommends a regimen of an InSTI in combination with 2 NRTIs for most patients with HIV-1; other regimens, including a boosted protease inhibitor (PI) or an NNRTI, may be preferred in certain clinical situations.
- The International Antiviral Society-USA recommends an InSTI plus 2 NRTIs as initial regimens for most patients; other effective regimens include NNRTIs or boosted PIs with 2 NRTIs (2018 recommendations [Ref. 5.4: 0508DT]).
- Other treatment guidelines such as the World Health Organization (2018) [Ref. 5.4: 05084L]) and the European AIDS Clinical Society (EACS) (2017) [Ref. 5.4: 04MZSY]) include the NNRTI class (including efavirenz [EFV] and rilpivirine [RPV]) as a recommended regimen in addition to InSTI- and PI-based regimens.

Rationale for DOR

As a class, NNRTIs have been commercially available since 1996 and are highly efficacious against HIV-1 in treatment-naïve individuals [Ref. 5.4: 04PB3J]. However, most NNRTIs have various tolerability, safety, and efficacy limitations. In addition, given the need for lifelong treatment and the increased frequency of co-morbidities as HIV-1-infected adults age, there is a need for new NNRTIs such as DOR that are efficacious, safe, and well tolerated and allow convenient dosing, lack significant drug-drug interactions, and have resistance profiles distinct from that of other NNRTIs.

Efavirenz and RPV are commonly prescribed in the US and in the EU. However, EFV is associated with treatment-limiting neuropsychiatric adverse events (AEs) [Ref. 5.4: 04PB39] and the efficacy of RPV is suboptimal in individuals with baseline HIV-1 RNA >100,000 copies/mL or $CD4^+$ T-cell counts <200 cells/mm^3 [Ref. 5.4: 04LK3B]. Etravirine and nevirapine (NVP) are less commonly prescribed, primarily due to specific side effects, lower efficacy, and/or a more complicated dosing schedule. Management of serum lipid levels is particularly important in HIV-1-infected individuals due to the increased cardiovascular risk inherent to HIV-1 infection. Some marketed NNRTIs, however, including EFV, are associated with dyslipidemia. Viral drug resistance is another limitation of many NNRTIs. Because a single viral mutation may confer resistance against one or several currently available NNRTIs, there is an ongoing need to continue development of NNRTIs with differing resistance profiles.

DOR addresses many of the limitations of other NNRTIs. As presented in the original marketing applications, DOR and DOR/3TC/TDF provide robust efficacy, a favorable safety profile, and convenient treatment options for HIV-1-infected adults. The data provided in this Supplemental Application demonstrate the durable efficacy of DOR and DOR/3TC/TDF through 96 weeks, the low rate of development of viral drug resistance, and maintenance of a favorable safety profile. These data support an update of the current Prescribing Information to reflect the efficacy and safety results for DOR and DOR/3TC/TDF through 96 weeks.

1.5 Overview of the Clinical Development Program

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials, including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.

The clinical development program for DOR included parallel development of DOR as a single agent to be used in combination with other antiretroviral agents and as an FDC (DOR/3TC/TDF) for the treatment of HIV-1 infection in adults aged 18 years and older.

The clinical development program for DOR and DOR/3TC/TDF includes 36 completed Phase 1 trials, 1 completed Phase 2b trial (P007), and 2 ongoing Phase 3 trials (P018, P021) that contributed data to the Original Application. Two additional Phase 2 trials (P028, P030) and 1 Phase 3 trial (P024) are ongoing [Sec. 2.7.3-trtmtnve96wk: 1.2].

Consistent with the formal guidance received from the FDA and the EMA CHMP, the clinical development program for DOR and DOR/3TC/TDF proceeded as follows:

1. Demonstration of in vivo HIV-1 antiretroviral activity (P005).

2. Selection of the clinical dose in Phase 2b trial P007, a multicenter, double-blind, randomized, dose-ranging trial in 340 HIV-1-infected, treatment-naïve adults: this trial was conducted to support dose selection for subsequent Phase 2 and 3 trials and to provide 96-week efficacy and safety data for the selected dose. Assessment of safety included an evaluation of DOR compared with EFV with respect to the proportion of participants with CNS events at Weeks 8 and 24.

3. Demonstration of efficacy and safety in the pivotal Phase 3 trials P018 (DRIVE-FORWARD) and P021 (DRIVE-AHEAD) in HIV-1-infected treatment-naïve adults. Both trials were designed to evaluate the non-inferior efficacy of DOR 100 mg at 48 weeks and to provide efficacy and safety data through 96 weeks of treatment, as well as additional longer-term safety data through open-label study extensions (summarized in [Table 2.5-trtmtnve96wk: 1].

    - In P018, DOR was evaluated as a single agent compared with the PI darunavir boosted with ritonavir (DRV+r). DOR was used in combination with either emtricitabine (FTC)/TDF (administered in the trial as TRUVADA™) or abacavir (ABC) plus 3TC (ABC/3TC; administered as either EPZICOM™ or KIVEXA™), as selected by the investigator.

    - In P021, DOR was evaluated as the fixed-dose combination DOR/3TC/TDF compared with the EFV-based regimen EFV/FTC/TDF (administered as ATRIPLA™).

4. Additional characterization of the clinical profile of DOR in trials P024, P028, and P030; each of these is ongoing (enrollment complete) at the time of this supplemental application:

    - P028 is a Phase 2 trial in which 86 HIV-1-infected participants, virologically suppressed on EFV/FTC/TDF and experiencing EFV-associated central nervous system (CNS) toxicity, were switched to DOR/3TC/TDF to assess whether CNS toxicities resolve or improve.

    - P030 is a Phase 2 trial in which 10 HIV-1-infected, treatment-naïve participants with the most commonly transmitted NNRTI resistance mutations (specifically, RT K103N, Y181C, or G190A) are treated with open-label DOR/3TC/TDF to assess antiretroviral activity.

    - P024 is a Phase 3 trial in which 673 HIV-1-infected participants, virologically suppressed on regimens that included a ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir), cobicistat-boosted elvitegravir, or an NNRTI (specifically, EFV, nevirapine or RPV), were switched to DOR/3TC/TDF to assess antiretroviral activity. These data have been submitted in a separate supplemental application.

Table 2.5-trtmtnve96wk: 1

Summary of the Phase 3 Clinical Trials Supporting the Current Supplemental Application

Protocol Phase Location	Population	Status	Primary Endpoint	Key Secondary Endpoints	Design and Duration	DOR Regimen	N Treated	Comparator	N Treated
018 Phase 3 Global	HIV-1-infected, treatment-naïve adults (18 years of age or older) with HIV-1 RNA of ≥1,000 copies/mL at screening	Base study (through Week 96) complete; open-label extension ongoing.	Proportion of participants achieving HIV-1 RNA <50 copies/mL at Week 48; associated key endpoint: threshold of <40 copies/mL.	Proportions of participants with HIV-1 RNA <50 copies/mL and <40 copies/mL at Week 96. Change from baseline in $CD4^+$ T-cell count at Week 48 and at Week 96.	Multicenter, double-blind, randomized, active-controlled trial in HIV-1-infected, treatment-naïve men and women. Two sequential open-label extensions ongoing; each lasts ~96 weeks.	DOR 100 mg QD	383	DRV+r	383
021 Phase 3 Global	HIV-1-infected, treatment-naïve adults (18 years of age or older) with HIV-1 RNA of ≥1,000 copies/mL at screening	Base study (through Week 96) complete; open-label extension ongoing.	Proportion of participants achieving HIV-1 RNA <50 copies/mL at Week 48; associated key endpoint: threshold of <40 copies/mL. Proportion of participants with neuropsychiatric AEs in the following categories by Week 48: - Dizziness - Sleep disorders and disturbances - Altered sensorium.	Proportions of participants with HIV-1 RNA <50 copies/mL and <40 copies/mL at Week 96. Change from baseline in $CD4^+$ T-cell count at Week 48 and at Week 96.	Multicenter, double-blind, randomized, active-controlled trial in HIV-1-infected, treatment-naïve men and women. Two sequential open-label extensions ongoing; each lasts ~96 weeks.	DOR/3TC/TDF QD	364	EFV/FTC/TDF	364

Abbreviations: 3TC = lamivudine; DOR = doravirine; DRV = darunavir; EFV = efavirenz; FTC = emtricitabine; r = ritonavir (as used to boost darunavir); TDF = tenofovir disoproxil fumarate.

Source: [Ref. 5.3.5.1: P018MK1439], [Ref. 5.3.5.1: P021MK1439A]

1.6 Regulatory Guidance and Advice

Regulatory agency advice was obtained at key points during the development program. Formal guidance received from the FDA and the EMA is summarized below.

1.6.1 FDA Regulatory Interactions

An [redacted] was held with the FDA on [redacted] for DOR and DOR/3TC/TDF. The FDA agreed with [redacted] On [redacted], the FDA agreed with the Applicant's proposal [redacted] full description of FDA advice obtained during development of P018 and P021 is found in the original application [Sec. 2.5-trtmtnve48wk: 1.6].

On [redacted], Merck informed the Agency of its plan to submit supplemental applications to the DOR and DOR/3TC/TDF NDAs to update the Prescribing Information to include a switch indication based on safety and efficacy data through Week 48 from Protocol 024, to submit a supplement to the DOR NDA to update the Prescribing Information to include Week 96 safety and efficacy data from Protocols 018 and 021, and to submit a supplement to the DOR/3TC/TDF NDA to update the Prescribing Information to include Week 96 data from Protocol 021. Merck proposed to submit a single Safety Update Report (SUR) in support of both Switch and Week 96 supplemental applications, given that these applications would be submitted within 1 to 2 months of each other. The Agency agreed with this proposal on [redacted].

1.6.2 European Regulatory Interactions

Prior to submission of the original MAA, CHMP [redacted] was obtained for DOR and DOR/3TC/TDF on [redacted]. In summary, the CHMP agreed with [redacted] In [redacted] CHMP [redacted] obtained on [redacted], the CHMP maintained its recommendation that [redacted] A full description of CHMP advice obtained during development of P018 and P021 is found in the Original Application [Sec. 2.5-trtmtnve48wk: 1.6].

During the CHMP's assessment of the original MAA, the Applicant was requested to provide the Week 96 data from P018 and P021, as these data had become available during the course

of the review. The Applicant provided the Week 96 data for P018 with the Day 120 responses, and the Week 96 data for P021 with the Day 180 responses, together with the P018 Week 96 CSR. The SmPC was updated, at the time of the Day 180 Responses, with Week 96 efficacy and safety data from both studies provided therein and assessed by CHMP. The P021 Week 96 CSR is being provided with this submission.

2 OVERVIEW OF BIOPHARMACEUTICS

No new biopharmaceutics information has been obtained since the original marketing applications were submitted. The biopharmaceutics program included:

- A bioequivalence trial (P039) evaluating the pharmacokinetics (PK) of the uncoated (Phase 3) formulation and of the coated DOR final market image tablet;
- Two biopharmaceutics trials supporting development of DOR/3TC/TDF conducted with the DOR/3TC/TDF final market image (P026 and P029); and
- Two trials evaluating the effect of food on DOR (P037) and DOR/3TC/TDF (P029) PK.

3 OVERVIEW OF CLINICAL PHARMACOLOGY

No new clinical pharmacology information has been obtained since the original marketing applications were submitted. A total of 36 Phase 1 trials were conducted to assess the safety, tolerability, PK (including drug-drug interactions and the effect of intrinsic and extrinsic factors on PK), biopharmaceutics, and pharmacodynamics of DOR and DOR/3TC/TDF.

The clinical pharmacology trials were conducted primarily with DOR, administered as the single-agent tablet. Following administration of the DOR/3TC/TDF final market image, the DOR, 3TC, and TDF components demonstrated similar PK compared with coadministration of each component administered as a single agent in a relative bioavailability trial (P026). Therefore, the clinical pharmacology profile for each individual component administered as a single agent is applicable to the FDC of DOR/3TC/TDF.

4 OVERVIEW OF EFFICACY

Data from the pivotal Phase 3 trials (P018 and P021) and from the Phase 2 trial (P007), presented in the original application, demonstrate that DOR 100 mg QD, as either the single agent in combination with 2 NRTIs or as DOR/3TC/TDF, has potent and durable efficacy with respect to viral suppression and increase in $CD4^+$ T-cell count in HIV-1-infected, treatment-naïve adults. This efficacy was shown in P018 and P021 to be non-inferior to that of 2 well-established comparators – one each from the NNRTI class (EFV) and from the PI class (DRV+r) (both in combination with 2 NRTIs) – through 48 weeks of treatment. Results through 96 weeks of treatment with DOR (in combination with 2 NRTIs) or with DOR/3TC/TDF, presented in this supplemental application, support the non-inferiority previously established at Week 48 with respect to each of these comparators.

4.1 Summary of Approach to Assessment of Efficacy

This overview summarizes efficacy data from 96 weeks of treatment in the individual Phase 3 trials (P018 and P021) and in the pooled data from those trials. Supportive efficacy data from 96 weeks of treatment in the Phase 2b trial (P007) were provided in the original application.

4.2 Relevance of the Patient Population

The participants in the Phase 3 trials are representative of the HIV-1-infected population, thus supporting the proposed indication in patients from diverse geographic and ethnic backgrounds. Specifically, participants in these trials had a broad range of baseline $CD4^+$ T-cell counts, a broad range of baseline HIV-1 RNA levels, and presented with and without a history of AIDS and with and without hepatitis B/C co-infections.

4.3 Methods for Efficacy Assessment

4.3.1 Clinical Trial Design

The study designs of the pivotal Phase 3 trials, P018 and P021, are described in [Sec. 2.7.3-trtmtnve96wk: 2.1.1] and in [Sec. 2.7.3-trtmtnve96wk: 2.2.1].

4.3.2 Clinical Efficacy Endpoints

The key efficacy endpoint in the P018 and P021 trials presented in this summary is virologic efficacy at Week 96, as measured by proportions of participants with HIV-1 RNA <50 copies/mL. Additional endpoints included proportions of participants with HIV-1 RNA <40 and <200 copies/mL at Week 96. Of note, proportions of participants with HIV-1 RNA <40 copies/mL is the EMA primary endpoint.

Immunologic efficacy was assessed by the change in $CD4^+$ T-cell count from baseline to various time points through Week 96. Additional evaluations included assessment of protocol-defined virologic failure (PDVF), time to loss of virologic response (TLOVR), and development of viral drug resistance.

4.3.3 Statistical Methodology

The statistical approach to analyzing the efficacy of DOR and DOR/3TC/TDF in this Supplemental Application is consistent with current scientific and regulatory guidelines; details are provided in [Sec. 2.7.3-trtmtnve96wk: 1.4.2] and summarized below.

Analysis Population

Efficacy analyses were based on the Full Analysis Set (FAS) for the individual P018 and P021 trials and for the pooled data. The FAS consists of all participants who received at least 1 dose of study treatment and had baseline data (for those analyses that required baseline data). Participants are included in the treatment group to which they were randomized.

Data from the Phase 3 trials were pooled because P018 and P021 are similar in design and have the same efficacy endpoints, definition of PDVF, and approach to handling participants with PDVF.

Missing Data Approaches

Two approaches were used to address missing values in the individual Phase 3 trials (P018 and P021) as well as the pooled data:

- FDA Snapshot approach: all participants with missing data were considered to be failures regardless of reason.
- Observed Failure (OF) approach: participants who prematurely discontinued assigned treatment due to lack of efficacy were considered to be failures thereafter; participants with other types of missing data were excluded from the analysis.

The primary approach for the analysis of the proportion of participants achieving virologic suppression (HIV-1 RNA <40 copies/mL, <50 copies/mL, and <200 copies/mL) was the FDA snapshot approach. The OF approach was applied as a sensitivity analysis.

Immunologic efficacy and virologic efficacy by prognostic and demographic factors were analyzed using the OF approach.

4.4 Efficacy Results

4.4.1 P018 Efficacy Results

A total of 769 participants were randomized 1:1 in P018 to receive DOR or DRV+r together with either FTC/TDF or ABC/3TC. A total of 766 participants (383 in each treatment group) received at least 1 dose of study medication.

Efficacy Summary at Week 96

At Week 96, antiretroviral efficacy in the DOR treatment group was higher than that in the DRV+r treatment group with regard to proportion of participants with HIV-1 RNA <50 copies/mL, using the FDA snapshot approach; this finding supports the non-inferiority of DOR to DRV+r previously established at Week 48. Specifically, 73.1% and 66.0% of participants in the DOR and DRV+r treatment groups, respectively, achieved HIV-1 RNA <50 copies/mL, with an estimated treatment difference of 7.1% (95% CI: 0.5, 13.7) [Table 2.5-trtmtnve96wk: 2].

Results for treatment-group differences in proportion of participants achieving HIV-1 RNA <40 copies/mL were similar to those for the endpoint of HIV-1 RNA <50 copies/mL. Specifically, 72.0% and 64.4% of participants in the DOR and DRV+r treatment groups, respectively, achieved HIV-1 RNA <40 copies/mL using the FDA snapshot approach, with an estimated treatment difference of 7.6% (95% CI: 1.0, 14.2) [Table 2.5-trtmtnve96wk: 2].

Comparable proportions of participants in each treatment group achieved HIV-1 RNA <50 copies/mL regardless of whether screening plasma HIV-1 RNA was ≤100,000 or >100,000 copies/mL and regardless of whether background therapy was FTC/TDF or ABC/3TC [Ref. 5.3.5.1: P018MK1439: 11.1.3.1].

Analysis of the change from baseline in $CD4^+$ T-cell count produced comparable results for both treatment groups, with a mean increase from baseline at Week 96 of 224 cells/mm^3 in the DOR group and 207 cells/mm^3 in the DRV+r group [Table 2.5-trtmtnve96wk: 2].

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Table 2.5-trtmtnve96wk: 2

P018: Efficacy Analysis at Week 96
Base Study (Double Blind)

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (Doravirine - Darunavir)[‡]	
		Doravirine 100 mg QD n/N (%)	Darunavir 800 mg + ritonavir 100 mg QD n/N (%)	Estimated Difference	95% CI
Primary					
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	277/379 (73.1)	248/376 (66.0)	7.082	(0.508, 13.656)
Secondary and Exploratory					
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	277/342 (81.0)	248/323 (76.8)	4.007	(-2.201, 10.214)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	273/379 (72.0)	242/376 (64.4)	7.606	(0.980, 14.232)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	273/342 (79.8)	242/323 (74.9)	4.662	(-1.663, 10.988)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	286/379 (75.5)	257/376 (68.4)	7.076	(0.642, 13.510)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	286/342 (83.6)	257/323 (79.6)	3.899	(-2.028, 9.825)
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	224.1 (200.8, 247.4)	206.7 (184.9, 228.5)	17.4	(-14.5, 49.3)

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach. Subjects with missing HIV-1 RNA due to Abbott manufacture agent recall were excluded from the analysis.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum. The 95% CI for mean difference in CD4 change was based on t-distribution.

Analysis of post-baseline data includes laboratory records collected after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Note: Doravirine 100 mg QD and Darunavir 800 mg + ritonavir 100 mg QD were administered with FTC/TDF or ABC/3TC.

n = Number of subjects in each subcategory.

N = Number of subjects in each treatment group.

Source: [P018MK1439: analysis-adsl; adcd4; adrna]

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Protocol-Defined Virologic Failure and Development of Viral Drug Resistance

Rates of PDVF (defined in [Sec. 2.7.3-trtmtnve96wk: 1.4.1.3]) through Week 96 were low and comparable in the DOR (8.9%) and DRV+r (11.2%) treatment groups, with most participants with PDVF in each treatment group being rebounders who had initially responded to treatment. Additional details are in [Table 2.7.3-trtmtnve96wk: 4].

Among participants who met criteria for PDVF (either rebounders or non-responders), 11 of 34 in the DOR treatment group had samples available and results reported for genotypic and/or phenotypic viral drug resistance testing [Ref. 5.3.5.1: P018MK1439: 11.1.4.2.1]. Virus from 1 of the 11 DOR-treated participants with resistance-testing results was found to have primary genotypic and phenotypic resistance to DOR (via RT V106A and P225H mutations) and to FTC/3TC at Week 72.

Among participants who discontinued for reasons other than viral failure, 4 of 61 in the DOR group had samples available and results reported for viral genotypic and/or phenotypic viral drug resistance testing [Ref. 5.3.5.1: P018MK1439: 11.1.4.2.2]. Virus from 1 of the 4 DOR-treated participants with results from resistance testing, who was discontinued at Week 24 due to noncompliance, was found to have resistance mutations to DOR (RT V106I, H221Y, and F227C) and to FTC/3TC.

Listings by participant detailing viral resistance are provided in [Ref. 5.3.5.1: P018MK1439: 16.2.6].

4.4.2 P021 Efficacy Results

A total of 734 participants were randomized 1:1 in P021 to receive DOR/3TC/TDF or EFV/FTC/TDF. A total of 728 participants (364 in each treatment group) received at least 1 dose of study medication.

Efficacy Summary at Week 96

At Week 96, antiretroviral efficacy in the DOR treatment group was comparable to that in the EFV/FTC/TDF treatment group with regard to proportion of participants with HIV-1 RNA <50 copies/mL, using the FDA snapshot approach; this finding supports the non-inferiority of DOR/3TC/TDF to EFV/FTC/TDF previously established at Week 48. Specifically, 77.5% and 73.6% of participants in the DOR/3TC/TDF and EFV/FTC/TDF treatment groups, respectively, achieved HIV-1 RNA <50 copies/mL, with an estimated treatment difference of 3.8% (95% CI: -2.4, 10.0) [Table 2.5-trtmtnve96wk: 3].

Results for treatment-group differences in proportion of participants achieving HIV-1 RNA <40 copies/mL were similar to those for the endpoint of HIV-1 RNA <50 copies/mL.

Analysis of the change from baseline in $CD4^+$ T-cell count produced comparable results for both treatment groups, with a mean increase from baseline at Week 96 of 238 cells/mm^3 in the DOR group and 223 cells/mm^3 in the EFV/FTC/TDF group [Table 2.5-trtmtnve96wk: 3].

Table 2.5-trtmtnve96wk: 3

PN021: Efficacy Analysis at Week 96
Base Study (Double Blind)

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (DOR/3TC/TDF - EFV/FTC/TDF)[‡]	
		DOR/3TC/TDF QD n/N (%)	EFV/FTC/TDF QD n/N (%)	Estimated Difference	95% CI
Primary					
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	282/364 (77.5)	268/364 (73.6)	3.815	(-2.412, 10.042)
Secondary and Exploratory					
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	282/337 (83.7)	268/312 (85.9)	-2.186	(-7.707, 3.335)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	277/364 (76.1)	265/364 (72.8)	3.268	(-3.057, 9.593)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	277/337 (82.2)	265/312 (84.9)	-2.710	(-8.411, 2.991)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	292/364 (80.2)	272/364 (74.7)	5.471	(-0.592, 11.533)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	292/337 (86.6)	272/312 (87.2)	-0.509	(-5.727, 4.708)
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI
Change from Baseline in CD4 Cell Count (cells/mm3)	OF	237.7 (214.9, 260.6)	223.0 (198.4, 247.6)	14.7	(-18.7, 48.2)

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum. The 95% CI for mean difference in CD4 change was based on t-distribution.

Analysis of post-baseline data includes laboratory records collected after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

n = Number of subjects in each subcategory.

N = Number of subjects in each treatment group.

Source: [P021MK1439A: analysis-adsl; adcd4; adrna]

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Protocol-Defined Virologic Failure and Development of Viral Drug Resistance

Rates of PDVF through Week 96 were low and comparable in the DOR/3TC/TDF (9.3%) and EFV/FTC/TDF (7.7%) treatment groups; the majority of participants with PDVF in each treatment group were rebounders [Table 2.7.3-trtmtnve96wk: 6].

Among participants who met the criteria for PDVF (either rebound or non-response), 22 of 34 in the DOR/3TC/TDF group and 16 of 28 in the EFV/FTC/TDF group had samples available and results reported for genotypic and/or phenotypic drug resistance testing. Isolates from 7 of the 34 DOR/3TC/TDF-treated participants with PDVF were found to have primary genotypic resistance to DOR, with 6 of these also having phenotypic resistance to DOR. The most common resistance mutation was in the RT V106 codon (5 of the 7 isolates had V106I, V106V/I, V106A, or V106M/T substitutions in combination with 1 or more of the following substitutions: A98A/G, H221H/Y, P225P/H, F227C or F227C/R, Y318Y/F), while 1 isolate had genotypic resistance conferred through a Y188L mutation alone. Six of the 7 isolates also had mutations associated with resistance to the NRTIs 3TC and/or tenofovir [Ref. 5.3.5.1: P021MK1439: 11.1.4.2.1.1].

Among participants who discontinued for reasons other than virologic failure, 13 of 39 in the DOR/3TC/TDF treatment group and 22 of 62 in the EFV/FTC/TDF group had samples available for testing and results reported for genotypic and/or phenotypic drug resistance testing [Ref. 5.3.5.1: P021MK1439: 11.1.4.2.2]. An isolate from 1 DOR/3TC/TDF-treated participant was found to have primary genotypic resistance, specifically a RT V106I mutation, but no phenotypic resistance; this participant had been randomized with this exclusionary mutation and was discontinued at Week 4.

All participants who received DOR/3TC/TDF and developed resistance to study drugs did so by Week 48; no additional resistance was observed between Weeks 48 and 96. Listings by participant detailing viral resistance are provided in [Ref. 5.3.5.1: P021MK1439: 16.2.6].

4.4.3 Efficacy Results in the Pooled Population

This section presents efficacy analyses based on pooled data from P018 and P021, comparing data from the combined DOR group (n=747) with data from both the DRV+r group from P018 (n=383) and the EFV/FTC/TDF group from P021 (n=364). Participants who received DOR in P018 or DOR/3TC/TDF in P021 are referred to as the “DOR Regimen” group.

4.4.3.1 Study Population (Disposition and Baseline Subject Characteristics – Pooled Population)

The disposition of participants in the Phase 3 trials included in this submission is presented in [Sec. 2.7.3-trtmtnve96wk: 3.2]. Data from P018 and P021 represent subject status through Week 96.

In the pooled efficacy analyses, comparable proportions of participants across treatment groups discontinued from the trial for any reason by Week 96 (21.1% in the DOR Regimen group to 28.6% in the DRV+r group). While proportions of participants who discontinued due to specific reasons were also generally balanced across treatment groups, a higher

proportion discontinued due to AE in the EFV/FTC/TDF group compared with the DOR Regimen group (7.1% and 2.3%, respectively) [Table 2.7.3-trtmtnve96wk: 7].

Demographic and prognostic characteristics were comparable across the DOR Regimen group and both comparator groups, with the exception of various racial and regional subgroups; these differences reflect the worldwide enrollment of the pivotal trials [Table 2.5-trtmtnve96wk: 4]. Most participants were male and white; the proportion of enrolled women (14.6% to 16.5%) is consistent with that in other Phase 3 clinical trials in HIV-1-infected patients. Approximately 75% of participants in each treatment group were in the stratum of screening HIV-1 RNA ≤100,000 copies/mL. The numbers of elderly (≥65 years of age) participants and participants with hepatitis B or C co-infection were limited.

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Table 2.5-trtmtnve96wk: 4

Subject Baseline Characteristics
Efficacy Pool (P018 and P021 Combined)

	DOR Regimen (P018, P021) (N = 747)	DRV+r (P018) (N = 383)	EFV/FTC/TDF (P021) (N = 364)
Gender n (%)			
Male	624 (83.5)	326 (85.1)	311 (85.4)
Female	123 (16.5)	57 (14.9)	53 (14.6)
Race n (%)			
American Indian or Alaska Native	12 (1.6)	3 (0.8)	6 (1.6)
Asian	66 (8.8)	7 (1.8)	65 (17.9)
Black or African American	154 (20.6)	88 (23.0)	68 (18.7)
Multiple	58 (7.8)	2 (0.5)	55 (15.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)	2 (0.5)	0 (0.0)
White	456 (61.0)	280 (73.1)	170 (46.7)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
Ethnicity n (%)			
Hispanic or Latino	219 (29.3)	86 (22.5)	119 (32.7)
Not Hispanic or Latino	522 (69.9)	290 (75.7)	239 (65.7)
Unknown	6 (0.8)	7 (1.8)	6 (1.6)
Region n (%)			
Africa	60 (8.0)	22 (5.7)	27 (7.4)
Asia/Pacific	71 (9.5)	3 (0.8)	62 (17.0)
Europe	258 (34.5)	179 (46.7)	94 (25.8)
Latin America	127 (17.0)	33 (8.6)	87 (23.9)
North America	231 (30.9)	146 (38.1)	94 (25.8)
Age (years)			
18 to 64	743 (99.5)	379 (99.0)	362 (99.5)
>=65	4 (0.5)	4 (1.0)	2 (0.5)
Mean (SD)	34.2 (10.5)	35.7 (10.7)	32.7 (9.9)
Median (min, max)	32.0 (18, 70)	34.0 (18, 69)	30.0 (18, 69)
Baseline CD4 Cell Count (cells/mm^3)			
N†	747	383	364
Mean (SD)	433.7 (212.9)	411.9 (229.6)	415.5 (210.6)
Median (min, max)	412.0 (19, 1822)	393.0 (19, 1303)	388.0 (19, 1452)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	15 (2.0)	19 (5.0)	10 (2.7)
>50 cells/mm^3 and <=200 cells/mm^3	71 (9.5)	48 (12.5)	36 (9.9)
>200 cells/mm^3	661 (88.5)	316 (82.5)	318 (87.4)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)			
N†	747	382	364
Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.5 (0.7)
Median (min, max)	4.4 (2.0, 6.4)	4.4 (2.4, 6.5)	4.5 (2.6, 6.4)

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Subject Baseline Characteristics
Efficacy Pool (P018 and P021 Combined)

	DOR Regimen (P018, P021) (N = 747)	DRV+r (P018) (N = 383)	EFV/FTC/TDF (P021) (N = 364)
Baseline Plasma HIV-1 RNA (copies/mL)			
N[†]	747	382	364
Geometric Mean	25299.9	26532.4	29087.1
Median (min, max)	25406.0 (105, 2776658)	27357.0 (235, 3272236)	29732.5 (403, 2692740)
Baseline Plasma HIV-1 RNA n (%)			
<=100,000 copies/mL	591 (79.1)	309 (80.7)	282 (77.5)
>100,000 copies/mL	156 (20.9)	73 (19.1)	82 (22.5)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
Baseline Plasma HIV-1 RNA n (%)			
<=500,000 copies/mL	720 (96.4)	370 (96.6)	346 (95.1)
>500,000 copies/mL	27 (3.6)	12 (3.1)	18 (4.9)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
History of AIDS n (%)			
Yes	82 (11.0)	37 (9.7)	53 (14.6)
No	665 (89.0)	346 (90.3)	311 (85.4)
Stratum n (%)			
Screening HIV-1 RNA<= 100,000	565 (75.6)	289 (75.5)	274 (75.3)
Screening HIV-1 RNA> 100,000	182 (24.4)	94 (24.5)	90 (24.7)
Baseline Hepatitis Status[††]			
Hep B and/or C Positive	22 (2.9)	18 (4.7)	9 (2.5)
Hep B Positive Only	13 (1.7)	12 (3.1)	8 (2.2)
Hep C Positive Only	9 (1.2)	6 (1.6)	1 (0.3)
Hep B and C Negative	725 (97.1)	365 (95.3)	355 (97.5)
Viral Subtype n (%)			
Clade B	498 (66.7)	272 (71.0)	253 (69.5)
Non-Clade B	247 (33.1)	111 (29.0)	111 (30.5)
Missing	2 (0.3)	0 (0.0)	0 (0.0)

[†] Subjects with missing results excluded.
[††] Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C virus.
N = Number of subjects randomized and treated in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

Source: [ISE: analysis-adsl]

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4.4.3.2 Efficacy Summary at Week 96: Virologic and Immunologic Responses

Efficacy Summary at Week 96 and Over Time

Antiretroviral efficacy in the DOR Regimen group at Week 96 was comparable to that in both comparator groups: using the FDA snapshot approach, 75.2%, 66.0%, and 73.6% of participants in the DOR Regimen, DRV+r, and EFV/FTC/TDF groups, respectively, had <50 copies/mL HIV-1 RNA [Table 2.5-trtmtnve96wk: 5]. Similar results were seen when the 40 copies/mL and 200 copies/mL thresholds were used, as well as when the OF approach was used with each of these thresholds.

Immunologic efficacy in the DOR Regimen group at Week 96 was also comparable to that in both comparator groups: mean increase from baseline in $CD4^+$ T-cell count was 231, 207, and 223 cells/mm^3 in the DOR Regimen, DRV+r, and EFV/FTC/TDF groups, respectively [Table 2.5-trtmtnve96wk: 5].

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Table 2.5-trtmtnve96wk: 5

Efficacy Analysis at Week 96
Efficacy Pool (P018 and P021 Combined)

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		
		DOR Regimen (P018, P021) n/N (%)	DRV+r (P018) n/N (%)	EFV/FTC/TDF (P021) n/N (%)
Primary				
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	559/743 (75.2)	248/376 (66.0)	268/364 (73.6)
Secondary and Exploratory				
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	559/679 (82.3)	248/323 (76.8)	268/312 (85.9)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	550/743 (74.0)	242/376 (64.4)	265/364 (72.8)
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	550/679 (81.0)	242/323 (74.9)	265/312 (84.9)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	578/743 (77.8)	257/376 (68.4)	272/364 (74.7)
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	578/679 (85.1)	257/323 (79.6)	272/312 (87.2)
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	230.9 (214.6, 247.2)	206.7 (184.9, 228.5)	223.0 (198.4, 247.6)

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach. P018 subjects with missing HIV-1 RNA due to Abbott manufacture agent recall were excluded from the analysis.
Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.
n = Number of subjects in each subcategory.
N = Number of subjects in each treatment group.

Source: [ISE: analysis-adsl; adcd4; adrna]

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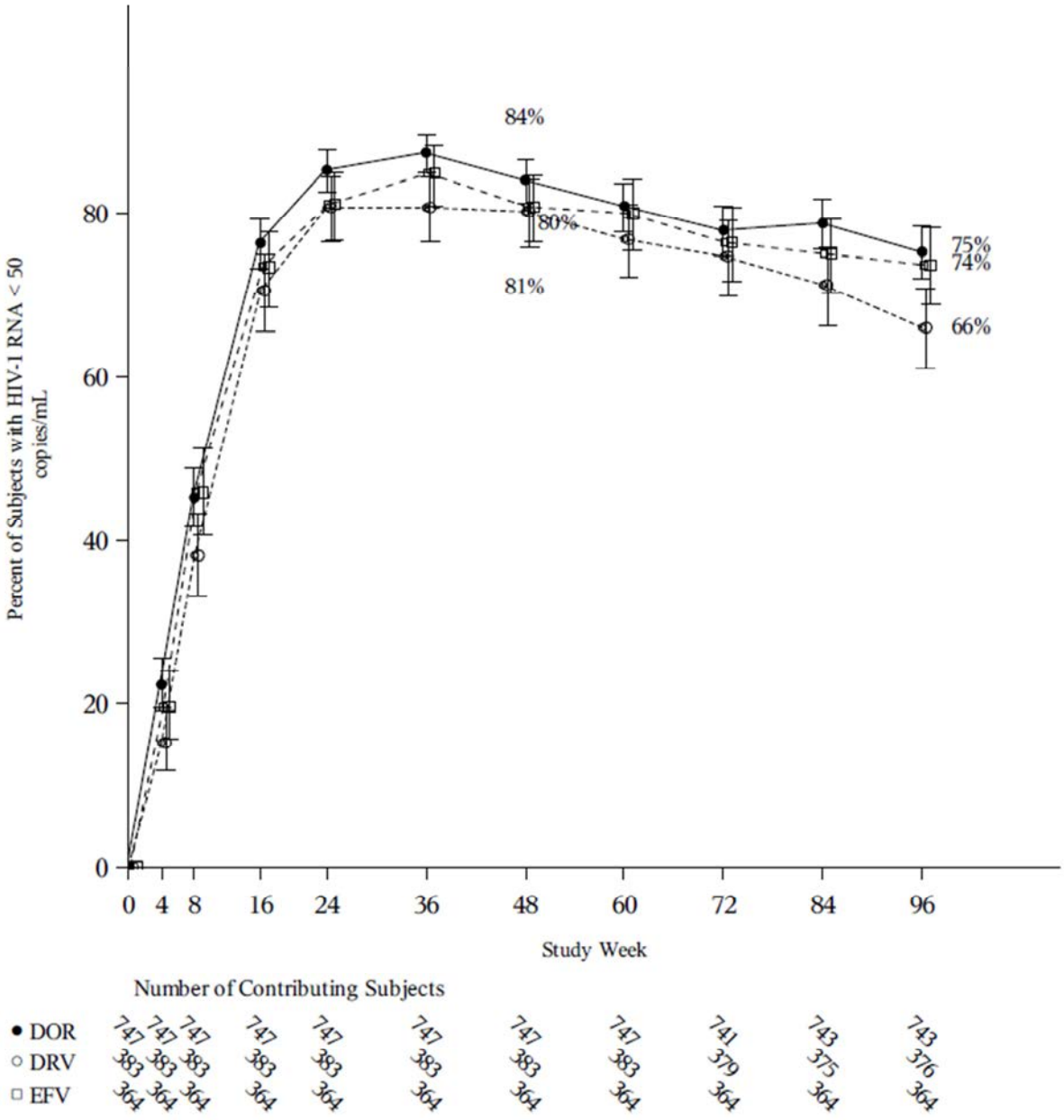
Persistence of Efficacy

At each time point through Week 96, the response was robust and comparable in the DOR Regimen group and each of the comparator groups. This response was sustained through Week 96 in each of the individual Phase 3 trials (P018 and P021) and in the integrated efficacy dataset. Results using the FDA snapshot approach and the threshold of 50 copies/mL HIV-1 RNA are shown in [Figure 2.5-trtmtnve96wk: 1]; consistent patterns of virologic response over time across all treatment groups were also seen when thresholds of 40 and 200 copies/mL were used, and when the OF approach to missing data was used to analyze each of these thresholds. As described in the original application, durable efficacy through Week 96 was seen in the Phase 2 trial P007 as well. Consistent with the above results, the risk of loss-of-response in the pooled analysis was comparable across the DOR Regimen, DRV+r, and EFV/FTC/TDF groups, with no clinically meaningful difference seen [Sec. 2.7.3-trtmtnve96wk: 3.3.3].

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Figure 2.5-trtmtnve96wk: 1

Proportion of Subjects With HIV-1 RNA < 50 copies/mL Over Time
Efficacy Pool (P018 and P021 Combined)
FDA Snapshot Approach
Weeks 0-96, Base Study (Double Blind)



DOR=DOR Regimen (P018, P021); DRV=DRV+r (P018); EFV=EFV/FTC/TDF (P021)
Source: [ISE: analysis-adsl; adrna]

Protocol-Defined Virologic Failure and Development of Viral Drug Resistance

Proportions of participants who met the criterion for PDVF by Week 96 were low and comparable across the DOR Regimen, the DRV+r, and the EFV/FTC/TDF groups (9.1%, 11.2%, and 7.7%, respectively); the majority of PDVF cases were due to rebound rather than non-response [Table 2.7.3-trtmtnve96wk: 11]. Notably, between half and two-thirds of participants in each treatment group had low-level viremia, ie, HIV-1 RNA between 50 and 200 copies/mL, at the time of virologic failure confirmation. This observation is consistent with the possibility that this low-level viremia meeting PDVF criteria was due to noncompliance with study medication.

Among participants in P018 and P021 in the DOR Regimen group who met PDVF criteria or who discontinued for a reason other than PDVF, 47 had genotype and/or phenotypic testing results available. A total of 10 of these DOR-treated participants had viral isolates with primary genotypic resistance mutations, of which 8 also had phenotypic resistance [Figure 2.7.3-trtmtnve96wk: 12]. All but one of these cases of resistance among DOR-treated participants developed by Week 48. The most common substitution was at the RT V106 codon (V106A, V106I, or V106M/T, with V106I being the most frequently observed); phenotypic resistance was seen when one of these V106 substitutions was combined with 1 or more of the following substitutions: A98G, H221Y, P225H, F227C or F227R, Y318Y/F. In a single case, phenotypic resistance was seen when Y188L occurred alone [Table 2.7.3-trtmtnve96wk: 12].

Efficacy in Subgroups

Both virologic and immunologic efficacy were comparable across the subgroups defined by various demographic and prognostic factors and analyzed using the OF approach. No clinically meaningful differences across subgroups in antiretroviral efficacy were seen in the DOR Regimen or either comparator group, whether the 50 copies/mL HIV-1 RNA threshold was used or the 40 or 200 copies/mL thresholds were used. Similarly, no clinically meaningful differences in immunologic efficacy were seen in the DOR Regimen or comparator groups for all demographic and prognostic factors.

4.5 Rationale for Applicability of Foreign Data to the United States Population

As highlighted in [Sec. 2.5-trtmtnve96wk: 4.4.3.1], 30.9% of the pooled population (P018 and P021) were from the North American region (the majority of participants in the North American region were from the United States). In the integrated dataset, efficacy results were consistent among participants from North America and participants from other regions [Sec. 2.7.3-trtmtnve96wk: 3.4]. In addition, DOR and DOR/3TC/TDF were generally well tolerated and had a safety profile that was similar among participants from North America and participants from other regions [Sec. 2.7.4-trtmtnve96wk: 5.1]. The Applicant considers foreign data to be applicable to the population in the United States.

4.6 Efficacy Conclusions for Doravirine and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

Analysis of the pooled dataset at Week 96 showed antiretroviral efficacy in the DOR Regimen group at Week 96 was comparable to that in both the DRV+r and EFV/FTC/TDF groups, using the FDA snapshot approach to missing data and the 50 copies/mL HIV-1 RNA endpoint. Consistent results were seen using the OF missing-data approach and additional HIV-1 RNA thresholds (40 and 200 copies/mL). In P018 at Week 96, antiretroviral efficacy in the DOR treatment group was higher than that in the DRV+r treatment group with regard to observed proportion of participants with HIV-1 RNA <50 copies/mL (as well as <40 and <200 copies/mL) using the FDA snapshot approach. In P021 at Week 96, antiretroviral efficacy in the DOR treatment group was comparable to that in the EFV/FTC/TDF treatment group for all 3 HIV-1 RNA thresholds, using both missing-data approaches. These findings support the non-inferiority of DOR with regard to both DRV+r and EFV/FTC/TDF previously established at Week 48.

Immunologic efficacy in the DOR Regimen group at Week 96 was also comparable to that in both comparator groups; the mean increase from baseline in $CD4^+$ T-cell count was 231, 207, and 223 cells/mm^3 in the DOR Regimen, DRV+r, and EFV/FTC/TDF groups, respectively.

Rates of PDVF through Week 96 were low and comparable in the DOR/3TC/TDF (9.3%) and EFV/FTC/TDF (7.7%) treatment groups. Rates of development of viral genotypic and phenotypic drug resistance to DOR in the DOR Regimen group by Week 96 were also low (10/747 [1.3%] and 8/747 [1.1%], respectively). Most participants who received DOR or DOR/3TC/TDF and developed resistance to study drugs did so by Week 48; only 1 participant, in P018, developed resistance to DOR between Week 48 and Week 96.

5 OVERVIEW OF SAFETY

The safety data reported in [Sec. 2.7.4-trtmtnve96wk] provide an analysis of the safety profile of DOR and DOR/3TC/TDF in 979 treatment-naïve participants who received DOR or DOR/3TC/TDF in the Phase 2b/3 trials [P007, P018, and P021] through 96 weeks treatment. Results of Phase 1 trials were reported in the Original Application. Overall, the safety analyses demonstrate that DOR, both as a single agent and as DOR/3TC/TDF, was generally well-tolerated through 96 weeks of treatment. The safety profiles of DOR and DOR/3TC/TDF demonstrate safety benefits over DRV+r and EFV-containing regimens; see [Sec. 2.5-trtmtnve96wk: 6.2].

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5.1 Summary of Approach to Safety Assessment

Analysis Populations

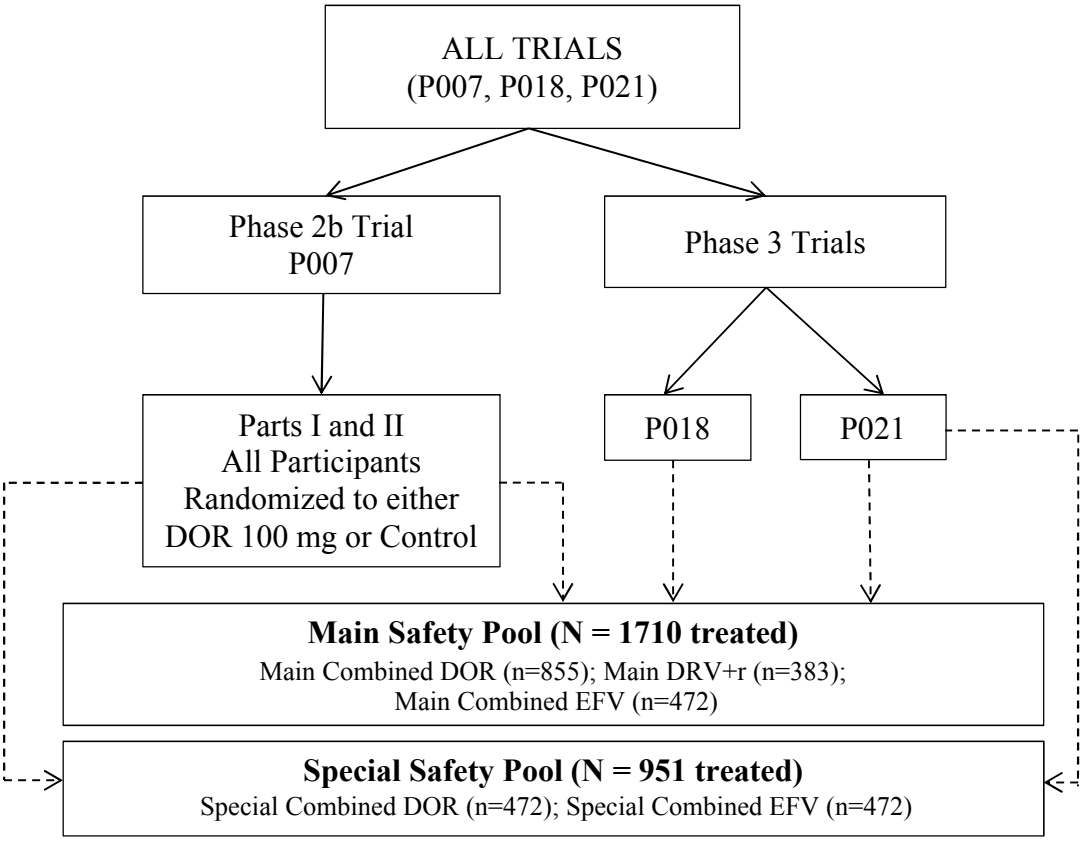
Safety analyses were based on the All Participants as Treated (ASaT) population (all randomized participants who received at least 1 dose of any study medication). This Supplemental Application provides analyses of safety data from 96 weeks' treatment in the Phase 2 and Phase 3 trials, with integrated safety analyses conducted on 2 pools of participants: the Main Safety Pool (MSP) and the Special Safety Pool (SSP) [Figure 2.5-trtmtnve96wk: 2].

- The MSP consists of 1710 participants: all treated participants in P018 and P021 and those participants in P007 initially randomized (in Part I or Part II) to the DOR 100-mg group. The MSP was the primary pool for evaluation of all AEs.
- The SSP consists of 944 participants: all treated participants in P021 and those participants in P007 initially randomized (in Part I or Part II) to the DOR 100-mg or EFV groups. The SSP was primarily used to assess proportion of participants discontinuing due to AEs by Week 96, time to discontinuation due to AEs by Week 96, and neuropsychiatric events using prespecified categories of AEs. A predefined list of neuropsychiatric AEs in the following categories was examined: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders.

See [Sec. 2.7.4-trtmtnve96wk: 1.1.2] for further details regarding the MSP and SSP.

Figure 2.5-trtmtnve96wk: 2

Integrated Safety Populations



Main Combined DOR Treatment Group (P018, P021 and 100-mg arm of P007): DOR 100 mg administered with FTC/TDF or ABC/3TC or as DOR/3TC/TDF (100/300/300 mg).

Special Combined DOR Treatment Group (P021 and 100-mg arm of P007): DOR 100 mg administered with FTC/TDF or as DOR/3TC/TDF (100/300/300 mg).

Main DRV+r Treatment Group (from P018): DRV+r 800/100 mg administered with FTC/TDF or ABC/3TC.

Main and Special Combined EFV Treatment Groups (P021 and 100-mg arm of P007): EFV 600 mg administered with FTC/TDF, or EFV/FTC/TDF.

Assessment of Safety

Assessment of AEs for the individual Phase 2b and Phase 3 trials and for the integrated safety data included review of commonly reported AEs, deaths, other SAEs, AEs leading to discontinuation, and AEs of special interest, specifically, central nervous system (CNS)/neuropsychiatric AEs (for comparison of DOR with EFV in P007 and P021).

Evaluations of laboratory values included review of Pre-Defined Limit of Change (PDLC) results and assessment of change from baseline for laboratory parameters. Among the parameters evaluated were specified fasting lipid values in the P018 and P021 trials individually and in the integrated safety data.

5.2 Extent of Exposure

A total of 979 participants received DOR in the Phase 2 and 3 trials: 232 participants in P007 (of whom 108 received 100 mg QD for up to 96 weeks), 383 participants in P018 (100 mg for up to 96 weeks), and 364 participants in P021 (as DOR/3TC/TDF [100 mg/300 mg/ 300 mg]) for up to 96 weeks) [Table 2.7.4-trtmtnve96wk: 2]. The mean duration of exposure to any dose of DOR in P007 and P018 was 573.8 days [Table 2.7.4-trtmtnve96wk: 3], while the mean duration of exposure to DOR/3TC/TDF in P021 was 587.4 days [Table 2.7.4-trtmtnve96wk: 4].

5.3 Analysis of Adverse Experiences

The current Supplemental Application focuses on analysis of AEs in the integrated data from the MSP and the SSP. AE data from Phase 1 trials were presented and analyzed in the Original Application. For the Phase 2b/3 trials, grading of laboratory abnormality severity was based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS Criteria) [Ref. 5.4: 04MB77].

Analyses of AEs in the Phase 2 P007 trial and the Phase 3 trials, P18 and P021, are found in the individual CSRs [Ref. 5.3.5.1: P007MK1439] [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A].

5.3.1 Adverse Events in the Main Safety Pool (Protocols 007, 018, and 021)

While the overall incidences of AEs and SAEs in the Main Combined DOR, Main DRV+r, and Main Combined EFV groups through Week 96 were comparable, the frequencies of drug-related AEs (including SAEs) and discontinuations due to AE (including drug-related AE) in the Main Combined DOR group were lower than in the Main Combined EFV group [Table 2.5-trtmtnve96wk: 6]. (Incidences of all categories of AEs were comparable in the Main Combined DOR and Main DRV+r groups.)

Table 2.5-trtmtnve96wk: 6

Adverse Event Summary
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-96, Base Study (Double Blind)

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
with one or more adverse events	742	(86.8)	317	(82.8)	443	(93.9)
with no adverse event	113	(13.2)	66	(17.2)	29	(6.1)
with drug-related† adverse events	277	(32.4)	123	(32.1)	299	(63.3)
with serious adverse events	59	(6.9)	33	(8.6)	43	(9.1)
with serious drug-related adverse events	2	(0.2)	1	(0.3)	7	(1.5)
who died	1	(0.1)	1	(0.3)	2	(0.4)
discontinued‡ due to an adverse event	22	(2.6)	13	(3.4)	38	(8.1)
discontinued due to a drug-related adverse event	15	(1.8)	8	(2.1)	34	(7.2)
discontinued due to a serious adverse event	5	(0.6)	3	(0.8)	5	(1.1)
discontinued due to a serious drug-related adverse event	1	(0.1)	1	(0.3)	4	(0.8)

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Main Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.

Main Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Source: [ISS: analysis-adsl] [ISS: tabulations-aeplus]

The most frequently reported AEs (incidence ≥10%) through Week 96 in the Main Combined DOR group and the Main DRV+r group (in descending order for the Main Combined DOR group) were diarrhea, headache, nasopharyngitis, upper respiratory tract infection, and nausea. The most frequently reported AE in the Main Combined EFV group was dizziness, with a higher frequency (36.2%) than in the Main Combined DOR and Main DRV+r groups (8.5% and 5.0%, respectively). Abnormal dreams was also a frequently reported AE in the Main Combined EFV group (13.3%) but not in the Main Combined DOR and Main DRV+r groups (<5% of participants in each), as was rash (11.4% in the Main Combined EFV group, <5% in the Main Combined DOR and Main DRV+r groups) [Table 2.5-trtmtnve96wk: 7].

Table 2.5-trtmtnve96wk: 7

Subjects With Adverse Events
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-96, Base Study (Double Blind)

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
with one or more adverse events	742	(86.8)	317	(82.8)	443	(93.9)
with no adverse events	113	(13.2)	66	(17.2)	29	(6.1)
Ear and labyrinth disorders	**24**	**(2.8)**	**6**	**(1.6)**	**26**	**(5.5)**
Eye disorders	**24**	**(2.8)**	**10**	**(2.6)**	**24**	**(5.1)**
Gastrointestinal disorders	**345**	**(40.4)**	**174**	**(45.4)**	**199**	**(42.2)**
Diarrhoea	129	(15.1)	91	(23.8)	76	(16.1)
Nausea	89	(10.4)	52	(13.6)	53	(11.2)
Vomiting	43	(5.0)	11	(2.9)	36	(7.6)
General disorders and administration site conditions	**159**	**(18.6)**	**64**	**(16.7)**	**89**	**(18.9)**
Fatigue	62	(7.3)	23	(6.0)	31	(6.6)
Infections and infestations	**522**	**(61.1)**	**222**	**(58.0)**	**276**	**(58.5)**
Bronchitis	39	(4.6)	29	(7.6)	27	(5.7)
Nasopharyngitis	115	(13.5)	52	(13.6)	56	(11.9)
Pharyngitis	47	(5.5)	14	(3.7)	23	(4.9)
Syphilis	46	(5.4)	23	(6.0)	22	(4.7)
Upper respiratory tract infection	102	(11.9)	30	(7.8)	42	(8.9)
Injury, poisoning and procedural complications	**79**	**(9.2)**	**31**	**(8.1)**	**68**	**(14.4)**
Investigations	**105**	**(12.3)**	**46**	**(12.0)**	**73**	**(15.5)**
Metabolism and nutrition disorders	**70**	**(8.2)**	**41**	**(10.7)**	**54**	**(11.4)**
Musculoskeletal and connective tissue disorders	**165**	**(19.3)**	**59**	**(15.4)**	**88**	**(18.6)**
Back pain	52	(6.1)	11	(2.9)	28	(5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**46**	**(5.4)**	**15**	**(3.9)**	**36**	**(7.6)**
Nervous system disorders	**240**	**(28.1)**	**84**	**(21.9)**	**235**	**(49.8)**
Dizziness	73	(8.5)	19	(5.0)	171	(36.2)
Headache	128	(15.0)	46	(12.0)	71	(15.0)
Somnolence	17	(2.0)	6	(1.6)	29	(6.1)

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Subjects With Adverse Events
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-96, Base Study (Double Blind)

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**179**	**(20.9)**	**65**	**(17.0)**	**187**	**(39.6)**
Abnormal dreams	30	(3.5)	3	(0.8)	63	(13.3)
Depression	21	(2.5)	15	(3.9)	24	(5.1)
Insomnia	53	(6.2)	20	(5.2)	44	(9.3)
Nightmare	23	(2.7)	5	(1.3)	28	(5.9)
Reproductive system and breast disorders	**49**	**(5.7)**	**14**	**(3.7)**	**36**	**(7.6)**
Respiratory, thoracic and mediastinal disorders	**139**	**(16.3)**	**48**	**(12.5)**	**66**	**(14.0)**
Cough	48	(5.6)	10	(2.6)	26	(5.5)
Skin and subcutaneous tissue disorders	**176**	**(20.6)**	**69**	**(18.0)**	**143**	**(30.3)**
Rash	30	(3.5)	5	(1.3)	54	(11.4)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Main Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.
Main Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.
Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Source: [ISS: analysis-adsl] [ISS: tabulations-aeplus]

5.3.2 Prespecified Safety Endpoints in the Special Safety Pool (P007 and P021)

The SSP (participants in the P007 100-mg DOR group and P021) was used for the analyses of the proportion of participants who discontinued due to AE through Week 96, the time to discontinuation from the trials due to AE through Week 96, and neuropsychiatric events using a prespecified list of AEs.

5.3.2.1 Discontinuation and Time to Discontinuation Due to Adverse Events

Through Week 96 in the SSP, a lower proportion of participants discontinued the trial due to AE in the Special Combined DOR treatment group compared with the Special Combined EFV treatment group [Table 2.5-trtmtnve96wk: 8].

Table 2.5-trtmtnve96wk: 8

Analysis of Proportion of Subjects Discontinuing from the Study Due to Adverse Event
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)
Weeks 0-96, Base Study (Double Blind)

	Special Combined DOR		Special Combined EFV		Treatment Difference (Special Combined DOR - Special Combined EFV)
	n/N	(%)	n/N	(%)	Estimate (95% CI)[†]
Discontinuation Due to an Adverse Event	16/472	(3.4)	37/472	(7.8)	-4.4 (-7.6, -1.6)

[†] Based on Miettinen & Nurminen method with weights proportional to the size of each protocol (P007, P021).
Special Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Special Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.
n = Number of subjects in each subcategory.
N = Number of subjects in each treatment group.

Source: [ISS: analysis-adsl; adtte]

The cumulative discontinuation rate over time was lower in the Special Combined DOR group than in the Special Combined EFV group. Results of the log-rank test identified a treatment difference (nominal $p = 0.006$, unadjusted for multiplicity) by Week 96 in time to discontinuation due to AE [Figure 2.7.4-trtmtnve96wk: 2].

5.3.2.2 Neuropsychiatric Events

At Week 96, the proportions of participants with overall neuropsychiatric events were lower in the Special Combined DOR group compared with the Special Combined EFV group (28.4% vs. 57.6%) [Table 2.5-trtmtnve96wk: 9]. The majority of participants who reported neuropsychiatric events in this analysis had already reported them by Week 8 (20.3% vs. 50.6%), with most of the remainder reporting them by Week 48. The subcategories of dizziness and sleep disorders and disturbances had lower proportions of participants reporting neuropsychiatric events in the Special Combined DOR group compared with the Special Combined EFV group.

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Table 2.5-trtmtnve96wk: 9

Analysis of Subjects with Neuropsychiatric Adverse Events by Week 96
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR (N=472)		Special Combined EFV (N=472)		Treatment Difference (Special Combined DOR - Special Combined EFV)
	n	%	n	%	Estimate (95% CI)[†]
Subjects in population	472		472		
with one or more neuropsychiatric adverse events	134	(28.4)	272	(57.6)	-29.2 (-35.2, -23.1)
with no neuropsychiatric adverse events	338	(71.6)	200	(42.4)	29.2 (23.1, 35.2)
Dizziness	53	(11.2)	171	(36.2)	-25.0 (-30.2, -19.8)
Sleep Disorders and Disturbances	74	(15.7)	138	(29.2)	-13.6 (-18.8, -8.3)
Altered Sensorium	21	(4.4)	33	(7.0)	-2.5 (-5.7, 0.4)
Depression and Suicide/self-injury	27	(5.7)	41	(8.7)	-3.0 (-6.4, 0.3)
Psychosis and Psychotic Disorders	5	(1.1)	8	(1.7)	-0.6 (-2.4, 1.0)

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 20.1. Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a category is counted a single time for that category.

[†] The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each protocol (P007, P021).

Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Special Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Special Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; adcns]

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5.4 Clinical Laboratory Evaluations

Analyses of laboratory evaluations in the Phase 2 P007 trial and the Phase 3 trials, P18 and P021, are found in the individual CSRs [Ref. 5.3.5.1: P007MK1439] [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A].

In the MSP, the proportions of participants at Week 96 with clinical laboratory results meeting PDLC criteria for select laboratory parameters were generally similar; between-group differences for any given parameter did not exceed 2% across the 3 treatment groups [Sec. 2.7.4-trtmtnve96wk: 3.1.1] with few notable exceptions:

- A higher observed proportion of participants in the Main Combined DOR treatment group met the PDLC criteria for Grade 1 and Grade 2 total bilirubin (5.9% and 1.9%, respectively) compared with the Main DRV+r (1.9%, 0.3%) and the Main Combined EFV (0.6%, 0%) groups. In both P018 and P021, more DOR- or DOR/3TC/TDF-treated than comparator-treated participants had Grade 1 and Grade 2 bilirubin elevations. The majority of Grade 1 bilirubin elevations in the Main Combined DOR group were either single, transient elevations or 2 nonconsecutive Grade 1 elevations. The majority of participants with Grade 2 values had predose Grade 1 values and values that fluctuated between Grade 1 and Grade 2 during the trial. In both trials, none of the bilirubin elevations resulted in discontinuation from the trial, and no common etiology has been identified. These findings are similar to findings through Week 48, as reported in the original application. Specifically, among DOR-treated participants, the incidence of Grade 1 bilirubin elevations increased from 4.5% at Week 48 to 5.9% at Week 96 (ie, by 12 participants), and the incidence of Grade 2 bilirubin elevations increased from 1.8% to 1.9% (ie, by 1 participant). Grade 3 and 4 bilirubin elevations remained ≤0.2% (1 to 2 participants) among DOR-treated participants.
- A higher proportion of participants in the Main Combined EFV group met the PDLC Grade 1 criteria for both ALT (18.6%) and alkaline phosphatase (9.2%) compared with the Main Combined DOR group (12.9% and 2.8%, respectively).

When changes in laboratory parameters from baseline were evaluated in the MSP for fasting lipids, DOR was associated with decreases from baseline to Week 96 in mean values for LDL-C, non-HDL-C, and triglycerides, compared with increases in these values for both DRV+r and EFV [Table 2.5-trtmtnve96wk: 10]. A small mean increase in fasting cholesterol was noted in the Main Combined DOR group, relative to larger mean increases in the Main DRV+r and Main Combined EFV groups. Small increases in fasting HDL-C values were noted for each of the treatment groups.

Table 2.5-trtmtnve96wk: 10

Change From Baseline in Fasting Lipids at Week 96
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-96

Main Combined DOR			Main DRV+r			Main Combined EFV		
N	Baseline Mean	Mean Change (SD)	N	Baseline Mean	Mean Change (SD)	N	Baseline Mean	Mean Change (SD)
Fasting LDL Cholesterol (mg/dL)								
655	91.67	-0.53 (23.59)	317	91.86	14.00 (26.86)	306	90.79	10.78 (24.60)
Fasting Non-HDL Cholesterol (mg/dL)								
660	114.33	-1.32 (25.45)	324	114.56	17.65 (30.26)	315	114.92	14.95 (28.11)
Fasting Cholesterol (mg/dL)								
660	157.16	1.98 (27.67)	324	157.85	21.88 (32.89)	315	156.29	23.38 (29.06)
Fasting Triglyceride (mg/dL)								
660	115.20	-5.42 (72.04)	324	117.15	22.52 (81.42)	315	123.15	18.78 (90.27)
Fasting HDL Cholesterol (mg/dL)								
660	42.83	3.30 (11.22)	324	43.28	4.23 (11.48)	315	41.37	8.43 (11.26)
Total Cholesterol to HDL Ratio								
660	3.91	-0.15 (1.39)	324	3.94	0.10 (1.14)	315	4.03	-0.10 (1.31)

The Last Observation Carry Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Main Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of doravirine/ lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.

Main Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

N = Number of subjects with baseline and at least one postbaseline test result.

Source: [ISS: analysis-adsl; adlpd]

5.5 Safety in Special Groups and Situations

The safety of DOR and DOR/3TC/TDF at Week 96 was assessed in the MSP based on examination of intrinsic and extrinsic factors, as well as other situations (eg, overdose, use in pregnant or lactating women) likely to be encountered in the clinical practice of treating individuals with HIV-1 infection.

5.5.1 Intrinsic Factors

Clinical and laboratory AEs were reviewed for subgroups of participants based on age, gender, race, ethnicity, hepatitis B/C infection status, and baseline $CD4^+$ T-cell count [Sec. 2.7.4-trtmtnve96wk: 5.1]. AE and laboratory abnormality profiles were generally similar across treatment groups within each of the subgroups defined by gender, race/ethnicity, and age.

Small sample sizes for subgroups of participants defined by age ≥65 years (no participants were >70 years of age), female gender, certain races, and positive hepatitis B and/or C status preclude useful comparisons across treatment groups.

5.5.2 Extrinsic Factors and Drug-Drug Interactions

While the extrinsic factor of geographic region was not evaluated at Week 96, the analysis at Week 48 did not reveal any notable differences based on this factor.

Results of all Phase 1 trials, including those studying drug-drug interactions, were reported in the original application.

AE data from the MSP were analyzed for subgroups defined by the use of moderate or strong CYP3A4 inhibitors: while the overall incidence of AEs and AEs in various categories (SAEs, drug-related AEs, etc) was not affected by use of this drug class, proportions of participants with specific AEs (eg, diarrhea, nausea, headache, bronchitis, and pharyngitis) differed between these subgroups [Sec. 2.7.4-trtmtnve96wk: 5.3]. This finding is likely confounded by the underlying condition necessitating the use of a concomitant CYP3A inhibitor, as well as the concomitant therapy itself. These results are not indicative of a new safety concern.

5.5.3 Overdose

In the Phase 3 trials, there was a single report of overdose of DOR in the MSP: in P018, 1 participant reported an accidental overdose of 300 mg DOR on Day 399 [Ref. 5.3.5.1: P018MK1439: 12.2.6.1]. No AEs were reported with any of the overdoses, and no participant discontinued due to overdose.

5.5.4 Use in Pregnancy and Lactation

Females who were pregnant and/or lactating were excluded from enrollment into any of the clinical trials. In total, 8 treated participants (1 in the DOR 50-mg group in P007, 2 in the DOR group and 1 in the DRV+r group in P018, and 2 each in the DOR/3TC/TDF and EFV/FTC/TDF groups in P021) became pregnant during these trials and discontinued due to the pregnancy or to an associated AE. The outcomes of these pregnancies among the 5 DOR-treated participants were: a live birth with no congenital anomalies for 3 pregnancies (the participant in P007 and both participants in P018) and a spontaneous abortion for the other 2 pregnancies (both in P021). Neither of the spontaneous abortions was considered related to study drug. Additional information is provided in [Sec. 2.7.4-trtmtnve96wk: 5.3].

The use of DOR and DOR/3TC/TDF during pregnancy and lactation is not recommended. Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission.

5.6 Limitations of the Safety Database

The safety database in this application has no data or insufficient data for the following populations: treatment-experienced patients, patients above the age of 65, and pregnant or nursing women. Additionally, in the population examined, potential long-term safety signals

are unknown as there is limited safety data beyond 96 weeks of therapy. The Phase 3 trials (P018, P021) are continuing with open-label study extensions, and additional safety findings from this longer duration of follow-up will be analyzed.

5.6.1 Risk Management Plan

No changes have been made to the risk profile based on evaluation of the Week 96 safety data; therefore, there is no change to the Risk Management Plan provided in the Original Application.

5.7 Safety Conclusions for Doravirine and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

DOR and DOR/3TC/TDF were generally well tolerated in 855 HIV-1-infected, treatment-naïve participants treated for at least 96 weeks.

In the SSP, a lower proportion of DOR/3TC/TDF-treated participants compared to EFV/FTC/TDF-treated participants reported neuropsychiatric AEs by Week 96 in 2 of 5 prespecified categories (dizziness and sleep disorders/disturbances). Lower proportions of DOR/3TC/TDF-treated participants reported AEs in the other 3 categories (altered sensorium, depression and suicide/self-injury, and psychosis/psychotic disorders), although the 95% CI around the treatment difference included 0.

In the SSP, a lower proportion of DOR- DOR/3TC/TDF-treated participants discontinued the trial due to AE compared with EFV/FTC/TDF-treated participants. In addition, the cumulative discontinuation rate over time was lower in the Special Combined DOR group than in the Special Combined EFV group.

In the MSP, DOR and DOR/3TC/TDF were associated with decreases from baseline to Week 96 in mean values for LDL-C, non-HDL-C, and triglycerides, compared with increases in these values for both DRV+r and EFV. A small mean increase in fasting cholesterol was noted in the Main Combined DOR group, relative to larger mean increases in the Main DRV+r and Main Combined EFV groups. Small increases in fasting HDL-C values were noted for each of the treatment groups, including DOR.

In both P018 and P021, more DOR- or DOR/3TC/TDF-treated than comparator-treated participants had Grade 1 and Grade 2 bilirubin elevations, similar to findings through Week 48, as reported in the original application. None of the bilirubin elevations resulted in discontinuation from the trial, and no common etiology has been identified.

6 BENEFITS AND RISKS CONCLUSIONS

DOR and DOR/3TC/TDF have positive benefit/risk profiles that support the recommended dose regimens.

6.1 Therapeutic Context

6.1.1 Disease or Condition

Background information regarding HIV-1 infection, including the epidemiology and public health burden of HIV-1 infection, is found in [Sec. 2.5-trtmtnve96wk: 1.4] of this document.

6.1.2 Current Therapies

Background information regarding current HIV-1 therapies for treatment-naive patients is found in [Sec. 2.5-trtmtnve96wk: 1.4] of this document.

6.1.3 Medical Need

Lifelong ART is needed for HIV-1-infected patients, and as people living with HIV age, they commonly have multiple co-morbidities. There continues to be a need for HIV-1 therapies that are efficacious, safe, well tolerated, convenient for patients, with a distinct resistance profile, and without significant food effect or drug-drug interactions.

6.2 Benefits

The clinical benefits of treatment with DOR or DOR/3TC/TDF of HIV-1-infected, treatment-naïve patients are supported by the robust clinical trial data in a diverse population.

DOR and DOR/3TC/TDF showed:

- Non-inferior efficacy through Week 96 as compared with DRV+r and EFV in the 2 pivotal Phase 3 trials, as measured by the proportion of participants achieving HIV-1 RNA <50 copies/mL;
- Consistent efficacy across demographic and prognostic factors, including participants with high baseline HIV-1 RNA (>100,000 copies/mL) and low $CD4^+$ T-cell count (<200 cells/mm^3); and
- Robust immunological response with increases in $CD4^+$ T-cell counts from baseline similar to DRV+r and EFV.

DOR and DOR/3TC/TDF showed a favorable resistance profile with the following aspects:

- Potent in vitro antiviral activity against wild-type virus and the most common NNRTI-resistant variants: in 100% normal human serum, wild-type HIV-1 had an EC_{50} of 12 nM, with similarly low EC_{50}s of 21, 31, and 55 nM against HIV-1 mutants containing the most frequently transmitted NNRTI mutations RT K103N, Y181C, and G190A, respectively; and

- A low rate of resistance in Phase 2 and 3 trials with a unique resistance pathway that commonly requires more than 1 substitution to confer DOR resistance.

DOR and DOR/3TC/TDF demonstrated an overall safety profile similar to that seen at Week 48, specifically:

- DOR and DOR/3TC/TDF were generally well tolerated in HIV-1-infected, treatment-naïve adults for at least 96 weeks;
- A lower proportion of participants treated with DOR or DOR/3TC/TDF discontinued due to an AE by Week 96 compared with the combined EFV/FTC/TDF group;
- A superior neuropsychiatric profile with significantly fewer neuropsychiatric AEs compared with EFV-based regimens; and
- A favorable profile for fasting LDL-C and non-HDL-C through Week 96 when compared with EFV and DRV+r, with marked between-group differences favoring DOR.

6.3 Risks

As detailed above, the safety database has the following limitations:

- Limited data beyond 96 weeks (potential long-term safety signals may not be known).
- Very limited data in women who are pregnant/lactating.
- Minimal data in participants ≥65 years of age.

6.4 Benefit-risk Assessment

DOR, in combination with other antiretroviral therapies, and DOR/3TC/TDF have been shown to be efficacious in HIV-1-infected, treatment-naïve patients. Integrated safety analysis of DOR and DOR/3TC/TDF demonstrates that DOR is generally well tolerated and has a favorable safety profile with no untoward risks identified. Risks have been extensively analyzed and were found to be limited and can be safely managed by clinicians. A table summarizing the favorable and unfavorable effects in the Phase 2b/3 trials is provided in [Appendix 2.5-trtmtnve96wk: 1].

The efficacy and safety profiles for DOR and DOR/3TC/TDF, with new data through Week 96 supplied in the current supplemental application, show sufficient benefit to justify the update of data in the clinical efficacy and safety sections of the Prescribing Information.

7 LITERATURE REFERENCES

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[Ref. 5.4: 05084L] Department of HIV. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance. Geneva (Switzerland): World Health Organization (WHO); 2018 Jul. 14 p.

[Ref. 5.4: 0508DT] Saag MS, Benson CA, Gandhi RT, Hoy JF, Landovitz RJ, Mugavero MJ, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society–USA panel. JAMA. 2018 Jul 24-31;320(4):379-96.

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[Ref. 5.4: 053CRN] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV: Oct 2018. Washington (DC): U.S. Department of Health and Human Services (HHS); [last updated: 2018 Oct 25]. 331 p.

Appendix 1 Summary of Favorable and Unfavorable Effects in Doravirine Phase 2b and 3 Studies (P007, P018 and P021) in This Supplemental Application

Effect	Short Description	Unit	DOR Regimen	Comparator	Uncertainties / Strength of evidence	References
Favorable						
Proportion of subjects achieving HIV-1 RNA <50 copies/mL	Robust efficacy higher than that of DRV+r and comparable to that of EFV in Phase 3 trials	%	75.2	66.0 (DRV+r); 73.6 (EFV/FTC/TDF)		[Table 2.5-trtmtnve96wk: 2], [Table 2.5-trtmtnve96wk: 3], [Table 2.5-trtmtnve96wk: 5]
Proportion of subjects achieving HIV-1 RNA <40 copies/mL	Robust efficacy higher than that of DRV+r and comparable to that of EFV through Week 96 in Phase 3 trials	%	74.0	64.4 (DRV+r); 72.8 (EFV/FTC/TDF)		[Table 2.5-trtmtnve96wk: 2], [Table 2.5-trtmtnve96wk: 3], [Table 2.5-trtmtnve96wk: 5]
Mean increase in $CD4^+$ T-cell counts from baseline	A robust immunological response in Phase 3 trials	cells/mm^3	230.9	206.7 (DRV+r); 223.0 (EFV/FTC/TDF)		[Table 2.5-trtmtnve96wk: 5]
Proportion of subjects with neuropsychiatric AEs	Fewer neuropsychiatric AEs compared to EFV-based regimens in the Special Safety Population through Week 96	%	20.3 at Week 8; 25.0 at Week 48; 28.4 at Week 96	50.6 at Week 8 (EFV Group); 55.9 at Week 48 (EFV Group) 57.6 at Week 96 (EFV Group)		[Sec. 2.5-trtmtnve96wk: 5.3.2.2]
	Fewer neuropsychiatric AEs in the DOR regimen compared with EFV-based regimens in P021 through Week 96	%	26.4	58.5 (EFV/FTC/TDF)		[Ref. 5.3.5.1: P021MK1439A: Table 12-2]
Mean change from baseline in fasting lipids	More favorable lipid profile and superior LDL-C and non-HDL-C profile when compared with EFV and DRV+r at Week 96					[Table 2.5-trtmtnve96wk: 10]
	Fasting LDL cholesterol	mg/dL	-0.53	14.00 (DRV+r); 10.78 (EFV/FTC/TDF)		
	Fasting non-LDL cholesterol	mg/dL	-1.32	17.65 (DRV+r); 14.95 (EFV/FTC/TDF)		
	Fasting cholesterol	mg/dL	1.98	21.88 (DRV+r); 23.38 (EFV/FTC/TDF)		
	Fasting triglyceride	mg/dL	-5.42	22.52 (DRV+r) 18.78 (EFV/FTC/TDF)		
Rate of discontinuations due to AEs	A lower rate of discontinuations through Week 96 due to AEs and SAEs when compared with Special Combined EFV Group	%	3.4	7.8 (EFV Group)		[Table 2.5-trtmtnve96wk: 8]
Unfavorable						
Not Applicable						

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